Breast cancer Risk Reduction

Clinical Practice Guidelines in Oncology

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Breast cancer is the most commonly diagnosed cancer in American women with 209,060 and 54,010 estimated cases of invasive breast cancer and female carcinoma in situ, respectively, in 2010. Approximately 39,840 women will die of breast cancer in the United States in 2010.1

Risk factors for the development of breast cancer can be grouped into categories, including familial/genetic factors (family history, known or suspected BRCA1/2, TP53, PTEN, or other gene mutation associated with breast cancer risk); factors related to...
demographics (e.g., age, ethnicity/race); reproductive history (age at menarche, parity, age at first live birth, age at menopause); environmental factors (prior thoracic irradiation before age 30 years [e.g., to treat Hodgkin disease], hormone replacement therapy [HRT], alcohol consumption); and other factors (e.g., number of breast biopsies, atypical hyperplasia or lobular carcinoma in situ [LCIS], breast density, body mass index).

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 (e.g., 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 for breast cancer must balance the demonstrated benefits with the potential morbidities of the interventions, because surgical risk reduction strategies (e.g., risk reduction bilateral mastectomy) may have psychosocial consequences, and agents, such as tamoxifen and raloxifene, used for nonsurgical risk reduction have been associated with certain adverse effects. To assist women who have an increased risk of developing breast cancer and their physicians in
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FAMILIAL RISK ASSESSMENTa

- Familial/genetic factors
- Criteria for further risk evaluation:
  - Family historyb
  - Early-age-onset breast cancerc
  - Two breast primariesd or breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual
  - Two or more breast primariesd or breast and ovarian/fallopian tube/primary peritoneal cancers in close relative(s) from the same side of family (maternal or paternal)
  - A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations, or leukemia/lymphoma on the same side of family
  - Member of a family with a known mutation in a breast cancer susceptibility gene
  - Populations at riskf
  - Male breast cancer
  - Ovarian/fallopian tube/primary peritoneal cancer
  - Known BRCA1/2, p53, PTEN, or other gene mutation associated with breast cancer risk

See NCCN Clinical Practice Guidelines in Oncology (NCCN Oncology) for Genetic/Familial High-Risk Assessment: Breast and Ovarian* and NCCN Guidelines for Breast Cancer Screening and Diagnosis*

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

aThe management of ductal carcinoma in situ (DCIS) is not covered by the NCCN Guidelines for Breast Cancer Risk Reduction. See the NCCN Guidelines for Breast Cancer.bThe maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Should include 3 generations (including proband, offspring, paternal and maternal generations) and include ages of cancer diagnoses. Note if family structure limits evaluation (small family, few surviving females).
cClinically use age ≤ 50 y because studies define early onset as either ≤ 40 or ≤ 50 y. For the purposes of these guidelines, invasive and DCIS breast cancers should be included.dTwo breast primaries, including bilateral disease or when 2 or more clearly separate ipsilateral primary tumors are present.eFor lobular breast cancer and diffuse gastric cancer, CDH1 gene testing can be considered.fFor populations at risk, requirements for inclusion may be lessened (e.g., women of Ashkenazi Jewish descent with breast or ovarian cancer at any age).
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FAMILIAL RISK ASSESSMENT

Woman meets one or more of the criteria → Referral to cancer genetics professional recommended → Lifetime risk > 20% based on models largely dependent on family history or Pedigree suggestive of genetic predisposition or Known gene mutation associated with breast cancer risk and Life expectancy ≥ 10 y

- Yes → Risk reduction counseling h

- No → See Risk Assessment (page 1116)

See Woman Does Not Desire Risk Reduction Therapy (page 1117)

See Woman Desires Risk Reduction Therapy (page 1118)

For a reference point, the life expectancy of the average 78-year-old woman in the United States is 10.2 y.

hSee Components of Risk/Benefit Assessment and Counseling (page 1121).

For a reference point, the life expectancy of the average 78-year-old woman in the United States is 10.2 y.
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### Elements of Risk

- **Demographics**
  - Age
  - Body mass index
- **Reproductive history**
  - Parity
  - Age at menarche
  - Age at first live birth
  - Age at menopause
- **Environmental factors**
  - Current or prior estrogen and progesterone hormone replacement therapy
  - Alcohol consumption
- **Other**
  - Atypical hyperplasia
  - Number of prior breast biopsies
  - Procedure done with the intent to diagnose cancer; multiple biopsies of the same lesion are scored as one biopsy
  - Breast density
  - Prior thoracic RT
  - History of lobular carcinoma in situ (LCIS)

### Risk Assessment

- **Prior thoracic RT**
- **History of LCIS**
- Life expectancy ≥ 10 y

### 5-y Breast Cancer Risk

- 1.7% for 10 y life expectancy

### Contraindication

- To tamoxifen or raloxifene

### Risk Reduction Counseling

See NCCN Guidelines for Breast Cancer Screening and Diagnosis. For a reference point, the life expectancy of the average 78-year-old woman in the United States is 10.2 y.

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9 For a reference point, the life expectancy of the average 78-year-old woman in the United States is 10.2 y.

8 See Components of Risk/Benefit Assessment and Counseling (page 1121).

7 The clinical utility and role of random periareolar fine needle aspiration, nipple aspiration, or ductal lavage are being still being evaluated and should only be used in the context of a clinical trial.

3 The NCI Breast Cancer Risk Assessment Tool is a computer-based version of the modified Gail model and may be obtained through the NCI Web site. There are circumstances in which the Gail model underestimates risk for development of breast cancer; for instance: BRCA1/2 carriers and those with a strong family history of breast cancer or family history of ovarian cancer in the maternal or paternal family lineage or non-white women. The Claus model may be particularly helpful in determining risk for breast cancer in women with strong family history of breast cancer or family history of ovarian cancer.

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

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*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.*
**RISK REDUCTION COUNSELING/SCREENING**

- **Known BRCA1/2, p53, PTEN, or other gene mutation associated with breast cancer risk**
  - or
  - Pedigree suggestive of genetic predisposition or
  - Lifetime risk > 20%

- **History of LCIS**

- **Prior thoracic RT**

- **5-y breast cancer risk ≥ 1.7%**
  - and
  - Life expectancy ≥ 10 y

See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian* and NCCN Guidelines for Breast Cancer Screening and Diagnosis*

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For a reference point, the life expectancy of the average 78-year-old woman in the United States is 10.2 y.

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

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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. All recommendations are category 2A unless otherwise indicated.

