

DISCUSSION GUIDE

Breast cancer risk reduction for women at increased risk of breast cancer

This Discussion Guide is meant to assist health care providers in their discussions of potential risk reduction agents with women at increased risk for breast cancer,¹ so they can make informed decisions together. In this Discussion Guide, women at increased risk are defined as having five-year projected breast cancer risk $\geq 1.66\%$ (according to the National Cancer Institute Breast Cancer Risk Assessment Tool¹) or with lobular carcinoma in situ (LCIS). It is based on recommendations from the American Society of Clinical Oncology (ASCO) updated clinical practice guideline on the use of tamoxifen, raloxifene, aromatase inhibitors, or retinoids to lower a woman's risk of breast cancer.

The Discussion Guide includes data on the risks and benefits of tamoxifen and raloxifene in women who are at increased risk of breast cancer and is divided into four sections:

1. The benefits and risks of taking tamoxifen,
2. The benefits and risks of taking raloxifene,
3. The benefits and risks of taking raloxifene compared to tamoxifen, and
4. Help for women in thinking through the available options

¹ (The National Cancer Institute Breast Cancer Risk Assessment Tool is available at: <http://www.cancer.gov/bcrisktool>)

This Discussion Guide is derived in part from recommendations in the American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction. This Discussion Guide is a practice tool based on ASCO[®] practice guidelines and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the practice guidelines and this Discussion Guide is voluntary. The practice guidelines and additional information are available at <http://www.asco.org/guidelines/bcrr>. Copyright © 2009 by the American Society of Clinical Oncology. All rights reserved.



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MEDICATIONS TO LOWER BREAST CANCER RISK

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) that interferes with the actions of estrogen on breast tissue. It has been shown to decrease the risk of developing breast cancer, and is also used in the treatment of breast cancer. Four clinical trials have compared tamoxifen (20 mg daily for 5 years) with placebo (no treatment) for reducing breast cancer risk.² These trials are the National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP-P1, also known as the Breast Cancer Prevention Trial [BCPT]), the International Breast Cancer Intervention Study I (IBIS-I), the Royal Marsden Tamoxifen Prevention Trial, and the Italian Randomized Tamoxifen Prevention Trial. **Tamoxifen was consistently associated with a reduction in estrogen receptor positive (ER+) invasive breast cancer risk in each of these trials.**

Quick Facts

Who can and cannot take tamoxifen?

- Tamoxifen is a drug or medication which blocks the action of estrogen on breast cells and is an option for women who are pre- or postmenopausal and are at increased risk for breast cancer.
- Tamoxifen is not recommended for women with a prior history of deep venous thrombosis (blood clots), pulmonary embolus (blood clots in the lung), stroke, or transient ischemic attack (a kind of stroke).

What else is important to know?

- Tamoxifen was originally approved by the FDA for the treatment of advanced breast cancer. The FDA then extended that approval to women with early stage breast cancer with ER+ invasive breast cancer. Due to its overall benefit in reducing contralateral breast cancer, studies were designed to test its efficacy for lowering breast cancer risk in women at increased risk.
- Tamoxifen can reduce the risk of invasive breast cancer—especially ER+ breast cancer—for up to 10 years, even when taken for only 5 years.
- The benefit of taking tamoxifen for more than five years for risk reduction is unknown and is not recommended.
- There is an increase in vasomotor and gynecological symptoms like hot flashes, sweats, and menstrual irregularities, but these do not appear to continue after treatment across all age groups.
- Risks and benefits of tamoxifen can vary according to a woman's general health and age, baseline risk for developing breast cancer, and whether she has had a prior hysterectomy, which are important to consider fully.
- Due to inconsistent evidence, it is not routinely recommended for women to take tamoxifen and hormone therapy at the same time. If women are taking hormone therapy (e.g. hormone replacement) or are considering it and also considering taking tamoxifen, they and their doctor should discuss this.
- Tamoxifen for premenopausal women can be associated with bone loss.
- If taking tamoxifen, the guidelines recommend that women should have a gynecological exam before starting and yearly while on tamoxifen.
- A woman experiencing any abnormal vaginal bleeding while taking tamoxifen should report this to a health care provider.
- It is not known whether tamoxifen prolongs survival when taken to reduce breast cancer risk, as the studies were not designed to look at this. However, even delaying the onset of breast cancer is a potential benefit.

