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Breast Cancer Risk Reduction

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NCCN Guidelines Panel Disclosures

Ω Gynecologic oncology
† Medical oncology
‡ Internal medicine, including family, preventive medicine
α Allergy/Immunology
¶ Surgery/Surgical oncology
Δ Genetics
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≠ Pathology
δ Endocrinology
& Epidemiology

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## Breast Cancer Risk Reduction

### NCCN Breast Cancer Risk Reduction Panel Members

### Summary of the Guidelines Updates

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

To find clinical trials online at NCCN Member Institutions, [click here](nccn.org/clinical_trials/physician.html).

### NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

## Discussion

### Familial Risk Assessment (BRISK-1)

### Elements of Risk, Risk Assessment (BRISK-3)

### Woman Does Not Desire Risk Reduction Therapy (BRISK-4)

### Woman Desires Risk Reduction Therapy: Baseline Assessment, Intervention, and Follow-up (BRISK-5)

### Clinical Symptoms and Management While on Tamoxifen orRaloxifene Therapy (BRISK-6)

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

### Breast Cancer Risk Reduction Agents (BRISK-B)
Updates in the 2013 version of the NCCN Guidelines for Breast Cancer Risk Reduction from the 2012 version include:

**BRISK-1**
- Under Family history:
  - 2nd sub-bullet was reorganized and modified as follows:
    - ≥2 breast primaries in single individual
    - ≥2 individuals with breast primaries on the same side of family (maternal or paternal)
  - 6th sub-bullet was reorganized and modified as follows:
    - ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of GI tract; diffuse gastric cancer.
  - 7th sub-bullet was modified:
    - From a population at “increased” risk.
- Footnote “F” was added: “For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, STK11 testing should be considered. See NCCN Guidelines for Colorectal Cancer Screening: Peutz-Jeghers Syndrome.”
- Footnote “H” modified to include, for populations at “increased” risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with breast or ovarian, or “pancreatic” cancer at any age).

**BRISK-3**
- Under Body Mass Index there are 3 new sub-bullets:
  - Risk factor in Caucasian women.
  - BMI and breast cancer risk in African American women is complex.
  - Obesity is a risk factor in postmenopausal women.
- Under Reproductive history modified the following:
  - “Younger” age at menarche
  - “Lower” parity
  - “Older” age at first live birth
  - “Older” age at menopause
- Under Other, first sub-bullet modified to include “(ductal and lobular)” for Atypical hyperplasia.

**BRISK-5**
- Fourth column under Risk Reduction Therapy, added a second bullet, which reads: “Baseline bone density evaluation (for post-menopausal women only).”
- Two new footnotes were added to “Bilateral total mastectomy ± reconstruction.” They are as follows:
  - Footnote “dd” Discuss risks and benefits of nipple-areolar sparing surgery.
  - Footnote “ee” Axillary node assessment is not part of the risk reduction procedure.

**BRISK-A**
- Added a new link to 3rd bullet under Healthy lifestyle: See the American Cancer Society Guidelines.
FAMILIAL RISK ASSESSMENT\textsuperscript{a}

- Familial/genetic factors\textsuperscript{b}
  
  **Criteria for further genetic risk evaluation:**\textsuperscript{c}
  
  - **Family history**
    - Member of a family with a known mutation in a breast cancer susceptibility gene
    - \( \geq 2 \) breast primaries\textsuperscript{d} in single individual
    - \( \geq 2 \) individuals with breast primaries on the same side of family (maternal or paternal)
    - \( \geq 1 \) ovarian primary from the same side of family (maternal or paternal)
    - First- or second-degree relative with breast cancer \( \leq 45 \) y
    - \( \geq 1 \) family member on same side of family with a combination of breast cancer and \( \geq 1 \) of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score \( \geq 7 \)), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations\textsuperscript{e}, and/or macrocephaly, hamartomatous polyps of GI tract; diffuse gastric cancer\textsuperscript{f}
    - From a population at increased risk\textsuperscript{h}
    - Male breast cancer
    - Ovarian/fallopian tube/primary peritoneal cancer

\textsuperscript{a}See NCCN Guidelines for Genetic/Familial High-Risk Assessment.

\textsuperscript{b}See BRISK-2 for women with a known genetic predisposition for breast cancer (BRCA 1/2, p53, PTEN, or other gene mutation).

\textsuperscript{c}The criteria for further genetic risk assessment and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

\textsuperscript{d}Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

\textsuperscript{e}For dermatologic manifestations, see NCCN Guidelines for Genetic/Familial High-Risk Assessment - Cowden Syndrome (See COVID-1).

\textsuperscript{f}For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, STK11 testing should be considered.

\textsuperscript{g}For lobular breast cancer with a family history of diffuse gastric cancer, CDH1 gene testing should be considered.

\textsuperscript{h}For populations at increased risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age).

\textbf{Note:} All recommendations are category 2A unless otherwise indicated.

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

ADDITIONAL RISK ASSESSMENT

Woman meets one or more of the familial risk criteria → Referral to cancer genetics professional recommended

- Lifetime risk >20% based on models largely dependent on family history\(^a\) or
- Pedigree suggestive of/or known genetic predisposition\(^a,b\)
- Life expectancy \(\geq 10\) y\(^k\)

Yes → Risk reduction counseling\(^i\)

Woman Does Not Desire Risk Reduction Therapy (See BRISK-4)

No → (See BRISK-3)

Woman Desires Risk Reduction Therapy (See BRISK-5)

See NCCN Guidelines for Genetic/Familial High-Risk Assessment.

See BRISK-2 for women with a known genetic predisposition for breast cancer (BRCA 1/2, p53, PTEN, or other gene mutation).

\(^a\) A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome. Genetic counseling is highly recommended when genetic testing is offered and after results are disclosed.

\(^b\) Risk models that are largely dependent on family history (eg, Claus, BRCAPRO, BOADICEA, Tyrer-Cuzick).

\(^k\) For a reference point, the life expectancy of the average 78-y-old woman in the United States is 10.2 years. (See NCCN Guidelines for Senior Adult Oncology).

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

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**ELEMENTS OF RISK**

- **Demographics**
  - Age
    - Utility of risk reduction agents for breast cancer risk reduction in women <35 years of age is unknown.
  - Ethnicity/race
    - For example, there is an increased incidence of specific BRCA1/2 mutations in women of Ashkenazi Jewish decent.
  - Body mass index (BMI)
    - Risk factor in Caucasian women
    - BMI and breast cancer risk in African American women is complex
    - Obesity is a risk factor in postmenopausal women
  - Reproductive history
    - Younger age at menarche
    - Lower parity
    - Older age at first live birth
    - Older age at menopause
  - Environmental factors
    - Current or prior estrogen and progesterone hormone therapy
    - Alcohol consumption
  - Other
    - Atypical hyperplasia (ductal and lobular)
    - Number of prior breast biopsies
      - Procedure done with the intent to diagnose cancer; multiple biopsies of the same lesion are scored as one biopsy.
    - Mammographic breast density
    - Prior thoracic RT <30 y of age
    - History of lobular carcinoma in situ (LCIS)

- **Risk Assessment**
  - Prior thoracic RT <30 y of age
  - History of LCIS
  - Breast cancer risk assessment (e.g., modified Gail Model for women ≥35 y of age)
  - Life expectancy <10 y
  - 5-y breast cancer risk ≥1.7% and Life expectancy ≥10 y
  - 5-y breast cancer risk <1.7% or Life expectancy <10 y
  - Contraindication to endocrine risk reduction therapies

- **Risk Management**
  - See NCCN Guidelines for Breast Cancer Screening and Diagnosis
  - Woman Does Not Desire Risk Reduction Therapy (See BRISK-4)
  - Woman Desires Risk Reduction Therapy (See BRISK-5)

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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.
**NCCN Guidelines Version 1.2013**

**Breast Cancer Risk Reduction**

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**Discussion**

**SCREENING/FOLLOW-UP**

- **Pedigree suggestive of/or known genetic predisposition**, or **Lifetime risk >20% based on models largely dependent on family history**

**RISK ASSESSMENT**

- **History of LCIS**
- **Prior thoracic RT <30 y of age**
- **5 y breast cancer risk ≥1.7%**

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\( ^a \) See NCCN Guidelines for Genetic/Familial High-Risk Assessment.

\( ^b \) See BRISK-2 for women with a known genetic predisposition for breast cancer (BRCA 1/2, p53, PTEN, or other gene mutation).

\( ^i \) Risk models that are largely dependent on family history (eg, Claus, BRCAPRO, BOADICEA, Tyrer-Cuzick).

\( ^k \) For a reference point, the life expectancy of the average 78-y-old woman in the United States is 10.2 years. (See NCCN Guidelines for Senior Adult Oncology).

\( ^n \) The management for women with LCIS is available in the NCCN Guidelines for Breast Cancer.

\( ^q \) 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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**BRISK-4**
# NCCN Guidelines Version 1.2013

## Breast Cancer Risk Reduction

### Risk Reduction Therapy Desired

- **Woman desires risk reduction therapy and life expectancy ≥10 y**
  - **Normal**
    - **Baseline assessment**
      - **Risk reduction mastectomy desired?**
      - **Risk reduction bilateral salpingo-oophorectomy desired?** (Limited to those with known or strongly suspected BRCA1/2 mutations)
    - **Risk reduction agent**
      - Baseline gynecologic assessment (for women with intact uterus)
      - Baseline bone density evaluation (for post-menopausal women only)
  - **Abnormal**
    - See NCCN Guidelines for Breast Cancer Screening and Diagnosis

### Risk Reduction Intervention

- **Bilateral total mastectomy ± reconstruction**
- **Bilateral salpingo-oophorectomy with peritoneal washings. Pathologic assessment should include fine sectioning of ovaries and fallopian tubes**

### Follow-Up

- **Clinical trial† or Tamoxifen‡ (category 1)**
  - Premenopausal
  - Postmenopausal

### Discussion

- Surveillance according to NCCN Guidelines for Breast Cancer Screening and Diagnosis for women at increased risk for breast cancer.
- Annual gynecologic assessment (for women with intact uterus on tamoxifen).
- Ophthalmology exam if cataracts or vision problems.
- For management while on tamoxifen or raloxifene therapy, see BRISK-6.