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**NON-SURGICAL RISK REDUCTION THERAPY**

**MONITORING**

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

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

1 See Breast Cancer Risk Reduction Agents (page 1122).
MONITORING, FINDINGS, AND MANAGEMENT

Asymptomatic

- Continue tamoxifen or raloxifene

Hot flashes or other tamoxifen or raloxifene-related symptoms

- 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 endometrial pathology found, reinitiation of tamoxifen or raloxifene may be considered after hysterectomy if early stage disease
  - See NCCN Guidelines for Uterine Neoplasms* for management
  - If no endometrial pathology (carcinoma or hyperplasia with or without atypia) found, continue tamoxifen or raloxifene and reevaluate if symptoms persist or recur

Anticipated elective surgery

- Consider discontinuing tamoxifen or raloxifene 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

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

Some serotonin reuptake inhibitors (SSRIs) decrease the formation of endoxifen, the active metabolite of tamoxifen. However, citalopram and venlafaxine seem to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is unknown.
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 Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.*

- Tamoxifen or raloxifene - see Table 3 and Table 5 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, current pregnancy or pregnancy potential without effective method of contraception, or known inherited clotting trait.
  - 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 possibly 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 to less than 1 drink per day
  - Exercise
  - Weight control

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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# BREAST CANCER RISK-REDUCTION AGENTS

## PREMENOPAUSAL
- **Tamoxifen**
  - Data regarding tamoxifen risk reduction are limited to women aged 35 y or older with a Gail model 5-year breast cancer risk of ≥ 1.7% or a history of LCIS.
  - Tamoxifen: 20 mg/d for 5 years was shown to reduce risk of breast cancer by 49%. Among women with a history of atypical hyperplasia, this dose and duration of tamoxifen was associated with an 86% reduction in breast cancer risk.\(^2\)
  - Limited data are currently available regarding the efficacy of tamoxifen risk reduction in women who are carriers of BRCA1/2 mutations or who have undergone prior thoracic radiation.
  - For other high-risk premenopausal women, data regarding the risk/benefit ratio for tamoxifen appears relatively favorable (category 1).
  - Use of raloxifene, an aromatase inhibitor, or other agents for breast cancer risk reduction is inappropriate unless as part of a clinical trial.

## POSTMENOPAUSAL
- **Tamoxifen or Raloxifene**
  - Data regarding tamoxifen or raloxifene risk reduction are limited to women aged 35 y or older with a Gail model 5-year breast cancer risk ≥ 1.7% or a history of LCIS.
  - Limited data are currently available regarding the efficacy of tamoxifen or raloxifene in women who are carriers of BRCA1/2 mutations or who have undergone prior thoracic radiation.
  - 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.
  - At a median follow-up of approximately 8 y, raloxifene was shown to be about 76% as effective as tamoxifen in reducing the risk of invasive breast cancer (relative risk ratio, 1.24; 95% CI, 1.05-1.47). The relative risk of noninvasive breast cancer for patients in the raloxifene arm compared with those receiving tamoxifen was 1.22 (95% CI, 0.95-1.59).\(^3\)
  - Use of an aromatase inhibitor or other agents for breast cancer risk reduction is inappropriate unless part of a clinical trial.

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\(^1\) Limited data are available regarding > 5 y of tamoxifen or raloxifene use in breast cancer prevention. Moreover, there may be safety concerns related to the use of tamoxifen for > 5 y. Based on the recent update of the STAR trial data, continuing raloxifene beyond 5 y may be an approach to maintain the risk reduction activity of the agent.


the application of individualized strategies to reduce breast cancer risk, the NCCN developed the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Risk Reduction (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Risk Assessment

Estimation of breast cancer risk for an individual woman begins with an initial assessment of familial/genetic factors associated with increased breast cancer risk to determine whether more extensive genetic risk assessment and counseling should be undertaken. The first step in this primary assessment is a broad and flexible evaluation of the personal and family history of the woman, primarily with respect to breast and/or ovarian cancer.\(^{2,3}\) The magnitude of risk increases with the number of affected relatives in the family and the closeness of the relationship, and is affected by the age at which the affected relative was diagnosed.\(^{4,5}\) The younger the age at diagnosis, the more likely a genetic component is present. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Genetic/Familial High-Risk Assessment: Breast and Ovarian; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Hereditary cancers are often characterized by mutations associated with a high probability of cancer development (i.e., a high penetrance genotype), vertical transmission through either mother or father, and an association with other types of tumors.\(^{6,7}\) They often have an early age of onset, and occur when the individual has a germline mutation in only one copy of a gene. Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.\(^{8-11}\)

If an individual or a close family member of that individual meets one or more of the criteria present-
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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.\textsuperscript{24–26}

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 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 Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT)\textsuperscript{27} and the Study of Tamoxifen and Raloxifene (STAR) trial.\textsuperscript{28,29}

The criteria used to determine risk by the modified Gail model are described in Figure 1 (available online, in these guidelines, at www.NCCN.org [MS-22]. The Gail model, as modified by the NSABP investigators, is available on the NCI Web site or at www.breastcancerprevention.com.

Recently, the Gail model was updated using combined data from the Women’s Contraceptive and Reproductive Experiences (CARE) Study and the SEER database, and causes of death from the National Center of Health Statistics, to provide a more accurate determination of risk for African-American women.\textsuperscript{30} Application of the Gail model to recent immigrants from Japan or China may overestimate the risk of breast cancer.

As previously mentioned, the Gail model is not an appropriate breast cancer risk assessment tool for women who underwent prior thoracic irradiation for treatment of Hodgkin disease (e.g., mantle radiation) or those with LCIS. In the Late Effects Study Group trial, the overall risk of breast cancer associated with prior thoracic irradiation at a young age was found to be 56.7-fold (55.5-fold for female patients) greater than the risk of breast cancer in the general population.\textsuperscript{31,32} In that study, the relative risk according to follow-up interval was: 0 at 5 to 9 years; 71.3 at 10 to 14 years; 90.8 at 15 to 19 years; 50.9 at 20 to 24 years; 41.2 at 25 to 29 years; and 24.5 at more than 29 years.\textsuperscript{32} Results from a 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.\textsuperscript{33} Women with a history of thoracic radiation for treatment of Hodgkin’s disease are at a high risk of breast cancer based on radiation exposure alone.\textsuperscript{34–37} Women with a history of LCIS are also at substantially increased risk for invasive breast cancer in both the affected and contralateral breast.\textsuperscript{38,39} Women with a diagnosis of ductal carcinoma in situ (DCIS) should be managed according to recommendations in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Women with a life expectancy of 10 years or greater and no diagnosis/history of breast cancer who are considered to be at increased risk of breast cancer based on any of these assessments should receive counseling on strategies for decreasing breast cancer risk that are individually tailored (e.g., risk-reduction surgery in BRCA1/2 mutation carriers; tamoxifen or raloxifene only in those without a contraindication to these risk-reduction agents; breast screening as detailed in the NCCN Guidelines for Breast Cancer Screening and Diagnosis [to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org]).

Risk Reduction Interventions

Risk Reduction Surgery

**Bilateral Total Mastectomy:** The lifetime risk of breast cancer in BRCA1/2 mutation carriers has been estimated to be 56% to 84%.\textsuperscript{40–43} Retrospective analyses with median follow-up periods of 13 to 14 years have indicated that bilateral risk reduction mastectomy (RRM) decreased the risk for developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA1/2 mutation carriers.\textsuperscript{44,45} An analysis of results from one of these studies\textsuperscript{44} determined that the number of women at high risk for breast cancer needed to treat (NNT) with RRM to prevent one case of breast cancer was equal to 6.\textsuperscript{46} Results from smaller prospective studies with shorter follow-up periods have provided support for concluding that RRM provides a high degree of protection against breast cancer in women with a BRCA1/2 mutation.\textsuperscript{47,48}

The panel supports the use of RRM for carefully selected women at high risk for developing breast
cancer who desire this intervention (e.g., women with a BRCA1/2, TP53, or PTEN mutation or, possibly, those with a history of LCIS). Although the panel consensus is that consideration of RRM is an option for a woman with LCIS without additional risk factors, it is not a recommended approach for most of these women. No data are available on RRM in women with prior mantle radiation exposure.

Women considering RRM 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 (i.e., 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.49 After RRM, women with a BRCA1/2 mutation should be monitored according to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian. Women found to have invasive breast cancer or DCIS at RRM should be treated according to the NCCN Guidelines for Breast Cancer (in this issue and at www.NCCN.org). All other women should be followed up with routine health maintenance after RRM. (The most recent versions of these and other guidelines are available on the NCCN Web site at www.NCCN.org.)

