

# Tamoxifen for women at high risk of breast cancer

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**Abstract:** Tamoxifen has been used as a treatment for women who have been diagnosed with breast cancer for roughly four decades and has been approved as chemoprevention for over ten years. Although tamoxifen has been proven to be beneficial in preventing breast cancer in high-risk women, its use has not been widely embraced. To some extent, this is due to several of its side effects, including an increased risk of endometrial cancer and pulmonary embolism, but these serious side effects are rare. The risks and benefits of tamoxifen chemoprevention should be considered for each patient.

**Keywords:** tamoxifen, breast cancer, women, chemoprevention

## Introduction

A large proportion of breast cancers express the estrogen receptor (ER), and the progression of these cancers is dependent on intact estrogen signaling. Treatment of ER-positive breast cancers usually includes a therapy that is designed to block estrogen signaling. Tamoxifen is an ER antagonist that has been used as a treatment for patients with breast cancer since the early 1970s.<sup>1</sup> A collaborative meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group found that, for women with ER-positive breast cancer, 5 years of tamoxifen therapy reduces the annual breast cancer death rate by 31%.<sup>2</sup> In addition, tamoxifen lowers the risk of developing a contralateral breast cancer by as much as one half.<sup>3</sup> This observation led scientists to believe that tamoxifen might be effective as a chemopreventive agent in healthy women who are at increased risk of developing the disease.<sup>1</sup> Several randomized trials have been conducted to test this hypothesis and these support the use of tamoxifen as a chemopreventive agent in high-risk women. As a result, the National Institute for Health and Care Excellence (NICE) in the UK recently updated its cancer prevention guidelines for women who are at high risk of developing the disease.<sup>4</sup> They recommend that women who have a strong family history of breast cancer but who have not been diagnosed with the disease be offered 5 years of chemoprevention with tamoxifen or raloxifene.<sup>4</sup> NICE also advocates for more women to be tested for genetic mutations that are known to cause cancer (*BRCA1* and *BRCA2*) and proposed more inclusive criteria for genetic testing.<sup>4</sup> This policy update in the UK is due in part to the greater acceptance of the value of chemoprevention in high-risk women, including those who carry a *BRCA* mutation.

It is important to consider the risks associated with tamoxifen use and to determine the risks and benefits for each group of women. Four groups of women who

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are at high risk of developing breast cancer are discussed here, including women with a family history of the disease, women with a *BRCA1* or *BRCA2* mutation, women with atypical hyperplasia in their breast tissue, and women with high density mammograms.