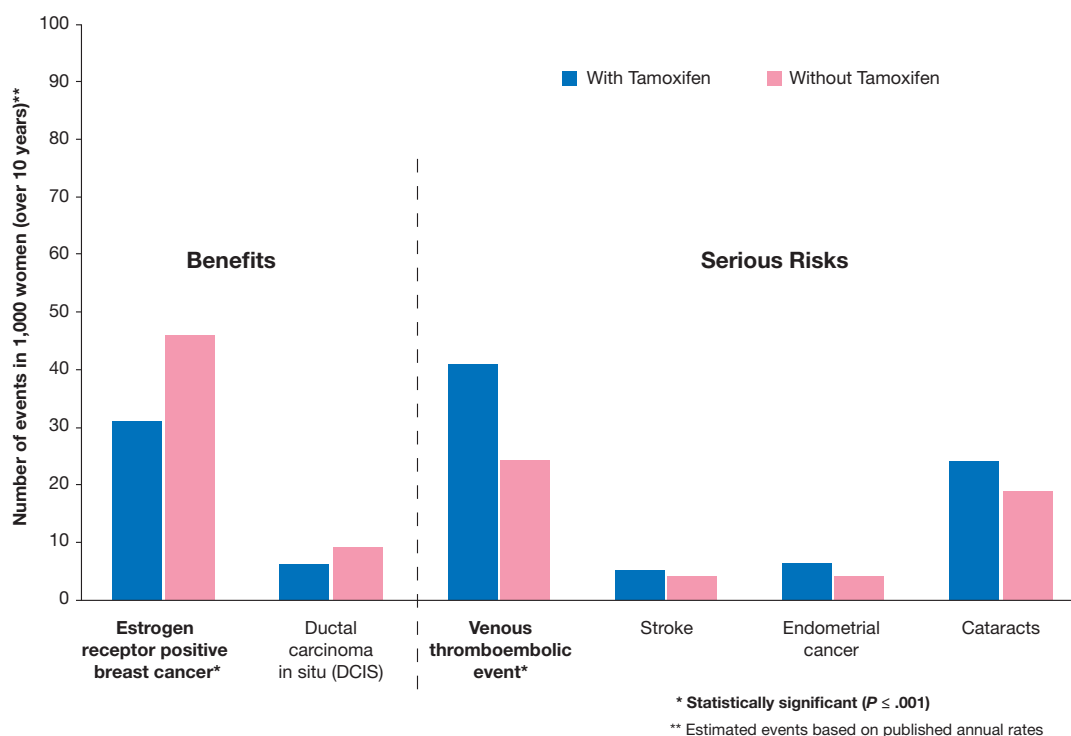
² References available at www.asco.org/guidelines/bcrr

Risks and Benefits of Tamoxifen Treatment

Before making a decision about taking tamoxifen to lower breast cancer risk, it is suggested a woman weigh all the risks and benefits. A woman who has an increased risk of breast cancer and a low risk of having side effects from a drug is likely to receive the most benefit.

The following information about absolute risks and benefits is based on the results from one clinical trial called IBIS-I, with over 7,000 women at increased risk of breast cancer, which has the longest follow-up so far, for up to 10 years. About half of these women took tamoxifen and the other half took a placebo (no treatment) for 5 years. Risks assessed include venous thromboembolism, stroke, endometrial cancer, and cataracts, and the effect of tamoxifen on bone health.

Long-term Benefits and Risks of Tamoxifen Use (Results after 10 years of IBIS-I Trial)



This graph reports the number of possible events (benefits or risks) in 1000 women over a 10 year follow up period, based on the results of the IBIS-I trial. For example, for every 1,000 women on tamoxifen for 5 years, 31 of them developed estrogen positive breast cancer (green/darker column); while 46 women who had a placebo (no treatment) developed ER+ breast cancer over the same period (orange/lighter column). Thus, tamoxifen could potentially have prevented 15 breast cancers in 1,000 women over the 10 year period.

