National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer Risk Reduction

NCCN Evidence Blocks™

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NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Evidence Blocks™

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NCCN Guidelines Panel Disclosures

& Epidemiology
Δ Genetics
Ω Gynecologic oncology
‡ Hematology
Þ Internal medicine, including family, preventive medicine
† Medical oncology
# Nursing
¥ Patient advocacy
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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NCCN Breast Cancer Risk Reduction Panel Members
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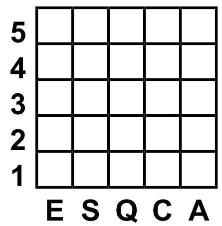
Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

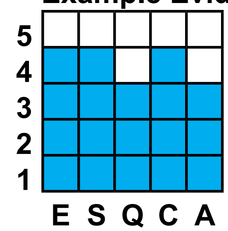
See NCCN Categories of Evidence and Consensus.

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

FAMILIAL RISK ASSESSMENT[a]

Familial/genetic factors

- **Known germline pathogenic/likely pathogenic variants conferring elevated risk for breast cancer[b]; for full list, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate** → **BRISK-2**

- **For further genetic risk evaluation of individuals with no personal history of invasive breast cancer or ductal carcinoma in situ (DCIS),[c] see criteria outlined in NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate** → **Individual meets one or more of the familial/genetic risk criteria outlined in NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate**
  - **Yes** → **Referral to genetic counselor or other health professional with expertise and experience in cancer genetics[d,e] AND See BRISK-2**
  - **No** → **BRISK-3**

[a] NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[b] Individuals who are identified as having a variant of uncertain significance should be treated on the basis of their family history.
[c] The criteria for further genetic risk assessment and genetic testing are not identical. For the purposes of evaluating family history in individuals with no personal history of breast cancer, having a family history of invasive breast cancer or DCIS should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.
[d] For further details regarding the nuances of genetic counseling and testing, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[e] If not tested, treatment should be based on family history and other risk factors listed on BRISK-3.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

ADDITIONAL FAMILIAL RISK ASSESSMENT[f]

- **Known genetic predisposition[a,g]**
  or
- **Pedigree suggestive of genetic predisposition[a,g,h]**
  or
- **Personal history of atypical hyperplasia (AH)/lobular carcinoma in situ (LCIS) or a strong family history of breast cancer[g,i]**
- **Elevated risk of breast cancer based on validated risk estimation[f,j] models (BRISK-C)**
  and
  Life expectancy ≥10 y[g,k]

→ **Counsel on healthy lifestyles and risk reduction options[l,m]**

→ **Individual desires risk-reducing therapy**
and
Life expectancy ≥10 y[k] → **BRISK-5**

→ **Individual does not desire risk-reducing therapy (BRISK-7)**

[a] NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[f] The use of polygenic risk scores (PRS) as part of standard of care in breast cancer risk assessment is discouraged. Further validation is required to understand interaction of single nucleotide polymorphisms (SNPs) with environmental or hormonal risk factors and disease subtype in diverse populations. Ongoing research will shed light on utility of PRS in comprehensive risk assessment models to guide personalized therapy.
[g] In patients with at least one intact breast for whom risk-reducing therapy is recommended.
[h] Individual meets one or more of the familial risk criteria (BRISK-1).
[i] For risk models that are largely dependent on family history (eg, Tyrer-Cuzick, BRCAPro, CanRisk/BOADICEA), see Comparison of Risk Assessment Models (BRISK-C). For breast cancer screening recommendations, see NCCN Guidelines for Breast Cancer Screening and Diagnosis.
[j] A change in personal or family history should prompt re-calculation of risk. A diagnosis of new pathogenic germline variant or AH should be considered outside of risk models as they may not accurately estimate breast cancer risk (eg, the Gail model underestimates risk for individuals with AH while Tyrer-Cuzick model overestimates risk). Reassess any variant of uncertain significance (VUS) to determine if it has been re-classified to pathogenic/likely pathogenic variant.
[k] See life expectancy calculator (www.eprognosis.com). For a reference point, the life expectancy of the average 78-year-old patient assigned female at birth (AFAB) in the United States is 10.2 years. See NCCN Guidelines for Older Adult Oncology.
[l] Components of Risk/Benefit Assessment and Counseling (BRISK-A).
[m] See BRISK-B for risk reduction agents and details on dosing.

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ELEMENTS OF RISK[n]

Individual does not meet any of the familial risk criteria or tests negative for a genetic predisposition →

Elements that increase risk[o]
- Family history
- Increasing age
- Ethnicity/race[p]
- Lifestyle factors
  - Increased body mass index (BMI)
  - Alcohol consumption
  - Current or prior combined estrogen and progesterone hormone agents[q]
- Reproductive history
  - Younger age at menarche
  - Nulliparity/lower parity
  - Older age at first live birth
  - Older age at menopause
- Other
  - History of LCIS; AH (ductal and/or lobular)
  - Number of prior breast biopsies
    - ◊ Procedure done with the intent to diagnose cancer; multiple biopsies (needle/excision) of the same lesion are scored as one biopsy
  - Mammographic breast density (heterogeneously and/or extremely dense breasts)
  - Prior thoracic radiation therapy (RT) 10–30 y of age

Elements that decrease risk
- Menopause before age 45 y
- Prior risk-reducing agent
- Exercise
- Breastfeeding

→ **For breast cancer risk assessment and management, see BRISK-4**

[n] The management of DCIS and invasive breast cancer is available in the NCCN Guidelines for Breast Cancer.
[o] See Table 2 in Nattinger AB, et al. Breast Cancer Screening and Prevention. Ann Intern Med 2016;164:ITC81-TTC96.
[p] There are differences in risk associated with race and ethnicity. Further studies are needed for social determinants of health and existing health care disparities to better understand this relationship.
[q] Based on the observational data, hormonal intrauterine devices (IUDs) have very low systemic absorption and very low associated breast cancer risk. There are insufficient data regarding the use of testosterone (through any route of administration) and its impact on breast cancer risk at this time.

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NON-FAMILIAL RISK ASSESSMENT[f]

RISK MANAGEMENT

Individuals with atypical hyperplasia or history of LCIS and Life expectancy ≥10 y[g,k] →
- **Risk-reducing agent is strongly recommended[s] (BRISK-6 and BRISK-B)**
  - **If the individual does not desire risk-reducing therapy, see BRISK-7 for surveillance recommendations**
- **Counsel on healthy lifestyles[l] (BRISK-A)**

Prior thoracic RT 10–30 y of age[g,r] and Life expectancy ≥10 y[g,k]

Elevated risk of breast cancer based on validated risk estimation[f,s] models (BRISK-C) and Life expectancy ≥10 y[g,k]

→ **Counsel individuals on healthy lifestyles and risk reduction options[l,m] (BRISK-A)**
- → **Individual desires risk-reducing therapy (BRISK-5)**
- → **Individual does not desire risk-reducing therapy (BRISK-7)**

If individuals have any of the assessed (familial and non-familial) risks but life expectancy <10 y[k] → **Counsel regarding healthy lifestyles[l] (BRISK-A)**

[f] The use of PRS as part of standard of care in breast cancer risk assessment is discouraged. Further validation is required to understand interaction of SNPs with environmental or hormonal risk factors and disease subtype in diverse populations. Ongoing research will shed light on utility of PRS in comprehensive risk assessment models to guide personalized therapy.
[g] In patients with at least one intact breast for whom risk-reducing therapy is recommended.
[k] See life expectancy calculator (www.eprognosis.com). For a reference point, the life expectancy of the average 78-year-old patient AFAB in the United States is 10.2 years. See NCCN Guidelines for Older Adult Oncology.
[l] Components of Risk/Benefit Assessment and Counseling (BRISK-A).
[m] See BRISK-B for risk reduction agents and details on dosing.
[r] These individuals are at a significantly elevated risk for breast cancer and risk reduction options should be strongly considered. Bhatia S, et al. Clin Cancer Res 2021;27:967-974.
[s] Individuals with AH have an 86% reduction in risk with an endocrine agent. LCIS has a >50% reduction in risk with an endocrine agent. Risk-reducing endocrine agents should be strongly recommended for individuals with AH and LCIS (for risk-reducing endocrine therapy agent options, see BRISK-6).

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All recommendations are category 2A unless otherwise indicated.

RISK-REDUCING THERAPY DESIRED	BASELINE ASSESSMENT		RISK-REDUCING INTERVENTION	
Individual desires risk-reducing therapy • Baseline gynecologic assessment (for individuals with intact uterus)[t] • Baseline bone density evaluation[u] (for post-menopausal individuals only) →	Breast screening as per NCCN Guidelines for Breast Cancer Screening and Diagnosis if not done in previous year	Normal →	If considering risk-reducing agent[m,v,w] →	BRISK-6
			Discuss option of risk-reducing mastectomy[x] for only those individuals meeting criteria →	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate
		Abnormal →		See NCCN Guidelines for Breast Cancer Screening and Diagnosis

[m] See BRISK-B for risk reduction agents and details on dosing.
[t] The purpose of baseline gynecologic assessment is to ensure no abnormal bleeding that requires evaluation before beginning treatment.
[u] To guide choice of risk-reducing endocrine agent (eg, low baseline bone density—choose raloxifene over aromatase inhibitors).
[v] Although risk-reducing agents can be considered and should be discussed when the 5-year risk by modified Gail model is ≥1.7%, it should be recommended when the 5-year risk by Gail model is at least 3% or a 10-year risk by the International Breast Cancer Intervention Study (IBIS)/Tyrer-Cuzick is at least 5%. For risk models that are largely dependent on family history (eg, Tyrer-Cuzick, BRCAPro, CanRisk/BOADICEA), see Comparison of Risk Assessment Models (BRISK-C).
[w] *CYP2D6* genotype testing is not recommended in individuals considering tamoxifen.
[x] Risk-reducing mastectomy should be discussed and can be considered as an option in individuals with a germline pathogenic/likely pathogenic variants in high-penetrance breast cancer susceptibility genes (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate), compelling family history, or those with a history of chest wall radiation before 30 years of age. While risk-reducing mastectomy has previously been considered for LCIS, the currently preferred approach for LCIS is close monitoring and therapy with a risk-reducing endocrine agent. Risk estimation is a complex and individualized process; the NCCN Panel does not recommend a specific risk cutoff for decision-making regarding risk-reducing mastectomy. Thus, individualizing management is highly encouraged.

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All recommendations are category 2A unless otherwise indicated.

RISK-REDUCING AGENT

Premenopausal[y] →
- **Clinical trial**[z]
- **or**
- **Tamoxifen**[m,y] **(category 1)**[aa]

Postmenopausal[u,y] →
- **Clinical trial**[z]
- **or**
- **Tamoxifen**[m,z] **(category 1)**[aa]
- **or**
- **Raloxifene**[m] **(category 1)**[aa]
- **or**
- **Aromatase inhibitors**[m] **(category 1)**[aa]

→

SURVEILLANCE

- **Surveillance according to NCCN Guidelines for Breast Cancer Screening and Diagnosis for those at increased risk for breast cancer**
- **Routine age-appropriate gynecologic screening (for individuals with intact uterus on tamoxifen)**[bb]
- **Ophthalmology exam if cataracts or vision problems**
- **For management while on endocrine agent, see BRISK-8**
- **Monitor bone density while on aromatase inhibitors**

See Evidence Blocks on EB-1

[m] See BRISK-B for risk reduction agents and details on dosing.
[u] To guide choice of risk-reducing endocrine agent (eg, low baseline bone density—choose raloxifene over aromatase inhibitors).
[y] 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 years; age <60 years and amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, or toremifene; or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range. If taking tamoxifen or toremifene and age <60 y, reasonable criteria include FSH and plasma estradiol level in postmenopausal ranges.
[z] Individuals in a clinical trial should have a baseline exam, follow-up, and monitoring as per protocol.
[aa] For patients with a known genetic predisposition or prior thoracic RT, the recommendation for the use of risk-reducing agents is category 2A.
[bb] Routine endometrial ultrasound and biopsy are not recommended for individuals in the absence of other symptoms.

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All recommendations are category 2A unless otherwise indicated.

RISK-REDUCING THERAPY NOT DESIRED

RISK ASSESSMENT → **SCREENING/FOLLOW-UP**

Individual does not desire risk-reducing therapy

and

Life expectancy ≥10 y[k]

- **Pedigree suggestive of/or known genetic predisposition[a,g]** **or** **Personal history of AH/LCIS or a strong family history of breast cancer[g,h,s]** → See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate **and** NCCN Guidelines for Breast Cancer Screening and Diagnosis
- **AH/LCIS**
- **Prior thoracic RT at 10–30 y of age**
- **5-y breast cancer risk ≥1.7%[cc]**

→ (AH/LCIS; Prior thoracic RT at 10–30 y of age; 5-y breast cancer risk ≥1.7%) See NCCN Guidelines for Breast Cancer Screening and Diagnosis

[a] NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[g] In patients with at least one intact breast for whom risk-reducing therapy is recommended.
[h] Individual meets one or more of the familial risk criteria (BRISK-1).
[i] For risk models that are largely dependent on family history (eg, Tyrer-Cuzick, BRCAPro, CanRisk/BOADICEA), see Comparison of Risk Assessment Models (BRISK-C). For breast cancer screening recommendations, see NCCN Guidelines for Breast Cancer Screening and Diagnosis.
[k] See life expectancy calculator (www.eprognosis.com). For a reference point, the life expectancy of the average 78-year-old patient AFAB in the United States is 10.2 years. See NCCN Guidelines for Older Adult Oncology.
[s] Individuals with AH have an 86% reduction in risk with an endocrine agent. LCIS has a >50% reduction in risk with an endocrine agent. Risk-reducing endocrine agents should be strongly recommended for individuals with AH and LCIS (for risk-reducing endocrine therapy agent options, see BRISK-6).
[cc] The definition of risk as defined by the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP BCPT). See Valero MG, et al. Ann Surg Oncol 2020;27:736-740.

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CLINICAL SCENARIOS → **MANAGEMENT WHILE ON RISK-REDUCING AGENT**

Asymptomatic → Continue risk-reducing agent → Continue follow-up

Arthralgias (exemestane, anastrozole) → Symptomatic treatment, if persist:
- Try a different aromatase inhibitor (AI)
- Acupuncture and exercise
- Reevaluate role of risk-reducing agent

→ Continue risk-reducing agent → Continue follow-up

Osteopenia/osteoporosis → Monitor bone density with periodic dual-energy x-ray absorptiometry (DEXA) scans (every 1–2 years depending on risk) while on AI[dd] → Continue follow-up

Hot flashes or other risk-reducing, agent-related symptoms (tamoxifen, raloxifene, exemestane, anastrozole) → Symptomatic treatment, if persist,
- Non-hormonal treatment
- Reevaluate role of risk-reducing agent

→ Continue risk-reducing agent → Continue follow-up

Abnormal vaginal bleeding (while on tamoxifen) → Prompt evaluation for endometrial cancer if uterus intact (pause tamoxifen during evaluation)
- → If endometrial pathology found, reinitiation of tamoxifen may be considered after hysterectomy if early-stage disease; for management, see NCCN Guidelines for Uterine Neoplasms → Continue follow-up
- → If no endometrial pathology (carcinoma or hyperplasia with atypia) found, continue tamoxifen and reevaluate if symptoms persist or recur → Continue follow-up

Vaginal symptoms (dryness, dyspareunia, and urinary symptoms) → Consider non-hormonal moisturizers as well as lubricants or low-dose topical vaginal estrogen[ee]
Referral to a gynecologist is recommended

Deep vein thrombosis, pulmonary embolism, cerebrovascular accident, or prolonged immobilization (tamoxifen and raloxifene) → Discontinue tamoxifen or raloxifene, treat underlying condition

[dd] Weight-bearing exercise and consideration of a bisphosphonate (oral/IV) or denosumab is acceptable to maintain or to improve bone mineral density and reduce risk of fractures in individuals receiving aromatase inhibitors. Individuals treated with a bisphosphonate or denosumab should undergo a dental examination with preventive dentistry prior to the initiation of an agent, and should take vitamin D and get adequate calcium. An FDA-approved biosimilar is an appropriate substitute for denosumab.

[ee] Consider avoiding bioidentical hormones or dehydroepiandrosterone (DHEA).

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COMPONENTS OF RISK/BENEFIT ASSESSMENT AND COUNSELING

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

- **Genetic testing**
  - **If an individual is at elevated risk for breast cancer due to a personal history of ovarian cancer, pancreatic cancer, or breast cancer, or if the individual has a strong family history of cancer, genetic counseling should be offered. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.**
- **Lifestyle factors for breast cancer risk reduction**
  - **Exercise[1]**
    - **Be active daily; avoid being sedentary. Take part in 150–300 minutes of moderate-intensity physical activity per week; exceeding the upper limit is optimal.**
  - **Weight control**
    - **In postmenopausal individuals, a BMI >25 can incrementally increase breast cancer risk.**
  - **Diet**
    - **Adopt a predominantly plant-based diet (vegetables, fruits, legumes, whole grains), favor healthy fats (monounsaturated, such as olive or avocado oils and omega-3 fats, such as found in fatty fish and flaxseed), and limit high fat foods, which are rich in saturated fats.**
    - **Avoid processed foods, especially meats, refined carbohydrates and sugary foods, and high-calorie low-nutrient foods; and limit red meat.**
  - **Any alcohol intake increases the risk for breast cancer and is best avoided. Patients who choose to drink alcohol should limit their consumption to no more than one drink equivalent in a day and no more than three drinks per week.**
- **Risk-reducing agents (see Discussion)**
  - **Discussion of relative and absolute risk reduction with tamoxifen, raloxifene, or aromatase inhibitors.[2]**
  - **Contraindications to tamoxifen or raloxifene: history of deep vein thrombosis, pulmonary embolus, thrombotic stroke, transient ischemic attack, or known inherited clotting trait.**
  - **Hormonal intrauterine devices (IUDs) are not contraindicated with tamoxifen. There are limited data on the risk reduction benefit of tamoxifen in those on oral contraceptives.**
  - **Contraindications to tamoxifen and raloxifene[2]: current pregnancy or pregnancy potential without effective non-hormonal method of contraception.**
  - **There are common and serious adverse effects of tamoxifen, raloxifene, or aromatase inhibitors[2] with emphasis on age-dependent risks.**
- **Risk-reducing surgery**
  - **Risk-reducing mastectomy should be discussed and can be considered as an option in individuals with a pathogenic/likely pathogenic germline variants in high-penetrance breast cancer susceptibility genes (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate), compelling family history, or those with history of chest wall radiation before 30 years of age. While risk reducing mastectomy has previously been considered for LCIS, the currently preferred approach for LCIS is close monitoring and therapy with a risk-reducing endocrine agent. Risk estimation is a complex and individualized process; the NCCN Panel does not recommend a specific risk cutoff for decision-making regarding risk-reducing mastectomy. Thus, individualizing management is highly encouraged.**
  - **Whether the decision is made to spare the nipple or not, the completeness of the mastectomy is critical for optimal risk reduction.**
- **General Considerations**
  - **Option of participation in clinical research for screening, risk assessment, or other risk-reducing intervention**
  - **The use of polygenic risk scores (PRS) as part of standard of care in breast cancer risk assessment is discouraged. Further validation is required to understand interaction of single nucleotide polymorphisms (SNPs) with environmental or hormonal risk factors and disease subtypes in diverse populations. Ongoing research will shed light on utility of PRS in comprehensive risk assessment models to guide personalized therapy.**
  - **Combined estrogen-progesterone menopausal hormonal therapy is associated with an increase in breast cancer risk. The risk varies based on age at initiation, duration of use, and the type of estrogen and progesterone formulation. A comprehensive breast cancer risk assessment should be performed prior to initiation of hormone therapy and its use in individuals with high-risk is discouraged.**

[1] American Cancer Society Guidelines.
[2] See BRISK-B for details and dosing.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

BREAST CANCER RISK-REDUCING AGENTS

Tamoxifen[a,b,c]	Raloxifene[a,b]	Aromatase Inhibitors (exemestane and anastrozole)
• Data regarding tamoxifen risk reduction are limited to pre- and postmenopausal individuals ≥35 years of age with a Gail Model 5-year breast cancer risk of ≥1.7% or a 10-year risk by IBIS/Tyrer-Cuzick[e] of ≥5% or a history of LCIS. • Tamoxifen: 20 mg per day for 5 years was shown to reduce risk of breast cancer by 49%. Among individuals with a history of AH, this dose and duration of tamoxifen were associated with an 86% reduction in breast cancer risk. Low-dose tamoxifen (5 mg per day or 10 mg every other day for 3–5 years)[d] is an option if patient is symptomatic on the 20-mg dose or if patient is unwilling or unable to take standard-dose 20 mg per day tamoxifen.[1] This low dosage needs further investigation in premenopausal individuals. • The efficacy of tamoxifen risk reduction in individuals who are carriers of germline *BRCA1/2* and other pathogenic variants is less well studied than in other risk groups. Limited data suggest there may be a benefit, likely a larger benefit, for *BRCA2* carriers. • For healthy, premenopausal individuals at elevated risk for breast cancer, data regarding the risk/benefit ratio for tamoxifen appear relatively favorable (category 1). • For postmenopausal individuals at elevated risk for breast cancer, 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.	• Data regarding raloxifene risk reduction are limited to postmenopausal individuals ≥35 years of age with a Gail Model 5-year breast cancer risk ≥1.7% or a 10-year risk by IBIS/Tyrer-Cuzick[e] of ≥5% 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 individuals with an intact uterus. • There are no data regarding the use of raloxifene in individuals who are carriers of germline *BRCA1/2* and other pathogenic variants or who have had prior thoracic radiation. • For postmenopausal individuals at elevated risk for breast cancer, 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 individuals is inappropriate unless part of a clinical trial.	• Data regarding exemestane are from a single large randomized study limited to postmenopausal individuals ≥35 years of age with a Gail Model 5-year breast cancer risk ≥1.7% or a 10-year risk by IBIS/Tyrer-Cuzick[e] of ≥5% or a history of LCIS. • Data regarding anastrozole are from a single large randomized study limited to postmenopausal individuals 40 to 70 years of age with the following risk compared with the general population: ‣ Aged 40 to 44 years - 4 times higher ‣ Aged 45 to 60 years - ≥2 times higher ‣ Aged 60 to 70 years - ≥1.5 times higher Individuals who did not meet these criteria but had a Tyrer-Cuzick[e] model 10-year breast cancer risk >5% were also included. • Exemestane: 25 mg per day was found to reduce the relative incidence of invasive breast cancer by 65% from 0.55% to 0.19% with a median follow-up of 3 years. • Anastrozole: 1 mg per day was found to reduce the relative incidence of breast cancer by 53% with a median follow-up of 5 years. • There are retrospective data that aromatase inhibitors can reduce the risk of contralateral breast cancer in *BRCA1/2* patients with ER-positive breast cancer who take aromatase inhibitors as adjuvant agents. • For postmenopausal individuals at elevated risk for breast cancer, data regarding the risk/benefit ratio for aromatase inhibitor agents are influenced by age and comorbid conditions such as osteoporosis (category 1). There are insufficient data on ethnicity and race. • Use of aromatase inhibitors for breast cancer risk reduction in premenopausal individuals is inappropriate unless part of a clinical trial. Footnotes and Reference on BRISK-B 2 of 2

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

FOOTNOTES AND REFERENCES

Footnotes

[a] There are no 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 >5 years, and it is not recommended. 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-reducing activity of the agent. Utility of tamoxifen or raloxifene for breast cancer risk reduction in individuals <35 years of age is unknown. Raloxifene is only for postmenopausal patients >35 years. 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 those with an intact uterus. Tamoxifen is a teratogen and is contraindicated during pregnancy or in individuals planning a pregnancy.