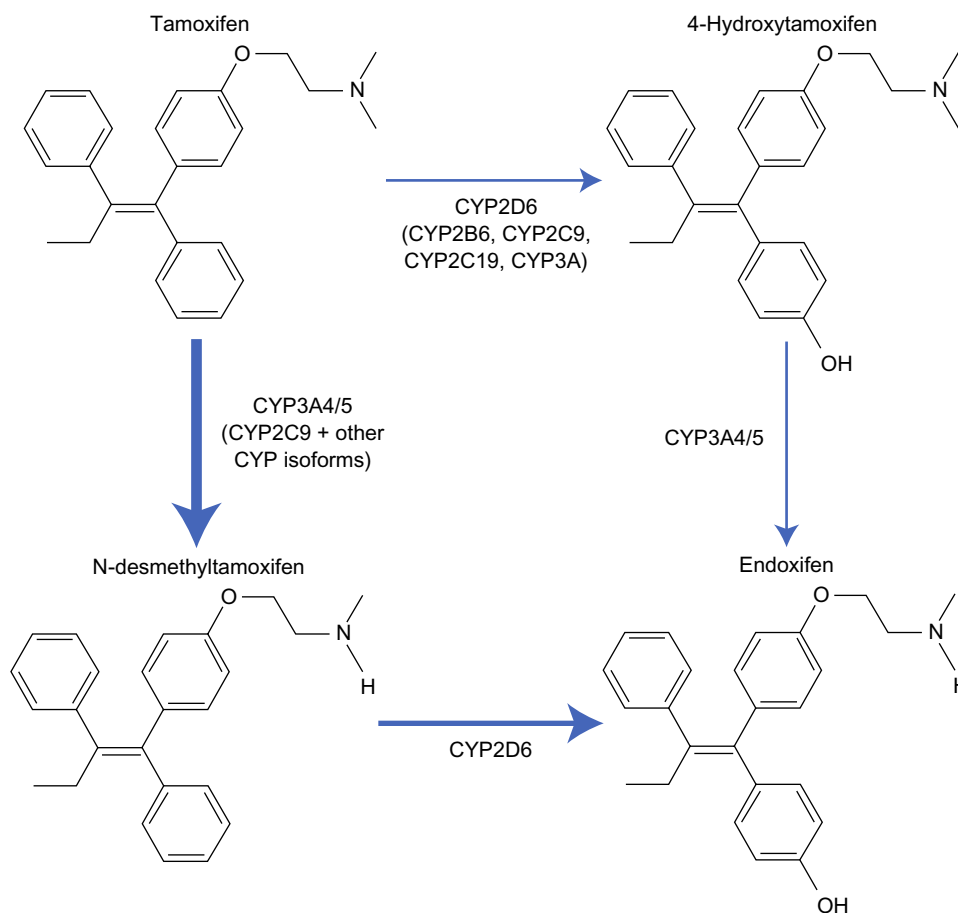
## Tamoxifen metabolism

Estrogen binds to hormone receptors and causes increased cell proliferation in the breast tissue. Tamoxifen blocks estrogen by binding to these receptors, and is therefore classified as an ER antagonist with respect to breast tissue. Tamoxifen itself has a weak affinity for the ER.<sup>5</sup> It is converted to active and inactive metabolites, which have a higher affinity for such receptors.<sup>5</sup> N-dimethyl-tamoxifen is the primary metabolite, which is subsequently metabolized into  $\alpha$ -hydroxy-tamoxifen, N-didesmethyl-tamoxifen, and 4-hydroxy-N-desmethyl-tamoxifen (also known as endoxifen).<sup>5</sup> Tamoxifen is also converted to 4-hydroxy-tamoxifen; a reaction catalyzed by many enzymes, including cytochrome P450 2D6, as can be

seen in Figure 1.<sup>5</sup> Endoxifen and 4-hydroxy-tamoxifen have at least a 10-fold higher affinity for ERs than tamoxifen.<sup>5</sup> In fact, in patients receiving tamoxifen therapy, endoxifen is found in serum concentrations 6–12-fold higher than 4-hydroxy-tamoxifen.<sup>5</sup> Thus, endoxifen is likely the most important metabolite required for tamoxifen activity.<sup>5</sup>

## High-risk groups

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial was designed to observe the effectiveness of tamoxifen as a chemopreventive agent in high-risk women. Eligibility was based on risk level and required that the participants have either a history of lobular carcinoma in situ, be aged 60 years or older, or have a  $\geq 1.66\%$  risk of breast cancer over the next 5 years. A total of 13,338 women at high risk of breast cancer were randomized to receive either oral tamoxifen or placebo for 5 years. Tamoxifen use resulted in a 43% reduction in invasive breast cancer (hazards ratio [HR] 0.57, 95% confidence interval [CI]



**Figure 1** Overview of tamoxifen metabolism pathway and the main enzymes involved. Thickness of the arrow demonstrates the relative contribution of each pathway.

**Note:** Adapted from Springer and *Current Oncology Reports*, 12,2010,7–15, CYP2D6 polymorphisms and tamoxifen metabolism: clinical relevance, Higgins MJ, Stearns V, figure number 1, with kind permission from Springer Science and Business Media.

**Abbreviations:** CYP, cytochrome P450; OH, hydroxide.

0.46–0.70).<sup>6</sup> The reduction was only seen for ER-positive cancers (HR 0.38, 95% CI 0.28–0.50). The magnitude of risk reduction varied by subgroup: women with a history of atypical hyperplasia experienced a risk reduction of 75% (HR 0.25, 95% CI 0.10–0.52).<sup>6</sup> The study investigators planned to evaluate the protective effect separately for white and black women but there were too few black women enrolled in the study to generate an estimate for this subgroup.