**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 lower than the risk of breast cancer in BRCA1/2 mutation carriers (e.g., estimated lifetime risks of 36%–46% and 10%–27% in BRCA1 and BRCA2 mutation carriers, respectively40,41,50–52), the absence of reliable methods for 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 study by Rebbeck et al.,53 the mean age at diagnosis of ovarian cancer was 50.8 years for BRCA1/2 carriers.

Several studies have shown the effectiveness of RRSO in reducing the risk of ovarian cancer in carriers of a BRCA1/2 mutation. For example, results of a meta-analysis involving 10 studies of BRCA1/2 mutation carriers showed an approximately 80% reduction in the risk of ovarian or fallopian cancer after RRSO.54 However, a 1% to 4.3% residual risk of a primary peritoneal carcinoma has been reported in some studies.53–58

RRSO is also reported to reduce the risk of breast cancer by approximately 50% in BRCA1/2 mutation carriers.53,54,58,59 In an international case-control study, Eisen et al.59 reported breast cancer risk reductions of 56% (odds ratio [OR], 0.44; 95% CI, 0.29–0.66) and 46% (OR, 0.57; 95% CI, 0.28–1.15) after RRSO in BRCA1 and BRCA2 mutation carriers, respectively. Hazard ratios (HRs) of 0.47 (95% CI, 0.29–0.77)53 and 0.30 (95% CI, 0.11–0.84)57 were reported in 2 other studies comparing breast cancer risk in BRCA1/2 mutation carriers who had undergone RRSO and those who opted for surveillance only. These studies are further supported by a recent meta-analysis that found similar reductions in breast cancer risk of approximately 50% for BRCA1 and BRCA2 mutation carriers after RRSO,54 although results of a recent prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for BRCA1 mutation carriers compared with BRCA2 mutation carriers.60

Reductions in breast cancer risk for BRCA1/2 mutation carriers who undergo RRSO may be associated with decreased hormonal exposure after surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a BRCA1 mutation who underwent an RRSO at age 40 years or younger (OR, 0.36; 95% CI, 0.20–0.64) relative to BRCA1 carriers aged 41 to 50 years who had this procedure (OR, 0.50; 95% CI, 0.27–0.92).59 A nonsignificant reduction in breast cancer risk was found for women aged 51 or older, although only a small number was included in this group.59 However, results from Rebbeck et al.58 also suggest that RRSO after 50 years of age is not associated with a substantial decrease in breast cancer risk.

Although data are limited regarding an optimal age for RRSO, a recently published Monte Carlo simulation model provides estimates of the survival impact of breast and ovarian risk reduction strategies (e.g., mammographic/MRI breast screening; risk reduction surgery) in BRCA1/2 mutation carriers according to the type of BRCA mutation present, the specific risk-reduction interventions, and the age of the women at intervention.61 Survival estimates generated from this model...
can facilitate shared decision-making regarding choice of a risk reduction approach (see Table 1, available online, in these guidelines, at www.NCCN.org [MS-23]).

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 additional benefit of concurrent hysterectomy is currently unclear. Women who undergo RRSO should continue with routine health maintenance.

Risk Reduction Agents
Risk reduction agents (i.e., tamoxifen, raloxifene) are recommended only for women aged 35 years or older. **Tamoxifen for Risk Reduction:** The benefits of tamoxifen, a selective estrogen receptor modulator (SERM), for 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 women with breast cancer has shown a reduction in the incidence of contralateral second primary breast cancer.62–65 The Early Breast Cancer Trialists’ meta-analysis confirmed that the risk of developing contralateral primary breast cancer is substantially reduced (i.e., a statistically significant annual recurrence rate ratio of 0.59) after 5 years of tamoxifen therapy in women with first breast cancers that are estrogen receptor–positive or whose estrogen receptor status is unknown.66

**NSABP BCPT:** 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 to 59 with a 1.7% or greater cumulative 5-year risk for developing breast cancer, or with a history of LCIS.27 Both pre- and postmenopausal women were enrolled in the trial, and randomized in a double-blinded fashion to 5 years of treatment with either tamoxifen, 20 mg daily, or placebo. Invasive breast cancer incidence was the primary study end point; high-priority secondary end points 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 takes into account 7 years of follow-up data subsequent to the point where the study was unblinded. However, nearly one third of the participants taking placebo 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.67

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 2).27 Risk reduction benefits were seen across all age groups (Table 2). The difference in average annual rates for invasive breast cancer was 3.30 cases per 1000 women (i.e., 6.76 cases per 1000 women in the placebo group and 3.43 cases per 1000 women in the group taking tamoxifen). The absolute risk reduction was 21.4 cases per 1000 women over 5 years.27 In terms of NNT, 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.67

The reduction in invasive breast cancer risk for participants with atypical hyperplasia was particularly striking (risk ratio, 0.14; 95% CI, 0.03–0.47) in the initial study analysis (Table 2), 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 bone fractures (Table 3). However, as was anticipated from the experience in studies of women taking tamoxifen after breast cancer diagnosis, major toxicities included hot flashes, invasive endometrial cancer in postmenopausal women, and cataracts (Table 3). A significant increase in the incidence of pulmonary embolism was also observed in women aged 50 years or older taking tamoxifen (Table 3). No differences were observed in overall rates of mortality among treatment groups, with a follow-up period out to 7 years. The initial study analysis showed that average annual mortality from all causes in tamoxifen-treated women was 2.17 per 1000 women compared with 2.71 per 1000 in the placebo-treated group, for a risk ratio of 0.81 (95% CI, 0.56–1.16).27 Annual mortality after 7 years of follow-up was 2.80 per 1000 women compared with 3.08 per 1000 women in the tamoxifen and placebo groups, respectively, for a risk ratio of 1.10 (95% CI, 0.85–1.43).67

An evaluation of the subset of patients with a BRCA1/2 mutation in the BCPT study showed that breast cancer risk was reduced by 62% in study pa-
tients with a BRCA2 mutation receiving tamoxifen compared with those taking 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 carriers of 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 FDA approved tamoxifen for breast cancer risk reduction in women at increased risk of developing 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 aged 30 to 70 years who were at an increased risk for developing breast cancer based largely on their family history. Women in the trial were allowed to continue or initiate postmenopausal HRT. With 2471 participants available for interim analysis, no difference in the frequency of breast cancer was observed between the study groups. Moreover, the toxicity experienced by the groups did not show statistically significant differences. However, an analysis of updated findings from the Royal Marsden study showed a nonsignificant breast cancer risk reduction benefit with tamoxifen use (i.e., 62 cases of breast cancer in 1238 women receiving tamoxifen vs. 75 cases of breast cancer in 1233 women in the placebo arm).

Most recently, an analysis of blinded results from the Royal Marsden trial at 20-year follow-up showed no difference in breast cancer incidence between the groups randomly assigned to tamoxifen or placebo (HR, 0.78; 95% CI, 0.58–1.04; P = .1). However, the incidence of estrogen receptor–positive breast cancer was significantly lower in the tamoxifen arm than in the placebo arm (HR, 0.61; 95% CI, 0.43–0.86; P = .005). Importantly, the difference between the arms became significant only in the posttreatment period (i.e., after 8 years of treatment).

The Italian Tamoxifen Prevention Study randomized 5408 women aged 35 to 70 years without breast cancer and who had undergone a previous hysterectomy to receive either tamoxifen or placebo for 5 years. Women in the trial were allowed to receive HRT. No significant difference in the occurrence of breast cancer in the overall study population was identified at median follow-up periods of 46, 81.2, and 109.2 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 HRT and were classified at increased breast cancer risk based on reproductive and hormonal characteristics were found to have a significantly reduced risk of developing breast cancer when undergoing tamoxifen therapy. However, only approximately 13% of the patients in the trial were at high risk for breast cancer.

