Breast Cancer Risk Reduction

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Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Consensus: All recommendations are Category 2A unless otherwise specified.
See NCCN Categories of Consensus

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### Qualitative Risk Assessment:
- Age
- Ethnicity/race
- Family history
- Age at menarche
- Parity
- Age at first live birth
- Age at menopause
- Prior breast biopsies
- Atypical hyperplasia or LCIS
- Prior thoracic irradiation (e.g., Hodgkin’s disease)
- Known or suspected BRCA1, BRCA2, p53, PTEN, or other gene mutation associated with breast cancer risk

### Quantitative Risk Assessment:
- Known or suspected BRCA1, BRCA2, p53, PTEN or other gene mutation associated with breast cancer risk
- Close relatives with breast and/or ovarian cancer
- Prior thoracic irradiation
- History of lobular carcinoma in situ
- Breast cancer risk assessment (modified Gail Model for women > 35 y of age)

#### RISK STATUS

- Risk-reduction therapy counseling
- 5 y breast cancer risk ≥ 1.7% and Life expectancy ≥ 10 y and No contraindication to tamoxifen
- 5 y breast cancer risk < 1.7% or Life expectancy < 10 y or Contraindication to tamoxifen

#### RISK ASSESSMENT

- Woman does not desire risk reduction therapy (See BRISK-2)
- Woman desires risk reduction therapy (See BRISK-3)

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**PREVENTIVE COUNSELING/SCREENING**

- **Known or suspected BRCA1, BRCA2, p53, PTEN or other gene mutation associated with breast cancer risk**
- **Close relatives with breast and/or ovarian cancer**

**Woman does not desire risk-reduction therapy**

- **History of lobular carcinoma in situ**

**Prior thoracic irradiation**

- **5 y breast cancer risk ≥ 1.7%**
- **and life expectancy ≥ 10 y**
- **and no contraindication to tamoxifen**

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- **See NCCN Genetics/Familial High Risk Assessment Guidelines and Breast Cancer Screening and Diagnosis Guidelines**
- **See NCCN Breast Cancer Screening and Diagnosis Guidelines**
- **See NCCN Breast Cancer Screening and Diagnosis Guidelines**

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See the NCCN Genetics/Familial High Risk Assessment Guidelines.

See Components of Risk/Benefit Assessment and Counseling (BRISK-A).

The definition of risk as defined by the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP BCPT).

As a reference point, the life expectancy of the average 78 y old woman in the US is 10.2 years.

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Breast Cancer Risk Reduction

BASELINE EXAM

Risk reduction bilateral salpingo-oophorectomy desired (Limited to those with known or strongly suspected BRCA1 and BRCA2 mutations)

MONITORING FINDINGS AND MANAGEMENT

Risk reduction bilateral salpingo-oophorectomy and with peritoneal washings. Pathologic assessment should include fine sectioning of ovaries and fallopian tubes

Routine follow-up as clinically indicated

Woman desires risk-reduction therapy

Clinical breast exam
Bilateral mammogram if not done in prior 6 mo

Normal

Risk reduction mastectomy desired

Bilateral mastectomy ± reconstruction

Routine follow-up as clinically indicated

Abnormal

See NCCN Breast Cancer Screening and Diagnosis Guidelines

Non-surgical risk reduction desired

Clinical trial or Tamoxifen

PM

Pelvic exam
Consider ophthalmology exam if cataracts or poor vision
Consider monitoring for bone mineral density loss if premenopausal (category 2B)

See Non-surgical risk reduction therapy (BRISK-4)

Utility of tamoxifen for breast cancer risk reduction in women under 35 years of age is unknown.

Women in clinical trial should have baseline exam, follow-up, and monitoring as per protocol.

Risk reduction mastectomy should generally be considered only in women with very high risk, such as BRCA1 or BRCA2 mutations, or women with LCIS. Evaluation should include consultation with surgery and reconstructive surgery. Psychological consultation may also be considered.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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**Non-Surgical Risk Reduction Therapy**

Tamoxifen<sup>a,m</sup>

- 20 mg/day for 5 y (category 1)

**Monitoring on Tamoxifen**

- H&P every 6 months or for symptoms
- Annual mammography
- Annual pelvic exam including age-appropriate Pap smear (optional if post-hysterectomy)
- Ophthalmology exam if cataracts or vision problems
- Consider monitoring for bone mineral density loss if premenopausal (category 2B)
- Monthly breast self-exam (category 2B)<sup>o</sup>

<sup>a</sup>Utility of tamoxifen for breast cancer risk reduction in women under 35 years of age is unknown.

<sup>m</sup>See Breast Cancer Risk Reduction Agents (BRISK-B).