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- For a reference point, the life expectancy of the average 78-y-old woman in the United States is 10.2 years. (See NCCN Guidelines for Senior Adult Oncology)
- Risk reduction mastectomy should generally be considered only in women with BRCA1/2, or other strongly predisposing gene mutation, compelling family history, or possibly with LCIS or prior thoracic radiation therapy at <30 y of age. Women considering risk reduction mastectomy should receive multidisciplinary counseling including consultation with genetics if not already done. Psychological consultation may also be of value.
- The additional benefit of concurrent hysterectomy is not clear at this time.
- There are no data regarding the use of risk reduction agents in women with prior thoracic radiation therapy.
- CYP2D6 genotype testing is not recommended in women considering tamoxifen.
- See Breast Cancer Risk Reduction Agents (BRISK-B).
- Bone density may play a role in choice of therapy.

### Clinical Trials

- Clinical trials in breast cancer have utilized a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following: Prior bilateral oophorectomy; age ≥60 y; age <60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range. If taking tamoxifen or toremifene and age <60 y, FSH and plasma estradiol level in postmenopausal ranges.
- Clinical trials in breast cancer have utilized a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following: Prior bilateral oophorectomy; age ≥60 y; age <60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range. If taking tamoxifen or toremifene and age <60 y, FSH and plasma estradiol level in postmenopausal ranges.
- Women in clinical trial should have baseline exam, follow-up, and monitoring as per protocol.
- Utility of tamoxifen or raloxifene for breast cancer risk reduction in women <35 years of age is unknown. Raloxifene is only for post-menopausal women ≥35 y. While raloxifene in long-term follow-up appears to be less efficacious in risk reduction than tamoxifen, consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in women with an intact uterus.
- Other aromatase inhibitors have shown prevention of contralateral breast cancer and there are ongoing clinical trials.
- Routine endometrial ultrasound and biopsy are not recommended for women in the absence of other symptoms.
- Discuss risks and benefits of nipple-areolar sparing surgery.
- Axillary node assessment is not part of the risk reduction procedure.

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CLINICAL SYMPTOMS

Asymptomatic

- Continue risk reduction agent

Hot flashes or other risk reduction agent-related symptoms

- Symptomatic treatment
  - If persist, reevaluate role of risk reduction agent
  - If endometrial pathology found, reinitiation of tamoxifen may be considered after hysterectomy if early-stage disease; for management, see NCCN Guidelines for Uterine Neoplasms Treatment

Abnormal vaginal bleeding

- Prompt evaluation for endometrial cancer if uterus intact
  - If no endometrial pathology (carcinoma or hyperplasia with or without atypia) found, continue tamoxifen 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

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

- Risk reduction agents - See the Discussion section.
  - Discussion of relative and absolute risk reduction with tamoxifen, raloxifene, or exemestane.
  - Contraindications to tamoxifen or raloxifene: history of deep vein thrombosis, pulmonary embolus, thrombotic stroke, transient ischemic attack, or known inherited clotting trait.
  - Contraindications to tamoxifen, raloxifene, and exemestane: current pregnancy or pregnancy potential without effective nonhormonal method of contraception.
  - Common and serious adverse effects of tamoxifen, raloxifene, or exemestane 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 mutation, compelling family history, or possibly women with LCIS or prior thoracic RT <30 y of age. Evaluation should include consultation with surgery and reconstructive surgery. Psychological consultation may also be considered.
  - Discussion regarding the risk for 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 therapy
  - Limit alcohol consumption to less than 1 drink per day
  - Exercise
  - Weight control

2 See American Cancer Society Guidelines.

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BREAST CANCER RISK REDUCTION AGENTS

Tamoxifen¹,²
- Data regarding tamoxifen risk reduction are limited to pre- and postmenopausal women 35 y of age or older with a Gail model 5-year breast cancer risk of ≥1.7% or a history of LCIS.
- Tamoxifen: 20 mg per day 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.
- Limited data are currently available regarding the efficacy of tamoxifen risk reduction in women who are carriers of BRCA 1/2 mutations or who have had prior thoracic radiation.
- For high-risk premenopausal women, data regarding the risk/benefit ratio for tamoxifen appear relatively favorable (category 1).
- For high-risk postmenopausal women, data regarding the risk/benefit ratio for tamoxifen are influenced by age, presence of uterus, or comorbid conditions (category 1). There are insufficient data on ethnicity and race.

Raloxifene¹,²
- Data regarding raloxifene risk reduction are limited to postmenopausal women 35 y of age or older with a Gail model 5-year breast cancer risk ≥1.7% or a history of LCIS.
- Raloxifene: 60 mg per day was found to be equivalent to tamoxifen for breast cancer risk reduction in the initial comparison. While raloxifene in long-term follow-up appears to be less efficacious in risk reduction than tamoxifen, consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in women with an intact uterus.
- There are no data regarding the use of raloxifene in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation.
- For high-risk postmenopausal women, data regarding the risk/benefit ratio for raloxifene are influenced by age or comorbid conditions (category 1). There are insufficient data on ethnicity and race.
- Use of raloxifene for breast cancer risk reduction in premenopausal women is inappropriate unless part of a clinical trial.

Exemestane⁴
- Data regarding exemestane are from a single large randomized study limited to postmenopausal women 35 years of age or older with a Gail model 5-year breast cancer risk ≥1.7% or a history of LCIS.
- Exemestane: 25 mg per day was found to reduce the relative incidence of invasive breast cancers by 65% from 0.55% to 0.19% with a median follow-up of 3 years. There are ongoing trials evaluating prolonged aromatase inhibitor therapy in postmenopausal healthy women at risk for breast cancer.
- There are no data regarding the use of exemestane in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation.
- For high-risk postmenopausal women, data regarding the risk/benefit ratio for exemestane therapy are influenced by age and comorbid conditions such as osteoporosis (category 1). There are insufficient data on ethnicity and race.
- Use of exemestane for breast cancer risk reduction in premenopausal women is inappropriate unless part of a clinical trial.

¹There are limited data regarding ≥5 years of tamoxifen or raloxifene use in breast cancer prevention. Moreover, there may be safety concerns related to use of tamoxifen for greater than 5 years. Based on the recent update of the STAR trial data, continuing raloxifene beyond 5 years (there are no high-level experience or clinical trial data evaluating these agents for risk reduction beyond 5 years) may be an approach to maintain the risk reduction activity of the agent.
⁴Exemestane is not currently FDA approved for breast cancer risk reduction. There are currently no data comparing the benefits and risks of exemestane to those of tamoxifen or raloxifene.

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NCCN Guidelines Version 1.2013
Breast Cancer Risk Reduction

Discussion
This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/09/12

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

Breast cancer is the most commonly diagnosed cancer in American women, with 229,060 estimated cases of invasive breast cancer in the year 2012. Approximately 39,920 women will die of breast cancer in the United States in 2012.1

Risk factors for the development of breast cancer can be grouped into categories including familial/genetic factors (family history, known or suspected BRCA 1/2, TP53, PTEN, or other gene mutation associated with breast cancer risk), factors related to demographics (eg, age, ethnicity/race); reproductive history (age at menarche, parity, age at first live birth, age at menopause); environmental factors (such as current or prior hormone therapy, alcohol consumption); and other factors (eg, number of breast biopsies, atypical hyperplasia or lobular carcinoma in situ [LCIS], breast density, body mass index [BMI], prior thoracic irradiation before age 30 [eg, to treat Hodgkin’s disease]).

Estimating breast cancer risk for the individual woman is difficult, and most breast cancers are not attributable to risk factors other than female gender and increased age. The development of effective strategies for the reduction of breast cancer incidence has also been difficult because few of the existing risk factors are modifiable and some of the potentially modifiable risk factors have social implications extending beyond concerns for breast cancer (eg, age at first live birth). Nevertheless, effective breast cancer risk reduction strategies such as use of risk reduction agents, and risk reduction surgery, have been identified. However, women and their physicians who are considering interventions to reduce risk of breast cancer must balance the demonstrated benefits with the potential morbidities of the interventions; surgical risk reduction strategies (eg, risk reduction bilateral mastectomy) may have psychosocial and/or physical consequences for the woman, and risk reduction agents, used for non-surgical risk reduction, are associated with certain adverse effects.2,3 To assist women at increased risk of breast cancer and their physicians in the application of individualized strategies to reduce breast cancer risk, the NCCN has developed these guidelines for breast cancer risk reduction.

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 for the purpose of determining 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 individual, primarily with respect to breast and/or ovarian cancer.4,5 The magnitude of the risk increases with the number of affected relatives in the family, the closeness of the relationship, and is affected by the age at which the affected relative was diagnosed.6-8 The younger the age at diagnosis, the more likely it is that a genetic component is present. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer (see NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian).

Hereditary cancers are often characterized by gene mutations associated with a high probability of cancer development (ie, a high penetrance genotype), vertical transmission through either mother or father, and an association with other types of tumors.9,10 They often have an early age of onset, and exhibit an autosomal dominant inheritance pattern (i.e., they 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.11-14

If an individual or a close family member of that individual meets one or more of the criteria listed in the NCCN Breast Cancer Risk Reduction algorithm under “Familial Risk Assessment” (and also NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian), that individual may be at increased risk for familial/hereditary breast cancer, and referral for formal genetic assessment/counseling is recommended. A cancer genetic professional should be involved in determining whether the individual has a lifetime risk of breast cancer greater than 20% based on models dependent on family history (eg, Claus,15 Tyrer-Cuzick,16 and others17-19). BRCAPRO20 and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)21 are more commonly used to estimate the risk based on BRCA mutations. Strong genetic association between breast and ovarian cancer has been demonstrated in some families by linkage analyses. The Claus tables may be useful in providing breast cancer risk estimates for white women without a known cancer-associated gene mutation who have one or two first or second degree female relatives with breast cancer.15 and ovarian cancer.22 Based on this risk assessment, women with a BRCA1/2, TP53, or PTEN gene mutation, or a pedigree strongly suggestive of genetic predisposition to breast cancer, may be identified. The NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian also describe management strategies for women with a known or suspected BRCA1/2, TP53, or PTEN mutation or a pedigree strongly suggestive of genetic predisposition to breast cancer.

