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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer Risk Reduction

Version 1.2025 — August 28, 2024

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

See NCCN Categories of Evidence and Consensus.

Updates in Version 1.2025 of the NCCN Guidelines for Breast Cancer Risk Reduction from Version 2.2024 include:

BRISK-1
Familial Risk Assessment
Familial/genetic factors
- Bullet 1, modified: for list of *relevant* ~~pathogenic/likely pathogenic~~ gene mutations, see...
- Column 4, modified: Referral to genetic *counselor or* other health professional...

BRISK-2
Additional Familial Risk Assessment
- Column 1, bullet 3, modified: ~~Compelling~~ Personal history of atypical hyperplasia (AH)/lobular carcinoma in situ (LCIS) or a *strong* family history of breast cancer (Also for BRISK-7)
  - Bullet 4, modified: ~~Breast cancer risk~~ Elevated *risk of breast cancer* based on validated risk estimation models... (Also for BRISK-4)

Footnotes
- f, new: The routine use of polygenic risk scores (PRS) 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. (Also for BRISK-4, BRISK-A)
- i, modified: For risk models that are largely dependent on family history (eg, Tyrer-Cuzick, BRCAPro, *CanRisk/BOADICEA*)...(Also for BRISK-5, BRISK-7, BRISK-B 2 of 2)
- j, moved from BRISK-4: A change in family history, or a recent breast biopsy, would affect risk estimate and should prompt re-calculation of breast cancer risk. Consider periodic re-calculation of risk as individual ages.

BRISK-3
Elements of Risk
- Bullet 4, sub-bullet 3 modified, Current or prior *combined* estrogen and progesterone hormone agents
- Bullet 6, sub-bullet 4 modified, Prior thoracic radiation therapy (RT) ~~<30~~ *10–30* y of age (Also for BRISK-7)

Footnotes
- q, modified: 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 it's impact on breast cancer risk at this time.*

BRISK-4
***Non-Familial* Risk Assessment**
Added *Non-Familial* to the header to read Non-Familial Risk Assessment
- Column 1, row 2 modified: Prior thoracic RT *10*-30 y of age
  - Row 4 modified, If individuals have any of the assessed (*familial and non-familial*) risks but life expectancy <10 y
- Column 2, bottom pathway removed: and NCCN Guidelines for Breast Cancer Screening and Diagnosis

Footnotes
- j, removed: See BRISK-B for risk reduction agents and details on dosing.
- q, removed: A change in family history, or a recent breast biopsy, would affect risk estimate and should prompt re-calculation of breast cancer risk. Consider periodic re-calculation of risk as individual ages.

Updates in Version 1.2025 of the NCCN Guidelines for Breast Cancer Risk Reduction from Version 2.2024 include:

BRISK-6
- Headers modified:
  - ~~Candidate for~~ Risk-Reducing Agent
  - ~~Baseline Assessment~~ Surveillance

BRISK-A
Components of Risk/Benefit Assessment and Counseling
- Bullet 1, subbullet 1, modified: If an individual is at elevated risk for breast cancer due to a personal history of ovarian cancer, pancreatic cancer, or ~~early-onset~~ breast cancer

BRISK-B (1 of 2)
- Bullet 2, modified: Low-dose tamoxifen (5 mg per day *or 10 mg every other day* for 3–5 years) 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.

BRISK-C (1 of 5)
Comparison of Risk Assessment Models
Benefits
- Bullet 1, modified: Predicts individual and combined probabilities for *carrying germline pathogenic or likely pathogenic variants in BRCA1/2* genes
- Bullet 2, new: Incorporates ethnicity and mastectomy

Limitations
- Bullet 3, modified: ~~Statistics for~~ *Performance characteristics in* minority ~~patient~~ populations need *further validation* ~~improvement~~

BRISK-C (5 of 5)
Limitations
- Bullet 3, modified: Routine *clinical* use of PRS in risk assessment is not encouraged.

FAMILIAL RISK ASSESSMENT[a]

Familial/genetic factors

- **Known pathogenic/likely pathogenic gene mutations conferring elevated risk for breast cancer[b]; for list of relevant gene mutations, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic** → **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, and Pancreatic** → **Individual meets one or more of the familial/genetic risk criteria outlined in NCCN Guidelines for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic**
  - **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, and Pancreatic.
[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, and Pancreatic.
[e] If not tested, treatment should be based on family history and other risk factors listed on BRISK-3.

Note: 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, and Pancreatic.
[f] The routine use of polygenic risk scores (PRS) 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 family history, or a recent breast biopsy, would affect risk estimate and should prompt re-calculation of breast cancer risk. Consider periodic re-calculation of risk as individual ages.
[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 it's 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)**
- **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 routine use of PRS 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 (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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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**	**NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**
		Abnormal		**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 generally be considered in individuals with a pathogenic/likely pathogenic genetic variant in high-penetrance breast cancer susceptibility genes (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic), compelling family history, or those receiving chest wall radiation before 30 years of age. There is no established benefit of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic variants in moderate- or low-penetrance breast cancer susceptibility genes in the absence of a compelling family history. 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 risk-reducing mastectomy. Individualizing management is important.

Note: 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**

[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.

Note: 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[f,h,s]
  → **NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**
  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]**
  → **NCCN Guidelines for Breast Cancer Screening and Diagnosis**

[a] NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[f] In patients with at least one intact breast for whom risk-reducing therapy is recommended.
[g] Individual meets one or more of the familial risk criteria (BRISK-1).
[h] 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 (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.

Note: All recommendations are category 2A unless otherwise indicated.