Chart based on Cuzick J, Forbes JF, Sestak I, et al: Longterm results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 99:272-282, 2007 and Personal Communication J. Cuzick, July 2009

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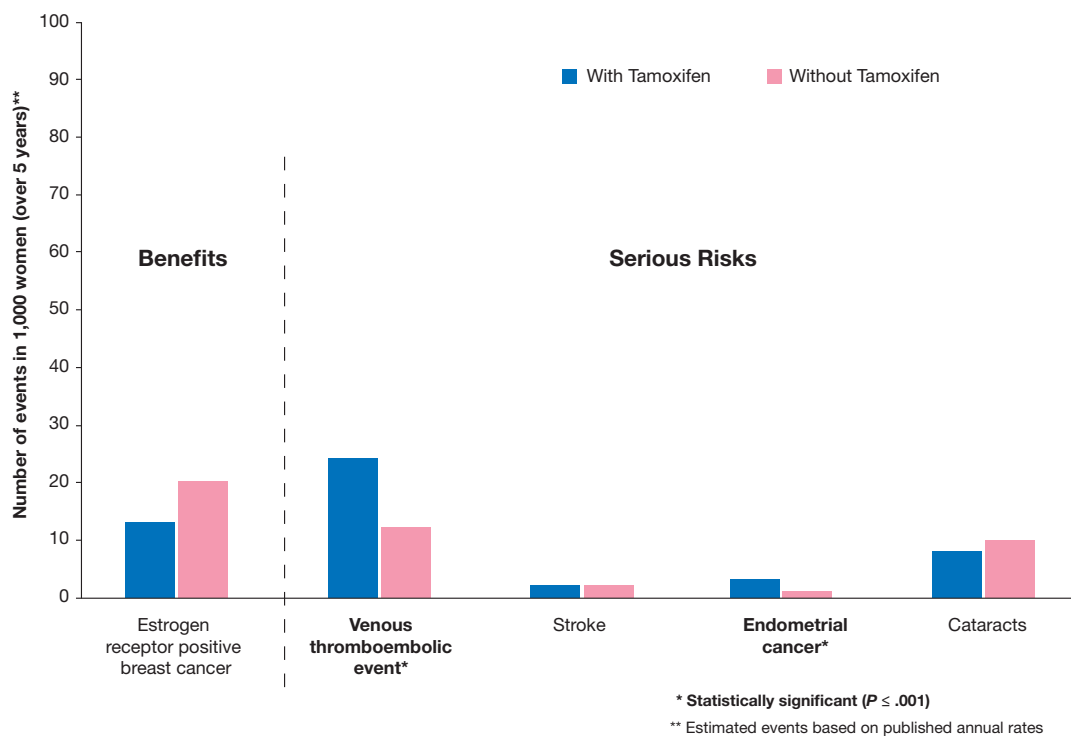
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Benefits and Risks During and After Tamoxifen Use

The risks and benefits can be further broken down as those that are more likely to occur (1) during five years of tamoxifen treatment and (2) after treatment.

