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NCCN Clinical Practice Guidelines in Oncology™

Breast Cancer Risk Reduction

V.2.2010

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

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

See NCCN Categories of Evidence

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SUMMARY OF UPDATES

Summary of changes in the 2.2010 version of the Breast Cancer Risk Reduction Guidelines from the 1.2010 version include:

DISCUSSION

- **The Discussion section has been updated to correspond with the recently updated algorithm.**

BRISK-3

- **Under Elements of Risk/Other - 2 new sub-bullets "History of lobular carcinoma in situ (LCIS) or atypical hyperplasia"; "Prior thoracic RT"**
- **Under Risk Assessment - Removed "Claus model, etc."**

BRISK-4

- **Changed "Close relatives with breast and/or ovarian cancer" to "Pedigree suggestive of genetic predisposition"; Moved "Lifetime risk > 20%" from bottom to top group.**

BRISK-B

- **Under "Premenopausal and Postmenopausal: - 1st sub-bullet: Changed to read - "Data regarding tamoxifen risk reduction are limited to women 35 y of age or older with a Gail model 5 year breast cancer risk of ≥ 1.7% or a history of LCIS."**
- **Under "Postmenopausal" – 4th sub-bullet under "Raloxifene": Changed to read - "At a median follow-up of approximately 8 years, raloxifene was shown to be about 76% as effective as tamoxifen in reducing the risk of invasive breast cancer (relative risk ratio=1.24; 95% CI, 1.05-1.47). The relative risk of noninvasive breast cancer for patients in the raloxifene arm compared with those receiving tamoxifen was 1.22 (95% CI, 0.95-1.59) (Cancer Prev Res 2010;3:696-706).**
- **Footnote 1: Changed 2nd sentence to read: "Moreover, there may be safety concerns related to use of tamoxifen for greater than 5 years." Added 3rd sentence: "Based on the recent update of the STAR trial data, continuing raloxifene beyond 5 years may be an approach to maintain the risk reduction activity of the agent."**

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FAMILIAL RISK ASSESSMENT[a]

Family history of cancer

Yes →

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

  See NCCN Genetic/ Familial High Risk Assessment Guidelines and NCCN Breast Cancer Screening and Diagnosis Guidelines

→ **Yes** → **See Familial Risk Assessment (BRISK-2)**

→ **No** → **See Risk Assessment (BRISK-3)**

No → **See Risk Assessment (BRISK-3)**

[a] The management of DCIS is not covered by the NCCN Breast Cancer Risk Reduction Guidelines. See the NCCN Breast Cancer Treatment Guidelines.

[b] The maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Should include 3 generations, (including proband, offspring, paternal and maternal generations) and include ages of cancer diagnoses. Note if family structure limits evaluation (small family, few surviving females).

[c] Clinically use age ≤ 50 y because studies define early onset as either ≤ 40 or ≤ 50. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[d] Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

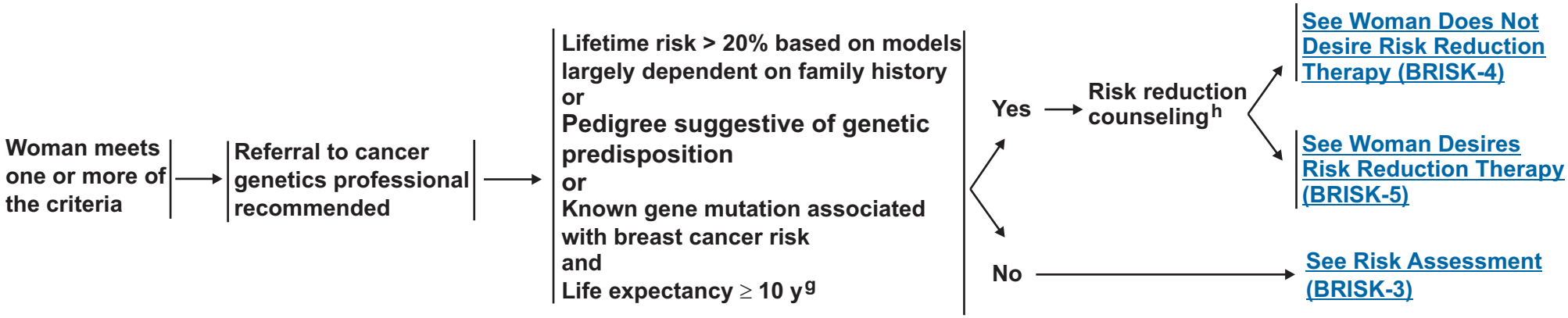
[e] For lobular breast cancer and diffuse gastric cancer, CDH1 gene testing can be considered.

[f] For populations at risk, requirements for inclusion may be lessened (eg, women of Ashkenazi Jewish descent with breast or ovarian cancer at any age.)

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FAMILIAL RISK ASSESSMENT



[g] For a reference point, the life expectancy of the average 78 y old woman in the US is 10.2 yrs

[h] See Components of Risk/Benefit Assessment and Counseling (BRISK-A).

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ELEMENTS OF RISK

Woman does not meet any of the family history criteria →

- Demographics
  - Age
    - Utility of tamoxifen or raloxifene for breast cancer risk reduction in women under 35 years of age is unknown.
  - Ethnicity/race
    - For example there is an increased incidence of specific BRCA1/2 mutations in Ashkenazi Jewish individuals.
  - Body mass index
- Reproductive history
  - Age at menarche
  - Parity
  - Age at first live birth
  - Age at menopause
- Environmental factors
  - Current or prior estrogen and progesterone hormone replacement therapy
  - Alcohol consumption
- Other
  - Atypical Hyperplasia
  - Number of prior breast biopsies
    - Procedure done with the intent to diagnose cancer, multiple biopsies of the same lesion are scored as one biopsy.
  - Breast density
  - Prior thoracic RT
  - History of lobular carcinoma in situ (LCIS)

RISK ASSESSMENT[i]

- Prior thoracic RT
- History of lobular carcinoma in situ (LCIS)

[See NCCN Breast Cancer Screening and Diagnosis] and [NCCN Breast Cancer Treatment Guidelines].

→ Life expectancy ≥ 10 y[g] →

Risk reduction counseling[h] →

- [Woman Does Not Desire Risk Reduction Therapy (BRISK-4)]
- [Woman Desires Risk Reduction Therapy (BRISK-5)]

Breast cancer risk assessment[h,j] (eg, modified Gail Model for women ≥ 35 y of age)

→ 5 y breast cancer risk ≥ 1.7%[k] and Life expectancy ≥ 10 y[g] → Risk reduction counseling[h]

→ 5 y breast cancer risk < 1.7%[k] or Life expectancy < 10 y[g] or Contraindication to tamoxifen or raloxifene[h] → [See NCCN Breast Cancer Screening and Diagnosis Guidelines]

[g] For a reference point, the life expectancy of the average 78 y old woman in the US is 10.2 yrs.

[h] See Components of Risk/Benefit Assessment and Counseling (BRISK-A).

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

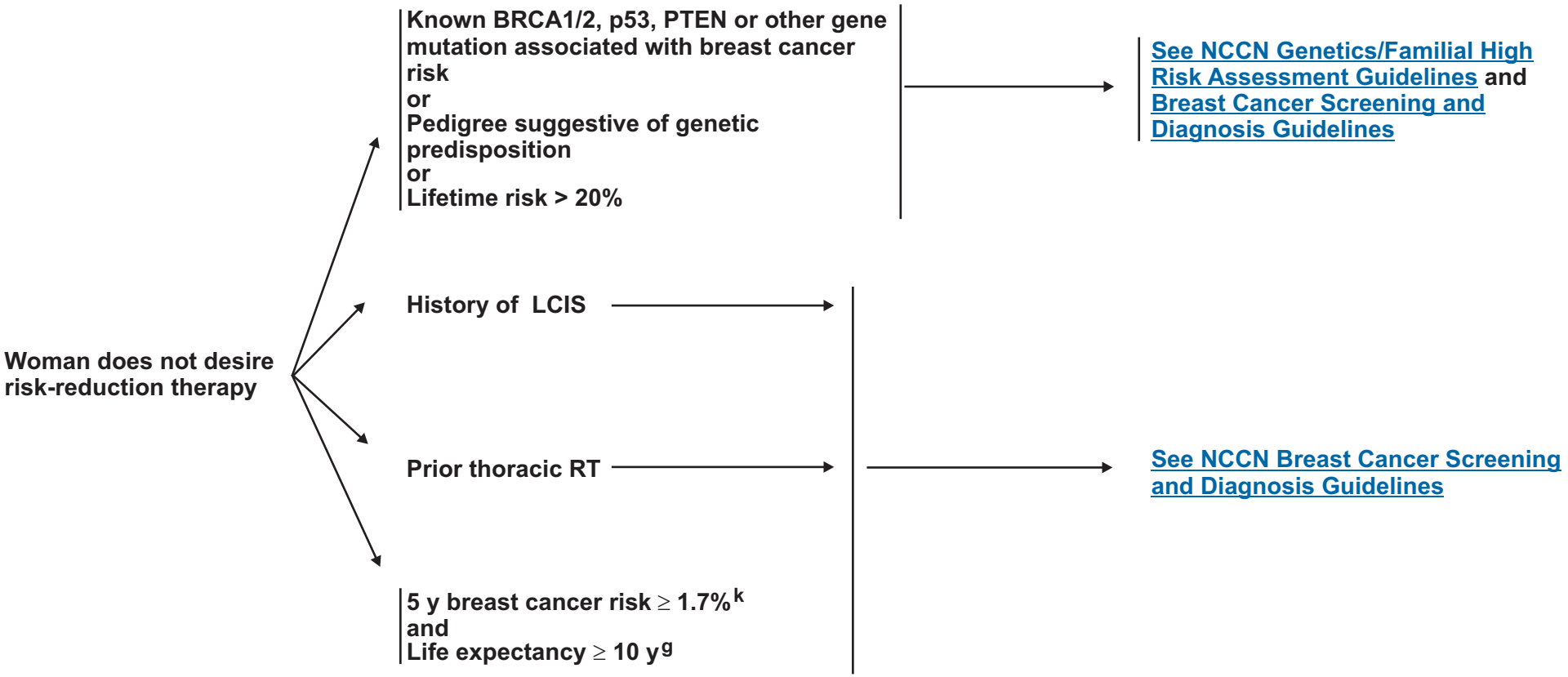
[j] The NCI Breast Cancer Risk Assessment Tool is a computer-based version of the modified Gail model and may be obtained through the NCI Web site. There are circumstances in which the Gail model underestimates risk for development of breast cancer-for instance, BRCA1/2 carriers and those with a strong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

[k] 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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RISK REDUCTION COUNSELING/SCREENING



[g] For a reference point, the life expectancy of the average 78 y old woman in the US is 10.2 years.
[k] The definition of risk as defined by the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP BCPT).