For women not considered to be at risk of familial/hereditary breast cancer, an evaluation of the breast cancer risk factors related to demographics (eg, age, ethnicity/race, reproductive history (age at menarche, parity, age at first live birth, age at menopause); environmental factors (such as current or prior hormone therapy, alcohol consumption); and other factors such as number of breast biopsies, prior thoracic irradiation before age 30 (eg, to treat Hodgkin’s disease), atypical hyperplasia or lobular carcinoma in situ (LCIS), body mass index (BMI), including changes in breast density23; is recommended. Breast density is not included in any of the commonly used risk assessment models/tools.18 However, dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.24, 25 For example, a report of a large case-cohort study of women 35 years and older with no history of breast cancer who underwent mammographic screening at baseline and at an average of 6 years later suggested that longitudinal changes in breast density are associated with changes in breast cancer risk.25

Women ≥ 35 years of age without a BRCA1/2, TP53, or PTEN mutation, with a strong family history of breast cancer, a history of thoracic radiation before the age of 30, or a history of LCIS should have their risk for breast cancer estimated according to the modified Gail model.26-28 The modified Gail model is a computer-based multivariate logistic regression model that uses age, race, age at menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous breast biopsies, and histology of the breast biopsies to produce actuarial estimates of future breast cancer risk.26,29,30 The criteria used to determine risk by the modified Gail model are described in Figure 1. The Gail model, as modified by the NSABP investigators, is
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 NCCN Breast Cancer Risk Reduction Panel has adopted the 1.7% or greater 5-year actuarial risk of breast cancer as defined by the modified Gail model, which was used to identify women eligible for the National Surgical Adjuvant Bowel and Breast Project (NSABP) Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR) trial.

The Gail model was updated using combined data from the Women’s Contraceptive and Reproductive Experiences (CARE) study and the Surveillance Epidemiology and End Results (SEER) database, as well as causes of death from the National Center of Health Statistics, to provide a more accurate determination of risk for African-American women. The model was updated using data from the Asian American Breast Cancer Study (AABCS) and the SEER database to provide a more accurate risk assessment for Asian and Pacific Islander women in the United States. 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 received prior thoracic radiation to treat Hodgkin’s disease (eg, 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. In that study, the relative risk according to follow-up interval were: 0 at 5-9 years; 71.3 at 10-14 years; 90.8 at 15-19 years; 50.9 at 20-24 years; 41.2 at 25-29 years; and 24.5 at > 29 years. Results from a case-control study of women treated at a young age (30 years or younger) 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% confidence interval [CI], 20.2%-40.1%) for a woman treated at 25 years of age with 40 Gy of radiation and no alkylating agents. Women with a history of treatment with thoracic radiation for Hodgkin’s disease are at a high risk of breast cancer on the basis of radiation exposure alone.

Women with a life expectancy ≥10 years and no diagnosis/history of breast cancer who are considered to be at increased risk of breast cancer based on any of the above mentioned assessments should receive counseling, that is tailored to the individual, to decrease breast cancer risk eg, risk-reduction surgery in BRCA1/2 mutation carriers; therapy with risk reduction agents in those without a contraindication to these agents (see section below on ‘Components of Risk Reduction Counseling’, page MS-18); and should undergo breast screening as detailed in the see NCCN Guidelines for Breast Cancer Screening and Diagnosis.

If life expectancy is <10 yrs, there is probably minimal if any benefit to risk reduction therapy or screening (see NCCN Guidelines for Breast Cancer Screening and Diagnosis and NCCN Guidelines for Breast Cancer).

Women with a diagnosis of DCIS should be managed according to recommendations in the NCCN Guidelines for Breast Cancer.
Risk Reduction Interventions

Life Style Modifications

Evidence from immigration studies indicate that in addition to family history and genetics, environmental factors play a significant role. Lifestyle modifications such as diet, body weight, exercise, and alcohol consumption are some of the modifiable components of breast cancer risk. While there is no clear evidence that specific dietary components can effectively reduce breast cancer risk, weight gain and obesity in adulthood are risk factors for the development of postmenopausal breast cancer.\textsuperscript{45-47} Alcohol consumption, even at moderate levels, increases breast cancer risk.\textsuperscript{47-51} Patients should be encouraged to maintain a healthy lifestyle and to remain up-to-date with recommendations for screening and surveillance (see section on “Counseling regarding lifestyle modifications” on MS-21).

Risk Reduction Surgery

Bilateral Total Mastectomy

The lifetime risk of breast cancer in BRCA1/2 mutation carriers has been estimated to be 56%-84%.\textsuperscript{52-54} Retrospective analyses with median follow-up periods of 13-14 years have indicated that bilateral risk reduction mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA1/2 mutation carriers.\textsuperscript{55, 56} An analysis of results from the study by Hartmann et al.,\textsuperscript{55} determined that the number of women at high risk of breast cancer needed to treat with RRM to prevent one case of breast cancer was equal to 6.\textsuperscript{57} 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{58, 59} The NCCN Breast Cancer Risk Reduction Panel supports the use of RRM for carefully selected women at high risk of breast cancer who desire this intervention (eg, women with a BRCA1/2, TP53, or PTEN mutation or, possibly, for women with a history of LCIS). Although the consensus of the NCCN Breast Cancer Risk Reduction Panel 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. There are no data regarding 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 (ie, a total mastectomy). Women undergoing RRM do not require an axillary lymph node dissection unless breast cancer is identified on pathologic evaluation of the mastectomy specimen.\textsuperscript{60} Following RRM, women who carry a BRCA1/2 mutation should be monitored according to the NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian. Women found to have invasive breast cancer or DCIS at the time of RRM should be treated according to the NCCN Guidelines for Breast Cancer. All other women should be followed up with routine health maintenance following RRM. Most health maintenance recommendations are not related to the breast. For monitoring the breast health, women should continue with annual exams of the chest/reconstructed breast as there is still a small risk of developing breast cancer. Mammograms are not recommended in this situation.

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 a BRCA1/2 mutation carrier (eg, estimated lifetime risks of 36%-46% and 10%-27%
in \textit{BRCA1} and \textit{BRCA2} mutation carriers, respectively\textsuperscript{53, 61-64}), the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have lent support for the performance of bilateral risk reduction salpingo-oophorectomy (RRSO) after completion of childbearing in these women. In the studies of Rebbeck et al., the mean age at diagnosis of ovarian cancer was 50.8 years for \textit{BRCA1/2} carriers.\textsuperscript{65}

The effectiveness of RRSO in reducing the risk of ovarian cancer in carriers of a \textit{BRCA1/2} mutation has been demonstrated in a number of studies. For example, results of a meta-analysis involving 10 studies of \textit{BRCA1/2} mutation carriers showed an approximately 80\% reduction in the risk of ovarian or fallopian cancer following RRSO.\textsuperscript{66} However, a 1-4.3\% residual risk of a primary peritoneal carcinoma has been reported in some studies.\textsuperscript{65-70}

RRSO is also reported to reduce the risk of breast cancer in carriers of a \textit{BRCA1/2} mutation by approximately 50\%.\textsuperscript{65, 66, 70, 71} In the case-control international study by Eisen et al., a 56\% (odds ratio = 0.44; 95\% CI, 0.29-0.66) and a 46\% (odds ratio = 0.57; 95\% CI, 0.28-1.15) breast cancer risk reduction was reported following RRSO in carriers of a \textit{BRCA1} and a \textit{BRCA2} mutation, respectively.\textsuperscript{71} Hazard ratios of 0.47 (95\% CI, 0.29-0.77)\textsuperscript{66; and 0.30 (95\% CI, 0.11-0.84)\textsuperscript{69} were reported in two other studies comparing breast cancer risk in women with a \textit{BRCA1/2} mutation who had undergone RRSO with carriers of these mutations who opted for surveillance only. These studies are further supported by a meta-analysis which found similar reductions in breast cancer risk of approximately 50\% for \textit{BRCA1} and \textit{BRCA2} mutation carriers following RRSO.\textsuperscript{66} The results of a prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for \textit{BRCA1} mutation carriers compared with \textit{BRCA2} mutation carriers.\textsuperscript{72}

Reductions in breast cancer risk for carriers of a \textit{BRCA1/2} mutation after RRSO may be associated with decreased hormonal exposure following surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a \textit{BRCA1} mutation who had a RRSO at age 40 years or younger (odds ratio = 0.36, 95\% CI, 0.20-0.64) relative to \textit{BRCA1} carriers aged 41-50 years who had this procedure (odds ratio = 0.50, 95\% CI, 0.27-0.92).\textsuperscript{71} Nonsignificant reduction in risk for developing breast cancer was found for women aged 51 or older although only a small number of women were included in this group.\textsuperscript{71} However, results from Rebbeck et al also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.\textsuperscript{70}

Although data are limited regarding an optimal age for RRSO, the Monte Carlo simulation model provides estimates of the survival impact of breast and ovarian risk reduction strategies (eg, mammographic/MRI breast screening; risk reduction surgery) in women who are carriers of \textit{BRCA1/2} mutations according to the type of \textit{BRCA} mutation present, the specific risk-reduction intervention(s), and the age of the women at the time of the intervention(s).\textsuperscript{73} Survival estimates generated from this model can facilitate shared decision-making regarding choice of a risk reduction approach (see Table 1).

A prospective multicenter study reported the benefit of risk-reducing procedures for women with strong genetic predispositions for breast cancer.\textsuperscript{74} The study involved 2482 women diagnosed with \textit{BRCA1/2} gene mutations, almost half of whom chose either RRSO or RRM. During the 3 years of follow up, no cases of breast cancer occurred in the women who opted for RRM. In the same time period, 7\% of the women who adopted other approaches received a breast cancer diagnosis. In \textit{BRCA2}-mutation carriers, no cases of ovarian cancer occurred after salpingo-oophorectomy over a 6-year follow-up period,
whereas 3% of those who did not undergo the same surgery were diagnosed with ovarian cancer. None of the women who underwent RRM developed breast cancer. RRSO was associated with a reduction in overall mortality (hazard ratio [HR] = 0.40), breast cancer–specific mortality (HR = 0.44), and ovarian cancer–specific mortality (HR = 0.21). Among women who underwent RRSO, only 1.1% developed ovarian cancer.

The NCCN Breast Cancer Risk Reduction 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 not clear at this time. Women who undergo RRSO should continue with routine health maintenance and breast screening as per the NCCN Guidelines for Breast Cancer unless the woman has had RRM.

Risk Reduction Agents
Risk reduction agents (ie, tamoxifen, raloxifene, exemestane) are recommended for women ≥35 years of age only, as the utility of these agents in women younger than 35 years is unknown.