<sup>o</sup>Prospective trials of breast self examination in high-risk populations have not been performed. However, the use of breast self-examination is generally encouraged.
MONITORING FINDINGS AND MANAGEMENT

Asymptomatic → Continue tamoxifen

Abnormal vaginal bleeding → Prompt evaluation for endometrial cancer if uterus intact
- If endometrial cancer found, reinitiation of tamoxifen may be considered after hysterectomy if early stage disease. See NCCN Endometrial Cancer Treatment Guidelines for management
- If no endometrial cancer found, continue tamoxifen and reevaluate if symptoms persist or recur

Hot flashes or other symptoms → Symptomatic treatment. If persists, reevaluate role of tamoxifen → Continue tamoxifen

Deep vein thrombosis, pulmonary embolism, cerebrovascular accident → Discontinue tamoxifen, treat underlying condition

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
COMPONENTS OF RISK/BENEFIT ASSESSMENT AND COUNSELING

Options for risk reduction should be discussed in a non-directive counseling environment. For breast cancer risk reduction, elements of this discussion include:

• Discussion of overall health status, including health risks/benefits of estrogen or hormone replacement therapy vs. risk reduction options.

• If a woman is at high-risk secondary to a strong family history or very early onset of breast or ovarian cancer, special genetic counseling should be offered. See NCCN Genetic/Familial High Risk Assessment Guidelines.

• Tamoxifen:
  › Use of tamoxifen in combination with hormone replacement therapy (HRT) is not recommended outside a clinical trial, given the uncertainty regarding long-term side effects of the combination and the association of HRT with increased breast cancer risk. (Estring is permitted, category 3)
  › Discussion of relative and absolute risk reduction with tamoxifen.
  › Contraindications to tamoxifen: history of deep vein thrombosis, pulmonary embolus, thrombotic stroke, transient ischemic attack, pregnancy or pregnancy potential without effective method of contraception.
  › Common and serious adverse effects of tamoxifen, with emphasis on age-dependent risks. See Table 2 (MS-10)
  › Prior hysterectomy.

• Risk reduction surgery
  › Discussion of risk reduction mastectomy in high-risk women. Risk reduction mastectomy should generally be considered only in women with very high risk, such as BRCA1, BRCA2 carriers, or women with LCIS. Evaluation should include consultation with surgery and reconstructive surgery. Psychological consultation may also be considered.
  › Discussion regarding the risk of breast or ovarian cancer and the option of risk reduction bilateral salpingo-oophorectomy.

• Option of participation in clinical research for screening or risk assessment (e.g., screening MRI and ductal lavage studies) or chemoprevention (e.g. NSABP Study of Tamoxifen and Raloxifene or other studies).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
BREAST CANCER RISK-REDUCTION AGENTS

- Insufficient data are currently available regarding tamoxifen risk reduction in women who are carriers of BRCA1 or BRCA2 mutations or who have had prior thoracic irradiation.

- Data regarding tamoxifen risk reduction is limited to women 35 y of age or older.

- For high-risk premenopausal women, data regarding the risk/benefit ratio for tamoxifen appears relatively favorable (category 1)

- For high-risk postmenopausal women, data regarding the risk/benefit ratio for tamoxifen appears less favorable than that for premenopausal women and is influenced by age, race, and presence of uterus (category 1).

- Raloxifene for breast cancer risk reduction is inappropriate unless as part of a clinical trial.
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NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Breast cancer is the most commonly diagnosed cancer in American women, with 203,500 cases and 39,600 deaths estimated in 2002 in the United States alone.¹ Major risk factors for the development of breast cancer have been identified and include:

- female gender
- increasing age
- early menarche
- late menopause
- nulliparity
- older age at first live birth
- family history of breast cancer
- personal history of proliferative benign breast disease
- history of radiation exposure
- BRCA1, BRCA2, p53, or PTEN mutations.

Estimating risk for the individual woman is difficult, and most breast cancers are not attributable to risk factors other than female gender and increased age. The modified Gail model is a computer-based multivariate logistic regression model that uses age, race, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, number of previous breast biopsies, and histology of the breast biopsies to produce actuarial estimates of future breast cancer risk.²⁻⁴

In women with a strong family history of breast cancer, women who are known carriers of BRCA1, BRCA2, p53, or PTEN mutations, or women who have had previous exposure to therapeutic doses of thoracic radiation, the modified Gail model may underestimate future risk for breast cancer. Models for risk estimation based on family history of breast cancer exist, including the Klaus model, which is especially effective in estimating risk of breast cancer in women with a positive family history of breast cancer.⁵ The development of effective strategies for the reduction of breast cancer incidence has been difficult, because few of the existing risk factors are modifiable and many of the potentially modifiable risk factors have social implications extending beyond concerns for breast cancer (e.g., age at first live birth).

