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Family, Preventive Medicine
σ Allergy/Immunology
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These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2008.
Summary of changes in the 1.2008 version of the Breast Cancer Risk Reduction Guidelines from the 1.2007 version include:

BRISK-1

- Added footnote f: The management of DCIS is not covered by the NCCN Breast Cancer Risk Reduction Guidelines. Please refer to the NCCN Breast Cancer Treatment Guidelines.
- Following breast cancer risk assessment (eg modified Gail Model for women ≥ 35 y of age, Claus model, etc), "No contraindication to tamoxifen or raloxifene" was replaced with "lifetime risk of breast cancer greater than 20%."

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.
ELEMENTS OF RISK
- Age
- Ethnicity/race
- Family history
- Age at menarche
- Parity
- Age at first live birth
- Age at menopause
- Number of prior breast biopsies
- Atypical hyperplasia or LCIS
- Prior thoracic RT (e.g., Hodgkin’s disease)
- Known or suspected BRCA1/2, p53, PTEN, or other gene mutation associated with breast cancer risk
- Close relatives with breast and/or ovarian cancer
- Prior thoracic RT
- History of atypical hyperplasia or lobular carcinoma in situ (LCIS)
- Known or suspected BRCA1/2, p53, PTEN or other gene mutation associated with breast cancer risk
- Current or prior estrogen and progesterone hormone replacement therapy
- Body mass index (BMI)
- Breast density
- Alcohol consumption

RISK ASSESSMENT
- Known or suspected BRCA1/2, p53, PTEN or other gene mutation associated with breast cancer risk
- Close relatives with breast and/or ovarian cancer
- Prior thoracic RT
- History of atypical hyperplasia or lobular carcinoma in situ (LCIS)
- Breast cancer risk assessment (e.g., modified Gail Model for women ≥ 35 y of age, Claus model, etc.)

RISK STRATEGY

See the NCCN Genetic/Familial High Risk Assessment Guidelines.

Risk-reduction counseling

- 5 y breast cancer risk ≥ 1.7% or
- Lifetime risk > 20% and
- Life expectancy ≥ 10 y

See NCCN Breast Cancer Risk Reduction Therapy Guidelines

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

Woman desires risk reduction therapy (See BRISK-3)

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RISK REDUCTION COUNSELING/SCREENING

- Known or suspected BRCA1/2, p53, PTEN or other gene mutation associated with breast cancer risk or Close relatives with breast and/or ovarian cancer
  - See NCCN Genetics/Familial High Risk Assessment Guidelines and Breast Cancer Screening and Diagnosis Guidelines

- History of atypical hyperplasia or LCIS
  - See NCCN Breast Cancer Screening and Diagnosis Guidelines

- Woman does not desire risk-reduction therapy
  - Prior thoracic RT
  - 5 y breast cancer risk ≥ 1.7% or Lifetime risk > 20% and Life expectancy ≥ 10 y
  - See NCCN Genetics/Familial High Risk Assessment Guidelines, Breast Cancer Screening and Diagnosis Guidelines

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See the NCCN Genetics/Familial High Risk Assessment Guidelines.

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.
**BASELINE ASSESSMENT**

**Risk reduction mastectomy desired**

**NORMAL**

Breast screening as per NCCN Breast Cancer Screening and Diagnosis Guidelines if not done in previous year

**Abnormal**

Risk reduction agent

**RISK REDUCTION INTERVENTION**

Risk reduction bilateral salpingo-oophorectomy desired (Limited to those with known or strongly suspected BRCA1/2 mutations)

Baseline assessment (for women with intact uterus)

**MONITORING, FINDINGS AND MANAGEMENT**

Bilateral total mastectomy ± reconstruction

Routine follow-up as clinically indicated

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

Routine follow-up as clinically indicated

**MONITORING, FINDINGS AND MANAGEMENT**

Clinical trial P or Tamoxifen (category 1) a,m

Clinical trial P or Raloxifene (category 1) a,m

See Non-surgical Risk Reduction Therapy BRISK-4)

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

**m** See Breast Cancer Risk Reduction Agents (BRISK-B).

**n** Risk reduction mastectomy should generally be considered only in women with BRCA1/2, or other strongly predisposing gene, compelling family history, or women with LCIS. Evaluation should include consultation with surgery and reconstructive surgery. Psychological consultation may also be considered.

**o** The benefit of bilateral salpingo-oophorectomy with concurrent hysterectomy is not clear at this time.

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

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MONITORING

- Surveillance according to NCCN Breast Cancer Screening and Diagnosis Guidelines for women at increased risk of breast cancer
- Annual gynecologic assessment (for women with intact uterus)
- Ophthalmology exam if cataracts or vision problems

See Monitoring, Findings and Management (BRISK-5)

NON-SURGICAL RISK REDUCTION THERAPY

Tamoxifen or Raloxifene

See Breast Cancer Risk Reduction Agents (BRISK-B).

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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.
MONITORING, FINDINGS AND MANAGEMENT

Asymptomatic ➔ Continue tamoxifen or raloxifene

Hot flashes or other tamoxifen or raloxifene-related symptoms ꞏ Symptomatic treatment
If persist, reevaluate role of tamoxifen or raloxifene ➔ Continue tamoxifen or raloxifene

Abnormal vaginal bleeding ➔ Prompt evaluation for endometrial cancer if uterus intact
If no endometrial pathology found, continue tamoxifen or raloxifene and reevaluate if symptoms persist or recur

Anticipated elective surgery ➔ Consider discontinuing tamoxifen or raloxifene 2-4 weeks prior to elective surgery ➔ Resume tamoxifen or raloxifene postoperatively when ambulation is normal

Deep vein thrombosis, pulmonary embolism, cerebrovascular accident, or prolonged immobilization ➔ Discontinue tamoxifen or raloxifene, treat underlying condition

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q Some serotonin reuptake inhibitors (SSRIs) decrease the formation of endoxifen, the active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.

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COMPONENTS OF RISK/BENEFIT ASSESSMENT AND COUNSELING

Options for risk reduction should be discussed in a shared decision-making environment. For breast cancer risk reduction, elements of this discussion include:

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

- Tamoxifen or raloxifene - See Table 2 and Table 4 in the manuscript section.
  - Discussion of relative and absolute risk reduction with tamoxifen or raloxifene.
  - Contraindications to tamoxifen or raloxifene: 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 or raloxifene, with emphasis on age-dependent risks.

- Surgery
  - Discussion of risk reduction mastectomy in high-risk women. Risk reduction mastectomy should generally be considered only in women with BRCA1/2, or other strongly predisposing gene, compelling family history, 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, risk assessment, or other risk reduction intervention.

- Healthy lifestyle
  - Consider breast cancer risks associated with hormone replacement therapy
  - Limit alcohol consumption
  - Exercise
  - Weight control

Note: All recommendations are category 2A unless otherwise indicated.
BREAST CANCER RISK-REDUCTION AGENTS

<table>
<thead>
<tr>
<th>PREMENOPAUSAL</th>
<th>POSTMENOPAUSAL</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
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<tr>
<td>Data regarding tamoxifen risk reduction are limited to women 35 y of age or older with a Gail model 5 year breast cancer risk of $\geq 1.7%$. Data regarding tamoxifen risk reduction are limited to women 35 y of age or older with a Gail model 5-year breast cancer risk $\geq 1.7%$.</td>
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<tr>
<td>Limited data are currently available regarding the efficacy of tamoxifen risk reduction in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation. Limited data are currently available regarding the efficacy of tamoxifen or raloxifene risk reduction in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation.</td>
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<tr>
<td>For other 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 or raloxifene is influenced by age, presence of uterus or comorbid conditions (category 1). There are insufficient data on ethnicity and race.</td>
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<tr>
<td>Use of raloxifene, an aromatase inhibitor, or other agents for breast cancer risk reduction is inappropriate unless as part of a clinical trial. Use of an aromatase inhibitor or other agents for breast cancer risk reduction is inappropriate unless part of a clinical trial.</td>
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</table>

1There are limited data regarding > 5 years of tamoxifen or raloxifene use in breast cancer prevention. Moreover, there may be safety concerns related to use of these agents for greater than 5 years.