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

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

The results of the P-1 study showed that treatment with tamoxifen decreased the short-term risk for breast cancer by 49% in healthy women aged 35 years or older who had an increased risk for the disease (Table 1). Risk reduction benefits were demonstrated across all age groups (Table 2). The difference in average annual rates for invasive breast cancer was 3.30 cases per 1,000 women (ie, 6.76 cases per 1,000 women in the placebo group and 3.43 cases per 1,000 women in the tamoxifen group).
women in the group taking tamoxifen). The absolute risk reduction was 21.4 cases per 1,000 women over 5 years. In terms of numbers needed to treat, this corresponds to treatment of 47 women with tamoxifen to prevent 1 case of invasive breast cancer. Updated results indicate that breast cancer risk was reduced by 43% in this population after 7 years of follow-up. The reduction in invasive breast cancer risk in 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 following a diagnosis of breast cancer, 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 ≥ 50 years of age taking tamoxifen (Table 3). No differences were observed in overall rates of mortality by treatment group with a follow-up period out to 7 years. The initial study analysis revealed that average annual mortality from all causes in the tamoxifen group was 2.17 per 1,000 women compared with 2.71 per 1,000 women treated with placebo, for a risk ratio of 0.81 (95% CI, 0.56-1.16) 

An evaluation of the subset of patients with a BRCA1/2 mutation in the P-1 study revealed that breast cancer risk was reduced by 62% in study patients with a BRCA2 mutation receiving tamoxifen relative to placebo (risk ratio = 0.38; 95% CI, 0.06-1.56). However, tamoxifen use was not associated with a reduction in breast cancer risk in patients with a BRCA1 mutation. These findings may be related to the greater likelihood for development of ER-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 [P-1] study results, in October 1998 the U.S. Food and Drug Administration (FDA) approved tamoxifen for breast cancer risk reduction for women at increased risk of breast cancer.

**European Studies of Tamoxifen**

Three European studies comparing tamoxifen with placebo for breast cancer risk reduction have also been reported. The Royal Marsden Hospital study was a pilot trial of tamoxifen versus placebo in women ages 30 to 70 years who were at increased breast cancer risk based largely on their family history. Women in the trial were allowed to continue or to initiate postmenopausal hormone therapy. With 2,471 participants available for interim analysis, no difference in the frequency of breast cancer was observed between the 2 study groups. Moreover, the toxicity experienced by the 2 groups did not show statistically significant differences. An analysis of updated findings from the Royal Marsden study did demonstrate a nonsignificant breast cancer risk reduction benefit with tamoxifen use (i.e., 62 cases of breast cancer in 1238 women receiving tamoxifen versus 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 ER-positive breast cancer was significantly lower in the tamoxifen arm vs. placebo arm of the trial (HR = 0.61; 95% CI, 0.43-0.86; P=.005). Importantly, the difference between the 2 arms became significant only in the posttreatment period (i.e., after 8 years of treatment).
Breast Cancer Risk Reduction

The Italian Tamoxifen Prevention Study randomized 5,408 women ages 35 to 70 without breast cancer, who had undergone a previous hysterectomy, to receive tamoxifen or placebo for 5 years. Women in the trial were allowed to receive hormone therapy. 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 women treated with tamoxifen. A subset of women in the Italian Tamoxifen Prevention Study who had used hormone therapy and were classified as at increased breast cancer risk based on reproductive and hormonal characteristics were found to have a significantly reduced risk of breast cancer with tamoxifen therapy. However, only approximately 13% of the patients in the trial were at high risk for breast cancer.

It is unclear why no overall breast cancer risk reduction was observed in the Italian Tamoxifen Prevention study. Possible reasons include concurrent use of hormone therapy, and different study populations (ie, populations at lower risk of breast cancer).

The first International Breast Cancer Intervention Study (IBIS-I) randomized 7,152 women aged 35-70 years at increased risk for breast cancer to receive either tamoxifen or placebo for 5 years. Tamoxifen provided a breast cancer (invasive or ductal carcinoma in situ) risk reduction of 32% (95% CI, 8-50; \(P=0.013\)). Thromboembolic events increased with tamoxifen (odds ratio = 2.5; 95% CI, 1.5-4.4; \(P=0.001\)), and endometrial cancer showed a nonsignificant increase (\(P=0.2\)). An excess of deaths from all causes was seen in the tamoxifen treated women (\(P=0.028\)).

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; \(P=0.004\)). Although no difference in the risk of ER-negative invasive tumors was observed between the 2 groups, those in the tamoxifen arm were found to have a 34% lower risk of ER-positive invasive breast cancer. Slightly higher risk reduction with tamoxifen was observed for premenopausal patients. Importantly, the increased risk of venous thromboembolism (VTE) observed with tamoxifen during the treatment period was no longer significant in the posttreatment period. Gynecologic and vasomotor side effects associated with active tamoxifen treatment were not observed during the posttreatment follow-up. These results provide randomized evidence that the benefits of tamoxifen continue following cessation of treatment while many of the side effects diminish or disappear.

The use of tamoxifen as a breast cancer risk reduction agent has most recently been evaluated in the STAR Trial (see section on The STAR Trial below, MS-11).

### Raloxifene for Risk Reduction

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

The **MORE Trial**

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was designed to determine whether 3 years of raloxifene treatment reduced...
the risk of fracture in postmenopausal women with osteoporosis. A total of 7,705 postmenopausal women 31-80 years of age were randomized to receive placebo, 60 mg/day of raloxifene, or 120 mg/day of raloxifene for 3 years. At study entry, participants were required to have osteoporosis (defined as a bone density at least 2.5 standard deviations below the mean for young women) or a history of osteoporotic fracture. The study showed a reduction in the vertebral fracture risk and an increase in bone mineral density in the femoral neck and spine for the women treated with raloxifene, compared with those who received placebo.

After a median follow-up of 40 months in the MORE trial, breast cancer was reported in 40 patients: 27 cases in 2,576 women on placebo and 13 cases in 5,129 women on raloxifene. The relative risk of developing invasive breast cancer on raloxifene, compared with placebo, was 0.24 (95% CI, 0.13-0.44). Raloxifene markedly decreased the risk of ER-positive cancers (relative risk = 0.10; 95% CI, 0.04-0.24) but did not appear to influence the risk of developing an ER-negative cancer (relative risk = 0.88; 95% CI, 0.26-3.0). Although incidence of breast cancer was a secondary endpoint in the MORE trial, it is important to note that breast cancer risk was not a prospectively determined characteristic for the women enrolled and stratified into treatment arms in this study. 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 [P-1] study.

Side effects associated with the use of raloxifene included hot flashes, influenza-like syndromes, endometrial cavity fluid, peripheral edema, and leg cramps. In addition, there was an increased incidence of deep venous thromboses (DVT) (0.7% for women receiving 60 mg/day raloxifene vs 0.2% for placebo) and pulmonary emboli (0.3% for women receiving 120 mg/day raloxifene vs 0.1% for placebo) associated with raloxifene treatment. However, there was no increase in the risk of endometrial cancer associated with raloxifene.

The CORE Trial
The early findings relating to breast cancer risk in the MORE trial led to the continuation of this trial under the name Continuing Outcomes Relevant to Evista (CORE) trial. Because breast cancer incidence was a secondary endpoint in the MORE trial, CORE was designed to assess the effect of 4 additional years of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis. A secondary endpoint was the incidence of invasive ER-positive breast cancer. Data from the CORE Trial were reported in 2004.

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 to placebo, reduced the incidence of invasive ER-positive breast cancer by 66% (HR = 0.34; 95% CI, 0.18-0.66) but had no effect on invasive ER-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 to placebo, 8 years of raloxifene reduced the incidence of invasive ER-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 the CORE trial were similar to those seen in the MORE trial. There was a nonsignificant increase in the risk of thromboembolism (relative risk = 2.17; 95% CI, 0.83-5.70) in the raloxifene group of the CORE trial compared to the placebo group. There was no statistical significant difference in endometrial events...
(bleeding, hyperplasia and cancer) between the raloxifene and placebo groups during the 4 years of CORE or the 8 years of MORE and CORE. During the 8 years of the MORE and CORE trials, raloxifene increased the risk for hot flushes and leg cramps compared with placebo; these risks were observed during the MORE trial but not during the additional 4 years of therapy in CORE. While it is possible that hot flushes and leg cramps are early events that do not persist with continued therapy, it is also possible that an increased risk of these adverse events was not observed in the CORE trial as a result of selection bias (i.e., women who experienced these symptoms in the MORE trial may have chosen not to continue in the CORE trial).

The results from the CORE trial are not entirely straightforward because of the complex design of the trial. 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 in favor of the treatment group. In the CORE trial, the researchers did not randomize the patients again (1286 in the placebo arm, 2725 in the raloxifene arm) maintaining 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. Invasive breast cancer incidence was another primary endpoint 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. Raloxifene did not reduce risk of cardiovascular events but there was a 44% decrease in the incidence of invasive breast cancer in the raloxifene arm (HR=0.56; 95% CI, 0.38-0.83), with a 55% lower incidence of ER-positive breast cancer (HR=0.45; 95% CI, 0.28-0.72).

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) which was initiated in 1999; initial results became available in 2006. In the STAR Trial, 19,747 postmenopausal women 35 years or older at increased risk for invasive breast cancer as determined by the modified Gail model or with a personal history of LCIS were enrolled into one of two treatment arms (no placebo arm). The primary study endpoint was invasive breast cancer; secondary endpoints included quality of life, and incidences of noninvasive breast cancer, DVT, pulmonary embolism, endometrial cancer, stroke, cataracts, and death. At an average follow-up of approximately 4 years, no statistically significant differences between patients receiving 20 mg/day tamoxifen or 60 mg/day raloxifene were observed with respect to invasive breast cancer risk reduction (risk ratio = 1.02; 95% CI, 0.82-1.28). Because there was no placebo arm, it was not possible to determine a raloxifene versus placebo risk ratio for invasive breast cancer; however, tamoxifen was shown in the BCPT [P-1] 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,

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.
although the observed difference was not statistically significant (risk ratio = 1.40; 95% CI, 0.98-2.00).31

At a median follow-up of nearly 8 years (81 months) involving 19,490 women, raloxifene was shown to be about 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 by age group), suggesting that tamoxifen has greater long-term benefit with respect to lowering invasive breast cancer risk.33 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 2 groups. In the initial analysis of the STAR trial data, invasive endometrial cancer occurred less frequently in the group receiving raloxifene compared with the tamoxifen group, although the difference did not reach statistical significance. It is important to note, however, that the incidence of endometrial hyperplasia and hysterectomy were significantly lower in the raloxifene group compared to the tamoxifen group. However, at long-term follow-up, the risk of endometrial cancer was significantly lower in the raloxifene arm (see Table 5).