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
  - 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 while on aromatase inhibitors[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, and Pancreatic.**

- **Healthy lifestyle for breast cancer risk reduction**
  - **Consider breast cancer risks associated with combined estrogen/ progesterone agents ≥3–5 year's duration of use.**
  - **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.**
  - **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.**

- **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.**
  - **Contraindications to tamoxifen[2]: current pregnancy or pregnancy potential without effective nonhormonal method of contraception.**
  - **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 nonhormonal 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 generally be considered in individuals with a pathogenic/likely pathogenic genetic variant in high-penetrance breast cancer susceptibility genes (see NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic), compelling family history, or those receiving chest wall radiation before 30 years of age. There is no established benefit of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic variants in moderate- or low-penetrance breast cancer susceptibility genes in the absence of a compelling family history. 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 risk-reducing mastectomy. Individualizing management is important.**
  - **Whether the decision is made to spare the nipple or not, the completeness of the mastectomy is critical for optimal risk reduction.**

- **Option of participation in clinical research for screening, risk assessment, or other risk-reducing intervention**
- **Routine use of polygenic risk scores (PRS) 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.**

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

Note: 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 *BRCA1/2* and other pathogenic mutations 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 *BRCA1/2* and other pathogenic mutations 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 references on BRISK-B 2 of 2

Note: 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).

References

[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: 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 pathogenic or likely pathogenic variants in *BRCA1/2* genes. • 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: 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: 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 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 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: 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 mutations 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: 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 (hormone replacement therapy [HRT] duration). • 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 Evalutation 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: All recommendations are category 2A unless otherwise indicated.

ABBREVIATIONS

AFAB	assigned female at birth
AH	atypical hyperplasia
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
HRT	hormone replacement therapy
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 scores
SEER	Surveillance, Epidemiology, and End Results
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor

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 is being updated to correspond with the newly updated algorithm. Last updated 04/23/18

Table of Contents

Overview

Breast cancer is the most commonly diagnosed cancer in American females, with an estimated 268,670 cases of invasive breast cancer and an estimated death toll of 41,400 in 2018.[1] This highlights the need for effective breast cancer screening and risk-reduction 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 finding flat epithelial atypia (FEA), atypical hyperplasia (AH), or lobular carcinoma in situ (LCIS), breast density, or thoracic irradiation before 30 years of age (eg, to treat Hodgkin's disease).

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.[2] In the United States, 266,120 females are diagnosed with invasive breast cancer annually, compared with approximately 2550 cases that occur annually in males.[1]

The development of effective strategies for the reduction of breast cancer incidence has also been difficult, because few of the existing risk factors are modifiable and some of the potentially modifiable risk factors have social implications extending beyond concerns for breast cancer (eg, age at first live birth). Nevertheless, effective breast cancer risk-reduction strategies such as use of risk-reduction agents and risk-reduction surgery have been identified. 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-reduction strategies (eg, risk-reduction bilateral mastectomy) may have psychosocial and/or physical consequences and risk-reduction 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.

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; 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 on the NCCN webpage.

Elements of Risk and Risk Assessment

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/Genetic Risk Factors

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.[6,7]

Genetic predispositions conferring a high risk for breast cancer include hereditary breast and ovarian cancer (*BRCA1/2*),[8,9] Li-Fraumeni syndrome (*TP53*),[10] Peutz-Jeghers syndrome (*STK11*),[11] Cowden syndrome (*PTEN*),[12,13] and hereditary diffuse gastric cancer (*CDH1*).[14]

If the individual has a known genetic predisposition for breast cancer such as mutations in *BRCA1/2, TP53, PTEN*, or other genes associated with breast cancer risk, that individual must be counseled about risk reduction options.

If the familial/genetic factors are not known, a thorough evaluation must be performed. The magnitude of the risk increases with the number of affected relatives in the family, the closeness of the relationship, and the age at which the affected relative was diagnosed.[15-17] The younger the age at diagnosis of the first- or second-degree relative, the more likely it is that a genetic component is present. The maternal *and* paternal sides of the family should be considered independently for familial patterns of cancer (see NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian).

Hereditary cancers are often characterized by gene mutations associated with a high probability of cancer development (ie, a high penetrance genotype), vertical transmission through either mother or father, and an association with other types of tumors.[18,19] They often have an early age of onset and exhibit an autosomal-dominant inheritance pattern (ie, they occur when the individual has a germline mutation in only one copy of a gene).

Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or age of onset consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.[20-23]

If an individual or a close family member of that individual meets one or more of the criteria listed in the NCCN Guidelines for Breast Cancer Risk Reduction under "Familial Risk Assessment" (and also NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian), that individual may be at increased risk for familial/hereditary breast cancer, and referral for formal genetic assessment/counseling is recommended.

A cancer genetics professional should be involved in determining whether the individual has a lifetime risk for breast cancer greater than 20% based on models dependent on family history (eg, Claus,[24] Tyrer-Cuzick,[25] others[26-28]). The Claus tables may be useful in providing breast cancer risk estimates for white females with no known cancer-associated gene mutation but who have one or two first- or second-degree female relatives with breast cancer[24] and ovarian cancer.[29]

BRCAPRO[30] and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)[31] are more commonly used to estimate the risk of a *BRCA* mutation. Strong genetic association between breast and ovarian cancer has been demonstrated in some families by linkage analyses. Based on a risk assessment using one or more of these models, those with a *BRCA1/2*, *TP53*, or *PTEN* gene mutation, or a pedigree strongly suggestive of genetic predisposition to breast cancer, may be identified. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian describe management strategies for individuals with a known or suspected *BRCA1/2, TP53, or PTEN* mutation or a pedigree strongly suggestive of genetic predisposition to breast cancer.

Other Elements of 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.[32]

Reproductive history is another factor to consider. Risk factors linked to reproductive history include nulliparity,[33-35] prolonged interval between menarche and age at first live birth (eg, early menarche or late age at first live birth),[33-35] onset of menarche at a younger age, or onset of menopause at older age.[36,37]

Body mass index (BMI) is an independent risk factor for breast cancer, especially in Caucasians. Several studies have established the association between high BMI and adult weight gain and increased risk for breast cancer in postmenopausal individuals.[38-48] This increase in risk has been attributed to increase in circulating endogenous estrogen levels from fat tissue.[44-46] In addition, the association between BMI and risk for postmenopausal breast cancer is stronger for hormone-positive tumors.[40-43] A meta-analysis of more than 1000 epidemiologic studies looked at cancer risk with excess body fat. Those with higher BMI experienced an increased risk of postmenopausal breast cancer (relative risk [RR] 1.1 per 5 BMI units, 95% CI 1.1–1.2).[49] Lifestyle factors such as current or prior hormone therapy (HT),[50-54] alcohol consumption,[48,55-62] and, to a lesser extent, smoking[63,64] also contribute to the risk of developing breast cancer.