Why no overall breast cancer risk reduction was observed in the Italian Tamoxifen Prevention Study is unclear. Possible reasons include concurrent use of HRT, and different study populations (i.e., populations at lower risk for breast cancer).

The first International Breast Cancer Intervention Study (IBIS-I) randomized 7152 women aged 35 to 70 years at increased risk for breast cancer to receive either tamoxifen or placebo for 5 years. Tamoxifen provided a breast cancer (invasive or DCIS) risk reduction of 32% (95% CI, 8–50; P = .013). Thromboembolic events increased with tamoxifen (OR, 2.5; 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.

### Table 2 Rates of Breast Cancer in the NSABP Breast Cancer Prevention Trial

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Raloxifene vs. Tamoxifen)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
</tr>
<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 y</td>
<td>0.56</td>
<td>0.37–0.85</td>
</tr>
<tr>
<td>50–59 y</td>
<td>0.49</td>
<td>0.29–0.81</td>
</tr>
<tr>
<td>≥ 60 y</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>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All women</td>
<td>0.50</td>
<td>0.33–0.77</td>
</tr>
</tbody>
</table>

95% CI, 1.5–4.4; \( P = .001 \)), and endometrial cancer showed a nonsignificant increase (\( P = .2 \)). An excess of deaths from all causes was seen in the tamoxifen-treated women (\( P = .028 \)).

In an updated analysis of the blinded IBIS-I trial at a median follow-up of 96 months, the relative risk of breast cancer for the tamoxifen arm compared with placebo was 0.73 (95% CI, 0.58–0.91; \( P = .004 \)).\(^9\) Although no difference in the risk of estrogen receptor–negative invasive tumors was observed between the groups, those in the tamoxifen arm were found to have a 34% lower risk of estrogen receptor–positive invasive breast cancer. Slightly higher risk reduction with tamoxifen was observed for premenopausal patients. Importantly, the increased risk of venous thromboembolism observed with tamoxifen during the treatment period was no longer significant in the posttreatment period, and gynecologic and vaso-motor side effects associated with active tamoxifen treatment were not observed in posttreatment follow-up. These results provide randomized evidence that the benefits of tamoxifen continue after cessation of treatment, whereas many of the side effects diminish or disappear.

The use of tamoxifen as a breast cancer risk reduction agent was most recently evaluated in the STAR trial (see The STAR Trial, page 1130).\(^{28,29}\)

**Tamoxifen Recommendations:** The panel recommends tamoxifen (20 mg/d) as an option to reduce breast cancer risk in healthy pre- and postmenopausal women aged 35 years or older who have a 1.7% or greater 5-year risk for breast cancer as determined using the modified Gail model, or who have had LCIS (category 1; see pages 1118 and 1122). The panel consensus 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 post-
menopausal women is influenced by age, presence of uterus, or other comorbid conditions (category 1). Early studies suggest that lower doses of tamoxifen over shorter treatment periods may reduce breast cancer risk in postmenopausal women, but these findings must be validated in phase III clinical trials.80 Because only limited data are currently available regarding the efficacy of tamoxifen for risk reduction in BRCA1/2 mutation carriers and in women who have received prior thoracic radiation, use of tamoxifen in these populations is designated as a category 2A recommendation. The efficacy of tamoxifen as a breast cancer risk reduction agent in women younger than 35 years is unknown. Data are insufficient on the influence of ethnicity and race on the efficacy and safety of tamoxifen as a risk reduction agent.

Evidence shows that certain drugs 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.81 The consensus of the panel is that alternative medications that have minimal or no impact on plasma levels of endoxifen should be substituted when possible.81 Certain CYP2D6 genotypes have also been reported to be markers of poor tamoxifen metabolism.82,83 Nevertheless, the consensus of the panel is that further validation of this biomarker is needed before it can be used to select patients for tamoxifen therapy.

**Raloxifene for Risk Reduction:** Raloxifene is a second-generation SERM that is chemically different from tamoxifen and seems to have similar antiestrogenic effects with considerably less endometrial stimulation. The efficacy of raloxifene as a breast cancer risk reduction agent has been evaluated in several clinical studies. In 2007, the FDA expanded the indications for raloxifene to include reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer.84

**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.85 A total of 7705 postmenopausal women aged 31 to 80 years 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 2576 women on placebo and 13 cases in 5129 women on raloxifene.86 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 seem 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 end point in the MORE trial, breast cancer risk was not a prospectively determined characteristic for the women enrolled and stratified into treatment arms in this study.77 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, an increased incidence was seen for deep venous thromboses (0.7% for women receiving 60 mg/d raloxifene vs. 0.2% for placebo) and pulmonary emboli (0.3% for women receiving 120 mg/d raloxifene vs. 0.1% for placebo) associated with raloxifene treatment. However, no increase was seen 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 end point 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 end point was the incidence of invasive estrogen receptor–positive breast cancer. Data from the CORE trial were reported in 2004.87

During the CORE trial, the 4-year incidence
of invasive breast cancer was reduced by 59% (HR, 0.41; 95% CI, 0.24–0.71) in the raloxifene group compared with the placebo group. Raloxifene, compared with placebo, reduced the incidence of invasive estrogen receptor–positive breast cancer by 66% (HR, 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% (HR, 0.34; 95% CI, 0.22–0.50) in the raloxifene group compared with the placebo group. Compared with placebo, 8 years of raloxifene reduced the incidence of invasive estrogen receptor–positive breast cancer by 76% (HR, 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 (HR, 1.78; 95% CI, 0.37–8.61).

The adverse events in CORE were similar to those seen in MORE. A nonsignificant increase was seen in the risk of thromboembolism (relative risk, 2.17; 95% CI, 0.83–5.70) in the raloxifene group of the CORE trial compared with the placebo group. No statistical significant difference was seen 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. Although hot flushes and leg cramps may be early events that do not persist with continued therapy, the reason an increased risk of these adverse events was not observed in the CORE trial may be because 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 results from the CORE trial are not entirely straightforward because of the complex design. Of the 7705 patients randomized in the MORE trial, only 4011 chose to continue, blinded to therapy, in CORE; this drop-off likely introduces bias favoring the treatment group. In the CORE trial, the researchers did not re-randomize patients (1286 in the placebo arm, 2725 in the raloxifene arm) and maintained the double-blinding of the original trial.

The RUTH Trial: In the Raloxifene Use for The Heart (RUTH) trial, postmenopausal women with an increased risk of coronary heart disease were randomly assigned to raloxifene or placebo arms.\textsuperscript{88,89} Invasive breast cancer incidence was a coprimary end point of the trial, although only approximately 40% of the study participants had an increased risk of breast cancer according to the Gail model. Median exposure to study drug was 5.1 years and median duration of follow-up was 5.6 years.\textsuperscript{89} Raloxifene did not reduce risk of cardiovascular events, but a 44% decrease in the incidence of invasive breast cancer was seen in the raloxifene arm (HR, 0.56; 95% CI, 0.38–0.83), with a 55% lower incidence of estrogen receptor–positive breast cancer (HR, 0.45; 95% CI, 0.28–0.72). No reduction in the risk of noninvasive breast cancer was found for patients receiving raloxifene, in agreement with the initial results of the STAR trial, although only 7% of breast cancers in the RUTH trial were noninvasive.