(1) Possible Risks and Benefits of Tamoxifen during 5 Years of Treatment

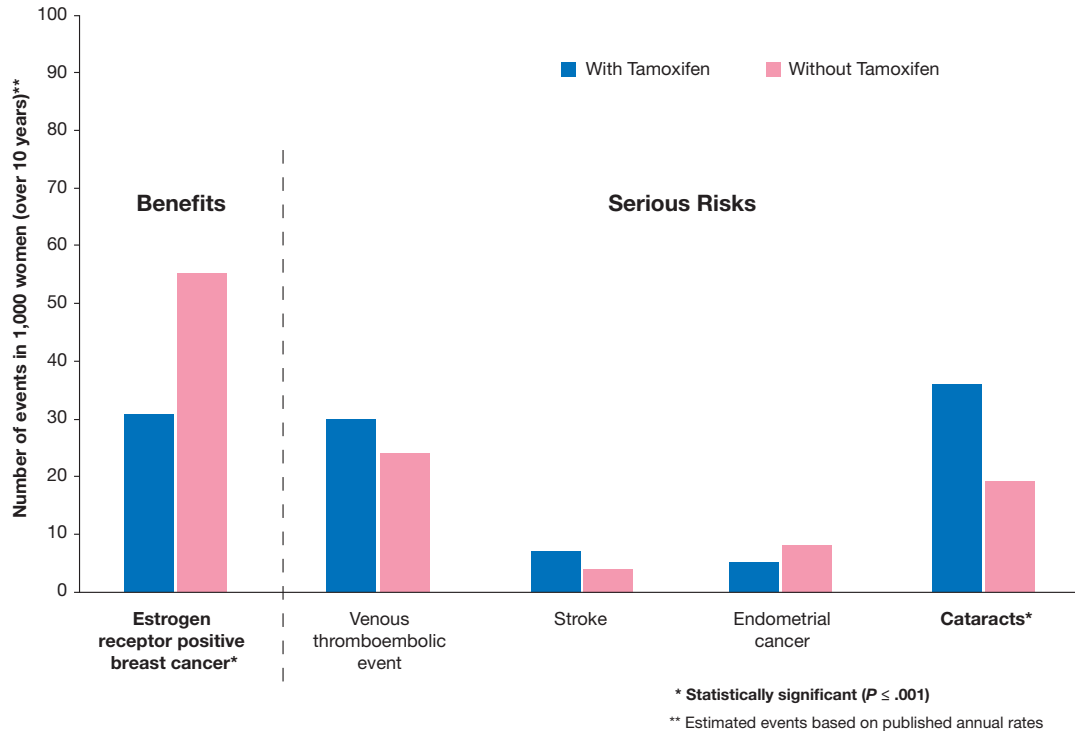


Other commonly reported side effects during treatment:

During treatment, women who take tamoxifen also report an increase in hot flashes and gynecological symptoms like vaginal discharge, dryness, and menstrual irregularities. Once tamoxifen treatment is finished, these symptoms appear to decline.

Chart based on Cuzick J, Forbes JF, Sestak I, et al: Longterm results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 99:272-282, 2007 and Personal Communication J. Cuzick, July 2009

(2) Possible Risks and Benefits of Tamoxifen after 5 Years of Treatment



Quality of Life

There is no information to suggest that tamoxifen treatment will have a serious impact on quality of life. Women taking tamoxifen report more vasomotor and gynecological symptoms like hot flashes, sweats, and menstrual irregularities. These symptoms increase during treatment and decline once women stop taking tamoxifen. Women who take tamoxifen report fewer breast complaints and headaches, especially during treatment. After treatment, women who had taken tamoxifen experience slightly more headaches. Women taking tamoxifen do not appear to have more weight gain or depression than women who are not taking tamoxifen in the few studies that have looked at this. There are some reports of a slight increase in problems related to sexual functioning in women taking tamoxifen (e.g., decreased interest in sex, decreased enjoyment, and painful intercourse).

More information for patients on risks and benefits of tamoxifen is available at www.cancer.net, www.cancer.gov/cancertopics/druginfo/tamoxifencitrate and www.cancer.org/docroot/CDG/content/CDG_tamoxifen.asp.

Chart based on Cuzick J, Forbes JE, Sestak I, et al: Longterm results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 99:272-282, 2007 and Personal Communication J. Cuzick, July 2009

Raloxifene

Raloxifene is another option for women at elevated risk for breast cancer, but only in those who are postmenopausal. Raloxifene is also a SERM that interferes with the actions of estrogen on breast tissue. The US FDA has approved it for treatment of osteoporosis and for reducing the risk of developing breast cancer for women who are postmenopausal.

Four clinical trials have evaluated raloxifene compared to placebo for reducing breast cancer risk.³ Breast cancer risk reduction was the primary endpoint of two trials: the National Surgical Adjuvant Breast and Bowel Project P2 Study of Tamoxifen and Raloxifene (STAR) trial and Raloxifene Use for The Heart (RUTH) trial; and a secondary endpoint of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. It was also the primary endpoint of the Continuing Outcomes Relevant to Evista (CORE) trial, which followed a subgroup of participants from the MORE trial. Although the eligibility criteria for these trials differed, raloxifene use was consistently associated with a reduction in breast cancer risk.

Quick Facts

Who can and cannot take raloxifene?

- Only women who have been through menopause may take raloxifene (60 mg every day for 5 years) to reduce their risk of invasive breast cancer. Raloxifene is not recommended for women who are premenopausal.
- Women with osteoporosis, in whom breast cancer risk reduction is an additional benefit, can take raloxifene.
- Raloxifene is not recommended in women with a prior history of deep venous thrombosis (blood clots), pulmonary embolus (blood clots in the lung), stroke, or transient ischemic attack (a kind of stroke).

What else is important to know?

- Raloxifene was originally approved by the FDA for the treatment of osteoporosis. It has since been approved to reduce the risk of breast cancer in postmenopausal women (60 mg every day).
- There are risks and benefits with raloxifene, and these are important to consider fully.
- Women with osteoporosis, in whom breast cancer risk reduction is an additional benefit, may take raloxifene for longer than 5 years.
- It is not known whether raloxifene prolongs survival when taken to reduce breast cancer risk, because the studies were not designed to look at this. However, even delaying the onset of breast cancer could be a benefit.