Tamoxifen for Risk Reduction

The benefits of tamoxifen in the treatment of breast cancer in the adjuvant and metastatic settings are well documented.
Retrospective analysis of randomized, controlled clinical trials comparing tamoxifen with no tamoxifen in the adjuvant treatment of breast cancer has shown a reduction in the incidence of contralateral second primary breast cancer. The Early Breast Cancer Trialists' meta-analysis confirms that 5 years of tamoxifen therapy reduces the risk of contralateral second primary breast cancers by 47%.

The effectiveness of tamoxifen in this setting gave rise to the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial, a randomized clinical trial of healthy women aged 35 or older with a 1.7% or greater cumulative 5-year risk for developing breast cancer. Women enrolled in the trial were randomized in a double-blinded fashion to treatment with tamoxifen, 20 mg daily for 5 years, or placebo. Breast cancer incidence and mortality were the primary end points of the study; high-priority secondary end points included the occurrence of thromboembolic disease, cardiovascular disease, bone fracture, and endometrial cancer. The breast cancer risk reductions demonstrated in the NSABP Breast Cancer Prevention Trial are presented in Table 1.

The results show that treatment with tamoxifen decreases the short-term risk for future development of breast cancer by 49% in healthy women over the age of 35 who have an increased risk for developing breast cancer (Table 1). The median follow-up in the NSABP Breast Cancer Prevention Trial was 54.6 months; thus, no definite conclusions regarding long-term risk reduction can yet be drawn. The benefits in terms of risk reduction exist across all age groups (Table 1). The risk reduction in participants with atypical hyperplasia was particularly striking (risk ratio, 0.14; 95% confidence interval [CI], 0.03-0.47). However, as was anticipated from the experience in women taking tamoxifen for breast cancer, the drug was associated with toxicities, including hot flashes, increased risk of thromboembolic disease, an increased risk of invasive endometrial cancer in postmenopausal women, and an increased risk of cataracts (Table 2). An additional benefit of tamoxifen was a decrease in bony fractures (Table 2). Average annual mortality from all causes in tamoxifen-treated women was 2.17 per 1,000 women compared with 2.71 per 1,000 women in placebo-treated women, for a risk ratio of 0.81 (95% CI, 0.56-1.16).

Based on the results of the NSABP Breast Cancer Prevention Trial, the U.S. Food and Drug Administration approved tamoxifen for use in the reduction of breast cancer incidence in October 1998.

European Studies of Tamoxifen

Three reported European studies comparing tamoxifen with placebo for the reduction of breast cancer risk have also been reported. The Royal Marsden Hospital is performing an 8-year extended pilot trial of tamoxifen versus placebo in women ages 30 to 70 who are at increased risk for breast cancer based largely on their family history. Women in the trial are allowed to continue or to initiate postmenopausal hormone replacement therapy. With 2,471 participants available for analysis, no difference between the 2 study groups in the frequency of breast cancer has been observed. Moreover, the toxicity experience between the 2 groups is not significantly different statistically.

The Italian Tamoxifen Prevention Study randomized 5,408 women ages 35 to 70 without breast cancer, who had undergone a previous hysterectomy, to receive tamoxifen or placebo for 5 years. Women in the trial were allowed to receive hormone replacement therapy. With a median follow-up of 30.5 months, no difference in the occurrence of breast cancer has been identified. Thromboembolic
events, predominantly superficial thrombophlebitis, increased in the tamoxifen-treated women.

The reason that the Royal Marsden Trial and the Italian Tamoxifen Prevention Study failed to show the risk reduction shown in the NSABP Breast Cancer Prevention Trial is not clear. However, the European trials are smaller, allow for the concurrent use of hormone replacement therapy, and enroll different study populations. At the time of the interim report, only 149 women had completed 5 years of treatment in the Italian Tamoxifen Prevention Trial.

The first International Breast Cancer Intervention Study (IBIS-I) randomized 7,152 women at increased risk for breast cancer and ages 35 to 70 to receive either tamoxifen or placebo for 5 years (International Breast Cancer Intervention Study, 2002). Tamoxifen provided a risk reduction for breast cancer (invasive or in situ) of 32% (95% CI 8-50; $P = .013$). Thromboembolic events increased with tamoxifen (odds ratio 2.5 [95% CI 1.5-4.4], $P = .001$), and endometrial cancer increased nonsignificantly ($P = .2$). An excess of deaths from all causes was seen in the tamoxifen treated women ($P = .028$).