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 STAR trial (P-2) initiated in 1999; initial results became available in 2006.\textsuperscript{28} In the STAR trial, 19,747 postmenopausal women aged 35 years or older at increased risk for invasive breast cancer as determined by the modified Gail model were enrolled into 1 of 2 treatment arms (there was no placebo arm). The primary study end point was invasive breast cancer; secondary end points 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/d of tamoxifen or 60 mg/d of raloxifene were observed with respect to invasive breast cancer risk reduction (risk ratio, 1.02; 95% CI, 0.82–1.28). Because no placebo arm was included, a raloxifene-versus-placebo risk ratio for invasive breast cancer could not be determined; however, tamoxifen was shown in the BCPT study to reduce breast cancer risk by nearly 50%. 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 (risk ratio, 1.40; 95% CI, 0.98–2.00).27

At a median follow-up of nearly 8 years (81 months) involving 19,490 women, raloxifene was shown to be approximately 76% as effective as tamoxifen in reducing the risk of invasive breast cancer (risk ratio, 1.24; 95% CI, 1.05–1.47; see Table 4 for risk ratios according to age group), suggesting that tamoxifen has greater long-term benefit with respect to lowering invasive breast cancer risk.29 Raloxifene remained as effective as tamoxifen in reducing the risk of invasive cancer in women with LCIS, but was less effective than tamoxifen for those with a history of atypical hyperplasia (see Table 4). Interestingly, at long-term follow-up, the risk of noninvasive cancer in the raloxifene arm grew closer to that observed for the group receiving tamoxifen (risk ratio, 1.22; 95% CI, 0.95–1.50; see Table 4). No significant differences in mortality were observed between the groups.

In the initial analysis of the STAR trial data, invasive endometrial cancer occurred less frequently in the group receiving raloxifene than in the tamoxifen group, although the difference did not reach statistical significance. However, the incidences of endometrial hyperplasia and hysterectomy were significantly lower in the raloxifene group than in the tamoxifen group. At long-term follow-up, the risk of endometrial cancer was significantly lower in the raloxifene arm (see Table 5).29

The lower incidences of thromboembolic events and cataract development observed in the raloxifene group compared with the tamoxifen group when the STAR trial results were initially analyzed were maintained at long-term follow-up (see Table 5). The incidences of stroke, ischemic heart disease, and bone fracture were similar in the groups. In the initial report, overall quality of life was reported to be similar for patients in both groups, although patients receiving tamoxifen reported better sexual function.30

**Raloxifene Recommendations:** The panel recommends raloxifene use (60 mg/d) as an option to reduce breast cancer risk in healthy postmenopausal women aged 35 years or older who have a 1.7% or greater 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1; see pages 1118 and 1122). The panel consensus 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). Because no data are currently available regarding the efficacy of raloxifene risk reduction in BRCA1/2 mutation carriers and those who have undergone prior thoracic radiation, raloxifene use 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 usefulness of raloxifene as a breast cancer risk reduction agent in women younger than 35 years is not known. Data are insufficient regarding the influence of ethnicity and race on the efficacy and safety of raloxifene as a risk reduction agent.

**Aromatase Inhibitors for Risk Reduction:** Several 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 (ATAC) trial, randomized postmenopausal women with invasive breast cancer to anastrozole versus tamoxifen versus anastrozole plus tamoxifen in a double-blinded fashion.91 The occurrence

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**Table 4 Rates of Breast Cancer in the NSABP Study of Tamoxifen and Raloxifene (STAR) Trial – 81 Months Median Follow-Up**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Raloxifene vs. Tamoxifen)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All women</td>
<td>1.24</td>
<td>0.105–1.47</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 y</td>
<td>1.53</td>
<td>0.64–3.80</td>
</tr>
<tr>
<td>50–59 y</td>
<td>1.23</td>
<td>0.97–1.57</td>
</tr>
<tr>
<td>≥ 60 y</td>
<td>1.22</td>
<td>0.95–1.58</td>
</tr>
<tr>
<td>History of LCIS</td>
<td>1.13</td>
<td>0.76–1.69</td>
</tr>
<tr>
<td>History of atypical hyperplasia</td>
<td>1.48</td>
<td>1.06–2.09</td>
</tr>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All women</td>
<td>1.22</td>
<td>0.95–1.59</td>
</tr>
</tbody>
</table>

of contralateral second primary breast cancers was a study end point. With 47 months median follow-up, a nonsignificant reduction in contralateral breast cancers was observed in women treated with anastrozole alone compared with tamoxifen (OR, 0.62; 95% CI, 0.38–1.02; \( P = .062 \)) and a significant reduction in contralateral breast cancers was seen in the subset of women with hormone receptor–positive first cancers (OR, 0.56; 95% CI, 0.32–0.98; \( P = .04 \)).

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. 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 the letrozole arm compared with the tamoxifen arm.

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, National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MAP.36 and IBIS-II trials are evaluating exemestane and anastrozole, respectively, compared with placebo for the prevention of breast cancer in postmenopausal women at increased risk of developing breast cancer.

Use of an aromatase inhibitor as an agent for reduction of breast cancer risk in healthy women is inappropriate unless it’s part of a clinical trial (see page 1122).

### 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 pages 1119 and 1120). 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 Guidelines for Breast Cancer Screening and Diagnosis (to view the most recent version of these guidelines, visit www.NCCN.org). The population of women eligible for risk reduction therapy with tamoxifen or raloxifene is at sufficiently increased risk for breast cancer to warrant, at a minimum, yearly bilateral mammography, a clinical breast examination every 6 months, and encouragement of breast awareness (see page 1119).

### Endometrial Cancer

Results from the BCPT study indicate that women aged 50 years or older treated with tamoxifen have an increased risk of developing invasive endometrial cancer (Table 3). This study did not show an increased risk of endometrial cancer in women aged

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**Table 5  Toxicity Experience in Women Enrolled in the NSABP Study of Tamoxifen and Raloxifene (STAR) Trial – 81 Months Median Follow-Up**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Annual Rate per 1000 Patients</th>
<th>Tamoxifen</th>
<th>Raloxifene</th>
<th>Risk Ratio (Raloxifene vs. Tamoxifen)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive endometrial cancer</td>
<td>2.25</td>
<td>1.23</td>
<td>0.55</td>
<td>0.36–0.83</td>
<td></td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>4.40</td>
<td>0.84</td>
<td>0.19</td>
<td>0.12–0.29</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy during follow-up</td>
<td>12.08</td>
<td>5.41</td>
<td>0.45</td>
<td>0.37–0.54</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>3.30</td>
<td>2.47</td>
<td>0.75</td>
<td>0.60–0.93</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.93</td>
<td>1.38</td>
<td>0.55</td>
<td>0.54–0.95</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.36</td>
<td>1.09</td>
<td>0.27</td>
<td>0.57–1.11</td>
<td></td>
</tr>
<tr>
<td>Cataracts developed during follow-up</td>
<td>14.58</td>
<td>11.69</td>
<td>0.80</td>
<td>0.72–0.89</td>
<td></td>
</tr>
<tr>
<td>Cataracts developed and underwent surgery</td>
<td>11.18</td>
<td>8.85</td>
<td>0.79</td>
<td>0.70–0.90</td>
<td></td>
</tr>
</tbody>
</table>

49 years or younger treated with tamoxifen.\textsuperscript{27,67} Although the only death from endometrial cancer in the NSABP BCPT occurred in a placebo-treated subject,\textsuperscript{27,67} analyses of the NSABP data have shown a small number of uterine sarcomas among the patients with an intact uterus taking tamoxifen. Uterine sarcoma is a rare form of uterine malignancy reported in 2% to 4% of all patients with uterine cancer.\textsuperscript{98} Compared with other uterine cancers, uterine sarcomas present at a more advanced stage and thus may have a worse prognosis in terms of disease-free and overall survival.\textsuperscript{99,100}

Updated results from the NSABP BCPT indicate that the incidence of endometrial adenocarcinoma per 1000 women-years was 2.20 for women receiving tamoxifen and 0.71 for those in the placebo arm.\textsuperscript{101} The incidence rate of uterine sarcoma was 0.17 and 0.0 per 1000 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 for developing uterine sarcoma.\textsuperscript{99–103} A black box FDA warning is included on the package insert of tamoxifen to highlight the associated risk for development of endometrial cancer (both epithelial endometrial cancer and uterine sarcoma).\textsuperscript{101,104}

Use of raloxifene was not found to be associated with an increased incidence of endometrial cancer in the MORE trial.\textsuperscript{86} Long-term results from the STAR trial showed the incidence of invasive endometrial cancer to be significantly lower in the group receiving raloxifene compared with the tamoxifen group (Table 5).

For women with an intact uterus, a baseline gynecologic assessment is recommended before administration of the risk reduction agent, and follow-up gynecologic assessments should be performed at each visit\textsuperscript{105} (see page 1119). Most women with tamoxifen-associated endometrial cancer present with vaginal spotting as an early symptom of cancer. Therefore, prompt evaluation of vaginal spotting in postmenopausal women is essential.

Evidence is currently insufficient to recommend the performance of uterine ultrasonography or endometrial biopsy for routine screening in asymptomatic women.\textsuperscript{106–108} Women diagnosed with endometrial cancer while taking a risk reduction agent should discontinue the drug until the cancer is 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**
Tamoxifen has been reported to be associated with the occurrence of retinopathy, although most of this information has come from case studies.\textsuperscript{109,110} Furthermore, the randomized controlled trials of tamoxifen have not confirmed these reports. A relative risk of 1.14 for 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 3).\textsuperscript{27} After 7 years of follow-up in the BCPT study, the relative risks of cataract formation and cataract surgery were similar to those initially reported.\textsuperscript{67} 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).\textsuperscript{111} In the STAR trial, the incidence of cataract development and occurrence of cataract surgery was significantly higher in the group receiving tamoxifen than in the group receiving raloxifene (Table 5). Thus, patients experiencing visual symptoms while undergoing treatment with tamoxifen should seek ophthalmologic evaluation (see page 1119).

**Bone Mineral Density**
Bone is an estrogen-responsive tissue, on which tamoxifen can act as either an estrogen agonist or estrogen antagonist, depending on the menstrual status of a woman.\textsuperscript{112–114} In premenopausal women, tamoxifen may oppose the more potent effects of estrogen on the bone and potentially increase the risk for osteoporosis, whereas tamoxifen in the presence of typically lower estrogen levels in postmenopausal women is associated with an increase in bone mineral density.\textsuperscript{27,67} However, the panel did not recommend monitoring of bone mineral density (BMD) in premenopausal patients on tamoxifen, because development of osteopenia/osteoporosis in this population was considered unlikely.

Compared with placebo, raloxifene has been shown to increase bone mineral density and reduce the incidence of vertebral bone fracture in postmenopausal women.\textsuperscript{35,88} Results from the STAR trial did not show any difference in the incidence of bone fracture in the groups of postmenopausal women taking either raloxifene or tamoxifen.\textsuperscript{28,29}
Thromboembolic Disease and Strokes

Tamoxifen and raloxifene have been associated with an increased risk of thromboembolic events, such as deep venous thrombosis, pulmonary embolism (see Tables 3 and 5), or stroke. Increased incidences of venous thromboembolism were observed in the tamoxifen arms of all of the placebo-controlled randomized risk reduction trials. Although not statistically significant, all of these trials, except the Royal Marsden trial (which enrolled only younger women), also showed an increased risk for stroke in women receiving tamoxifen, with this risk found to be significantly elevated in 2 meta-analyses of randomized controlled trials evaluating tamoxifen for breast cancer risk reduction or treatment. A comparison of the raloxifene and tamoxifen arms in the STAR trial did not show a difference in incidence of stroke, and the risk of fatal stroke was significantly higher for women in the RUTH trial with underlying heart disease receiving raloxifene.

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 with women without these mutations. 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 about 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 undergo 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. In the STAR trial, women receiving tamoxifen reported a significantly increased incidence of vasomotor symptoms relative to those receiving raloxifene, although raloxifene use also has been associated with an increase in hot flash severity and/or frequency when compared with placebo. 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 treating hot flashes for women taking a risk reduction agent outside of a clinical trial.

Gabapentin, a γ-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. The mode of action of gabapentin is believed to be through central temperature regulatory centers. A double-blinded, placebo-controlled study involving the use of gabapentin to treat hot flashes randomized 420 women with breast cancer to either 300 mg/d of gabapentin, 900 mg/d of gabapentin, or 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 lower-dose gabapentin arm reported reductions of 33% and 31% and those in the higher-dose arm reported reductions of 49% and 46% 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.

Venlafaxine, a serotonin and norepinephrine inhibitor antidepressant, was shown to be effective in managing hot flashes 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, 75, and 150 mg) compared with placebo; incremental improvement was seen at 75 versus 37.5 mg (P = .03). 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 to 75 mg after 1 week if a greater degree of symptom control is desired. However, this study followed subjects for only 4 weeks.

Another antidepressant, paroxetine, a selective serotonin reuptake inhibitor (SSRI), has also been studied for the relief of hot flashes. A double-blinded, placebo-controlled trial randomized 165 menopausal women to receive either placebo; paroxetine, 12.5 mg/d; or paroxetine, 25 mg/d. After 6 weeks, significant reductions in composite hot flash scores were noted for both dosages of paroxetine (62% for 12.5 mg and 65% for 25 mg); no significant differences were seen between dose levels.124 Adverse events, reported by 54% of subjects receiving placebo and 58% receiving paroxetine, generally included nausea, dizziness, and insomnia.

In a stratified, randomized, double-blinded, crossover, placebo-controlled study, 151 women reporting a history of hot flashes were randomized to 1 of 4 treatment arms (10 or 20 mg of paroxetine for 4 weeks followed by 4 weeks of placebo, or 4 weeks of placebo followed by 4 weeks of 10 or 20 mg of paroxetine).125 Hot flash frequency and composite score were reduced by 40.6% and 45.6%, respectively, for patients receiving 10 mg of paroxetine, compared with 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, respectively, were seen 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 20 mg of paroxetine relative to the other arms, and a greater percentage of patients receiving the higher dose of paroxetine discontinued treatment.

Although these reports seem promising, further randomized studies of the use of these agents in women experiencing hot flash symptoms, especially those also taking tamoxifen, are needed to assess long-term effectiveness and safety. In this context, recent evidence suggests that concomitant use of tamoxifen with certain SSRIs (e.g., paroxetine and fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.81,126 These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen through inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, citalopram and venlafaxine seem to have only minimal effects on tamoxifen metabolism.

Of interest in this context are results of a recent retrospective evaluation of data from the Women’s Healthy Eating and Living randomized trial, which suggest an inverse association between hot flashes and breast cancer recurrence in women with a history of breast cancer taking tamoxifen. These results suggest that hot flashes in women receiving tamoxifen may be an indicator of the biologic availability, and thus effectiveness, of the drug, although additional studies are needed to further elucidate whether hot flashes are predictive of benefit from tamoxifen.127

A recent report of 2 nonrandomized parallel study cohorts of women with DCIS or those at high risk for breast cancer (e.g., those with LCIS, atypical hyperplasia, or a ≥ 1.7% 5-year breast cancer risk according to the Gail model) comparing tamoxifen alone and concomitant with HRT (mean duration of HRT at start of study, approximately 10 years) did not show a difference in the rate of tamoxifen-induced hot flashes.128 The panel recommends against the use of HRT in women taking tamoxifen or raloxifene outside of a clinical trial.

Various other substances for the control of hot flashes have been described.129 Both the oral and transdermal formulations of clonidine reduce hot flashes in a dose-dependent manner.130–132 Toxicities associated with clonidine include dry mouth, Constipation, and drowsiness. Anecdotal evidence suggests that the use of several 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 showed that this agent was associated with only a very modest improvement in hot flashes compared with placebo.133 Results from a recent double-blinded, 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.134 Some herbal or food supplements contain active estrogenic compounds, the activity and safety of which are unknown. Other strategies for managing hot flashes, such as relaxation training, acupuncture, avoidance of caffeine and alcohol, and exercise, although potentially beneficial, remain unsupported.135
Breast Cancer Risk Reduction

The observed placebo effect in the treatment of hot flashes is considerable, typically in the range 25% or more, suggesting that a considerable proportion of patients might be helped through 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. In addition, a study of women receiving tamoxifen for early-stage breast cancer showed a decrease in hot flashes over time.

Risk Reduction Counseling

Women should be monitored according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at www.NCCN.org). Women with a known or suspected BRCA1/2, TP53, PTEN, or other gene mutation associated with breast cancer risk, or those with close relatives with breast and/or ovarian cancer, should be managed according to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at www.NCCN.org), despite whether they choose to undergo risk reduction therapy (see pages 1114 and 1117). Women who have abnormal results from their clinical breast examination or bilateral mammogram should be managed according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis or, if results indicate malignancy, should be treated according to the NCCN Guidelines for Breast Cancer (in this issue and at www.NCCN.org). Although the panel recommends that women with LCIS be managed according to these guidelines, risk reduction strategies for patients with LCIS are also described in the NCCN Guidelines for Breast Cancer. (The most recent versions of these and other guidelines are available on the NCCN Web site at www.NCCN.org.)

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 (see page 1121). 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 (e.g., hysterectomy status, prior venous thromboembolic event, current use of hormones or SSRI, previous use of a SERM); 2) absolute and relative breast cancer risk reduction achieved with the risk reduction intervention; 3) risks of risk reduction therapy, with emphasis on age-dependent risks; 4) the contraindications to therapy with tamoxifen and raloxifene (e.g., history of venous thromboembolism, history of thrombotic stroke, history of transient ischemic attack, pregnancy or pregnancy potential without an effective nonhormonal method of contraception); and 5) the common and serious side effects of tamoxifen and raloxifene (see page 1121).

The recently updated guidelines from ASCO comparing the effectiveness of breast cancer risk reduction agents provide some estimates of the NNT to prevent breast cancer or the number needed to harm (NNH) by causing a specific side effect in a single patient receiving a specific risk reduction agent. Both NNT and NNH can be useful aids in communicating risks and benefits of tamoxifen and raloxifene in this setting (e.g., using long-term data from the IBIS-1 trial, the NNH with respect to venous thromboembolism was determined to be 73 with tamoxifen, whereas it was 150 for patients receiving raloxifene using data from the RUTH study). A summary of other strategies to facilitate a more quantitative discussion of the impact of these agents is also described in the ASCO guidelines.

Risk Reduction Agents

Counseling sessions with women who are considering nonsurgical options for 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 profile of tamoxifen is much more favorable in younger women, and the benefits in relative risk reduction are similar across all age and risk groups (Tables 2 and 3). The tamoxifen treatment risk/benefit ratio is especially favorable in women between ages 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 50 years and younger versus older than 50 years. 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 noninvasive breast cancer.
(Table 4), although the difference is not statistically significant at long-term follow-up.28,29 Furthermore, tamoxifen was reported by patients in the STAR trial to be associated with better sexual function than raloxifene.90 However, tamoxifen has been associated with an increased incidence of invasive endometrial cancer relative to placebo in women aged 50 years or older27,67 (Table 3) and an increased incidence of endometrial hyperplasia and invasive endometrial cancer relative to raloxifene,28,29 possibly making it a less attractive choice in women with a uterus. Postmenopausal women with a uterus or those at risk for developing cataracts may prefer raloxifene for reducing breast cancer risk.

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. Contraindications to tamoxifen or raloxifene include history of venous thromboembolism, thrombotic stroke, transient ischemic attack, current pregnancy or pregnancy potential without effective method of contraception, and known inherited clotting trait.

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.66 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.27,28 However, based on the updated STAR results, which showed that the benefits of raloxifene diminished after cessation of therapy,29 continuing raloxifene beyond 5 years may maintain the risk reduction activity of the agent.

Based on studies of animal models, some concerns exist regarding the potential for interference with subsequent raloxifene efficacy in patients who previously completed a 5-year course of tamoxifen.139 Conversely, questions also exist regarding the safety and efficacy of administering tamoxifen to patients who previously took raloxifene for treatment or prevention of osteoporosis. Until further information is available, a period of 5 years for tamoxifen therapy seems to be appropriate 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 are not known. After completing 5 years of tamoxifen therapy, women should continue to be monitored according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis (to view the most recent version, visit www.NCCN.org) and should continue to undergo monitoring for late toxicity, especially for endometrial cancer and cataracts.

The prolonged effectiveness of tamoxifen as an agent to reduce breast cancer risk, particularly with respect to the development of estrogen receptor–positive disease, is supported by long-term follow-up results of several placebo-controlled randomized trials.57,72 The recent results from the STAR trial suggest that although a 5-year course of raloxifene retains considerable benefit in preventing invasive breast cancer at a median follow-up of 81 months, the breast cancer preventive benefit of tamoxifen therapy for 5 years seems to be sustained for a longer period.29

Risk Reduction Surgery

For women at very high risk of breast cancer who are considering bilateral RRM, the potential psychosocial effects of RRM must be addressed, although these effects have not been well studied.140–142 This 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 before surgery, and should include a surgeon familiar with the natural history and therapy of benign and malignant breast disease,143 to enable the woman to become well informed regarding treatment alternatives, the risks and benefits of surgery, and surgical breast reconstruction options. Immediate breast reconstruction is an option for many women after RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction.144 Psychological consultation may also be considered.

The risk of ovarian cancer and the option of bilateral RRSO for breast and ovarian cancer risk reduction should also be discussed with women who are known carriers of a BRCA1/2 mutation. Other topics that should be addressed with respect to RRSO include the increased risk of osteoporosis and cardiovascular disease associated with premature menopause, and the potential effects of possible cogn-
Breast Cancer Risk Reduction

Recent studies involving 16,608 women with intact uteri at baseline randomized to receive estrogen plus progestin or placebo,151 and one trial of 10,739 women who had undergone prior hysterectomy randomized to receive estrogen alone or placebo.152 The former trial was terminated early because of 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 (HR, 1.26; 95% CI, 1.00–1.59). Of greater concern is that the breast cancers were more advanced in the treatment group than in the placebo group,153 although the increased risk of breast cancer declined rapidly after cessation of HRT.154

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.155 Results from long-term follow-up (i.e., mean, 7.1 years) of women from the WHI study who received estrogen alone support the conclusion that no significant difference was seen in breast cancer incidence between the treatment and placebo groups (HR, 0.80; 95% CI, 0.62–1.04; P = .09). However, an increased incidence of abnormal mammograms was observed in the group of women receiving estrogen,156 and a doubling of the risk of benign proliferative breast disease.157 A more recent analysis of the data from this randomized controlled WHI trial showed that use of estrogen alone significantly increased mammographic breast density compared with use of placebo, and this effect was observed for at least a 2-year period.157 An 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.158

Contrary to the results from the WHI randomized controlled trials, 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, in which use of estrogen alone for 10 years or longer was associated with increased risk of invasive breast cancer (relative risk, 1.41; 95% CI, 0.95–2.10)159; the Million Women Study of women aged 50 to 64 years, which showed an association between current use of estrogen-only HRT and increased risk

Studies have reported that short-term hormone replacement in women undergoing RRSO did not negate the reduction in breast cancer risk associated with the surgery.149 In addition, results of a recent case-control study of BRCA1 mutation carriers showed no association between HRT and increased breast cancer risk in postmenopausal BRCA1 mutation carriers.146 However, the consensus of the panel is that caution should be used when considering HRT in mutation carriers after RRSO, given the limitations inherent in nonrandomized studies (see Breast Cancer Risks Associated with HRT, below).147,148 A prospective randomized study on the use of RRSO for breast cancer risk reduction is unlikely to be performed. Whether the resulting reduction in the risk of breast cancer from this procedure is preferable to a RRM will probably remain a personal decision.149 Table 1 (available online, in these guidelines, at www.NCCN.org [MS-23]) provides estimates based on a Model Carlo simulation model of the survival impact of breast and ovarian risk reduction strategies; these data can be used as a tool to facilitate shared decision-making regarding choice of a risk reduction approach, particularly with respect to issues related to risk reduction surgery (see Table 1, available at www.NCCN.org).

Healthy Lifestyle
Evidence indicates that certain lifestyle characteristics, such as obesity, increased alcohol consumption, and use of certain types of HRT, are risk factors or markers for an elevated risk of breast cancer.150 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 to 79 years of age into a set of clinical trials from 1993 to 1998. Two of these trials were randomized controlled studies involving the use of HRT in primary disease prevention: one trial involving 16,608 women with intact uteri at baseline randomized to receive estrogen plus progestin or placebo, and one trial of 10,739 women who had undergone prior hysterectomy randomized to receive estrogen alone or placebo. The former trial was terminated early because of 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 (HR, 1.26; 95% CI, 1.00–1.59). Of greater concern is that the breast cancers were more advanced in the treatment group than in the placebo group, although the increased risk of breast cancer declined rapidly after cessation of HRT.

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Contrary to the results from the WHI randomized controlled trials, 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, in which use of estrogen alone for 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); the Million Women Study of women aged 50 to 64 years, which showed an association between current use of estrogen-only HRT and increased risk...
Numerous studies have shown that the intake of moderate amounts of alcohol (1–2 drinks per day) is associated with a 30% to 50% increase in the incidence of breast cancer. A population-based study of 51,847 postmenopausal women provided evidence supporting an association between increased alcohol consumption and an increased likelihood of development of estrogen receptor–positive breast cancer. However, the effect of a reduction in alcohol consumption on the incidence of breast cancer has not been well studied. The panel consensus is that alcohol consumption should be limited to less than 1 drink per day.

**Exercise:** Increased levels of physical activity have been associated with a decreased risk of breast cancer. For example, the effect of exercise on risk of breast cancer was evaluated in a population-based study of 90,509 women between the ages of 40 and 65 years. A relative risk of 0.62 (95% CI, 0.49–0.78) was observed for women who reported more than 5 hours of vigorous exercise per week compared with women who did not participate in recreational activities. These results are supported by another population-based, case-control study of 4538 case patients with newly diagnosed invasive breast cancer and control patients grouped according to race (e.g., 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 compared with inactive women (OR, 0.82; 95% CI, 0.71–0.93).

In addition, a prospective assessment evaluating the association of physical activity among 45,631 women showed the greatest reduction in breast cancer risk for women who reported walking/hiking for 10 or more hours per week (relative risk, 0.57; 95% CI, 0.34–0.95). Recently, a study of 320 postmenopausal sedentary women randomly assigned to either 1 year of aerobic exercise or a control group showed modest but significant changes in serum levels of estradiol and sex hormone–binding globulin from baseline (i.e., a decrease and an increase in these levels, respectively). However, experts have suggested that other unidentified mechanisms are more likely to be responsible for the association between increased activity level and decreased risk of breast cancer.

**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 for breast cancer did not show a statistically significant reduction in the incidence of invasive breast cancer in women who adhered to a low-fat diet over an average of 8.1 years (HR, 0.91; 95% CI; 0.83–1.01). Limitations of this type of study include inherent difficulties in assuring compliance with dietary interventions, recall biases, the relatively short duration of the follow-up period, and the likelihood of insufficient differences between the arms with respect to fat intake. Furthermore, the impact of certain diets on breast cancer risk may depend on the age of the study population. For example, results of several population-based studies have suggested that the effect of diet composition on breast cancer risk may be much greater during adolescence and early adulthood. Nevertheless, diets in which the main sources of dietary fat are nonhydrogenated and unsaturated have been shown to have cardiovascular benefits.

Recent epidemiologic studies suggest that vitamin D (from dietary sources and the sun) may have a protective role through decreasing risk for breast cancer development. Furthermore, some evidence suggests that this protection is greatest for women who had more prolonged exposure of skin to sunlight and higher dietary intake of sources of vitamin D during adolescence, although additional studies are needed to further evaluate this finding.

**Weight/Body Mass Index:** A substantial amount of evidence indicates that overweight or obese women have a higher risk for developing postmenopausal breast cancer.

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 suggest that women who experienced a weight gain of 25.0 kg or more since 18 years of age have an increased risk of breast cancer compared with women who have maintained their weight (relative risk, 1.45; 95% CI, 1.27–1.66). Furthermore, women who never used postmenopausal HRT 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). Interestingly, evidence shows that the risk of breast cancer is lower in premenopausal women who are overweight compared with those who are not overweight.

Results from a case-control study of 1073 pairs of women with BRCA1/2 mutations indicated that a weight loss of 10 or more pounds in women between the ages of 18 and 30 years with the BRCA1 mutation was associated with a decreased risk of developing breast cancer between the ages of 30 and 40 years (OR, 0.35; 95% CI, 0.18–0.67).

**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 substantially decreases the future risk of breast cancer provides an opportunity for a risk reduction intervention. However, the risks and benefits associated with tamoxifen or raloxifene use should be evaluated and discussed with each 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 carriers of a BRCA1/2 mutation, in whom the risk of breast cancer is very high, a bilateral mastectomy or bilateral salpingo-oophorectomy may be considered for breast cancer risk reduction. Women considering either surgery should undergo multidisciplinary consultations before surgery to become well informed about all treatment alternatives, the risks and benefits associated with 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 to decrease 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.

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Breast Cancer Risk Reduction


### Individual Disclosures for the NCCN Breast Cancer Risk Reduction Panel

<table>
<thead>
<tr>
<th>Panel Member</th>
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<td>Loretta Loftus, MD, MBA</td>
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<td>Deborah J. MacDonald, PhD, RN, APNG</td>
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<td>Martin C. Mahoney, MD, PhD</td>
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The NCCN guidelines staff have no conflicts to disclose.