Opportunities and Strategies for Breast Cancer Prevention Through Risk Reduction

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ABSTRACT Due to the high incidence of breast cancer among US females, risk-reduction strategies are essential. Before considering approaches to breast cancer risk reduction, it is important for clinicians to complete individualized qualitative and quantitative assessments of risk for their patients in order to inform physicians’ clinical decision making and management and to engage patients collaboratively in a thorough discussion of risks and benefits. This review will summarize information on potential pharmacologic, nutritional, surgical, and behavioral approaches to reducing breast cancer risk.

While there is no clear evidence that specific dietary components can effectively reduce breast cancer risk, weight gain and obesity in adulthood are risk factors for the development of postmenopausal breast cancer. Alcohol consumption, even at moderate levels, increases breast cancer risk, although some of the detrimental effects may be reduced by sufficient folate intake. Women at increased risk of breast cancer can opt to reduce their breast cancer risk through the use of tamoxifen or raloxifene; other chemopreventive agents remain under investigation. Surgical approaches to risk reductions are restricted to those patients with a substantially increased risk of developing breast cancer. Patients should be encouraged to maintain a healthy lifestyle for their overall well-being and to remain up to date with recommendations for screening and surveillance. (CA Cancer J Clin 2008;58:347–371.) © American Cancer Society, Inc., 2008.

INTRODUCTION

While decreases in both breast cancer incidence and breast cancer mortality have been apparent in recent years, the societal and economic impact of this malignancy continues to be huge. A 3.9% decrease in breast cancer incidence has been observed between 2001 to 2004, along with a 2.2% decrease in breast cancer mortality between 1990 to 2004. Although a constellation of breast cancer risk factors has been identified, many of these are not easily modified. Further, many women worry about the potential impact of a breast cancer diagnosis on themselves and their families. As a result, interest in strategies to prevent breast cancer remains strong.

EPIDEMIOLOGY OF BREAST CANCER

Estimates from the American Cancer Society (ACS) project 184,450 new cases of breast cancer and 40,480 deaths due to breast cancer among US women during 2008. Breast cancer continues to be the most commonly diagnosed malignancy among females in the United States. A woman’s lifetime risk of developing breast cancer is about 1 in 8 or approximately 12%. As shown in Figure 1, marked disparities are apparent with regard to both incidence and mortality patterns. A comprehensive overview of trends in breast cancer epidemiology has been published.

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Age-specific incidence rates increase dramatically beginning at age 40 years, with peak incidence generally occurring among women aged between 75 and 79 years; incidence peaks are not as pronounced among non-Whites (see Figure 2). The median age at diagnosis among all breast cancer cases in the United States is 61 years.

As illustrated in Figure 3, the lifetime probability of being diagnosed with breast cancer tends to diminish as increased age ranges are achieved. For example, at age 30 years, a woman’s lifetime risk of breast cancer is 12.5%; at age 50 years, the lifetime risk of breast cancer is 11.1%; and at age 70 years, the lifetime risk of breast cancer is...
The reason that the lifetime risk of breast cancer declines with advancing age is that the area under the age-specific incidence curve decreases as one ages.

A review of incidence data shows that the average annual age-specific rate of breast cancer for a White female aged between 60 to 64 years is 388.0 cases per 100,000 population or 3.8 cases per 1,000 women in the age interval; in other words, 996 of these 1,000 women will not develop breast cancer. As shown in Figure 4, the probability of an average-risk women developing breast cancer between the ages of 55 and 59 years is 1.4%.

Population surveys, based on both the National Health Interview Survey and the Behavioral Risk Factor Survey, have been used to assess trends in cancer screening behaviors such as completion of mammography and identification of subgroups who may require a targeted focus. Data suggest a recent slight dip in the proportion of women aged 40 years and older who report having completed at least one mammogram in the past 2 years; in 2000, the proportion was 76.4% compared with 74.6% in 2005. While this dip appears to be consistent across White, Black, and Hispanic women, survey data are unable to explain reasons for this decrease nor whether the trend will continue. Despite this recent modest change in mammography rates, breast cancer is typically diagnosed at an early stage (61% local and 31% regional). Overall, 87.3% of women diagnosed with breast cancer remain alive at 5 years, and 79.9% are alive at 10 years following diagnosis. During the period of 1988 to 2003, relative survival rates for localized breast cancer were 97.6% and 93.5% at 5 years and 10 years, respectively, while for regional disease, survival rates were 80.0% and 67%, respectively. As of 2004, it was estimated there were 2,407,943 female breast cancer survivors in the United States.