Based on studies including women with osteoporosis that compared raloxifene to placebo and showed a decreased risk of breast cancer, the STAR trial was conducted comparing raloxifene and tamoxifen in which all of the women were at increased risk of breast cancer. The information below is based on that trial.

More information for patients on risks and benefits of raloxifene is available at www.cancer.net, <http://www.cancer.gov/cancertopics/druginfo/raloxifenehydrochloride> and http://www.cancer.org/docroot/CDG/content/CDG_raloxifene.asp.

3 References available at www.asco.org/guidelines/bcrr

Comparing Tamoxifen and Raloxifene

The following information provides results from the STAR trial (NSABP-P2) that included almost 20,000 **postmenopausal** women at increased risk of breast cancer. The results compare the risks and benefits of raloxifene to tamoxifen after 6 years of follow-up.

Quick Facts

- Raloxifene and tamoxifen work equally well to reduce the risk of ER+ invasive breast cancer in women who have been through menopause.
- Side effects affecting women who take either tamoxifen or raloxifene can include gynecological symptoms (such as vaginal discharge), vasomotor symptoms (hot flashes), leg cramps, and bladder control problems, venous thromboembolic events, stroke, endometrial cancer, fracture, and cataracts.
- Raloxifene may have fewer serious side effects than tamoxifen, including thromboembolic events, benign uterine conditions, and cataracts.

Differences were seen in the outcomes below, however they were small and may not be clinically meaningful.

- Women on tamoxifen may have more gynecological symptoms, vasomotor symptoms, leg cramps, and bladder control problems compared to women on raloxifene.
- Women taking raloxifene reported more musculoskeletal problems (muscle and joint pain) and weight gain compared to women taking tamoxifen.
- Women taking raloxifene reported slightly more problems related to sexual activity, sexual interest, sexual arousal, sexual enjoyment, and in painful intercourse.

Comparing the Benefits and Risks

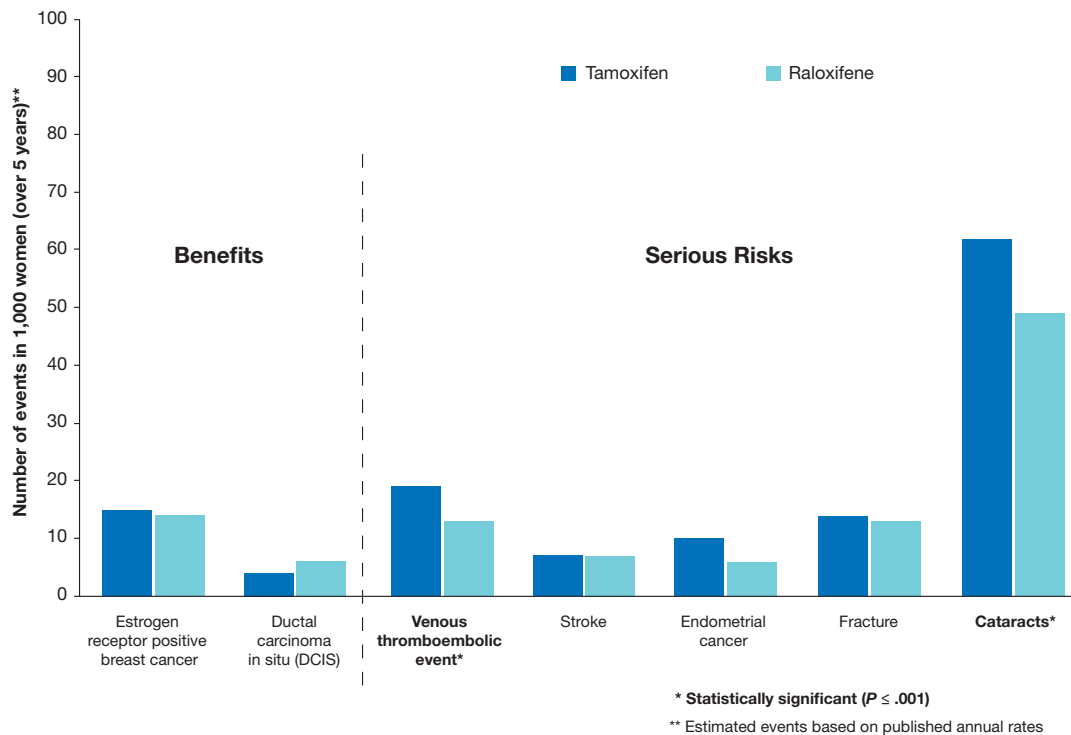


Chart based on Vogel VG, Costantino JP, Wickerham DL, et al: Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 295:2727-2741, 2006

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WEIGHING YOUR OPTIONS

After you have spoken with your doctor about taking tamoxifen or raloxifene, the following page is intended to help you organize your thoughts in five areas. You may want to do this on your own, with your healthcare provider, or with someone else (for example, family, friends, or other caregivers outside of this health care provider's office).