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Breast Cancer Risk Reduction

Overview

Breast cancer is the most commonly diagnosed cancer in American women, with 214,640 cases and 41,430 deaths estimated in 2006 in the United States.¹ 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
- BRCA1/2, p53, or PTEN gene mutations
- Current or prior estrogen and progesterone hormone replacement therapy
- High body mass index (BMI)
- Alcohol consumption
- Increased breast density

Estimating breast cancer 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 development of effective strategies for the reduction of breast cancer incidence has also been difficult because few of the existing risk factors are modifiable and some of the potentially modifiable risk factors have social implications extending beyond concerns for breast cancer (eg, age at first live birth). Nevertheless, effective breast cancer risk reduction agents/strategies, such as tamoxifen, raloxifene, and risk reduction surgery, have been identified. However, women and their physicians who are considering interventions to reduce risk of breast cancer must balance the demonstrated benefits with the potential morbidities of the interventions, since surgical risk reduction strategies (eg, risk reduction bilateral mastectomy) may have psychosocial consequences for the woman, and agents, such as tamoxifen and raloxifene, used for non-surgical risk reduction have been associated with certain adverse effects. To assist women at increased risk of breast cancer and their physicians in the application of individualized strategies to reduce breast cancer risk, the NCCN has developed these Breast Cancer Risk Reduction Guidelines.

Risk Assessment

Estimation of breast cancer risk for an individual woman begins with an evaluation of the breast cancer risk factors described in the previous section, many of which, including breast density,² may be associated with hormonal levels (see BRISK-1). Based on this risk assessment, women with a known BRCA1/2, p53, or PTEN gene mutation, or more than 2 first-degree relatives with breast cancer or ovarian cancer, may be identified. Women with a BRCA1/2 mutation or a strong family

¹Estimates made by the American Cancer Society. See ref. 1
²Estimates from American Cancer Society. See ref. 2

NCCN Categories of Evidence and Consensus

Category 1: Based on high-level evidence and uniform consensus.
Category 2A: Based on lower-level evidence including clinical experience and uniform consensus.
Category 2B: Based on lower-level evidence including clinical experience and nonuniform consensus (but no major disagreement).
Category 3: Based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.
Breast Cancer Risk Reduction

History of breast cancer should be evaluated and managed according to the NCCN Genetics/Familial High-Risk Assessment Guidelines. These women may also be appropriate candidates for risk reduction strategies.

Women with a history of lobular carcinoma in situ (LCIS) are also at substantially increased risk for invasive breast cancer in both the affected and contralateral breast, and are thus appropriate candidates for risk reduction interventions as may be women with a history of thoracic irradiation, especially at a young age.

Women ≥35 years of age without a BRCA1/2, p53, or PTEN mutation, a strong family history of breast cancer, a history of thoracic radiation, or a history of LCIS should have their risk for breast cancer estimated according to the modified Gail model. The modified Gail model is a computer-based multivariate logistic regression model that uses age, race, age at menarche, age at first live birth or nulliparity, 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.

The risk threshold 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 threshold, the panel has adopted the 1.7% or greater 5-year actuarial risk of breast cancer as defined by the modified Gail model, which was used to identify women eligible for the National Surgical Adjuvant Bowel and Breast Project (NSABP) Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR) trial.

The criteria used to determine risk by the modified Gail model are described in Figure 1. The Gail model, as modified by the NSABP investigators, is available on the National Cancer Institute website or at www.breastcancerprevention.com.

The Gail model as a tool for the assessment of breast cancer risk is inappropriate for women with a predisposing gene mutation, or strong family history of breast or ovarian cancers. Furthermore, application of the Gail model to African American women may underestimate breast cancer risk in this population, and the breast cancer risk of women from certain ethnic groups, such as recent immigrants from Japan or China may be overestimated by the Gail model. The Claus tables may be useful in providing breast cancer risk estimates for white women without a known cancer-associated gene mutation who have one or two first or second degree female relatives with breast cancer. Neither the Gail model nor the Claus tables are appropriate breast cancer risk assessment tools for women with a history of thoracic radiation. Results from a recent case-control study of women treated at a young age for Hodgkin lymphoma with thoracic radiation indicated that the estimated cumulative absolute risk of breast cancer at 55 years of age was 29.0% (95% CI, 20.2%-40.1%) for a woman treated at 25 years of age with 40 Gy of radiation and no alkylating agents. Women with a history of treatment with thoracic radiation are at a high risk of breast cancer on the basis of radiation exposure alone.

Risk Reduction Interventions (BRISK-3)

Risk Reduction Surgery

Bilateral Total Mastectomy

Retrospective analyses with median follow-up periods of 13-14 years have indicated that bilateral risk reduction mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA1/2 mutation carriers. Results from smaller prospective studies with shorter follow-up periods have provided support for concluding that RRM
Breast Cancer Risk Reduction

provides a high degree of protection against breast cancer in women with a BRCA1/2 mutation.20,21

The panel supports the use of RRM for carefully selected women at high risk of breast cancer who desire this intervention (eg, women with a BRCA1/2, p53, or PTEN mutation, or women with a history of LCIS or thoracic radiation, who have additional breast cancer risk factors or extreme anxiety associated with the diagnosis). These women should first have appropriate multidisciplinary consultations and a clinical breast examination and bilateral mammogram if not performed within the past 6 months. If results are normal, women who choose RRM may undergo the procedure with or without immediate breast reconstruction. Bilateral mastectomy performed for risk reduction should involve removal of all breast tissue (ie, a total mastectomy). Women undergoing RRM do not require an axillary lymph node dissection unless breast cancer is identified on pathologic evaluation of the mastectomy specimen. Following RRM, women who carry a BRCA1/2 mutation should be monitored according to the NCCN Genetics/Familial High-Risk Assessment Guidelines. Women found to have invasive breast cancer or ductal carcinoma in situ at the time of RRM should be treated according to the NCCN Breast Cancer Guidelines. All other women should be followed up with routine health maintenance following RRM.

Bilateral Salpingo-oophorectomy

Women with a BRCA1/2 mutation are at increased risk for both breast and ovarian cancers (including fallopian tube cancer). Although the risk of ovarian cancer is considerably lower than the risk of breast cancer in a BRCA1/2 mutation carrier, the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have lent support for the performance of bilateral risk reduction salpingo-oophorectomy (RRSO) after completion of childbearing in these women. In the studies of Rebbeck et al, the mean age at diagnosis of ovarian cancer was 50.8 years for BRCA1/2 carriers.22

The effectiveness of RRSO in reducing the risk of ovarian cancer in carriers of a BRCA1/2 mutation has been demonstrated in several studies, although a 1-4.3% residual risk of a primary peritoneal carcinoma has been reported.22-26

RRSO is also reported to reduce the risk of breast cancer in carriers of a BRCA1/2 mutation by approximately 50% 22,26,27 In the case-control international study of Eisen et al., a 56% (odds ratio=0.44; 95% CI, 0.29-0.66) and a 46% (odds ratio=0.57; 95% CI, 0.28-1.15) breast cancer risk reduction was reported following RRSO in carriers of a BRCA1 and a BRCA2 mutation, respectively.27 Hazard ratios of 0.47 (95% CI, 0.29-0.77)22, and 0.30 (95% CI, 0.11-0.84)25 were reported in two other studies comparing breast cancer risk in women with a BRCA1/2 mutation who had undergone RRSO with carriers of these mutations who opted for surveillance only.