**ASSESSING BREAST CANCER RISK**

It is important for clinicians to determine whether a female patient is at “general population risk” or at “increased risk” of developing breast cancer since this information can impact patient management decisions. General population risk refers to women who are not known to have any medical conditions, family history of malignancy, or specific exposures that would increase the risk of developing breast cancer above that of the general population. Screening tests are used for the early diagnosis of disease...
in otherwise healthy persons at general population risk. Mammography, performed at recommended intervals, is used to identify breast cancers among women aged 40 years and older in the general population not known to be at increased risk of developing breast cancer.

In contrast, “increased risk” refers to persons who are known or are suspected to be at increased risk of developing a certain cancer due to personal and/or family history of medical conditions, exposures, and/or prior cancers. For example, a woman with a close relative (e.g., mother or sister) who has been diagnosed with breast cancer before age 60 years may warrant surveillance based on clinical examination and use of other imaging studies at specific intervals due to an increased risk of developing breast cancer compared with others without this family/medical history. Surveillance refers to explicit strategies for assessment and/or examination at precise time intervals among persons at increased disease risk. It is important to note that levels of increased risk vary and that surveillance plans are frequently individualized. Guidelines on the use of breast magnetic resonance imaging (MRI) for breast cancer detection among women at high risk (>20% lifetime risk) are available. Screening MRI is recommended as an adjunct to annual mammography for women with an estimated 20% to 25% or greater lifetime risk of breast cancer based on risk models, including women with a strong family history of breast or ovarian cancer, women who were treated with chest irradiation for Hodgkin disease (HD), and other clinical considerations. Women judged to be at moderately increased breast cancer risk (15% to 20% lifetime risk) should consult with their physicians about the benefits and limitations of adding MRI screening to their yearly mammogram. Yearly MRI screening is not recommended for women whose lifetime risk of breast cancer is estimated to be less than 15%.

In general, personal or family histories of cancer that may suggest increased susceptibility for certain types of cancer include (i) 2 or more affected individuals on the same side of the family (i.e., maternal or paternal lineage) with the same or “related” cancers (such as breast and ovarian cancers or colon and uterine cancers); (ii) age of cancer diagnosis is earlier than the average age of onset in the general population in at least one individual; (iii) presence of more than one primary cancer in an individual (not including metastases); and/or (iv) a history of specific medical conditions associated with an increased risk of developing...
certain types of cancer. Patients and/or families with a history suggestive of increased susceptibility should consider evaluation by a genetics professional to determine the significance of this family history and specific recommendations for surveillance and/or cancer risk management. Guidelines to assist clinicians in making decisions about referral for genetic risk assessments and counseling for women with a family history marked by increased breast cancer susceptibility have been developed by a number of organizations, including the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the US Preventive Services Task Force.

**QUALITATIVE BREAST CANCER RISK ASSESSMENT**

As indicated earlier, multiple risk factors for breast cancer have been identified. A comprehensive medical history review can be used to stratify women by level of breast cancer risk. Women with known breast cancer gene mutations or a history of chest irradiation would be classified at high risk. Women with multiple risk factors or a strong family history of breast cancer would be at moderate risk, while those not in either of the 2 former groups would be classified as being at general population risk of developing breast cancer. As summarized in Figure 5, breast cancer risk factors can be divided into those that cannot be modified and those that are modifiable (or potentially modifiable).

**Personal Risk Factors**

Breast cancer incidence rates vary by age group and by race/ethnicity. Beyond age and race, a variety of risk factors contribute to an individual’s risk of developing breast cancer. Risk of breast cancer is impacted by family history (relative risk [RR] = 1.8 for woman with a first-degree relative aged 50 years or older with postmenopausal breast cancer; RR = 3.3 for woman with a first-relative with premenopausal breast cancer; RR = 1.5 for woman with a second-degree relative with breast cancer; and RR = 3.6 for woman with 2 first-degree relatives with breast cancer)15; genetic factors (carriers of breast cancer 1 [BRCA1] and/or breast cancer 2 [BRCA2] mutations, lifetime risk of breast cancer between 40% to 80%)16; reproductive factors (eg, late age at first live birth [RR = 1.7 to 1.9])15; breastfeeding history (4.3% reduction in risk, 95% confidence interval [CI], 2.9% to 5.8%, for each year of breastfeeding)17; menstrual history (eg, early age at menarche [RR = 1.3], late menopause [RR = 1.2 to 1.5])15; and medical history (eg, woman with Hodgkin lymphoma treated at age 25 years with a chest radiation dose of at least 40 Gray, cumulative absolute risk of breast cancer by age 55 years = 29.0% [95% CI, 20.2% to 40.1%]).18 In addition, breast density on mammograms is predictive of breast cancer risk (odds ratio [OR] = 5.23; 95% CI, 1.70 to 16.13).19 Other risk factors for breast cancer have the potential of being modifiable: overweight (80th percentile versus 20th percentile of body mass index, RR = 1.2 to 1.9)15; physical activity (for postmenopausal women risk reduction of 20% [range 20% to 80%]; no clear relationship among premenopausal women)20; alcohol consumption (2 drinks daily versus none, RR = 1.2)15; and use of exogenous hormones (current user of estrogen + progestin for at least 5 years, RR = 1.2).15

For postmenopausal breast cancer, strong evidence for risk reductions of at least 20% was noted for leisure time physical activity (range, 20% to 80%). For pre- and postmenopausal breast cancer combined, the evidence for an association with leisure time or total activity was much weaker (nil and indecisive, respectively) using our a priori set criteria for defining levels...
of evidence. However, when the criteria were changed to a risk estimate below 0.85 (instead of 0.80), the evidence was strong and moderate, respectively, indicating a 15% to 20% overall breast cancer risk reduction. For premenopausal breast cancer, the evidence for an association with physical activity was indecisive. Evidence for a dose-response relationship was observed in approximately half of the higher-quality studies that reported a decreased risk.

**Genetics**

Families with 2 or more persons diagnosed with breast cancer and other related malignancies (ovarian) are suggestive of increased risk. Mutations involving the tumor-suppressor genes BRCA1 and/or BRCA2 are present in 1% to 2% of Ashkenazi Jews and confer a lifetime risk of breast cancer ranging between 40% and 80%, as well as an increased risk of ovarian and colon cancers. The prevalence of BRCA1 mutations among non-Hispanic White populations without Ashkenazi heritage has been estimated to be 0.24%, suggesting that more than 500,000 non-Ashkenazi Whites are at substantially increased risk of breast cancer; the prevalence of BRCA2 mutations is lower and would account for a lower number of susceptible individuals. In addition to high-penetrance genes such as BRCA1 and BRCA2, several low-penetrance genes affect the risk of breast malignancies.

**Medical Conditions**

Increased rates of breast cancer have been observed among female survivors of HD treated with chest irradiation. Risk is proportional to the radiation dose to the breasts and the age at time of treatment. As an example, a female diagnosed with Hodgkin lymphoma at age 20 years and treated with >40 Gray of chest irradiation and no alkylating agents has an estimated cumulative breast cancer risk of 19.1% (95% CI, 13.0% to 27.4%) over the next 30 years. Surveillance guidelines for women with a history of HD recommend annual mammograms beginning either 8 years following treatment or beginning at age 25 years.

**Quantitative Breast Cancer Risk Assessment**

Breast cancer risk-assessment tools can be useful for quantifying the magnitude of risk for individual patients; the Gail and Claus models are among the most widely known examples of these risk-assessment tools. These models were developed based on 2 different studies (the Cancer and Steroid Hormone Project for the Claus model and the Breast Cancer Detection and Demonstration Project for the Gail model).

Components of the Gail model (http://www.cancer.gov/bcrisktool/), which provides a risk estimate for the next 5 years and an estimate of lifetime risk, include age at menarche, age at first live birth, number of first-degree relatives with invasive breast cancer, patient age, and number of prior breast biopsies and result(s) (atypical hyperplasia: yes, no, unknown). The Gail model was initially developed based on a cohort of White women. Recently, the model was updated using data from the Contraceptive and Reproductive Experiences Study to provide more accurate determination of risk for Black women. (The Gail model is not applicable to patients with a prior history of invasive breast cancer, lobular carcinoma in situ [LCIS], or ductal carcinoma in situ [DCIS].)

The Claus model includes information on up to 2 first- and/or second-degree relatives with invasive breast cancer, along with specification as to maternal or paternal lineage, age of patient, and age of relatives at time of breast cancer diagnosis. An advantage of the Claus model is the inclusion of expanded family history information; however, it can only be used among women with a family history of breast cancer.

DCIS and LCIS of the breast are defined as noninvasive breast cancers, and both DCIS and LCIS cases are excluded from risk calculations in both the Gail and Claus models. These exclusions likely result in an underestimation of actual risk. Neither the Gail nor Claus model includes a family history of ovarian or other related cancers when predicting the risk of developing breast cancer. This is significant because studies have linked a family history of ovarian cancer to the diagnosis of breast cancer. Finally, race/ethnicity also presents a limitation as Gail only considers
Black, White, and Hispanic race/ethnicity, while Claus does not include race/ethnicity.

In attempting to compare these 2 models, the Gail model includes reproductive factors plus breast biopsies, histology, and first-degree family history but does not include information about the ages of affected relatives, breast cancers among second-degree relatives, or cases on the paternal side. The Claus model includes information about up to 2 affected second-degree relatives, including paternal cases, but does not include data on the patient’s history of atypical hyperplasia, menarche, or age at first live birth. It can only be used among women who report a history of breast cancer in a first- or second-degree relative. Both the Gail and Claus models were developed before the BRCA1 and BRCA2 susceptibility genes for breast cancer were identified, although additional models are available to estimate an individual’s risk of carrying these deleterious mutations. Newer risk-prediction models include additional variables, such as weight, body mass index, breast density, and use of hormone therapy (HT), but require further validation. These other breast cancer risk-assessment models include additional variables on family history, hormonal factors, and benign breast disease, as well as low-penetrance genes. The Cuzick-Tyrer model performed most accurately, compared with the Gail, Claus, and BRCA1/2 models, when tested against a data set of women followed in a breast cancer screening program for about 5 years.

**Selective Estrogen-receptor Modulators**

Several recent studies have reported on the use of selective estrogen–receptor modulators (SERMs) to reduce breast cancer risk. This class of drugs, including tamoxifen (Nolvadex) and raloxifene (Evista), act as both estrogen agonists and antagonists. Tamoxifen citrate is a first-generation SERM that competes with circulating estrogen for binding to the estrogen receptor (ER). Depending on the target tissue, tamoxifen acts as an estrogen agonist or an estrogen antagonist. Like tamoxifen, raloxifene, a second-generation SERM, has both estrogen agonist and estrogen antagonist properties. Raloxifene differs from tamoxifen principally by its lack of stimulation of the endometrium.

**Tamoxifen**

The demonstration that tamoxifen prevented the development of contralateral breast cancers among women with a history of breast cancer serves as a model for the prevention of new breast cancers in healthy women. For more than 30 years, tamoxifen has been used in the treatment of breast cancer to reduce the risk of both recurrence and contralateral breast cancers. In addition to reducing the incidence of recurrent breast cancer by 42%, tamoxifen given for 5 years reduced the incidence of contralateral breast cancer by 47%. For this reason, tamoxifen was selected for further study as a potential breast cancer chemopreventive agent. Table 1 summarizes the results of selected clinical trials of tamoxifen as a breast cancer preventive agent.

In 1992, the National Surgical Adjuvant Breast and Bowel Project, with the support of the National Cancer Institute, launched the landmark Breast Cancer Prevention Trial (BCPT), also known as the P-1 trial or the tamoxifen prevention trial, to investigate the value of tamoxifen in reducing the risk of primary invasive breast cancer among women at increased risk for the disease. A total of 13,388 women aged 35 years or older who were at increased risk for breast cancer were enrolled in the trial and randomly assigned to receive either tamoxifen 20 mg or placebo daily for 5 years. Increased risk was defined as a personal history of LCIS, a 5-year risk of developing breast cancer of at least 1.7% as calculated using the modified Gail model, or age 60 years and older.

In the BCPT, tamoxifen reduced the risk of developing invasive breast cancer by 49% (risk ratio = 0.51; 95% CI, 0.39 to 0.66) (see Table 1). Tamoxifen also reduced the risk of noninvasive breast cancer by 50% (risk ratio = 0.50; 95%
CI, 0.33 to 0.77). Updated results from the P-1 study based on 7 years of follow up noted similar reductions in breast cancer incidence. The follow-up analysis demonstrated that tamoxifen had a persisting effect on breast cancer incidence, with 43% fewer breast cancers in the tamoxifen arm (risk ratio = 0.57; 95% CI, 0.46 to 0.70) compared with placebo.

Women with a history of LCIS showed a nonsignificant decrease in breast cancer risk (risk ratio = 0.44; 95% CI, 0.16 to 1.06); however, women with a history of atypical hyperplasia demonstrated an 86% risk reduction (risk ratio = 0.14; 95% CI, 0.03 to 0.47). The incidence of ER-positive breast cancers was reduced 69% in the tamoxifen group (risk ratio = 0.31; 95% CI, 0.22 to 0.45) without any significant change in the incidence of ER-negative breast cancers (risk ratio = 1.22; 95% CI, 0.74 to 2.03).

In addition to the BCPT, 3 European tamoxifen prevention trials have been completed and have reported long-term follow-up data of the effects of tamoxifen on breast cancer incidence. The initial paper from the Italian Randomized Tamoxifen Prevention Trial presented a preliminary analysis lacking statistical power to meaningfully examine differences in breast cancer incidence. Two subsequent publications from the Italian Trial reported no reduction in the risk of breast cancer with tamoxifen use in women with a history of LCIS showed a nonsignificant decrease in breast cancer risk (risk ratio = 0.44; 95% CI, 0.16 to 1.06); however, women with a history of atypical hyperplasia demonstrated an 86% risk reduction (risk ratio = 0.14; 95% CI, 0.03 to 0.47). The incidence of ER-positive breast cancers was reduced 69% in the tamoxifen group (risk ratio = 0.31; 95% CI, 0.22 to 0.45) without any significant change in the incidence of ER-negative breast cancers (risk ratio = 1.22; 95% CI, 0.74 to 2.03).39

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### TABLE 1 Summary of Selected Breast Cancer Chemopreventive Clinical Trials Using Tamoxifen

| Study (Publication)/Subjects/Eligibility/Follow Up | Outcome |
|-------------------------------------------------|---------|
| NSABP (BCPT, P-1) (Fisher B, Costantino JP, Wickham DL, et al)13, 388 women/eligibility: 5-year Gail risk ≥ 1.66% or history of LCIS/6 years of follow up; median follow up 54.6 months | Invasive breast cancers |
| | Placebo | TAM (95% CI) (Favors TAM) |
| | 6.76 | 3.43 |
| | 0.51 (0.39 to 0.66) | −3.33 |
| | NNT | 300 |
| Italian Tamoxifen Trial (Veronesi U, Maisonneuve P, Rotmensz N, et al)2, 4, 37, 43/5, 408 women/eligibility: normal-risk women with prior hysterectomy; 48% with oophorectomy/median follow up of 6.75 years | Invasive breast cancers |
| | Placebo | TAM |
| | 2.07 | 2.48 |
| | 0.84 (0.60 to 1.17) | No difference |
| Italian Tamoxifen Trial (Veronesi U, Maisonneuve P, Rotmensz N, et al)2, 4/midterm follow up of 11 years | Invasive breast cancers |
| | Placebo | TAM |
| | 4.98 | 4.71 |
| | 0.94 (0.59 to 1.42) | No difference |
| Royal Marsden Trial (Powles T, Eeles R, Ashley S, et al)2, 42/2, 494 women/eligibility: women at increased risk due to family history of breast cancer/midterm follow up of 5.83 years | Invasive breast cancers |
| | Placebo | TAM |
| | 6.48 | 5.09 |
| | 0.78 (0.58 to 1.04) | No difference |
| Royal Marsden Trial (Powles TJ, Ashley S, Tidy A, et al)2, 42/midterm follow up of 11 years | Invasive breast cancers |
| | Placebo | TAM |
| | 5.36 | 3.58 |
| | 0.61 (0.43 to 0.86) | −1.78 |
| | NNT | 562 |
| International Breast Cancer Intervention Study, IBIS-I (Cuzick J, Forbes J, Edwards R, et al)46/7, 152 women/eligibility: women at increased risk of breast cancer/midterm follow up of 4.17 years | Invasive breast cancers, DCIS |
| | Placebo | TAM |
| | 6.79 | 4.36 |
| | 0.68 (0.50 to 0.92) | −2.43 |
| | NNT | 412 |
| International Breast Cancer Intervention Study, IBIS-I (Cuzick J, Forbes JF, Sestak I, et al)47/median follow up of 11 years | Invasive breast cancers, DCIS |
| | Placebo | TAM |
| | 6.82 | 4.97 |
| | 0.73 (0.58 to 0.91) | −1.85 |
| | NNT | 541 |

All trials administered either placebo or tamoxifen 20 milligrams daily for 5 years except for Royal Marsden trial, where duration of treatment was between 5 and 8 years.

Abbreviations: TAM, tamoxifen; CI, confidence interval; Risk Ratio, ratio of rates between treatment groups; NNT, number needed to treat to prevent one case of breast cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; P-1, Breast Cancer Prevention Trial; LCIS, lobular carcinoma in situ; ER+, estrogen receptor positive; DCIS, ductal carcinoma in situ.
otherwise healthy women who had undergone hysterectomy.\textsuperscript{42,43} However, the updated report, based on 11 years of follow up, did show a reduction in breast cancer incidence in the tamoxifen arm (hazard ratio = 0.24; 95% CI, 0.10 to 0.59) among women at high risk of developing hormone receptor-positive breast cancers (high risk defined as >median height among study participants, at least one intact ovary, <14 years at menarche, and no full-term pregnancy before age 24 years).\textsuperscript{42} The Royal Marsden Hospital Tamoxifen Prevention Pilot Trial randomized women at increased risk of breast cancer resulting from a positive family history to tamoxifen or placebo for 8 years. Initial results, at a median of 5.83 years of follow up, showed no decrease in breast cancer risk.\textsuperscript{44} Analyses after 11 years of observation also failed to demonstrate any significant reduction in the overall incidence of invasive breast cancer (hazard ratio = 0.78; 95% CI, 0.58 to 1.04); however, a significant reduction in ER-positive invasive breast cancers was noted (hazard ratio = 0.61; 95% CI, 0.43 to 0.86).\textsuperscript{45} The International Breast Cancer Intervention Study randomized women at increased risk of breast cancer to tamoxifen or placebo for 5 years. Initial results showed a 32% reduced risk of invasive breast cancer (OR = 0.68; 95% CI, 8 to 50; \(P = .013\))\textsuperscript{46}; recent follow-up data showed a 27% reduction in invasive breast cancer (OR = 0.73; 95% CI, 0.58 to 0.91).\textsuperscript{47} The preventive effect of tamoxifen was fairly constant for the entire follow-up period, and no diminution of benefit was observed for up to 10 years after randomization.\textsuperscript{46,47} A meta-analysis of all the tamoxifen prevention studies demonstrated that tamoxifen reduced the risk of breast cancer by 38\% (95% CI 28 to 46; \(P < .0001\)) and confirmed the risks of endometrial cancer and venous thromboembolic events.\textsuperscript{48}

As summarized in Table 2, use of tamoxifen has potential risks that must be considered when evaluating its use in healthy women. The National Surgical Adjuvant Breast and Bowel Study Breast Cancer Prevention Trial, which included more than 13,000 participants, noted an increased risk of endometrial cancer (risk ratio = 2.53; 95% CI, 1.35 to 4.97) and pulmonary embolus (PE) (risk ratio = 3.01; 95% CI, 1.15 to 9.27) for those participants assigned to use of tamoxifen. However, stratified analyses revealed that these risks, while present for all women in the trial, were restricted to women aged more than 50 years. Also, increased risks of cataract development (risk ratio = 1.14; 95% CI, 1.01 to 1.29), as well as the need for cataract surgeries (risk ratio = 1.57; 95% CI, 1.16 to 2.14), were seen in this trial. In terms of potential harms resulting from use of tamoxifen, 437 women aged more than 50 years would need to be treated to cause one case of endometrial cancer, and 1,449 women aged more than 50 years would need to be treated to cause one case of PE. One cataract would be expected to occur among every 323 women treated with tamoxifen. To put these risks into perspective, the protective benefit of tamoxifen in preventing breast cancers resulted in an absolute-risk reduction of 3.33 per 1,000, meaning that 300 women would have to be treated with tamoxifen to prevent one breast cancer.