The next three pages include four steps:

1. Weigh the risks and benefits.
2. What decision do you need to make?
3. What information do you need to make the decision?
4. What kind of help do you need to think over the decision?
5. What are the next steps?

Weighing the Risks and Benefits

This table is for thinking about the information provided by the health care provider, including the graphs, and thinking about how it matters to you, personally.

In the following table, use the stars (*) to show how important each benefit and risk is to you. If you circle five stars, then the risk or benefit matters a lot to you. If you circle no stars, then the risk or benefit matters very little to you. Finally, please think about what you think is most likely to happen and underline those. Circle the benefit that matters the most (most stars) and that you think is most likely to happen (underlined).

	How much does this matter to you? Please circle the number of stars* (no stars = not at all, 5 stars = a lot)	For your notes and to weigh your options about treatment (tamoxifen, raloxifene [if eligible], or no intervention) by keeping in mind the risks and benefits (see pages 2-7 above)
BENEFITS:		
Reducing the risk of getting ER+ invasive breast cancer	* * * * *	
Reducing the risk of fracture	* * * * *	
Other:	* * * * *	
	* * * * *	
	* * * * *	
RISKS:		
Gynecological symptoms, such as vaginal dryness	* * * * *	
Hot flashes	* * * * *	
Blood clots	* * * * *	
Cataracts (cloudiness in the front of the eye)	* * * * *	
Cancer of the uterus (endometrial cancer)	* * * * *	
Stroke	* * * * *	
Benign uterine problems, such as fibroids	* * * * *	
Leg cramps	* * * * *	
Trouble controlling your bladder	* * * * *	
Pain during sexual intercourse	* * * * *	
Other:	* * * * *	
	* * * * *	

Pages 8-10 adapted from the Ottawa Personal Decision Guide Copyright O'Connor, Stacey, Jacobsen 2004.

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2. What decision do you need to make?

By when do you want to make a choice? _____

Do you know what your risk is for getting breast cancer? _____

Have you had your period in the last year? _____

Do you know how your risk compares to other women's risk? _____

Do you understand how tamoxifen or raloxifene may lower your risk? _____

3. What information and other resources do you need to make the decision?

Do you have enough support and advice from other people to make a choice? _____

Are you choosing your treatment option without pressure from others? _____

Do you have enough facts to make a choice? _____

Do you know who will be available if you have questions or problems? Do you know how to contact them?

Do you know which options you have? _____

Do you know the benefits and risks of each option? _____

Do you understand what the benefits and risks might mean to you personally? Do you understand what impact they can be expected to have on your health and expectations for quality in your life? _____

Are you clear about which benefits and risks matter most to you? _____

Is cost of the drug a concern for you? (e.g., do you know this information? do you have insurance? does it cover these medications?) _____

In the following space, write down any other things that you think are important to your decision (for example, your age, money issues, etc.):

4. What kind of help do you need to think over the decision?

Are there any people you would like to help you make this decision?

NAME(S): _____

How can this person or these people help you? _____

5. What are the next steps?

Consider planning your next steps based on your needs:

1. If you feel you do not have enough support and/or if you feel pressure from others—you may want to look for more support. Your doctor or health care institution may be able to refer you to others who could give you support.
2. If you feel you do not have enough facts—you may want to get more facts. For example, you could review “What To Know: ASCO’s Guideline on Drugs to Reduce Breast Cancer Risk,” visit cancer.net, visit cancer.gov, and/or call 1-800-4-Cancer.
3. If you are not sure what matters most to you—you may want to review this Discussion Guide, talk to family or friends, look for others who have made this decision and learn about their decisions, including what matters to them, especially those who have made this decision and/or have experienced the benefits and/or side effects.
4. What else do you need to help with your decision? Consider the things you are willing to try to get that help.

After filling out these pages, write any questions you have in the space below or on another page:

