



## Medications To Reduce the Risk of Primary Breast Cancer in Women

This guide summarizes the effectiveness and safety of two medications used to reduce the risk of primary breast cancer: tamoxifen and raloxifene. Both of these medications are approved by the U.S. Food and Drug Administration (FDA) to reduce the risk of primary breast cancer (defined as invasive breast cancer in women without pre-existing breast cancer). This guide does not contain information about surgical approaches to breast cancer prevention, such as prophylactic mastectomy or oophorectomy. It also does not cover adjuvant therapy for women with a personal history of invasive or noninvasive breast cancer.

### Clinical Issue

Breast cancer is the most commonly diagnosed noncutaneous cancer among women in the United States. In 2008, nearly 200,000 cases of invasive breast cancer were diagnosed and over 40,000 women died from the disease.

Tamoxifen and raloxifene are both selective estrogen receptor modulators (SERMs). Tamoxifen is widely used to treat early and advanced hormone-receptor positive breast cancer. Raloxifene is primarily used for the prevention and treatment of osteoporosis.

Although both of these medications are approved for the prevention of primary breast cancer, currently they are rarely used for this purpose in the United States.

Tamoxifen was approved for prevention of primary breast cancer in 1998. Raloxifene was approved for this indication more recently, in 2007. Tamoxifen for primary prevention is approved for both pre- and postmenopausal women; raloxifene, for postmenopausal women only. The dose and price of both drugs are listed on the back page.

The ideal candidate for chemoprevention is a woman who has a higher than average risk of breast cancer and who is willing to accept the risk of harm from long-term use (up to 5 years) of either drug. Decisions to use either drug need to balance the potential benefits with the potential for harm.

### Clinical Bottom Line

Tamoxifen and raloxifene are both effective at reducing the risk of primary invasive breast cancer in women age 35–70.

*Level of Confidence:* ●●●

Raloxifene and tamoxifen reduce the likelihood of a woman developing breast cancer by a similar amount.

*Level of Confidence:* ●●○

Neither tamoxifen nor raloxifene reduce all-cause mortality.

*Level of Confidence:* ●●●

Raloxifene and tamoxifen both increase the risk of thromboembolic events (deep vein thrombosis and pulmonary embolism).

*Level of Confidence:* ●●●

Tamoxifen increases the risk of endometrial cancer.

*Level of Confidence:* ●●●

#### Confidence Scale

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

High ●●● There are consistent results from good quality studies. Further research is very unlikely to change the conclusions.

Medium ●●○ Findings are supported, but further research could change the conclusions.

Low ●○○ There are very few studies or existing studies are flawed.



## Effectiveness

Evidence of tamoxifen's and raloxifene's effectiveness to reduce the risk of primary breast cancer comes from generally well-designed clinical trials. The trials also examined mortality rates and did not find that either tamoxifen or raloxifene prolongs survival. However, the trials were not necessarily designed to detect changes in all-cause mortality, or even breast cancer mortality. They generally lasted 3–5 years. Larger and longer studies might detect a survival benefit. It is also possible that these drugs may prevent cases of breast cancer that have more favorable prognoses and would be easier to treat.

## Primary Breast Cancer

### Invasive Breast Cancer

- Both tamoxifen and raloxifene reduce primary estrogen-receptor positive invasive breast cancer.  
*Level of Confidence:* ●●●
- Tamoxifen and raloxifene do not reduce rates of estrogen-receptor negative breast cancer.  
*Level of confidence:* ●●○
- In a head-to-head trial, the incidence of primary breast cancer was about the same among women using raloxifene or tamoxifen.  
*Level of Confidence:* ●●○

### Noninvasive Breast Cancer

- Raloxifene does not reduce the rate of noninvasive breast cancer.  
*Level of confidence:* ●●○
- Evidence is *insufficient* to determine whether tamoxifen reduces the rate of noninvasive breast cancer.

## Mortality

- Neither tamoxifen nor raloxifene reduces all-cause mortality.  
*Level of Confidence:* ●●●
- Tamoxifen does not lower the number of deaths caused by breast cancer.  
*Level of confidence:* ●●○
- Evidence is *insufficient* to determine whether raloxifene reduces breast cancer deaths.

## Fracture Prevention

Both tamoxifen and raloxifene inhibit osteoclastic activity and reduce the risk of osteoporotic fracture among women.

- Raloxifene reduces vertebral fractures but does not reduce hip or other nonvertebral fractures.  
*Level of Confidence:* ●●●
- Tamoxifen reduces hip and other nonvertebral fractures.  
*Level of Confidence:* ●●○
- Evidence is *insufficient* to determine whether tamoxifen reduces vertebral fractures.

## Adverse Events

**Tamoxifen and raloxifene have adverse event profiles that may influence decisions on their use (see Table 1).** Hot flashes are a common side effect of both drugs. Vaginal symptoms, such as discharge, itching, and dryness, are common side effects of tamoxifen. Leg cramps are a common side effect of raloxifene.

**Table 1. Adverse Events With Use of Tamoxifen or Raloxifene<sup>1</sup>**

Vascular events	
Coronary artery disease	No harm for both drugs
Stroke <sup>2</sup>	No harm for both drugs
Thromboembolic events (DVT and PE)	<b>Increased risk for both drugs</b>
Uterine events	
Endometrial cancer	<b>Increased risk for tamoxifen</b> No harm for raloxifene

<sup>1</sup>Findings are based on meta-analyses of six placebo-controlled trials. Findings are  
*Level of Confidence* ●●○ or ●●●

<sup>2</sup> Based on the results of single trials, the U.S. Food and Drug Administration warns of an increased risk of stroke with both tamoxifen and raloxifene.

DVT= deep vein thrombosis.

PE= pulmonary embolism.

## Balancing the Benefits and Harms

In counseling women about whether to take a medication to lower the risk of breast cancer, the factors influencing the decision include:

- The probability the woman will develop breast cancer.
- The amount this risk is lowered by tamoxifen or raloxifene.
- The risk of serious adverse events when taking either drug.

A woman's individual risk of breast cancer depends on multiple factors, including age, family history, and genetic mutations. Other risk factors include high mammographic breast density and a personal history of atypical ductal or lobular hyperplasia. In the clinical trials of tamoxifen and raloxifene, the participants had varying individual risks of breast cancer. Age is an important predictor of risk, and the estimated 10-year risk of breast cancer for women of different ages is shown in Table 2.

Multiple models exist for predicting breast cancer risk. Although they provide good estimates of breast cancer risk for population groups, they all have been shown to be only marginally better than age alone in predicting an **individual's** risk of developing breast cancer.

The study results provide an overall estimate of the magnitude of risk reduction but do not permit calculation of the protection provided for individual women. Overall, for every 1,000 women taking either tamoxifen or raloxifene for 5 years, there will be about 8 fewer cases of breast cancer (absolute risk reduction of 0.8 percent).

The clinical trials also provide estimates of serious adverse events for women who take either drug for 5 years. Compared with women not taking a drug to reduce the risk of breast cancer, the absolute additional risk of a serious adverse event (deep vein thrombosis, pulmonary embolism, or endometrial cancer) when taking either drug is also about 0.8 percent.

**Table 2. Estimated 10-Year Risk of Primary Invasive Breast Cancer Based on Current Age for Women Not Treated With Tamoxifen or Raloxifene**

Age	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79
Risk <sup>1</sup>	0.4%	1.4%	2.4%	3.4%	3.7%

<sup>1</sup>Risk data from Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review, 1975–2005, National Cancer Institute.

## About the Studies

The evidence about the effectiveness of tamoxifen and raloxifene for reducing the risk of primary breast cancer comes from seven large randomized controlled trials with over 55,000 participants. Four trials compared tamoxifen with placebo, two compared raloxifene with placebo, and one was a head-to-head trial that compared raloxifene with tamoxifen. The majority of study participants were white, and trials did not report outcomes by race or ethnic group.