The risk for breast cancer associated with FEA is similar to that of benign proliferative disease without atypia. The data are not as strong with respect to the degree of risk or the benefits of risk-reduction therapy in this population. Proliferative lesions with atypia include atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and LCIS. These lesions are associated with an increased risk of developing breast cancer.[65-67] Individuals with LCIS are at substantially increased risk for breast cancer. In a population-based study of 19,462 females diagnosed with LCIS from the SEER database between 1983 and 2014 in whom 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.[68] 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.[68] Other factors to consider are number of breast biopsies, done with the intent to diagnose cancer.

Individuals receiving early thoracic irradiation encompassing the chest/breast area before age 30 (eg, to treat Hodgkin's disease) 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.[69] In that study, the 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.[69] 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.[70] Those with a history of treatment with thoracic radiation for Hodgkin's disease are at high risk for breast cancer on the basis of radiation exposure alone.[69-74]

Change in breast density has been suggested as a risk factor for breast cancer.[75] Dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.[76-80] For example, a report of a large case-cohort study of females 35 years and older 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.[79]

There are many elements that may reduce the risk of cancer. Breast feeding has been shown to have a protective effect in many studies.[81-85] 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%.[82]

Exercise has also been shown to reduce the risk of breast cancer, especially in post-menopausal individuals.[86-90] A most recent 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).[90]

Oophorectomy before age 45 years and risk-reduction 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).[91]

Cancer Risk Assessment

The modified Gail model is a computer-based, multivariate, logistic regression model that uses age, race, age at menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous breast biopsies, and histology of the breast biopsies to produce actuarial estimates of future breast cancer risk.[92-95] The criteria used to determine risk by the modified Gail model are described in Table 1.

The Gail model was initially modified by the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators. It has subsequently been updated using combined data from the Contraceptive and Reproductive Experiences (CARE) study and the SEER database, as well as causes of death from the National Center for Health Statistics, to provide a more accurate determination of risk for those who are African American .[96] The model was also updated using data from the Asian American Breast Cancer Study (AABCS) and the SEER database to provide a more accurate risk assessment for Asian and Pacific Islander females in the United States.[97] Application of the Gail model to recent immigrants from Japan or China may overestimate the risk for breast cancer.[97] The most recent version of the Gail model is available on the National Cancer Institute website (http://www.cancer.gov/bcrisktool/Default.aspx).

Females ≥35 years of age should have their risk for breast cancer estimated according to the modified Gail model.[92,93,98] The Gail model is not an appropriate breast cancer risk assessment tool for those with a *BRCA1/2*, *TP53*, or *PTEN* mutation; a strong family history of breast cancer; who received thoracic radiation to treat Hodgkin disease (eg, mantle radiation); or those with LCIS.[99] While the Gail model can overestimate the risk for some and in others, notably those with AH, it can underestimate their risk making them appear to be ineligible for risk-reduction therapy. The Gail model does not apply to individuals with FEA.

The risk threshold required to consider the use of risk-reduction strategies must depend on an evaluation of the efficacy, morbidity, and expense of the proposed intervention. As a reasonable discriminating threshold, the NCCN Breast Cancer Risk Reduction Panel has adopted the 1.7% or greater 5-year actuarial breast cancer risk as defined by the modified Gail model, which was used to identify those eligible for the NSABP Breast Cancer Prevention Trial (BCPT)[100,101] and the Study of Tamoxifen and Raloxifene (STAR) trial.[102,103]

The Tyrer-Cuzick model, in addition to considering risk due to a *BRCA* mutation, also estimates her risk of developing breast cancer using family history, epidemiologic variables including a personal history of AH or LCIS. Individuals with AH or a history of LCIS are also at substantially increased risk for invasive breast cancer in both the affected and contralateral breast.[65-67,104,105]

In an analysis of the Mayo Clinic cohort of more than 300 patients with AH, the Gail model underestimated breast cancer risk in those with AH,[99] whereas the Tyrer-Cuzick model overestimated this risk.[106] Breast density is not included in any of the commonly used risk assessment models/tools.[27]

Individuals with life expectancy ≥10 years with no prior diagnosis/history of breast cancer and considered to be at increased risk for breast cancer based on any of the above-mentioned assessments, should receive counseling and should undergo breast screening as detailed in the NCCN Guidelines for Breast Cancer Screening and Diagnosis. 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) (see section below on *Components of Risk-Reduction Counseling*).

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

Diagnosis of DCIS should be managed according to recommendations outlined in the NCCN Guidelines for Breast Cancer.

Risk-Reduction Interventions

Lifestyle Modifications

Evidence from immigration studies indicates that in addition to family history and genetics, environmental factors play a significant role. As discussed under *Other Elements of Risk*, life style factors such as lack of exercise and alcohol consumption are linked with risk of developing breast cancer and are some of the modifiable components.

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-Reduction Surgery

Risk-reducing mastectomy (RRM) should generally be considered only in those with a genetic mutation conferring a high-risk for breast cancer.

Data have supported a protective effect of bilateral oophorectomy, although now there are conflicting reports that challenge that observation.[107] The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian discuss the recommendations for risk-reduction surgery (mastectomy and bilateral oophorectomy) in detail.

Risk-Reduction Agents

Risk-reduction agents (ie, tamoxifen, raloxifene, anastrozole, exemestane) are recommended for individuals ≥35 years of age only, as the utility of these agents in those younger than 35 years is unknown. Tamoxifen is the only agent indicated for premenopausal patients, whereas all 4 agents may be used in those who are postmenopausal.