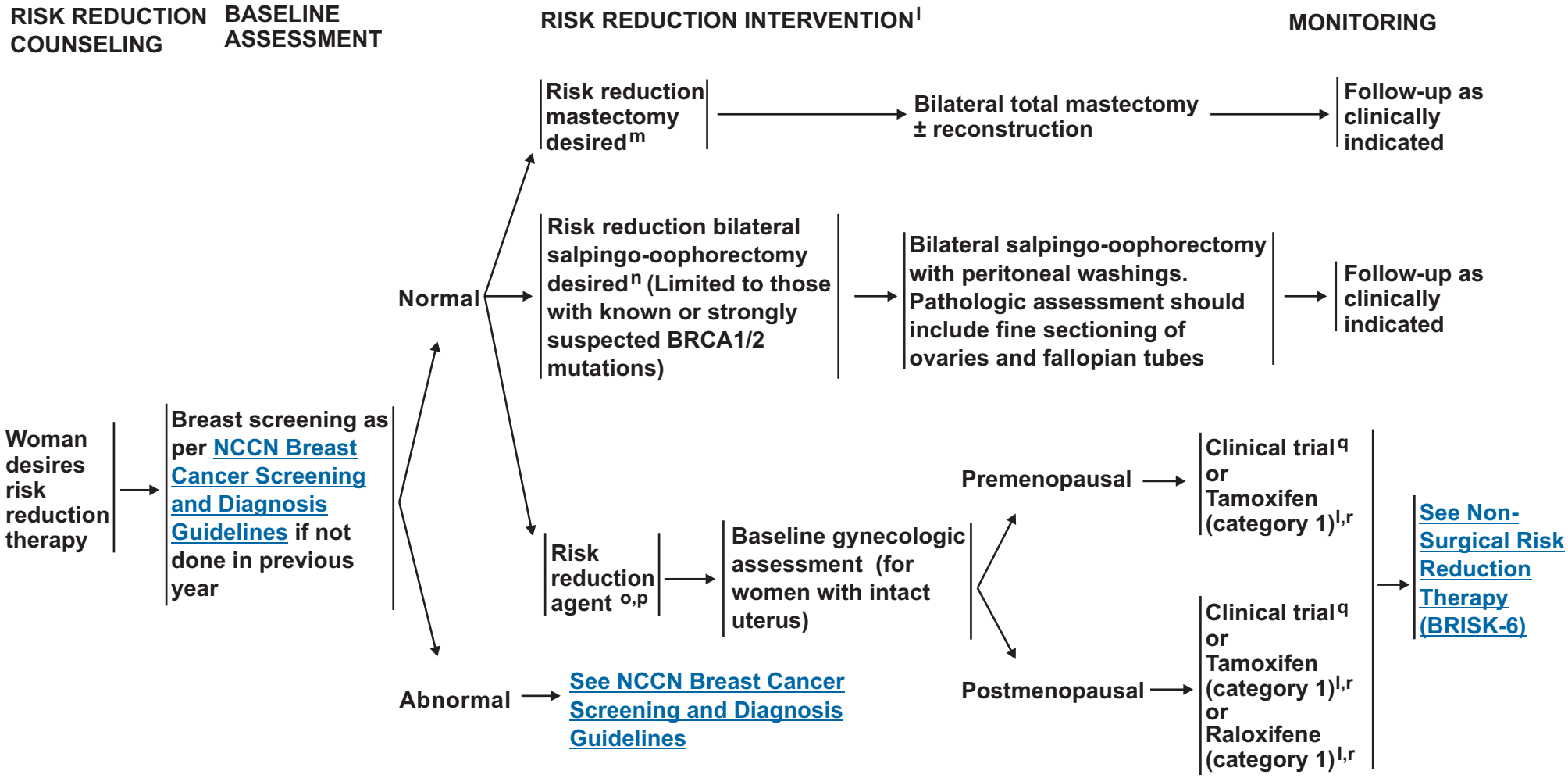
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[l] See Breast Cancer Risk Reduction Agents (BRISK-B).

[m] Risk reduction mastectomy should generally be considered only in women with BRCA1/2, or other strongly predisposing gene, compelling family history, or possibly women with LCIS. Women considering risk reduction mastectomy should receive multidisciplinary counseling including consultation with genetics if not already done. Psychological consultation may also be of value.

[n] The additional benefit of concurrent hysterectomy is not clear at this time

[o] There are no data regarding the use of risk reduction agents in women with prior thoracic RT

[p] CYP2D6 genotype testing is not recommended in women considering tamoxifen.

[q] Women in clinical trial should have baseline exam, follow-up, and monitoring as per protocol.

[r] Utility of tamoxifen or raloxifene for breast cancer risk reduction in women under 35 years of age is unknown. Raloxifene is only for post-menopausal women > 35 y.

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NON-SURGICAL RISK REDUCTION THERAPY[I]

MONITORING

Tamoxifen or Raloxifene →

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

→ See Monitoring, Findings and Management (BRISK-7)

[I] See Breast Cancer Risk Reduction Agents (BRISK-B).

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MONITORING, FINDINGS AND MANAGEMENT

Asymptomatic → **Continue tamoxifen or raloxifene** → **Continue follow-up**

Hot flashes or other tamoxifen or raloxifene-related symptoms[s] → **Symptomatic treatment If persist, reevaluate role of tamoxifen or raloxifene** → **Continue tamoxifen or raloxifene** → **Continue follow-up**

Abnormal vaginal bleeding → **Prompt evaluation for endometrial cancer if uterus intact**

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

Anticipated elective surgery → **Consider discontinuing tamoxifen or raloxifene prior to elective surgery** → **Resume tamoxifen or raloxifene postoperatively when ambulation is normal**

Deep vein thrombosis, pulmonary embolism, cerebrovascular accident, or prolonged immbolization → **Discontinue tamoxifen or raloxifene, treat underlying condition**

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

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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 Genetic/Familial High Risk Assessment Guidelines.**

- **Tamoxifen or raloxifene - See Table 3 and Table 5 in the manuscript section.**
  - **Discussion of relative and absolute risk reduction with tamoxifen or raloxifene.**
  - **Contraindications to tamoxifen or raloxifene: history of deep vein thrombosis, pulmonary embolus, thrombotic stroke, transient ischemic attack, current pregnancy or pregnancy potential without effective method of contraception, or known inherited clotting trait.**
  - **Common and serious adverse effects of tamoxifen or raloxifene, with emphasis on age-dependent risks.**

- **Surgery**
  - **Discussion of risk reduction mastectomy in high-risk women. Risk reduction mastectomy should generally be considered only in women with BRCA1/2, or other strongly predisposing gene, compelling family history, or possibly women with LCIS. Evaluation should include consultation with surgery and reconstructive surgery. Psychological consultation may also be considered.**
  - **Discussion regarding the risk of breast or ovarian cancer and the option of risk reduction bilateral salpingo-oophorectomy.**

- **Option of participation in clinical research for screening, risk assessment, or other risk reduction intervention.**

- **Healthy lifestyle**
  - **Consider breast cancer risks associated with hormone replacement therapy**
  - **Limit alcohol consumption to less than 1 drink per day.[1]**
  - **Exercise**
  - **Weight control**

[1] Mahoney MC, Bevers T, Linos E, Willett WC. Opportunities and strategies for breast cancer prevention through risk reduction. CA Cancer J Clin 2008 Nov-Dec;58(6):347-71. Epub 2008 Nov 3.

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BREAST CANCER RISK-REDUCTION AGENTS[1]

PREMENOPAUSAL

- **Tamoxifen**
  - Data regarding tamoxifen risk reduction are limited to women 35 y of age or older with a Gail model 5 year breast cancer risk of ≥ 1.7% or a history of LCIS.
  - Tamoxifen: 20 mg per day for 5 years was shown to reduce risk of breast cancer by 49%. Among women with a history of atypical hyperplasia, this dose and duration of tamoxifen was associated with an 86% reduction in breast cancer risk. (Fisher JNCI, 1998)
  - 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.
  - For other high-risk premenopausal women, data regarding the risk/benefit ratio for tamoxifen appears relatively favorable (category 1).
  - Use of raloxifene, an aromatase inhibitor, or other agents for breast cancer risk reduction is inappropriate unless as part of a clinical trial.