[b] When counseling postmenopausal patients regarding the risk/benefit of tamoxifen and raloxifene, refer to tables in Freedman AN, Binbing Y, Gail MH, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. J Clin Oncol 2011;29:2327-2333.

[c] Some selective 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. Based on current data, the Panel recommends against *CYP2D6* gene testing for patients being considered for tamoxifen therapy.

[d] 10 mg every other day since 5-mg dose is not available in the United States.

[e] For risk models that are largely dependent on family history (eg, Tyrer-Cuzick, BRCAPro, CanRisk/BOADICEA), see Comparison of Risk Assessment Models (BRISK-C).

Reference

[1] DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. J Clin Oncol 2019;37:1629-1637.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

COMPARISON OF RISK ASSESSMENT MODELS

BRCA Mutation Carrier Risk Models			
	Factors Included	Benefits	Limitations
BRCAPro[1]	• Bayesian model assuming autosomal-dominant inheritance, based on family history incorporating unaffected relatives compared with SEER data. *BRCA1/2* penetrance/prevalence data are based on a systematic review of the literature.	• Predicts individual and combined probabilities for carrying germline *BRCA1/2* pathogenic/likely pathogenic variants. • Incorporates ethnicity and mastectomy.	• Underestimates carrier frequency in families with ovarian cancer. • Underestimates carrier frequency in families with prostate cancer. • Performance characteristics in minority populations need further validation. • Does not allow incorporation of third-degree relatives. • Excludes limited or unknown information about family. • Ages must be estimated, if they are not known. • Does not consider any genes besides *BRCA1/2*. • Not freely available without registering.

[1] Parmigiani G, Berry D, Aguilar O, et al. Determining carrier probabilities for breast cancer-susceptibility genes *BRCA1* and *BRCA-2*. Am J Hum Genet 1998;62:145-158.

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

COMPARISON OF RISK ASSESSMENT MODELS

	Description	Factors Included	Benefits	Limitations
The Breast Cancer Surveillance Consortium (BCSC) Risk Calculator version 3.0	• Interactive tool designed to estimate 5-year risk of developing invasive breast cancer in those assigned female at birth (AFAB), including benign breast disease diagnoses and to estimate both 5-year and 10-year breast cancer risk. • May have limited applicability for extensive family history beyond first-degree relatives.	• Five- and 10-year breast cancer risk calculations are based on five factors: ▸ Age ▸ Race/ethnicity ▸ Family history of breast cancer in a first-degree relative (parent, sibling, or child) ▸ History of a breast biopsy (core biopsy, excisional biopsy, or fine-needle aspiration [FNA]) with benign breast disease diagnosis if known ▸ Breast Imaging Reporting and Data System (BI-RADS) breast density (radiologic assessment of the density of breast tissue by a radiologist who interprets mammograms)	• Accessible online	• The calculator is NOT applicable to individuals who meet any of the following criteria: ▸ Does not take into account beyond first-degree relatives ▸ <35 years or >74 years ▸ Previous diagnosis of the following: ◊ Breast cancer ◊ DCIS ◊ Breast augmentation ◊ Mastectomy

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

COMPARISON OF RISK ASSESSMENT MODELS

BRCA Mutation Carrier Risk Models			
	Factors Included	**Benefits**	**Limitations**
CanRisk Tool (BOADICEA v6)* (https://canrisk.org)	• Models the risks of breast and ovarian cancer based on family history and genotypes for germline variants in *BRCA1/2, PALB2, CHEK2, ATM, BARD1, RAD51C,* and *RAD51D.* • Incorporates the effects of common genetic variants (summarized as PRS), lifestyle, hormonal and clinical features, breast density, and disease pathology. Prospectively validated, both for the prediction of carrier probabilities and prediction of subsequent cancer risk.	• Accessible online. • Includes personal and lifestyle risk factors. • Includes family history of breast/non-breast cancers in immediate/distant relatives. • Provides risk estimates for breast and ovarian cancer. • Inclusive of patients with personal history of breast cancer (tumor pathology). • Can be used with susceptibility germline variants of high/moderate risk other than *BRCA1/2*. • Incorporates risk estimates from SNPs (PRS), if available.	• Routine use of PRS in risk assessment is not encouraged. • Non-white population • Does not take into account personal risk factors such as breastfeeding, prior breast biopsy, and atypia. • Does not include mantle radiation.

*The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

COMPARISON OF RISK ASSESSMENT MODELS[a]

	Description	Factors Included	Benefits	Limitations
Gail Model	• Individualized breast cancer risk assessment computed based on SEER-specific breast cancer risk data with inclusion of personalized risk factors • Provides both 5-year and lifetime risk assessment. Five-year risk assessment ≥1.67% used to assess eligibility for a risk-reducing agent.	• Age • Age at menarche • Age at first live birth • Family history of breast cancer in first-degree relatives AFAB • Number of previous breast biopsies • Diagnoses of AH	• Validated across multiple studies and cohorts • Accessible online • Available to assess eligibility for a risk-reducing agent • Periodic updates based on changes in breast cancer incidence data • Accounts for competing risks of mortality other than breast cancer	• Limited use in individuals of non-European (non-white) ethnicity. • Cannot be used for individuals <35 years. • Considers only a fraction of family history data: ‣ Only includes first-degree relative AFAB (paternal family history excluded). ‣ Does not include ages of diagnoses of relatives' breast cancers. ‣ Does not include family history of other cancer diagnoses outside breast cancer. ‣ Does not include mantle radiation. • Underestimates risk for development of breast cancer in: ‣ Those with germline variants in known breast cancer predisposition genes such as *BRCA1/2* ‣ Those with a strong family history of breast cancer ‣ Those with a family history of ovarian cancer in the maternal or paternal family linage ‣ Non-white individuals ‣ Those with AH

[a] The Claus Model is obsolete and therefore is not listed on this table.

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

COMPARISON OF RISK ASSESSMENT MODELS

	Description	Factors Included	Benefits	Limitations
International Breast Cancer Intervention Study [IBIS]/ Tyrer-Cuzick (version 8)[b]	• Computerized model based on initial data from the United Kingdom Thames Cancer Registry 2005–2009. • Attribution of risk based on family history data[2] • Provides personalized breast cancer risk assessment based on individual risk factors and family history information. • Both lifetime breast cancer risk (to age 85 in v7+) and 10-year risk estimations are available.	• Age • Reproductive history (ie, age at menarche, age at first live birth, age at menopause) • BMI • Exogenous hormone exposure (menopause hormone therapy) • Family history (comprehensive, see Benefits) • History of breast biopsies and results (including AH and LCIS) • Breast density • Genetic test results (*BRCA1/2* only)	• Can be used in individuals <35 years. • Accessible online. • Simultaneous computation of risk for *BRCA1/2* pathogenic mutation. • Comprehensive incorporation of family history and overall family structures. Includes: ‣ Affected first-, second-, and third- (first cousins) degree relatives ‣ Ovarian cancer diagnoses ‣ Breast cancer diagnosis in those assigned male at birth (AMAB) ‣ Unaffected relatives • Periodic updates based on breast cancer incidence data. • Accounts for competing risks of mortality other than breast cancer (have to select option). • Incorporates risk estimates from SNPs (PRS), if available.	• Does not consider risk from mantle radiation. • Overestimates risk for the development of breast cancer in: ‣ Hispanic individuals as this model was validated in primarily white individuals in the United Kingdom ‣ AH[3-5] ‣ LCIS[6] ‣ Dense breast • Routine clinical use of PRS in risk assessment is not encouraged.

[b] With permission IBIS Breast Cancer Risk Evaluation Tool. Developed by Cuzick J, Tyrer J, Brentnall A. Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6Bq, https://ems-trials.org/riskevaluator/.

[2] Anderson H, Bladström A, Olsson H, et al. Familial breast and ovarian cancer: a Swedish population-based register study. Am J of Epidemiol 2000;152:1154-1163.
[3] Boughey JC, Hartmann LC, Anderson SS, et al. Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) model for breast cancer risk prediction in women with atypical hyperplasia. J Clin Oncol 2010;28:3591-3596.
[4] Laitman Y, Simeonov M, Keinan-Boker L, et al. Breast cancer risk prediction accuracy in Jewish Israeli high-risk women using the BOADICEA and IBIS risk models. Genet Res 2013;95:174-177.
[5] Lo LL, Milne RL, Liao Y, et al. Validation of the IBIS breast cancer risk evaluator for women with lobular carcinoma in-situ. Br J Cancer 2018;119:36-39.
[6] Valero MG, Zabor EC, Park A, et al. The Tyrer-Cuzick model inaccurately predicts invasive breast cancer risk in women with LCIS. Ann Surg Oncol 2020;27:736-740.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

EVIDENCE BLOCKS FOR RISK REDUCTION AGENTS

	Postmenopausal	Premenopausal
Anastrozole 1 mg/d		—
Exemestane 25 mg/d		—
Raloxifene 60 mg/d		—
Tamoxifen 5 mg/d		
Tamoxifen 20 mg/d		

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

ABBREVIATIONS

AFAB	assigned female at birth
AH	atypical hyperplasia
AI	aromatase inhibitor
AMAB	assigned male at birth
BCSC	Breast Cancer Surveillance Consortium
BI-RADS	Breast Imaging Reporting and Data System
BMI	body mass index
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
DCIS	ductal carcinoma in situ
DEXA	dual-energy x-ray absorptiometry
FNA	fine-needle aspiration
FSH	follicle-stimulating hormone
IBIS	International Breast Cancer Intervention Study
IUD	intrauterine device
LCIS	lobular carcinoma in situ
NSABP BCPT	National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial
PRS	polygenic risk score
SEER	Surveillance, Epidemiology, and End Results
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
VUS	variant of uncertain significance

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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 indicated.

Discussion

This discussion has been updated to correspond with the newly updated algorithm. Last updated: 08/29/25

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NCCN Guidelines Version 1.2026
Breast Cancer Risk Reduction

Overview

Breast cancer is the most commonly diagnosed cancer in American females, with an estimated 316,950 cases of invasive breast cancer and an estimated death toll of 42,680 in 2025.[1] This highlights the need for effective breast cancer screening and risk-reducing strategies.

For an individual who does not have a personal history of breast cancer, the risk factors for the development of breast cancer can be grouped into categories, including familial/genetic factors; factors related to demographics; reproductive history; lifestyle factors; and other factors such as number of breast biopsies, especially those done with the intent to diagnose cancer (multiple biopsies [needle/excision] of the same lesion are scored as one biopsy); history of ductal or lobular atypical hyperplasia (AH) or lobular carcinoma in situ (LCIS); mammographic breast density; or prior thoracic irradiation between 10 to 30 years of age (eg, to treat Hodgkin lymphoma).

Estimating breast cancer risk for an individual is difficult, and most breast cancers are not attributable to risk factors other than female gender and increasing age. In the United States, 310,720 females are diagnosed with invasive breast cancer annually, compared with approximately 2790 cases that occur annually in males.[2]

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-reducing strategies such as the use of risk-reducing agents and risk-reducing surgery have been identified. Patients and their physicians considering interventions to reduce risk for breast cancer must balance the demonstrated benefits with the potential morbidities of the interventions.

Surgical risk-reducing strategies (eg, risk-reducing bilateral mastectomy) may have psychosocial and/or physical consequences and risk-reducing agents used for non-surgical risk reduction are associated with certain adverse effects.[3-5] To assist those who are at increased risk of developing breast cancer and their physicians in the application of individualized strategies to reduce breast cancer risk, NCCN has developed these guidelines for breast cancer risk reduction.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Clinical Practice Guidelines (NCCN Guidelines®) are available on the NCCN website (www.NCCN.org).

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines® for Breast Cancer Risk Reduction, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: Breast Cancer Risk Assessment; Breast Cancer Risk Reduction; and Breast Cancer Risk Reduction Therapies. The search results were narrowed by selecting studies in humans published in English. An updated search was carried out before the publication of this document. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

Search results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Clinical Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search citations over the past year was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and/or discussed by the Panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[6] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Elements of Risk and Risk Assessment

Susceptibility to breast cancer is multifactorial and many genetic variants and other factors such as reproductive, hormonal, and lifestyle are known to be associated with the risk of developing the disease. A personal history of breast cancer increases the risk of developing an invasive breast cancer in the contralateral breast.