The lower incidences of thromboembolic events and cataract development observed in the raloxifene group compared to 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 two 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.98

**Aromatase Inhibitors for Risk Reduction**

A number of clinical trials testing the use of aromatase inhibitors in the adjuvant therapy of postmenopausal women with invasive breast cancer have been reported. The first of these studies, the Arimidex, Tamoxifen Alone or in Combination Trial (ATAC Trial) randomized postmenopausal women with invasive breast cancer to anastrozole versus tamoxifen versus anastrozole plus tamoxifen in a double-blinded fashion.99 The occurrence of contralateral second primary breast cancers was a study endpoint. With 47 months median follow-up, a nonsignificant reduction in contralateral breast cancers was observed in women treated with anastrozole alone compared with tamoxifen (odds ratio = 0.62; 95% CI, 0.38-1.02; P=0.62) and a significant reduction in contralateral breast cancers was seen in the subset of women with hormone receptor-positive first cancers (odds ratio= 0.56; 95% CI, 0.32-0.98; P=.04).100 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.101, 102

In the Breast International Group (BIG) 1-98 trial postmenopausal women with early stage breast cancer were randomized to receive 5 years of treatment with one of the following therapeutic regimens: letrozole; sequential letrozole followed by tamoxifen; tamoxifen; or sequential tamoxifen followed by letrozole. Risk of breast cancer recurrence was lower in women in the letrozole arm relative to the tamoxifen arm.103

The results of the MAP.3 trial show promising use of exemestane in the breast cancer prevention setting. MAP.3 is a randomized double blind
placebo controlled multicentre, multinational trial in which 4560 women were randomly assigned to either exemestane (2285 patients) or placebo (2275 patients). The study authors reported that about 5% in each group had discontinued the protocol treatment. The major reasons for early discontinuation of the protocol treatments were toxic effects (15.4% in the exemestane groups vs. 10.8% in the placebo group, \( P < .001 \)) and patient refusal (6.9% vs. 6.0%, \( P = .22 \)). After a median follow-up of 3 years, compared to the placebo exemestane was found to reduce the relative incidence of invasive breast cancers by 65%, from 0.55% to 0.19% [hazard ratio, 0.35 with exemestane; 95% CI, 0.18 to 0.70].

**NCCN Breast Cancer Risk Reduction Panel Recommendations for Risk Reduction Agents**

Based on the data from BCPT and STAR trials, Freedman et al have developed tables of benefit/risk indices to compare raloxifene versus no treatment (placebo) and tamoxifen versus no treatment. The risk and benefit of treatment with either tamoxifen or raloxifene depends on age, race, breast cancer risk, and history of hysterectomy. There are separate tables in the paper listing the level of 5-year invasive breast cancer risk by age group for non-Hispanic women white women with and without a uterus, for black women with and without a uterus, and also for Hispanic women with and without a uterus. The NCCN Breast Cancer Risk Reduction Panel recommends using these tables while counseling postmenopausal women regarding use of raloxifene and tamoxifen for breast cancer risk reduction.

**Tamoxifen Recommendations**

The NCCN Breast Cancer Risk Reduction Panel recommends tamoxifen (20 mg/day), as an option to reduce breast cancer risk in healthy pre- and postmenopausal women \( \geq 35 \) years of age, whose life expectancy is greater than to equal to 10 years, and who have a \( \geq 1.7\% \) 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1). The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for tamoxifen use in premenopausal women at increased risk of breast cancer is relatively favorable (category 1), and that the risk/benefit ratio for tamoxifen use in postmenopausal women is influenced by age, presence of uterus or other comorbid conditions (category 1). Early studies suggest that lower doses of tamoxifen over shorter treatment periods may reduce breast cancer risk in postmenopausal women, but these findings need to be validated in phase III clinical trials. Only limited data are currently available regarding the efficacy of tamoxifen risk reduction in BRCA1/2 mutation carriers and women who have received prior thoracic radiation. The utility of tamoxifen as a breast cancer risk reduction agent in women <35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of tamoxifen as a risk reduction agent.

There is evidence that certain drugs (eg. Serotonin reuptake inhibitors) 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. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that alternative medications which have minimal or no impact on plasma levels of endoxifen should be substituted when possible. Citalopram and venlafaxine do not disrupt tamoxifen metabolism.

It has also been reported that certain CYP2D6 genotypes are markers of poor tamoxifen metabolism. Nevertheless, the consensus of the NCCN Breast Cancer Risk Reduction Panel is that further validation of this biomarker is needed before it can be used to select patients for tamoxifen therapy.
**Raloxifene Recommendations**
The NCCN experts serving on the Breast Cancer Risk Reduction Panel feel strongly that tamoxifen is a superior choice of risk reduction agent for most postmenopausal women desiring non-surgical risk reduction therapy. This is based on the updated STAR trial results that showed diminished benefits of raloxifene compared to tamoxifen after cessation of therapy. However consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in some women.

If raloxifene is chosen, the NCCN Breast Cancer Risk Reduction Panel recommends use of 60 mg/day. Data regarding use of raloxifene to reduce breast cancer risk is limited to healthy postmenopausal women ≥ 35 years who have a ≥ 1.7% 5-year risk for breast cancer as determined by the modified Gail model, or who have a history of LCIS. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for raloxifene use in postmenopausal women at increased risk for breast cancer is influenced by age, bone density, and comorbid conditions (category 1). Since there are no currently available data regarding the efficacy of raloxifene risk reduction in BRCA1/2 mutation carriers, and women who have received prior thoracic radiation, use of raloxifene in these populations is designated as a category 2A recommendation by the NCCN Breast Cancer Risk Reduction Panel. Use of raloxifene to reduce breast cancer risk in premenopausal women is inappropriate unless part of a clinical trial. The utility of raloxifene as a breast cancer risk reduction agent in women < 35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of raloxifene as a risk reduction agent.

**Exemestane Recommendations**
The NCCN experts serving on the Breast Cancer Risk Reduction Panel have included exemestane as one of the choices of risk reduction agent for most postmenopausal women desiring non-surgical risk reduction therapy (category 1). This is based on the results of the MAP.3 trial. If exemestane is chosen, the NCCN Breast Cancer Risk Reduction Panel recommends use of 25 mg/day. Data regarding use of exemestane to reduce breast cancer risk is limited to postmenopausal women 35 years of age or older with a Gail model 5-year risk score > 1.66% or a history of LCIS. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for exemestane use in postmenopausal women at increased risk for breast cancer is influenced by age, bone density, and comorbid conditions. Use of exemestane to reduce breast cancer risk in premenopausal women is inappropriate unless part of a clinical trial. The utility of exemestane as a breast cancer risk reduction agent in women < 35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of raloxifene as a risk reduction agent.

Exemestane is not currently FDA approved for breast cancer risk reduction. There is currently no data comparing the benefits and risks of exemestane to those of tamoxifen or raloxifene. Ongoing trials are evaluating the use of other aromatase inhibitors as risk reduction agents in healthy women at increased risk for future breast cancer. For example, the IBIS-II trial is evaluating anastrozole compared with placebo for the prevention of breast cancer in postmenopausal women at increased risk of developing breast cancer.

**Monitoring Patients on Risk Reduction Agents**
Follow-up of women treated with risk reduction agents for breast cancer risk reduction should focus on the early detection of breast cancer and the management of adverse symptoms or complications. Appropriate monitoring for breast cancer and the evaluation of breast abnormalities should be performed according to the guidelines described for high risk women in the NCCN Guidelines for Breast Cancer Screening and
Diagnosis. The population of women eligible for risk reduction therapy with tamoxifen, raloxifene, or exemestane is at sufficiently increased risk of breast cancer to warrant, at a minimum, yearly bilateral mammography, a clinical breast examination every 6 months, and encouragement of breast awareness.

Endometrial Cancer
Results from the BCPT [P-1] study indicated that women ≥50 years of age treated with tamoxifen have an increased risk of developing invasive endometrial cancer (Table 3). An increased risk of endometrial cancer was not observed in women ≤49 years of age treated with tamoxifen in this study.31, 81 Although the only death from endometrial cancer in the NSABP BCPT [P-1] occurred in a placebo treated subject,31, 81 analyses of the NSABP data have revealed a small number of uterine sarcomas among the number of patients with an intact uterus taking tamoxifen. Uterine sarcoma is a rare form of uterine malignancy reported to occur in 2% to 4% of all patients with uterine cancer.109 Compared with other uterine cancers, uterine sarcomas present at a more advanced stage and thus may carry a worse prognosis in terms of disease free and overall survival.110, 111

Updated results from the NSABP studies indicate that incidence of both endometrial adenocarcinoma and uterine sarcoma is increased in women taking tamoxifen when compared to the placebo arm.112 Several other studies have also supported an association between tamoxifen therapy and an increased risk of developing uterine sarcoma.110, 111, 113, 114 A “black box” FDA warning has been included on the package insert of tamoxifen to highlight the endometrial cancer risk (both epithelial endometrial cancer and uterine sarcoma) of tamoxifen.115

Use of raloxifene was not found to be associated with an increased incidence of endometrial cancer in the MORE trial.94 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 prior to administration of the risk reduction agent, and follow-up gynecologic assessments should be performed at each visit.116 The vast majority of women with tamoxifen-associated endometrial cancer present with vaginal spotting as an early symptom of cancer. Therefore, prompt evaluation of vaginal spotting in the postmenopausal woman is essential.

At present, there is insufficient evidence to recommend the performance of uterine ultrasonography or endometrial biopsy for routine screening in asymptomatic women.117-119 In women diagnosed with endometrial cancer while taking a risk reduction agent, the drug should be discontinued until the endometrial cancer has been fully treated. The NCCN Breast Cancer Risk Reduction Panel believes that it is safe and reasonable to resume therapy with a risk reduction agent after completion of treatment for early stage endometrial cancer.

Retinopathy and Cataract Formation
There have been reports of tamoxifen being associated with the occurrence of retinopathy, although most of this information has come from case studies.120, 121 Furthermore, these reports have not been confirmed in the randomized controlled trials of tamoxifen. A 1.14 relative risk of cataract formation (95% CI, 1.01-1.29), compared with placebo has been reported in the BCPT [P-1] 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).31 After 7 years of follow-up in the BCPT [P-1] study, relative risks of cataract formation and cataract surgery were similar to those initially
reported. 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). In the STAR trial, the incidence of cataract development and occurrence of cataract surgery was significantly higher in the group receiving tamoxifen compared with the group receiving raloxifene. Thus, patients experiencing visual symptoms while undergoing treatment with tamoxifen should seek ophthalmologic evaluation.