POSTMENOPAUSAL

- **Tamoxifen**
  or
- **Raloxifene**
  - Data regarding tamoxifen or raloxifene risk reduction are limited to women 35 y of age or older with a Gail model 5-year breast cancer risk ≥ 1.7% or a history of LCIS.
  - Limited data are currently available regarding the efficacy of tamoxifen or raloxifene in women who are carriers of BRCA1/2 mutations or who have had prior thoracic radiation.
  - For high-risk postmenopausal women, data regarding the risk/benefit ratio for tamoxifen or raloxifene is influenced by age, presence of uterus or comorbid conditions (category 1). There are insufficient data on ethnicity and race.
  - At a median follow-up of approximately 8 years, raloxifene was shown to be about 76% as effective as tamoxifen in reducing the risk of invasive breast cancer (relative risk ratio=1.24; 95% CI, 1.05-1.47). The relative risk of noninvasive breast cancer for patients in the raloxifene arm compared with those receiving tamoxifen was 1.22 (95% CI, 0.95-1.59) (Cancer Prev Res 2010;3:696-706).
  - Use of an aromatase inhibitor or other agents for breast cancer risk reduction is inappropriate unless part of a clinical trial.

[1] There 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 may be an approach to maintain the risk reduction activity of the agent.

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Discussion

NCCN Categories of Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Breast cancer is the most commonly diagnosed cancer in American women, with 209,060 and 54,010 estimated cases of invasive breast cancer and female carcinoma in situ, respectively in 2010. Approximately 39,840 women will die of breast cancer in the United States in 2010.[1]

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

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 agents/strategies, such as tamoxifen, raloxifene, and risk reduction surgery, have been identified. However, women and their physicians who are considering interventions to reduce risk of breast cancer must balance the demonstrated benefits with the potential morbidities of the interventions, since surgical risk reduction strategies (eg, risk reduction bilateral mastectomy) may have psychosocial consequences for the woman, and agents, such as tamoxifen and raloxifene, used for non-surgical risk reduction have been associated with certain adverse effects. To assist women at increased risk of breast cancer and their physicians in the application of individualized strategies to reduce breast cancer risk, the NCCN has developed these Breast Cancer Risk Reduction Guidelines.

Risk Assessment

Estimation of breast cancer risk for an individual woman begins with an initial assessment of familial/genetic factors associated with increased breast cancer risk for the purpose of determining whether more extensive genetic risk assessment and counseling should be undertaken. The first step in this primary assessment is a broad and flexible evaluation of the personal and family history of the individual, primarily with respect to breast and/or ovarian cancer.[2,3] The magnitude of the risk increases with the number of affected relatives in the family,

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the closeness of the relationship, and is affected by the age at which the affected relative was diagnosed.[4,5] The younger the age at diagnosis, the more likely 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 Genetic/Familial Risk Assessment: Breast and Ovarian Cancer Guidelines).

Hereditary cancers are often characterized by 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.[6,7] They often have an early age of onset, and occur when the individual has a germline mutation in only one copy of a gene. Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.[8-11]

If an individual or a close family member of that individual meets one or more of the criteria presented on BRISK-1 that individual may be at increased risk for famililal/hereditary breast cancer, and referral for formal genetic assessment/counseling is recommended (see BRISK-2). A cancer genetic professional should be involved in determining whether the individual has a lifetime risk of breast cancer > 20% based on models largely dependent on family history (eg, BRCAPRO,[12] BOADICEA,[13] and others)[14-18] and/or meets criteria for genetic testing. The Claus tables may be useful in providing breast cancer risk estimates for white women without a known cancer-associated gene mutation who have one or two first or second degree female relatives with breast cancer.[16] Based on this risk assessment, women with a *BRCA1/2*, *TP53*, or *PTEN* gene mutation, or close relatives with breast cancer or ovarian cancer, may be identified. The NCCN Genetics/Familial High-Risk Assessment Guidelines also describe management strategies for women with a known or suspected *BRCA1/2, TP53, or PTEN* mutation or a pedigree strongly suggestive of genetic predisposition to breast cancer.

For women not considered to be at risk of familial/hereditary breast cancer, an evaluation of the breast cancer risk factors described in the previous section (eg, reproductive history), many of which, including breast density,[19] may be associated with hormonal levels is recommended (see BRISK-3). Dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.[20,21] For example, a recent report of a large case-cohort study of women 35 years and older with no history of breast cancer who underwent mammographic screening at baseline and at an average of 6 years later suggested that longitudinal changes in breast density are associated with changes in breast cancer risk.[21] Nevertheless, breast density is not included in any of the commonly used risk assessment models/tools.[17]

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, or a history of LCIS should have their risk for breast cancer estimated according to the modified Gail model.[22-24] 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.[24-26]

The risk threshold required for a woman to consider the use of risk reduction strategies must depend on an evaluation of the efficacy,

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morbidity, and expense of the proposed intervention. As a reasonable discriminating threshold, the Panel has adopted the 1.7% or greater 5-year actuarial risk of breast cancer as defined by the modified Gail model, which was used to identify women eligible for the National Surgical Adjuvant Bowel and Breast Project (NSABP) Breast Cancer Prevention Trial (BCPT)[27] and the Study of Tamoxifen and Raloxifene (STAR) trial.[28,29]

The criteria used to determine risk by the modified Gail model are described in Figure 1. The Gail model, as modified by the NSABP investigators, is available on the National Cancer Institute website or at www.breastcancerprevention.com.

Recently, the Gail model was updated using combined data from the Women's Contraceptive and Reproductive Experiences (CARE) Study and the Surveillance Epidemiology and End Results (SEER) database, as well as causes of death from the National Center of Health Statistics, to provide a more accurate determination of risk for African-American women.[30] Application of the Gail model to recent immigrants from Japan or China may overestimate the risk of breast cancer.

As previously mentioned, the Gail model is not an appropriate breast cancer risk assessment tool for women who received prior thoracic radiation to treat Hodgkin's disease (eg, mantle radiation) or those with LCIS. In the Late Effects Study Group trial, the overall risk of breast cancer associated with prior thoracic irradiation at a young age was found to be 56.7–fold (55.5-fold for female patients) greater than the risk of breast cancer in the general population.[31,32] In that study, the relative risk according to follow-up interval was: 0 at 5-9 years; 71.3 at 10-14 years; 90.8 at 15-19 years; 50.9 at 20-24 years; 41.2 at 25-29 years; and 24.5 at > 29 years.[32] Results from a case-control study of women treated at a young age for Hodgkin lymphoma with thoracic radiation indicated that the estimated cumulative absolute risk of breast cancer at 55 years of age was 29.0% (95% CI, 20.2%-40.1%) for a woman treated at 25 years of age with 40 Gy of radiation and no alkylating agents.[33] Women with a history of treatment with thoracic radiation for Hodgkin's disease are at a high risk of breast cancer on the basis of radiation exposure alone.[34-37] Women with a history of lobular carcinoma in situ (LCIS) are also at substantially increased risk for invasive breast cancer in both the affected and contralateral breast.[38,39] Women with a diagnosis of ductal carcinoma in situ (DCIS) should be managed according to recommendations in the NCCN Breast Cancer Treatment Guidelines.

Women with a life expectancy ≥ 10 years and no diagnosis/history of breast cancer who are considered to be at increased risk of breast cancer based on any of these assessments should receive counseling regarding strategies to decrease breast cancer risk that are tailored to the individual (eg, risk-reduction surgery in *BRCA1/2* mutation carriers; tamoxifen or raloxifene only in those without a contraindication to these risk-reduction agents; breast screening as detailed in the NCCN Breast Cancer Screening and Diagnosis Guidelines, etc.)

Risk Reduction Interventions (BRISK-5)

Risk Reduction Surgery

Bilateral Total Mastectomy

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

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concluding that RRM provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation.[47,48]

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

Women considering RRM should first have appropriate multidisciplinary consultations and a clinical breast examination and bilateral mammogram if not performed within the past 6 months. If results are normal, women who choose RRM may undergo the procedure with or without immediate breast reconstruction. Bilateral mastectomy performed for risk reduction should involve removal of all breast tissue (ie, a total mastectomy). Women undergoing RRM do not require an axillary lymph node dissection unless breast cancer is identified on pathologic evaluation of the mastectomy specimen.[49] Following RRM, women who carry a *BRCA1/2* mutation should be monitored according to the NCCN Genetics/Familial High-Risk Assessment Guidelines. Women found to have invasive breast cancer or ductal carcinoma in situ (DCIS) at the time of RRM should be treated according to the NCCN Breast Cancer Guidelines. All other women should be followed up with routine health maintenance following RRM.

Bilateral Salpingo-oophorectomy

Women with a *BRCA1/2* mutation are at increased risk for both breast and ovarian cancers (including fallopian tube cancer). Although the risk of ovarian cancer is lower than the risk of breast cancer in a *BRCA1/2* mutation carrier (eg, estimated lifetime risks of 36%-46% and 10%-27% in *BRCA1* and *BRCA2* mutation carriers, respectively.[40,43,50-52]), the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have lent support for the performance of bilateral risk reduction salpingo-oophorectomy (RRSO) after completion of childbearing in these women. In the studies of Rebbeck et al., the mean age at diagnosis of ovarian cancer was 50.8 years for *BRCA1/2* carriers.[53]

The effectiveness of RRSO in reducing the risk of 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 the risk of ovarian or fallopian cancer following RRSO.[54] However, a 1-4.3% residual risk of a primary peritoneal carcinoma has been reported in some studies.[53-58]

RRSO is also reported to reduce the risk of breast cancer in carriers of a *BRCA1/2* mutation by approximately 50% [53,54, 58,59] In the case-control international study of Eisen et al., a 56% (odds ratio=0.44; 95% CI, 0.29-0.66) and a 46% (odds ratio=0.57; 95% CI, 0.28-1.15) breast cancer risk reduction was reported following RRSO in carriers of a BRCA1 and a BRCA2 mutation, respectively.[59] Hazard ratios of 0.47 (95% CI, 0.29-0.77)[53]; and 0.30 (95% CI, 0.11-0.84)[57] 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 recent meta-analysis which found similar reductions in breast cancer risk of approximately 50% for *BRCA1* and *BRCA2* mutation carriers following RRSO,[54] although results of a recent prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA1* mutation carriers compared with *BRCA2* mutation carriers.[60]

Reductions in breast cancer risk for carriers of a *BRCA1/2* mutation who undergo RRSO may be associated with decreased hormonal

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exposure following surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a *BRCA1* mutation who had a 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).[59] A nonsignificant reduction in breast cancer risk was found for women aged 51 or older although only a small number of women were included in this group.[59] However, results from Rebbeck et al (1999) also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.[58]

Although data are limited regarding an optimal age for RRSO, a recently published Monte Carlo simulation model provides estimates of the survival impact of breast and ovarian risk reduction strategies (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).[61] Survival estimates generated from this model can facilitate shared decision-making regarding choice of a risk reduction approach (see Table 1).

The Panel recommends limiting RRSO to women with a known or strongly suspected *BRCA1/2* mutation. Peritoneal washings should be performed at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes. The additional benefit of concurrent hysterectomy is not clear at this time. Women who undergo RRSO should continue with routine health maintenance.

Risk Reduction Agents

Risk reduction agents (ie, tamoxifen, raloxifene) are recommended for women ≥35 years of age only.

Tamoxifen for Risk Reduction

The benefits of tamoxifen, a selective estrogen receptor 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.[62-65] The Early Breast Cancer Trialists' meta-analysis confirmed that the risk of contralateral primary breast cancer is substantially reduced (i.e. a statistically significant annual recurrence rate ratio=0.59) by 5 years of tamoxifen therapy in women with first breast cancers that are estrogen receptor-positive or have an unknown estrogen receptor status.[66]

NSABP Breast Cancer Prevention Trial

The effectiveness of tamoxifen in the setting of breast cancer treatment gave rise to the NSABP BCPT (P-1), a randomized clinical trial of healthy women aged 60 years or older, aged 35-59 with a 1.7% or greater cumulative 5-year risk for developing breast cancer, or with a history of LCIS.[27] 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.[67]

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The results of the BCPT study showed that treatment with tamoxifen decreased the short-term risk for breast cancer by 49% in healthy women aged 35 years or older who had an increased risk for the disease (Table 2).[27] Risk reduction benefits were demonstrated across all age groups (Table 2). The difference in average annual rates for invasive breast cancer was 3.30 cases per 1,000 women (ie, 6.76 cases per 1,000 women in the placebo group and 3.43 cases per 1,000 women in the group taking tamoxifen). The absolute risk reduction was 21.4 cases per 1,000 women over 5 years.[27] 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.[67] The reduction in invasive breast cancer risk in participants with atypical hyperplasia was particularly striking (risk ratio=0.14; 95% confidence interval (CI), 0.03-0.47) in the initial study analysis (Table 2), and a risk ratio of 0.25 (95% CI, 0.10-0.52) was found after 7 years of follow-up. An additional benefit of tamoxifen was a decrease in bone fractures (Table 3). However, as was anticipated from the experience in studies of women taking tamoxifen following a diagnosis of breast cancer, major toxicities included hot flashes, invasive endometrial cancer in postmenopausal women, and cataracts (Table 3). A significant increase in the incidence of pulmonary embolism was also observed in women ≥ 50 years of age taking tamoxifen (Table 3). No differences were observed in overall rates of mortality by treatment group with a follow-up period out to 7 years. The initial study analysis revealed that average annual mortality from all causes in tamoxifen-treated women was 2.17 per 1,000 women compared with 2.71 per 1,000 women in placebo-treated women, for a risk ratio of 0.81 (95% CI, 0.56-1.16)[27]; annual mortality after 7 years of follow-up was 2.80 per 1,000 women compared with 3.08 per 1,000 women in the tamoxifen and placebo groups, respectively, for a risk ratio of 1.10 (95% CI, 0.85-1.43).[67]

An evaluation of the subset of patients with a *BRCA1/2* mutation in the BCPT study revealed that breast cancer risk was reduced by 62% in study patients with a *BRCA2* mutation receiving tamoxifen relative to placebo (risk ratio, 0.38; 95% CI, 0.06-1.56). However, tamoxifen use was not associated with a reduction in breast cancer risk in patients with a *BRCA1* mutation.[68] These findings may be related to the greater likelihood for development of estrogen receptor-positive tumors in *BRCA2* mutation carriers relative to *BRCA1* mutation carriers. However, this analysis was limited by the very small number of patients with a *BRCA1/2* mutation.

Based on the BCPT study results, in October 1998 the U.S. Food and Drug Administration (FDA) approved tamoxifen for breast cancer risk reduction for women at increased risk of breast cancer.[69]

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.[70,71] Women in the trial were allowed to continue or to initiate postmenopausal hormone replacement therapy. With 2,471 participants available for interim analysis, no difference in the frequency of breast cancer was observed between the 2 study groups. Moreover, the toxicity experienced by the 2 groups did not show statistically significant differences.[70] An analysis of updated findings from the Royal Marsden study did demonstrate a nonsignificant breast cancer risk reduction benefit with tamoxifen use (ie, 62 cases of breast cancer in 1238 women receiving tamoxifen versus 75 cases of breast cancer in 1233 women in the placebo arm).[71]

Most recently, an analysis of blinded results from the Royal Marsden trial at 20 year follow-up showed no difference in breast cancer incidence between the groups randomly assigned to tamoxifen or

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placebo (hazard ratio=0.78; 95% CI, 0.58-1.04; P=0.1).[72] However, the incidence of estrogen receptor-positive breast cancer was significantly lower in the tamoxifen arm vs. placebo arm of the trial (hazard ratio=0.61; 95% CI, 0.43-0.86; P=0.005). 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 5,408 women ages 35 to 70 without breast cancer, who had undergone a previous hysterectomy, to receive tamoxifen or placebo for 5 years.[73] Women in the trial were allowed to receive hormone replacement therapy. No significant difference in the occurrence of breast cancer in the overall study population was identified at median follow-up periods of 46, 81.2, and 109.2 months.[73-75] Thromboembolic events, predominantly superficial thrombophlebitis, were increased in the tamoxifen-treated women. A subset of women in the Italian Tamoxifen Prevention Study who had used hormone replacement therapy (HRT) and were classified as at increased breast cancer risk based on reproductive and hormonal characteristics were found to have a significantly reduced risk of breast cancer with tamoxifen therapy.[75,76] However, only approximately 13% of the patients in the trial were at high risk for breast cancer.

It is unclear why no overall breast cancer risk reduction was observed in the Italian Tamoxifen Prevention study. Possible reasons include concurrent use of hormone replacement therapy, and different study populations (ie, populations at lower risk of breast cancer).[77]

The first International Breast Cancer Intervention Study (IBIS-I) randomized 7,152 women aged 35-70 years at increased risk for breast cancer to receive either tamoxifen or placebo for 5 years.[78] Tamoxifen provided a breast cancer (invasive or ductal carcinoma in situ) risk reduction of 32% (95% CI, 8-50; P=0.013). Thromboembolic events increased with tamoxifen (odds ratio= 2.5; 95% CI, 1.5-4.4; P=0.001), and endometrial cancer showed a nonsignificant increase (P=0.2). An excess of deaths from all causes was seen in the tamoxifen treated women (P=0.028).

In an updated analysis of the blinded IBIS-I trial at a median follow-up of 96 months, the relative risk of breast cancer for the tamoxifen arm compared with placebo was 0.73 (95% CI, 0.58-0.91; P=0.004).[79] Although no difference in the risk of ER-negative invasive tumors was observed between the 2 groups, those in the tamoxifen arm were found to have a 34% lower risk of ER-positive invasive breast cancer. Slightly higher risk reduction with tamoxifen was observed for premenopausal patients. Importantly, the increased risk of venous thromboembolism observed with tamoxifen during the treatment period was no longer significant in the posttreatment period, and gynecologic and vasomotor side effects associated with active tamoxifen treatment were not observed in posttreatment follow-up. These results provide randomized evidence that the benefits of tamoxifen continue 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 Study of Tamoxifen and Raloxifene (STAR) Trial.[28,29] (see section on The STAR Trial).

Tamoxifen Recommendations

The Panel recommends tamoxifen (20 mg/day) as an option to reduce breast cancer risk in healthy pre- and postmenopausal women ≥ 35 years of age who have a ≥ 1.7% 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1) (see BRISK-5; BRISK-B). The consensus of the Panel is that the risk/benefit ratio for tamoxifen use in premenopausal women at increased risk of breast cancer is relatively favorable (category 1), and that the risk/benefit ratio for tamoxifen use in postmenopausal women is influenced by age, presence of uterus or other comorbid conditions (category 1). Early studies suggest that lower doses of tamoxifen over shorter treatment periods may reduce breast cancer risk in

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postmenopausal women, but these findings need to be validated in phase III clinical trials.[80] Since 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, use of tamoxifen in these populations is designated as a category 2A recommendation. 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 interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen.[81] The consensus of the Panel is that alternative medications which have minimal or no impact on plasma levels of endoxifen should be substituted when possible.[81] It has also been reported that certain CYP2D6 genotypes are markers of poor tamoxifen metabolism.[82,83] Nevertheless, the consensus of the Panel is that further validation of this biomarker is needed before it can be used to select patients for tamoxifen therapy.