The studies differed in the groups of women who were enrolled. The tamoxifen trials were designed to study breast cancer rates and included only younger women (average ages 47–51) having elevated risk of breast cancer, usually on the basis of a family history. The single trial comparing tamoxifen with raloxifene also enrolled women with elevated risk of breast cancer. However, none of these trials used BRCA1 or BRCA2 as an eligibility criterion.

The trials comparing raloxifene with placebo were designed to examine the effectiveness of raloxifene for reducing rates of osteoporotic fractures or cardiac events. The rate of breast cancer was a secondary outcome in these studies. The women included in these trials were older (average age 67) than the women who participated in the tamoxifen studies.

**Tibolone:** One placebo-controlled trial of tibolone was included in the review. Tibolone currently is *not* approved by the FDA for use in the United States but is used in many European countries for treatment of menopausal symptoms and prevention of osteoporosis. The trial found that tibolone reduced the risk of invasive breast cancer but increased the risk of stroke.

## Dose and Price

Drug Name	Brand Name	Dose <sup>1</sup>	Route	Price Per Month <sup>2</sup>	
				Generic	Brand
Raloxifene	Evista®	60 mg once a day <sup>3</sup>	Oral	NA	\$115
Tamoxifen	Nolvadex®	20 mg daily for 5 years	Oral	\$115	\$245

<sup>1</sup>Dosing for primary prevention of breast cancer.

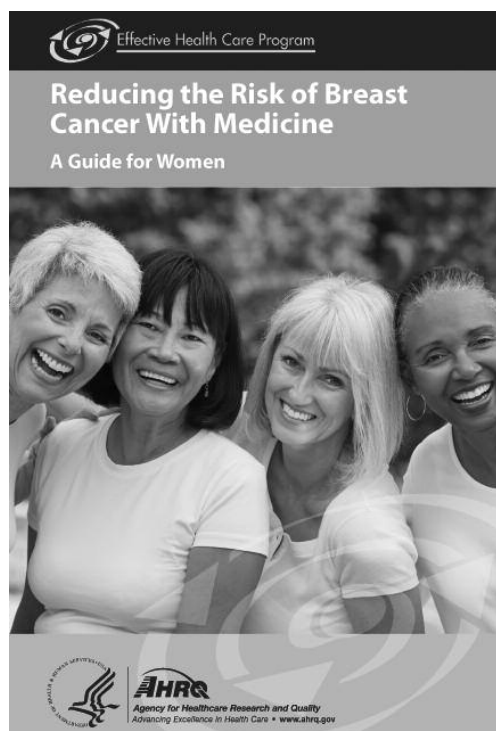
<sup>2</sup>Average Wholesale Price from *Red Book*, 2009.

<sup>3</sup>Optimum duration of treatment is not known.

NA = not available.

## Resource for Patients

*Reducing the Risk of Breast Cancer with Medicine: A Guide for Women* is a companion to this clinician guide. It can help women talk with their health care professional about medications that reduce the risk of primary breast cancer. It provides information about a woman's risk of breast cancer, effectiveness of risk-reducing medications, and adverse effects.



## For More Information

For electronic copies of the consumer guide, this clinician guide, and the full systematic review, visit this Web site: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

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AHRQ created the John M. Eisenberg Center at Oregon Health & Science University to make research useful for decisionmakers. This guide was written by Bruin Ruge, M.D., Erin Davis, B.A., Martha Schechtel, R.N., and David Hickam, M.D., of the Eisenberg Center.

## Source

The source material for this guide is a systematic review of 123 research articles published between 1989 and 2008. The review, *Comparative Effectiveness of Medications To Reduce the Risk of Primary Breast Cancer in Women* (2009), was prepared by the Oregon Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts. The full systematic review is available at [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov).