**Raloxifene for Risk Reduction**

Raloxifene is another selective estrogen receptor modulator that is chemically different from tamoxifen. Like tamoxifen, it binds to the estrogen receptor and blocks estrogen-mediated DNA transcription. Unlike tamoxifen, experience with raloxifene in patients with documented breast cancer has been very limited, and this agent currently has no established role in the treatment of women with breast cancer.

**The MORE Trial**

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was designed to determine whether 3 years of raloxifene treatment reduced the risk of fracture in postmenopausal women with osteoporosis. A total of 7,705 postmenopausal women younger than age 80 were randomized to receive placebo, 60 mg/d of raloxifene, or 120 mg/d of raloxifene for 3 years. At study entry, participants were required to have osteoporosis (defined as a bone density at least 2.5 standard deviations below the mean for young women) or a history of osteoporotic fracture. The study showed a reduction in the vertebral fracture risk and an increase in bone mineral density in the femoral neck and spine for the raloxifene-treated women, compared with those who received placebo.

After a median follow-up of 40 months in the MORE trial, breast cancer was reported in 40 patients: 27 cases in 2,576 women on placebo and 13 cases in 5,129 women on raloxifene. The relative risk of developing invasive breast cancer on raloxifene, compared with placebo, was 0.24; (95% CI, 0.13-0.44). Raloxifene markedly decreased the risk of estrogen receptor-positive cancers (relative risk, 0.10; 95% CI, 0.04-0.24) but did not appear to influence the risk of developing an estrogen receptor-negative cancer (relative risk, 0.88; 95% CI, 0.26-3.00).

Side effects associated with the use of raloxifene included hot flashes, influenza-like syndromes, endometrial cavity fluid, peripheral edema, and leg cramps. In addition, there were more deep vein thromboses (0.7% for raloxifene vs 0.2% for placebo) and pulmonary emboli (0.3% for raloxifene vs 0.1% for placebo) associated with raloxifene treatment. However, there was no increase in the risk of endometrial cancer associated with raloxifene. The results from this trial led to the initiation of the NSABP Study of...
Tamoxifen and Raloxifene (STAR) trial, which is comparing the 2 drugs in postmenopausal women who are at increased risk of developing breast cancer.

**Prophylactic Mastectomy for Risk Reduction**

The use of bilateral prophylactic mastectomy has not been subjected to prospective, randomized study as a means of decreasing breast cancer risk. However, bilateral prophylactic mastectomy has been estimated in a retrospective analysis to decrease the risk of developing breast cancer by approximately 90% in moderate- and high-risk women. The psychosocial effect of prophylactic bilateral mastectomy on women has not been adequately studied. Such surgery would be expected to negatively impact perceptions of body image, ease of forming new relationships, and the quality of existing relationships. Moreover, the procedure also eliminates the breast as a sexual organ. Bilateral prophylactic mastectomy should be limited to those at very high risk, such as patients with lobular carcinoma in situ (LCIS) or those who are known carriers of BRCA1 or BRCA2 mutations.

Women and their physicians who are considering tamoxifen or prophylactic mastectomy to reduce the risk of breast cancer must balance the demonstrated benefits with the morbidity of the interventions. Furthermore, the monitoring of patients undergoing tamoxifen therapy is complex, because several organ systems are at risk for adverse events. To assist patients and their physicians with risk reduction strategies, the NCCN has developed these guidelines for breast cancer risk reduction.

**Risk Assessment**

Qualitative risk assessment includes the assessment of known risk factors for the development of breast cancer. Based on the qualitative risk assessment, women with known risk factors, such as BRCA1, BRCA2, p53, or PTEN mutations, or more than 2 first-degree relatives with breast cancer or ovarian cancer, may be identified. Patients with BRCA1 or BRCA2 mutations or with a strong family history of breast cancer should be evaluated and managed according to the NCCN Genetic/Familial High-Risk Screening Guidelines. These women may also be appropriate candidates for risk reduction therapy.

Women with a history of thoracic irradiation, especially if it was administered at a young age, are also at greatly increased risk for the future development of breast cancer, and are appropriate candidates for risk reduction strategies. Women with a history of LCIS are also known to be at substantially increased risk for the future development of invasive breast cancer in both the ipsilateral and contralateral breast, and are thus appropriate candidates for risk reduction therapy.

Women without BRCA1, BRCA2, p53, or PTEN mutations, a strong family history of breast cancer, LCIS, or a history of thoracic radiation should have their risk for future breast cancer estimated according to the modified Gail model. As estimated by the modified Gail model, the threshold risk required for a woman to consider the use of risk reduction strategies must depend on an evaluation of the efficacy, morbidity, and expense of the proposed intervention. As a reasonable discriminating risk threshold, the panel has adopted the estimated 1.7% or greater 5-year actuarial risk of breast cancer.
used to identify women eligible for the NSABP Breast Cancer Prevention Trial. The Claus model provides estimation of risk for future breast cancer in women with a strong family history of breast cancer.