Raloxifene for Risk Reduction

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

The MORE Trial

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was designed to determine whether 3 years of raloxifene treatment reduced the risk of fracture in postmenopausal women with osteoporosis.[85] A total of 7,705 postmenopausal women 31-80 years of age were randomized to receive placebo, 60 mg/day of raloxifene, or 120 mg/day of raloxifene for 3 years. At study entry, participants were required to have osteoporosis (defined as a bone density at least 2.5 standard deviations below the mean for young women) or a history of osteoporotic fracture. The study showed a reduction in the vertebral fracture risk and an increase in bone mineral density in the femoral neck and spine for the raloxifene-treated women, compared with those who received placebo.

After a median follow-up of 40 months in the MORE trial, breast cancer was reported in 40 patients: 27 cases in 2,576 women on placebo and 13 cases in 5,129 women on raloxifene.[86] The relative risk of developing invasive breast cancer on raloxifene, compared with placebo, was 0.24 (95% CI, 0.13-0.44). Raloxifene markedly decreased the risk of estrogen receptor-positive cancers (relative risk=0.10; 95% CI, 0.04-0.24) but did not appear to influence the risk of developing an estrogen receptor-negative cancer (relative risk=0.88; 95% CI, 0.26-3.0). Although incidence of breast cancer was a secondary 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.[77] Furthermore, the patients enrolled in the MORE trial were, on average, at lower risk for breast cancer and older than the patients enrolled in the NSABP BCPT.

Side effects associated with the use of raloxifene included hot flashes, influenza-like syndromes, endometrial cavity fluid, peripheral edema, and leg cramps. In addition, there was an increased incidence of deep venous thromboses (0.7% for women receiving 60 mg/day raloxifene vs

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

The CORE Trial

The early findings relating to breast cancer risk in the MORE trial led to the continuation of this trial under the name Continuing Outcomes Relevant to Evista (CORE) trial. Because breast cancer incidence was a secondary endpoint in the MORE trial, CORE was designed to assess the effect of 4 additional years of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis. A secondary endpoint was the incidence of invasive estrogen receptor-positive breast cancer. Data from the CORE Trial were reported in 2004.[87]

During the CORE trial, the 4-year incidence of invasive breast cancer was reduced by 59% (hazard ratio =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 estrogen receptor-positive breast cancer by 66% (hazard ratio =0.34; 95% CI, 0.18-0.66) but had no effect on invasive estrogen receptor-negative breast cancers. Over the 8 years of both trials (MORE + CORE), the incidence of invasive breast cancer was reduced by 66% (hazard ratio =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 estrogen receptor-positive breast cancer by 76% (hazard ratio=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 (hazard ratio = 1.78; 95% CI, 0.37-8.61).

The adverse events in CORE were similar to those seen in MORE. There was a nonsignificant increase in the risk of thromboembolism (relative risk =2.17; 95% CI, 0.83-5.70) in the raloxifene group of the CORE trial compared to the placebo group. There was no statistical significant difference in endometrial events (bleeding, hyperplasia and cancer) between the raloxifene and placebo groups during the 4 years of CORE or the 8 years of MORE and CORE. During the 8 years of the MORE and CORE trials, raloxifene increased the risk for hot flushes and leg cramps compared with placebo; these risks were observed during the MORE trial but not during the additional 4 years of therapy in CORE. While it is possible that hot flushes and leg cramps are early events that do not persist with continued therapy, it is also possible that an increased risk of these adverse events was not observed in the CORE trial as a result of selection bias (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 re-randomize patients (1286 in the placebo arm, 2725 in the raloxifene arm) and maintained the double blinding of the original trial.

The RUTH Trial

In the Raloxifene Use for The Heart (RUTH) Trial, postmenopausal women with an increased risk of coronary heart disease were randomly assigned to raloxifene or placebo arms.[88,89] Invasive breast cancer incidence was a co-primary endpoint of the trial, although only approximately 40% of the study participants had an increased risk of breast cancer according to the Gail model. Median exposure to study drug was 5.1 years and median duration of follow-up was 5.6 years.[89] Raloxifene did not reduce risk of cardiovascular events but there was a 44% decrease in the incidence of invasive breast cancer in the

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raloxifene arm (HR=0.56; 95% CI, 0.38-0.83], with a 55% lower incidence of estrogen-receptor positive breast cancer (HR=0.45; 95% CI, 0.28-0.72). No reduction in the risk of noninvasive breast cancer was found for patients receiving raloxifene, in agreement with the initial results of the STAR trial, although only 7% of breast cancers in the RUTH trial were noninvasive.

The STAR Trial

Despite issues of trial design, the results from the CORE trial and the previous MORE study provided support for concluding that raloxifene may be an effective breast cancer risk reduction agent. However, neither of these studies was designed to directly evaluate the efficacy of raloxifene versus tamoxifen in this regard. This issue was addressed in the NSABP Study of Tamoxifen and Raloxifene (STAR) Trial (P-2) which was initiated in 1999; initial results became available in 2006.[28]

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 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, deep venous thrombosis, pulmonary embolism, endometrial cancer, stroke, cataracts, and death. At an average follow-up of approximately 4 years, no statistically significant differences between patients receiving 20 mg/day tamoxifen or 60 mg/day raloxifene were observed with respect to invasive breast cancer risk reduction (risk ratio=1.02;95% CI, 0.82-1.28). Because there was no placebo arm, it was not possible to determine a raloxifene versus placebo risk ratio for invasive breast cancer; however, tamoxifen was shown in the BCPT study to reduce breast cancer risk by nearly 50%. In addition, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive cancer in the subset of patients with a history of LCIS or atypical hyperplasia. However, raloxifene was not as effective as tamoxifen in reducing the risk of noninvasive breast cancer, although the observed difference was not statistically significant (risk ratio=1.40; 95% CI, 0.98-2.00).[27]

At a median follow-up of nearly 8 years (81 months) involving 19,490 women, raloxifene was shown to be about 76% as effective as tamoxifen in reducing the risk of invasive breast cancer (risk ratio=1.24; 95% CI, 1.05-1.47; see Table 4 for risk ratios by age group), suggesting that tamoxifen has greater long-term benefit with respect to lowering invasive breast cancer risk.[29] Raloxifene remained as effective as tamoxifen in reducing the risk of invasive cancer in women with LCIS, but was less effective than tamoxifen for those with a history of atypical hyperplasia (see Table 4). Interestingly, at long-term follow-up, the risk of noninvasive cancer in the raloxifene arm grew closer to that observed for the group receiving tamoxifen (risk ratio=1.22; 95% CI, 0.95-1.50; see Table 4). No significant differences in mortality were observed between the 2 groups. In the initial analysis of the STAR trial data, invasive endometrial cancer occurred less frequently in the group receiving raloxifene compared with the tamoxifen group, although the difference did not reach statistical significance. It is important to note, however, that the incidence of endometrial hyperplasia and hysterectomy were significantly lower in the raloxifene group compared to the tamoxifen group. However, at long-term follow-up, the risk of endometrial cancer was significantly lower in the raloxifene arm (see Table 5).

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

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similar for patients in both groups, although patients receiving tamoxifen reported better sexual function.[90]

Raloxifene Recommendations

The Panel recommends use of raloxifene (60 mg/day) as an option to reduce breast cancer risk in healthy postmenopausal women ≥ 35 years who have a ≥ 1.7% 5-year risk for breast cancer as determined by the modified Gail model, or who have had LCIS (category 1) (see BRISK-5; BRISK-B). The consensus of the 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 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.

Aromatase Inhibitors for Risk Reduction

A number of clinical trials testing the use of aromatase inhibitors in the adjuvant therapy of postmenopausal women with invasive breast cancer have been reported. The first of these studies, the Arimidex, Tamoxifen Alone or in Combination Trial (ATAC Trial) randomized postmenopausal women with invasive breast cancer to anastrozole versus tamoxifen versus anastrozole plus tamoxifen in a double-blinded fashion.[91] The occurrence of contralateral second primary breast cancers was a study endpoint. With 47 months median follow-up, a nonsignificant reduction in contralateral breast cancers was observed in women treated with anastrozole alone compared with tamoxifen (odds ratio= 0.62; 95% CI, 0.38-1.02; P=0.062) 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=0.04).[92] Similar reductions in the risk of contralateral breast cancer have been observed with sequential tamoxifen followed by exemestane compared with tamoxifen alone and with sequential tamoxifen followed by letrozole compared with tamoxifen followed by placebo.[93,94]

In the Breast International Group (BIG) 1-98 trial postmenopausal women with early stage breast cancer were randomized to receive 5 years of treatment with one of the following therapeutic regimens: letrozole; sequential letrozole followed by tamoxifen; tamoxifen; or sequential tamoxifen followed by letrozole. Risk of breast cancer recurrence was lower in women in the letrozole arm relative to the tamoxifen arm.[95]

Ongoing trials are evaluating the use of the aromatase inhibitors as risk reduction agents in healthy women at increased risk for future breast cancer. For example, National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MAP.3[96] and IBIS-II[97] trials are evaluating exemestane and anastrozole, respectively, compared with placebo for the prevention of breast cancer in postmenopausal women at increased risk of developing breast cancer.

Use of an aromatase inhibitor as an agent for reduction of breast cancer risk in healthy women is inappropriate unless part of a clinical trial (see BRISK-B).

Monitoring Patients on Risk-Reduction Agents

Follow-up of women treated with tamoxifen or raloxifene for breast cancer risk reduction should focus on the early detection of breast cancer and the management of adverse symptoms or complications (see BRISK-6; BRISK-7). Appropriate monitoring for breast cancer and the evaluation of breast abnormalities should be performed according

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to the guidelines described for high risk women in the NCCN Breast Cancer Screening and Diagnosis Guidelines. The population of women eligible for risk reduction therapy with tamoxifen or raloxifene is at sufficiently increased risk of breast cancer to warrant, at a minimum, yearly bilateral mammography, a clinical breast examination every 6 months, and encouragement of breast awareness (see BRISK-6).

Endometrial Cancer

Results from the BCPT study indicated that women ≥ 50 years of age treated with tamoxifen have an increased risk of developing invasive endometrial cancer (Table 3). An increased risk of endometrial cancer was not observed in women ≤ 49 years of age treated with tamoxifen in this study.[27, 67] Although the only death from endometrial cancer in the NSABP BCPT occurred in a placebo-treated subject,[27,67] 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.[98] 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.[99, 100]

Updated results from the NSABP BCPT indicate that the incidence of endometrial adenocarcinoma per 1,000 women-years was 2.20 for women receiving tamoxifen and 0.71 for women in the placebo arm.[101] The incidence rate of uterine sarcoma was 0.17 and 0.0 per 1,000 women-years for women in the tamoxifen and placebo arms, respectively. Several other studies have also supported an association between tamoxifen therapy and an increased risk of developing uterine sarcoma.[99-103] 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.[101,104]

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

For women with an intact uterus, a baseline gynecologic assessment is recommended prior to administration of the risk reduction agent, and follow-up gynecologic assessments should be performed at each visit[105] (see BRISK-6). 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.[106-108] 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 Panel believes that it is safe and reasonable to resume therapy with a risk reduction agent after completion of treatment for early stage endometrial cancer.

Retinopathy and Cataract Formation

There have been reports of tamoxifen being associated with the occurrence of retinopathy, although most of this information has come from case studies.[109,110] 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 study and individuals developing cataracts while on tamoxifen have a relative risk for cataract surgery of 1.57 (95% CI, 1.16-2.14), compared with placebo (Table 3).[27] After 7 years of follow-up in the BCPT study, relative risks

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of cataract formation and cataract surgery were similar to those initially reported.[67] In the MORE trial, raloxifene use was not associated with an increase in the incidence of cataracts compared with placebo (relative risk=0.9; 95% CI, 0.8-1.1).[111] 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 (Table 5). Thus, patients experiencing visual symptoms while undergoing treatment with tamoxifen should seek ophthalmologic evaluation (see BRISK-6).

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 women.[112-114] In premenopausal women, tamoxifen may oppose the more potent effects of estrogen on the bone and potentially increase the risk of osteoporosis, whereas tamoxifen in the presence of typically lower estrogen levels in postmenopausal women is associated with an increase in bone mineral density.[27,67] However, the Panel did not recommend monitoring of bone mineral density (BMD) in premenopausal patients on tamoxifen since development of osteopenia/osteoporosis in this population was considered unlikely.

Raloxifene has been shown to increase BMD and to reduce incidence of vertebral bone fracture in postmenopausal women when compared with placebo.[85,88] 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.[28,29] [Reference to table removed here.]

Thromboembolic Disease and Strokes

Tamoxifen and raloxifene have been associated with an increased risk of thromboembolic events (ie, deep venous thrombosis, pulmonary embolism) (Table 3; Table 5) and stroke.[27,28,29,67,86,115] Increased incidences of VTE were observed in the tamoxifen arms of all of the placebo-controlled randomized risk reduction trials. Although not statistically significant, all of these trials with the exception of the Royal Marsden trial (which enrolled only younger women) also showed an increase in risk of stroke for women receiving tamoxifen, and this risk was found to be significantly elevated in 2 meta-analyses of randomized controlled trials evaluating tamoxifen for breast cancer risk reduction or treatment.[116,117] A comparison of the raloxifene and tamoxifen arms of the STAR trial did not show a difference with respect to incidence of stroke,[28,29] and the risk of fatal stroke was significantly higher for women in the RUTH trial with underlying heart disease receiving raloxifene.[89] However, recent evidence has shown that women with a Factor V Leiden or prothrombin G20210 → A mutation receiving tamoxifen therapy in the BCPT study were not at increased risk of developing a venous thromboembolism compared to women without these mutations.[118] Although prospective screening of women for Factor V Leiden or prothrombin mutations or intermittent screening of women for thromboembolic disease is unlikely to be of value, women taking tamoxifen or raloxifene should be educated regarding the symptoms associated with deep venous thrombosis and pulmonary emboli. They should also be informed that prolonged immobilization may increase risk of venous thromboembolism, and instructed to contact their physicians immediately if they develop symptoms of deep venous thrombosis or pulmonary emboli. Women with documented thromboembolic disease should 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 study, hot flashes occurred in approximately 81% of tamoxifen-treated women and 69% of placebo-treated women.[27] In the STAR trial, women

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receiving tamoxifen reported a significantly increased incidence of vasomotor symptoms relative to women receiving raloxifene,[90] although raloxifene use has also been associated with an increase in hot flash severity and/or frequency when compared with placebo.[86] In women whose quality of life is diminished by hot flashes, an intervention to eliminate or minimize hot flashes should be undertaken. Estrogens and/or progestins have the potential to interact with SERMs and are not recommended by the Panel for 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.[119-122] It has been hypothesized that the mode of action of gabapentin is via central temperature regulatory centers.[119,121] 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.[122]

Venlafaxine, a serotonin and norepinephrine inhibitor antidepressant has been shown to be effective in the management of hot flash symptoms in a group of breast cancer survivors of which nearly 70% were taking tamoxifen. Significant declines were observed for both hot flash frequency and severity scores for all doses of venlafaxine (37.5 mg, 75 mg and 150 mg) compared to placebo; incremental improvement was seen at 75 mg versus 37.5 mg (P=0.03).[123] 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, a selective serotonin reuptake inhibitor (SSRI), has also been studied for the relief of hot flash symptoms. A double blind, placebo-controlled trial recruited 165 menopausal women who were randomized into 3 arms (placebo, paroxetine 12.5 mg daily or paroxetine 25 mg daily). After 6 weeks, significant reductions in composite hot flash scores were noted for both dosages of paroxetine (12.5 mg, 62% reduction and 25 mg, 65% reduction); there were no significant differences between dose levels.[124] Adverse events, reported by 54% of subjects receiving placebo and 58% receiving paroxetine, generally included nausea, dizziness and insomnia.

In a stratified, randomized, double-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 20mg 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).[125] Hot flash frequency and composite score were reduced by 40.6% and 45.6%, respectively, for patients receiving 10 mg paroxetine compared to reductions of 13.7% and 13.7% in the placebo group. Likewise, reductions of 51.7% and 56.1% in hot flash frequency and score were found for women receiving 20 mg paroxetine compared with values of 26.6% and 28.8% in the

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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 20mg 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, an active metabolite of tamoxifen.[81,126] These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, citalopram and venlafaxine, appear to have only minimal effects on tamoxifen metabolism.

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

A recent report of 2 nonrandomized parallel study cohorts of women with ductal carcinoma in situ (DCIS) or those at high-risk of breast cancer (eg, those with LCIS, atypical hyperplasia, or ≥ 1.7% 5-year breast cancer risk by the Gail model) comparing women receiving tamoxifen alone with women receiving tamoxifen concomitant with hormone replacement therapy (HRT) (mean duration of HRT at start of study approximately 10 years) did not show a difference in the rate of tamoxifen-induced hot flashes.[128] The Panel recommends against the use of HRT 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.[129] Both the oral and transdermal formulations of clonidine reduce hot flashes in a dose-dependent manner.[130-132] Toxicities associated with clonidine include dry mouth, constipation, and drowsiness. Anecdotal evidence suggests that the use of 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.[133] Results from a recent 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.[134] 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.[135]

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,[120-125] suggesting that a considerable proportion of patients might be helped through a trial of limited duration. However, not all women who experience hot flashes require medical intervention, and the decision to intervene requires consideration of the efficacy and toxicity of the intervention. In addition, a study of women receiving tamoxifen

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for early-stage breast cancer showed a decrease in hot flashes over time.[136]

Risk Reduction Counseling

Women should be monitored according to the NCCN Breast Cancer Screening and Diagnosis Guidelines. Women with a known or suspected *BRCA 1/2, TP53, PTEN*, or other gene mutation associated with breast cancer risk or those with close relatives with breast and/or ovarian cancer should be followed according to the NCCN Genetics/Familial High Risk Assessment Guidelines whether or not they choose to undergo risk reduction therapy (see BRISK-1;BRISK-4). Women who have abnormal results from their clinical breast examination or bilateral mammogram should be managed according to the NCCN Breast Cancer Screening and Diagnosis Guidelines or, if results indicate malignancy, the women should be treated according to the NCCN Breast Cancer Treatment Guidelines. Although the 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 Breast Cancer Treatment Guidelines.

All women who are appropriate candidates for breast cancer risk reduction intervention should undergo counseling that provides a description of the available strategies, including a healthy lifestyle, to decrease breast cancer risk (see BRISK-A).[137] 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 a venous thromboembolic event, current use of hormones or SSRI or previous use of a SERM); (2) absolute and relative breast cancer risk reduction achieved with the risk reduction intervention; (3) risks of risk reduction therapy with an emphasis on age-dependent risks; (4) the contraindications to therapy with tamoxifen and raloxifene (eg, history of venous thromboembolism, history of thrombotic stroke, history of transient ischemic attack, and pregnancy or pregnancy potential without an effective nonhormonal method of contraception; (5) the common and serious side effects of tamoxifen and raloxifene (see BRISK-A).