**Bone Mineral Density**

Bone is an estrogen responsive tissue, and tamoxifen can act as either an estrogen agonist or estrogen antagonist with respect to bone, depending on the menstrual status of a woman. In premenopausal women, tamoxifen may oppose the more potent effects of estrogen on the bone and potentially increase the risk of osteoporosis, whereas tamoxifen in the presence of typically lower estrogen levels in postmenopausal women is associated with an increase in bone mineral density. However, the NCCN Breast Cancer Risk Reduction Panel does not recommend monitoring bone mineral density (BMD) in premenopausal patients on tamoxifen since development of osteopenia/osteoporosis in this population is considered unlikely. Changes in BMD are of concern in women on aromatase inhibitor therapy. Therefore, a baseline BMD scan is recommended before initiating therapy with an aromatase inhibitor such as exemestane.

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

**Thromboembolic Disease and Strokes**

Tamoxifen and raloxifene have been associated with an increased risk of thromboembolic events (ie, DVT, pulmonary embolism) and stroke. Increased incidences of VTE were observed in the tamoxifen arms of all the placebo controlled randomized risk reduction trials. Although not statistically significant, all of these trials with the exception of the Royal Marsden trial (which enrolled only younger women) also showed an increase in risk of stroke for women receiving tamoxifen, and this risk was found to be significantly elevated in 2 meta analyses of randomized controlled trials evaluating tamoxifen for breast cancer risk reduction or treatment. Comparison of the raloxifene and tamoxifen arms of the STAR trial did not show a difference with respect to 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, evidence has shown that women with a Factor V Leiden or prothrombin G20210 → A mutation, receiving tamoxifen therapy in the BCPT [P-1] study were not at increased risk of developing VTE compared to 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 regarding the symptoms associated with DVT and pulmonary emboli. They should also be informed that prolonged immobilization may increase risk of VTE, and instructed to contact their physicians immediately if they develop symptoms of DVT or pulmonary emboli. Women with documented thromboembolic disease should receive appropriate treatment for the thromboembolic condition and should permanently discontinue tamoxifen or raloxifene therapy.
Managing Side Effects of Risk Reduction Agents

Hot flashes are a common menopausal complaint. In the BCPT [P-1] study, hot flashes occurred in approximately 81% of women treated with tamoxifen and 69% of women treated with placebo. In the STAR trial, women receiving tamoxifen reported a significantly increased incidence of vasomotor symptoms relative to women receiving raloxifene, although raloxifene use has also 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 NCCN Breast Cancer Risk Reduction Panel for the treatment of hot flashes for women on a risk reduction agent outside of a clinical trial.

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

Venlafaxine, a serotonin and norepinephrine inhibitor antidepressant has been shown to be effective in the management of hot flash symptoms in a group of breast cancer survivors of which nearly 70% were taking tamoxifen. Significant declines were observed for both hot flash frequency and severity scores for all doses of venlafaxine (37.5 mg, 75 mg and 150 mg) compared to placebo; incremental improvement was seen at 75 mg versus 37.5 mg (P=.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, as necessary after one week, to 75 mg if a greater degree of symptom control is desired. However, this study followed subjects for only 4 weeks.

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

In a stratified, randomized, double-blind, cross-over, placebo controlled study, 151 women reporting a history of hot flashes were randomized to one of 4 treatment arms (10 mg or 20 mg of paroxetine for 4 weeks
followed by 4 weeks of placebo or 4 weeks of placebo followed by 4 weeks of 10 mg or 20 mg of paroxetine. Hot flash frequency and composite score were reduced by 40.6% and 45.6%, respectively, for patients receiving 10 mg paroxetine compared to reductions of 13.7% and 13.7% in the placebo group. Likewise, reductions of 51.7% and 56.1% in hot flash frequency and score were found for women receiving 20 mg paroxetine compared with values of 26.6% and 28.8% in the placebo group. No significant differences in efficacy were observed with the lower and higher paroxetine doses. Rates of the most commonly reported side effects did not differ among the 4 arms, although nausea was significantly increased in women receiving 20 mg paroxetine relative to the other arms, and a greater percentage of patients receiving the higher dose of paroxetine discontinued treatment.

While these reports appear 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 the long-term effectiveness and safety of these agents. In this context it should be noted that recent evidence has suggested that concomitant use of tamoxifen with certain SSRIs (eg, paroxetine and fluoxetine) may decrease plasma levels of endoxifen and 4-OH tamoxifen, active metabolites of tamoxifen, and may impact its efficacy. These SSRIs may interfere with the enzymatic conversion of tamoxifen to its active metabolites by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. Caution is advised about co-administration of these drugs with tamoxifen. Citalopram and venlafaxine, appear to have only minimal effects on tamoxifen metabolism.

Of interest in this context are results of a 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 for women with a history of breast cancer on 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.

A recent report of 2 nonrandomized parallel study cohorts of women with DCIS or those at high-risk of breast cancer (eg, those with LCIS, atypical hyperplasia, or ≥1.7% 5-year breast cancer risk by the Gail model) comparing women receiving tamoxifen alone with women receiving tamoxifen concomitant with hormone therapy (HT) (mean duration of HT at start of study approximately 10 years) did not show a difference in the rate of tamoxifen-induced hot flashes. The NCCN Breast Cancer Risk Reduction Panel recommends against the use of HT for women taking tamoxifen or raloxifene outside of a clinical trial.

A variety of other substances for the control of hot flashes have been described. Both the oral and transdermal formulations of clonidine reduce hot flashes in a dose-dependent manner. Toxicities associated with clonidine include dry mouth, constipation, and drowsiness. Anecdotal evidence suggests that the use of a number of different herbal or food supplements may alliviate hot flashes. Vitamin E may decrease the frequency and severity of hot flashes, but results from a randomized clinical trial demonstrated that only a very modest improvement in hot flashes was associated with this agent compared with placebo. Results from a double-blind, randomized placebo controlled crossover trial of the use of black cohosh to treat hot flashes did not show significant differences between groups with respect to improvement in hot flash symptoms. Some herbal or food supplements contain active estrogenic compounds, the activity and safety of which are unknown. Other strategies such as relaxation
training, acupuncture, avoidance of caffeine and alcohol and exercise for the management of hot flashes, while potentially beneficial, remain unsupported.\textsuperscript{146}

It should be noted that the observed placebo effect in the treatment of hot flashes is considerable, typically falling in the range 25\% or more,\textsuperscript{130,132-136} suggesting that a considerable proportion of patients might be helped through a trial of therapy 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.\textsuperscript{147}

**Components of Risk Reduction Counseling**

Women should be monitored according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis. Women with known or suspected BRCA 1/2, TP53, PTEN, or other gene mutations associated with breast cancer risk or those with close relatives with breast and/or ovarian cancer should also be followed according to the NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian whether or not they choose to undergo risk reduction therapy. 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, the women should be treated according to the NCCN Guidelines for Breast Cancer. Although the NCCN Breast Cancer Risk Reduction Panel recommends that women with LCIS be managed according to the NCCN Breast Cancer Risk Reduction Guidelines, risk reduction strategies for patients with LCIS are also described in the NCCN Guidelines for Breast Cancer.

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.\textsuperscript{148} Options for breast cancer risk reduction should be discussed in a shared decision-making environment. The counseling should include a discussion and consideration of (1) the individual’s overall health status, including menopausal status, medical history, and medication history (eg, hysterectomy status, prior history of VTE, current use of hormones or SSRI or 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 an emphasis on age dependent risks; (4) the contraindications to therapy with tamoxifen and raloxifene (eg, history of VTE, history of thrombotic stroke, history of transient ischemic attack, and pregnancy or pregnancy potential without an effective nonhormonal method of contraception; (5) the common and serious side effects of tamoxifen and raloxifene.

The recently updated guidelines from the American Society of Clinical Oncology (ASCO) comparing the effectiveness of breast cancer risk reduction agents provide some estimates of the number either needed to treat (NNT) to prevent breast cancer or number needed to harm (NNH) by causing a specific side effect in a single patient receiving a specific risk reduction agent.\textsuperscript{149} Both NNT and NNH can be useful aids in communicating risks and benefits of tamoxifen and raloxifene in this setting (eg, using long-term data from the IBIS-1 trial, NNH with respect to VTE was determined to be 73 with tamoxifen, whereas this value 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.
**Counseling prior to therapy with risk reduction agents**

Counseling sessions with women who are considering non-surgical breast cancer risk reduction should incorporate an explanation of data from the BCPT [P-1], STAR, and/or MAP.3 trial as appropriate.

**Counseling on use of a SERM for breast cancer risk reduction**

The BCPT [P-1] 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 groups and risk groups (Table 2; Table 3).31 The tamoxifen treatment risk/benefit ratio is especially favorable in women between the ages of 35 and 50 years. Unfortunately, individualized data regarding the risk/benefit ratio for tamoxifen are not generally available except for the broad age categories of ages 50 years and younger versus older than 50 years of age. Tamoxifen, unlike raloxifene, is a risk reduction agent that can be used by premenopausal women. In addition, tamoxifen may be more effective than raloxifene in reducing the incidence of non-invasive breast cancer (Table 4), although the difference is not statistically significant at long-term follow-up.32, 33 Further, tamoxifen was reported by patients in the STAR trial to be associated with better sexual function than raloxifene.98 However, tamoxifen has been associated with an increased incidence of invasive endometrial cancer relative to placebo in women ≥ 50 years of age,31, 81 (Table 3) and an increased incidence of endometrial hyperplasia and invasive endometrial cancer relative to raloxifene,32, 33 possibly making it a less attractive choice in women with a uterus. Use of raloxifene to reduce breast cancer risk may be preferred by postmenopausal women with a uterus or those at risk for developing cataracts. All women receiving a breast cancer risk reduction agent should be counseled with respect to signs and symptoms of possible side effects associated with use of these agents, and the recommended schedules for monitoring for the presence of certain adverse events. Contraindications to tamoxifen or raloxifene include history of VTE, thrombotic stroke, transient ischemic attack, current pregnancy or pregnancy potential without effective method of contraception, or known inherited clotting trait.

The optimal duration of SERM therapy for breast cancer risk reduction is not known. In the overview by the Early Breast Cancer Trialists' Collaborative Group, continuing tamoxifen therapy for up to 5 years resulted in an increasingly reduced risk for the development of contralateral primary breast cancer.80 Use of tamoxifen for more than 5 years provided no greater benefit but incurred continued risks of therapy. In addition, the BCPT [P-1] and STAR trials only studied 5 years of risk reduction therapy with either tamoxifen or raloxifene.31, 32 However, based on the updated STAR results which showed that the benefits of raloxifene diminished after cessation of therapy,33 continuing raloxifene beyond 5 years might be an approach to maintain the risk reduction activity of the agent.

There have been some concerns based on studies of animal models regarding the potential for interference with subsequent raloxifene efficacy in patients who had previously completed a 5-year course of tamoxifen.146 Conversely, questions also exist regarding the safety and efficacy of administering tamoxifen to a patient who had previously taken raloxifene for treatment or prevention of osteoporosis. Until further information is available, a period of 5 years appears to be appropriate for tamoxifen therapy when the agent is used to reduce the risk of cancer. Women should be counseled that the benefits and safety of further therapy with raloxifene is not known. After completing 5 years of tamoxifen therapy, women should continue to be monitored according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis 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 ER-positive disease, is supported by results of several placebo controlled randomized trials at long-term follow-up. The recent results from the STAR trial suggest that although a 5-year course of raloxifene retains considerable benefit with respect to the prevention of invasive breast cancer at a median follow-up of 81 months, the breast cancer preventive benefit of tamoxifen therapy for 5 years appears to be sustained for a longer period of time.

The NCCN Breast Cancer Risk Reduction Panel recommends using the tables from the Freedman et al publication while counseling postmenopausal women regarding use of raloxifene and tamoxifen for breast cancer risk reduction.

Counseling on use of exemestane for breast cancer risk reduction
Currently, there is no data comparing the benefits and risks of exemestane to those of tamoxifen or raloxifene. Data regarding exemestane are from the single large randomized MAP.3 trial limited to postmenopausal women 35 years of age or older with a Gail model 5-year breast cancer risk 1.7% or a history of LCIS which may be used while counseling patients. The data shows that exemestane has a completely different toxicity profile than the SERMs. Compared to the placebo group in the MAP.3 trial, exemestane had no increased risk of serious side effects. The incidence of osteoporosis, cardiac events, and bone fractures were identical for women in the MAP.3 trial taking exemestane and for those taking the placebo. Women taking exemestane had a small, but not statistically significant increase in menopausal symptoms, such as hot flashes (18.3% vs 11.9) and arthritis (6.5% vs 4.0%). The optimal duration of exemestane therapy is currently unknown. Changes in BMD are of concern in women on aromatase inhibitor therapy. Therefore, a baseline BMD scan is recommended before initiating therapy exemestane. The role of calcium, vitamin D, and maintaining healthy lifestyle in maintaining bone health must be emphasized in healthy postmenopausal women who are receiving exemestane.

Counseling prior to risk reduction surgery
For women at very high risk of breast cancer who are considering RRM, it is important that the potential psychosocial effects of RRM are addressed, although these effects have not been well studied. Such surgery has the potential to negatively impact perceptions of body image, ease of forming new relationships, and the quality of existing relationships. Moreover, the procedure also eliminates the breast as a sexual organ. Multidisciplinary consultations are recommended prior to surgery, and should include a surgeon familiar with the natural history and therapy of benign and malignant breast disease 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 following RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction. Psychological consultations may also be considered.

Discussions regarding the risk of ovarian cancer and the option of RRSO for breast and ovarian cancer risk reduction should also be undertaken with women who are known carriers of a BRCA1/2 mutation. Other topics which should be addressed with respect to RRSO include the increased risk of osteoporosis and cardiovascular disease associated with premature menopause, as well as the potential effects of possible cognitive changes, accelerated bone loss, and vasomotor symptoms on quality of life. Furthermore, the surgery itself may have some associated complications.
It has been reported that short-term hormone therapy in women undergoing RRSO did not negate the reduction in breast cancer risk associated with the surgery.\textsuperscript{155} In addition, results of a recent case-control study of BRCA1 mutation carriers showed no association between use of HT and increased breast cancer risk in postmenopausal BRCA1 mutation carriers.\textsuperscript{156} However, the consensus of the NCCN Breast Cancer Risk Reduction Panel is that caution should be used when considering use of HT in mutation carriers following RRSO; given the limitations inherent in nonrandomized studies (see also section below on “Breast Cancer Risks Associated with HT”).\textsuperscript{156, 157} It is unlikely that a prospective randomized study on the use of RRSO for breast cancer risk reduction will be performed. Whether the resulting reduction in the risk of breast cancer from this procedure is preferable to a RRM is likely to remain a personal decision.\textsuperscript{158} Table 1 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).

**Counseling regarding lifestyle modifications**

There is evidence to indicate that certain lifestyle characteristics, such as obesity, increased alcohol consumption, and use of certain types of HT, are factors or markers for an elevated risk of breast cancer.\textsuperscript{47} 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 Hormone Therapy**

The Women’s Health Initiative (WHI) enrolled 161,809 postmenopausal women 50-79 years of age into a set of clinical trials from 1993-1998. Two of these trials were randomized controlled studies involving the use of HT (estrogen plus progestin) in primary disease prevention: a trial involving 16,608 women with intact uteri at baseline randomized to receive estrogen plus progestin or placebo,\textsuperscript{159} and a trial of 10,739 women with prior hysterectomy randomized to receive estrogen alone or placebo.\textsuperscript{160} The former trial was terminated early due to evidence for breast cancer harm, along with a global index associated with overall harm. In that study, a 26\% increased incidence of breast cancer was observed in the treatment group (HR =1.26; 95\% CI, 1.00-1.59). 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.\textsuperscript{161} Of greater concern is that HT was associated with significant increase in rates of both incidence of breast cancer and breast cancer related mortality,\textsuperscript{162} although the increased risk of breast cancer declined rapidly following cessation of HT.\textsuperscript{163}

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.\textsuperscript{160} The lower incidence of breast cancer seen among women randomized to estrogen alone during the intervention period became statistically significant with extended follow-up for mean of 10.7 years.\textsuperscript{164} However, an increased incidence of abnormal mammograms was observed in the group of women receiving estrogen,\textsuperscript{165} as well as a doubling of the risk of benign proliferative breast disease.\textsuperscript{166} Analysis of the data from this
randomized controlled WHI trial showed use of estrogen alone to significantly increase mammographic breast density compared with women receiving placebo, and this effect was observed for at least a 2 year period.\textsuperscript{167} Contrary to the results from the WHI randomized controlled trials, results from several prospective, population based, observational studies have shown use of estrogen only HT to be associated with increased risks of breast cancer. These studies include the Black Women’s Health Study where use of estrogen alone for a duration of 10 years or longer was associated with a nonsignificant increase in risk of invasive breast cancer (relative risk = 1.41; 95% CI, 0.95-2.10),\textsuperscript{168} the Million Women Study of women 50-64 years of age which showed an association between current use of estrogen only HT and increased risk of breast cancer (relative risk = 1.30; 95% CI, 1.21-1.40; \textit{P}<.0001),\textsuperscript{169} and the Nurses’ Health Study which demonstrated a significantly increased breast cancer risk after long-term use (20 years or longer) of estrogen alone (relative risk = 1.42; 95% CI, 1.13-1.77).\textsuperscript{170}

It has been noted that there are important differences in the populations enrolled in the WHI randomized clinical trials relative to the women followed in the observational studies with respect to duration of exposure to HT and age at initiation of HT.\textsuperscript{171} For example, many of women in the WHI clinical trials did not start receiving HT until years after menopause whereas those in the population based studies were more likely to initiate HT at menopause and to have been exposed to such treatment for longer periods of time. One hypothesis put forward to explain the apparent contradictions in the summary of studies of HT described above is that short-term use of estrogen following a period of estrogen deprivation may decrease breast cancer risk by inducing apoptosis of occult breast cancer tumors, whereas long-term use of estrogen may initiate and promote the growth of new tumors, thereby increasing breast cancer risk.\textsuperscript{172} However, further studies are needed to evaluate this hypothesis. Another possible explanation for the decrease in breast cancer risk observed in the first 2 years of the WHI randomized controlled trial of postmenopausal women receiving estrogen plus progestin may be related to effects of HT on breast tissue and subsequent interference with the ability of mammography to detect new breast cancer tumors.\textsuperscript{171}

The use of estrogen/progestin therapy and estrogen therapy alone has also been associated with increased risks of cardiovascular disease (eg, stroke) and decreased risk of bone fractures.\textsuperscript{159, 160} However, a more recent secondary analysis from the WHI randomized controlled trials showed a trend for more effective reduction in the risk of cardiovascular disease with initiation of HT closer to menopause compared with administration of HT to women who experienced a greater time gap between menopause and the start of such therapy.\textsuperscript{173} Nevertheless, recent results from a large French cohort control study show a significantly increased risk of breast cancer in women receiving short-term (ie, 2 years or less) estrogen and progestagen shortly after menopause when compared with nonusers.\textsuperscript{174}

The NCCN Breast Cancer Risk Reduction Panel recommends against the use of HT for women taking tamoxifen, raloxifene or exemestane outside of a clinical trial.

\textbf{Alcohol Consumption}

Numerous studies have demonstrated that the intake of moderate amounts of alcohol (one to two drinks per day) is associated with an increase in the risk of breast cancer.\textsuperscript{47, 48, 49} A 10% increase in breast cancer risk for every 10 grams of alcohol consumed each day was seen in analyses of two cohort studies.\textsuperscript{50, 51} A population based study of 51,847 postmenopausal women provided evidence to support an
association between increased alcohol consumption and an increased likelihood of development of ER-positive breast cancer. However, the effect of a reduction in alcohol consumption on the incidence of breast cancer has not been well studied. Even one drink per day modestly elevates breast cancer risk. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that alcohol consumption should be limited to < 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 five hours of vigorous exercise per week compared to 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 (eg, 1605 black and 2933 white patients). Both black and white women with annual lifetime exercise activity levels exceeding the median activity level for active control subjects were found to have a 20% lower risk of breast cancer when compared to inactive women (odds ratio = 0.82; 95% CI, 0.71-0.93). 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 hours per week (relative risk = 0.57; 95% CI, 0.34-0.95). Recently, a study of 320 postmenopausal sedentary women randomly assigned to 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 (ie, a decrease and an increase in these levels, respectively). However, it has been suggested that other, as yet 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 of breast cancer did not show a statistically significant reduction in the incidence of invasive breast cancer in women who followed a low-fat diet over an average of 8.1 years (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 2 arms with respect to fat intake. Furthermore, it is possible that the impact of certain diets on breast cancer risk may be dependent on the age of the study population. For example, results of a number of 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 non hydrogenated and unsaturated have been shown to have cardiovascular benefits.