Tamoxifen for Risk Reduction

The benefits of tamoxifen, a selective estrogen receptor (ER) modulator (SERM), in the treatment of breast cancer in the adjuvant and metastatic settings are well documented. Retrospective analysis of randomized, controlled, clinical trials comparing tamoxifen to no tamoxifen in the adjuvant treatment of breast cancer has shown a reduction in the incidence of contralateral second primary breast cancer.[108-111] 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.[112]

NSABP Breast Cancer Prevention Trial

The effectiveness of tamoxifen in the setting of breast cancer treatment gave rise to the NSABP BCPT study, also known as the P-1 study. It was a randomized clinical trial of healthy individuals aged 60 years or older, aged 35 to 59 years with a 1.7% or greater cumulative 5-year risk for developing breast cancer, or with a history of LCIS.[100] 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 trial was unblinded and initial findings were reported in 1998. A subsequent report on this trial has been published, which takes into account 7 years of follow-up data subsequent to the point where the study was unblinded. However, nearly one-third of the participants on placebo began taking a SERM when the study was unblinded, which decreased the proportion in the placebo group relative to the tamoxifen group, potentially confounding the long-term results.[101] The results of the P-1 study showed that treatment with tamoxifen decreased the short-term risk for breast cancer by 49% in healthy individuals aged 35 years or older who had an increased risk for the disease.[100] Risk-reduction benefits were demonstrated across all age groups, in pre-menopausal and post-menopausal 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.[100] 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.[101] 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).[100]

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 treated with placebo, for an RR of 0.81 (95% CI, 0.56–1.16).[100] Annual mortality after 7 years of follow-up was 2.80 per 1,000 compared with 3.08 per 1000 in the tamoxifen and placebo groups respectively, for an RR of 1.10 (95% CI, 0.85–1.43).[101]

An evaluation of the subset of patients with a *BRCA1/2* mutation in the P-1 study revealed that breast cancer risk was reduced by 62% in study patients with a *BRCA2* mutation receiving tamoxifen relative to placebo (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.[113] 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.

Based on the P-1study results, in October 1998 the FDA approved tamoxifen for breast cancer risk reduction for those at increased risk for breast cancer.

European Studies of Tamoxifen

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.[114,115] 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 2 study groups. Moreover, the toxicity experienced by the 2 groups did not show statistically significant differences.[115] 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).[114]

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).[116] However, the incidence of ER-positive breast cancer was significantly lower in the tamoxifen arm vs. placebo arm of the trial (HR, 0.61; 95% CI, 0.43–0.86; *P* = .005). Importantly, the difference between the 2 arms became significant only in the posttreatment period (ie, after 8 years of treatment).

The Italian Tamoxifen Prevention Study randomized 5408 patietnts ages 35 to 70 years without breast cancer, who had undergone a previous hysterectomy, to receive tamoxifen or placebo for 5 years.[117] 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.[117-119] 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.[119,120] 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).[121]

The first International Breast Cancer Intervention Study (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.[122] 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.[123] 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.[123] 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, 0.53–0.91; *P* = .009]).[124] 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 [0.77–7.82]; *P* = .13).[124]

The use of tamoxifen as a breast cancer risk-reduction agent has been evaluated in the STAR trial[102,103] (see *The STAR Trial* below).

Raloxifene for Risk Reduction

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

The MORE Trial

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was designed to determine whether 3 years of raloxifene treatment reduced the risk of fracture in postmenopausal patients with osteoporosis.[125] 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.[126] 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.[121] 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 P-1 study.

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

The CORE Trial

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. Data from the CORE trial were reported in 2004.[127]

During the CORE trial, the 4-year incidence of invasive breast cancer was reduced by 59% (HR, 0.41; 95% CI, 0.24–0.71) in the raloxifene group compared with the placebo group. Raloxifene, compared to placebo, reduced the incidence of invasive ER-positive breast cancer by 66% (HR, 0.34; 95% CI, 0.18–0.66) but had no effect on invasive ER-negative breast cancers.[127] 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).[127]

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.

The RUTH 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.[128,129] 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 study drug was 5.1 years and median duration of follow-up was 5.6 years.[129] 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.

The STAR Trial

Despite issues of trial design, the results from the CORE trial and the previous MORE study provided support for concluding that raloxifene may be an effective breast cancer risk-reduction agent. However, neither of these studies was designed to directly evaluate the efficacy of raloxifene versus tamoxifen in this regard. This issue was addressed in the NSABP STAR trial (P-2), which was initiated in 1999; initial results became available in 2006.[102]

In the STAR trial, 19,747 postmenopausal patients 35 years or older at increased risk for invasive breast cancer as determined by the modified Gail model or with a personal history of LCIS were enrolled into one of two treatment arms (no placebo arm). The primary study endpoint was invasive breast cancer; secondary endpoints included quality of life, and incidences of noninvasive breast cancer, DVT, pulmonary embolism, endometrial cancer, stroke, cataracts, and death. At an average follow-up of approximately 4 years, no statistically significant differences between patients receiving 20 mg/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 P-1 study to reduce breast cancer risk by nearly 50%. In addition, raloxifene was shown to be as effective as tamoxifen in reducing the risk 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).[100]

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.[103] 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 2 groups. In the initial analysis of the STAR trial data, invasive endometrial cancer occurred less frequently in the group receiving raloxifene compared with the tamoxifen group, although the difference did not reach statistical significance. It is important to note, however, that the incidence of endometrial hyperplasia and hysterectomy were significantly lower in the raloxifene group compared to the tamoxifen group. However, at long-term follow-up, the risk 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.[103] 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.[130]

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.[131] The occurrence of contralateral second primary breast cancers was a study endpoint. At 47 months median follow-up, a nonsignificant 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).[132] 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.[133,134]

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.[135]

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]

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]

There are retrospective data that AIs can reduce the risk of contralateral breast cancer in *BRCA-1/2* patients with ER-positive breast cancer who take AIs as adjuvant therapy.[136]

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

Based on data from the BCPT[100] and STAR[102] trials, Freedman et al have developed tables of benefit/risk indices for patients aged 50 years and older to compare raloxifene versus no treatment (placebo) and tamoxifen versus no treatment.[3] The risk and benefit of treatment with either tamoxifen or raloxifene depends on age, race, breast cancer risk, and history of hysterectomy. There are separate tables in the 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. The NCCN Breast Cancer Risk Reduction Panel recommends using these tables[3] while counseling postmenopausal patients regarding use of raloxifene and tamoxifen for breast cancer risk reduction. It should be noted that these tables do not consider the greater risk reduction achieved in patients with proliferative breast lesions such as AH.