The recently updated guidelines from the American Society of Clinical Oncology (ASCO) comparing the effectiveness of breast cancer risk reduction agents provide some estimates of the number needed to either treat (NNT) to prevent breast cancer or harm (NNH) by causing a specific side effect in a single patient receiving a specific risk reduction agent.[138] Both NNT and NNH can be useful aids in communicating risks and benefits of tamoxifen and raloxifene in this setting (eg, using long-term data from the IBIS-1 trial, NNH with respect to VTE was determined to be 73 with tamoxifen, whereas this value was 150 for patients receiving raloxifene using data from the RUTH study). A summary of other strategies to facilitate a more quantitative discussion of the impact of these agents is also described in the ASCO guidelines.

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 and/or STAR trial, as appropriate. The BCPT study showed that the toxicity profile of tamoxifen is much more favorable in younger women, and the benefits in relative risk reduction are similar across all age groups and risk groups (Table 2; Table 3).[27] 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

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addition, tamoxifen may be more effective than raloxifene in reducing the incidence of non-invasive breast cancer (Table 4), although the difference is not statistically significant at long-term follow-up. [28,29] Further, tamoxifen was reported by patients in the STAR trial to be associated with better sexual function than raloxifene.[90] However, tamoxifen has been associated with an increased incidence of invasive endometrial cancer relative to placebo in women ≥ 50 years of age,[27,67] (Table 3) and an increased incidence of endometrial hyperplasia and invasive endometrial cancer relative to raloxifene,[28,29] possibly making it a less attractive choice in women with a uterus. Use of raloxifene to reduce breast cancer risk may be preferred by postmenopausal women with a uterus or those at risk for developing cataracts. All women receiving a breast cancer risk reduction agent should be counseled with respect to signs and symptoms of possible side effects associated with use of these agents, and the recommended schedules for monitoring for the presence of certain adverse events. Contraindications to tamoxifen or raloxifene include history of VTE, thrombotic stroke, transient ischemic attack, current pregnancy or pregnancy potential without effective method of contraception, or known inherited clotting trait.

The optimal duration of SERM therapy for breast cancer risk reduction is not known. In the Early Breast Cancer Trialists' most recent overview analysis, continuing tamoxifen therapy for up to 5 years resulted in an increasingly reduced risk for the development of contralateral primary breast cancer.[66] Use of tamoxifen for more than 5 years provided no greater benefit but incurred continued risks of therapy. In addition, the BCPT and STAR trials only studied 5 years of risk reduction therapy with either tamoxifen or raloxifene.[27, 28] However, based on the updated STAR results which showed that the benefits of raloxifene diminished after cessation of therapy,[29] continuing raloxifene beyond 5 years might be an approach to maintain the risk reduction activity of the agent.

There have been some concerns based on studies of animal models regarding the potential for interference with subsequent raloxifene efficacy in patients who had previously completed a 5-year course of tamoxifen.[139] Conversely, questions also exist regarding the safety and efficacy of administering tamoxifen to a patient who had previously taken raloxifene for treatment or prevention of osteoporosis. Until further information is available, a period of 5 years appears to be appropriate for tamoxifen therapy when the agent is used to reduce the risk of cancer. Women should be counseled that the benefits and safety of further therapy with raloxifene is not known. After completing 5 years of tamoxifen therapy, women should continue to be monitored according to the NCCN Breast Cancer Screening and Diagnosis Guidelines and should continue to undergo monitoring for late toxicity, especially for endometrial cancer and cataracts.

The prolonged effectiveness of tamoxifen as an agent to reduce breast cancer risk, particularly with respect to the development of estrogen receptor-positive disease, is supported by results of several placebo-controlled randomized trials at long-term follow-up.[67,72,79] 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.[29]

Risk Reduction Surgery

For women at very high risk of breast cancer who are considering risk reduction bilateral mastectomy (RRM), it is important that the potential psychosocial effects of RRM are addressed, although these effects have not been well studied.[140-142] Such surgery has the potential to negatively impact perceptions of body image, ease of forming new relationships, and the quality of existing relationships. Moreover, the procedure also eliminates the breast as a sexual organ.

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Multidisciplinary consultations are recommended prior to surgery, and should include a surgeon familiar with the natural history and therapy of benign and malignant breast disease[143] to enable the woman to become well informed regarding treatment alternatives, the risks and benefits of surgery, and surgical breast reconstruction options. Immediate breast reconstruction is an option for many women following RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction.[144] Psychological consultation may also be considered.

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

It has been reported that short-term hormone replacement in women undergoing RRSO did not negate the reduction in breast cancer risk associated with the surgery.[145] In addition, results of a recent case-control study of *BRCA1* mutation carriers showed no association between use of HRT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers.[146] However, the consensus of the Panel is that caution should be used when considering use of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies (see also section on Breast Cancer Risks Associated with HRT).[147,148] It is unlikely that a prospective randomized study on the use of RRSO for breast cancer risk reduction will be performed. Whether the resulting reduction in the risk of breast cancer from this procedure is preferable to a RRM is likely to remain a personal decision.[149] Table 1 provides estimates based on a Model Carlo simulation model of the survival impact of breast and ovarian risk reduction strategies; these data can be used as a tool to facilitate shared decision-making regarding choice of a risk reduction approach, particularly with respect to issues related to risk reduction surgery (see Table 1).

Healthy Lifestyle

There is evidence to indicate that certain lifestyle characteristics, such as obesity, increased alcohol consumption, and use of certain types of hormone replacement therapy (HRT), are risk factors or markers for an elevated risk of breast cancer.[150] However, the association between a lifestyle modification and a change in breast cancer risk is not as clear. Nevertheless, a discussion of lifestyle characteristics associated with increased risk of breast cancer also provides “a teachable moment” for the promotion of overall health, and an opportunity to encourage women to make choices and changes compatible with a healthy lifestyle.

Breast Cancer Risks Associated with HRT

The Women’s Health Initiative (WHI) enrolled 161,809 postmenopausal women 50-79 years of age into a set of clinical trials from 1993-1998. Two of these trials were randomized controlled studies involving the use of HRT in primary disease prevention: a trial involving 16,608 women with intact uteri at baseline randomized to receive estrogen plus progestin or placebo,[151] and a trial of 10,739 women with prior hysterectomy randomized to receive estrogen alone or placebo.[152] The former trial was terminated early due to evidence for breast cancer harm, along with a global index associated with overall harm. In that study, a 26% increased incidence of breast cancer was observed in the treatment group (hazard ratio=1.26; 95% CI, 1.00-1.59). Of greater concern is that the breast cancers were more advanced in the

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treatment group compared to placebo,[153] although the increased risk of breast cancer declined rapidly following cessation of HRT.[154]

However, an increased risk of breast cancer was not observed in the trial of women who had undergone hysterectomies and were receiving unopposed estrogen. In fact, the rate of breast cancer was lower in the group receiving estrogen relative to the placebo group, although this difference was not considered to be statistically significant.[152] Results from long-term follow-up (ie, mean 7.1 years) of women from the WHI study who received estrogen alone have supported the conclusion of no significant difference in breast cancer incidence between the treatment and placebo groups (hazard ratio=0.80; 95% CI, 0.62-1.04; P=0.09). However, an increased incidence of abnormal mammograms was observed in the group of women receiving estrogen,[155] as well as a doubling of the risk of benign proliferative breast disease.[156] A more recent analysis of the data from this randomized controlled WHI trial showed use of estrogen alone to significantly increase mammographic breast density compared with women receiving placebo, and this effect was observed for at least a 2 year period.[157] An increased incidence of abnormal mammograms was also observed for women in the WHI who received estrogen plus progestin, and was attributed to an increase in breast density.[158]

Contrary to the results from the WHI randomized controlled trials, results from several prospective, population-based, observational studies have shown use of estrogen-only HRT to be associated with increased risks of breast cancer. These studies include the Black Women's Health Study where use of estrogen alone for a duration of 10 years or longer was associated with a nonsignificant increase in risk of invasive breast cancer (relative risk=1.41; 95% CI, 0.95-2.10),[159] the Million Women Study of women 50-64 years of age which showed an association between current use of estrogen-only HRT and increased risk of breast cancer (relative risk=1.30; 95% CI, 1.21-1.40; P<0.0001),[160] 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).[161]

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 HRT and age at initiation of HRT.[154] For example, many of women in the WHI clinical trials did not start receiving HRT until years after menopause whereas those in the population-based studies were more likely to initiate HRT 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 HRT 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.[162] However, further studies are needed to evaluate this hypothesis. Another possible explanation for the decrease in breast cancer risk observed in the first 2 years of the WHI randomized controlled trial of postmenopausal women receiving estrogen plus progestin may be related to effects of HRT on breast tissue and subsequent interference with the ability of mammography to detect new breast cancer tumors.[154]

The use of estrogen/progestin therapy and estrogen therapy alone has also been associated with increased risks of cardiovascular disease (eg, stroke) and decreased risk of bone fractures.[151,152] However, a more recent secondary analysis from the WHI randomized controlled trials showed a trend for more effective reduction in the risk of cardiovascular disease with initiation of HRT closer to menopause compared with administration of HRT to women who experienced a greater time gap between menopause and the start of such therapy.[163]