## Family history

Approximately 8% of breast cancer patients have an affected first-degree relative.<sup>7</sup> Women with a strong family history of breast cancer are a natural group to use to study chemopreventive agents for several reasons. These women tend to be motivated to participate as they have an increased risk of developing the disease and personal experience of breast cancer in a family member. Second, studies of high-risk women are more efficient with regards to cost. If there are side effects associated with chemoprevention, using women at high risk will optimize the risk/benefit ratio. The three main studies that have been conducted to study the effect of chemopreventive tamoxifen in women with a strong family history of breast cancer are The Royal Marsden Trial, The International Breast Cancer Intervention Study, and the Milan study.

The Royal Marsden Trial accrued 2,494 women between the ages of 30 and 70 years who had an increased risk of developing breast cancer due to a strong family history.<sup>8</sup> Participants were randomly assigned to either tamoxifen 20 mg/day or a placebo for 8 years and were followed for an additional 8 years. After patients were followed for up to 16 years, the risk of ER-positive invasive breast cancer was significantly lower in the tamoxifen group than in the placebo group (HR 0.61, 95% CI 0.43–0.86,  $P=0.005$ );<sup>8</sup> the risk of ER-negative breast cancer was not significantly lower in the tamoxifen group (HR 1.4, 95% CI 0.7–2.6,  $P=0.3$ ). The HR for any invasive cancer was 0.78 (95% CI 0.58–1.04) and was not statistically significant ( $P=0.1$ ).

In 2008, the International Breast Cancer Intervention Study randomly assigned 7,145 women aged 35–70 years who were at increased risk of breast cancer to receive tamoxifen 20 mg/day or placebo for 5 years.<sup>9</sup> Of these women, 3,433 had a first-degree relative with early-onset breast cancer and 4,410 had two or more first-degree or second-degree relatives with breast cancer.<sup>9</sup> After a median follow-up of 96 months, 142 women in the tamoxifen group were diagnosed with breast cancer compared with 195 women in the placebo group (HR 0.73, 95% CI 0.58–0.91,  $P=0.004$ ).<sup>9</sup> The reduction was limited to ER-positive cancers (HR 0.66, 95% CI 0.50–0.87).

A third study was initiated in Milan, Italy, in 1992 to assess the benefit of tamoxifen as a chemopreventive agent in Italian women with a strong family history of breast cancer. Because of the concern for endometrial cancer, only women who had a hysterectomy were included. Women were randomized to receive tamoxifen 20 mg/day or placebo for 5 years. After 11 years of follow-up, a total of 136 women had developed breast cancer (74 in the placebo group and 62 in the tamoxifen group).<sup>10</sup> The overall association with tamoxifen was not significant (HR 0.84, 95% CI 0.60–1.17), nor was there a significant reduction in the risk of ER-positive cancers (HR 0.77, 95% CI 0.51–1.16).

## BRCA mutations

The lifetime risk of a woman developing breast cancer is about 70% for a *BRCA1* mutation carrier and 60% for a *BRCA2* mutation carrier.<sup>11</sup> Women who undergo genetic testing and are found to be positive for a mutation have several options for risk management, including prophylactic surgery (mastectomy and/or oophorectomy) or chemopreventive drugs such as tamoxifen.

The Hereditary Breast Cancer Clinical Study Group conducted a case-control study matching 285 women with bilateral breast cancer and known *BRCA* mutation to 751 *BRCA* mutation carriers with unilateral breast cancer.<sup>12</sup> The results of this study showed that tamoxifen use was associated with a 50% reduction in the risk of developing a contralateral breast cancer in mutation carriers (odds ratio 0.50, 95% CI 0.30–0.85).<sup>12</sup> Researchers observed a benefit of tamoxifen for up to 4 years of use.<sup>12</sup>

Metcalf et al conducted a historical cohort study observing the protective effect of tamoxifen on women with a *BRCA1* or *BRCA2* mutation. Recruited were 491 women with stage I or stage II breast cancer, for whom a *BRCA1* or *BRCA2* mutation was identified in the family. The results showed a moderate decrease in the risk of contralateral breast cancer associated with tamoxifen use (HR 0.59, 95% CI 0.35–1.01,  $P=0.05$ ).<sup>13</sup> A greater protective effect was observed for *BRCA1* carriers (HR 0.57) than for *BRCA2* carriers (HR 0.73).<sup>13</sup> However, this difference was not statistically significant.<sup>13</sup>

A recent study was conducted by Phillips et al to determine if adjuvant tamoxifen therapy is associated with a reduced risk of contralateral breast cancer in women with a *BRCA1* or *BRCA2* mutation.<sup>14</sup> In total, 383 of 1,583 *BRCA1* mutation carriers and 454 of 881 *BRCA2* mutation carriers took tamoxifen after being diagnosed with breast cancer.<sup>14</sup> Analysis of combined historical and prospective data showed

a significant reduction in the risk of contralateral breast cancer with the use of tamoxifen in *BRCA1* mutation carriers (HR 0.38,  $P < 0.001$ ) and in *BRCA2* mutation carriers (HR 0.33,  $P < 0.001$ ).<sup>14</sup>

The findings of Metcalfe et al and Phillips et al indicate that adjuvant tamoxifen therapy reduces the risk of contralateral breast cancer in women who have been diagnosed with breast cancer and are *BRCA1* or *BRCA2* mutation carriers. However, to date, there are no prospective studies specifically designed to study chemoprevention for primary breast cancer in *BRCA1* or *BRCA2* carriers. Very few mutation carriers choose to use tamoxifen due to the perceived side effects associated with treatment. A small prospective study of chemoprevention for primary breast cancer in *BRCA* mutation carriers was conducted in 2001. King et al<sup>8</sup> tested 288 women who developed breast cancer in the randomized NSABP Breast Cancer Prevention Trial of *BRCA* mutations. Of these 288 women, eight were found to have a *BRCA1* mutation and eleven were found to have a *BRCA2* mutation.<sup>15</sup> Tamoxifen reduced the breast cancer risk by 62% in *BRCA2* carriers,<sup>15</sup> but did not reduce the risk of breast cancer in healthy women with a *BRCA1* mutation.<sup>15</sup>

In summary, the results of large studies in *BRCA1* and *BRCA2* carriers differ substantially from those in noncarriers, in that among mutation carriers the protective effect of tamoxifen does not appear to be limited to prevention of ER-positive cancers. This is a consistent observation across the four randomized trials conducted in noncarriers (Table 1), including those in which most study subjects had a strong family history of breast cancer.

## Atypical hyperplasia

Atypical hyperplasia is the accumulation of abnormal cells in breast tissue due to an increased proliferation of breast tissue cells. It can occur in one or both breasts and is usually found at breast biopsy. It is classified as a benign condition, but it increases the risk of subsequent breast cancer by 4–5 times.<sup>16</sup> The NSABP P-1 study reported a 75% reduction in the incidence of breast cancer in women with atypical hyperplasia who received tamoxifen rather than placebo.<sup>6</sup> Shortly after closing of the NSABP P-1 trial, researchers continued to follow women whose breast tissue showed atypical hyperplasia or lobular carcinoma in situ.<sup>6</sup> The incidence of invasive breast cancer in 1,000 women with atypical hyperplasia was 10.1 in the placebo group, compared with 1.4 in the tamoxifen group (relative risk [RR] 0.14, 95% CI 0.03–0.47).<sup>6</sup> This estimates a 5-year breast cancer rate of approximately 5.0%.<sup>6</sup> Similarly, the incidence of invasive breast cancer per 1,000 women with lobular carcinoma in situ was 13.0 in the placebo group compared with 5.7 in the tamoxifen group (RR 0.44, 95% CI 0.16–1.06).<sup>6</sup> These findings confirm that tamoxifen significantly reduces the risk of invasive breast cancer in women with atypical hyperplasia or lobular carcinoma in situ.

Another recent trial studying the effect of tamoxifen in women with atypical hyperplasia yielded a similar result. Coopey et al reviewed the breast pathology reports of 42,950 women from 1987 to 2010 in order to determine the benefit of chemoprevention in patients with atypical breast lesions.<sup>17</sup> They identified 2,459 women with atypical breast lesions without prior or concurrent breast cancer, and of these

**Table 1** Summary of major randomized trials of tamoxifen prevention

Study (reference)	Study subjects (n)	Subject age, years	Events (n)		RR (95% CI)
			Placebo	Tamoxifen	
NSABP <sup>6</sup>	13,388	35–80			
All invasive			250	145	0.57 (0.46–0.70)
ER-positive			182	70	0.38 (0.28–0.50)
ER-negative			42	56	1.31 (0.86–2.01)
Royal Marsden Trial <sup>8</sup>	2,494	30–70			
All invasive			104	82	0.78 (0.58–1.04)
ER-positive			86	53	0.61 (0.43–0.86)
ER-negative			17	24	1.4 (0.7–2.6)
International Breast Cancer Intervention Study <sup>9</sup>	7,145	35–70			
ER-positive			195	142	0.73 (0.58–0.91)
ER-negative					132
			35		1.00 (0.53–1.87)
Milan study <sup>10</sup>	5,408	35–70			
ER-positive			74	62	0.84 (0.60–1.17)
ER-negative			52	40	0.77 (0.51–1.16)
			19	21	1.10 (0.59–2.05)

**Abbreviations:** CI, confidence interval; ER, estrogen receptor; RR, relative risk; NSABP, National Surgical Adjuvant Breast and Bowel Project.

women, 466 were treated with chemoprevention, primarily with tamoxifen, and 1,472 were not.<sup>17</sup> The results showed a significant decrease in risk of breast cancer with tamoxifen ( $P < 0.001$ ).<sup>17</sup> Women over the age of 50 years with atypia were found to have a significant reduction in breast cancer risk with chemoprevention (HR 0.34,  $P = 0.001$ ).<sup>17</sup> For women under the age of 50 years, the reduction was smaller and not statistically significant (HR 0.70;  $P = 0.33$ ).<sup>17</sup> These findings suggest that tamoxifen therapy is particularly beneficial in reducing the risk of breast cancer in patients with atypical breast lesions.

### High-density mammograms

Extensive dense breast tissue visible on a mammogram is a strong risk factor for breast cancer.<sup>18</sup> High-density mammograms are an indicator of a higher proportion of glandular and connective tissue in the breast relative to fat. Women with high-density mammograms have a cancer risk up to six times that of women with low-density mammograms.<sup>19</sup>

Studies have shown that tamoxifen reduces mammographic breast density. The 2008 International Breast Cancer Intervention Study showed that the mean reduction in mammographic breast density amongst women in the tamoxifen arm was 8.2%, and 48% of women had a  $\geq 10\%$  reduction in breast density at their 12–18-month mammogram.<sup>18</sup> In comparison, the mean density reduction amongst women in the placebo group was 3.8%, and only 26% of these women experienced a  $\geq 10\%$  reduction in breast density at their 12–18-month mammogram.<sup>18</sup> In comparison with women in the placebo group, those who took tamoxifen and experienced a  $\geq 10\%$  reduction in breast density had a RR reduction in breast cancer risk of 63% (odds ratio 0.37, 95% CI 0.20–0.69,  $P = 0.002$ ).<sup>18</sup> Women who were taking hormone replacement therapy did not experience a reduction in breast cancer risk with tamoxifen.<sup>18</sup>

In 2012, Chen et al conducted a study using three-dimensional magnetic resonance imaging to examine the effect of tamoxifen therapy on breast density. The results showed that tamoxifen therapy causes a significant reduction in breast density, and this reduction is positively correlated with treatment duration and baseline breast density.<sup>19</sup> The findings from these studies suggest that tamoxifen therapy is beneficial in reducing breast density, and reduces the risk of invasive breast cancer in this high-risk group. Nevertheless, more research is needed to confirm that a reduction in breast density due to tamoxifen is accompanied by a commensurate reduction in breast cancer risk and that tamoxifen is ineffective in the absence of a reduction in breast density.

### Risks of tamoxifen use

Although tamoxifen has shown clear benefit in the prevention of breast cancer in high-risk women, many patients are apprehensive about taking this drug due to its side effect profile. There are several risks associated with use of tamoxifen, which may be attributed to its estrogenic activity in human endometrial tissue.<sup>1</sup> During the NSABP P-1 trial, 51 invasive endometrial cancers occurred in the active phase of treatment, ie, 15 in the placebo arm and 36 in the tamoxifen arm (RR 1.13, 95% CI 0.44–2.93,  $P = 0.003$ ).<sup>20</sup> Age has been shown to predict the risk of developing invasive endometrial cancer. The NSABP trial showed that in women  $\geq 50$  years of age, the RR of developing endometrial cancer was 3.86 (95% CI 1.69–8.86), whereas in women  $< 50$  years of age, the RR of endometrial cancer was 1.13 (95% CI 0.44–2.93).<sup>20</sup> The NSABP trial also found that the use of tamoxifen in breast cancer patients resulted in an increased risk of 7.5-fold for endometrial tumors and a 1.4–5-fold increased risk of endometrial cancer in healthy women without breast cancer who were taking tamoxifen.<sup>21</sup>

Tamoxifen has also been shown to increase the incidence of deep vein thrombosis, pulmonary embolism, and cataracts.<sup>1,21</sup> Both deep vein thrombosis and pulmonary embolism pose significant health risks, and can lead to heart attacks, ischemic stroke, and death. During the NSABP-P1 trial, 57 women reported a deep vein thrombosis; 22 in the placebo arm and 35 in the tamoxifen arm (RR 1.60, 95% CI 0.94–2.72,  $P = 0.1$ ).<sup>20</sup> Twenty-four pulmonary emboli were reported, ie, six in the placebo arm and 18 in the tamoxifen arm (RR 3.01, 95% CI 1.20–1.58,  $P = 0.02$ ).<sup>20</sup> The increase in the annual rate of pulmonary embolism was not statistically significant in women  $< 50$  years of age ( $P = 0.4$ ) but was significant in women aged  $> 50$  years ( $P = 0.01$ ), suggesting that age is a factor when determining the risk of pulmonary emboli in these patients.<sup>20</sup>

### Attitudes of women and physicians towards use of tamoxifen

Although tamoxifen has been used as a treatment for breast cancer since the early 1970s, there is only limited enthusiasm for the drug in the preventive setting. The results of a multi-ethnic study of breast cancer risk reduction therapies indicated that even though 54% of women have heard of tamoxifen, only 4% have discussed it with their physicians.<sup>22</sup>

The recommended course of tamoxifen for prevention is 5 years; however, many women stop earlier than this. Land et al conducted a study to assess tamoxifen adherence in the NSABP-P1 trial. They found that 75% of study participants

continued to take the recommended dose of the drug after one month, but only 41% of participants were still taking the recommended dose after 36 months.<sup>23</sup> When asked why they chose to discontinue tamoxifen, most participants reported adverse effects.<sup>23</sup> The study also found that participants who were 60 years or older were more likely to complete treatment than women younger than 60 years.<sup>23</sup> Thus, despite the benefits associated with tamoxifen therapy for breast cancer prevention, widespread knowledge and adherence to such use of the drug is inadequate.

Armstrong et al conducted a study to assess factors affecting the prescription of tamoxifen as a chemopreventive agent among primary care physicians. Researchers mailed a survey to 350 primary care physicians, including those specializing in family practice, general internal medicine, and obstetrics and gynecology.<sup>24</sup> The purpose of the survey was to collect information regarding prescription of tamoxifen, intention to prescribe tamoxifen in certain situations, and factors affecting willingness to prescribe the drug to women at high risk of breast cancer. The study found that 27.4% of the 350 physicians reported having prescribed tamoxifen as a chemopreventive agent for breast cancer at least once in the past year.<sup>24</sup> The likelihood of prescribing tamoxifen was associated with the physician having a family member who had been diagnosed with breast cancer, the belief that the benefits of tamoxifen outweighed the risks, eligibility that was easy to determine, and patients who asked for more information about the drug.<sup>24</sup> Thus, it is evident that few physicians prescribe tamoxifen as a chemopreventive agent to women who are at high risk of breast cancer, and their decision to prescribe the drug is affected by their perception of the effectiveness of the drug, their personal experience with breast cancer, patient interest, and their ability to determine the eligibility of their patients.