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). Early studies suggest that lower doses of tamoxifen over shorter treatment periods may reduce breast cancer risk in postmenopausal patients, but these findings need to be validated in phase III clinical trials.[137] 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.[113]

The utility of tamoxifen as a breast cancer risk-reduction agent in individuals <35 years of age is not known. 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-reduction 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.[138] 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.[138] Citalopram and venlafaxine do not disrupt tamoxifen metabolism.

It has also been reported that certain CYP2D6 genotypes are markers of poor tamoxifen metabolism.[139,140] Nevertheless, the consensus of the NCCN Breast Cancer Risk Reduction Panel is that further validation of this biomarker is needed before it can be used to select patients for tamoxifen therapy.

Raloxifene Recommendations

The NCCN experts serving on the Breast Cancer Risk Reduction Panel feel strongly that tamoxifen is a superior choice of risk-reduction agent for most postmenopausal patients desiring non-surgical risk-reduction therapy. This is based on the updated STAR trial results that showed diminished benefits of raloxifene compared to tamoxifen after cessation of therapy.[103] 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 is limited to healthy postmenopausal patients ≥35 years who have a ≥1.7% 5-year risk for breast cancer as determined by the modified Gail model, or who have a history of LCIS. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for raloxifene use in those who are postmenopausal and at increased risk for breast cancer is influenced by age and comorbid conditions (category 1). There are no currently 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-reduction 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-reduction agent.

Overall, risk-reduction therapy with tamoxifen and raloxifene has been vastly underutilized.[141] The benefits of risk-reduction therapy far outweigh harms for those with AH (both ductal and lobular types) and LCIS.[67,100] Those with AH and LCIS have a significantly higher risk of developing invasive breast cancer. The initial and follow-up results of the P-1 study (described in sections above) demonstrated a significant risk reduction with tamoxifen in those with AH.[100,101] Despite this, a study has documented that only 44% with AH or LCIS received risk-reduction therapy.[67] Considering the opportunity that exists for a significant impact of risk-reduction therapy on reducing the incidence of breast cancer, the NCCN Panel *strongly* recommends risk-reduction 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 of risk-reduction agent for most postmenopausal individuals desiring non-surgical risk-reduction 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 or older with a Gail model 5-year risk score >1.66% or a history of LCIS. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for use of an AI in postmenopausal patients at increased risk for breast cancer is influenced by age, bone density, and comorbid conditions. 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-reduction 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-reduction 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

Follow-up after treatment with risk-reduction agents for breast cancer risk reduction should focus on the early detection of breast cancer and the management of adverse symptoms or complications. Appropriate monitoring for breast cancer and the evaluation of breast abnormalities should be performed according to the guidelines described for high-risk individuals in the NCCN Guidelines for Breast Cancer Screening and Diagnosis. The population eligible for risk-reduction therapy with tamoxifen, raloxifene, anastrozole, or exemestane is at sufficiently increased risk for breast cancer to warrant, at a minimum, yearly bilateral mammography with consideration for tomosynthesis, a clinical breast examination every 6 to 12 months, and encouragement of breast awareness. Supplemental screening with breast MRI may be indicated for certain individuals at increased risk of breast cancer (see NCCN Guidelines for Breast Cancer Screening and Diagnosis).

Endometrial Cancer

Results from the P-1 study indicated 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).[100,101] 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).[100,101] Although the only death from endometrial cancer in the P-1 study occurred in a placebo-treated subject,[100,101] 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.[142] 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.[143,144]

Updated results from the NSABP studies have indicated that incidence of both endometrial adenocarcinoma and uterine sarcoma is increased in those taking tamoxifen when compared to the placebo arm.[145] Several other studies have also supported an association between tamoxifen therapy and an increased risk of developing uterine sarcoma.[143,144,146,147] 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.[148] 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.[126] 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).[103]

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.[149] Tamoxifen-associated endometrial cancer typically present with vaginal spotting as an early symptom of cancer. Therefore, prompt evaluation of vaginal spotting in the 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.[150-152] If endometrial cancer is diagnosed while taking a risk-reduction agent, the drug should be discontinued until the endometrial cancer has been fully treated. The NCCN Breast Cancer Risk Reduction Panel believes that it is safe and reasonable to resume therapy with a risk-reduction agent after completion of treatment for early-stage endometrial cancer.

Retinopathy and Cataract Formation

There have been reports of tamoxifen being associated with the occurrence of retinopathy, although most of this information has come from case studies.[153,154] 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 P-1 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.[100] After 7 years of follow-up in the P-1 study, RRs of cataract formation and cataract surgery were similar to those initially reported.[101] 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).[155] 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.[103,155] 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.[103,155] 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.[115,156-158] 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.[100,101] 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.[125,128] 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.[102,103]

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.

Thromboembolic Disease and Strokes

Tamoxifen and raloxifene have been associated with an increased risk of thromboembolic events (ie, DVT, pulmonary embolism) and stroke.[100, 101-103,126,159] Increased incidences of VTE were observed in the tamoxifen arms of all the placebo-controlled, randomized, risk-reduction trials. Although not statistically significant, all of these trials with the exception of the Royal Marsden trial (which enrolled only younger 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.[160,161] Comparison of the raloxifene and tamoxifen arms of the STAR trial did not show a difference with respect to incidence of stroke,[102,103] and the risk of fatal stroke was significantly higher for those in the RUTH trial with underlying heart disease receiving raloxifene.[129] However, evidence has shown that patients with a Factor V Leiden or prothrombin G20210A mutation receiving tamoxifen therapy in the P-1 study were not at increased risk of developing VTE compared to patients without these mutations.[162] 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 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.

Managing Side Effects of Risk-Reduction Agents

Hot flashes are a common menopausal complaint. In the P-1 study, hot flashes occurred in approximately 81% of patients treated with tamoxifen and 69% treated with placebo.[100] In the STAR trial, those receiving tamoxifen reported a significantly increased incidence of vasomotor symptoms relative to those receiving raloxifene,[130] although raloxifene use has also been associated with an increase in hot flash severity and/or frequency when compared with placebo.[126] 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-reduction agent outside of a clinical trial.

Gabapentin, a gamma-aminobutyric acid (GABA) analog used primarily for seizure control and management of neuropathic pain, has been reported to moderate both the severity and duration of hot flashes.[163-166] It has been hypothesized that the mode of action of gabapentin is via central temperature regulatory centers.[163,164] 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.[166]

Venlafaxine, a serotonin and norepinephrine inhibitor anti-depressant, 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).[167] Participants receiving venlafaxine reported mouth dryness, reduced appetite, nausea, and constipation with increased prevalence at increased dosages. Based on these findings the authors suggested a starting dose of 37.5 mg with an increase, as necessary after one week, to 75 mg if a greater degree of symptom control is desired. However, this study followed subjects for only 4 weeks.

Another antidepressant, paroxetine, an SSRI, has also been studied for the relief of hot flash symptoms. A double-blind, placebo-controlled trial recruited 165 menopausal patients who were randomized into 3 arms (placebo, paroxetine 12.5 mg daily, or paroxetine 25 mg daily). After 6 weeks, significant reductions in composite hot flash scores were noted for both dosages of paroxetine (12.5 mg, 62% reduction and 25 mg, 65% reduction); there were no significant differences between dose levels.[168] Adverse events, reported by 54% of subjects receiving placebo and 58% receiving paroxetine, generally included nausea, dizziness, and insomnia.

In a stratified, randomized, double-blind, cross-over, placebo-controlled study, 151 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).[169] 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 commonly reported side effects did not differ among the 4 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.[138,170] These SSRIs may interfere with the enzymatic conversion of tamoxifen to its active metabolites by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. Caution is advised about co-administration of these drugs with tamoxifen. Citalopram and venlafaxine appear to have only minimal effects on tamoxifen metabolism.

Of interest in this context are results of a retrospective 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.[171]

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 start of study was approximately 10 years) did not show a difference in the rate of tamoxifen-induced hot flashes.[172] 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.[173] Both the oral and transdermal formulations of clonidine reduce hot flashes in a dose-dependent manner.[174-176] 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.[177] 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.[178] 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.[179]

It should be noted that the observed placebo effect in the treatment of hot flashes is considerable, typically falling in the range 25% or more,[163,165-169] 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.[180]

Weight-bearing exercise or use of a bisphosphonate (oral/IV) or denosumab is acceptable to maintain or to improve BMD and reduce risk of fractures in postmenopausal patients.

Components of Risk-Reduction Counseling

Patients should be monitored according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis. Those with known or suspected *BRCA1/2, TP53, PTEN*, or other gene mutations associated with breast cancer risk or those with 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 and Ovarian whether or not they choose to undergo risk-reduction therapy. Those with abnormal results from their clinical breast examination or bilateral mammogram or those with a history of LCIS should be treated according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis. Appropriate candidates for breast cancer risk-reduction intervention should undergo counseling that provides a description of the available strategies, including a healthy lifestyle, to decrease breast cancer risk.[181] 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-reduction intervention; 3) risks of risk-reduction therapy with an emphasis on age-dependent risks; 4) the contraindications to therapy with tamoxifen and raloxifene (eg, history of VTE, history of thrombotic stroke, history of transient ischemic attack, pregnancy or pregnancy potential without an effective nonhormonal method of contraception); and 5) the common and serious side effects of tamoxifen and raloxifene.

The 2009 ASCO Guidelines comparing the effectiveness of breast cancer risk-reduction agents provide some estimates of either the number needed to treat (NNT) to prevent breast cancer or the number needed to harm (NNH) by causing a specific side effect in a single patient receiving a specific risk-reduction agent.[182] Both NNT and NNH can be useful aids in communicating risks and benefits of tamoxifen and raloxifene in this setting (eg, using long-term data from the IBIS-1 trial, NNH with respect to VTE was determined to be 73 with tamoxifen, whereas this value was 150 for patients receiving raloxifene using data from the RUTH study).

Counseling Prior to Therapy with Risk-Reduction Agents

Counseling sessions for those considering non-surgical breast cancer risk reduction should incorporate an explanation of data from the P-1, STAR, MAP.3, and/or IBIS-II trial as appropriate.

Germline mutations in *PTEN* occur in 85% of patients with Cowden syndrome, an inherited condition associated with increased endometrial carcinoma risk. Therefore, increased risk for endometrial cancer in patients with *PTEN* mutations should be discussed while considering tamixifen.

Counseling on Use of a SERM for Breast Cancer Risk Reduction

The P-1 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.[100] 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 generally available except for the broad age categories of ages 50 years and younger versus older than 50 years of age. Tamoxifen, unlike raloxifene, is a risk-reduction agent that can be used by premenopausal 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.[102,103] Further, tamoxifen was reported by patients in the STAR trial to be associated with better sexual function than raloxifene.[130] However, tamoxifen has been associated with an increased incidence of invasive endometrial cancer relative to placebo in patients ≥50 years of age,[100,101] and an increased incidence of endometrial hyperplasia and invasive endometrial cancer relative to raloxifene,[102,103] 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 a breast cancer risk-reduction agent should be counseled with respect to signs and symptoms of possible side effects associated with use of these agents, and the recommended schedules for monitoring for the presence of certain adverse events. Contraindications to tamoxifen or raloxifene include history of VTE, thrombotic stroke, transient ischemic attack, current pregnancy or pregnancy potential without effective method of contraception, or known inherited clotting trait.

The optimal duration of SERM therapy for breast cancer risk reduction is not known. The P-1 and STAR trials studied 5 years of risk-reduction therapy with either tamoxifen or raloxifene.[100,102] However, based on the updated STAR results, which showed that the benefits of raloxifene diminished after cessation of therapy,[103] continuing raloxifene beyond 5 years might be an approach to maintain the risk-reduction activity of the agent.

The use of tamoxifen for periods longer than 5 years has been evaluated in the *adjuvant treatment* setting. Results of two randomized trials on extended adjuvant tamoxifen treatment[183,184] 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 now recommended for both premenopausal and postmenopausal patients for preventing cancer recurrence in the NCCN Guidelines for Breast Cancer and the ASCO Guidelines.[185] There are limited data on tamoxifen use for more than 5 years in the risk-reduction setting. Until further information is available, a period of 5 years appears to be 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 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.[101,116,123] 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.[103]

The NCCN Breast Cancer Risk Reduction Panel recommends using the tables from the Freedman et al publication[3] while counseling postmenopausal patients regarding use of raloxifene and tamoxifen for breast cancer risk reduction.

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 or older 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 exemestane has a completely different toxicity profile than the SERMs. Compared to the placebo group in the MAP.3 trial, exemestane had no increased risk of serious side effects. The incidence of osteoporosis, cardiac events, and bone fractures were identical for 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]

Data regarding anastrozole are from a single, large, randomized trial, IBIS-II.[5] The trial included postmenopausal patients 40 to 70 years of age with a higher risk of developing cancer compared with the general population. Patients who did not meet these criteria but had a Tyrer-Cuzick model 10-year breast cancer risk >5% were also included.[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] 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 exemestane 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 exemestane.

Counseling Prior to Risk Reduction Surgery

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.[186-188] 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[189] 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.[190] Psychological consultations may also be considered.

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

It has been reported that short-term HT in individuals undergoing RRSO did not negate the reduction in breast cancer risk associated with the surgery.[191] In addition, results of a case-control study of *BRCA1* mutation carriers showed no association between use of HT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers.[191] However, the consensus of the NCCN Breast Cancer Risk Reduction Panel is that caution should be used when considering HT use in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies (see also section below on *Breast Cancer Risks Associated with Hormone Therapy*).[192,193] It is unlikely that a prospective randomized study on the use of RRSO for breast cancer risk reduction will be performed. Whether the resulting reduction in the risk for breast cancer from this procedure is preferable to an RRM is likely to remain a personal decision.[194] Table 2 provides estimates based on a Monte Carlo simulation model of the survival impact of breast and ovarian risk-reduction strategies. These data can be used as a tool to facilitate shared decision-making regarding choice of a risk-reduction approach, particularly with respect to issues related to risk-reduction surgery (see Table 2).

Counseling Regarding Lifestyle Modifications

There is evidence to indicate that certain lifestyle characteristics, such as obesity, increased alcohol consumption, and use of certain types of HT, are factors or markers for an elevated risk for breast cancer. However, the association between a lifestyle modification and a change in breast cancer risk is not as clear. Nevertheless, a discussion of lifestyle characteristics associated with increased risk 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.

Breast Cancer Risks Associated with Hormone Therapy

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) in primary disease prevention: a trial involving 16,608 patients with intact uteri at baseline randomized to receive estrogen plus progestin or placebo,[195] and a trial of 10,739 patients with prior hysterectomy randomized to receive estrogen alone or placebo.[196] The former trial was terminated early due to evidence of breast cancer harm, along with a global index associated with overall harm. In that study, a 26% increased incidence of breast cancer was observed in the treatment group (HR, 1.26; 95% CI, 1.00–1.59). An increased incidence of abnormal mammograms was also observed in those who received estrogen plus progestin, and was attributed to an increase in breast density.[197] Of greater concern is that HT was associated with a significant increase in rates of both breast cancer incidence and breast cancer-related mortality,[198] although the increased risk for breast cancer rapidly declined following cessation of HT.[199]

An increased risk for breast cancer was not observed in those who had undergone hysterectomies and were receiving unopposed estrogen.[196] In fact, the rate of breast cancer was lower in the group receiving estrogen relative to the placebo group, although this difference was not considered to be statistically significant.[196] 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.[200] However, an increased incidence of abnormal mammograms was observed in the group receiving estrogen,[201] as well as a doubling of the risk for benign proliferative breast disease.[202] Analysis of the data from this randomized controlled WHI trial showed use of estrogen alone to significantly increase mammographic breast density compared with placebo; this effect was observed for at least a 2-year period.[203] Contrary to the results from the WHI randomized controlled trials, results from several prospective, population-based, observational studies have shown use of estrogen-only HT to be associated with increased risks for breast cancer. These studies include the Black Women's Health Study where use of estrogen alone for a duration of 10 years or longer was associated with a nonsignificant increase in risk for invasive breast cancer (RR = 1.41; 95% CI, 0.95–2.10);[204] the Million Women Study of patients 50 to 64 years of age, 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; $P < .0001$);[205] and the Nurses' Health Study, which demonstrated a significantly increased breast cancer risk after long-term use (20 years or longer) of estrogen alone (RR, 1.42; 95% CI, 1.13–1.77).[206]

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.[207] 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 put forward to explain the apparent contradictions in the summary of studies of HT described above is that short-term use of estrogen following a period of estrogen deprivation may decrease breast cancer risk by inducing apoptosis of occult breast cancer tumors, whereas long-term use of estrogen may initiate and promote the growth of new tumors, thereby increasing breast cancer risk.[208] 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.[207]

The use of estrogen/progestin therapy and estrogen therapy alone has also been associated with increased risk for cardiovascular disease (eg, stroke) and decreased risk for bone fractures.[195,196] 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.[209] Nevertheless, results from a large French cohort control study show a significantly increased risk for breast cancer in patients receiving short-term (ie, 2 years or less) estrogen and progesterone shortly after menopause when compared with nonusers.[210]

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

Alcohol Consumption

Numerous 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.[48,57-59] A 10% increase in breast cancer risk for every 10 grams of alcohol consumed each day was seen in analyses of 2 cohort studies.[56,60] 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 ER-positive breast cancer.[61] A meta-analysis of epidemiologic studies shows a small but significant association between breast cancer and light alcohol intake (RR, 1.05; 95% CI, 1.02–1.08).[62] Even one drink per day modestly elevates breast cancer risk.[48] However, the effect of a reduction in alcohol consumption on the incidence of breast cancer has not been well studied.

The consensus of the NCCN Breast Cancer Risk Reduction Panel is that alcohol consumption should be limited to ≤1 drink per day. The panel has defined one drink as 1 ounce of liquor, 6 ounces of wine, or 8 ounces of beer.

Exercise and BMI

Increased levels of physical activity have been associated with a decreased risk for breast cancer.[48,211-214] 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.[214] An RR of 0.62 (95% CI, 0.49–0.78) was observed for those who reported more than 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 subjects were found to have a 20% lower risk for breast cancer when compared to those who were inactive (OR, 0.82; 95% CI, 0.71–0.93).[211] 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).[212] 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).[215] 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.[216]

As discussed under the section on *Elements of Risk*, here is a substantial amount of evidence indicating that overweight or obese patients have a higher risk for postmenopausal breast cancer.

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 or more 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).[46] Furthermore, those who had never used postmenopausal HT and lost 10.0 kg or more since menopause and kept the weight off had a significantly lower risk 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 overweight compared with those who are not overweight.[48]

Results from a case-control study of individuals with *BRCA1/2* mutations indicated that a weight loss of 10 or more pounds in those with the *BRCA1* mutation between the ages of 18 and 30 was associated with a decreased risk of developing breast cancer between the ages of 30 and 40 years. (OR, 0.35; 95% CI, 0.18–0.67).[217]

Patients should be encouraged to exercise and stay active, and should be counseled on maintaining a healthy body weight and BMI.

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.[46-48] 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.[218,219]

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.[220] However, there is some evidence of decreased breast cancer risk with a diet high in fruits and vegetables.[221-223] 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.[224]

Epidemiologic studies suggest that vitamin D (from dietary sources and the sun) may play a protective role with respect to decreasing risk for breast cancer development.[218,225,226] Furthermore, there is some evidence to suggest that such protection is greatest for those who had more prolonged skin exposure to sunlight and higher dietary intake of sources of vitamin D during adolescence.[227,228] Studies are in progress to evaluate the role of vitamin D on breast cancer risk.

Other Lifestyle Changes

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.

Clinical Trials

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

Summary

Breast cancer risk assessment provides a means of identifying healthy individuals without a history of personal breast cancer, who are at increased risk for future development of this disease. 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. However, many of the risk factors for breast cancer are not modifiable. The demonstration that tamoxifen, raloxifene, anastrozole, or exemestane substantially decreases the future risk for breast cancer provides an opportunity for a risk-reduction intervention.

The risks and benefits associated with use of risk-reduction agents should be evaluated and discussed as part of a shared decision-making process. The benefits of risk-reduction therapy significantly exceed the harms in those with AH or LCIS. Therefore, the NCCN Panel strongly recommends risk-reduction therapy in these individuals. Patients taking a risk-reduction agent must be closely monitored for potential side effects associated with use of these agents. In special circumstances, such as in carriers of a BRCA1/2 mutation, where the risk for breast cancer is very high, the performance of a bilateral mastectomy or BSO may be considered for breast cancer risk reduction. Those considering either surgery should undergo multidisciplinary consultations prior to surgery so as to become well informed about all treatment alternatives, the risks and benefits of risk-reduction surgery, and, in the case of bilateral mastectomy, the various reconstruction options available. The NCCN Guidelines for Breast Cancer Risk Reduction Panel strongly encourages patients and health care providers to participate in clinical trials to test new strategies for decreasing the risk for breast cancer. Only through the accumulated experience gained from prospective and well-designed clinical trials will additional advances in breast cancer risk reduction be realized.

Table 1

Criteria Used in Calculation of 5-year Risk for Breast Cancer According to the Modified Gail Model
(Available at www.breastcancerprevention.org)

Question	Response
Age	____
Age at menarche (first menstrual period)	____
Age at first live birth or nulliparity	____
Number of breast biopsies	____
Atypical hyperplasia	Y / N
Number of first-degree relatives with breast cancer	____
Race/Ethnicity	Caucasian, African American, Hispanic, Other

Table 2

Survival Probability According to Breast/Ovarian Cancer Risk-Reduction Strategy at Age 70* for 25-Year-Old *BRCA1/2* Mutation Carrier

Variable	Survival Probability (%) in *BRCA1* Mutation Carriers	Survival Probability (%) in *BRCA2* Mutation Carriers
No intervention	53% [BCD=41%;OCD=36%]	71% [BCD=36%;OCD=20%]
RRSO only at age 40	68% [BCD=45%;OCD=12%]	77% [BCD=30%;OCD=4%]
RRSO only at age 50	61% [BCD=51%;OCD=20%]	75% [BCD=42%;OCD=6%]
RRM only at age 25	66% [BCD=5%;OCD=58%]	79% [BCD=4%;OCD=30%]
RRM only at age 40	64% [BCD=13%;OCD=53%]	78% [BCD=9%;OCD=28%]
Breast screening only from ages 25–69	59% [BCD=26%;OCD=46%]	75% [BCD=21%;OCD=25%]
RRSO at age 40 and RRM at age 25	79% [BCD=6%;OCD=21%]	83% [BCD=3%;OCD=6%]
RRSO at age 40 and breast screening from ages 25–69	74% [BCD=30%;OCD=15%]	80% [BCD=18%;OCD=5%]
RRSO at age 40, RRM at age 40, and breast screening from ages 25–39	77% [BCD=18%;OCD=18%]	82% [BCD=9%;OCD=6%]

*Survival probability for 70-year-old woman from general population = 84%[Probability of death as a result of breast cancer (BCD) or ovarian cancer (OCD); RRSO – risk-reducing bilateral salpingo-oophorectomy; RRM – risk-reducing bilateral mastectomy; Breast screening – annual mammography and MRI] Data from: Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for *BRCA1/2* mutation carriers. J Clin Oncol 2010;28:222-231.

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