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Nevertheless, recent results from a large French cohort-control study show a significantly increased risk of breast cancer in women receiving short-term (ie, 2 years or less) estrogen and progestagen shortly after menopause when compared with nonusers.[164]

The Panel recommends against the use of HRT for women taking tamoxifen or raloxifene 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 a 30%-50% increase in the incidence of breast cancer.[165] 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 estrogen-receptor-positive breast cancer.[166] However, the effect of a reduction in alcohol consumption on the incidence of breast cancer has not been well studied. The consensus of the Panel is that alcohol consumption should be limited to < 1 drink per day.[150]

Exercise

Increased levels of physical activity have been associated with a decreased risk of breast cancer.[150,167-170] For example, the effect of exercise on risk of breast cancer was evaluated in a population-based study of 90,509 women between the ages of 40 and 65 years.[169] A relative risk of 0.62 (95% CI, 0.49-0.78) was observed for women who reported more than five hours of vigorous exercise per week compared to women who did not participate in recreational activities. These results are supported by another population-based case-control study of 4538 case patients with newly diagnosed invasive breast cancer and control patients grouped according to race (eg, 1605 black and 2933 white patients). Both black and white women with annual lifetime exercise activity levels exceeding the median activity level for active control subjects were found to have a 20% lower risk of breast cancer when compared to inactive women (odds ratio=0.82; 95% CI, 0.71-0.93).[170] 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).[167] Recently, a study of 320 postmenopausal sedentary women randomly assigned to 1 year of aerobic exercise or a control group showed modest but significant changes in serum levels of estradiol and sex hormone-binding globulin from baseline (ie, a decrease and an increase in these levels, respectively).[171] However, it has been suggested that other, as yet unidentified, mechanisms are more likely to be responsible for the association between increased activity level and decreased risk of breast cancer.[172]

Diet

Results from the WHI controlled intervention trial of 48,835 postmenopausal women designed to test the effect of a low-fat diet (e.g. fat intake limited to 20% of total caloric intake per day, and increased consumption of fruits, vegetables, and grains) on risk of breast cancer did not show a statistically significant reduction in the incidence of invasive breast cancer in women who followed a low-fat diet over an average of 8.1 years (hazard ratio=0.91, 95% CI; 0.83-1.01).[173] Limitations of this type of study include inherent difficulties in assuring compliance with dietary interventions, recall biases, the relatively short duration of the follow-up period, and the likelihood of insufficient differences between the 2 arms with respect to fat intake.[174] Furthermore, it is possible that the impact of certain diets on breast cancer risk may be dependent on the age of the study population.[174,175] 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.[175,176] Nevertheless, diets in which the main sources of dietary fat are non-

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hydrogenated and unsaturated have been shown to have cardiovascular benefits.[175,177]

Recent epidemiologic studies suggest that vitamin D (from dietary sources and the sun) may play a protective role with respect to decreasing risk of the development of breast cancer.[175,178] Furthermore, there is some evidence to suggest that such protection is greatest for women who had more prolonged exposure of skin to sunlight and higher dietary intake of sources of vitamin D during adolescence,[179,180] although additional studies are need to further evaluate this finding.

Weight/BMI

There is a substantial amount of evidence indicating that overweight or obese women have a higher risk of postmenopausal breast cancer.[150]

Recent results from the Nurses' Health Study evaluating the effect of weight change on the incidence of invasive breast cancer in 87,143 postmenopausal women suggested that women experiencing a weight gain of 25.0 kg or more since age 18 have an increased risk of breast cancer when compared with women who have maintained their weight (relative risk=1.45; 95% CI, 1.27-1.66).[181] Furthermore, women who had never used postmenopausal hormone replacement therapy and lost 10.0 kg or more since menopause and kept the weight off had a significantly lower risk of breast cancer than women who had maintained their weight (relative risk= 0.43; 95% CI, 0.21-0.86). Interestingly, there is evidence that the risk of breast cancer is lower in premenopausal women who are overweight compared with women who are not overweight.[150]

Results from a case-control study of 1,073 pairs of women with *BRCA1/2* mutations indicated that a weight loss of 10 or more pounds in women with the *BRCA1* mutation between the ages of 18 and 30 was associated with a decreased risk of developing breast cancer between the ages of 30 and 40 years. (odds ratio=0.35; 95% CI, 0.18-0.67).[182]

Clinical Trials

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

Summary

Breast cancer risk assessment provides a means of identifying healthy women at increased risk for future development of this disease. However, many of the risk factors for breast cancer are not modifiable. The demonstration that use of tamoxifen or raloxifene for 5 years substantially decreases the future risk of breast cancer provides an opportunity for a risk reduction intervention. However, the risks and benefits associated with use of tamoxifen or raloxifene for an individual woman should be evaluated and discussed with the woman as part of a shared decision-making process. Women taking a risk reduction agent must be closely monitored for potential side effects associated with use of these agents. In special circumstances, such as in women who are carriers of a *BRCA1/2* mutation, where the risk of breast cancer is very high, the performance of a bilateral mastectomy or bilateral salpingo-oophorectomy may be considered for breast cancer risk reduction. Women considering either surgery should undergo multidisciplinary consultations prior to surgery so as to become well informed about all treatment alternatives, the risks and benefits of risk reduction surgery, and, in the case of bilateral mastectomy, the various reconstruction options available.

The Panel strongly encourages women and health care providers to participate in clinical trials to test new strategies for decreasing the risk of breast cancer. Only through the accumulated experience gained from prospective and well-designed clinical trials will additional advances in the reduction of breast cancer risk be realized.

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Figure 1

Criteria used in calculation of 5-year risk of 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

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Table 1

Survival Probability by Age 70 Years* According to Breast/Ovarian Cancer Risk Reduction Strategy for 25 Year Old BRCA1/2 Mutation Carrier. [Probability of death as a result of breast cancer (BCD) or ovarian cancer (OCD); RRSO-risk-reduction bilateral salpingo-oophorectomy; RRM – risk-reduction bilateral mastectomy; Breast screening – annual mammography and MRI]

Intervention	*BRCA1* mutation carrier	*BRCA2* mutation carrier
No intervention	53% [BCD=41%;OCD=36%]	71% [BCD=36%;OCD=20%]
RRSO at age 40 only	68% [BCD=45%;OCD=12%]	77% [BCD=30%;OCD=4%]
RRSO at age 50 only	61% [BCD=51%;OCD=20%]	75% [BCD=42%;OCD=6%]
RRM at age 25 only	66% [BCD=5%;OCD=58%]	79% [BCD=4%;OCD=30%]
RRM at age 40 only	64% [BCD=13%;OCD=53%]	78% [BCD=9%;OCD=28%]
Breast screening only from 25-69	59% [BCD=26%;OCD=46%]	75% [BCD=21%;OCD=25%]
RRSO at age 40 and PM at age 25	79% [BCD=6%;OCD=21%]	83% [BCD=3%;OCD=6%]
RRSO at age 40 and breast screening from 25-69	74% [BCD=30%;OCD=15%]	80% [BCD=18%;OCD=5%]
RRSO at age 40; breast screening from 25-39 followed by PM at age 40	77% [BCD=18%;OCD=18%]	82% [BCD=9%;OCD=6%]

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

Adapted 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, by permission of the American Society of Clinical Oncology.

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Table 2

Rates of Invasive Breast Cancer in the NSABP Breast Cancer Prevention Trial (BCPT)

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

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

Patient Characteristic	Risk Ratio (Tamoxifen vs Placebo)	95% CI
All women	0.50	0.33-0.77

Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for the 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, by permission of Oxford University Press.

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Table 3

Toxicity Experience in Women Enrolled in the NSABP Breast Cancer Prevention Trial (BCPT)

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

Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for the 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, by permission of Oxford University Press.

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Table 4

Rates of Invasive Breast Cancer in the NSABP Study of Tamoxifen and Raloxifene (STAR) Trial – 81 months median follow-up

Patient Characteristic	Risk Ratio (Raloxifene vs Tamoxifen)	95% Confidence Interval (CI)
All women	**1.24**	**0.1.05-1.47**
Age		
≤ 49 yr	1.53	0.64-3.80
50-59 yr	1.23	0.97-1.57
≥ 60 yr	1.22	0.95-1.58
History of LCIS	1.13	0.76-1.69
History of atypical hyperplasia	1.48	1.06-2.09

Rates of Noninvasive Breast Cancer in the STAR Trial

Patient Characteristic	Risk Ratio (Raloxifene vs Tamoxifen)	95% CI
All women	1.22	0.95-1.59

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 2010;3:696-706, by permission of the American Association for Cancer Research.

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Table 5

Toxicity Experience in Women Enrolled in the NSABP Study of Tamoxifen and Raloxifene (STAR) Trial – 81 months median follow-up

Toxicity	Annual Rate per 1,000 Patients			95% Confidence Interval (CI)
	Tamoxifen	Raloxifene	Risk Ratio (Raloxifene vs Tamoxifen)	
Invasive endometrial cancer	2.25	1.23	0.55	0.36-0.83
Endometrial hyperplasia	4.40	0.84	0.19	0.12-0.29
Hysterectomy during follow-up	12.08	5.41	0.45	0.37-0.54
Thromboembolic events	3.30	2.47	0.75	0.60-0.93
- **Deep vein thrombosis**	1.93	1.38	0.55	0.54-0.95
- **Pulmonary embolism**	1.36	1.09	0.27	0.57-1.11
Cataracts developed during follow-up	14.58	11.69	0.80	0.72-0.89
Cataracts developed and underwent surgery	11.18	8.85	0.79	0.70-0.90

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 2010;3:696-706, by permission of the American Association for Cancer Research.

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