Estimation of breast cancer risk for an individual who does not have a personal history of invasive breast cancer or ductal carcinoma in situ (DCIS) 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.

Familial Risk Assessment

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/fallopian tube or primary peritoneal cancer.[7,8]

Genetic predispositions conferring an elevated risk for breast cancer and the criteria for genetic evaluation of individuals with no personal history of invasive breast cancer or DCIS, are outlined in NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. A change in personal or family history should prompt re-calculation of risk. The current risk models may not accurately estimate breast cancer risk for new diagnosis of a pathogenic germline variant or AH. The Gail model underestimates risk for women with AH while the Tyrer-Cuzick model overestimates this risk.[9,10] Any variant of uncertain significance (VUS) must be reassessed to determine if these variants have been reclassified as pathogenic/likely pathogenic.

A strong family history of breast cancer or personal history of proliferative lesions such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and LCIS are associated with an increased risk of developing breast cancer.[11-13] Individuals with LCIS are at substantially increased risk for breast cancer. In a SEER database population-based study of 19,462 females diagnosed with LCIS between 1983 and 2014, the cumulative incidences of subsequent breast malignancy were 11.3% (95% CI, 10.7%–11.9%) and 19.8% (95% CI, 18.8%–20.9%) at 10 and 20 years, respectively.[14] At a median follow-up of 8.1 years (range, 0–30.9 years), primary breast cancer was diagnosed in 9.4% of the cohort.[14] Other factors to consider are number of breast biopsies performed with the intent to diagnose cancer.

Other Non-Familial/Genetic Elements of Risk

Elements That Increase Risk*:* For individuals not considered to be at risk for familial/hereditary breast cancer, an evaluation of other elements of risk that contribute to increased breast cancer risk is recommended. These include demographic factors such as female gender, age, and ethnicity/race. There is an increased incidence of *BRCA1/2* mutation reported in females of Ashkenazi Jewish decent.[15]

Reproductive history is another factor to consider. Risk factors linked to reproductive history include nulliparity,[16-18] prolonged interval between menarche and age at first live birth (eg, early menarche or late age at first live birth),[16-18] onset of menarche at a younger age, or onset of menopause at an older age.[19,20]

Individuals receiving early thoracic irradiation encompassing the chest/breast area between ages 10 to 30 (eg, to treat Hodgkin lymphoma) is a significant risk factor for the development of breast cancer. In the Late Effects Study Group trial, the overall risk for breast cancer associated with thoracic irradiation at a young age was found to be 56.7-fold (55.5-fold for female patients) greater than the risk for breast cancer in the general population.[21] In that study, the relative risk (RR) according to follow-up interval was: 0 at 5 to 9 years; 71.3 at 10 to 14 years; 90.8 at 15 to 19 years; 50.9 at 20 to 24 years; 41.2 at 25 to 29 years; and 24.5 at >29 years.[21] Results from a case-control study of females treated at a young age (≤30 years) for Hodgkin lymphoma with thoracic radiation indicated that the estimated cumulative absolute risk for breast cancer at 55 years of age was 29.0% (95% CI, 20.2%–40.1%) for an individual treated at 25 years of age with 40 Gy of radiation and no alkylating agents.[22] Those with a history of treatment with thoracic radiation for Hodgkin lymphoma are at high risk for breast cancer on the basis of radiation exposure alone.[21-26]

Change in breast density has been suggested as a risk factor for breast cancer.[27] Dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.[28-32] For example, a report of a large case-cohort study of females ≥35 years with no history of breast cancer who underwent mammographic screening, first at baseline and then at an average of 6 years later, suggested that longitudinal changes in breast density are associated with changes in breast cancer risk.[31]

Lifestyle factors such as increased body mass index (BMI), alcohol consumption, and current or prior exposure to combined estrogen and progesterone hormones play a role in increasing the risk for breast cancer.

Increased BMI and Physical Inactivity: BMI is an independent risk factor for breast cancer. Several studies have established the association between high BMI and adult weight gain and increased risk for breast cancer in postmenopausal individuals.[33-43] This increase in risk has been attributed to increase in circulating endogenous estrogen levels from fat tissue.[39-41] In addition, the association between BMI and risk for postmenopausal breast cancer is stronger for hormone-positive tumors.[35-38] A meta-analysis of >1000 epidemiologic studies looked at cancer risk

with excess body fat. Those with higher BMI experienced an increased risk of postmenopausal breast cancer (RR,1.1 per 5 BMI units; 95% CI, 1.1–1.2).[44]

Increased levels of physical activity have been associated with a decreased risk for breast cancer.[43,45-48] For example, the effect of exercise on breast cancer risk was evaluated in a population-based study of 90,509 individuals between the ages of 40 and 65 years.[48] An RR of 0.62 (95% CI, 0.49–0.78) was observed for those who reported >5 hours of vigorous exercise per week compared to those 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). Annual lifetime exercise activity levels exceeding the median activity level for active control patients were found to have a 20% lower risk for breast cancer when compared to those who were inactive (odds ratio [OR], 0.82; 95% CI, 0.71–0.93).[45] In addition, a prospective assessment evaluating the association of physical activity among 45,631 patients showed the greatest reduction in breast cancer risk for patients who reported walking/hiking for ≥10 hours per week (RR, 0.57; 95% CI, 0.34–0.95).[46] A study of 320 postmenopausal sedentary patients 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).[49] 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 for breast cancer.[50]

Results from the Nurses' Health Study evaluating the effect of weight change on the incidence of invasive breast cancer in 87,143 postmenopausal patients suggested that patients experiencing a weight gain of ≥25.0 kg since age 18 have an increased risk for breast cancer when compared with patients who have maintained their weight (RR, 1.45; 95% CI, 1.27–1.66).[41] Furthermore, those who had never used postmenopausal hormone therapy (HT) and lost ≥10.0 kg since menopause and kept the weight off had a significantly lower risk for breast cancer compared with those who had maintained their weight (RR, 0.43; 95% CI, 0.21–0.86). Interestingly, there is evidence that the risk for breast cancer is lower in premenopausal individuals who are affected by overweight compared with those who are not.[43]

Results from a case-control study of individuals with *BRCA1/2* mutations indicated that a weight loss of ≥10 pounds in those with the *BRCA1* mutation between the ages of 18 and 30 years was associated with a decreased risk of developing breast cancer between the ages of 30 and 40 years (OR, 0.35; 95% CI, 0.18–0.67).[51]

Hormone Therapy: HT, particularly estrogen alone and estrogen plus progestin, has been studied in relation to breast cancer risk.

The Women's Health Initiative (WHI) enrolled 161,809 postmenopausal patients 50 to 79 years of age into a set of clinical trials from 1993 through 1998. Two of these trials were randomized controlled studies involving the use of HT (estrogen with/without progestin, specifically conjugated equine estrogen [CEE] and medroxyprogesterone acetate [MPA]) in primary disease prevention: one was a trial involving 16,608 patients with intact uteri at baseline randomized to receive combined estrogen plus progestin (CEE + MPA) or placebo,[52] and the other a trial of 10,739 patients with prior hysterectomy randomized to receive CEE alone or placebo.[53] The former trial was terminated early due to evidence of breast cancer harm, along with a global index associated with overall harm.

With the use of combination estrogen-progestin (CEE + MPA), the risk of invasive breast cancer was increased at an average follow-up of 5.6 years

(HR, 1.2) compared with placebo.[54] Longer follow-up showed that there were more cases of invasive breast cancer in the combined HT compared with the placebo group (206 vs. 155 respectively; HR, 1.24; 95% CI, 1.01–1.53).[55]

An increased risk for breast cancer was not observed in those who had undergone hysterectomies and were receiving CEE alone.[53] In fact, the rate of breast cancer was lower in the group receiving CEE alone relative to the placebo group, although this difference was not considered to be statistically significant.[53] The lower incidence of breast cancer seen among patients randomized to estrogen alone during the intervention period became statistically significant with extended follow-up for a mean of 10.7 years.[56]

The use of combined CEE + MPA therapy was also associated with increased risk for cardiovascular disease (eg, stroke) and decreased risk for bone fractures.[52,53] However, a secondary analysis from the WHI randomized controlled trials showed a trend for more effective reduction in the risk for cardiovascular disease with initiation of HT closer to menopause compared with administration of HT to patients who experienced a greater time gap between menopause and the start of such therapy.[57]

With respect to mammographic densities, data from a subset of the WHI trial showed that mammographic density increased with combined CEE + MPA and with CEE alone. For combined therapy, breast density increased 4.9% in year 2 compared with a 0.8% decrease in the placebo group.[58] A significant increase in mammographic breast density was seen with the use of CEE alone as well compared with placebo; this effect was observed for at least a 2-year period (absolute difference 2.9% at 2 years).[59]

While results from WHI randomized controlled trials show a decrease in breast cancer risk and mortality with use of CEE alone, several prospective, observational studies have demonstrated a significant correlation of increased breast risk with prolonged use of estrogen only. These studies include the Black Women's Health Study where use of estrogen alone for a duration of ≥10 years was associated with a non-significant increase in risk for invasive breast cancer (RR = 1.41; 95% CI, 0.95–2.10)[60]; the Million Women Study of patients aged 50 to 64 years, which showed an association between current use of estrogen-only HT and increased risk for breast cancer (RR, 1.30; 95% CI, 1.21–1.40; $P < .0001$)[61]; and the Nurses' Health Study, which demonstrated a significantly increased breast cancer risk after long-term use (≥20 years) of estrogen alone (RR, 1.42; 95% CI, 1.13–1.77).[62] Results from a large French cohort control study show a significantly increased risk for breast cancer in patients receiving short-term (ie, ≤2 years) estrogen and progesterone shortly after menopause when compared with non-users.[63]

It has been noted that there are important differences in the populations enrolled in the WHI randomized clinical trials relative to those in the observational studies with respect to duration of exposure to HT and age at initiation of HT.[64] For example, many 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 for 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.[65] 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 patients receiving estrogen plus progestin may be related to HT effects on breast tissue and subsequent

interference with the ability of mammography to detect new breast cancer tumors.[64]

With respect to timing of initiation of HT, there are some data suggesting that initiation of HT (closer to the time of menopause) is associated with an increased breast cancer risk compared to starting therapy several years after menopause.[54,66,67] However, the risk associated with HT may vary depending on the duration of use and the specific type of HT (estrogen alone vs. estrogen plus progestin). The studies have evaluated time since menopause and not adjusted for the fact that those who start closer to menopause have longer durations of use; therefore, the increased risk may be due to duration rather than age at menopause. A recent pooled analysis of 459,476 female patients aged 16 to 54 years investigated the relationship between exogenous hormones and breast cancer. Over a median follow-up of 7.8 years, 2% of participants (n = 8455) were diagnosed with breast cancer before age 55. HT was reported by 15% of participants, with the most common regimens being estrogen plus progestin therapy (6%) and unopposed estrogen (5%).[68] No overall association was found between HT of any type and young-onset breast cancer (HR, 0.96; 95% CI, 0.88–1.04). However, the use of estrogen-only therapy was associated with a significantly lower risk (HR, 0.86; 95% CI, 0.75–0.98), corresponding to a 0.5% absolute risk reduction by age 55 (from 4.1% among non-hormone users to 3.5%).[68] In contrast, combined estrogen plus progestin therapy was associated with an elevated risk of young-onset breast cancer (HR, 1.10; 95% CI, 0.98–1.24), particularly with longer duration of use (>2 years; HR, 1.18; 95% CI, 1.01–1.38), especially among women with intact uteri and ovaries (HR, 1.15; 95% CI, 1.02–1.31).[68]

There are no data from randomized controlled trials regarding risk of breast cancer with the use of modern formulations (eg, transdermal estrogen and micronized progesterone) for menopause HT.

Alcohol Consumption: There is a large body of evidence showing that alcohol consumption is associated with a higher risk of breast cancer,[43,69-76] and, to a lesser extent, smoking[77,78] also contributes to the risk of developing breast cancer.