Reductions in breast cancer risk for carriers of a BRCA1/2 mutation who undergo RRSO may be associated with decreased hormonal exposure following surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a BRCA1 mutation who had a RRSO at age 40 years or younger (odds ratio=0.36, 95% CI, 0.20-0.64) relative to BRCA1 carriers aged 41-50 years who had this procedure (odds ratio=0.50, 95% CI, 0.27-0.92).27 A nonsignificant reduction in breast risk was found for women aged 51 or older although only a small number of women were included in this group.27 However, results from Rebbeck et al (1999) also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.26

The panel recommends limiting RRSO to women with a known or strongly suspected BRCA1/2 mutation. Peritoneal washings should be performed at surgery, and pathologic assessment should include fine
sectioning of the ovaries and fallopian tubes. The benefit of RRSO with concurrent hysterectomy is not clear at this time. Women who undergo RRSO should continue with routine health maintenance.

Risk Reduction Agents

**Tamoxifen for Risk Reduction**

The benefits of tamoxifen, a selective estrogen receptor modulator (SERM), in the treatment of breast cancer in the adjuvant and metastatic settings are well documented. Retrospective analysis of randomized, controlled clinical trials comparing tamoxifen to no tamoxifen in the adjuvant treatment of women with breast cancer has shown a reduction in the incidence of contralateral second primary breast cancer.28-31 The Early Breast Cancer Trialists’ meta-analysis confirmed that the risk of contralateral primary breast cancer is substantially reduced (i.e. a statistically significant annual recurrence rate ratio=0.59) by 5 years of tamoxifen therapy in women with first breast cancers that are estrogen receptor-positive or have an unknown estrogen receptor status.32

**NSABP Breast Cancer Prevention Trial**

The effectiveness of tamoxifen in the setting of breast cancer treatment gave rise to the NSABP BCPT (P-1), a randomized clinical trial of healthy women aged 60 years or older, aged 35-59 with a 1.7% or greater cumulative 5-year risk for developing breast cancer, or with a history of LCIS.14 Both premenopausal and postmenopausal women were enrolled in the trial, and randomized in a double-blinded fashion to treatment with tamoxifen, 20 mg daily for 5 years, or placebo. Invasive breast cancer incidence was the primary study endpoint; high-priority secondary endpoints included the occurrence of thromboembolic disease, cardiovascular disease, bone fracture, endometrial cancer, noninvasive breast cancer, and breast cancer mortality. The trial was unblinded and initial findings were reported in 1998. A subsequent report on this trial has been published which takes into account 7 years of follow-up data subsequent to the point where the study was unblinded. However, nearly one-third of the placebo participants began taking a SERM when the study was unblinded which decreased the proportion of women in the placebo group relative to the tamoxifen group, potentially confounding the long-term results.33

The results of the BCPT study showed that treatment with tamoxifen decreased the short-term risk for breast cancer by 49% in healthy women aged 35 years or older who had an increased risk for the disease (Table 1).14 Risk reduction benefits were demonstrated across all age groups (Table 1). The difference in average annual rates for invasive breast cancer was 3.30 cases per 1,000 women (ie, 6.76 cases per 1,000 women in the placebo group and 3.43 cases per 1,000 women in the group taking tamoxifen). The absolute risk reduction was 21.4 cases per 1,000 women over 5 years.14 In terms of numbers needed to treat, this corresponds to treatment of 47 women with tamoxifen to prevent 1 case of invasive breast cancer. Updated results indicate that breast cancer risk was reduced by 43% in this population after 7 years of follow-up.33 The reduction in invasive breast cancer risk in participants with atypical hyperplasia was particularly striking (risk ratio=0.14; 95% confidence interval (CI), 0.03-0.47) in the initial study analysis (Table 1), and a risk ratio of 0.25 (95% CI, 0.10-0.52) was found after 7 years of follow-up. An additional benefit of tamoxifen was a decrease in bony fractures (Table 2). However, as was anticipated from the experience in studies of women taking tamoxifen following a diagnosis of breast cancer, major toxicities, included hot flashes, invasive endometrial cancer in postmenopausal women, and cataracts (Table 2). A significant increase in the incidence of pulmonary embolism was also observed in women ≥ 50 years of age taking tamoxifen (Table 2). No differences were observed in overall rates of mortality by treatment group with a follow-up period out to 7 years. The initial study analysis revealed that average annual mortality from all causes in tamoxifen-treated women was 2.17 per 1,000 women.
Breast Cancer Risk Reduction

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); annual mortality after 7 years of follow-up was 2.80 per 1,000 women compared with 3.08 per 1,000 women in the tamoxifen and placebo groups, respectively, for a risk ratio of 1.10 (95% CI, 0.85-1.43).

An evaluation of the subset of patients with a BRCA1/2 mutation in the BCPT study revealed that breast cancer risk was reduced by 62% in study patients with a BRCA2 mutation receiving tamoxifen relative to placebo (risk ratio, 0.38; 95% CI, 0.06-1.56). However, tamoxifen use was not associated with a reduction in breast cancer risk in patients with a BRCA1 mutation. These findings may be related to the greater likelihood for development of estrogen receptor-positive tumors in BRCA2 mutation carriers relative to BRCA1 mutation carriers. However, this analysis was limited by the very small number of patients with a BRCA1/2 mutation.

Based on the BCPT study results, in October 1998 the U.S. Food and Drug Administration (FDA) approved tamoxifen for breast cancer risk reduction for women at increased risk of breast cancer.

European Studies of Tamoxifen
Three European studies comparing tamoxifen with placebo for breast cancer risk reduction have also been reported. The Royal Marsden Hospital study was a pilot trial of tamoxifen versus placebo in women ages 30 to 70 years who were at increased breast cancer risk based largely on their family history. Women in the trial were allowed to continue or to initiate postmenopausal hormone replacement therapy. With 2,471 participants available for interim analysis, no difference in the frequency of breast cancer was observed between the 2 study groups. Moreover, the toxicity experienced by the 2 groups did not show statistically significant differences. An analysis of updated findings from the Royal Marsden study did demonstrate a nonsignificant breast cancer risk reduction benefit with tamoxifen use (ie, 62 cases of breast cancer in 1238 women receiving tamoxifen versus 75 cases of breast cancer in 1233 women in the placebo arm).

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. No significant difference in the occurrence of breast cancer in the overall study population was identified at median follow-up periods of 46 and 81.2 months. Thromboembolic events, predominantly superficial thrombophlebitis, were increased in the tamoxifen-treated women. A subset of women in the Italian Tamoxifen Prevention Study who had used hormone replacement therapy (HRT) and were classified as at increased breast cancer risk based on reproductive and hormonal characteristics were found to have a significantly reduced risk of breast cancer with tamoxifen therapy. However, these findings involved only very small numbers of patients and require confirmation in larger studies.

It is unclear why the breast cancer risk reductions observed in the Royal Marsden and Italian Tamoxifen Prevention studies were not as great as those observed in the NSABP BCPT. Possible reasons include the smaller sample sizes, concurrent use of hormone replacement therapy, and different study populations (ie, populations at lower risk of breast cancer).

The first International Breast Cancer Intervention Study (IBIS-I) randomized 7,152 women aged 35-70 years at increased risk for breast cancer to receive either tamoxifen or placebo for 5 years. Tamoxifen provided a breast cancer (invasive or ductal carcinoma in situ) risk reduction of 32% (95% CI, 8.50; P=0.013). Thromboembolic events increased with tamoxifen (odds ratio= 2.5; 95% CI, 1.5-4.4; P=0.001), and endometrial cancer increased nonsignificantly (P=0.2). An excess
of deaths from all causes was seen in the tamoxifen treated women (P=0.028). An updated analysis of the IBIS-I study is planned in 2007.43 Results of a meta-analysis of all 4 tamoxifen prevention trials (BCPT, Royal Marsden, Italian Tamoxifen Prevention study, and IBIS-1) demonstrated a 38% reduction (95% CI, 28-46; P<0.0001) in breast cancer incidence and a 48% reduction (95% CI, 36-58; P<0.0001) in estrogen receptor-positive breast cancer in patients in the group receiving tamoxifen when compared with the placebo group.37

The use of tamoxifen as a breast cancer risk reduction agent has most recently been evaluated in the Study of Tamoxifen and Raloxifene (STAR) Trial.15 (see section on The STAR Trial).

Tamoxifen Recommendations
The panel recommends tamoxifen (20 mg/day) as an option to reduce breast cancer risk in healthy pre- and postmenopausal women ≥ 35 years of age who have a ≥ 1.7% 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1) (see BRISK-3; BRISK-B). The consensus of the panel is that the risk/benefit ratio for tamoxifen use in premenopausal women at increased risk of breast cancer is relatively favorable (category 1), and that the risk/benefit ratio for tamoxifen use in postmenopausal women is influenced by age, presence of uterus or other comorbid conditions (category 1). Since only limited data are currently available regarding the efficacy of tamoxifen risk reduction in BRCA1/2 mutation carriers, and women who have received prior thoracic radiation, use of tamoxifen in these populations is designated as a category 2A recommendation. The utility of tamoxifen as a breast cancer risk reduction agent in women < 35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of tamoxifen as a risk reduction agent.

Raloxifene for Risk Reduction
Raloxifene is a second generation SERM that is chemically different from tamoxifen and appears to have similar anti-estrogenic effects with considerably less endometrial stimulation. The efficacy of raloxifene as a breast cancer risk reduction agent has been evaluated in several clinical studies.

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.44 A total of 7,705 postmenopausal women 31-80 years of age were randomized to receive placebo, 60 mg/day of raloxifene, or 120 mg/day 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.45 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, 0.26-3.0). Although incidence of breast cancer was a secondary endpoint in the MORE trial, it is important to note that breast cancer risk was not a prospectively determined characteristic for the women enrolled and stratified into treatment arms in this study.41 Furthermore, the patients
enrolled in the MORE trial were, on average, at lower risk for breast cancer and older than the patients enrolled in the NSABP BCPT.

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 was an increased incidence of deep venous thromboses (0.7% for women receiving 60 mg/day raloxifene vs 0.2% for placebo) and pulmonary emboli (0.3% for women receiving 120 mg/day 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 CORE Trial
The early findings relating to breast cancer risk in the MORE trial led to the continuation of this trial under the name Continuing Outcomes Relevant to Evista (CORE) trial. Because breast cancer incidence was a secondary endpoint in the MORE trial, CORE was designed to assess the effect of 4 additional years of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis. A secondary endpoint was the incidence of invasive estrogen receptor-positive breast cancer. Data from the CORE Trial were reported in 2004.46

During the CORE trial, the 4-year incidence of invasive breast cancer was reduced by 59% (hazard ratio =0.41; 95% CI, 0.24-0.71) in the raloxifene group compared with the placebo group. Raloxifene, compared to placebo, reduced the incidence of invasive estrogen receptor-positive breast cancer by 66% (hazard ratio =0.34; 95% CI, 0.18-0.66) but had no effect on invasive estrogen receptor-negative breast cancers. Over the 8 years of both trials (MORE + CORE), the incidence of invasive breast cancer was reduced by 66% (hazard ratio =0.34; 95% CI, 0.22-0.50) in the raloxifene group compared with the placebo group. Compared to placebo, 8 years of raloxifene reduced the incidence of invasive estrogen receptor-positive breast cancer by 76% (hazard ratio=0.24; 95% CI, 0.15-0.40). Interestingly, the incidence of noninvasive breast cancer was not significantly different for patients in the raloxifene and placebo arms (hazard ratio = 1.78; 95% CI, 0.37-8.61).

The adverse events in CORE were similar to those seen in MORE. There was a nonsignificant increase in the risk of thromboembolism (relative risk =2.17; 95% CI, 0.83-5.70) in the raloxifene group of the CORE trial compared to the placebo group. There was no statistical significant difference in endometrial events (bleeding, hyperplasia and cancer) between the raloxifene and placebo groups during the 4 years of CORE or the 8 years of MORE and CORE. During the 8 years of the MORE and CORE trials, raloxifene increased the risk for hot flushes and leg cramps compared with placebo; these risks were observed during the MORE trial but not during the additional 4 years of therapy in CORE. While it is possible that hot flushes and leg cramps are early events that do not persist with continued therapy, it is also possible that an increased risk of these adverse events was not observed in the CORE trial as a result of selection bias, i.e., women who experienced these symptoms in the MORE trial may have chosen not to continue in the CORE trial.

The STAR Trial
Despite issues of trial design, the results from the CORE trial and the previous MORE study provided support for concluding that raloxifene may be an effective breast cancer risk reduction agent. However,
neither of these studies was designed to directly evaluate the efficacy of raloxifene versus tamoxifen in this regard. This issue was addressed in the NSABP Study of Tamoxifen and Raloxifene (STAR) Trial (P-2) which was initiated in 1999; initial results became available in 2006.\textsuperscript{15}

In the STAR Trial, 19,747 postmenopausal women 35 years or older at increased risk for invasive breast cancer as determined by the modified Gail model were enrolled into one of two treatment arms (no placebo arm). The primary study endpoint was invasive breast cancer; secondary endpoints included quality of life, and incidences of noninvasive breast cancer, deep venous thrombosis, pulmonary embolism, endometrial cancer, stroke, cataracts, and death. At an average follow-up of approximately 4 years, no statistically significant differences between patients receiving 20 mg/day tamoxifen or 60 mg/day raloxifene were observed with respect to invasive breast cancer risk reduction (\textsuperscript{Table 3}). In addition, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive cancer in the subset of patients with a history of LCIS or atypical hyperplasia. However, raloxifene was not as effective as tamoxifen in reducing the risk of noninvasive breast cancer, although the observed difference was not statistically significant (\textsuperscript{Table 3}). Because there was no placebo arm, it is not possible to determine a raloxifene versus placebo risk ratio for invasive breast cancer or adverse events. However, results of the STAR trial indicated that raloxifene is as effective as tamoxifen in reducing the incidence of breast cancer (which was shown in the BCPT study to reduce breast cancer risk by nearly 50%).\textsuperscript{14}

Invasive endometrial cancer occurred less frequently in the group receiving raloxifene compared with the tamoxifen group, although the difference did not reach statistical significance (\textsuperscript{Table 4}). It is important to note, however, that highly significant reductions in endometrial hyperplasia and hysterectomy were associated with the raloxifene group compared to the tamoxifen group and a significantly lower incidence of thromboembolic events occurred in the raloxifene group compared to the tamoxifen group. The incidences of stroke, ischemic heart disease, and bone fracture were similar in the two groups, whereas cataract development occurred significantly less frequently in the raloxifene group (\textsuperscript{Table 4}). Overall quality of life was reported to be similar for patients in both groups, although patients receiving tamoxifen reported better sexual function.\textsuperscript{47}

\textbf{Raloxifene Recommendations}

The panel recommends use of raloxifene (60 mg/day) as an option to reduce breast cancer risk in healthy postmenopausal women \textgeq 35 years at who have a \textgeq 1.7\% 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1) (see BRISK-3; BRISK-B). The consensus of the panel is that the risk/benefit ratio for raloxifene use in postmenopausal women at increased risk for breast cancer is influenced by age, and comorbid conditions (category 1). Since there are no currently available data regarding the efficacy of raloxifene risk reduction in \textit{BRCA1/2} mutation carriers, and women who have received prior thoracic radiation, use of raloxifene in these populations is designated as a category 2A recommendation by the panel. Use of raloxifene to reduce breast cancer risk in premenopausal women is inappropriate unless part of a clinical trial. The utility of raloxifene as a breast cancer risk reduction agent in women < 35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of raloxifene as a risk reduction agent.

\textbf{Aromatase Inhibitors for Risk Reduction}

A number of clinical trials testing the use of aromatase inhibitors in the adjuvant therapy of postmenopausal women with invasive breast cancer have been reported. The first of these studies, the Arimidex, Tamoxifen Alone or in Combination Trial (ATAC Trial) randomized postmenopausal women with invasive breast cancer to anastrozole versus tamoxifen versus anastrozole plus tamoxifen in a double-blinded...
fashion.48 The occurrence of contralateral second primary breast cancers was a study endpoint. With 47 months median follow-up, a nonsignificant reduction in contralateral breast cancers was observed in women treated with anastrozole alone compared with tamoxifen (odds ratio= 0.62; 95% CI, 0.38-1.02; P=0.062) and a significant reduction in contralateral breast cancers was seen in the subset of women with hormone receptor-positive first cancers (odds ratio= 0.56; 95% CI, 0.32-0.98; P=0.04).49 Similar reductions in the risk of contralateral breast cancer have been observed with sequential tamoxifen followed by exemestane compared with tamoxifen alone and with sequential tamoxifen followed by letrozole compared with tamoxifen followed by placebo.50,51

In the Breast International Group (BIG) 1-98 trial postmenopausal women with early stage breast cancer were randomized to receive 5 years of treatment with one of the following therapeutic regimens: letrozole; sequential letrozole followed by tamoxifen; tamoxifen; or sequential tamoxifen followed by letrozole. Risk of breast cancer recurrence was lower in women in the letrozole arm relative to the tamoxifen arm.52

Ongoing trials are evaluating the use of the aromatase inhibitors as risk reduction agents in healthy women at increased risk for future breast cancer. For example, the NSABP Study to Evaluate Letrozole and Raloxifene (STELLAR; P-4), anticipated to open in early 2007, will evaluate the efficacy and safety of these agents in postmenopausal women at increased risk of breast cancer. Use of an aromatase inhibitor as an agent for reduction of breast cancer risk in healthy women is inappropriate unless part of a clinical trial (see BRISK-B).

**Monitoring Patients on Risk-Reduction Agents**

Follow-up of women treated with tamoxifen or raloxifene for breast cancer risk reduction should focus on the early detection of breast cancer and the management of adverse symptoms or complications (see BRISK-4; BRISK-5). Appropriate monitoring for breast cancer and the evaluation of breast abnormalities should be performed according to the guidelines described for high risk women in the NCCN Breast Cancer Screening and Diagnosis Guidelines. The population of women eligible for risk reduction therapy with tamoxifen or raloxifene is at sufficiently increased risk of breast cancer to warrant, at a minimum, yearly bilateral mammography, a clinical breast examination every 6 months, and monthly breast self examination (see BRISK-4).

**Endometrial Cancer**

Results from the BCPT study indicated that women ≥ 50 years of age treated with tamoxifen have an increased risk of developing invasive endometrial cancer (Table 2). An increased risk of endometrial cancer was not observed in women ≤ 49 years of age treated with tamoxifen in this study.14, 33 Although the only death from endometrial cancer in the NSABP BCPT occurred in a placebo-treated subject,14, 33 analyses of the NSABP data have revealed a small number of uterine sarcomas among the number of patients with an intact uterus taking tamoxifen. Uterine sarcoma is a rare form of uterine malignancy reported to occur in 2% to 4% of all patients with uterine cancer.53 Compared with other uterine cancers, uterine sarcomas present at a more advanced stage and thus may carry a worse prognosis in terms of disease free and overall survival.54, 55

Updated results from the NSABP BCPT indicate that the incidence of endometrial adenocarcinoma per 1,000 women-years was 2.20 for women receiving tamoxifen and 0.71 for women in the placebo arm.56 The incidence rate of uterine sarcoma was 0.17 and 0.0 per 1,000 women-years for women in the tamoxifen and placebo arms, respectively. Several other studies have also supported an association between tamoxifen therapy and an increased risk of developing uterine sarcoma.54-58 A “black box” FDA warning has been included on the
package insert of tamoxifen to highlight the endometrial cancer risk (both epithelial endometrial cancer and uterine sarcoma) of tamoxifen.56,59

Use of raloxifene was not found to be associated with an increased incidence of endometrial cancer in the MORE trial.45 Results from the STAR trial showed the incidence of invasive endometrial cancer to be lower in the group receiving raloxifene compared with the tamoxifen group, although this difference was not statistically significant (Table 4). However, highly significant reductions in endometrial hyperplasia and hysterectomy during follow-up were associated with the group receiving raloxifene relative to the group receiving tamoxifen.15

For women with an intact uterus, a baseline gynecologic assessment is recommended prior to administration of the risk reduction agent, and follow-up gynecologic evaluations should be performed annually according to the guidelines of the American College of Obstetrics and Gynecology60 (see BRISK-4). 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.61-63 In women diagnosed with endometrial cancer while taking a risk reduction agent, the drug should be discontinued until the endometrial cancer has been fully treated. The panel believes that it is safe and reasonable to resume therapy with a risk reduction agent after completion of treatment for early stage endometrial cancer.

Retinopathy and Cataract Formation
There have been reports of tamoxifen being associated with the occurrence of retinopathy, although most of this information has come from case studies.64,65 Furthermore, these reports have not been confirmed in the randomized controlled trials of tamoxifen. A 1.14 relative risk of cataract formation (95% CI, 1.01-1.29), compared with placebo has been reported in the BCPT study and 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 (Table 2).14 After 7 years of follow-up in the BCPT study, relative risks of cataract formation and cataract surgery were similar to those initially reported.33 In the MORE trial, raloxifene use was not associated with an increase in the incidence of cataracts compared with placebo (relative risk=0.9; 95% CI, 0.8-1.1).66 In the STAR trial, the incidence of cataract development and occurrence of cataract surgery was significantly higher in the group receiving tamoxifen compared with the group receiving raloxifene (Table 4). Thus, patients experiencing visual symptoms while undergoing treatment with tamoxifen should seek prompt ophthalmologic evaluation (see BRISK-4).

Bone Mineral Density
Bone is an estrogen-responsive tissue, and tamoxifen can act as either an estrogen agonist or estrogen antagonist with respect to bone, depending on the menstrual status of a woman.67-69 In premenopausal women, tamoxifen may oppose the more potent effects of estrogen on the bone and potentially increase the risk of osteoporosis, whereas tamoxifen in the presence of typically lower estrogen levels in postmenopausal women is associated with an increase in bone mineral density.14,33 However, the panel did not recommend monitoring of bone mineral density (BMD) in premenopausal patients on tamoxifen since development of osteopenia/osteoporosis in this population was considered unlikely.

Raloxifene has been shown to increase BMD and to reduce incidence of bone fracture in postmenopausal women when compared with placebo.44 Results from the STAR trial did not reveal any difference in
the incidence of bone fracture in the groups of postmenopausal women on either raloxifene or tamoxifen (Table 4).15

**Thromboembolic Disease**

Tamoxifen and raloxifene have been associated with an increased risk of thromboembolic events, such as deep venous thrombosis, pulmonary embolism, or cerebrovascular accident (Table 2; Table 4).14,15,33,45,70 However, recent evidence has shown that women with a Factor V Leiden or prothrombin G20210 → A mutation receiving tamoxifen therapy in the BCPT study were not at increased risk of developing a venous thromboembolism compared to women without these mutations.71 Although prospective screening of women for Factor V Leiden or prothrombin mutations or intermittent screening of women for thromboembolic disease is unlikely to be of value, women taking tamoxifen or raloxifene should be educated regarding the symptoms associated with deep venous thrombosis and pulmonary emboli. They should also be informed that prolonged immobilization may increase risk of venous thromboembolism, and instructed to contact their physicians immediately if they develop symptoms of deep venous thrombosis or pulmonary emboli. Women with documented thromboembolic disease should receive appropriate treatment for the thromboembolic condition and should permanently discontinue tamoxifen or raloxifene therapy.

**Managing Side Effects of Risk Reduction Agents**

Hot flashes are a common menopausal complaint. In the BCPT study, hot flashes occurred in approximately 81% of tamoxifen-treated women and 69% of placebo-treated women.14 In the STAR trial, women receiving tamoxifen reported a significantly increased incidence of vasomotor symptoms relative to women receiving raloxifene,47 although raloxifene use has also been associated with an increase in hot flash severity and/or frequency when compared with placebo.45 In women whose quality of life is diminished by hot flashes, an intervention to eliminate or minimize hot flashes should be undertaken. Estrogens and/or progestins have the potential to interact with SERMs and are not recommended by the panel for the treatment of hot flashes for women on a risk reduction agent outside of a clinical trial.

Gabapentin, a gamma aminobutyric acid (GABA) analog used primarily for seizure control and management of neuropathic pain, has been reported to moderate both the severity and duration of hot flashes.72-75 It has been hypothesized that the mode of action of gabapentin is via central temperature regulatory centers.72,74 Results from a randomized, double-blind, placebo-controlled study involving the use of gabapentin to treat hot flashes in 420 women with breast cancer have been reported. The three treatment arms of the trial were as follows: 300 mg/day gabapentin; 900 mg/day gabapentin; and placebo. Study duration was 8 weeks, and most of the women in the study (68%-75% depending on treatment arm) were taking tamoxifen as adjuvant therapy. Women in the placebo group experienced reductions in severity of hot flashes of 21% and 15% at 4 and 8 weeks, respectively, whereas those in the treatment arms reported reductions of 33% and 31% with lower dose gabapentin, and 49% and 46% with higher dose gabapentin at 4 and 8 weeks, respectively. Only women receiving the higher dose of gabapentin had significantly fewer and less severe hot flashes. Side effects of somnolence or fatigue were reported in a small percentage of women taking gabapentin.75

Venlafaxine, a serotonin and norepinephrine inhibitor antidepressant has been shown to be effective in the management hot flash symptoms in a group of breast cancer survivors of which nearly 70% were taking tamoxifen. Significant declines were observed for both hot flash frequency and severity scores for all doses of venlafaxine (37.5 mg, 75 mg and 150 mg) compared to placebo; incremental improvement was seen at 75 mg versus 37.5 mg (P=0.03).76 Participants receiving venlafaxine reported mouth dryness, reduced appetite, nausea and
constipation with increased prevalence at increased dosages. Based on these findings the authors suggested a starting dose of 37.5 mg with an increase, as necessary after one week, to 75 mg if a greater degree of symptom control is desired. However, this study followed subjects for only 4 weeks.

Very recently, results have been reported from the North Central Cancer Treatment Group (NCCTG) Phase III trial comparing venlafaxine to depomedroxyprogesterone acetate (MPA) in the management of hot flashes. Very recently, results have been reported from the North Central Cancer Treatment Group (NCCTG) Phase III trial comparing venlafaxine to depomedroxyprogesterone acetate (MPA) in the management of hot flashes. One hundred nine patients in each of two treatment arms were randomized to receive either venlafaxine (37.5 mg/day for a week, then 75 mg/day) for 6 weeks or MPA (400 mg IM; single dose). Results for general analyses were available for 94 patients in each group. Reductions in hot flash scores (which combine number and severity of hot flashes) of 55% and 79% for the venlafaxine and MPA treatment arms (P< 0.0001), respectively, were reported at 6 weeks following randomization. Significantly higher frequencies of certain side effects, such as sleepiness, and constipation, were reported in the group receiving venlafaxine relative to the MPA group. Data on long-term control of hot flashes were accumulated from monthly follow-up phone calls made by nurses to some of the patients in the study who did not receive subsequent hot-flash therapy. These results indicated that 27% and 10% (P= 0.003) of patients in the MPA and venlafaxine treatment arms, respectively, experienced more than a 90% decrease in hot flash scores from baseline at 6 months after randomization. Based on these outcomes, the authors suggest that a single dose of MPA delivered intramuscularly is well tolerated and relieves hot flashes better than venlafaxine. However, the safety of MPA in women at either increased risk for breast cancer or the potential for interactions between MPA and tamoxifen or raloxifene remain uncertain.

Another antidepressant, paroxetine, a selective serotonin reuptake inhibitor (SSRI), has also been studied for the relief of hot flash symptoms. A double blind, placebo-controlled trial recruited 165 menopausal women who were randomized into 3 arms (placebo, paroxetine 12.5 mg daily or paroxetine 25 mg daily). After 6 weeks, significant reductions in composite hot flash scores were noted for both dosages of paroxetine (12.5 mg, 62% reduction and 25 mg, 65% reduction); there were no significant differences between dose levels. Adverse events, reported by 54% of subjects receiving placebo and 58% receiving paroxetine, generally included nausea, dizziness and insomnia.

In a stratified, randomized, double-blind, cross-over, placebo-controlled study, 151 women reporting a history of hot flashes were randomized to one of 4 treatment arms (10 mg or 20mg of paroxetine for 4 weeks followed by 4 weeks of placebo or 4 weeks of placebo followed by 4 weeks of 10 mg or 20 mg of paroxetine). Hot flash frequency and composite score were reduced by 40.6% and 45.6%, respectively, for patients receiving 10 mg paroxetine compared to reductions of 13.7% and 13.7% in the placebo group. Likewise, reductions of 51.7% and 56.1% in hot flash frequency and score were found for women receiving 20 mg paroxetine compared with values of 26.6% and 28.8% in the placebo group. No significant differences in efficacy were observed with the lower and higher paroxetine doses. Rates of the most commonly reported side effects did not differ among the 4 arms, although nausea was significantly increased in women receiving 20mg paroxetine relative to the other arms, and a greater percentage of patients receiving the higher dose of paroxetine discontinued treatment.
effectiveness and safety of these agents. In this context it should be noted that recent evidence has suggested that concomitant use of tamoxifen with certain SSRIs (eg, paroxetine and fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen. These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, citalopram and venlafaxine appear to have only minimal effects on tamoxifen metabolism.

A variety of other substances for the control of hot flashes have been described. 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. Anecdotal evidence suggests that the use of a number of different herbal or food supplements may alleviate hot flashes. Vitamin E may decrease the frequency and severity of hot flashes, but results from a randomized clinical trial demonstrated that only a very modest improvement in hot flashes was associated with this agent compared with placebo. Results from a recent double-blind, randomized placebo-controlled crossover trial of the use of black cohosh to treat hot flashes did not show significant differences between groups with respect to improvement in hot flash symptoms. Some herbal or food supplements contain active estrogenic compounds, the activity and safety of which are unknown. Other strategies such as relaxation training, acupuncture, avoidance of caffeine and alcohol and exercise for the management of hot flashes remain unsupported.

It should be noted that the observed placebo effect in the treatment of hot flashes is considerable, typically falling in the range 25% or more, suggesting that a considerable proportion of patients might be helped though a trial of limited duration. 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.

**Risk Reduction Counseling**

Women should be monitored according to the NCCN Breast Cancer Screening and Diagnosis Guidelines. Women with a known or suspected BRCA 1/2, p53, PTEN, or other gene mutation associated with breast cancer risk or those with close relatives with breast and/or ovarian cancer should be followed according to the NCCN Genetics/Familial High Risk Assessment Guidelines whether or not they choose to undergo risk reduction therapy (see BRISK-1; BRISK-2). Women who have abnormal results from their clinical breast examination or bilateral mammogram should be treated according to the NCCN Breast Cancer Screening and Diagnosis Guidelines or, if results indicate malignancy, the women should be treated according to the NCCN Breast Cancer Treatment Guidelines. Although the panel recommends that women with LCIS undergo evaluation according to the NCCN Breast Cancer Risk Reduction Guidelines, strategies for treating patients with LCIS are also described in the NCCN Breast Cancer Treatment Guidelines.

All women who are appropriate candidates for breast cancer risk reduction intervention should undergo counseling that provides a description of the available strategies, including a healthy lifestyle, to decrease breast cancer risk, as described in the NCCN Breast Cancer Risk Reduction Guidelines (see BRISK-A). Options for breast cancer risk reduction should be discussed in a shared decision-making environment. The counseling should include a discussion and consideration of (1) the individual’s overall health status, including menopausal status, medical history, and medication history (eg, hysterectomy status, prior history of a venous thromboembolic event, current use of hormones or SSRI or previous use of a SERM); (2) absolute and relative breast cancer risk reduction achieved with the risk
risk reduction intervention; (3) risks of risk reduction therapy with an emphasis on age-dependent risks; (4) the contraindications to therapy with tamoxifen and raloxifene (eg, history of venous thromboembolism, history of thrombotic stroke, history of transient ischemic attack, and pregnancy or pregnancy potential without an effective method of contraception; (5) the common and serious side effects of tamoxifen and raloxifene (see BRISK-A).

**Risk Reduction Agents**

Counseling sessions with women who are considering non-surgical breast cancer risk reduction should incorporate an explanation of data from the BCPT and/or STAR trial, as appropriate. The BCPT study showed that the toxicity experienced with tamoxifen is much more favorable in younger women, and the benefits in relative risk reduction are similar across all age groups and risk groups (Table 1; Table 2). The tamoxifen treatment risk/benefit ratio is especially favorable in women between the ages of 35 and 50 years. Unfortunately, individualized data regarding the risk/benefit ratio for tamoxifen are not generally available except for the broad age categories of ages 50 years and younger versus older than 50 years of age. Tamoxifen, unlike raloxifene, is a risk reduction agent that can be used by premenopausal women. In addition, tamoxifen may be more effective than raloxifene in reducing the incidence of non-invasive breast cancer (Table 3). Further, tamoxifen was reported by patients in the STAR trial to be associated with better sexual function than raloxifene. However, tamoxifen has been associated with an increased incidence of invasive endometrial cancer relative to placebo in women ≥ 50 years of age, (Table 2) and an increased incidence of endometrial hyperplasia relative to raloxifene, possibly making it a less attractive choice in women with a uterus. Use of raloxifene to reduce breast cancer risk may be preferred by postmenopausal women with a uterus or those at risk for developing cataracts. All women receiving a breast cancer risk reduction agent should be counseled with respect to signs and symptoms of possible side effects associated with use of these agents, and the recommended schedules for monitoring for the presence of certain adverse events.

The optimal duration of SERM therapy for breast cancer 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 the development of contralateral primary breast cancer. Use of tamoxifen for more than 5 years provided no greater benefit but incurred continued risks of therapy. In addition, the BCPT and STAR trials only studied 5 years of risk reduction therapy with either tamoxifen or raloxifene.

There have been some concerns based on studies of animal models regarding the potential for interference with subsequent raloxifene efficacy in patients who had previously completed a 5-year course of tamoxifen. Conversely, questions also exist regarding the safety and efficacy of administering tamoxifen to a patient who had previously taken raloxifene for treatment or prevention of osteoporosis. Until further information is available, a period of 5 years appears to be appropriate for SERM treatment when the agent is used to reduce the risk of cancer. Women should be counseled that the benefits and safety of further therapy with raloxifene is not known. 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 cancer and cataracts.

**Risk Reduction Surgery**

For women at very high risk of breast cancer who are considering risk reduction bilateral mastectomy (RRM), it is important that the potential psychosocial effects of RRM are addressed, although these effects have not been well studied. Such surgery has the potential 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.

Multidisciplinary consultations are recommended prior to surgery to enable the woman to become well informed regarding treatment alternatives, the risks and benefits of surgery, and surgical breast reconstruction options. Psychological consultation may also be considered.

Discussions regarding the risk of ovarian cancer and the option of risk reduction bilateral salpingo-oophorectomy (RRSO) for breast and ovarian cancer risk reduction should also be undertaken with women who are known carriers of a BRCA1/2 mutation. Other topics which should be addressed with respect to RRSO include the increased risk of osteoporosis and cardiovascular disease associated with premature menopause, as well as the potential effects of possible cognitive changes, accelerated bone loss, and vasomotor symptoms on quality of life. Furthermore, the surgery itself may have some associated complications.

Very recently, it has been reported that short-term hormone replacement in women undergoing RRSO did not negate the reduction in breast cancer risk associated with the surgery. It is unlikely that a prospective randomized study on the use of RRSO for breast cancer risk reduction will be performed. Whether the resulting reduction in the risk of breast cancer from this procedure is preferable to a RRM is likely to remain a personal decision.

Healthy Lifestyle

There is evidence to indicate that certain lifestyle characteristics, such as obesity, increased alcohol consumption, and use of certain types of hormone replacement therapy (HRT), are risk factors or markers for an elevated risk of breast cancer. However, the association between a lifestyle modification and a change in breast cancer risk is not as clear. Nevertheless, a discussion of lifestyle characteristics associated with increased risk of breast cancer also provides “a teachable moment” for the promotion of overall health, and an opportunity to encourage women to make choices and changes compatible with a healthy lifestyle.

Breast Cancer Risks Associated with HRT

The Women’s Health Initiative (WHI) enrolled 161,809 postmenopausal women 50-79 years of age into a set of clinical trials from 1993-1998. Two of these trials were randomized controlled studies involving the use of HRT in primary disease prevention: a trial involving 16,608 women with intact uteri at baseline randomized to receive estrogen plus progestin or placebo, and a trial of 10,739 women with prior hysterectomy randomized to receive estrogen alone or placebo. The former trial was terminated early due to evidence for breast cancer harm, along with a global index associated with overall harm. In that study, a 26% increased incidence of breast cancer was observed in the treatment group (hazard ratio=1.26; 95% CI, 1.00-1.59). Of greater concern is that the breast cancers were more advanced in the treatment group compared to placebo.

However, an increased risk of breast cancer was not observed in the trial of women who had undergone hysterectomies and were receiving unopposed estrogen. In fact, the rate of breast cancer was lower in the group receiving estrogen relative to the placebo group, although this difference was not considered to be statistically significant. Results from long-term follow-up studies of women from the WHI study who received estrogen alone have supported the conclusion that no significant difference in breast cancer incidence exists between the treatment and placebo groups (hazard ratio=0.80; 95% CI, 0.62-1.04; P=0.09). However, an increased incidence of abnormal mammograms was observed in the group of women receiving estrogen.
increased incidence of abnormal mammograms was also observed for women in the WHI who received estrogen plus progestin, and was attributed to an increase in breast density.95 Contrary to the results from the WHI, results from several prospective, population-based, observational studies have shown use of estrogen-only HRT to be associated with increased risks of breast cancer. These studies include the Black Women’s Health Study where use of estrogen alone for a duration of 10 years or longer was associated with a nonsignificant increase in risk of invasive breast cancer (relative risk=1.41; 95% CI, 0.95-2.10),96 the Million Women Study of women 50-64 years of age which showed an association between current use of estrogen-only HRT and increased risk of breast cancer (relative risk=1.30; 95% CI, 1.21-1.40; P<0.0001),97 and the Nurses’ Health Study which demonstrated a significantly increased breast cancer risk after long-term use (20 years or longer) of estrogen alone (relative risk=1.42; 95% CI, 1.13-1.77).98 The use of estrogen/progestin therapy and estrogen therapy alone has also been associated with increased risks of cardiovascular disease (e.g. stroke) and decreased risk of bone fractures.91,92 The panel recommends against the use of HRT for women taking tamoxifen or raloxifene outside of a clinical trial.

**Exercise**

The effect of exercise on risk of breast cancer was recently evaluated in a population-based study of 90,509 women between the ages of 40 and 65 years.101 A relative risk of 0.62 (95% CI, 0.49-0.78) was observed for women who reported more than five hours of vigorous exercise per week compared to women who did not participate in recreational activities. These results are supported by another recent population-based case-control study of 4538 case patients with newly diagnosed invasive breast cancer grouped according to race (eg, 1605 black and 2933 white patients). Both black and white women with annual lifetime exercise activity levels exceeding the median activity level for active control subjects were found to have a 20% lower risk of breast cancer when compared to inactive women (odds ratio=0.82; 95% CI, 0.71-0.93).102

**Diet**

Results from the WHI controlled intervention trial of 48,835 postmenopausal women designed to test the effect of a low-fat diet (e.g. fat intake limited to 20% of total caloric intake per day, and increased consumption of fruits, vegetables, and grains) on risk of breast cancer did not show a statistically significant reduction in the incidence of invasive breast cancer in women who followed a low-fat diet over an average of 8.1 years (hazard ratio=0.91, 95% CI; 0.83-1.01).103 However, the nonsignificant trends observed in the study suggest that additional follow up may provide evidence of a significant effect of a low-fat diet on breast cancer risk.

**Weight/BMI**

Recent results from the Nurses’ Health Study evaluating the effect of weight change on the incidence of invasive breast cancer in 87,143 postmenopausal women suggested that women experiencing a weight gain of 25.0 kg or more since age 18 have an increased risk of breast cancer when compared with women who have maintained their weight (relative risk=1.45; 95% CI, 1.27-1.66).104 Furthermore, women who...
had never used postmenopausal hormone replacement therapy and lost 10.0 kg or more since menopause and kept the weight off had a significantly lower risk of breast cancer than women who had maintained their weight (relative risk= 0.43; 95% CI, 0.21-0.86).

Results from a case-control study of 1,073 pairs of women with \textit{BRCA1/2} mutations indicated that a weight loss of 10 or more pounds in women with the \textit{BRCA1} mutation between the ages of 18 and 30 was associated with a decreased risk of developing breast cancer between the ages of 30 and 40 years. (odds ratio=0.35; 95% CI, 0.18-0.67).\textsuperscript{105}

Clinical Trials
Risk reduction counseling should include a discussion of breast cancer risk reduction interventions available in clinical trials.

Summary
Breast cancer risk assessment provides a means of identifying healthy women at increased risk for future development of this disease. However, many of the risk factors for breast cancer are not modifiable. The demonstration that use of tamoxifen or raloxifene for 5 years decreases the future risk of breast cancer by nearly 50% provides an opportunity for a risk reduction intervention. However, the risks and benefits associated with use of tamoxifen or raloxifene for an individual woman should be evaluated and discussed with the woman as part of a shared decision-making process. Women taking a risk reduction agent must be closely monitored for potential side effects associated with use of these agents. In special circumstances, such as in women who are carriers of a \textit{BRCA1/2} mutation, where the risk of breast cancer is very high, the performance of a bilateral mastectomy or bilateral salpingo-oophorectomy may be considered for breast cancer risk reduction. Women considering either surgery should undergo multidisciplinary consultations prior to surgery so as to become well informed about all treatment alternatives, the risks and benefits of risk reduction surgery, and, in the case of bilateral mastectomy, the various reconstruction options available.

The panel strongly encourages women 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 prospective and well-designed clinical trials will additional advances in the reduction of breast cancer risk be realized.

Disclosures
At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Amgen, AstraZeneca, Eli Lilly, Genentech, Genomic Health, Myriad, Novartis, Organon, Pfizer, Roche, Sanofi-Aventis, and Susan G. Komen Breast Cancer Foundation. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
Figure 1

Criteria used in calculation of 5-year risk of breast cancer according to the modified Gail model
(Available at [www.breastcancerprevention.com](http://www.breastcancerprevention.com))

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>_____</td>
</tr>
<tr>
<td>Age at menarche (First menstrual period)</td>
<td>_____</td>
</tr>
<tr>
<td>Age at first live birth or nulliparity</td>
<td>_____</td>
</tr>
<tr>
<td>Number of breast biopsies</td>
<td>_____</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>Y / N</td>
</tr>
<tr>
<td>Number of first-degree relatives with breast cancer</td>
<td>_____</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Caucasian, African American, Hispanic, Other</td>
</tr>
</tbody>
</table>
### Table 1

**Rates of Invasive Breast Cancer in the NSABP Breast Cancer Prevention Trial (BCPT)**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Tamoxifen vs Placebo)</th>
<th>95% Confidence Interval (CI)</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>History of LCIS</td>
<td>0.44</td>
<td>0.16-1.06</td>
</tr>
<tr>
<td>History of atypical hyperplasia</td>
<td>0.14</td>
<td>0.03-0.47</td>
</tr>
</tbody>
</table>

**Rates of Noninvasive Breast Cancer in the NSABP Breast Cancer Prevention Trial**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Tamoxifen vs Placebo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>0.50</td>
<td>0.33-0.77</td>
</tr>
</tbody>
</table>

# Breast Cancer Risk Reduction

## Table 2

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Placebo</th>
<th>Tamoxifen</th>
<th>Risk Ratio (Tamoxifen vs Placebo)</th>
<th>Annual Rate per 1,000 Patients</th>
<th>95% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive endometrial cancer</strong></td>
<td></td>
<td></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>
<td>0.41-3.60</td>
<td></td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>0.76</td>
<td>3.05</td>
<td>4.01</td>
<td>1.70-10.90</td>
<td></td>
</tr>
<tr>
<td><strong>Deep vein thrombosis</strong></td>
<td></td>
<td></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>
<td>0.51-3.99</td>
<td></td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>0.88</td>
<td>1.51</td>
<td>1.71</td>
<td>0.85-3.58</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></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>
<td>0.11-4.49</td>
<td></td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>1.26</td>
<td>2.20</td>
<td>1.75</td>
<td>0.98-3.20</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary embolism</strong></td>
<td></td>
<td></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>
<td>0.11-119.62</td>
<td></td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>0.31</td>
<td>1.00</td>
<td>3.19</td>
<td>1.12-11.15</td>
<td></td>
</tr>
<tr>
<td><strong>Bone fracture</strong></td>
<td></td>
<td></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>
<td>0.46-1.68</td>
<td></td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>7.27</td>
<td>5.76</td>
<td>0.79</td>
<td>0.60-1.05</td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic heart disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.37</td>
<td>2.73</td>
<td>1.15</td>
<td>0.81-1.64</td>
<td></td>
</tr>
<tr>
<td><strong>Cataracts developed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.72</td>
<td>24.82</td>
<td>1.14</td>
<td>1.01-1.29</td>
<td></td>
</tr>
<tr>
<td><strong>Cataracts developed and underwent surgery</strong></td>
<td>3.00</td>
<td>4.72</td>
<td>1.57</td>
<td>1.16-2.14</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3

**Rates of Invasive Breast Cancer in the NSABP Study of Tamoxifen and Raloxifene (STAR) Trial**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Raloxifene vs Tamoxifen)</th>
<th>95% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>1.15</td>
<td>0.37-3.74</td>
</tr>
<tr>
<td>50-59 yr</td>
<td>0.93</td>
<td>0.68-1.29</td>
</tr>
<tr>
<td>≥ 60 yr</td>
<td>1.11</td>
<td>0.80-1.55</td>
</tr>
<tr>
<td>History of LCIS</td>
<td>0.98</td>
<td>0.58-1.63</td>
</tr>
<tr>
<td>History of atypical hyperplasia</td>
<td>1.12</td>
<td>0.72-1.74</td>
</tr>
</tbody>
</table>

**Rates of Noninvasive Breast Cancer in the STAR Trial**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Raloxifene vs Tamoxifen)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>1.40</td>
<td>0.98-2.00</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Annual Rate per 1,000 Patients</th>
<th>Risk Ratio (Raloxifene vs Tamoxifen)</th>
<th>95% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive endometrial cancer</td>
<td>2.00</td>
<td>1.25</td>
<td>0.62</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>4.69</td>
<td>0.76</td>
<td>0.16</td>
</tr>
<tr>
<td>Hysterectomy during follow-up</td>
<td>13.57</td>
<td>6.04</td>
<td>0.44</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>3.71</td>
<td>2.61</td>
<td>0.70</td>
</tr>
<tr>
<td>- Deep vein thrombosis</td>
<td>2.29</td>
<td>1.69</td>
<td>0.74</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>1.41</td>
<td>0.91</td>
<td>0.64</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.39</td>
<td>1.33</td>
<td>0.96</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>2.73</td>
<td>2.51</td>
<td>0.92</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3.00</td>
<td>3.29</td>
<td>1.10</td>
</tr>
<tr>
<td>Cataracts developed</td>
<td>12.30</td>
<td>9.72</td>
<td>0.79</td>
</tr>
<tr>
<td>Cataracts developed and underwent surgery</td>
<td>8.03</td>
<td>6.62</td>
<td>0.82</td>
</tr>
</tbody>
</table>

References


Breast Cancer Risk Reduction