The Gail model, modified by the NSABP investigators, is available on a computer disk from the National Cancer Institute and may be ordered through the NCI website at www.cancer.gov.

Risk Reduction Counseling

After determining qualitative and quantitative risk of future breast cancer, women at relatively low risk (namely, women with less than a 1.7% risk of invasive breast cancer within 5 years) should be monitored according to the NCCN Breast Cancer Screening and Diagnosis Guidelines. Women with a risk of greater than 1.7% may be followed according to the NCCN screening guidelines if they (1) decline consideration of risk reduction interventions, (2) have a contraindication to risk reduction intervention (see BRISK-A), or (3) have an overall health status that predicts a life expectancy of less than 10 years. As a guideline, the life expectancy of the average 78-year-old woman in the United States is 10.2 years.

Women who are appropriate candidates for risk reduction intervention should undergo counseling that provides an estimate of the future risk of breast cancer and the available strategies to decrease that risk. Options for risk reduction should be discussed in a nondirective counseling environment. The counseling should include a discussion and consideration of (1) the individual's overall health status; (2) the relative and absolute breast cancer risk reduction achieved with tamoxifen; (3) the contraindications to tamoxifen therapy; (4) the common and serious side effects of tamoxifen, with an emphasis on age-dependent risks; and (5) the presence or absence of the patient's uterus.

Data from the NSABP Breast Cancer Prevention Trial show that the toxicity experienced with tamoxifen is much more favorable in younger than in older women, and the benefits in relative risk reduction are similar across all age groups and risk groups. Thus, the tamoxifen treatment risk/benefit ratio is especially favorable in women between the ages of 35 and 50. Although the ratio is less favorable in older women, it still generally favors the use of tamoxifen. Unfortunately, individualized data regarding the risk/benefit ratio for tamoxifen are not generally available except for the broad age categories of 50 and younger versus older than 50.

Postmenopausal women without a contraindication to tamoxifen may be eligible for the STAR trial. Women who submit a risk assessment form for the STAR trial receive a computer-generated estimate of their future risk of breast cancer using the modified Gail model, which is age, race, and breast cancer risk-factor specific and also projects risks (age and race specific) for the known, potentially serious complications of treatment with a selective estrogen-receptor modulator. Completion of this form (or a similar assessment) is encouraged. It provides an accurate estimate of an individual's risks and benefits and further encourages women to participate in ongoing breast cancer risk reduction clinical trials.

The risk reduction discussion should also cover the risks and benefits of bilateral prophylactic mastectomy in women at very high risk, such as those who are known carriers of BRCA1, BRCA2, p53, or PTEN mutations or LCIS (rare instances). If bilateral prophylactic mastectomy is considered, the evaluation and counseling should include input from surgery, reconstructive surgery, and psychiatry.
Discussion regarding the risk of ovarian cancer and the option of prophylactic oophorectomy should also be included. For women considered at increased risk because of genetic traits or very early onset of breast or ovarian cancer in their families, the evaluation should also include special genetic counseling, according to the NCCN Genetic/Familial High-Risk Screening Guidelines.

**Risk Reduction Therapy**

**Bilateral Mastectomy**

Carefully selected women at increased risk (ie, with LCIS or BRCA1, BRCA2, p53, or PTEN mutations) who have had appropriate multidisciplinary consultations and who desire risk reduction therapy should first undergo a clinical breast examination and bilateral mammogram if not performed within the past 6 months. If results are normal, patients who choose bilateral prophylactic mastectomy should undergo the procedure with or without immediate breast reconstruction. Women undergoing prophylactic mastectomy do not require an axillary lymph node dissection unless breast cancer is identified on pathologic evaluation of the mastectomy specimen. After prophylactic mastectomy, women who are carriers of BRCA1 or BRCA2 mutations should be monitored according to the NCCN Genetic/Familial High-Risk Screening Guidelines. Patients with LCIS who undergo bilateral mastectomy should be followed up with routine health maintenance. Patients found to have invasive breast cancer or ductal carcinoma in situ at the time of prophylactic mastectomy should be treated according to the NCCN Breast Cancer Treatment Guidelines.

**Bilateral Salpingo-oophorectomy**

Women with BRCA1 or BRCA2 mutations are at risk for developing breast and ovarian cancer. Although the risk of ovarian cancer is considerably lower than the risk of breast cancer in BRCA1 or BRCA2 mutation carriers, the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have supported the recommendation of bilateral prophylactic oophorectomy after completion of childbearing in these women. The risk of primary peritoneal cancer (cancer of the lining of the peritoneal cavity) may still persist after bilateral salpingo-oophorectomy in this setting.\(^{22-24}\)

Breast cancer risk reduction in patients undergoing bilateral prophylactic oophorectomy has been reported. Retrospective reports have indicated that in BRCA1 mutation carriers, a bilateral salpingo-oophorectomy may offer breast cancer risk reduction as well.\(^{25}\) Decreases in ovarian hormone exposure after surgical removal of the ovaries may alter breast cancer risk. This may reach 50% risk reduction, depending on the age of surgical menopause.

Two recent studies reported on bilateral salpingo-oophorectomy in carriers of BRCA1 or BRCA2 mutations.\(^{26,27}\) In both studies, the effectiveness of prophylactic oophorectomy in preventing ovarian cancer was noted. The persistent risk of peritoneal tumors was approximately 1% in both studies after bilateral oophorectomy. The mean age of diagnosis of ovarian cancer was 50.8 years, thus supporting the recommendation for delaying oophorectomy until after the completion of childbearing. Risk reduction for breast cancer was noted to be of the magnitude of 25% to 50% in the patients undergoing bilateral salpingo-oophorectomy.

The removal of the ovaries results in premature menopause with an associated increased risk of osteoporosis and cardiovascular disease. Vasomotor symptoms and cognitive changes associated with menopause may also substantially affect quality of life. The surgery itself may have some associated complications. Hormone
replacement in women undergoing bilateral salpingo-oophorectomy did not adversely affect risk reduction in breast cancer noted and is generally not recommended past the age of 50 years of age in BRCA carriers.

It is unlikely that a prospective randomized study on the use of bilateral salpingo-oophorectomy for breast cancer risk reduction will be performed. Therefore, discussion of the risk reduction offered by bilateral salpingo-oophorectomy is appropriate. Whether the resulting reduction in the risk of breast cancer from this procedure is preferable to a risk reducing bilateral mastectomy is likely to remain a personal decision.28

Nonsurgical Risk Reduction

Women without a known contraindication to tamoxifen who desire nonsurgical breast cancer risk reduction therapy should be treated with 20 mg/d of tamoxifen or enrolled in a clinical trial for breast cancer risk reduction. Women receiving tamoxifen as a risk reduction agent should undergo a pelvic examination with cervical cytology (Papanicolaou smear) if the uterus is intact and an ophthalmologic evaluation if they have had cataracts or poor vision. Because evidence regarding the effect of tamoxifen on bone mineral density in premenopausal women is contradictory, a baseline bone mineral density determination may be considered (category 2B).

The optimal duration of tamoxifen therapy for risk reduction is not known. In the Early Breast Cancer Trialists' most recent overview analysis, continuing tamoxifen therapy for up to 5 years resulted in an increasingly reduced risk for development of contralateral primary breast cancer.10 In addition, the NSABP Breast Cancer Prevention Trial, in which women received either placebo or tamoxifen for 5 years, demonstrated a favorable benefit/toxicity profile.4 Thus, 5 years appears to be a reasonable period for tamoxifen treatment when this agent is used to reduce the risk of breast cancer.

Patients who have abnormal results from their clinical breast examination or bilateral mammogram should be treated according to the NCCN Breast Screening and Diagnosis Guidelines or, if results indicate malignancy, the NCCN Breast Cancer Treatment Guidelines.

Raloxifene and Breast Cancer Risk Reduction

Despite the encouraging results from the MORE trial, raloxifene cannot be recommended for breast cancer risk reduction outside of a clinical trial. The number of breast cancer events in the MORE trial was relatively small, and the median follow-up was only 40 months. More importantly, the patient population included in the MORE trial was not at elevated risk of developing breast cancer (as confirmed by the small number of breast cancer events). It remains unknown whether raloxifene treatment would produce similar results in a group of women at elevated risk such as those included in the NSABP Breast Cancer Prevention Trial.

For these reasons, the panel does not endorse the routine use of raloxifene for breast cancer risk reduction in women who have an elevated risk of developing breast cancer. The NCCN panel's recommendation is similar to the conclusion drawn in the American Society of Clinical Oncology Technology Assessment.29,30

Monitoring Patients on Tamoxifen

Follow-up of women treated with tamoxifen for breast cancer risk reduction should focus on the early detection of breast cancer and the management of adverse symptoms or complications.
Appropriate monitoring for breast cancer and the evaluation of breast abnormalities should be performed according to the NCCN Breast Cancer Screening and Diagnosis Guidelines. The population of women eligible for tamoxifen risk reduction therapy is at sufficiently high risk to warrant, at a minimum, yearly bilateral mammography, a clinical breast examination every 6 months, and monthly breast self examination.

Endometrial Cancer

The increased risk for endometrial cancer in postmenopausal women treated with tamoxifen requires monitoring. Early reports that tamoxifen-associated endometrial cancer may be more aggressive than other endometrial cancers have not been confirmed on further study. In the NSABP Breast Cancer Prevention Trial, the only death from endometrial cancer occurred in a placebo-treated subject.

Recent analysis from the NSABP data has noted a small number of uterine sarcomas among the number of patients taking tamoxifen with an intact uterus. These patients have already been included in the reported number of patients diagnosed with endometrial cancer. Uterine sarcoma is a rare form of uterine malignancy occurring in 2% to 4% of all patients with uterine malignancy. It has an annual worldwide incidence of between 0.5 and 3.3 cases per 100,000 women. Uterine sarcomas arise from the stromal elements of the uterus and are classified on the basis of whether they are pure, containing only a malignant stromal element (i.e., leiomyosarcoma, stromal cell sarcoma), or mixed, containing an epithelial and stromal element (e.g., MMMT [malignant mixed Mullerian tumor] or carcinosarcoma).

In the NSABP trials (B-09, B-14, B-21, B-23, B-24, and P-1), a small number of uterine sarcomas (12) were noted among the number of patients diagnosed with endometrial cancer. Nine of the 12 patients were diagnosed with MMMT (carcinosarcoma). Overall, the rate of sarcoma in women taking tamoxifen was 0.17 per 1,000 women-years. This translates to less than one-tenth of 1%. AstraZeneca reviewed all available global data on tamoxifen through July 2001 for the occurrence of uterine malignancy. These data included worldwide literature reports. This study identified 942 uterine malignancies, of which 140 (15%) were uterine sarcomas. Seventy-three percent were the MMMT variant. Because of the malignant epithelial component noted in MMMT (carcinosarcoma), these are generally treated and staged as epithelial endometrial cancers. Compared with endometrial cancers, they present at a more advanced stage and thus may carry a worse prognosis in terms of disease free and overall survival.

Because patients with uterine sarcomas have been included in the estimation of risk for endometrial cancer, the detailed risk benefits statistics previously published do not need to be changed. These can be used to determine which women may benefit from tamoxifen for reduction of breast cancer risk. However, a new “black box” Food and Drug Administration warning on tamoxifen has been added to highlight the uterine cancer risk (both endometrial and uterine sarcoma) and will also include pulmonary embolism and stroke risks.

Annual pelvic examination should include an age-appropriate Papanicolaou smear if the woman has an intact uterus. The vast majority of women with tamoxifen-associated endometrial cancer present with vaginal spotting as an early symptom of cancer. Therefore, prompt evaluation of vaginal spotting in the postmenopausal woman is essential.

At present, there is insufficient evidence to recommend the performance of uterine ultrasonography or endometrial biopsy for
routine screening in asymptomatic women. In women diagnosed with endometrial cancer while taking tamoxifen, the drug should be discontinued until the endometrial cancer has been fully treated. The panel believes that it is safe and reasonable to resume tamoxifen therapy after completion of treatment for early stage endometrial carcinoma.

**Retinopathy and Cataract Formation**

Tamoxifen is associated with the rare occurrence of retinopathy and with a 1.14 relative risk of cataract formation (95% CI, 1.01-1.29), compared with placebo. Individuals developing cataracts while on tamoxifen have a relative risk for cataract surgery of 1.57 (95% CI, 1.16-2.14), compared with placebo. Thus, in patients experiencing visual symptoms, prompt ophthalmologic evaluation is appropriate.

**Bone Mineral Density**

Although tamoxifen is associated with an increase in bone mineral density in postmenopausal women, there is concern that it may be associated with a decrease in bone mineral density in premenopausal women. Thus, monitoring bone mineral density in premenopausal women may be considered.

**Thromboembolic Disease**

The prospective intermittent screening of women for thromboembolic disease is unlikely to be of value. However, women taking tamoxifen should be educated regarding the symptoms associated with deep vein thrombosis and pulmonary emboli. They should also be instructed to contact their physicians immediately if they develop symptoms of deep vein thrombosis or pulmonary emboli. Women with documented thromboembolic disease should be treated appropriately for the thromboembolic process and should discontinue tamoxifen permanently.

**Duration of Treatment**

The optimal duration of tamoxifen therapy for the reduction of breast cancer incidence has yet to be determined. Until further information is available, a treatment period of 5 years appears to be appropriate. After completing 5 years of therapy, women should continue to be monitored according to the NCCN Breast Cancer Screening and Diagnosis Guidelines and should continue to undergo monitoring for late toxicity, especially for endometrial carcinoma and cataracts.

**Management of Toxicity**

Hot flashes are a common complaint among older women. In the NSABP Breast Cancer Prevention Trial, hot flashes occurred in approximately 81% of tamoxifen-treated women and 69% of placebo-treated women. In women whose quality of life is diminished by the experience of hot flashes, an intervention to eliminate or minimize hot flashes should be undertaken. Although estrogen and/or progestins are effective in eliminating hot flashes in women taking tamoxifen, the safety of these agents is uncertain in women at increased risk for breast cancer, and there is a potential for interaction with tamoxifen that might affect its efficacy.

Anecdotal evidence suggests that vitamin E may decrease the frequency and severity of hot flashes, but a randomized clinical trial of this agent documents only a very modest improvement in hot flashes when compared with placebo. Both the oral and transdermal formulations of clonidine reduce hot flashes in a dose-dependent manner. Toxicities associated with clonidine include...
dry mouth, constipation, and drowsiness. Recently, a nonrandomized pilot study suggested that low-dose venlafaxine was successful in decreasing hot flashes.\textsuperscript{46}

However, not all women who experience hot flashes require medical intervention, and the decision to intervene requires consideration of the efficacy and toxicity of the intervention. Anecdotal evidence also suggests that the use of a number of different herbal or food supplements may alleviate hot flashes. Most of these herbal or food supplements contain active estrogenic compounds, the activity and safety of which are unknown. The panel, therefore, discourages the use of herbal or food supplements in the symptomatic treatment of hot flashes.

Summary

Breast cancer risk factor analysis allows the identification of women at very high risk for the future development of breast cancer. Many of the known risk factors are either not modifiable or are not reasonably modifiable because of social implications or other potential health benefits (e.g., those associated with hormone replacement therapy). Thus, effective strategies to decrease the risk of breast cancer are needed.

The recent demonstration that the use of tamoxifen for 5 years decreases the future risk of breast cancer by approximately 49% provides the opportunity for a risk reduction intervention. Women taking tamoxifen must be monitored for the occurrence of well-defined toxicities, including hot flashes and, more rarely, endometrial carcinoma, thromboembolic disease, and cataract formation. Strategies are available for the management of tamoxifen toxicity.

In special circumstances, such as in carriers of BRCA1 or BRCA2 mutations, the risk of future breast cancer is very high, and the performance of a bilateral prophylactic mastectomy may be considered. Women considering bilateral prophylactic mastectomy should undergo multidisciplinary consultation so that they may make a fully informed decision.

The panel strongly encourages patients and health care providers to participate in clinical trials to test new strategies for decreasing the risk of breast cancer. Only through the accumulated experience gained from well-designed, prospective clinical trials will additional advances in the reduction of breast cancer risk be realized.
### Table 1

Breast Cancer Risk Reduction in the NSABP Breast Cancer Prevention Trial

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (tamoxifen vs placebo)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>0.51</td>
<td>0.39–0.66</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>0.56</td>
<td>0.37–0.85</td>
</tr>
<tr>
<td>50-59 yr</td>
<td>0.49</td>
<td>0.29–0.81</td>
</tr>
<tr>
<td>≥ 60 yr</td>
<td>0.45</td>
<td>0.27–0.74</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>0.14</td>
<td>0.03–0.47</td>
</tr>
</tbody>
</table>

Table 2
Toxicity Experience in Women Enrolled in the NSABP Breast Cancer Prevention Trial

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Annual Rate Per 1,000 Subjects</th>
<th>Risk Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td><strong>Invasive endometrial cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>1.09</td>
<td>1.32</td>
<td>1.21</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>0.76</td>
<td>3.05</td>
<td>4.01</td>
</tr>
<tr>
<td><strong>Deep-vein thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>0.78</td>
<td>1.08</td>
<td>1.39</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>0.88</td>
<td>1.51</td>
<td>1.71</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>0.39</td>
<td>0.30</td>
<td>0.76</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>1.26</td>
<td>2.20</td>
<td>1.75</td>
</tr>
<tr>
<td><strong>Pulmonary embolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>0.10</td>
<td>0.20</td>
<td>2.03</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>0.31</td>
<td>1.00</td>
<td>3.19</td>
</tr>
<tr>
<td><strong>Bone fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>2.24</td>
<td>1.98</td>
<td>0.88</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>7.27</td>
<td>5.76</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Ischemic heart disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataracts developed</td>
<td>2.37</td>
<td>2.73</td>
<td>1.15</td>
</tr>
<tr>
<td>Cataracts developed and underwent surgery</td>
<td>21.72</td>
<td>24.82</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>4.72</td>
<td>1.57</td>
</tr>
</tbody>
</table>

References


**Recommended Reading**