## Possible alternatives

### Second-generation drugs

Second-generation drugs, such as raloxifene and exemestane, may be alternatives to tamoxifen, in particular if they are equally or more effective and/or have fewer side effects. One study showed that after 4 years of treatment, raloxifene reduced the risk of invasive ER-positive breast cancer by 84%.<sup>1</sup> In addition, raloxifene appears to be less estrogenic to the endometrium than tamoxifen.<sup>1</sup> However, it may not be as effective; in 2010, Vogel et al assessed the results of the NSABP Study of Tamoxifen and Raloxifene (STAR) and found that the rate of invasive breast cancer was approximately 24% higher in patients taking raloxifene than in those

taking tamoxifen (RR 1.24, 95% CI 1.05–1.47).<sup>25</sup> It was also found that the number of noninvasive breast cancer cases in the raloxifene group was twice that in the tamoxifen group (RR 2.00).<sup>25</sup> Although tamoxifen is more effective in preventing both invasive and noninvasive breast cancer in high-risk women, raloxifene has been found to have a more favorable side effect profile. The results of this study showed that the raloxifene group had a significantly lower risk of developing uterine cancer (RR 0.55, 95% CI 0.36–0.83,  $P=0.003$ ) and uterine hyperplasia (RR 0.19, 95% CI 0.12–0.29) than the tamoxifen group.<sup>25</sup> In addition, the incidence of thromboembolic disease was considerably lower in the raloxifene group (RR 0.75, 95% CI 0.60–0.93).<sup>25</sup>

Visvanathan et al conducted a meta-analysis to compare several different pharmacologic interventions for reduction of the risk of breast cancer. Their analysis confirmed that raloxifene results in fewer and less severe side effects than tamoxifen. Raloxifene was found to be associated with a lower risk of thromboembolic disease, uterine cancer, benign uterine hyperplasia, and cataracts.<sup>26</sup> It was also associated with a lower incidence of ovarian cysts, endometrial polyps, hot flashes, and vaginal bleeding.<sup>26</sup> It is clear that both raloxifene and tamoxifen are beneficial in preventing invasive breast cancer in high-risk women (with a risk reduction of 38% and 50%, respectively).<sup>25</sup>

Exemestane has also been considered for breast cancer prevention in healthy, high-risk women. Exemestane is an aromatase inhibitor that binds to and inhibits the enzyme aromatase, leading to a reduction in estrogen levels. A recent study showed that exemestane resulted in a 65% relative reduction in the annual incidence of invasive breast cancer compared with placebo and was associated with no serious toxic effects after 3 years of use.<sup>27</sup> However, more women in the exemestane group than in the tamoxifen group self-reported that their menopause-related vasomotor and sexual symptoms had worsened.<sup>27</sup> Since exemestane depletes estrogen completely, menopausal symptoms may be more severe and loss of bone mineral density may cause bone pain.<sup>27</sup> More severe side effects associated with exemestane include hypertension, hyperlipidemia, and cardiac failure.<sup>28</sup>

### Low-dose tamoxifen

Scientists have suggested that administering lower doses of tamoxifen may achieve the benefit but reduce the side effects associated with the drug. Data from a recent animal study indicated that decreasing the tamoxifen dose to the human equivalent of 1 mg per day does not reduce its antitumor

effect in breast tissue, since this effect reaches a plateau once the ERs are saturated.<sup>29</sup>

Decensi et al compared the effects of different doses of tamoxifen on several biomarkers that reflect the activity of tamoxifen on target tissues. These biomarkers included lipid and insulin-like growth factor levels, as well as tissue biomarkers such as Ki-67.<sup>30</sup> They studied 127 healthy women aged 35–70 years.<sup>30</sup> Participants were randomly assigned to a placebo, tamoxifen 20 mg/day, tamoxifen 10 mg/day, or tamoxifen 10 mg on alternate days.<sup>30</sup> A reduction in the dose of tamoxifen by up to 75% of the conventional dose had no impact on the activity of the drug on these biomarkers.<sup>30</sup> This observation has not been confirmed in a clinical setting. Research on this topic should be considered a priority.