Studies have demonstrated that the intake of moderate amounts of alcohol (1–2 drinks per day) is associated with an increased risk for breast cancer.[43,71-73] A population-based study of 51,847 postmenopausal patients provided evidence to support an association between increased alcohol consumption and an increased likelihood of development of estrogen receptor (ER)-positive breast cancer.[75] A meta-analysis showed that for every 10-gram increase in alcohol consumed per day on average, risk of breast cancer increased 5% among premenopausal individuals and 9% among postmenopausal individuals.[79] A standard drink contains approximately 14 grams of alcohol.[80]

Smoking: The association of cigarette smoking to breast cancer is complicated, as 50% of individuals who smoke also consume alcohol, which is a known risk factor.[81] However, in individuals who smoke but do not consume alcohol, a higher breast cancer risk has been observed.[81]

Elements That Increase Risk : There are many elements that may reduce the risk of cancer. Breast feeding has been shown to have a protective effect in many studies.[82-86] An analysis of 47 epidemiologic studies (50,302 patients with invasive breast cancer and 96,973 controls) estimated that for every 12 months of breastfeeding, RR for breast cancer decreases by 4.3%.[83]

Exercise has been shown to reduce the risk of breast cancer, especially in postmenopausal individuals.[87-91] A review of epidemiologic studies estimated that risk of breast cancer was reduced among those who were most physically active compared with those who were least active (RR, 0.88; 95% CI, 0.85–0.90).[91]

Menopause before age 45 years and risk-reducing therapy have a protective effect. A large prospective study examined associations of hysterectomy with bilateral salpingo-oophorectomy (BSO) and simple hysterectomy in 66,802 postmenopausal patients from the Cancer Prevention Study-II Nutrition Cohort. The results showed that hysterectomy with BSO performed at any age (n = 1892), compared with no hysterectomy (n = 5586), is associated with a 10% reduction in all cancers (RR, 0.90; 95% CI, 0.85–0.96).[92]

Diet: 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.[41-43] Results from 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.[93,94]

In a prospective study of 993,466 patients observed for 11 to 20 years, no association between total fruit and vegetable intake and overall risk of breast cancer was identified.[95] However, there is some evidence of decreased breast cancer risk with a diet high in fruits and vegetables.[96-98] A case-control study showed that a diet rich in fruits and vegetables may be associated with a decreased risk for breast cancer, including among those who were less physically active throughout their lifetimes.[99]

Risk Prediction Models

Comprehensive risk models/calculators that incorporate all known factors of increased risk help improve the ability to identify those at increased risk for breast cancer. There are many breast cancer risk assessment models. Some models concentrate more on family history while some include personal variables such as history of breast biopsies, parity, and mammographically determined breast density. Most of these models have been primarily validated in white populations. Therefore, they do not accurately estimate breast cancer risk in non-white individuals.

Risk assessment tools or models for assessing breast cancer risk in individuals incorporating family history and personal risk factors include Carrier Estimation Algorithm (BOADICEA also called CanRisk),[100-102] International Breast Cancer Intervention Study (IBIS) or Tyrer-Cuzick model (https://ems-trials.org/riskevaluator), and BRCAPro.

The BOADICEA or CanRisk is an online tool that models the risks of breast and ovarian cancer based on family history, genotypes for breast and ovarian cancer susceptibility genes, risk estimates from polygenic risk scores (PRS), and mammographic density.[101]

The IBIS or Tyrer-Cuzick model uses family history risk due to a *BRCA* mutation, risk estimates from PRS including single nucleotide polymorphisms (SNPs), and epidemiologic variables including a personal history of AH or LCIS. Individuals with AH or a history of LCIS are also at increased risk for invasive breast cancer in both the affected and contralateral breast.[11-13,103,104] The absolute annual risk of developing breast cancer in those with AH is 1%, which is significantly higher than the general population and this risk of breast cancer increases with the number of foci of AH.[12] The limitation of the IBIS or Tyrer-Cuzick model is that it overestimates risk for individuals with AH[9] compared to other models such as the National Cancer Institute's Breast Cancer Risk Assessment Tool (BCRAT) or Gail model, Breast Cancer Surveillance Consortium (BSCS) Risk Calculator, and BRCAPro.[105]

Although the CanRisk and IBIS models use PRS to calculate risk, further validation is required to understand the interaction of SNPs with environmental or hormonal risk factors and disease subtypes in diverse populations. Ongoing research will shed light on the utility of PRS in comprehensive risk assessment models to guide personalized therapy.

The NCCN Breast Cancer Risk Reduction Panel does not encourage the routine clinical use of PRS in risk assessment.

The BRCAPro predicts individual and combined probabilities for carrying germline pathogenic or likely pathogenic variants in *BRCA1/2* genes.

Other calculators for individuals at average risk include the BCSC Risk Calculator (https://tools.bcsc-scc.ucdavis.edu/BC5yearRisk/#) and the BCRAT or Gail Model (https://bcrisktool.cancer.gov/calculator.html).

The BCSC Risk Calculator version 3.0 is an interactive tool designed to estimate 5- to 10-year risk of developing breast cancer using personal and family history of breast cancer, race, and other individual factors such as age, breast density, menopausal status, BMI, and age at first live birth.[106]

The BCRAT or Gail model 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.[107-110] Unlike the Tyrer-Cuzick model that overestimates the risk for women with AH, the BCRAT or Gail model underestimates their breast cancer risk.[10]

Page BRISK-C outlines the factors included in all the above-mentioned models as well as their benefits and limitations. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (available at www.NCCN.org) describe management strategies for individuals with pathogenic/likely pathogenic gene mutations conferring elevated risk for breast cancer. It is important to note that risk assessment models are limited by moderate predictive accuracy and may overestimate or underestimate breast cancer risk for certain individuals. While their use can help guide discussion in individuals at high risk with known family history of breast cancer, they may not always represent the best way to ascertain an individual's risk for breast cancer.

Risk-Reducing Strategies

If an individual has a known pathogenic/likely pathogenic gene mutation conferring elevated risk for breast cancer or an individual meets one or more of the criteria outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (available at www.NCCN.org), referral to a genetic counselor or other health professional with expertise and experience in cancer genetics is recommended.

Individuals with a life expectancy ≥10 years with no prior diagnosis/history of breast cancer and considered to be at increased risk for breast cancer based on validated risk assessment models or who had received prior RT between the ages of 10 and 30 years, should receive counseling and should undergo breast screening as detailed in the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at www.NCCN.org). The counseling should be 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).

If life expectancy is <10 years, there is probably minimal if any benefit to risk-reduction therapy or screening (see the NCCN Guidelines for Breast Cancer Screening and Diagnosis and the NCCN Guidelines for Breast Cancer, available at www.NCCN.org). Diagnosis of DCIS should be managed according to recommendations outlined in the NCCN Guidelines for Breast Cancer (available at www.NCCN.org).

Lifestyle Modifications

Patients should be encouraged to maintain a healthy lifestyle and to remain up-to-date with recommendations for screening and surveillance (see *Counseling Regarding Lifestyle Modifications*).

Risk-Reducing Surgery

Risk-reducing mastectomy (RRM) should generally be considered only in those with a pathogenic/likely pathogenic genetic variant in high-penetrance breast cancer susceptibility genes, compelling family history, or those who received chest wall radiation before 30 years of age. In the absence of a compelling family history, there is no established benefit of RRM in individuals with pathogenic/likely pathogenic variants in either moderate- or low-penetrance breast cancer susceptibility genes.[111] While this approach has been previously considered for LCIS, the currently preferred approach for LCIS is a risk-reducing endocrine agent. Risk estimation is a complex and individualized process; the NCCN Panel does not recommend a specific risk cutoff for decision-making regarding RRM. Individualizing management is important. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (available at www.NCCN.org) discuss the recommendations for risk-reducing surgery (mastectomy) in detail.

Risk-Reducing Agents

Risk-reducing agents (ie, tamoxifen, raloxifene, anastrozole, exemestane) are recommended for individuals ≥35 years of age only, with a Gail model 5-year breast cancer risk of ≥1.7% or a 10-year risk by IBIS/Tyrer-Cuzick of ≥5% or a history of LCIS.

Tamoxifen is the only agent indicated for premenopausal patients, whereas all four agents may be used in those who are postmenopausal.

Tamoxifen for Risk Reduction

The benefits of tamoxifen, a selective 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 breast cancer has shown a reduction in the incidence of contralateral second primary breast cancer.[112-115] The meta-analyses by Early Breast Cancer Trialists' Collaborative Group confirmed that the risk for contralateral primary breast cancer is substantially reduced (ie, a statistically significant annual recurrence rate ratio = 0.59) by 5 years of tamoxifen therapy for first breast cancers that are ER-positive or have an unknown ER status.[116]

The effectiveness of tamoxifen in the setting of breast cancer treatment gave rise to the NSABP-P1 study. It was a randomized clinical trial of healthy individuals aged ≥60 years, aged 35 to 59 years with a ≥1.7% cumulative 5-year risk for developing breast cancer, or with a history of LCIS.[117] Both premenopausal and postmenopausal patients 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 results of the NSABP-P1 study showed that treatment with tamoxifen decreased the short-term risk for breast cancer by 49% in healthy individuals aged ≥35 years who had an increased risk for the disease.[117] Risk-reduction benefits were demonstrated across all age groups, in premenopausal and postmenopausal patients. The difference in average annual rates for invasive breast cancer was 3.30 cases per 1000 patients (ie, 6.76 cases per 1000 patients in the placebo group and 3.43 cases per 1000 patients in the group taking tamoxifen). The absolute risk reduction was 21.4 cases per 1000 over 5 years.[117] In terms of numbers needed to treat, this corresponds to treatment of 47 individuals 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.[118] The reduction in invasive breast cancer risk in participants

with AH was particularly striking (RR, 0.14; 95% CI, 0.03–0.47) in the initial study analysis, and an RR 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 (RR, 0.81; 95% CI, 0.63–1.05). However, as was anticipated from the experience in studies of patients taking tamoxifen after a breast cancer diagnosis, major toxicities included hot flashes, invasive endometrial cancer in postmenopausal patients, and cataracts. A significant increase in the incidence of pulmonary embolism was also observed in those ≥50 years of age taking tamoxifen. The average annual rates of pulmonary embolism per 1000 patients were 1.00 versus 0.31 (RR, 3.19; 95% CI, 1.12–11.15).[117]

No differences were observed in overall rates of mortality by treatment group with a follow-up period of up to 7 years. The initial study analysis revealed that average annual mortality from all causes in the tamoxifen group was 2.17 per 1000 patients compared with 2.71 per 1000 patients treated with placebo, for an RR of 0.81 (95% CI, 0.56–1.16).[117] Annual mortality after 7 years of follow-up was 2.80 per 1000 patients compared with 3.08 per 1000 patients in the tamoxifen and placebo groups, respectively, for an RR of 1.10 (95% CI, 0.85–1.43).[118]

An evaluation of the subset of patients with a *BRCA1/2* mutation in the NASBP-P1 study revealed that breast cancer risk was reduced by 62% in study patients with a *BRCA2* mutation receiving tamoxifen relative to placebo (RR, 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.[119] These findings may be related to the greater likelihood of 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. Currently, there are no prospective studies evaluating the risk-reductive effect of tamoxifen in *BRCA* mutation carriers.

Three European studies comparing tamoxifen with placebo for breast cancer risk reduction have been reported. The Royal Marsden Hospital study was a pilot trial of tamoxifen versus placebo in individuals ages 30 to 70 years who were at increased breast cancer risk based largely on their family history.[120,121] Patients in the trial were allowed to continue or to initiate postmenopausal HT. With 2471 participants available for interim analysis, no difference in the frequency of breast cancer was observed between the two study groups. The toxicity experienced by the 2 groups did not show statistically significant differences.[121] An analysis of updated findings from the Royal Marsden Hospital study demonstrated a nonsignificant breast cancer risk-reduction benefit with tamoxifen use (ie, 62 cases of breast cancer in 1238 patients receiving tamoxifen vs. 75 cases of breast cancer in 1233 patients in the placebo arm).[120]

An analysis of blinded results from the Royal Marsden Hospital study 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; $P = .10$).[122] However, the incidence of ER-positive breast cancer was significantly lower in the tamoxifen arm versus placebo arm of the trial (HR, 0.61; 95% CI, 0.43–0.86; $P = .005$). Importantly, the difference between the two arms became significant only in the post-treatment period (ie, after 8 years of treatment).

The Italian Tamoxifen Prevention Study randomized 5408 patients ages 35 to 70 years without breast cancer, who had undergone a previous hysterectomy, to receive tamoxifen or placebo for 5 years.[123] Patients in the trial were allowed to receive HT. No significant difference in breast cancer occurrence in the overall study population was identified at median follow-up periods of 46, 81.2, and 109.2 months.[123-125] Thromboembolic events, predominantly superficial thrombophlebitis, were increased in those treated with tamoxifen. A subset of individuals in the Italian Tamoxifen Prevention Study who had used HT and were classified as at

increased breast cancer risk based on reproductive and hormonal characteristics were found to have a significantly reduced risk for breast cancer with tamoxifen therapy.[125,126] 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 HT, and different study populations (ie, populations at lower risk for breast cancer).[127]

The first IBIS (IBIS-I) randomized 7152 patients aged 35 to 70 years at increased risk for breast cancer to receive either tamoxifen or placebo for 5 years.[128] Tamoxifen provided a breast cancer (invasive breast cancer or DCIS) risk reduction of 32% (95% CI, 8–50; *P* = .013). Thromboembolic events increased with tamoxifen (OR, 2.5; 95% CI, 1.5–4.4; *P* = .001), and endometrial cancer showed a nonsignificant increase (*P* = .20). An excess of deaths from all causes was seen in the tamoxifen-treated arm (*P* = .028).

After a median follow-up of 8 years a significant reduction for all types of invasive breast cancer was reported (RR, 0.73 [95% CI, 0.58–0.91; *P* = .004]) with tamoxifen.[129] Although no difference in the risk for ER-negative–invasive tumors was observed between the 2 groups, those in the tamoxifen arm were found to have a 34% lower risk for ER-positive invasive breast cancer.[129] Slightly higher risk reduction with tamoxifen was observed for premenopausal patients. Importantly, the increased risk for 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.

The updated analysis after a median follow-up of 16 years confirmed that the preventive effect of tamoxifen continues with a significant reduction in the first 10 years (HR, 0.72; 95% CI, 0.59–0.88; *P* = .001), and a slightly greater reduction in subsequent years (HR, 0.69; 95% CI, 0.53–0.91; *P* = .009).[130] A similar pattern was observed after the long-term follow-up for reduction in occurrence of invasive ER-positive breast cancer; a significant reduction for tamoxifen was also recorded for DCIS, but only in the first 10 years of follow-up. Interestingly, more ER-negative breast cancers were reported in the tamoxifen group after 10 years of follow-up than in the placebo group (HR, 2.45; 95% CI, 0.77–7.82; *P* = .13).[130]

The use of tamoxifen as a breast cancer risk-reduction agent has also been evaluated in the STAR trial[131,132] (details on the Star trial are discussed in a later section below).

Tamoxifen administered for 5 years at 20 mg/day is effective in breast cancer treatment and prevention, but toxicity has limited its broad use. In a trial of 500 women with intraepithelial neoplasia, patients who were randomly assigned to 3 years of 5 mg/day tamoxifen had half the neoplastic events (DCIS or invasive cancer) compared to those who received placebo, at a median follow-up of 5 years (HR, 0.48; 95% CI, 0.26–0.92).[133] At longer follow-up of a median of 9.7 years, there were 25 neoplastic events with tamoxifen and 41 with placebo (HR, 0.58; 95% CI, 0.35–0.95). The subgroup with DCIS also experienced benefits with low-dose tamoxifen (HR, 0.50; 95% CI, 0.28–0.91).[134] A trend towards greater improvement in post-menopausal patients compared with premenopausal patients was observed; this, however, was not statistically significant.[135]

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-reducing agent has been evaluated in several clinical studies. In 2007, the U.S. Food and Drug Administration (FDA) expanded the indications for raloxifene to include risk reduction for invasive breast

cancer in postmenopausal patients with osteoporosis, and risk for invasive breast cancer in postmenopausal patients at high risk for invasive breast cancer.

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 patients with osteoporosis.[136] A total of 7705 postmenopausal patients 31 to 80 years of age were randomized to receive placebo, 60 mg/d of raloxifene, or 120 mg/d of raloxifene for 3 years. At study entry, participants were required to have osteoporosis (defined as a bone density at least 2.5 standard deviations below the mean for young patients) or a history of osteoporotic fracture. The study showed a reduction in the vertebral fracture risk and an increase in bone mineral density (BMD) in the femoral neck and spine for the patients 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 2576 patients receiving placebo and 13 cases in 5129 patients receiving raloxifene.[137] The RR of developing invasive breast cancer on raloxifene, compared with placebo, was 0.24 (95% CI, 0.13–0.44). Raloxifene markedly decreased the risk for ER-positive cancers (RR, 0.10; 95% CI, 0.04–0.24) but did not appear to influence the risk of developing an ER-negative cancer (RR, 0.88; 95% CI, 0.26–3.0). Although breast cancer incidence 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 patients enrolled and stratified into treatment arms in this study.[127] 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-P1 study.

Side effects associated with 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 patients receiving 60 mg/d raloxifene vs. 0.2% for patients receiving placebo) and pulmonary emboli (0.3% for patients receiving 120 mg/d raloxifene vs. 0.1% patients receiving for placebo) associated with raloxifene treatment. However, there was no increase in the risk for endometrial cancer associated with raloxifene.

The early findings related 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, the CORE trial was designed to assess the effect of 4 additional years of raloxifene on the incidence of invasive breast cancer in postmenopausal patients with osteoporosis. A secondary endpoint was the incidence of invasive ER-positive breast cancer.

In 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.[138] 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).[138]

The adverse events in the CORE trial were similar to those seen in the MORE trial. There was a nonsignificant increase in the risk for thromboembolism (RR, 2.17; 95% CI, 0.83–5.70) in the raloxifene group of the CORE trial compared to the placebo group. There was no statistically significant difference in endometrial events (bleeding, hyperplasia, and

cancer) between the raloxifene and placebo groups during the 4 years of the CORE trial or the 8 years of the MORE and CORE trials. During the 8 years of the MORE and CORE trials, raloxifene increased the risk for hot flashes and leg cramps compared with placebo; these risks were observed during the MORE trial but not during the additional 4 years of therapy in the CORE trial. While it is possible that hot flashes and leg cramps are early events that do not persist with continued therapy, it is also possible that an increased risk for these adverse events was not observed in the CORE trial as a result of selection bias (ie, patients 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 the CORE trial; 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.

In the Raloxifene Use for The Heart (RUTH) trial, postmenopausal patients with an increased risk for coronary heart disease were randomly assigned to raloxifene or placebo arms.[139,140] Invasive breast cancer incidence was another primary endpoint of the trial, although only approximately 40% of the study participants had an increased risk for breast cancer according to the Gail model. Median exposure to the study drug was 5.1 years and median duration of follow-up was 5.6 years.[140] 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). No reduction in the risk for 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.

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-reducing 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.[131]

In the STAR trial, 19,747 postmenopausal patients ≥35 years 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/d of tamoxifen or 60 mg/d of raloxifene were observed with respect to invasive breast cancer risk reduction (RR, 1.02; 95% CI, 0.82–1.28). Because there was no placebo arm, it was not possible to determine a raloxifene-versus-placebo RR for invasive breast cancer; however, tamoxifen was shown in the NSABP-P1 study to reduce breast cancer risk by nearly 50%. In addition, raloxifene was shown to be as effective as tamoxifen in reducing the risk for invasive cancer in the subset of patients with a history of LCIS or AH. However, raloxifene was not as effective as tamoxifen in reducing the risk for noninvasive breast cancer, although the observed difference was not statistically significant (RR, 1.40; 95% CI, 0.98–2.00).[117]

At a median follow-up of nearly 8 years (81 months) involving 19,490 patients, raloxifene was shown to be about 24% less effective than tamoxifen in reducing the risk for invasive breast cancer (RR, 1.24; 95% CI, 1.05–1.47), suggesting that tamoxifen has greater long-term benefit

with respect to lowering invasive breast cancer risk.[132] Raloxifene remained as effective as tamoxifen in reducing the risk for invasive cancer in patients with LCIS (RR, 1.13; 95% CI, 0.76–1.69), but was less effective than tamoxifen for those with a history of AH (RR, 1.48; 95% CI, 1.06–2.09). Interestingly, at long-term follow-up, the risk for noninvasive cancer in the raloxifene arm grew closer to that observed for the group receiving tamoxifen (RR, 1.22; 95% CI, 0.95–1.50). No significant differences in mortality were observed between the two 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 for endometrial cancer was significantly lower in the raloxifene arm (RR, 0.55; 95% CI, 0.36–0.83).

The lower incidences of thromboembolic events (RR, 0.75; 95% CI, 0.60–0.93) and cataract development (RR, 0.80; 95% CI, 0.72–0.89) 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.[132] 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.[141]

Optional Duration of SERM for Risk Reduction

The optimal duration of SERM therapy for breast cancer risk reduction is not known. The NSABP-P1 and STAR trials studied 5 years of risk-reducing therapy with either tamoxifen or raloxifene.[117,131] However, based on the updated STAR results, which showed that the benefits of raloxifene diminished after cessation of therapy,[132] continuing raloxifene beyond 5 years might be an approach to maintain the risk-reducing activity of the agent.

The use of tamoxifen for periods >5 years has been evaluated in the *adjuvant treatment* setting. Results of two randomized trials on extended adjuvant tamoxifen treatment[142,143] have demonstrated that tamoxifen for up to 10 years is more effective than shorter durations at preventing cancer *recurrence* and improving breast cancer survival. The option of 10 years of adjuvant tamoxifen therapy is recommended for both premenopausal and postmenopausal patients for preventing cancer recurrence in the NCCN Guidelines for Breast Cancer (available at www.NCCN.org) and the ASCO Guidelines.[144] There are limited data on tamoxifen use for >5 years in the risk-reducing setting. Until further information is available, a period of 5 years is appropriate for tamoxifen therapy when the agent is used to reduce breast cancer risk.

After completing 5 years of tamoxifen therapy, patients should continue to be monitored according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at www.NCCN.org) and should continue to undergo monitoring for late toxicity, especially for endometrial cancer and cataracts.

The prolonged effectiveness of tamoxifen as an agent to reduce breast cancer risk, particularly with respect to the development of ER-positive disease, is supported by results of several placebo-controlled, randomized trials at long-term follow-up.[118,122,129] The 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 5 years of tamoxifen therapy is significantly greater.[132]

Aromatase Inhibitors for Risk Reduction

A number of clinical trials have tested the use of aromatase inhibitors (AIs) in the adjuvant therapy of postmenopausal patients with invasive breast cancer to reduce risk of recurrence. The first of these studies, the ATAC trial, randomized postmenopausal patients with invasive breast cancer to anastrozole versus tamoxifen versus anastrozole plus tamoxifen in a double-blinded fashion.[145] The occurrence of contralateral second primary breast cancers was a study endpoint. At a median follow-up of 47 months, a non-significant reduction in contralateral breast cancers was observed in patients treated with anastrozole alone compared with tamoxifen (OR, 0.62; 95% CI, 0.38–1.02; *P* = .062), and a significant reduction in contralateral breast cancers was seen in the subset of patients with hormone receptor-positive first cancers (OR, 0.56; 95% CI, 0.32–0.98; *P* = .04).[146] Similar reductions in the risk for 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.[147,148]

In the Breast International Group (BIG) 1-98 trial postmenopausal patients 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 for breast cancer recurrence was lower in patients in the letrozole arm relative to the tamoxifen arm.[149]

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, multicenter, multinational trial in which 4560 patients were randomly assigned to either exemestane (2285 patients) or placebo (2275 patients).[4] The study authors reported that about 5% of patients 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 group 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% (HR, 0.35 with exemestane; 95% CI, 0.18– 0.70).[4] 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 patients in the MAP.3 trial taking exemestane and for those taking the placebo. However, follow-up was only 35 months. Patients 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%).[4]

Similarly, the IBIS-II trial evaluated the role of anastrozole for breast cancer prevention. The IBIS-II study included 3864 postmenopausal patients at high risk for breast cancer, defined by family history of breast cancer or prior diagnosis of DCIS, LCIS, or ADH[5] (HR, 0.47; 95% CI, 0.32–0.68). The advantage of anastrozole was greater prevention of high-grade tumors (HR, 0.35; 95% CI, 0.16–0.74) compared with intermediate- or low-grade tumors. The follow-up period in this trial was longer than that for the MAP.3 trial. The cumulative incidence after 7 years was predicted to rise 2.8% in the anastrozole group compared with 5.6% in the placebo group.[5] Musculoskeletal and vasomotor events were reported in both arms of the trial and were found to be significantly higher in the anastrazole arm (*P* = .0001); fracture rates were similar in both arms.[5]

There are retrospective data that AIs can reduce the risk of contralateral breast cancer in *BRCA1/2* patients with ER-positive breast cancer who take AIs as adjuvant therapy.[150]

NCCN Breast Cancer Risk Reduction Panel Recommendations for Risk-Reducing Agents

Tamoxifen Recommendations

The NCCN Breast Cancer Risk Reduction Panel recommends tamoxifen (20 mg/d) as an option to reduce breast cancer risk in healthy pre- and postmenopausal patients ≥35 years of age, whose life expectancy is ≥10 years, and who have a ≥1.7% 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1). The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for tamoxifen use in premenopausal patients at increased risk for breast cancer is relatively favorable (category 1), and that the risk/benefit ratio for tamoxifen use in postmenopausal patients is influenced by age, presence of uterus, or other comorbid conditions (category 1).[151] Only limited data are currently available regarding the efficacy of tamoxifen risk reduction in *BRCA1/2* mutation carriers and patients who have received prior thoracic radiation; there are no prospective studies evaluating the risk-reductive effect of tamoxifen in patients with *BRCA* mutations. However, available data from a very small cohort suggest a benefit for individuals with a *BRCA2* mutation but possibly not with a *BRCA1* mutation.[119]

Low-dose tamoxifen (5 mg per day or 10 mg every other day for 3–5 years, since 5 mg is unavailable in the United States) is an option if the patient is symptomatic on the 20-mg dose or if the patient is unwilling or unable to take standard-dose 20-mg/d tamoxifen. This low dosage needs further investigation in premenopausal individuals.

Tamoxifen is a teratogen and is contraindicated during pregnancy or in individuals planning a pregnancy. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of tamoxifen as a risk-reducing agent.

There is evidence that certain drugs (eg, selective serotonin reuptake inhibitors [SSRIs]) interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P450 2D6 (CYP2D6) enzyme involved in the metabolism of tamoxifen.[152] The consensus of the NCCN Breast Cancer Risk Reduction Panel is that alternative medications that have minimal or no impact on plasma levels of endoxifen should be substituted when possible.[152] Citalopram and venlafaxine do not disrupt tamoxifen metabolism.

It has also been reported that certain CYP2D6 genotypes are markers of poor tamoxifen metabolism.[153,154] 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-reducing agent for most postmenopausal patients desiring a risk-reducing agent. This is based on the updated STAR trial results that showed diminished benefits of raloxifene compared to tamoxifen after cessation of therapy.[132] However, consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in some patients.

If raloxifene is chosen, the NCCN Breast Cancer Risk Reduction Panel recommends use of 60 mg/d. Data regarding use of raloxifene to reduce breast cancer risk are limited to healthy postmenopausal patients ≥35 years of age who have a ≥1.7% 5-year risk for breast cancer as determined by the modified Gail model, or who have a history of LCIS. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for raloxifene use in those who are postmenopausal and at increased risk for breast cancer is influenced by age and comorbid conditions (category 1). Currently, there are no available data regarding

the efficacy of raloxifene risk reduction in *BRCA1/2* mutation carriers and patients who have received prior thoracic radiation. Use of raloxifene to reduce breast cancer risk in those who are premenopausal is not appropriate unless part of a clinical trial. The utility of raloxifene as a breast cancer risk-reducing agent in individuals <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-reducing agent.

Overall, risk-reducing therapy with tamoxifen and raloxifene has been vastly underutilized.[155] The benefits of risk-reducing therapy far outweigh harms for those with AH (both ductal and lobular types) and LCIS.[13,117] Those with AH and LCIS have a significantly higher risk of developing invasive breast cancer. The initial and follow-up results of the NSABP-P1 study (described in sections above) demonstrated a significant risk reduction with tamoxifen in those with AH.[117,118] Despite this, a study has documented that only 44% with AH or LCIS received risk-reducing therapy.[13] Considering the opportunity that exists for a significant impact of risk-reducing therapy on reducing the incidence of breast cancer, the NCCN Panel *strongly* recommends risk-reducing therapy in those with AH.

AI Recommendations (Anastrozole and Exemestane)
The NCCN experts serving on the Breast Cancer Risk Reduction Panel have included exemestane and anastrozole as choices for risk-reducing agents for most postmenopausal individuals desiring non-surgical risk-reducing therapy (category 1). This is based on the results of the MAP.3 trial[4] and the IBIS-II trial.[5] The NCCN Breast Cancer Risk Reduction Panel recommends use of 25 mg/d of exemestane or 1 mg/d of anastrozole. Data regarding use of AI (exemestane and anastrozole) to reduce breast cancer risk are limited to postmenopausal individuals ≥35 years of age 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 use of an AI in postmenopausal patients at increased risk for breast cancer is influenced by age, bone density, and comorbid conditions (category 1). Use of an AI to reduce breast cancer risk in premenopausal patients is inappropriate unless part of a clinical trial. The utility of an AI as a breast cancer risk-reducing agent in those <35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of AIs as a risk-reducing agent.

Exemestane and anastrazole are not currently FDA approved for breast cancer risk reduction. Currently, there are no data comparing the benefits and risks of AI to those of tamoxifen or raloxifene.

Monitoring Patients on Risk Reduction Agents and Symptom Management

Follow-up during and after treatment with risk-reducing agents for breast cancer risk reduction should focus on the early detection of breast cancer and the management of adverse symptoms or complications.

Screening for Breast Cancer

Appropriate screening for breast cancer and the evaluation of breast abnormalities should be performed according to the guidelines described for individuals at high-risk in the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at www.NCCN.org).

Endometrial Cancer

Routine age-appropriate gynecologic screening is recommended for individuals with an intact uterus on tamoxifen. If there is abnormal vaginal bleeding while on tamoxifen, the patient should be evaluated for endometrial cancer.

Results from the NSABP-P1 study indicate that patients ≥50 years of age treated with tamoxifen have an increased risk of developing invasive endometrial cancer. The risk of developing endometrial cancer in those ≥50 years while on tamoxifen compared to placebo was increased (RR,

4.01; 95% CI, 1.70–10.90).[117,118] An increased risk for endometrial cancer was *not* observed in patients ≤49 years of age treated with tamoxifen in this study (RR, 1.21; 95% CI, 0.41–3.60).[117,118] Although the only death from endometrial cancer in the NSABP-P1 study occurred in a placebo-treated patient,[117,118] 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.[156] 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.[157,158]

Updated results from the NSABP-P1 studies have indicated that incidence of both endometrial adenocarcinoma and uterine sarcoma is increased in those taking tamoxifen when compared to the placebo arm.[159] Several other studies have also supported an association between tamoxifen therapy and an increased risk of developing uterine sarcoma.[157,158,160,161] 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.[162] Nonetheless, the absolute risk of developing endometrial cancer is low (absolute annual risk per 1000: placebo 0.91 vs. tamoxifen 2.30). Often, for those at increased risk for breast cancer, the reduction in the number of breast cancer events exceeds that of the increase in the number of uterine cancer events.

Use of raloxifene has not been associated with an increased incidence of endometrial cancer in the MORE trial.[137] 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 (RR, 0.55; CI, 0.36–0.83).[132]

For those with an intact uterus, a baseline gynecologic assessment is recommended prior to administration of tamoxifen and follow-up gynecologic assessments should be performed at each visit.[163] Tamoxifen-associated endometrial cancer typically presents with vaginal spotting as an early symptom of cancer. Therefore, prompt evaluation of vaginal spotting in postmenopausal patients is essential.

At present, there is insufficient evidence to recommend the performance of uterine ultrasonography or endometrial biopsy for routine screening in asymptomatic individuals.[164-166] If endometrial cancer is diagnosed while taking a risk-reducing 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-reducing agent after completion of treatment as per the NCCN Guidelines for Uterine Neoplasms 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.[167,168] Furthermore, these reports have not been confirmed in the randomized controlled trials of tamoxifen. A 1.14 RR of cataract formation (95% CI, 1.01–1.29), compared with placebo, has been reported in the NSABP-P1 study, and individuals developing cataracts while on tamoxifen have an RR for cataract surgery of 1.57 (95% CI, 1.16–2.14), compared with placebo.[117] After 7 years of follow-up in the NSABP-P1 study, RRs of cataract formation and cataract surgery were similar to those initially reported.[118] In the MORE trial, raloxifene use was not associated with an increase in the incidence of cataracts compared with placebo (RR, 0.9; 95% CI, 0.8–1.1).[169] In the STAR trial, the incidence of cataract development and occurrence of cataract surgery were significantly higher in the group receiving tamoxifen compared with the group receiving raloxifene.[132,169] The rate of cataract development (RR,

0.80; 95% CI, 0.72–0.89) and the rate of cataract surgery (RR, 0.79; 95% CI, 0.70–0.90) were about 20% less in the raloxifene group than in the tamoxifen group.[132,169] 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.[121,170-172] In premenopausal patients, tamoxifen may oppose the more potent effects of estrogen on the bone and potentially increase the risk for osteoporosis, whereas tamoxifen in the presence of typically lower estrogen levels in postmenopausal patients is associated with an increase in BMD.[117,118] However, the NCCN Breast Cancer Risk Reduction Panel does not recommend monitoring BMD in premenopausal patients on tamoxifen, since development of osteopenia/osteoporosis in this population is considered unlikely. Raloxifene has been shown to increase BMD and to reduce incidence of vertebral bone fracture in postmenopausal patients when compared with placebo.[136,139] Results from the STAR trial did not reveal any difference in the incidence of bone fracture in the groups of postmenopausal patients on either raloxifene or tamoxifen.[131,132]

Changes in BMD are of concern while on AI therapy. Therefore, a baseline BMD scan is recommended for postmenopausal patients before initiating therapy with an AI such as anastrozole or exemestane. According to the NCCN Panel consensus, bone density should be monitored with periodic dual-energy x-ray absorptiometry (DEXA) scans (every 1–2 years depending on risk) while on AIs.

Weight-bearing exercise and consideration of bisphosphonate (oral/IV) or denosumab is acceptable to maintain or to improve BMD and reduce risk of fractures in individuals receiving AIs. Individuals treated with bisphosphonate or denosumab should undergo a dental examination with preventive dentistry prior to the initiation of an agent and should take vitamin D and get adequate calcium. An FDA-approved biosimilar is an appropriate substitute for denosumab.

Thromboembolic Disease and Strokes

Tamoxifen and raloxifene have been associated with an increased risk of thromboembolic events (ie, DVT, pulmonary embolism) and stroke.[117,118,131,132,137,173] Increased incidences of VTE were observed in the tamoxifen arms of all the placebo-controlled, randomized, risk-reducing trials. Although not statistically significant, all these trials except for the Royal Marsden trial (which enrolled only younger patients) also showed an increase in risk for stroke for those receiving tamoxifen. 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.[174,175] Comparison of the raloxifene and tamoxifen arms of the STAR trial did not show a difference with respect to incidence of stroke,[131,132] and the risk of fatal stroke was significantly higher for those in the RUTH trial with underlying heart disease who were receiving raloxifene.[140] However, evidence has shown that patients with a Factor V Leiden or prothrombin G20210A mutation receiving tamoxifen therapy in the NSABP-P1 study were not at increased risk of developing VTE compared to patients without these mutations.[176] Although prospective screening for Factor V Leiden or prothrombin mutations or intermittent screening for thromboembolic disease is unlikely to be of value, those 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 the risk of VTE, and they should be instructed to contact their physicians immediately if they develop symptoms of DVT or pulmonary emboli. Patients with documented thromboembolic disease should receive appropriate

treatment for the thromboembolic condition and should permanently discontinue tamoxifen or raloxifene therapy.

Hot Flashes

Hot flashes are a common menopausal complaint. In the NSABP-P1 study, hot flashes occurred in approximately 81% of patients treated with tamoxifen and 69% treated with placebo.[117] In the STAR trial, those receiving tamoxifen reported a significantly increased incidence of vasomotor symptoms relative to those receiving raloxifene,[141] although raloxifene use has also been associated with an increase in hot flash severity and/or frequency when compared with placebo.[137] If 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 while on a risk-reducing 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.[177-180] It has been hypothesized that the mode of action of gabapentin is via central temperature regulatory centers.[177,178] Results from a randomized, double-blind, placebo-controlled study involving the use of gabapentin to treat hot flashes in 420 patients with breast cancer have been reported. The three treatment arms of the trial were as follows: 300 mg/d gabapentin; 900 mg/d gabapentin; and placebo. Study duration was 8 weeks, and most patients in the study (68%–75% depending on treatment arm) were taking tamoxifen as adjuvant therapy. Patients 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 those 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 patients taking gabapentin.[180]

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, 70% of whom 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).[181] 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 participants 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 patients who were randomized into three 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.[182] Adverse events, reported by 54% of patients receiving placebo and 58% receiving paroxetine, generally included nausea, dizziness, and insomnia.

In a stratified, randomized, double-blind, cross-over, placebo-controlled study, 151 patients 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).[183] 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 in patients 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 reported side effects did not differ among the four arms, although nausea was significantly increased in patients 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 patients 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 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.[152,184] 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 have only minimal effects on tamoxifen metabolism.

Of interest in this context are the results of a retrospective trial, which suggest an inverse association between hot flashes and breast cancer recurrence in patients with a history of breast cancer receiving tamoxifen. These results suggest that hot flashes in patients receiving tamoxifen may be an indicator of the biologic availability and, thus, effectiveness of the drug. However, additional studies are needed to further elucidate whether hot flashes are predictive of benefit from tamoxifen.[185]

A report of two nonrandomized, parallel study cohorts of patients with DCIS or those at high risk for breast cancer (eg, those with LCIS, AH, or ≥1.7% 5-year breast cancer risk by the Gail model) comparing patients receiving tamoxifen alone with patients receiving tamoxifen concomitantly with HT (mean duration of HT at the start of the study was approximately 10 years) did not show a difference in the rate of tamoxifen-induced hot flashes.[186] The NCCN Breast Cancer Risk Reduction Panel recommends against the use of HT for patients taking tamoxifen or raloxifene outside of a clinical trial.

A variety of other substances for the control of hot flashes have been described.[187] Both the oral and transdermal formulations of clonidine reduce hot flashes in a dose-dependent manner.[188-190] Toxicities associated with clonidine include dry mouth, constipation, and drowsiness. Anecdotal evidence suggests that the use of a number of different herbal or food supplements may alleviate hot flashes. Vitamin E may decrease the frequency and severity of hot flashes, but results from a randomized clinical trial demonstrated that only a very modest improvement in hot flashes was associated with this agent compared with placebo.[191] 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.[192] 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.[193]

It should be noted that the observed placebo effect in the treatment of hot flashes is considerable, typically falling in the range of ≥25%,[177,179-183] suggesting that a considerable proportion of patients might be helped through a trial of therapy of limited duration. However, not all patients 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 patients receiving tamoxifen for early-stage breast cancer showed a decrease in hot flashes over time.[194]

Components of Risk/Benefit Assessment and Counseling

Patients should be screened and monitored according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at www.NCCN.org). Those with known pathogenic/likely pathogenic gene mutations conferring elevated risk for breast cancer or a significant family history of breast and/or ovarian cancer should also be followed according to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (available at www.NCCN.org). Appropriate candidates for breast cancer risk-reducing intervention should undergo counseling that provides a description of the available strategies, including a healthy lifestyle, to decrease breast cancer risk.[195] 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 SSRIs, previous use of a SERM); 2) absolute and relative breast cancer risk reduction achieved with the risk-reducing intervention; 3) risks of risk-reducing 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, pregnancy or pregnancy potential without an effective non-hormonal method of contraception); and 5) the common and serious side effects of tamoxifen and raloxifene.[196]

Counseling Prior to Therapy with Risk-Reducing Agents

Counseling sessions for those considering non-surgical breast cancer risk reduction should incorporate an explanation of all available data as appropriate.

Based on data from the BCPT[117] and STAR[131] trials, Freedman et al have developed tables of benefit/risk indices for patients aged ≥50 years to compare raloxifene versus no treatment (placebo) and tamoxifen versus no treatment.[3] The risks and benefit of treatment with either tamoxifen or raloxifene depend on age, race, breast cancer risk, and history of hysterectomy. There are separate tables in the report listing the level of 5-year invasive breast cancer risk by age group for non-Hispanic white patients with and without a uterus, Black patients with and without a uterus, and Hispanic patients with and without a uterus.

Counseling on Use of a SERM for Breast Cancer Risk Reduction

The NSABP-P1 study showed that the toxicity profile of tamoxifen is much more favorable in younger patients, and the benefits in RR reduction are similar across all age groups and risk groups.[117] The tamoxifen treatment risk/benefit ratio is especially favorable in patients between the ages of 35 and 50 years. Unfortunately, individualized data regarding the risk/benefit ratio for tamoxifen are not available except for the broad age categories of ages ≤50 years versus >50 years of age. Tamoxifen, unlike raloxifene, is a risk-reducing agent that can be used by premenopausal patients. In addition, tamoxifen may be more effective than raloxifene in reducing the incidence of noninvasive breast cancer, although the difference is not statistically significant at long-term follow-up.[131,132] Further, tamoxifen was reported by patients in the STAR trial to be associated with better sexual function than raloxifene.[141] However, tamoxifen has been associated with an increased incidence of invasive endometrial cancer relative to placebo in patients ≥50 years of age,[117,118] and an increased incidence of endometrial hyperplasia and invasive endometrial cancer relative to

raloxifene,[131,132] possibly making it a less attractive choice in those with a uterus. Use of raloxifene to reduce breast cancer risk may be preferred by postmenopausal patients with a uterus or those at risk for developing cataracts. All those receiving breast cancer risk-reducing agents 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 a history of VTE, thrombotic stroke, transient ischemic attack, current pregnancy, or pregnancy potential without effective method of contraception or known inherited clotting trait.

Counseling on Use of an AI for Breast Cancer Risk Reduction

Currently, there are no data comparing the benefits and risks of AIs (exemestane or anastrozole) to those of tamoxifen or raloxifene. Data regarding exemestane are from the single, large, randomized MAP.3 trial[4] limited to postmenopausal patients ≥35 years of age with a Gail model 5-year breast cancer risk of 1.7% or a history of LCIS, which may be used while counseling patients. The data show that AIs have a completely different toxicity profile than SERMs.

The optimal duration of AI therapy is currently unknown. Changes in BMD are of concern in patients receiving AI therapy. Therefore, a baseline BMD scan is recommended before initiating AI therapy. The role of calcium, vitamin D, and a healthy lifestyle in maintaining bone health must be emphasized in healthy postmenopausal patients who are receiving AI.

Counseling Prior to Risk Reduction Surgery

RRM should generally be discussed and can be considered as an option in individuals with a pathogenic/likely pathogenic germline variant in high-penetrance breast cancer susceptibility genes (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate), compelling family history, or history of chest wall radiation before 30 years of age. While RRM has been previously considered for LCIS, the currently preferred approach for LCIS is close monitoring with consideration of a risk-reducing endocrine agent. Risk estimation is a complex and individualized process; the NCCN Panel does not recommend a specific risk cutoff for decision-making regarding RRM. Thus, individualizing management is highly encouraged.

For those at very high risk for 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.[197-199] 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[200] to become well informed regarding treatment alternatives, the risks and benefits of surgery, nipple-sparing mastectomy, and surgical breast reconstruction options. Immediate breast reconstruction is an option following RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction.[201] Psychological consultations may also be considered.

Counseling Regarding Lifestyle Modifications

Options for risk reduction should be discussed in a shared decision-making environment. For breast cancer risk reduction, elements of this discussion include risk assessment including genetic testing, healthy lifestyles changes, use of risk-reducing agents, and risk-reducing surgery.

As discussed under *Other Non-Familial/Genetic Elements of Risk*, 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 for breast cancer. However, the association between lifestyle modification and a change in breast cancer risk is not as clear. Nevertheless, a discussion of lifestyle characteristics associated with increased risk for breast cancer also provides "a teachable moment" for the promotion of overall health, and an opportunity to encourage making choices and changes compatible with a healthy lifestyle.

Alcohol Consumption: The consensus of the NCCN Breast Cancer Risk Reduction Panel is that alcohol consumption increases the risk for breast cancer and is best avoided. Patients who choose to drink alcohol should limit consumption to no more than one drink equivalent in a day and no more than three drinks per week.

Exercise and BMI: There is substantial evidence discussed under *Elements of Risk and Risk Assessment* indicating that increased BMI and physical inactivity have a higher risk for postmenopausal breast cancer. Patients should be encouraged to exercise and stay active and should be counseled on maintaining a healthy body weight and BMI.[93,202-205]

Diet: Adopting a predominantly plant-based diet (vegetables, fruits, legumes, and whole grains) should be encouraged.[206,207] A general recommendation is that choice of food items should include healthy fats (monounsaturated, such as olive or avocado oils and omega-3-fatty acids, found in fatty fish and flaxseed), limited saturated fats, and avoidance of processed foods, especially processed meats, refined carbohydrates and sugars, and foods that have a high-calorie, low-nutrient content.[208]

Other Factors: Counseling should also involve discussion of other factors that may have a protective effect, if appropriate, such as planning first childbirth at a younger age and encouraging breastfeeding.

Breast Cancer Risks Associated with Combined Estrogen/Progesterone Agents: Combined estrogen-progesterone menopausal HT is associated with an increase in breast cancer risk (as discussed above in the section on elements of increased risk). The risk varies based on age at initiation, duration of use, and the type of estrogen and progesterone formulation. Comprehensive breast cancer risk assessment should be performed prior to initiation of HT, and its use in individuals at high risk who are >50 years of age is discouraged.

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

Summary

Breast cancer risk assessment provides a means of identifying healthy individuals without a history of personal breast cancer, who are at increased risk for future development of this disease. While many of the risk factors for breast cancer are not modifiable there are many modifiable risks. Everyone should be counseled regarding healthy lifestyle recommendations to decrease breast cancer risk and to avoid lifestyles that would adversely impact their chance of developing the disease.

The risks and benefits associated with use of risk-reducing surgery and agents should be evaluated and discussed as part of a shared decision-making process. The benefits of risk-reducing therapy significantly exceed the risk in those with AH or LCIS. Therefore, the NCCN Panel strongly recommends risk-reducing therapy in these individuals. Patients taking a risk-reducing agent must be closely monitored for potential side effects associated with use of these agents. In special circumstances, such as in carriers of a *BRCA*1/2 mutation, where the risk for breast cancer is very high, the performance of a risk-reducing surgery may be considered for breast cancer risk reduction. Those considering either surgery should undergo multidisciplinary consultations

prior to surgery to become well informed about all treatment alternatives, 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 patients and health care providers to participate in clinical trials to test new strategies for decreasing the risk of breast cancer. Only through the accumulated experience gained from prospective and well-designed clinical trials will advances in breast cancer risk reduction be realized.

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