Epidemiologic studies suggest that vitamin D (from dietary sources and the sun) may play a protective role with respect to decreasing risk of the development of breast cancer. Furthermore, there is some evidence to suggest that such 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. Current studies are ongoing to evaluate the role of Vitamin D on breast cancer risk.
Weight/BMI

There is a substantial amount of evidence indicating that overweight or obese women have a higher risk of postmenopausal breast cancer.\(^{45-47}\)

Recent results from the Nurses’ Health Study evaluating the effect of weight change on the incidence of invasive breast cancer in 87,143 postmenopausal women suggested that women experiencing a weight gain of 25.0 kg or more since age 18 have an increased risk of breast cancer when compared with women who have maintained their weight (relative risk = 1.45; 95% CI, 1.27-1.66).\(^{46}\) Furthermore, women who had never used postmenopausal HT 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, there is evidence that the risk of breast cancer is lower in premenopausal women who are overweight compared with women who are not overweight.\(^{47}\)

Results from a case-control study of 1,073 pairs of women with \(BRCA1/2\) mutations indicated that a weight loss of 10 or more pounds in women with the \(BRCA1\) mutation between the ages of 18 and 30 was associated with a decreased risk of developing breast cancer between the ages of 30 and 40 years. (odds ratio = 0.35; 95% CI, 0.18-0.67).\(^{190}\)

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, raloxifene, or exemestane substantially decreases the future risk of breast cancer provides an opportunity for a risk reduction intervention. However, the risks and benefits associated with use of risk reduction agents for an individual woman should be evaluated and discussed with the woman as part of a shared decision-making process. Women taking a risk reduction agent must be closely monitored for potential side effects associated with use of these agents. In special circumstances, such as in women who are carriers of a \(BRCA1/2\) mutation, where the risk of breast cancer is very high, the performance of a bilateral mastectomy or bilateral salpingo-oophorectomy may be considered for breast cancer risk reduction. Women considering either surgery should undergo multidisciplinary consultations prior to surgery so as to become well informed about all treatment alternatives, the risks and benefits of risk reduction surgery, and, in the case of bilateral mastectomy, the various reconstruction options available. The NCCN Guidelines for Breast Cancer Risk Reduction Panel strongly encourages women and health care providers to participate in clinical trials to test new strategies for decreasing the risk of breast cancer. Only through the accumulated experience gained from prospective and well designed clinical trials will additional advances in the reduction of breast cancer risk be realized.
### Figure 1

Criteria used in calculation of 5-year risk of breast cancer according to the modified Gail model

(Available at [www.breastcancerprevention.com](http://www.breastcancerprevention.com))

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>___</td>
</tr>
<tr>
<td>Age at menarche (First menstrual period)</td>
<td>___</td>
</tr>
<tr>
<td>Age at first live birth or nulliparity</td>
<td>___</td>
</tr>
<tr>
<td>Number of breast biopsies</td>
<td>___</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>Y / N</td>
</tr>
<tr>
<td>Number of first-degree relatives with breast cancer</td>
<td>___</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Caucasian, African American, Hispanic, Other</td>
</tr>
</tbody>
</table>
### Table 1
Survival Probability According to Breast/Ovarian Cancer Risk Reduction Strategy at Age 70* for 25 Year Old *BRCA1/2* Mutation Carrier.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival probability (%) in <em>BRCA1</em> mutation carriers</th>
<th>Survival probability (%) in <em>BRCA2</em> mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention</td>
<td>53% [BCD=41%;OCD=36%]</td>
<td>71% [BCD=36%;OCD=20%]</td>
</tr>
<tr>
<td>RRSO only at age 40</td>
<td>68% [BCD=45%;OCD=12%]</td>
<td>77% [BCD=30%;OCD=4%]</td>
</tr>
<tr>
<td>RRSO only at age 50</td>
<td>61% [BCD=51%;OCD=20%]</td>
<td>75% [BCD=42%;OCD=6%]</td>
</tr>
<tr>
<td>RRM only at age 25</td>
<td>66% [BCD=5%;OCD=58%]</td>
<td>79% [BCD=4%;OCD=30%]</td>
</tr>
<tr>
<td>RRM only at age 40</td>
<td>64% [BCD=13%;OCD=53%]</td>
<td>78% [BCD=9%;OCD=28%]</td>
</tr>
<tr>
<td>Breast Screening only from 25-69</td>
<td>59% [BCD=26%;OCD=46%]</td>
<td>75% [BCD=21%;OCD=25%]</td>
</tr>
<tr>
<td>RRSO at age 40 and RRM at age 25</td>
<td>79% [BCD=6%;OCD=21%]</td>
<td>83% [BCD=3%;OCD=6%]</td>
</tr>
<tr>
<td>RRSO at age 40 and Breast Screening from 25-69</td>
<td>74% [BCD=30%;OCD=15%]</td>
<td>80% [BCD=18%;OCD=5%]</td>
</tr>
<tr>
<td>RRSO at age 40, RRM at age 40; and Breast Screening from 25-39</td>
<td>77% [BCD=18%;OCD=18%]</td>
<td>82% [BCD=9%;OCD=6%]</td>
</tr>
</tbody>
</table>

*Survival probability for 70 year old woman from general population=84%

[Probability of death as a result of breast cancer (BCD) or ovarian cancer (OCD); RRSO- risk-reduction bilateral salpingo-oophorectomy; RRM – risk-reduction bilateral mastectomy; Breast screening – annual mammography and MRI]

Table 2 Rates of Invasive Breast Cancer in the NSABP Breast Cancer Prevention Trial (BCPT) [P-1 study]

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Tamoxifen vs Placebo)</th>
<th>95% Confidence Interval (CI) for Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>0.51</td>
<td>0.39-0.66</td>
</tr>
<tr>
<td>Age ≤ 49 yr</td>
<td>0.56</td>
<td>0.37-0.85</td>
</tr>
<tr>
<td>Age 50-59 yr</td>
<td>0.49</td>
<td>0.29-0.81</td>
</tr>
<tr>
<td>Age ≥ 60 yr</td>
<td>0.45</td>
<td>0.27-0.74</td>
</tr>
<tr>
<td>History of LCIS</td>
<td>0.44</td>
<td>0.16-1.06</td>
</tr>
<tr>
<td>History of atypical hyperplasia</td>
<td>0.14</td>
<td>0.03-0.47</td>
</tr>
</tbody>
</table>

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

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

Table 3  Toxicity Experience in Women Enrolled in the NSABP Breast Cancer Prevention Trial (BCPT) [P-1 study]

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Annual Rate per 1,000 Patients</th>
<th>Placebo</th>
<th>Tamoxifen</th>
<th>Risk Ratio (Tamoxifen vs Placebo)</th>
<th>95% Confidence Interval for Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive endometrial cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td></td>
<td>1.09</td>
<td>1.32</td>
<td>1.21</td>
<td>0.41-3.60</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td></td>
<td>0.76</td>
<td>3.05</td>
<td>4.01</td>
<td>1.70-10.90</td>
</tr>
<tr>
<td><strong>Deep vein thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td></td>
<td>0.78</td>
<td>1.08</td>
<td>1.39</td>
<td>0.51-3.99</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td></td>
<td>0.88</td>
<td>1.51</td>
<td>1.71</td>
<td>0.85-3.58</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td></td>
<td>0.39</td>
<td>0.30</td>
<td>0.76</td>
<td>0.11-4.49</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td></td>
<td>1.26</td>
<td>2.20</td>
<td>1.75</td>
<td>0.98-3.20</td>
</tr>
<tr>
<td><strong>Pulmonary embolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td></td>
<td>0.10</td>
<td>0.20</td>
<td>2.03</td>
<td>0.11-119.62</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td></td>
<td>0.31</td>
<td>1.00</td>
<td>3.19</td>
<td>1.12-11.15</td>
</tr>
<tr>
<td><strong>Bone fracture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td></td>
<td>2.24</td>
<td>1.98</td>
<td>0.88</td>
<td>0.46-1.68</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td></td>
<td>7.27</td>
<td>5.76</td>
<td>0.79</td>
<td>0.60-1.05</td>
</tr>
<tr>
<td><strong>Ischemic heart disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.37</td>
<td>2.73</td>
<td>1.15</td>
<td>0.81-1.64</td>
</tr>
<tr>
<td><strong>Cataracts developed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.72</td>
<td>24.82</td>
<td>1.14</td>
<td>1.01-1.29</td>
</tr>
<tr>
<td><strong>Cataracts developed and underwent surgery</strong></td>
<td></td>
<td>3.00</td>
<td>4.72</td>
<td>1.57</td>
<td>1.16-2.14</td>
</tr>
</tbody>
</table>

### Table 4
Rates of Invasive 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% Confidence Interval (CI) for Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>1.24</td>
<td>1.05-1.47</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 yr</td>
<td>1.53</td>
<td>0.64-3.80</td>
</tr>
<tr>
<td>50-59 yr</td>
<td>1.23</td>
<td>0.97-1.57</td>
</tr>
<tr>
<td>≥ 60 yr</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>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Ratio (Raloxifene vs Tamoxifen)</th>
<th>95% CI for Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>1.22</td>
<td>0.95-1.59</td>
</tr>
</tbody>
</table>

### 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 1,000 Patients</th>
<th>Risk Ratio (Raloxifene vs Tamoxifen)</th>
<th>95% Confidence Interval for Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>Raloxifene</td>
<td></td>
</tr>
<tr>
<td>Invasive endometrial cancer</td>
<td>2.25</td>
<td>1.23</td>
<td>0.55</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>4.40</td>
<td>0.84</td>
<td>0.19</td>
</tr>
<tr>
<td>Hysterectomy during follow-up</td>
<td>12.08</td>
<td>5.41</td>
<td>0.45</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>3.30</td>
<td>2.47</td>
<td>0.75</td>
</tr>
<tr>
<td>- Deep vein thrombosis</td>
<td>1.93</td>
<td>1.38</td>
<td>0.55</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>1.36</td>
<td>1.09</td>
<td>0.27</td>
</tr>
<tr>
<td>Cataracts developed during follow-up</td>
<td>14.58</td>
<td>11.69</td>
<td>0.80</td>
</tr>
<tr>
<td>Cataracts developed and underwent surgery</td>
<td>11.18</td>
<td>8.85</td>
<td>0.79</td>
</tr>
</tbody>
</table>

References


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62. Antoniou A, Pharoah PDP, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined


