

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®])

Breast Cancer Risk Reduction

Version 1.2014

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Breast Cancer Risk Reduction

[NCCN Guidelines Index](#)
[Breast Cancer Risk Reduction TOC](#)
[Discussion](#)

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† Medical oncology	ø Endocrinology
▸ Internal medicine, including family, preventive medicine	& Epidemiology
σ Allergy/Immunology	Δ Genetics
¶ Surgery/Surgical oncology	* Writing Committee Member
‡ Hematology	



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NCCN Guidelines Version 1.2014 Table of Contents

Breast Cancer Risk Reduction

[NCCN Guidelines Index](#)
[Breast Cancer Risk Reduction TOC](#)
[Discussion](#)

[NCCN Breast Cancer Risk Reduction Panel Members](#)
[Summary of the Guidelines Updates](#)

[Familial Risk Assessment \(BRISK-1\)](#)

[Elements of Risk, Risk Management \(BRISK-3\)](#)

[Risk-Reduction Therapy Not Desired: Risk Assessment and
Screening/Follow-up \(BRISK-4\)](#)

[Risk-Reduction Therapy Desired: Baseline Assessment,
Intervention, and Follow-up \(BRISK-5\)](#)

[Clinical Symptoms and Management While on Tamoxifen or Raloxifene
Therapy \(BRISK-7\)](#)

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

[Breast Cancer Risk-Reduction Agents \(BRISK-B\)](#)

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

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

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

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Guidelines Version 1.2014 Updates Breast Cancer Risk Reduction

Updates in the 1.2014 version of the NCCN Guidelines for Breast Cancer Risk Reduction from the 1.2013 version include:

BRISK-1

- Under Familial/genetic factors:
- Known genetic predisposition for breast cancer (BRCA1/2, p53, PTEN, or other gene mutation) is new to the page,
 - Footnote “b” ~~See BRISK-1 for women with a known genetic predisposition for breast cancer (BRCA1/2, p53, PTEN, or other gene mutation)~~ has been deleted.
- Modified Criteria for further genetic risk evaluation to include, “for women who do not have a personal history of invasive breast cancer or DCIS”
- Under Family history:
 - 2nd sub sub-bullet was reorganized and modified:
 - ◊ ~~≥2 primaries breast cancers~~ in a single individual
 - 3rd sub sub-bullet was reorganized and modified:
 - ◊ ~~≥2 individuals with breast primaries cancers~~ on the same side of family (maternal or paternal)
 - 4th sub sub-bullet was reorganized and modified:
 - ◊ ~~≥1 ovarian/fallopian tube/primary peritoneal cancer~~ from the same side of family (maternal or paternal)
 - 7th sub sub-bullet was modified:
 - ◊ From a population at increased risk for *genetic predisposition*
- Corresponding footnote “g” was modified: For populations at increased risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with a *personal history* of breast, ovarian, or pancreatic cancer at any age).
- 2nd sub-bullet under Family history has been modified: *Personal history* of ovarian/fallopian tube/primary peritoneal cancer
- The branch off the 2nd column–
 - Yes: “Referral to cancer genetics professional recommended” is new to the page as is corresponding footnote “h”
 - No: reader is directed to BRISK-2

BRISK-2

- ~~Woman meets one or more of the familial risk criteria~~ has been deleted.
- ~~Referral to cancer genetics professional recommended~~ has been deleted.
- Known genetic predisposition is new to the page
- Woman meets one or more of the familial risk criteria (See BRISK-1) is a new footnote corresponding to “Pedigree suggestive of genetic predisposition.” (Also for BRISK-4)
- Footnote “k” has been modified to include: “See life expectancy calculator (www.eprognosis.com).” (Also for BRISK-3, 4, and 5)

BRISK-3

- Under Elements of Risk:
- ~~Demographics~~ has been replaced with *Elements that increase risk*
- 1st bullet “Increasing age,” is new to the page
 - ◊ ~~Utility of risk reduction agents for breast cancer risk reduction in women <35 years of age is unknown~~ has been deleted.
- 2nd bullet, “Ethnicity/race” has a new corresponding footnote: “For example, there is an increased incidence of specific BRCA1/2 mutations in women of Ashkenazi Jewish descent.”
- 3rd bullet, “Lifestyle factors” is new to the page.
 - Increased body mass index (BMI)
 - Alcohol consumption
 - Current or prior estrogen and progesterone hormone therapy
 - ◊ ~~Risk factor in caucasian women~~ has been deleted.
 - ◊ ~~BMI and breast cancer risk in African American women is complex~~
 - ◊ ~~Obesity is a risk factor in postmenopausal women~~ has been deleted.
- 4th bullet, 2nd sub-bullet, “Nulliparity” is new to the page.
- New to the page: *Elements that decrease risk*, and includes the following:
 - Prior oophorectomy
 - Prior risk-reduction therapy
 - Exercise

BRISK-5

- 6th column, bottom branch, changed Exemestane to *Aromatase inhibitors* with a corresponding footnote, “Exemestane and anastrozole are not currently FDA approved for breast cancer risk reduction. There are currently no data comparing the benefits and risks of exemestane and anastrozole to those of tamoxifen or raloxifene.” (Also for BRISK-A and BRISK-B)

BRISK-6 Footnotes:

- “s” has been modified: *Risk-reduction mastectomy should generally be considered only in women with a genetic mutation conferring a high risk for breast cancer (BRCA1/2, PTEN, TP53, CDH1, STK11), compelling family history, or possibly with LCIS or prior thoracic radiation therapy at <30 yrs of age. The value of risk-reducing mastectomy in women with deleterious mutations in other genes associated with a 2-fold or greater risk for breast cancer (based on large epidemiologic studies) in the absence of a compelling family history of breast cancer is unknown. Risk reduction mastectomy should generally be considered only in women with BRCA1/2, or other strongly predisposing gene mutation, compelling*



Guidelines Version 1.2014 Updates

Breast Cancer Risk Reduction

BRISK-6 Footnotes (continued)

~~family history, or possibly with LCIS or prior thoracic radiation therapy at <30 y of age. Women considering risk reduction mastectomy should receive multidisciplinary counseling including consultation with genetics if not already done. Psychological consultation may also be of value.~~

- ▶ ~~“aa” Other aromatase inhibitors have shown prevention of contralateral breast cancer and there are ongoing clinical trials.~~ has been deleted.
- ▶ ~~“y” Axillary node assessment has limited indication at the time of is not part of the risk reduction procedure surgery.~~

BRISK-7

- Footnote “ff”: “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.” The footnote was deleted from this page and moved to BRISK-B, corresponding to Tamoxifen.

BRISK-A

- ~~Exemestane~~ has been replaced with *aromatase inhibitors*.
- Under Surgery, 3rd sub-bullet, *Consider nipple-sparing mastectomy for risk reduction* is new to the page.
- Under Healthy lifestyle
 - ▶ 1st sub-bullet modified: Consider breast cancer risks associated with ~~hormone combined estrogen/progesterone~~ therapy
 - ▶ The reference that corresponds to “Limit alcohol consumption to less than 1 drink per day” has been deleted. ~~Mahoney MC, Bevers T, Lines E, Willett WC. Opportunities and strategies for breast cancer prevention through risk reduction. CA Cancer J Clin 2008;58(6):347-74.~~

BRISK-B

- Under Tamoxifen
 - ▶ 3rd sub-bullet modified: ~~Limited data are currently available regarding~~ The efficacy of tamoxifen risk reduction in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation *is less well studied than in other risk groups. Available data suggest a benefit.*
- 3rd column: ~~Exemestane~~ has been changed to *Aromatase inhibitors (Exemestane and Anastrozole)*

BRISK-B (continued)

- ▶ The following is new to the guidelines: 2nd sub-bullet, Data regarding anastrozole are from a single large randomized study limited to postmenopausal women 40-70 years of age with the following risk compared with the general population:
 - ♦ Aged 40-44 years - 4 times higher
 - ♦ Aged 45-60 years - ≥2 times higher
 - ♦ Aged 60-70 years - ≥1.5 times higher
 Women who did not meet these criteria but had a Tyrer-Cuzick 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. ~~There are ongoing trials evaluating prolonged aromatase inhibitor therapy in postmenopausal healthy women at risk for breast cancer.~~
- ▶ 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 no data regarding the use of ~~exemestane~~ *aromatase inhibitors* in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation.
- ▶ For high-risk postmenopausal women, data regarding the risk/benefit ratio for ~~exemestane~~ *aromatase inhibitor* therapy are influenced by age and comorbid conditions such as osteoporosis (category 1). There are insufficient data on ethnicity and race.
- ▶ Use of ~~exemestane~~ *aromatase inhibitors* for breast cancer risk reduction in premenopausal women is inappropriate unless part of a clinical trial.
- Reference 3 has been deleted: ~~Fisher B, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90(18):1371-88.~~

MS-1

- The Discussion section has been updated to reflect the changes to the algorithm.



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NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

[NCCN Guidelines Index](#)
[Breast Cancer Risk Reduction TOC](#)
[Discussion](#)

FAMILIAL RISK ASSESSMENT^a

Familial/genetic factors

- Known genetic predisposition for breast cancer (BRCA1/2, p53, PTEN, or other gene mutation)

→ [See BRISK-2](#)

- Criteria for further genetic risk evaluation for women who do not have a personal history of invasive breast cancer or ductal carcinoma in situ (DCIS):^b

► Family history

- ◊ Member of a family with a known mutation in a breast cancer susceptibility gene
- ◊ ≥2 primary breast cancers^c in a single individual
- ◊ ≥2 individuals with breast cancers on the same side of family (maternal or paternal)
- ◊ ≥1 ovarian/fallopian tube/primary peritoneal cancer from the same side of family (maternal or paternal)
- ◊ First- or second-degree relative with breast cancer ≤45 y
- ◊ ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma, thyroid cancer, dermatologic manifestations,^d and/or macrocephaly, hamartomatous polyps of GI tract,^e or diffuse gastric cancer^f
- ◊ From a population at increased risk for genetic predisposition^g
- ◊ Male breast cancer

- Personal history of ovarian/fallopian tube/primary peritoneal cancer

Woman meets one or more of the familial/genetic risk criteria

Yes
No

Referral to cancer genetics professional recommended^h
[See BRISK-2](#)

→ [See BRISK-2](#)

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

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

^cTwo breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

^dFor dermatologic manifestations, [see NCCN Guidelines for Genetic/Familial High-Risk Assessment - Cowden Syndrome \(See COWD-1\)](#).

^eFor hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, STK11 testing should be considered. [See NCCN Guidelines for Colorectal Cancer Screening](#): Peutz-Jeghers Syndrome.

^fFor lobular breast cancer with a family history of diffuse gastric cancer, *CDH1* gene testing should be considered.

^gFor populations at increased risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with a personal history of breast, ovarian, or pancreatic cancer at any age).

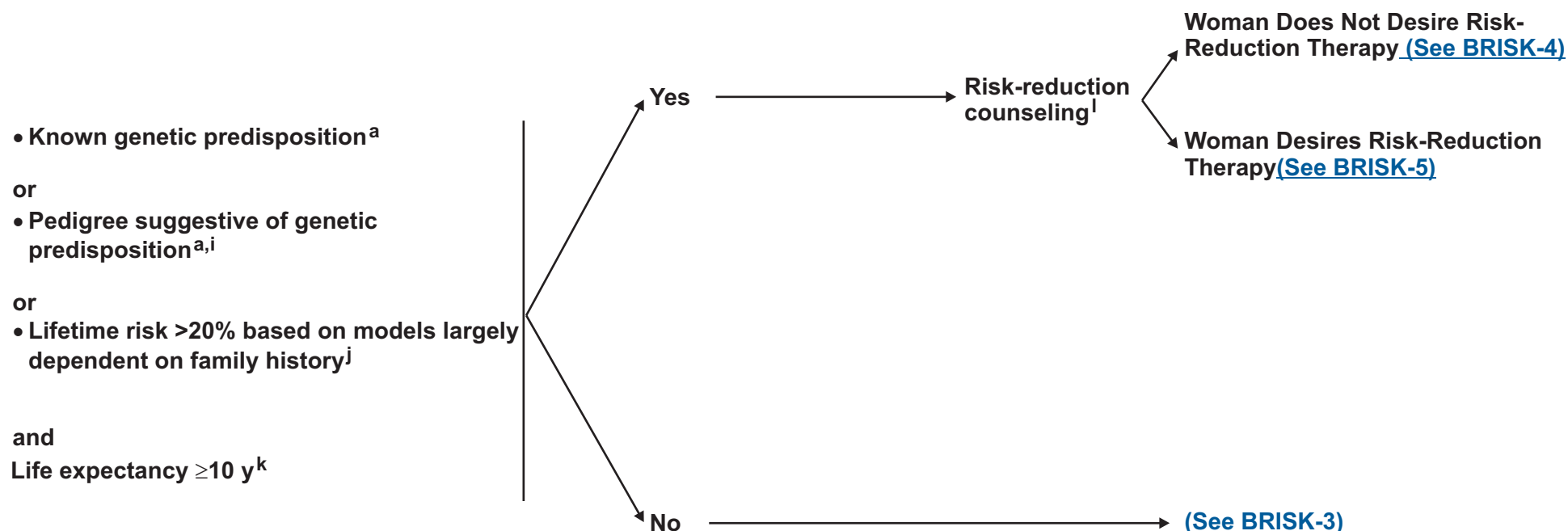
^hA genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome. Genetic counseling is highly recommended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

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

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ADDITIONAL RISK ASSESSMENT



^aSee [NCCN Guidelines for Genetic/Familial High-Risk Assessment](#).

ⁱWoman meets one or more of the familial risk criteria ([See BRISK-1](#)).

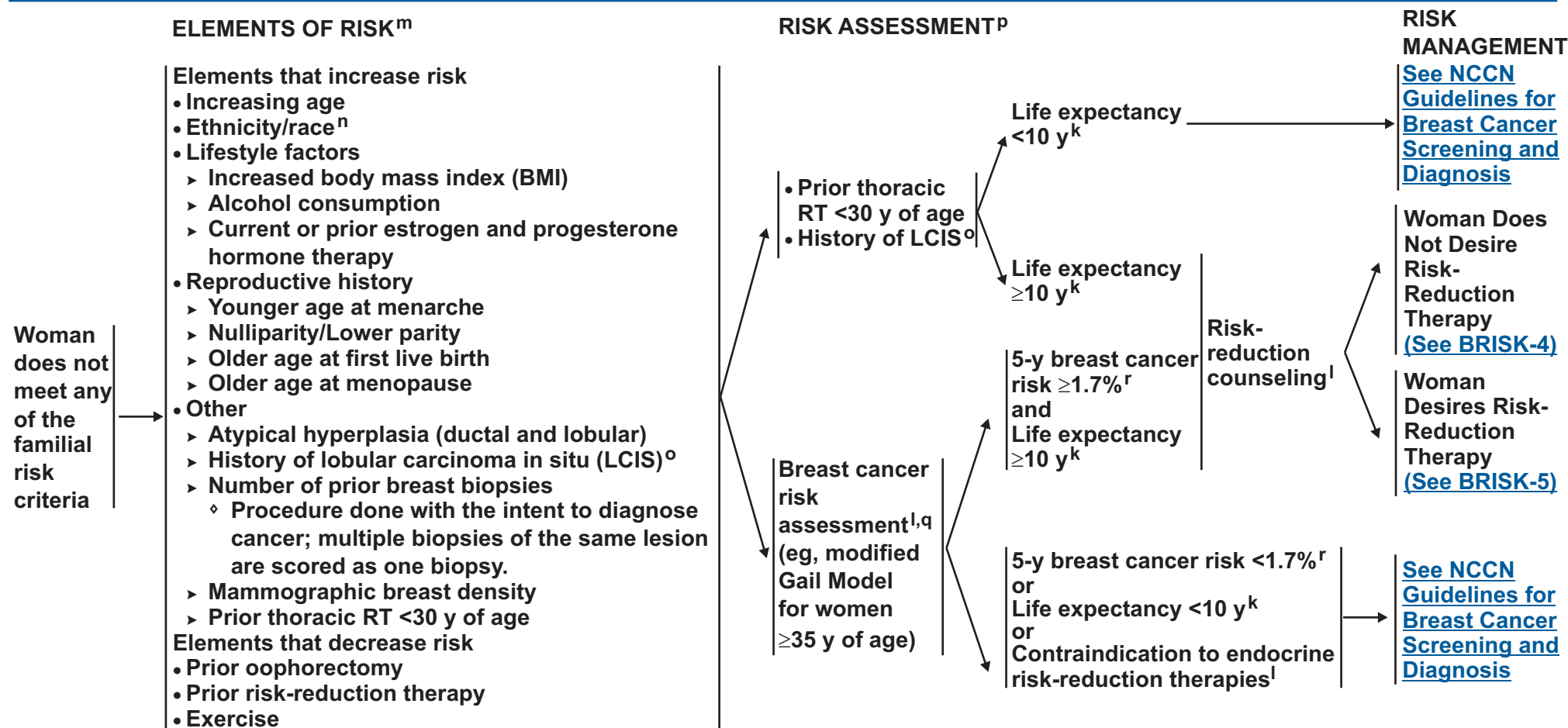
^jRisk models that are largely dependent on family history (eg, Claus, BRCAPRO, BOADICEA, Tyrer-Cuzick).

^kSee life expectancy calculator (www.eprognosis.com). For a reference point, the life expectancy of the average 78-y-old woman in the United States is 10.2 years. ([See NCCN Guidelines for Senior Adult Oncology](#)).

^lSee [Components of Risk/Benefit Assessment and Counseling \(BRISK-A\)](#).

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NCCN Guidelines Version 1.2014
Breast Cancer Risk Reduction[NCCN Guidelines Index](#)
[Breast Cancer Risk Reduction TOC](#)
[Discussion](#)

^kSee life expectancy calculator (www.e prognosis.com). For a reference point, the life expectancy of the average 78-y-old woman in the United States is 10.2 years. (See [NCCN Guidelines for Senior Adult Oncology](#)).

^lSee [Components of Risk/Benefit Assessment and Counseling \(BRISK-A\)](#).

^mThe management for women with DCIS is available in the [NCCN Guidelines for Breast Cancer](#).

ⁿFor example, there is an increased incidence of specific BRCA1/2 mutations in women of Ashkenazi Jewish descent.

^oThe management for women with LCIS is also available in the [NCCN Guidelines for Breast Cancer](#).

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

^qThe modified Gail Model (NCI Breast Cancer Risk Assessment Tool) is a computer-based version and may be obtained through the NCI website (<http://www.cancer.gov/bcrisktool/Default.aspx>). There are circumstances in which the Gail Model underestimates risk for development of breast cancer, for instance, BRCA1/2 carriers and those with a strong family history of breast cancer or family history of ovarian cancer in the maternal or paternal family lineage or non-white women. The Claus, BRCAPRO, Tyrer-Cuzick, and BOADICEA models may be particularly helpful in determining risk for breast cancer in women with a strong family history of breast, ovarian, or other cancers. See [Discussion, MS-2](#).

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

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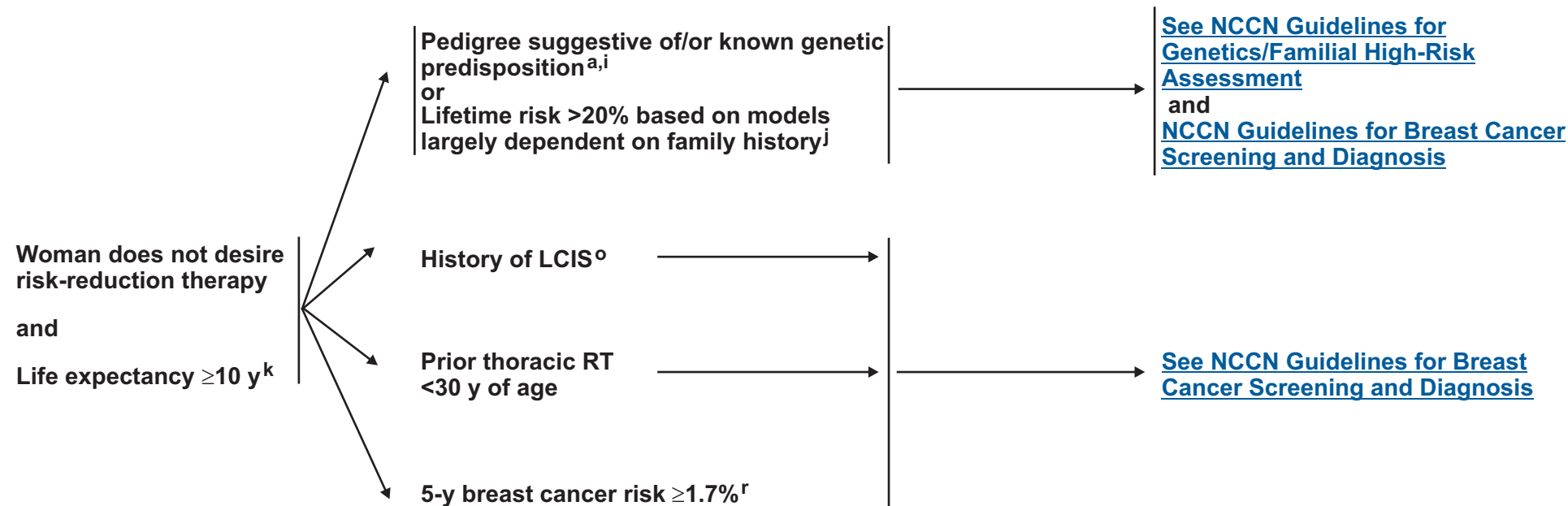
Breast Cancer Risk Reduction

[NCCN Guidelines Index](#)
[Breast Cancer Risk Reduction TOC](#)
[Discussion](#)

RISK-REDUCTION THERAPY NOT DESIRED

RISK ASSESSMENT

SCREENING/FOLLOW-UP



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

ⁱ Woman meets one or more of the familial risk criteria ([See BRISK-1](#)).

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

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

^o The management for women with LCIS is also available in the [NCCN Guidelines for Breast Cancer](#).

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

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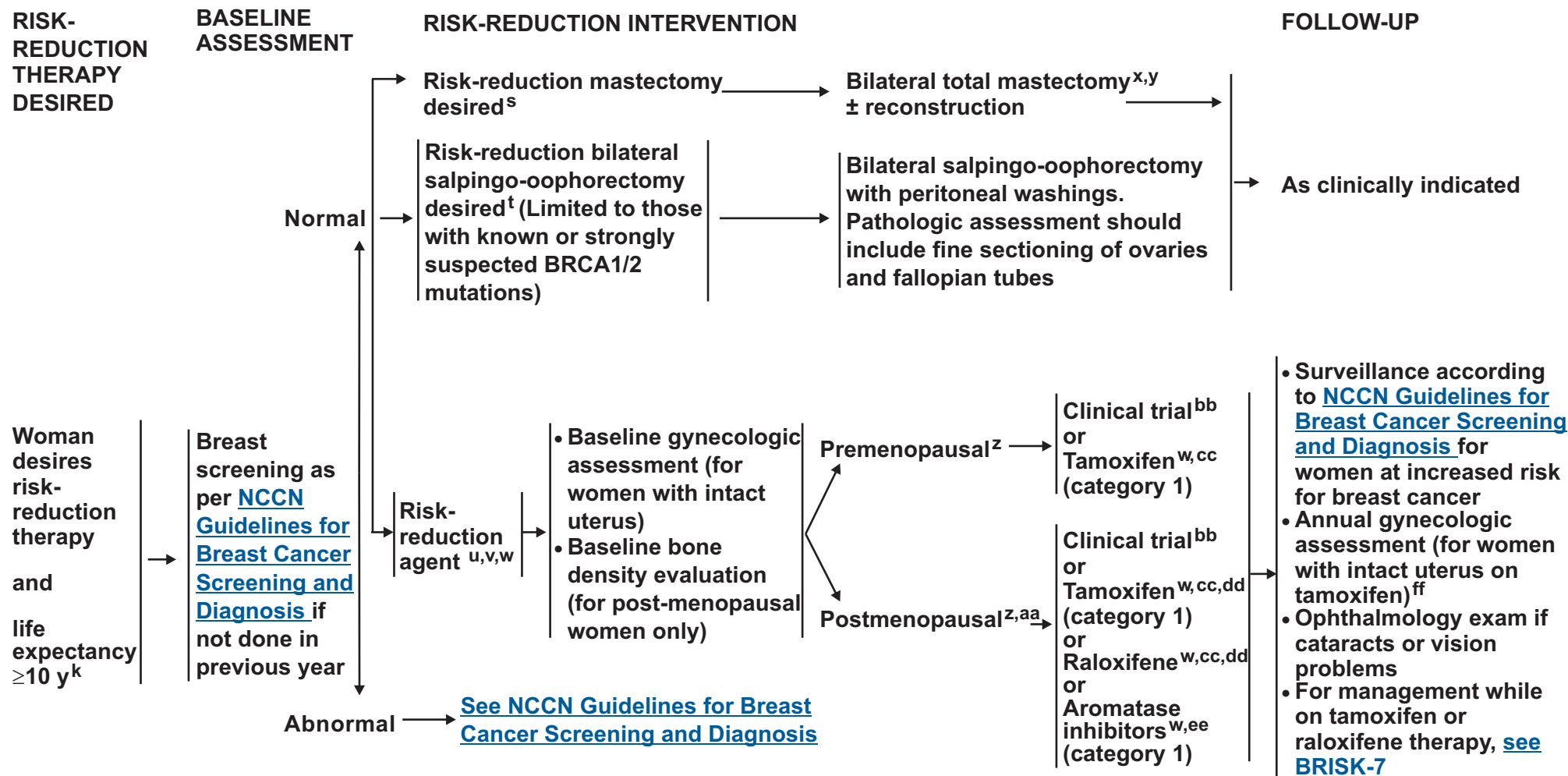


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NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

[NCCN Guidelines Index](#)
[Breast Cancer Risk Reduction TOC](#)
[Discussion](#)



See footnotes on [BRISK-6](#)

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FOOTNOTES FOR RISK-REDUCTION THERAPY

- ^kSee life expectancy calculator (www.eprognosis.com). For a reference point, the life expectancy of the average 78-y-old woman in the United States is 10.2 years. ([See NCCN Guidelines for Senior Adult Oncology](#)).
- ^sRisk-reduction mastectomy should generally be considered only in women with a genetic mutation conferring a high risk for breast cancer (ie, BRCA1/2, PTEN, TP53, CDH1, STK11), compelling family history, or possibly with LCIS or prior thoracic radiation therapy at <30 yrs of age. The value of risk-reducing mastectomy in women with deleterious mutations in other genes associated with a 2-fold or greater risk for breast cancer (based on large epidemiologic studies) in the absence of a compelling family history of breast cancer is unknown.
- ^tThe additional benefit of concurrent hysterectomy is not clear at this time.
- ^uThere are no data regarding the use of risk-reduction agents in women with prior thoracic radiation therapy.
- ^vCYP2D6 genotype testing is not recommended in women considering tamoxifen.
- ^w[See Breast Cancer Risk-Reduction Agents \(BRISK-B\)](#).
- ^xDiscuss risks and benefits of nipple-areolar sparing surgery.
- ^yAxillary node assessment has limited indication at the time of risk-reduction surgery.
- ^zClinical trials in breast cancer have utilized a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following: Prior bilateral oophorectomy; age ≥60 y; age <60 y; and amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range. If taking tamoxifen or toremifene and age <60 y, FSH and plasma estradiol level in postmenopausal ranges.
- ^{aa}Bone density may play a role in choice of therapy.
- ^{bb}Women in clinical trial should have baseline exam, follow-up, and monitoring as per protocol.
- ^{cc}Utility of tamoxifen or raloxifene for breast cancer risk reduction in women <35 years of age is unknown. Raloxifene is only for post-menopausal women >35 y. While raloxifene in long-term follow-up appears to be less efficacious in risk reduction than tamoxifen, consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in women with an intact uterus.
- ^{dd}When counseling postmenopausal women regarding the risk/benefit of tamoxifen and raloxifene, refer to tables in Freedman AN, 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(17):2327-2333.
- ^{ee}Exemestane and anastrozole are not currently FDA approved for breast cancer risk reduction. There are currently no data comparing the benefits and risks of exemestane and anastrozole to those of tamoxifen or raloxifene.
- ^{ff}Routine endometrial ultrasound and biopsy are not recommended for women in the absence of other symptoms.

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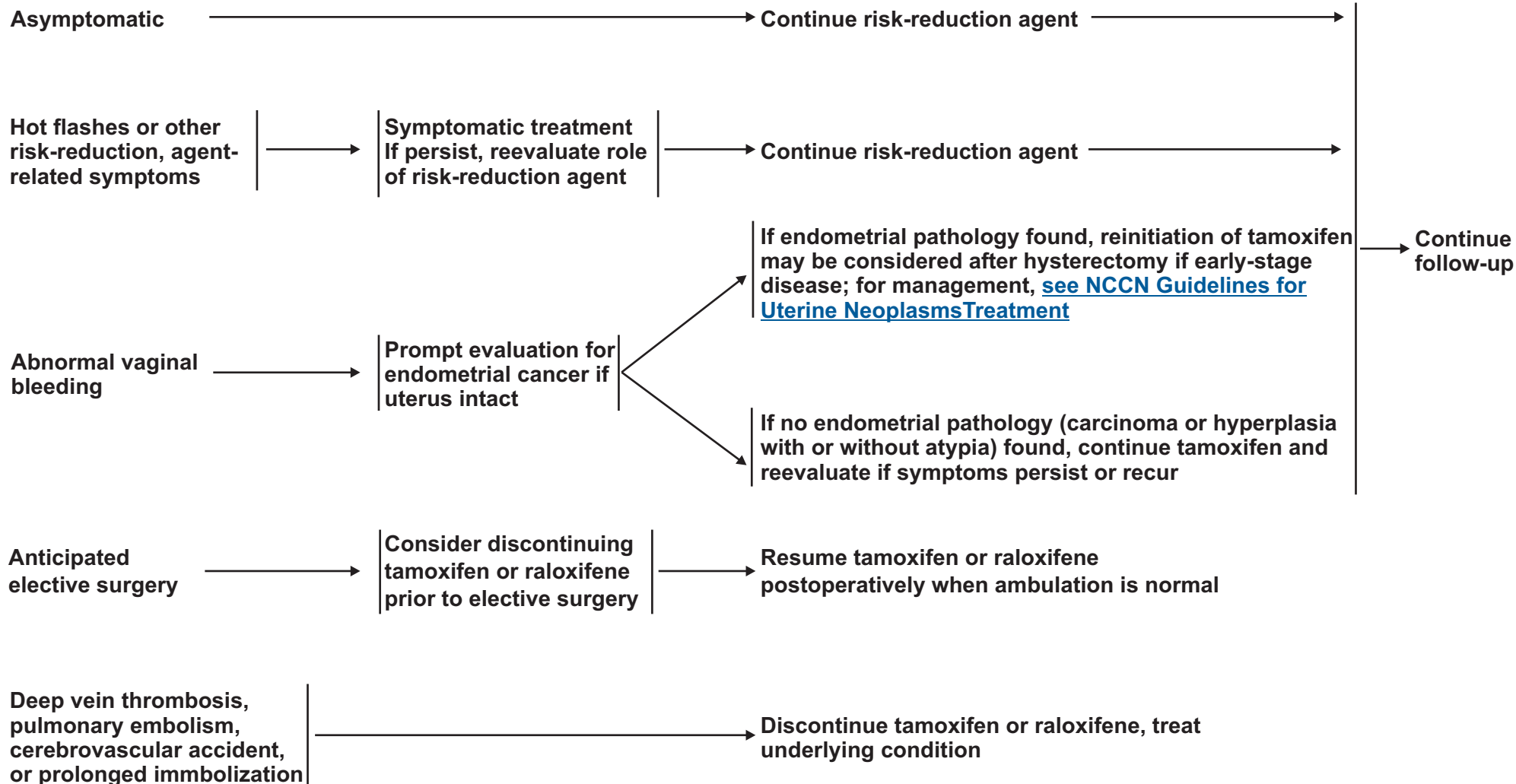
NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

[NCCN Guidelines Index](#)
[Breast Cancer Risk Reduction TOC](#)
[Discussion](#)

CLINICAL SYMPTOMS

MANAGEMENT WHILE ON TAMOXIFEN OR RALOXIFENE THERAPY



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COMPONENTS OF RISK/BENEFIT ASSESSMENT AND COUNSELING

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

- If a woman is at high risk secondary to a strong family history or very early onset of breast or ovarian cancer, genetic counseling should be offered. [See NCCN Guidelines for Genetic/Familial High-Risk Assessment.](#)
- Risk-reduction agents - See the [Discussion](#) section.
 - › Discussion of relative and absolute risk reduction with tamoxifen, raloxifene, or aromatase inhibitors¹.
 - › Contraindications to tamoxifen or raloxifene: history of deep vein thrombosis, pulmonary embolus, thrombotic stroke, transient ischemic attack, or known inherited clotting trait.
 - › Contraindications to tamoxifen, raloxifene, and aromatase inhibitors¹: current pregnancy or pregnancy potential without effective nonhormonal method of contraception.
 - › Common and serious adverse effects of tamoxifen, raloxifene, or aromatase inhibitors¹ with emphasis on age-dependent risks.
- Surgery
 - › Discussion of risk-reduction mastectomy in high-risk women. Risk-reduction mastectomy should generally be considered only in women with BRCA1/2, or other strongly predisposing gene mutation, compelling family history, or possibly women with LCIS or prior thoracic RT <30 y of age. Evaluation should include consultation with surgery and reconstructive surgery. Psychological consultation may also be considered.
 - › Discussion regarding the risk for breast or ovarian cancer and the option of risk-reduction bilateral salpingo-oophorectomy.
 - › Consider nipple-sparing mastectomy for risk reduction.
- Option of participation in clinical research for screening, risk assessment, or other risk-reduction intervention.
- Healthy lifestyle
 - › Consider breast cancer risks associated with combined estrogen/progesterone therapy
 - › Limit alcohol consumption to less than 1 drink per day
 - › Exercise²
 - › Weight control

¹Exemestane and anastrozole are not currently FDA approved for breast cancer risk reduction. There are currently no data comparing the benefits and risks of exemestane and anastrozole to those of tamoxifen or raloxifene.

²See [American Cancer Society Guidelines](#).

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BREAST CANCER RISK-REDUCTION AGENTS

• Tamoxifen^{1,2,3}

- Data regarding tamoxifen risk reduction are limited to pre- and postmenopausal women 35 y of age or older with a Gail Model 5-year breast cancer risk of $\geq 1.7\%$ or a history of LCIS.
- Tamoxifen: 20 mg per day for 5 years was shown to reduce risk of breast cancer by 49%. Among women with a history of atypical hyperplasia, this dose and duration of tamoxifen was associated with an 86% reduction in breast cancer risk.
- The efficacy of tamoxifen risk reduction in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation is less well studied than in other risk groups. Available data suggest a benefit.
- For high-risk premenopausal women, data regarding the risk/benefit ratio for tamoxifen appear relatively favorable (category 1).
- For high-risk postmenopausal women, data regarding the risk/benefit ratio for tamoxifen are influenced by age, presence of uterus, or comorbid conditions (category 1). There are insufficient data on ethnicity and race.

• Raloxifene^{1,2}

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

• Aromatase inhibitors (Exemestane and Anastrozole)⁴

- Data regarding exemestane are from a single large randomized study limited to postmenopausal women 35 years of age or older with a Gail model 5-year breast cancer risk $\geq 1.7\%$ or a history of LCIS.
- Data regarding anastrozole are from a single large randomized study limited to postmenopausal women 40-70 years of age with the following risk compared with the general population:
 - ◊ Aged 40-44 years - 4 times higher
 - ◊ Aged 45-60 years - ≥ 2 times higher
 - ◊ Aged 60-70 years - ≥ 1.5 times higher
 Women who did not meet these criteria but had a Tyrer-Cuzick 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 no data regarding the use of aromatase inhibitors in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation.
- For high-risk postmenopausal women, data regarding the risk/benefit ratio for aromatase inhibitor therapy 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 women is inappropriate unless part of a clinical trial.

¹There are limited data regarding >5 years of tamoxifen or raloxifene use in breast cancer prevention. Moreover, there may be safety concerns related to use of tamoxifen for greater than 5 years. Based on the recent update of the STAR trial data, continuing raloxifene beyond 5 years (there are no high-level experience or clinical trial data evaluating these agents for risk reduction beyond 5 years) may be an approach to maintain the risk-reduction activity of the agent.

²When counseling postmenopausal women regarding the risk/benefit of tamoxifen and raloxifene, refer to tables in Freedman AN, 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(17):2327-2333.

³Some 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.

⁴Exemestane and anastrozole are not currently FDA approved for breast cancer risk reduction. There are currently no data comparing the benefits and risks of exemestane and anastrozole to those of tamoxifen or raloxifene.

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

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview	MS-2
Risk Assessment	MS-2
Familial/Genetic Factors	MS-2
Other Elements of Risk	MS-3
Risk-Reduction Interventions	MS-5
Lifestyle Modifications	MS-5
Risk-Reduction Surgery	MS-5
Bilateral Total Mastectomy	MS-5
Bilateral Salpingo-oophorectomy	MS-6
Risk-Reduction Agents	MS-8
Tamoxifen for Risk Reduction	MS-8
Raloxifene for Risk Reduction	MS-10

Aromatase Inhibitors for Risk Reduction	MS-13
NCCN Panel Recommendations for Risk-Reduction Agents	MS-14
Tamoxifen Recommendations	MS-14
Raloxifene Recommendations	MS-15
AI Recommendations (Anastrozole and Exemestane)	MS-15
Monitoring Patients on Risk-Reduction Agents	MS-16
Endometrial Cancer	MS-16
Retinopathy and Cataract Formation	MS-17
Bone Mineral Density	MS-17
Thromboembolic Disease and Strokes	MS-17
Managing Side Effects of Risk-Reduction Agents	MS-18
Components of Risk-Reduction Counseling	MS-20
Counseling Prior to Therapy with Risk-Reduction Agents	MS-21
Counseling Prior to Risk-Reduction Surgery	MS-22
Counseling Regarding Lifestyle Modifications	MS-23
Summary	MS-26
Table 1	MS-28
Table 2	MS-29
References	MS-30

Overview

Breast cancer is the most commonly diagnosed cancer in American women, with an estimated 235,030 cases of invasive breast cancer and an estimated death of 40,430 women with breast cancer in 2014.¹ This highlights the need for effective breast cancer screening and risk-reduction strategies.

For a woman 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, atypical hyperplasia or lobular carcinoma in situ [LCIS], breast density, or prior thoracic irradiation before age 30 [eg, to treat Hodgkin's disease].

Estimating breast cancer risk for the individual woman is difficult, and most breast cancers are not attributable to risk factors other than female gender and increased age. The development of effective strategies for the reduction of breast cancer incidence has also been difficult, because few of the existing risk factors are modifiable and some of the potentially modifiable risk factors have social implications extending beyond concerns for breast cancer (eg, age at first live birth). Nevertheless, effective breast cancer risk-reduction strategies such as use of risk-reduction agents, and risk-reduction surgery, have been identified. However, women and their physicians who are considering interventions to reduce risk 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 for the woman, and risk-reduction agents, used for non-surgical risk reduction, are associated with certain adverse

effects.²⁻⁴ To assist women 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.

Risk Assessment

Estimation of breast cancer risk for an individual woman 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 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.^{5,6}

Genetic predispositions conferring a high risk for breast cancer include Hereditary Breast and Ovarian Cancer (*BRCA1/2*),^{7,8} Li-Fraumeni syndrome (*TP53*),⁹ Peutz-Jeghers syndrome (*STK11*),¹⁰ Cowden syndrome (*PTEN*),^{11,12} and Hereditary Diffuse Gastric Cancer (*CDH1*).¹³

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

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



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

age at which the affected relative was diagnosed.¹⁴⁻¹⁶ 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.^{17,18} 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 onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.¹⁹⁻²²

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 Risk Assessment: Breast and Ovarian](#)), that individual may be at increased risk for familial/hereditary breast cancer, and referral for formal genetic assessment/counseling is recommended.

A cancer genetic professional should be involved in determining whether the individual has a lifetime risk for breast cancer greater than 20% based on models dependent on family history (eg, Claus,²³ Tyrer-Cuzick,²⁴ and others²⁵⁻²⁷). BRCAPRO²⁸ and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)²⁹ are more commonly used to estimate the risk based on *BRCA* mutations. Strong genetic association between breast and ovarian cancer has been demonstrated in some families by linkage analyses. The Claus tables may be useful in providing breast cancer risk estimates for white women without a known cancer-associated gene mutation who have one or two first- or second-degree female relatives with breast cancer²³ and ovarian cancer.³⁰ Based on this risk assessment, women with a *BRCA1/2*, *TP53*, or *PTEN* gene mutation, or a pedigree strongly suggestive of genetic predisposition to breast cancer, may be identified. The [NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian](#) also describe management strategies for women with a known or suspected *BRCA1/2*, *TP53*, or *PTEN* mutation or a pedigree strongly suggestive of genetic predisposition to breast cancer.

Other Elements of Risk

For women 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 ethnicity/race. There is an increased incidence of *BRCA1/2* mutation reported in women of Ashkenazi Jewish descent.³¹ It also includes increasing age and reproductive history. Strong risk factors linked to reproductive history include nulliparity, current use of menopausal hormone therapy (HT), and prolonged interval between menarche and age at first birth.³²⁻³⁶



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

Body mass index (BMI) is an independent risk factor for breast cancer, especially in Caucasian women. Several studies have established the association between high BMI and adult weight gain to increased risk for breast cancer in postmenopausal women. This increase in risk has been attributed to increase in circulating endogenous estrogen levels from fat tissue.³⁷⁻³⁹ In addition, the association between BMI and risk for postmenopausal breast cancer is stronger for hormone-positive tumors.⁴⁰⁻⁴³

Lifestyle factors such as current or prior HT,³⁶ alcohol consumption,^{44,45} and smoking⁴⁶ also contribute to the risk of developing breast cancer. Other factors to consider are number of breast biopsies, prior thoracic irradiation before age 30 (eg, to treat Hodgkin's disease), atypical hyperplasia or LCIS, and changes in breast density.⁴⁷ Breast density is not included in any of the commonly used risk assessment models/tools.²⁶ However, dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.^{48,49} For example, a report of a large case-cohort study of women 35 years and older with no history of breast cancer who underwent mammographic screening, 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.⁴⁹

Women ≥ 35 years of age *without* a *BRCA1/2*, *TP53*, or *PTEN* mutation; a strong family history of breast cancer; a history of thoracic radiation before age 30; or a history of LCIS should have their risk for breast cancer estimated according to the modified Gail model.⁵⁰⁻⁵² 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.^{50,51,53,54} The criteria used to determine risk by the modified Gail model are described in [Table 1](#). The Gail model, as modified by the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators, is available on the National Cancer Institute website (<http://www.cancer.gov/bcrisktool/Default.aspx>).

The risk threshold required for a woman to consider the use of risk-reduction strategies must depend on an evaluation of the efficacy, morbidity, and expense of the proposed intervention. As a reasonable discriminating threshold, the NCCN Breast Cancer Risk Reduction Panel has adopted the 1.7% or greater 5-year actuarial breast cancer risk as defined by the modified Gail model, which was used to identify women eligible for the NSABP, Breast Cancer Prevention Trial (BCPT),^{55,56} and the Study of Tamoxifen and Raloxifene (STAR) trial.^{57,58}

The Gail model was updated using combined data from the Women's Contraceptive and Reproductive Experiences (CARE) study and the SEER database, as well as causes of death from the National Center of Health Statistics, to provide a more accurate determination of risk for African-American women.⁵⁹ The model was updated using data from the Asian American Breast Cancer Study (AABCS) and the SEER database to provide a more accurate risk assessment for Asian and Pacific Islander women in the United States.⁶⁰ Application of the Gail model to recent immigrants from Japan or China may overestimate the risk for breast cancer.⁶⁰

As previously mentioned, the Gail model is not an appropriate breast cancer risk assessment tool for women who received prior thoracic radiation to treat Hodgkin's disease (eg, mantle radiation) or those with LCIS. In the Late Effects Study Group trial, the overall risk for breast cancer associated with prior thoracic irradiation at a young age was



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

found to be 56.7-fold (55.5-fold for female patients) greater than the risk for breast cancer in the general population.⁶¹ In that study, the relative risk according to follow-up interval was: 0 at 5 to 9 years; 71.3 at 10 to 14 years; 90.8 at 15 to 19 years; 50.9 at 20 to 24 years; 41.2 at 25 to 29 years; and 24.5 at >29 years.⁶¹ Results from a case-control study of women treated at a young age (30 years or younger) for Hodgkin lymphoma with thoracic radiation indicated that the estimated, cumulative, absolute risk for breast cancer at 55 years of age was 29.0% (95% confidence interval [CI], 20.2%–40.1%) for a woman treated at 25 years of age with 40 Gy of radiation and no alkylating agents.⁶² Women with a history of treatment with thoracic radiation for Hodgkin's disease are at a high risk for breast cancer on the basis of radiation exposure alone.^{61–66} Women with a history of LCIS are also at substantially increased risk for invasive breast cancer in both the affected and contralateral breast.^{67,68}

Women with a life expectancy ≥ 10 years and no diagnosis/history of breast cancer who are considered to be at increased risk for breast cancer based on any of the above-mentioned assessments should receive counseling, that is tailored to the individual, to decrease breast cancer risk (eg, risk-reduction surgery in *BRCA1/2* mutation carriers; therapy with risk-reduction agents in those without a contraindication to these agents) (see section below on *Components of Risk-Reduction Counseling*, page MS-20), and should undergo breast screening as detailed in the [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#).

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](#)).

Women with a 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 indicate that in addition to family history and genetics, environmental factors play a significant role. Life style modifications such as diet, body weight, exercise, and alcohol consumption are some of the modifiable components of breast cancer risk. While there is no clear evidence that specific dietary components can effectively reduce breast cancer risk, weight gain and obesity in adulthood are risk factors for the development of postmenopausal breast cancer.^{39,69,70} Alcohol consumption, even at moderate levels, increases breast cancer risk.^{45,70–73} Patients should be encouraged to maintain a healthy lifestyle and to remain up-to-date with recommendations for screening and surveillance (see section on *Counseling regarding lifestyle modifications* on MS-24).

Risk-Reduction Surgery

Bilateral Total Mastectomy

The lifetime risk for breast cancer in *BRCA1/2* mutation carriers has been estimated to be 56% to 84%.^{74–76} Retrospective analyses with median follow-up periods of 13 to 14 years have indicated that bilateral risk-reducing mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known *BRCA1/2* mutation carriers.^{77,78} An analysis of results from the study by Hartmann et al,⁷⁷ determined that to prevent one case of breast cancer in women with high risk, the number of needed to be treated with RRM was equal to 6.⁷⁹ Results from smaller prospective studies with shorter follow-up periods have provided support for concluding that RRM provides a high degree of protection against



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

breast cancer in women with a *BRCA1/2* mutation.^{80,81} The NCCN Breast Cancer Risk Reduction Panel supports the use of RRM for carefully selected women at high risk for breast cancer who desire this intervention (eg, women with a *BRCA1/2*, *TP53*, *PTEN*, *CDH1*, or *STK11* mutation or, possibly, women with a history of LCIS). Although the consensus of the NCCN Breast Cancer Risk Reduction Panel is that consideration of RRM is an option for a woman with LCIS without additional risk factors, it is not a recommended approach for most of these women. There are no data regarding RRM in women with prior mantle radiation exposure. The value of RRM in women with deleterious mutations in other genes associated with a high risk for breast cancer (based on large epidemiologic studies) in the absence of a compelling family history of breast cancer is unknown.

Women considering RRM should first have appropriate multidisciplinary consultations and a clinical breast examination and bilateral mammogram if not performed within the past 6 months. If results are normal, women who choose RRM may undergo the procedure with or without immediate breast reconstruction. Bilateral mastectomy performed for risk reduction should involve removal of all breast tissue (ie, a total mastectomy). Axillary node assessment has limited utility at the time of RRM. Women undergoing RRM do not require an axillary lymph node dissection unless breast cancer is identified on pathologic evaluation of the mastectomy specimen.⁸²

Some patients may be at risk for an occult primary tumor, such as patients with abnormal imaging findings on either mammogram or breast MRI, who do not undergo biopsy, and patients with familial history who have not had a breast MRI prior to surgery. In such patients, a sentinel lymph node biopsy may be performed to stage the axilla for an occult cancer during the RRM, and a secondary axillary lymph node dissection could be avoided if an occult invasive cancer is

discovered. This procedure has not been found to increase the risk for lymphedema.⁸³

Following RRM, women who carry a *BRCA1/2* mutation should be monitored according to the [NCCN Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian](#). Women found to have invasive breast cancer or DCIS at the time of RRM should be treated according to the [NCCN Guidelines for Breast Cancer](#). All other women should be followed up with routine health maintenance following RRM. Most health maintenance recommendations are not related to the breast. For monitoring breast health, women should continue with annual exams of the chest/reconstructed breast as there is still a small risk of developing breast cancer. Mammograms are not recommended in this situation.

Bilateral Salpingo-oophorectomy

Women with a *BRCA1/2* mutation are at increased risk for both breast and ovarian cancers (including fallopian tube cancer). Although the risk for ovarian cancer is lower than the risk for breast cancer in a *BRCA1/2* mutation carrier (eg, estimated lifetime risks of 36%–46% and 10%–27% in *BRCA1* and *BRCA2* mutation carriers, respectively^{75,84–87}), the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have lent support for the performance of bilateral risk-reducing salpingo-oophorectomy (RRSO) after completion of childbearing in these women. In the studies of Rebbeck et al, the mean age at diagnosis of ovarian cancer was 50.8 years for *BRCA1/2* carriers.⁸⁸

The effectiveness of RRSO in reducing the risk for ovarian cancer in carriers of a *BRCA1/2* mutation has been demonstrated in a number of studies. For example, results of a meta-analysis involving 10 studies of *BRCA1/2* mutation carriers showed an approximately 80% reduction in



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

the risk for ovarian or fallopian cancer following RRSO.⁸⁹ However, a 1% to 4.3% residual risk for a primary peritoneal carcinoma has been reported in some studies.⁸⁸⁻⁹³

RRSO is also reported to reduce the risk for breast cancer in carriers of a *BRCA1/2* mutation by approximately 50%.^{88,89,93,94} In the case-control international study, a 56% (odds ratio = 0.44; 95% CI, 0.29–0.66) and a 46% (odds ratio = 0.57; 95% CI, 0.28–1.15) breast cancer risk reduction was reported following RRSO in carriers of a *BRCA1/2* mutation, respectively.⁹⁴ Hazard ratios of 0.47 (95% CI, 0.29–0.77)⁸⁸ and 0.30 (95% CI, 0.11–0.84)⁹² were reported in two other studies comparing breast cancer risk in women with a *BRCA1/2* mutation who had undergone RRSO with carriers of these mutations who opted for surveillance only. These studies are further supported by a meta-analysis that found similar reductions in breast cancer risk of approximately 50% for *BRCA1/2* mutation carriers following RRSO.⁸⁹ The results of a prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA1* mutation carriers compared with *BRCA2* mutation carriers.⁹⁵

Reductions in breast cancer risk for carriers of a *BRCA1/2* mutation after RRSO may be associated with decreased hormonal exposure following surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a *BRCA1* mutation who had an RRSO at age 40 years or younger (odds ratio = 0.36, 95% CI, 0.20–0.64) relative to *BRCA1* carriers aged 41–50 years who had this procedure (odds ratio = 0.50, 95% CI, 0.27–0.92).⁹⁴ Nonsignificant risk reduction of developing breast cancer was found for women aged 51 years or older, although only a small number of women were included in this group.⁹⁴ However, results from Rebbeck et al also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.⁹³

Although data are limited regarding an optimal age for RRSO, the Monte Carlo simulation model provides estimates of the survival impact of breast and ovarian risk-reduction strategies (eg, mammographic/MRI breast screening; risk-reduction surgery) in women who are carriers of *BRCA1/2* mutations according to the type of *BRCA* mutation present, the specific risk-reduction intervention(s), and the age of the women at the time of the intervention(s).⁹⁶ Survival estimates generated from this model can facilitate shared decision-making regarding choice of a risk-reduction approach (see [Table 2](#)).

A prospective multicenter study reported the benefit of risk-reducing procedures for women with strong genetic predispositions for breast cancer.⁹⁷ The study involved 2482 women diagnosed with *BRCA1/2* gene mutations, almost half of whom chose either RRSO or RRM. During the 3 years of follow up, no cases of breast cancer occurred in the women who opted for RRM. In the same time period, 7% of the women who adopted other approaches received a breast cancer diagnosis. In *BRCA2*-mutation carriers, no cases of ovarian cancer occurred after salpingo-oophorectomy over a 6-year follow-up period, whereas 3% of those who did not undergo the same surgery were diagnosed with ovarian cancer. None of the women who underwent RRM developed breast cancer. RRSO was associated with a reduction in overall mortality (hazard ratio [HR] = 0.40), breast cancer–specific mortality (HR = 0.44), and ovarian cancer–specific mortality (HR = 0.21). Among women who underwent RRSO, only 1.1% developed ovarian cancer.

The NCCN Breast Cancer Risk Reduction Panel recommends limiting RRSO to women with a known or strongly suspected *BRCA1/2* mutation. Peritoneal washings should be performed at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes.⁹⁸ The additional benefit of concurrent hysterectomy is



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

not clear at this time. Women who undergo RRSO should continue with routine health maintenance and breast screening as per the [NCCN Guidelines for Breast Cancer](#) unless a woman has had RRM.

Risk-Reduction Agents

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

Tamoxifen for Risk Reduction

The benefits of tamoxifen, a selective estrogen receptor (ER) modulator (SERM), in the treatment of breast cancer in the adjuvant and metastatic settings are well documented. Retrospective analysis of randomized, controlled, clinical trials comparing tamoxifen to no tamoxifen in the adjuvant treatment of women with breast cancer has shown a reduction in the incidence of contralateral second primary breast cancer.⁹⁹⁻¹⁰² 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 in women with first breast cancers that are ER-positive or have an unknown ER status.¹⁰³

NSABP Breast Cancer Prevention Trial

The effectiveness of tamoxifen in the setting of breast cancer treatment gave rise to the NSABP BCPT study, also known as the P-1 study. It was a randomized clinical trial of healthy women aged 60 years or older, aged 35 to 59 years with a 1.7% or greater cumulative 5-year risk for developing breast cancer, or with a history of LCIS.⁵⁵ Both premenopausal and postmenopausal women were enrolled in the trial and randomized in a double-blinded fashion to treatment with tamoxifen, 20 mg daily for 5 years, or placebo. Invasive breast cancer

incidence was the primary study endpoint; high-priority secondary endpoints included the occurrence of thromboembolic disease, cardiovascular disease, bone fracture, endometrial cancer, noninvasive breast cancer, and breast cancer mortality. The trial was unblinded and initial findings were reported in 1998. A subsequent report on this trial has been published, which takes into account 7 years of follow-up data subsequent to the point where the study was unblinded. However, nearly one-third of the placebo participants began taking a SERM when the study was unblinded, which decreased the proportion of women in the placebo group relative to the tamoxifen group, potentially confounding the long-term results.⁵⁶

The results of the P-1 study showed that treatment with tamoxifen decreased the short-term risk for breast cancer by 49% in healthy women aged 35 years or older who had an increased risk for the disease.⁵⁵ Risk-reduction benefits were demonstrated across all age groups, in pre-menopausal and post-menopausal women. The difference in average annual rates for invasive breast cancer was 3.30 cases per 1,000 women (ie, 6.76 cases per 1,000 women in the placebo group and 3.43 cases per 1,000 women in the group taking tamoxifen). The absolute risk reduction was 21.4 cases per 1,000 women over 5 years.⁵⁵ In terms of numbers needed to treat, this corresponds to treatment of 47 women with tamoxifen to prevent 1 case of invasive breast cancer. Updated results indicate that breast cancer risk was reduced by 43% in this population after 7 years of follow-up.⁵⁶ The reduction in invasive breast cancer risk in participants with atypical hyperplasia was particularly striking (risk ratio [RR], 0.14; 95% CI, 0.03–0.47) in the initial study analysis, and a 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



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

women taking tamoxifen following a breast cancer diagnosis, major toxicities included hot flashes, invasive endometrial cancer in postmenopausal women, and cataracts. A significant increase in the incidence of pulmonary embolism was also observed in women ≥ 50 years of age taking tamoxifen. The average annual rates of pulmonary embolism per 1000 women were 1.00 versus 0.31 (RR= 3.19; 95% CI, 1.12–11.15).⁵⁵

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 1,000 women compared with 2.71 per 1,000 women treated with placebo, for a RR of 0.81 (95% CI, 0.56–1.16).⁵⁵ Annual mortality after 7 years of follow-up was 2.80 per 1,000 women compared with 3.08 per 1,000 women in the tamoxifen and placebo groups, respectively, for a RR of 1.10 (95% CI, 0.85–1.43).⁵⁶

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.¹⁰⁴ These findings may be related to the greater likelihood for development of ER-positive tumors in *BRCA2* mutation carriers relative to *BRCA1* mutation carriers. However, this analysis was limited by the very small number of patients with a *BRCA1/2* mutation.

Based on the BCPT [P-1] study results, in October 1998 the U.S. Food and Drug Administration (FDA) approved tamoxifen for breast cancer risk reduction for women at increased risk for breast cancer.

European Studies of Tamoxifen

Three European studies comparing tamoxifen with placebo for breast cancer risk reduction have also been reported. The Royal Marsden Hospital study was a pilot trial of tamoxifen versus placebo in women ages 30 to 70 years who were at increased breast cancer risk based largely on their family history.^{105,106} Women 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.¹⁰⁶ An analysis of updated findings from the Royal Marsden Hospital study did demonstrate a nonsignificant breast cancer risk-reduction benefit with tamoxifen use (ie, 62 cases of breast cancer in 1238 women receiving tamoxifen vs. 75 cases of breast cancer in 1233 women in the placebo arm).¹⁰⁵

Most recently, an analysis of blinded results from the Royal Marsden Hospital trial at 20-year follow-up showed no difference in breast cancer incidence between the groups randomly assigned to tamoxifen or placebo (HR = 0.78; 95% CI, 0.58–1.04; $P = .10$).¹⁰⁷ 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 women ages 35 to 70 years without breast cancer, who had undergone a previous hysterectomy, to receive tamoxifen or placebo for 5 years.¹⁰⁸ Women 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.¹⁰⁸⁻¹¹⁰



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

Thromboembolic events, predominantly superficial thrombophlebitis, were increased in women treated with tamoxifen. A subset of women 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.^{110,111} 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).¹¹²

The first International Breast Cancer Intervention Study (IBIS-I) randomized 7152 women aged 35 to 70 years at increased risk for breast cancer to receive either tamoxifen or placebo for 5 years.¹¹³ Tamoxifen provided a breast cancer (invasive or ductal carcinoma in situ) risk reduction of 32% (95% CI, 8–50; $P = .013$). Thromboembolic events increased with tamoxifen (odds ratio = 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 women ($P = .028$).

In an updated analysis of the blinded IBIS-I trial at a median follow-up of 96 months, the relative risk for breast cancer for the tamoxifen arm compared with placebo was 0.73 (95% CI, 0.58–0.91; $P = .004$).¹¹⁴ 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. 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. These results provide randomized evidence that the benefits of tamoxifen continue following cessation of treatment while many of the side effects diminish or disappear.

The use of tamoxifen as a breast cancer risk-reduction agent has most recently been evaluated in the STAR Trial^{57,58} (see section on *The STAR Trial* below, MS-11).

Raloxifene for Risk Reduction

Raloxifene is a second-generation SERM that is chemically different from tamoxifen and appears to have similar anti-estrogenic effects with considerably less endometrial stimulation. The efficacy of raloxifene as a breast cancer risk-reduction agent has been evaluated in several clinical studies. In 2007, the FDA expanded the indications for raloxifene to include reduction in risk for invasive breast cancer in postmenopausal women with osteoporosis, and reduction in risk for invasive breast cancer in postmenopausal women 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 women with osteoporosis.¹¹⁵ A total of 7705 postmenopausal women 31 to 80 years of age were randomized to receive placebo, 60 mg/day of raloxifene, or 120 mg/day of raloxifene for 3 years. At study entry, participants were required to have osteoporosis (defined as a bone density at least 2.5 standard deviations below the mean for young women) or a history of



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

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 women treated with raloxifene, compared with those who received placebo.

After a median follow-up of 40 months in the MORE trial, breast cancer was reported in 40 patients: 27 cases in 2576 women receiving placebo and 13 cases in 5129 women receiving raloxifene.¹¹⁶ The relative risk of developing invasive breast cancer on raloxifene, compared with placebo, was 0.24 (95% CI, 0.13–0.44). Raloxifene markedly decreased the risk for ER-positive cancers (relative risk = 0.10; 95% CI, 0.04–0.24) but did not appear to influence the risk of developing an ER-negative cancer (relative risk = 0.88; 95% CI, 0.26–3.0). Although 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 women enrolled and stratified into treatment arms in this study.¹¹² Furthermore, the patients enrolled in the MORE trial were, on average, at lower risk for breast cancer and older than the patients enrolled in the NSABP BCPT [P-1] study.

Side effects associated with the 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 women receiving 60 mg/day raloxifene vs. 0.2% for placebo) and pulmonary emboli (0.3% for women receiving 120 mg/day raloxifene vs. 0.1% for placebo) associated with raloxifene treatment. However, there was no increase in the risk 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, CORE was designed to assess the effect of 4 additional years of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis. A secondary endpoint was the incidence of invasive ER-positive breast cancer. Data from the CORE trial were reported in 2004.¹¹⁷

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.¹¹⁷ 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).¹¹⁷

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 (relative risk = 2.17; 95% CI, 0.83–5.70) in the raloxifene group of the CORE trial compared to the placebo group. There was no statistically significant difference in endometrial events (bleeding, hyperplasia, and cancer) between the raloxifene and placebo groups during the 4 years of CORE or the 8 years of MORE and CORE. During the 8 years of the MORE and CORE trials, raloxifene increased the risk for hot flushes and leg cramps compared with placebo; these risks were observed during the MORE trial but not during the additional 4 years of therapy in CORE. While it is possible



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

that hot flushes and leg cramps are early events that do not persist with continued therapy, it is also possible that an increased risk of these adverse events was not observed in the CORE trial as a result of selection bias (ie, women who experienced these symptoms in the MORE trial may have chosen not to continue in the CORE trial).

The results from the CORE trial are not entirely straightforward because of the complex design of the trial. Of the 7705 patients randomized in the MORE trial, only 4011 chose to continue, blinded to therapy, in CORE; this drop off likely introduces bias in favor of the treatment group. In the CORE trial, the researchers did not randomize the patients again (1286 in the placebo arm, 2725 in the raloxifene arm), maintaining the double blinding of the original trial.

The RUTH Trial

In the Raloxifene Use for The Heart (RUTH) trial, postmenopausal women with an increased risk for coronary heart disease were randomly assigned to raloxifene or placebo arms.^{118,119} 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.¹¹⁹ 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 2006.⁵⁷

In the STAR trial, 19,747 postmenopausal women 35 years or older at increased risk for invasive breast cancer as determined by the modified Gail model or with a personal history of LCIS were enrolled into one of two treatment arms (no placebo arm). The primary study endpoint was invasive breast cancer; secondary endpoints included quality of life, and incidences of noninvasive breast cancer, DVT, pulmonary embolism, endometrial cancer, stroke, cataracts, and death. At an average follow-up of approximately 4 years, no statistically significant differences between patients receiving 20 mg/day of tamoxifen or 60 mg/day 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 BCPT [P-1] study to reduce breast cancer risk by nearly 50%. In addition, raloxifene was shown to be as effective as tamoxifen in reducing the risk for invasive cancer in the subset of patients with a history of LCIS or atypical hyperplasia. However, raloxifene was not as effective as tamoxifen in reducing the risk for noninvasive breast cancer, although the observed difference was not statistically significant (RR = 1.40; 95% CI, 0.98–2.00).⁵⁵

At a median follow-up of nearly 8 years (81 months) involving 19,490 women, raloxifene was shown to be about 76% as effective as



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

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.⁵⁸ Raloxifene remained as effective as tamoxifen in reducing the risk for invasive cancer in women with LCIS (RR, 1.13; 95% CI, 0.76–1.69), but was less effective than tamoxifen for those with a history of atypical hyperplasia (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.⁵⁸ 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.¹²⁰

Aromatase Inhibitors for Risk Reduction

A number of clinical trials testing the use of aromatase inhibitors (AIs) in the adjuvant therapy of postmenopausal women with invasive breast cancer have been reported. The first of these studies, the Arimidex, Tamoxifen, Alone or in Combination trial (ATAC trial), randomized postmenopausal women with invasive breast cancer to anastrozole versus tamoxifen versus anastrozole plus tamoxifen in a double-blinded fashion.¹²¹ 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 women treated with anastrozole alone compared with tamoxifen (odds ratio = 0.62; 95% CI, 0.38–1.02; $P = .062$) and a significant reduction in contralateral breast cancers was seen in the subset of women with hormone receptor-positive first cancers (odds ratio = 0.56; 95% CI, 0.32–0.98; $P = .04$).¹²² 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.^{123,124}

In the Breast International Group (BIG) 1-98 trial postmenopausal women with early-stage breast cancer were randomized to receive 5 years of treatment with one of the following therapeutic regimens: letrozole; sequential letrozole followed by tamoxifen; tamoxifen; or sequential tamoxifen followed by letrozole. Risk for breast cancer recurrence was lower in women in the letrozole arm relative to the tamoxifen arm.¹²⁵

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 women were randomly assigned to either exemestane (2285 patients) or



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

placebo (2275 patients).³ 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).³

The IBIS-II study included 3864 postmenopausal women at high risk for breast cancer, defined by family history of breast cancer or prior diagnosis of DCIS, LCIS, or atypical ductal hyperplasia.⁴ (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.⁴

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

Based on data from the BCPT⁵⁵ and STAR⁵⁷ trials, Freedman et al have developed tables of benefit/risk indices for women aged 50 years and older to compare raloxifene versus no treatment (placebo) and tamoxifen versus no treatment.² 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 women with and without a uterus, black women with and without a uterus, and Hispanic women with and without a uterus. The NCCN Breast Cancer Risk Reduction Panel recommends using

these tables² while counseling postmenopausal women regarding use of raloxifene and tamoxifen for breast cancer risk reduction.

Tamoxifen Recommendations

The NCCN Breast Cancer Risk Reduction Panel recommends tamoxifen (20 mg/day) as an option to reduce breast cancer risk in healthy pre- and postmenopausal women ≥ 35 years of age, whose life expectancy is ≥ 10 years, and who have a $\geq 1.7\%$ 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1). The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for tamoxifen use in premenopausal women at increased risk for breast cancer is relatively favorable (category 1), and that the risk/benefit ratio for tamoxifen use in postmenopausal women is influenced by age, presence of uterus, or other comorbid conditions (category 1). Early studies suggest that lower doses of tamoxifen over shorter treatment periods may reduce breast cancer risk in postmenopausal women, but these findings need to be validated in phase III clinical trials.¹²⁶ Only limited data are currently available regarding the efficacy of tamoxifen risk reduction in *BRCA1/2* mutation carriers and women who have received prior thoracic radiation. The efficacy of tamoxifen risk reduction in women with *BRCA1/2* mutations is less well studied than in other risk groups. However, available data suggest a benefit.¹⁰⁴

The utility of tamoxifen as a breast cancer risk-reduction agent in women < 35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of tamoxifen as a risk-reduction agent.

There is evidence that certain drugs (eg, serotonin reuptake inhibitors [SSRIs]) interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 2D6



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

enzyme (CYP2D6) involved in the metabolism of tamoxifen.¹²⁷ 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.¹²⁷ Citalopram and venlafaxine do not disrupt tamoxifen metabolism.

It has also been reported that certain CYP2D6 genotypes are markers of poor tamoxifen metabolism.^{128,129} Nevertheless, the consensus of the NCCN Breast Cancer Risk Reduction Panel is that further validation of this biomarker is needed before it can be used to select patients for tamoxifen therapy.

Raloxifene Recommendations

The NCCN experts serving on the Breast Cancer Risk Reduction Panel feel strongly that tamoxifen is a superior choice of risk-reduction agent for most postmenopausal women desiring non-surgical risk-reduction therapy. This is based on the updated STAR trial results that showed diminished benefits of raloxifene compared to tamoxifen after cessation of therapy.⁵⁸ However, consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in some women.

If raloxifene is chosen, the NCCN Breast Cancer Risk Reduction Panel recommends use of 60 mg/day. Data regarding use of raloxifene to reduce breast cancer risk is limited to healthy postmenopausal women ≥ 35 years who have a $\geq 1.7\%$ 5-year risk for breast cancer as determined by the modified Gail model, or who have a history of LCIS. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for raloxifene use in postmenopausal women at increased risk for breast cancer is influenced by age and comorbid conditions (category 1). Since there are no currently available data regarding the efficacy of raloxifene risk reduction in *BRCA1/2* mutation carriers and women who have received prior thoracic radiation, use of

raloxifene in these populations is designated as a category 2A recommendation by the NCCN Breast Cancer Risk Reduction Panel. Use of raloxifene to reduce breast cancer risk in premenopausal women is inappropriate unless part of a clinical trial. The utility of raloxifene as a breast cancer risk-reduction agent in women <35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of raloxifene as a risk-reduction agent.

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 women desiring non-surgical risk-reduction therapy (category 1). This is based on the results of the MAP.3 trial³ and the IBIS-II trial.⁴ The NCCN Breast Cancer Risk Reduction Panel recommends use of 25 mg/day of exemestane or 1 mg per day of anastrozole. Data regarding use of AI (exemestane and anastrozole) to reduce breast cancer risk are limited to postmenopausal women 35 years of age or older with a Gail model 5-year risk score $>1.66\%$ or a history of LCIS. The consensus of the NCCN Breast Cancer Risk Reduction Panel is that the risk/benefit ratio for use of an AI in postmenopausal women 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 women is inappropriate unless part of a clinical trial. The utility of an AI as a breast cancer risk-reduction agent in women <35 years of age is not known. There are insufficient data on the influence of ethnicity and race on the efficacy and safety of raloxifene as a risk-reduction agent.

Exemestane and anastrozole 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.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

Monitoring Patients on Risk Reduction Agents

Follow-up of women treated with risk-reduction agents for breast cancer risk reduction should focus on the early detection of breast cancer and the management of adverse symptoms or complications. Appropriate monitoring for breast cancer and the evaluation of breast abnormalities should be performed according to the guidelines described for high-risk women in the [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#). The population of women eligible for risk-reduction therapy with tamoxifen, raloxifene, anastrozole, or exemestane is at sufficiently increased risk for breast cancer to warrant, at a minimum, yearly bilateral mammography, a clinical breast examination every 6–12 months, and encouragement of breast awareness.

Endometrial Cancer

Results from the BCPT [P-1] study indicated that women ≥ 50 years of age treated with tamoxifen have an increased risk of developing invasive endometrial cancer. For women ≥ 50 years the risk of developing endometrial cancer while on tamoxifen compared to placebo was high (RR, 4.01, 95% CI 1.70–10.90).^{55,56} An increased risk for endometrial cancer was *not* observed in women ≤ 49 years of age treated with tamoxifen in this study (RR, 1.21, 95% CI, 0.41–3.60).^{55,56} Although the only death from endometrial cancer in the NSABP BCPT [P-1] occurred in a placebo-treated subject,^{55,56} 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.¹³⁰ 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.^{131,132}

Updated results from the NSABP studies have indicated that incidence of both endometrial adenocarcinoma and uterine sarcoma is increased in women taking tamoxifen when compared to the placebo arm.¹³³ Several other studies have also supported an association between tamoxifen therapy and an increased risk of developing uterine sarcoma.^{131,132,134,135} 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.¹³⁶

Use of raloxifene has not been associated with an increased incidence of endometrial cancer in the MORE trial.¹¹⁶ 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, 95% CI 0.36–0.83).⁵⁸ For women with an intact uterus, a baseline gynecologic assessment is recommended prior to administration of the risk-reduction agent, and follow-up gynecologic assessments should be performed at each visit.¹³⁷ The vast majority of women with tamoxifen-associated endometrial cancer present with vaginal spotting as an early symptom of cancer. Therefore, prompt evaluation of vaginal spotting in the postmenopausal woman is essential.

At present, there is insufficient evidence to recommend the performance of uterine ultrasonography or endometrial biopsy for routine screening in asymptomatic women.^{138–140} In women diagnosed with endometrial cancer while taking a risk-reduction agent, the drug should be discontinued until the endometrial cancer has been fully treated. The NCCN Breast Cancer Risk Reduction Panel believes that it is safe and reasonable to resume therapy with a risk-reduction agent after completion of treatment for early-stage endometrial cancer.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

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.^{141,142} Furthermore, these reports have not been confirmed in the randomized controlled trials of tamoxifen. A 1.14 relative risk of cataract formation (95% CI, 1.01–1.29), compared with placebo, has been reported in the BCPT [P-1] study, and individuals developing cataracts while on tamoxifen have a relative risk for cataract surgery of 1.57 (95% CI, 1.16–2.14), compared with placebo.⁵⁵ After 7 years of follow-up in the BCPT [P-1] study, relative risks of cataract formation and cataract surgery were similar to those initially reported.⁵⁶ In the MORE trial, raloxifene use was not associated with an increase in the incidence of cataracts compared with placebo (relative risk = 0.9; 95% CI, 0.8–1.1).¹⁴³ In the STAR trial, the incidence of cataract development and occurrence of cataract surgery was significantly higher in the group receiving tamoxifen compared with the group receiving raloxifene.^{58,143} 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.^{58,143} Thus, patients experiencing visual symptoms while undergoing treatment with tamoxifen should seek ophthalmologic evaluation.

Bone Mineral Density

Bone is an estrogen-responsive tissue, and tamoxifen can act as either an estrogen agonist or estrogen antagonist with respect to bone, depending on the menstrual status of a woman.^{106,144–146} In premenopausal women, tamoxifen may oppose the more potent effects of estrogen on the bone and potentially increase the risk for osteoporosis, whereas tamoxifen in the presence of typically lower estrogen levels in postmenopausal women is associated with an increase in BMD.^{55,56} 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. Changes in BMD are of concern in women on AI therapy. Therefore, a baseline BMD scan is recommended before initiating therapy with an AI such as anastrozole or exemestane.

Raloxifene has been shown to increase BMD and to reduce incidence of vertebral bone fracture in postmenopausal women when compared with placebo.^{115,118} Results from the STAR trial did not reveal any difference in the incidence of bone fracture in the groups of postmenopausal women on either raloxifene or tamoxifen.^{57,58}

Thromboembolic Disease and Strokes

Tamoxifen and raloxifene have been associated with an increased risk of thromboembolic events (ie, DVT, pulmonary embolism) and stroke.^{55, 56–58,116,147} Increased incidences of VTE were observed in the tamoxifen arms of all the placebo-controlled, randomized, risk-reduction trials. Although not statistically significant, all of these trials with the exception of the Royal Marsden trial (which enrolled only younger women) also showed an increase in risk for stroke for women 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.^{148,149} Comparison of the raloxifene and tamoxifen arms of the STAR trial did not show a difference with respect to incidence of stroke,^{57,58} and the risk of fatal stroke was significantly higher for women in the RUTH trial with underlying heart disease receiving raloxifene.¹¹⁹ However, evidence has shown that women with a Factor V Leiden or prothrombin G20210 → A mutation receiving tamoxifen therapy in the BCPT [P-1] study were not at increased risk of developing VTE compared to women without these mutations.¹⁵⁰ Although prospective screening of women for Factor V Leiden or



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

prothrombin mutations or intermittent screening of women for thromboembolic disease is unlikely to be of value, women taking tamoxifen or raloxifene should be educated regarding the symptoms associated with DVT and pulmonary emboli. They should also be informed that prolonged immobilization may increase risk of VTE, and should be instructed to contact their physicians immediately if they develop symptoms of DVT or pulmonary emboli. Women with documented thromboembolic disease should receive appropriate treatment for the thromboembolic condition and should permanently discontinue tamoxifen or raloxifene therapy.

Managing Side Effects of Risk-Reduction Agents

Hot flashes are a common menopausal complaint. In the BCPT [P-1] study, hot flashes occurred in approximately 81% of women treated with tamoxifen and 69% of women treated with placebo.⁵⁵ In the STAR trial, women receiving tamoxifen reported a significantly increased incidence of vasomotor symptoms relative to women receiving raloxifene,¹²⁰ although raloxifene use has also been associated with an increase in hot flash severity and/or frequency when compared with placebo.¹¹⁶ In women whose quality of life is diminished by hot flashes, an intervention to eliminate or minimize hot flashes should be undertaken. Estrogens and/or progestins have the potential to interact with SERMs and are not recommended by the NCCN Breast Cancer Risk Reduction Panel for the treatment of hot flashes for women on a risk-reduction agent outside of a clinical trial.

Gabapentin, a gamma-aminobutyric acid (GABA) analog used primarily for seizure control and management of neuropathic pain, has been reported to moderate both the severity and duration of hot flashes.¹⁵¹⁻¹⁵⁴ It has been hypothesized that the mode of action of gabapentin is via central temperature regulatory centers.^{151,152} Results from a

randomized, double-blind, placebo-controlled study involving the use of gabapentin to treat hot flashes in 420 women with breast cancer have been reported. The three treatment arms of the trial were as follows: 300 mg/day gabapentin; 900 mg/day gabapentin; and placebo. Study duration was 8 weeks, and most of the women in the study (68%–75% depending on treatment arm) were taking tamoxifen as adjuvant therapy. Women in the placebo group experienced reductions in severity of hot flashes of 21% and 15% at 4 and 8 weeks, respectively, whereas those in the treatment arms reported reductions of 33% and 31% with lower-dose gabapentin, and 49% and 46% with higher-dose gabapentin at 4 and 8 weeks, respectively. Only women receiving the higher dose of gabapentin had significantly fewer and less severe hot flashes. Side effects of somnolence or fatigue were reported in a small percentage of women taking gabapentin.¹⁵⁴

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 ($P = .03$).¹⁵⁵ Participants receiving venlafaxine reported mouth dryness, reduced appetite, nausea, and constipation with increased prevalence at increased dosages. Based on these findings the authors suggested a starting dose of 37.5 mg with an increase, as necessary after one week, to 75 mg if a greater degree of symptom control is desired. However, this study followed subjects for only 4 weeks.

Another antidepressant, paroxetine, an SSRI, has also been studied for the relief of hot flash symptoms. A double-blind, placebo-controlled trial recruited 165 menopausal women who were randomized into 3 arms



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

(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.¹⁵⁶ Adverse events, reported by 54% of subjects receiving placebo and 58% receiving paroxetine, generally included nausea, dizziness, and insomnia.

In a stratified, randomized, double-blind, cross-over, placebo-controlled study, 151 women reporting a history of hot flashes were randomized to one of 4 treatment arms (10 mg or 20 mg of paroxetine for 4 weeks followed by 4 weeks of placebo or 4 weeks of placebo followed by 4 weeks of 10 mg or 20 mg of paroxetine).¹⁵⁷ 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 women receiving 20 mg paroxetine compared with values of 26.6% and 28.8% in the placebo group. No significant differences in efficacy were observed with the lower and higher paroxetine doses. Rates of the most commonly reported side effects did not differ among the 4 arms, although nausea was significantly increased in women receiving 20 mg paroxetine relative to the other arms, and a greater percentage of patients receiving the higher dose of paroxetine discontinued treatment.

While these reports appear promising, further randomized studies of the use of these agents in women experiencing hot flash symptoms, especially those also taking tamoxifen, are needed to assess the long-term effectiveness and safety of these agents. In this context it should be noted that recent evidence has suggested that concomitant use of tamoxifen with certain SSRIs (eg, paroxetine and fluoxetine) may decrease plasma levels of endoxifen and 4-OH tamoxifen, active

metabolites of tamoxifen, and may impact its efficacy.^{127,158} These SSRIs may interfere with the enzymatic conversion of tamoxifen to its active metabolites by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. Caution is advised about co-administration of these drugs with tamoxifen. Citalopram and venlafaxine appear to have only minimal effects on tamoxifen metabolism.

Of interest in this context are results of a retrospective evaluation of data from the Women's Healthy Eating and Living randomized trial, which suggest an inverse association between hot flashes and breast cancer recurrence for women with a history of breast cancer receiving tamoxifen. These results suggest that hot flashes in women receiving tamoxifen may be an indicator of the biologic availability and, thus, effectiveness of the drug. However, additional studies are needed to further elucidate whether hot flashes are predictive of benefit from tamoxifen.¹⁵⁹

A recent report of 2 nonrandomized, parallel study cohorts of women with DCIS or those at high risk for breast cancer (eg, those with LCIS, atypical hyperplasia, or $\geq 1.7\%$ 5-year breast cancer risk by the Gail model) comparing women receiving tamoxifen alone with women receiving tamoxifen concomitantly with HT (mean duration of HT at start of study approximately 10 years) did not show a difference in the rate of tamoxifen-induced hot flashes.¹⁶⁰ The NCCN Breast Cancer Risk Reduction Panel recommends against the use of HT for women taking tamoxifen or raloxifene outside of a clinical trial.

A variety of other substances for the control of hot flashes have been described.¹⁶¹ Both the oral and transdermal formulations of clonidine reduce hot flashes in a dose-dependent manner.¹⁶²⁻¹⁶⁴ Toxicities associated with clonidine include dry mouth, constipation, and



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

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.¹⁶⁵ 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.¹⁶⁶ 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.¹⁶⁷

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,^{151,153-157} suggesting that a considerable proportion of patients might be helped through a trial of therapy of limited duration. However, not all women who experience hot flashes require medical intervention, and the decision to intervene requires consideration of the efficacy and toxicity of the intervention. In addition, a study of women receiving tamoxifen for early-stage breast cancer showed a decrease in hot flashes over time.¹⁶⁸

Components of Risk Reduction Counseling

Women should be monitored according to the [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#). Women with known or suspected *BRCA 1/2*, *TP53*, *PTEN*, or other gene mutations associated with breast cancer risk or those with close relatives with breast and/or ovarian cancer should also be followed according to the [NCCN](#)

[Guidelines for Genetic/Familial Risk Assessment: Breast and Ovarian](#) whether or not they choose to undergo risk-reduction therapy. Women who have abnormal results from their clinical breast examination or bilateral mammogram should be managed according to the [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#) or, if results indicate malignancy, the women should be treated according to the [NCCN Guidelines for Breast Cancer](#). Although the NCCN Breast Cancer Risk Reduction Panel recommends that women with LCIS be managed according to the NCCN Breast Cancer Risk Reduction Guidelines, risk-reduction strategies for patients with LCIS are also described in the [NCCN Guidelines for Breast Cancer](#).

All women who are appropriate candidates for breast cancer risk-reduction intervention should undergo counseling that provides a description of the available strategies, including a healthy lifestyle, to decrease breast cancer risk.¹⁶⁹ Options for breast cancer risk reduction should be discussed in a shared decision-making environment. The counseling should include a discussion and consideration of: 1) the individual's overall health status, including menopausal status, medical history, and medication history (eg, hysterectomy status, prior history of VTE, current use of hormones or SSRI, 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



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

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.¹⁷⁰ 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 with women who are considering non-surgical breast cancer risk reduction should incorporate an explanation of data from the BCPT [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 women with *PTEN* mutations should be discussed while considering a risk-reducing agent.

Counseling on Use of a SERM for Breast Cancer Risk Reduction

The BCPT [P-1] study showed that the toxicity profile of tamoxifen is much more favorable in younger women, and the benefits in relative risk reduction are similar across all age groups and risk groups.⁵⁵ The tamoxifen treatment risk/benefit ratio is especially favorable in women between the ages of 35 and 50 years. Unfortunately, individualized data regarding the risk/benefit ratio for tamoxifen are not generally available except for the broad age categories of ages 50 years and younger versus older than 50 years of age. Tamoxifen, unlike raloxifene, is a risk-reduction agent that can be used by premenopausal women. In addition, tamoxifen may be more effective than raloxifene in reducing the incidence of noninvasive breast cancer, although the difference is

not statistically significant at long-term follow-up.^{57,58} Further, tamoxifen was reported by patients in the STAR trial to be associated with better sexual function than raloxifene.¹²⁰ However, tamoxifen has been associated with an increased incidence of invasive endometrial cancer relative to placebo in women ≥ 50 years of age,^{55,56} and an increased incidence of endometrial hyperplasia and invasive endometrial cancer relative to raloxifene,^{57,58} possibly making it a less attractive choice in women with a uterus. Use of raloxifene to reduce breast cancer risk may be preferred by postmenopausal women with a uterus or those at risk for developing cataracts. All women receiving a breast cancer risk-reduction agent should be counseled with respect to signs and symptoms of possible side effects associated with use of these agents, and the recommended schedules for monitoring for the presence of certain adverse events. Contraindications to tamoxifen or raloxifene include history of VTE, thrombotic stroke, transient ischemic attack, current pregnancy or pregnancy potential without effective method of contraception, or known inherited clotting trait.

The optimal duration of SERM therapy for breast cancer risk reduction is not known. The BCPT [P-1] and STAR trials studied 5 years of risk-reduction therapy with either tamoxifen or raloxifene.^{55,57} However, based on the updated STAR results, which showed that the benefits of raloxifene diminished after cessation of therapy,⁵⁸ 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^{171,172} 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



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

now recommended for both premenopausal women and postmenopausal women for preventing cancer recurrence in the NCCN Guidelines for Breast Cancer and the recently updated ASCO Guidelines.¹⁷³ 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, women should continue to be monitored according to the [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#) and should continue to undergo monitoring for late toxicity, especially for endometrial cancer and cataracts.

The prolonged effectiveness of tamoxifen as an agent to reduce breast cancer risk, particularly with respect to the development of ER-positive disease, is supported by results of several placebo-controlled, randomized trials at long-term follow-up.^{56,107,114} The recent results from the STAR trial suggest that although a 5-year course of raloxifene retains considerable benefit with respect to the prevention of invasive breast cancer at a median follow-up of 81 months, the breast cancer preventive benefit of tamoxifen therapy for 5 years appears to be sustained for a longer period of time.⁵⁸

The NCCN Breast Cancer Risk Reduction Panel recommends using the tables from the Freedman et al publication² while counseling postmenopausal women 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 trial³ limited to postmenopausal women 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 women in the MAP.3 trial taking exemestane and for those taking the placebo. Women taking exemestane had a small, but not statistically significant increase in menopausal symptoms, such as hot flashes (18.3% vs. 11.9%) and arthritis (6.5% vs. 4.0%).³

Data regarding anastrozole are from a single, large, randomized trial, IBIS-II.⁴ The trial included postmenopausal women 40 to 70 years of age with a higher risk of developing cancer compared with the general population. Women who did not meet these criteria but had a Tyrer-Cuzick model 10-year breast cancer risk >5% were also included.⁴ Musculoskeletal and vasomotor events were reported in both arms of the trial and were found to be significantly higher in the anastrozole arm ($P = .0001$); fracture rates were similar in both arms.⁴ The optimal duration of AI therapy is currently unknown. Changes in BMD are of concern in women receiving AI therapy. Therefore, a baseline BMD scan is recommended before initiating exemestane therapy. The role of calcium, vitamin D, and maintaining a healthy lifestyle in maintaining bone health must be emphasized in healthy postmenopausal women who are receiving exemestane.

Counseling Prior to Risk Reduction Surgery

For women at very high risk 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.¹⁷⁴⁻¹⁷⁶ Such surgery has the potential to negatively impact perceptions of body image, ease of forming new relationships, and the quality of existing



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

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 disease¹⁷⁷ to enable the woman 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 for many women following RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction.¹⁷⁸ Psychological consultations may also be considered.

Discussions regarding the risk for ovarian cancer and the option of RRSO for breast and ovarian cancer risk reduction should also be undertaken with women who are known carriers of a *BRCA1/2* mutation. Other topics 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 women undergoing RRSO did not negate the reduction in breast cancer risk associated with the surgery.¹⁷⁹ In addition, results of a recent case-control study of *BRCA1* mutation carriers showed no association between use of HT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers.¹⁷⁹ 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*).^{180,181} 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 a RRM is likely to remain a personal decision.¹⁸² 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.⁷⁰ 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 women to make choices and changes compatible with a healthy lifestyle.

Breast Cancer Risks Associated with Hormone Therapy

The Women’s Health Initiative (WHI) enrolled 161,809 postmenopausal women 50 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 women with intact uteri at baseline randomized to receive estrogen plus progestin or placebo,¹⁸³ and a trial of 10,739 women with prior hysterectomy randomized to receive estrogen alone or placebo.¹⁸⁴ The former trial was terminated early due to evidence for breast cancer harm, along with a global index associated with overall harm. In that study, a 26% increased incidence



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

of breast cancer was observed in the treatment group (HR = 1.26; 95% CI, 1.00–1.59). An increased incidence of abnormal mammograms was also observed for women in the WHI who received estrogen plus progestin, and was attributed to an increase in breast density.¹⁸⁵ Of greater concern is that HT was associated with significant increase in rates of both breast cancer incidence and breast cancer–related mortality,¹⁸⁶ although the increased risk for breast cancer rapidly declined following cessation of HT.¹⁸⁷

However, an increased risk for breast cancer was not observed in the trial of women who had undergone hysterectomies and were receiving unopposed estrogen. In fact, the rate of breast cancer was lower in the group receiving estrogen relative to the placebo group, although this difference was not considered to be statistically significant.¹⁸⁴ The lower incidence of breast cancer seen among women randomized to estrogen alone during the intervention period became statistically significant with extended follow-up for a mean of 10.7 years.¹⁸⁸ However, an increased incidence of abnormal mammograms was observed in the group of women receiving estrogen,¹⁸⁹ as well as a doubling of the risk for benign proliferative breast disease.¹⁹⁰ Analysis of the data from this randomized controlled WHI trial showed use of estrogen alone to significantly increase mammographic breast density compared with women receiving placebo; this effect was observed for at least a 2-year period.¹⁹¹ 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 (relative risk = 1.41; 95% CI, 0.95–2.10);¹⁹² the Million Women Study of women 50 to 64 years of age, which showed

an association between current use of estrogen-only HT and increased risk for breast cancer (relative risk = 1.30; 95% CI, 1.21–1.40; $P < .0001$);¹⁹³ and the Nurses' Health Study, which demonstrated a significantly increased breast cancer risk after long-term use (20 years or longer) of estrogen alone (relative risk = 1.42; 95% CI, 1.13–1.77).¹⁹⁴

It has been noted that there are important differences in the populations enrolled in the WHI randomized clinical trials relative to the women followed in the observational studies with respect to duration of exposure to HT and age at initiation of HT.¹⁹⁵ For example, many of the women in the WHI clinical trials did not start receiving HT until years after menopause, whereas those in the population-based studies were more likely to initiate HT at menopause and to have been exposed to such treatment for longer periods of time. One hypothesis put forward to explain the apparent contradictions in the summary of studies of HT described above is that short-term use of estrogen following a period of estrogen deprivation may decrease breast cancer risk by inducing apoptosis of occult breast cancer tumors, whereas long-term use of estrogen may initiate and promote the growth of new tumors, thereby increasing breast cancer risk.¹⁹⁶ However, further studies are needed to evaluate this hypothesis. Another possible explanation for the decrease in breast cancer risk observed in the first 2 years of the WHI randomized controlled trial of postmenopausal women receiving estrogen plus progestin may be related to HT effects on breast tissue and subsequent interference with the ability of mammography to detect new breast cancer tumors.¹⁹⁵

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.^{183,184} However, a more recent secondary analysis from the WHI randomized controlled trials showed a trend for more effective reduction in the risk for



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

cardiovascular disease with initiation of HT closer to menopause compared with administration of HT to women who experienced a greater time gap between menopause and the start of such therapy.¹⁹⁷ Nevertheless, recent results from a large French cohort control study show a significantly increased risk for breast cancer in women receiving short-term (ie, 2 years or less) estrogen and progesterone shortly after menopause when compared with nonusers.¹⁹⁸

The NCCN Breast Cancer Risk Reduction Panel recommends against the use of HT for women 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 (one to two drinks per day) is associated with an increased risk for breast cancer.^{70,71,72} A 10% increase in breast cancer risk for every 10 grams of alcohol consumed each day was seen in analyses of two cohort studies.^{45,73} A population-based study of 51,847 postmenopausal women provided evidence to support an association between increased alcohol consumption and an increased likelihood of development of ER-positive breast cancer.¹⁹⁹ However, the effect of a reduction in alcohol consumption on the incidence of breast cancer has not been well studied. Even one drink per day modestly elevates breast cancer risk.⁷⁰ The consensus of the NCCN Breast Cancer Risk Reduction Panel is that alcohol consumption should be limited to <1 drink per day.

Exercise

Increased levels of physical activity have been associated with a decreased risk for breast cancer.^{70,200-203} For example, the effect of exercise on breast cancer risk was evaluated in a population-based study of 90,509 women between the ages of 40 and 65 years.²⁰³ A

relative risk of 0.62 (95% CI, 0.49–0.78) was observed for women who reported more than five hours of vigorous exercise per week compared to women who did not participate in recreational activities. These results are supported by another population-based, case-control study of 4538 case patients with newly diagnosed invasive breast cancer and control patients grouped according to race (eg, 1605 black and 2933 white patients). Both black and white women with annual lifetime exercise activity levels exceeding the median activity level for active control subjects were found to have a 20% lower risk for breast cancer when compared to inactive women (odds ratio = 0.82; 95% CI, 0.71–0.93).²⁰⁰ In addition, a prospective assessment evaluating the association of physical activity among 45,631 women showed the greatest reduction in breast cancer risk for women who reported walking/hiking for ≥10 hours per week (relative risk = 0.57; 95% CI, 0.34–0.95).²⁰¹ A study of 320 postmenopausal sedentary women randomly assigned to 1 year of aerobic exercise or a control group showed modest but significant changes in serum levels of estradiol and sex hormone-binding globulin from baseline (ie, a decrease and an increase in these levels, respectively).²⁰⁴ 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.²⁰⁵

Diet

Results from the WHI controlled intervention trial of 48,835 postmenopausal women designed to test the effect of a low-fat diet (eg, fat intake limited to 20% of total caloric intake per day, and increased consumption of fruits, vegetables, and grains) on risk for breast cancer did not show a statistically significant reduction in the incidence of invasive breast cancer in women who followed a low-fat diet over an average of 8.1 years (HR = 0.91, 95% CI, 0.83–1.01).²⁰⁶ Limitations of



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

this type of study include inherent difficulties in assuring compliance with dietary interventions, recall biases, the relatively short duration of the follow-up period, and the likelihood of insufficient differences between the 2 arms with respect to fat intake.²⁰⁷ Furthermore, it is possible that the impact of certain diets on breast cancer risk may be dependent on the age of the study population.^{207,208} For example, results of a number of population-based studies have suggested that the effect of diet composition on breast cancer risk may be much greater during adolescence and early adulthood.^{208,209} Nevertheless, diets in which the main sources of dietary fat are non-hydrogenated and unsaturated have been shown to have cardiovascular benefits.^{208,210}

Epidemiologic studies suggest that vitamin D (from dietary sources and the sun) may play a protective role with respect to decreasing risk of breast cancer development.^{208,211} Furthermore, there is some evidence to suggest that such protection is greatest for women who had more prolonged skin exposure to sunlight and higher dietary intake of sources of vitamin D during adolescence.^{212,213} Current studies are ongoing to evaluate the role of vitamin D on breast cancer risk.

Weight/BMI

There is a substantial amount of evidence indicating that overweight or obese women have a higher risk for postmenopausal breast cancer.^{39,69,70}

Recent results from the Nurses' Health Study evaluating the effect of weight change on the incidence of invasive breast cancer in 87,143 postmenopausal women suggested that women experiencing a weight gain of 25.0 kg or more since age 18 have an increased risk for breast cancer when compared with women who have maintained their weight (relative risk = 1.45; 95% CI, 1.27–1.66).³⁹ Furthermore, women who had never used postmenopausal HT and lost 10.0 kg or more since

menopause and kept the weight off had a significantly lower risk for breast cancer than women who had maintained their weight (relative risk = 0.43; 95% CI, 0.21–0.86). Interestingly, there is evidence that the risk for breast cancer is lower in premenopausal women who are overweight compared with women who are not overweight.⁷⁰

Results from a case-control study of 1073 pairs of women with *BRCA1/2* mutations indicated that a weight loss of 10 or more pounds in women with the *BRCA1* mutation between the ages of 18 and 30 was associated with a decreased risk of developing breast cancer between the ages of 30 and 40 years. (odds ratio = 0.35; 95% CI, 0.18–0.67).²¹⁴

Clinical Trials

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

Summary

Breast cancer risk assessment provides a means of identifying healthy women without a history of personal breast cancer, who are at increased risk for future development of this disease. All women 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 use of tamoxifen, raloxifene, anastrozole, or exemestane substantially decreases the future risk for breast cancer provides an opportunity for a risk-reduction intervention. However, the risks and benefits associated with use of risk-reduction agents for an individual woman should be evaluated and discussed with the woman as part of a shared decision-making process. Women taking a risk-reduction agent must be closely monitored for potential side effects associated with use of these



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

agents. In special circumstances, such as in women who are carriers of a *BRCA1/2* mutation, where the risk for breast cancer is very high, the performance of a bilateral mastectomy or bilateral salpingo-oophorectomy may be considered for breast cancer risk reduction. Women considering either surgery should undergo multidisciplinary consultations prior to surgery so as to become well informed about all treatment alternatives, the risks and benefits of risk-reduction surgery, and, in the case of bilateral mastectomy, the various reconstruction options available. The NCCN Guidelines for Breast Cancer Risk Reduction Panel strongly encourage women 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.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

Table 1

Criteria Used in Calculation of 5-year Risk for Breast Cancer According to the Modified Gail Model

(Available at www.breastcancerprevention.com)

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



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

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

Variable	Survival probability (%) in <i>BRCA1</i> mutation carriers	Survival probability (%) in <i>BRCA2</i> 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.



References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24399786>.
2. Freedman AN, Yu B, 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21537036>.
3. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011;364:2381-2391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21639806>.
4. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 2014;383:1041-1048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24333009>.
5. Murff HJ, Byrne D, Syngal S. Cancer risk assessment: quality and impact of the family history interview. *Am J Prev Med* 2004;27:239-245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15450637>.
6. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. *JAMA* 2004;292:1480-1489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15383520>.
7. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature* 1995;378:789-792. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8524414>.
8. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994;266:66-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7545954>.
9. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 1990;250:1233-1238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1978757>.
10. van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol* 2010;105:1258-1264; author reply 1265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20051941>.
11. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res* 2012;18:400-407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22252256>.
12. Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. *J Med Genet* 2013;50:255-263. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23335809>.
13. Berx G, Staes K, van Hengel J, et al. Cloning and characterization of the human invasion suppressor gene E-cadherin (CDH1). *Genomics* 1995;26:281-289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7601454>.
14. Colditz GA, Willett WC, Hunter DJ, et al. Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. *JAMA* 1993;270:338-343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8123079>.
15. Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. *JAMA* 1993;270:1563-1568. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8371466>.
16. Colditz GA, Kaphingst KA, Hankinson SE, Rosner B. Family history and risk of breast cancer: nurses' health study. *Breast Cancer Res*



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

Treat 2012. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22350789>.

17. Lynch HT, Watson P, Conway TA, Lynch JF. Clinical/genetic features in hereditary breast cancer. *Breast Cancer Res Treat* 1990;15:63-71. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/2322650>.

18. Pharoah PD, Day NE, Duffy S, et al. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997;71:800-809. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9180149>.

19. Berliner JL, Fay AM. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *J Genet Couns* 2007;16:241-260. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17508274>.

20. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med* 2008;359:2143-2153. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19005198>.

21. Pharoah PD, Antoniou A, Bobrow M, et al. Polygenic susceptibility to breast cancer and implications for prevention. *Nat Genet* 2002;31:33-36. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11984562>.

22. Trepanier A, Ahrens M, McKinnon W, et al. Genetic cancer risk assessment and counseling: recommendations of the national society of genetic counselors. *J Genet Couns* 2004;13:83-114. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15604628>.

23. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* 1994;73:643-651. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8299086>.

24. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med* 2004;23:1111-1130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15057881>.

25. Amir E, Evans DG, Shenton A, et al. Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. *J Med Genet* 2003;40:807-814. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14627668>.

26. Evans DG, Howell A. Breast cancer risk-assessment models. *Breast Cancer Res* 2007;9:213. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17888188>.

27. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2007;57:75-89. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17392385>.

28. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet* 1998;62:145-158. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9443863>.

29. Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br J Cancer* 2008;98:1457-1466. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18349832>.

30. Claus EB, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. *Breast Cancer Res Treat* 1993;28:115-120. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8173064>.

31. Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* 1996;14:185-187. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8841191>.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

32. Li CI, Malone KE, Daling JR, et al. Timing of menarche and first full-term birth in relation to breast cancer risk. *Am J Epidemiol* 2008;167:230-239. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17965112>.

33. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst* 2011;103:250-263. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21191117>.

34. Islam T, Matsuo K, Ito H, et al. Reproductive and hormonal risk factors for luminal, HER2-overexpressing, and triple-negative breast cancer in Japanese women. *Ann Oncol* 2012;23:2435-2441. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22328736>.

35. Li CI, Beaber EF, Tang MT, et al. Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20-44 years of age. *Breast Cancer Res Treat* 2013;137:579-587. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23224237>.

36. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-3253. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12824205>.

37. Han D, Nie J, Bonner MR, et al. Lifetime adult weight gain, central adiposity, and the risk of pre- and postmenopausal breast cancer in the Western New York exposures and breast cancer study. *Int J Cancer* 2006;119:2931-2937. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17016824>.

38. Kawai M, Minami Y, Kuriyama S, et al. Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study. *Br J Cancer* 2010;103:1443-1447. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20842123>.

39. Eliassen AH, Colditz GA, Rosner B, et al. Adult weight change and risk of postmenopausal breast cancer. *JAMA* 2006;296:193-201. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16835425>.

40. Suzuki R, Iwasaki M, Inoue M, et al. Body weight at age 20 years, subsequent weight change and breast cancer risk defined by estrogen and progesterone receptor status--the Japan public health center-based prospective study. *Int J Cancer* 2011;129:1214-1224. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21064092>.

41. Suzuki R, Rylander-Rudqvist T, Ye W, et al. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. *Int J Cancer* 2006;119:1683-1689. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16646051>.

42. Feigelson HS, Patel AV, Teras LR, et al. Adult weight gain and histopathologic characteristics of breast cancer among postmenopausal women. *Cancer* 2006;107:12-21. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16718671>.

43. Vrieling A, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat* 2010;123:641-649. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20711809>.

44. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* 2001;286:2143-2151. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11694156>.

45. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 2002;87:1234-1245. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12439712>.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

46. Rosenberg L, Boggs DA, Bethea TN, et al. A prospective study of smoking and breast cancer risk among African-American women. *Cancer Causes Control* 2013;24:2207-2215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24085586>.

47. Greendale GA, Reboussin BA, Slone S, et al. Postmenopausal hormone therapy and change in mammographic density. *J Natl Cancer Inst* 2003;95:30-37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12509398>.

48. Chiu SY, Duffy S, Yen AM, et al. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. *Cancer Epidemiol Biomarkers Prev* 2010;19:1219-1228. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20406961>.

49. Vachon CM, Sellers TA, Scott CG, et al. Longitudinal breast density and risk of breast cancer [abstract]. *Cancer Research* 2011;70:Abstract 4828. Available at: http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/70/8_MeetingAbstracts/4828.

50. Costantino JP, Gail MH, Pee D, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst* 1999;91:1541-1548. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10491430>.

51. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879-1886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2593165>.

52. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. *J Natl Cancer Inst* 1994;86:600-607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8145275>.

53. Gail MH, Costantino JP. Validating and improving models for projecting the absolute risk of breast cancer. *J Natl Cancer Inst* 2001;93:334-335. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11238688>.

54. Rockhill B, Spiegelman D, Byrne C, et al. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. *J Natl Cancer Inst* 2001;93:358-366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11238697>.

55. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371-1388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9747868>.

56. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005;97:1652-1662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16288118>.

57. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2727-2741. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16754727>.

58. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. *Cancer Prev Res (Phila)* 2010;3:696-706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20404000>.

59. Gail MH, Costantino JP, Pee D, et al. Projecting individualized absolute invasive breast cancer risk in African American women. *J Natl Cancer Inst* 2007;99:1782-1792. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18042936>.



60. Matsuno RK, Costantino JP, Ziegler RG, et al. Projecting Individualized Absolute Invasive Breast Cancer Risk in Asian and Pacific Islander American Women. J Natl Cancer Inst 2011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21562243>.

61. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 2003;21:4386-4394. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14645429>.

62. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005;97:1428-1437. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16204692>.

63. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 1993;85:25-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8416252>.

64. Hudson MM, Poquette CA, Lee J, et al. Increased mortality after successful treatment for Hodgkin's disease. J Clin Oncol 1998;16:3592-3600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9817280>.

65. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003;95:971-980. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12837833>.

66. Yahalom J, Petrek JA, Biddinger PW, et al. Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathologic analysis of 45 events in 37 patients. J Clin Oncol 1992;10:1674-1681. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1403050>.

67. Rosen PP, Kosloff C, Lieberman PH, et al. Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. Am J Surg Pathol 1978;2:225-251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/210682>.

68. Haagensen C, Bodian C, Haagensen D, Jr. Breast carcinoma: Risk and detection. Philadelphia, PA: W.B. Saunders; 1981.

69. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000;152:514-527. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10997541>.

70. Mahoney MC, Bevers T, Linos E, Willett WC. Opportunities and strategies for breast cancer prevention through risk reduction. CA Cancer J Clin 2008;58:347-371. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18981297>.

71. Zhang SM, Lee IM, Manson JE, et al. Alcohol consumption and breast cancer risk in the Women's Health Study. Am J Epidemiol 2007;165:667-676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17204515>.

72. Terry MB, Zhang FF, Kabat G, et al. Lifetime alcohol intake and breast cancer risk. Ann Epidemiol 2006;16:230-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16230024>.

73. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279:535-540. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9480365>.

74. Antoniou AC, Pharoah PD, Easton DF, Evans DG. BRCA1 and BRCA2 cancer risks. J Clin Oncol 2006;24:3312-3313; author reply 3313-3314. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16829658>.

75. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676-689. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9497246>.



76. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997;336:1401-1408. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9145676>.

77. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med* 1999;340:77-84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9887158>.

78. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst* 2001;93:1633-1637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11698567>.

79. Hamm RM, Lawler F, Scheid D. Prophylactic mastectomy in women with a high risk of breast cancer. *N Engl J Med* 1999;340:1837-1838; author reply 1839. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10366319>.

80. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001;345:159-164. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11463009>.

81. Rebbeck TR, Friebe T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2004;22:1055-1062. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14981104>.

82. Boughey JC, Khakpour N, Meric-Bernstam F, et al. Selective use of sentinel lymph node surgery during prophylactic mastectomy. *Cancer* 2006;107:1440-1447. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16955504>.

83. Miller CL, Specht MC, Skolny MN, et al. Sentinel lymph node biopsy at the time of mastectomy does not increase the risk of lymphedema: implications for prophylactic surgery. *Breast Cancer Res Treat*

2012;135:781-789. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22941538>.

84. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br J Cancer* 2000;83:1301-1308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11044354>.

85. Antoniou A, Pharoah PDP, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003;72:1117-1130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12677558>.

86. King M-C, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;302:643-646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14576434>.

87. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clin Cancer Res* 2002;8:3776-3781. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12473589>.

88. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 2002;346:1616-1622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12023993>.

89. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst* 2009;101:80-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19141781>.

90. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

a BRCA1 or BRCA2 Mutation. JAMA 2006;296:185-192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16835424>.

91. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609-1615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12023992>.

92. Kemei Y, Kauff ND, Robson ME, et al. Four-year follow-up of outcomes following risk-reducing salpingo-oophorectomy in BRCA mutation carriers [abstract]. ASCO Meeting Abstracts 2005;23:Abstract 1013. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/1013.

93. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 1999;91:1475-1479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10469748>.

94. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol 2005;23:7491-7496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16234515>.

95. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol 2008;26:1331-1337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18268356>.

96. 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19996031>.

97. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer

risk and mortality. JAMA 2010;304:967-975. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20810374>.

98. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol 2005;23:127-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15625367>.

99. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish Trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. Lancet 1987;2:171-175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2885637>.

100. Cyclophosphamide and tamoxifen as adjuvant therapies in the management of breast cancer. CRC Adjuvant Breast Trial Working Party. Br J Cancer 1988;57:604-607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2900646>.

101. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 1989;320:479-484. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2644532>.

102. Rutqvist LE, Cedermark B, Glas U, et al. Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoxifen therapy. J Natl Cancer Inst 1991;83:1299-1306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1886157>.

103. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-1717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15894097>.

104. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

P1) Breast Cancer Prevention Trial. JAMA 2001;286:2251-2256.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11710890>.

105. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003;361:296-300.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12559863>.

106. Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 1998;352:98-101. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9672274>.

107. Powles TJ, Ashley S, Tidy A, et al. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 2007;99:283-290. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17312305>.

108. Veronesi U, Maisonneuve P, Sacchini V, et al. Tamoxifen for breast cancer among hysterectomised women. Lancet 2002;359:1122-1124. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11943263>.

109. Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. Lancet 1998;352:93-97. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9672273>.

110. Veronesi U, Maisonneuve P, Rotmensz N, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 2007;99:727-737. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17470740>.

111. Veronesi U, Maisonneuve P, Rotmensz N, et al. Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. J Natl Cancer Inst 2003;95:160-165. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12529349>.

112. Bevers TB. Breast cancer chemoprevention: current clinical practice and future direction. Biomed Pharmacother 2001;55:559-564.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11769967>.

113. Cuzick J, Forbes J, Edwards R, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet 2002;360:817-824. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12243915>.

114. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer--96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 2007;99:272-282. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17312304>.

115. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637-645. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10517716>.

116. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189-2197. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10376571>.

117. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004;96:1751-1761. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15572757>.

118. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;355:125-137. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16837676>.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

119. Grady D, Cauley JA, Geiger MJ, et al. Reduced incidence of invasive breast cancer with raloxifene among women at increased coronary risk. *J Natl Cancer Inst* 2008;100:854-861. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18544744>.

120. Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2742-2751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16754728>.

121. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359:2131-2139. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12090977>.

122. Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003;98:1802-1810. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14584060>.

123. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004;350:1081-1092. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15014181>.

124. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349:1793-1802. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14551341>.

125. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast

cancer. *N Engl J Med* 2005;353:2747-2757. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16382061>.

126. Decensi A, Gandini S, Serrano D, et al. Randomized dose-ranging trial of tamoxifen at low doses in hormone replacement therapy users. *J Clin Oncol* 2007;25:4201-4209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17709798>.

127. Sideras K, Ingle JN, Ames MM, et al. Coprescription of tamoxifen and medications that inhibit CYP2D6. *J Clin Oncol* 2010;28:2768-2776. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20439629>.

128. Higgins MJ, Stearns V. CYP2D6 polymorphisms and tamoxifen metabolism: clinical relevance. *Curr Oncol Rep* 2010;12:7-15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20425602>.

129. Lash TL, Rosenberg CL. Evidence and practice regarding the role for CYP2D6 inhibition in decisions about tamoxifen therapy. *J Clin Oncol* 2010;28:1273-1275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20124162>.

130. Curtin J, Kavanagh J. Corpus: Mesenchymal tumors. In: Hoskins W, Perez C, Young R, eds. *Principles and Practice of Gynecologic Oncology* (ed 3rd). Philadelphia, PA; 2000:961-979.

131. Bergman L, Beelen ML, Gallee MP, et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet* 2000;356:881-887. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11036892>.

132. Curtis RE, Freedman DM, Sherman ME, Fraumeni JF, Jr. Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004;96:70-74. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14709741>.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

133. Wickerham DL, Fisher B, Wolmark N, et al. Association of tamoxifen and uterine sarcoma. J Clin Oncol 2002;20:2758-2760. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12039943>.

134. Bouchardy C, Verkooyen HM, Fioretta G, et al. Increased risk of malignant mullerian tumor of the uterus among women with breast cancer treated by tamoxifen. J Clin Oncol 2002;20:4403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12409344>.

135. Rieck GC, Freitas ON, Williams S. Is tamoxifen associated with high-risk endometrial carcinomas? A retrospective case series of 196 women with endometrial cancer. J Obstet Gynaecol 2005;25:39-41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16147692>.

136. Wysowski DK, Honig SF, Beitz J. Uterine sarcoma associated with tamoxifen use. N Engl J Med 2002;346:1832-1833. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12050351>.

137. ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. Obstet Gynecol 2006;107:1475-1478. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16738185>.

138. Barakat RR, Gilewski TA, Almadrones L, et al. Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. J Clin Oncol 2000;18:3459-3463. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11032585>.

139. Fung MF, Reid A, Faught W, et al. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol 2003;91:154-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14529676>.

140. Gerber B, Krause A, Muller H, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J Clin Oncol 2000;18:3464-3470. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11032586>.

141. Gorin MB, Costantino JP, Kulacoglu DN, et al. Is tamoxifen a risk factor for retinal vaso-occlusive disease? Retina 2005;25:523-526. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15933605>.

142. Nayfield SG, Gorin MB. Tamoxifen-associated eye disease. A review. J Clin Oncol 1996;14:1018-1026. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8622006>.

143. Grady D, Ettinger B, Moscarelli E, et al. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol 2004;104:837-844. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15458908>.

144. Powles TJ, Hickish T, Kanis JA, et al. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996;14:78-84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8558225>.

145. Sverrisdottir A, Fornander T, Jacobsson H, et al. Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. J Clin Oncol 2004;22:3694-3699. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15365065>.

146. Vehmanen L, Elomaa I, Blomqvist C, Saarto T. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. J Clin Oncol 2006;24:675-680. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16446340>.

147. Decensi A, Maisonneuve P, Rotmensz N, et al. Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. Circulation 2005;111:650-656. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15699284>.

148. Braithwaite RS, Chlebowski RT, Lau J, et al. Meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

Med 2003;18:937-947. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14687281>.

149. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology* 2004;63:1230-1233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15477543>.

150. Abramson N, Costantino JP, Garber JE, et al. Effect of Factor V Leiden and prothrombin G20210-->A mutations on thromboembolic risk in the national surgical adjuvant breast and bowel project breast cancer prevention trial. *J Natl Cancer Inst* 2006;98:904-910. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16818854>.

151. Guttuso T, Jr., Kurlan R, McDermott MP, Kiebert K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337-345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12576259>.

152. Guttuso TJ, Jr. Gabapentin's effects on hot flashes and hypothermia. *Neurology* 2000;54:2161-2163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10851385>.

153. Loprinzi L, Barton DL, Sloan JA, et al. Pilot evaluation of gabapentin for treating hot flashes. *Mayo Clin Proc* 2002;77:1159-1163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12440550>.

154. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005;366:818-824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16139656>.

155. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059-2063. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11145492>.

156. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized

controlled trial. *JAMA* 2003;289:2827-2834. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12783913>.

157. Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005;23:6919-6930. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16192581>.

158. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 2005;97:30-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15632378>.

159. Mortimer JE, Flatt SW, Parker BA, et al. Tamoxifen, hot flashes and recurrence in breast cancer. *Breast Cancer Res Treat* 2008;108:421-426. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17541741>.

160. Osborne CR, Duncan A, Sedlacek S, et al. The addition of hormone therapy to tamoxifen does not prevent hot flashes in women at high risk for developing breast cancer. *Breast Cancer Res Treat* 2009;116:521-527. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19139988>.

161. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057-2071. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16670414>.

162. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155-158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8270972>.

163. Laufer LR, Erlik Y, Meldrum DR, Judd HL. Effect of clonidine on hot flashes in postmenopausal women. *Obstet Gynecol* 1982;60:583-586. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7145250>.



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

164. Nagamani M, Kelder ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. *Am J Obstet Gynecol* 1987;156:561-565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3826200>.

165. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16:495-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9469333>.

166. Pockaj BA, Gallagher JG, Loprinzi CL, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. *J Clin Oncol* 2006;24:2836-2841. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16782922>.

167. Carpenter JS. Hot flashes and their management in breast cancer. *Semin Oncol Nurs* 2000;16:214-225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10967794>.

168. Fallowfield LJ, Bliss JM, Porter LS, et al. Quality of life in the intergroup exemestane study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer. *J Clin Oncol* 2006;24:910-917. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16484701>.

169. Mahoney MC. Breast cancer risk reduction and counseling: lifestyle, chemoprevention, and surgery. *J Natl Compr Canc Netw* 2007;5:702-710. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17927927>.

170. Visvanathan K, Chlebowski RT, Hurley P, et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. *J Clin Oncol* 2009;27:3235-3258. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19470930>.

171. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23219286>.

172. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *ASCO Meeting Abstracts* 2013;31:5. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/18_suppl/5.

173. Burstein HJ, Temin S, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *J Clin Oncol* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24868023>.

174. Bresser PJC, Van Gool AR, Seynaeve C, et al. Who is prone to high levels of distress after prophylactic mastectomy and/or salpingo-oophorectomy? *Ann Oncol* 2007;18:1641-1645. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17660493>.

175. Patenaude AF, Orozco S, Li X, et al. Support needs and acceptability of psychological and peer consultation: attitudes of 108 women who had undergone or were considering prophylactic mastectomy. *Psychooncology* 2008;17:831-843. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18636423>.

176. van Dijk S, van Roosmalen MS, Otten W, Stalmeier PF. Decision making regarding prophylactic mastectomy: stability of preferences and the impact of anticipated feelings of regret. *J Clin Oncol* 2008;26:2358-2363. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18467728>.

177. Giuliano AE, Boolbol S, Degnim A, et al. Society of Surgical Oncology: position statement on prophylactic mastectomy. Approved by the Society of Surgical Oncology Executive Council, March 2007. *Ann*



NCCN Guidelines Version 1.2014

Breast Cancer Risk Reduction

Surg Oncol 2007;14:2425-2427. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17597344>.

178. Morrow M, Mehrara B. Prophylactic mastectomy and the timing of breast reconstruction. Br J Surg 2009;96:1-2. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19109821>.

179. Rebbeck TR, Friebe T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23:7804-7810. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16219936>.

180. Chlebowski RT, Prentice RL. Menopausal hormone therapy in BRCA1 mutation carriers: uncertainty and caution. J Natl Cancer Inst 2008;100:1341-1343. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18812547>.

181. Garber JE, Hartman A-R. Prophylactic oophorectomy and hormone replacement therapy: protection at what price? J Clin Oncol 2004;22:978-980. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/14981100>.

182. Grann VR, Jacobson JS, Thomason D, et al. Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. J Clin Oncol 2002;20:2520-2529. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12011131>.

183. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-333. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12117397>.

184. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA

2004;291:1701-1712. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15082697>.

185. McTiernan A, Martin CF, Peck JD, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. J Natl Cancer Inst 2005;97:1366-1376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16174858>.

186. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 2010;304:1684-1692. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20959578>.

187. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 2009;360:573-587. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19196674>.

188. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA 2011;305:1305-1314. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21467283>.

189. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006;295:1647-1657. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16609086>.

190. Rohan TE, Negassa A, Chlebowski RT, et al. Conjugated equine estrogen and risk of benign proliferative breast disease: a randomized controlled trial. J Natl Cancer Inst 2008;100:563-571. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18398105>.

191. McTiernan A, Chlebowski RT, Martin C, et al. Conjugated equine estrogen influence on mammographic density in postmenopausal women in a substudy of the women's health initiative randomized trial. J



Clin Oncol 2009;27:6135-6143. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19901118>.

192. Rosenberg L, Palmer JR, Wise LA, Adams-Campbell LL. A prospective study of female hormone use and breast cancer among black women. Arch Intern Med 2006;166:760-765. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16606813>.

193. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419-427. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12927427>.

194. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med 2006;166:1027-1032. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16682578>.

195. Chlebowski RT. Menopausal hormone therapy, hormone receptor status, and lung cancer in women. Semin Oncol 2009;36:566-571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19995648>.

196. Santen RJ, Allred DC. The estrogen paradox. Nat Clin Pract Endocrinol Metab 2007;3:496-497. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17519914>.

197. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-1477. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17405972>.

198. Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? J Clin Oncol 2009;27:5138-5143. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19752341>.

199. Suzuki R, Ye W, Rylander-Rudqvist T, et al. Alcohol and postmenopausal breast cancer risk defined by estrogen and

progesterone receptor status: a prospective cohort study. J Natl Cancer Inst 2005;97:1601-1608. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16264180>.

200. Bernstein L, Patel AV, Ursin G, et al. Lifetime recreational exercise activity and breast cancer risk among black women and white women. J Natl Cancer Inst 2005;97:1671-1679. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16288120>.

201. Howard RA, Leitzmann MF, Linet MS, Freedman DM. Physical activity and breast cancer risk among pre- and postmenopausal women in the U.S. Radiologic Technologists cohort. Cancer Causes Control 2009;20:323-333. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18941914>.

202. Lahmann PH, Friedenreich C, Schuit AJ, et al. Physical activity and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 2007;16:36-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17179488>.

203. Tehard B, Friedenreich CM, Oppert J-M, Clavel-Chapelon F. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:57-64. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16434587>.

204. Friedenreich CM, Woolcott CG, McTiernan A, et al. Alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among postmenopausal women. J Clin Oncol 2010;28:1458-1466. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20159820>.

205. Chlebowski RT, Chen Z, Cauley JA, et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol 2010;28:3582-3590. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20567009>.



NCCN Guidelines Version 1.2014 Breast Cancer Risk Reduction

206. Prentice RL, Manson JE, Langer RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. *Am J Epidemiol* 2009;170:12-23. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19468079>.

207. Michels KB, Willett WC. The Women's Health Initiative Randomized Controlled Dietary Modification Trial: a post-mortem. *Breast Cancer Res Treat* 2009;114:1-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18373274>.

208. Linos E, Willett WC. Diet and breast cancer risk reduction. *J Natl Compr Canc Netw* 2007;5:711-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17927928>.

209. Tretli S, Gaard M. Lifestyle changes during adolescence and risk of breast cancer: an ecologic study of the effect of World War II in Norway. *Cancer Causes Control* 1996;7:507-512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8877047>.

210. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 2002;288:2569-2578. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12444864>.

211. Bertone-Johnson ER, Chen WY, Holick MF, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1991-1997. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16103450>.

212. Blackmore KM, Lesosky M, Barnett H, et al. Vitamin D from dietary intake and sunlight exposure and the risk of hormone-receptor-defined breast cancer. *Am J Epidemiol* 2008;168:915-924. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18756015>.

213. Knight JA, Lesosky M, Barnett H, et al. Vitamin D and reduced risk of breast cancer: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2007;16:422-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17372236>.

214. Kotsopoulos J, Olopado OI, Ghadirian P, et al. Changes in body weight and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res* 2005;7:R833-843. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16168130>.