Studies have been conducted to observe the effectiveness of combining low-dose tamoxifen with other agents to reduce the risk of breast cancer in healthy but high-risk women. However, these studies have shown that such combinations do not increase the efficacy of the drug. One study showed that the combination of low-dose tamoxifen and fenretinide did not reduce neoplastic breast events compared with placebo, whereas both single agents showed significant reduction of breast neoplasms.<sup>31</sup> Another study found that a combination of tamoxifen and aromatase inhibitors results in less efficacy than tamoxifen alone.<sup>31</sup> Use of tamoxifen alone is more effective than the combination of tamoxifen with other agents, as demonstrated in studies to date.

### Short-duration tamoxifen

While tamoxifen has been shown to reduce the mortality rate in women with invasive breast cancer and to decrease the incidence of breast cancer in healthy, high-risk women, the optimal duration of tamoxifen therapy in the preventive setting remains controversial. The recommended dose and duration for prevention was based on studies of adjuvant tamoxifen and the main endpoint was cancer recurrence. A study was conducted by Alkner et al in 2009 using 564 premenopausal women with stage II breast cancers to analyze the effect of adjuvant tamoxifen therapy for a duration of 2 years.<sup>32</sup> The results showed a significant reduction of contralateral breast cancer in premenopausal women with invasive breast cancer (HR 0.5,  $P=0.02$ ).<sup>32</sup> The idea that short-duration tamoxifen is beneficial in reducing the risk of developing contralateral breast cancer has led some scientists to believe that 2 years of tamoxifen therapy may be sufficient to prevent invasive breast cancer in healthy, high-risk women. Further research is required to confirm the benefit of short-duration tamoxifen for chemoprevention.

### Topical tamoxifen

Scientists have suggested the use of topical tamoxifen as an alternative to oral administration. When delivered transdermally, a drug has longer retention in local tissue.<sup>29</sup> Tamoxifen requires hepatic activation, so its more active metabolites should be used when it is administered transdermally. The tamoxifen metabolite 4-OHT can be concentrated directly in breast tissue.<sup>29</sup> One study showed that the maximal concentration of both tamoxifen and 4-OHT in breast tissue was reached 24 hours after topical application, with 4-OHT being retained in breast tissue for a much longer period than tamoxifen.<sup>29</sup> Rouanet et al<sup>33</sup> conducted a study which found that when 1 mg or 2 mg of 4-OHT was applied to breast skin daily, sufficient concentrations of 4-OHT were reached in the breast tissue in order to achieve the same degree of inhibition of tumor cells as seen with 20 mg/day of oral tamoxifen.<sup>29</sup> The benefit of transdermal 4-OHT is that it results in much lower plasma levels compared with oral tamoxifen, possibly reducing toxicity, thus resulting in fewer side effects.<sup>29</sup>

### Conclusion

Tamoxifen has been shown to be an effective chemopreventive agent for women who are at high risk of developing breast cancer. However, the risk/benefit ratio must be assessed for each woman. Women who would benefit from chemopreventive tamoxifen include those with a *BRCA1* or *BRCA2* mutation, atypical hyperplasia, and/or a high-density mammogram. Women with a strong family history of breast cancer but with no *BRCA* mutation are candidates for tamoxifen but are often reluctant to take it due to perceived side effects. Possible alternatives include raloxifene, low-dose tamoxifen, short-term tamoxifen, and topical tamoxifen. These alternatives may minimize toxicity while retaining activity. Further studies are needed to evaluate the effectiveness of such alternatives.

### Disclosure

The authors report no conflicts of interest in this work.

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