Commonly reported side effects with tamoxifen use included hot flashes (77.7\% versus 65.0\% for tamoxifen and placebo groups, respectively), night sweats (66.8\% versus 54.9\%), vaginal discharge (58.8\% versus 34.1\%), and genital itching (47.1\% versus 38.3\%). Weight gain and depression were not associated with use of tamoxifen therapy.\textsuperscript{49} No effect was seen on the incidence of ischemic heart disease, fractures, deep vein thrombus (DVT), or stroke.

**Raloxifene**

Raloxifene has reduced the incidence of breast cancer in preclinical models and several clinical trials that evaluated this agent for the prevention of osteoporosis and heart disease.\textsuperscript{50–56} The results of selected clinical trials, which included the use of raloxifene as a breast cancer preventive agent, are presented in Table 3. Raloxifene was initially Food and Drug Administration (FDA)-approved for the prevention and treatment of osteoporosis in postmenopausal women. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, use of raloxifene was associated with a 30\% (relative risk = 0.7; 95% CI, 0.5 to 0.8) reduction in the risk of vertebral fracture in postmenopausal women with osteoporosis.\textsuperscript{53} The MORE trial studied selected bone outcomes among postmenopausal women with osteoporosis (3 treatment groups: placebo,
raloxifene 60 mg per day, or raloxifene 120 mg per day); breast cancer was a secondary endpoint in this study. After 4 years of follow up, a 62% reduction in breast cancer incidence was seen among the raloxifene-treated group. The Continuing Outcomes Relevant to Evista (CORE) trial extended the MORE trial to examine an additional 4 years of raloxifene (20 mg per day) on breast cancer incidence. Results showed a 50% reduction in the incidence of breast cancers among the raloxifene-treated group; the CIs for the rates of breast cancers and ER-positive invasive breast cancers overlapped for the MORE and CORE trials. The number needed to treat to prevent one case of breast cancer based on the MORE and CORE studies was in the range of ~300 to 350. When 8 years of follow up (both MORE and CORE) was examined, the incidence rates for venous thromboembolic events was 2.2 per 1,000 person years in the raloxifene and 1.3 per 1,000 person years in the placebo group (number needed to harm = 1,111).

Because women in the MORE trial were not selected based on specific breast cancer risk factors, their breast cancer risk was not calculated. The results of this study led investigators to conduct a Phase III, comparative, randomized trial of raloxifene versus tamoxifen in 19,747 postmenopausal women at increased risk for breast cancer. In the Study of Tamoxifen and Raloxifene (STAR) trial, increased risk was defined as a personal history of LCIS or a 5-year predicted risk of breast cancer of at least 1.66% as determined by the Gail model. Women were randomly assigned to receive either tamoxifen 20 mg or raloxifene 60 mg daily for 5 years. The primary endpoint was the incidence of breast cancer. Raloxifene was found to be equivalent to tamoxifen in reducing the incidence of breast cancer in postmenopausal women at increased risk.

### TABLE 2 Summary of Selected Outcomes in the NSABP Breast Cancer Prevention Trial (P-1)

| Comparing Placebo Versus Tamoxifen (n=13,388 Subjects) | Absolute Rate Difference per 1,000 |
|-------------------------------------------------------|-----------------------------------|
| **Outcome**                                           | **Annual Rate/1,000**              | **Risk Ratio (95% CI)** | **(Favors Placebo)** | **(Favors Tamoxifen)** | **NNH (Favors Placebo)** | **NNT (Favors Tamoxifen)** |
|-------------------------------------------------------|-----------------------------------|-------------------------|----------------------|----------------------|------------------------|--------------------------|
| Endometrial cancer                                    | Age                               | Placebo | Tamoxifen | 1.09 | 1.32 | 1.21 (0.41 to 3.60) | 2.29 | 437 |
|                                                       | ≤50 years                         | 0.76    | 3.05     | 4.10 (1.70 to 10.90) |                       |                        |                        |
| Deep vein thrombosis                                  | ≤49 years                         | 0.78    | 1.08     | 1.39 (0.51 to 3.99)  |                       |                        |                        |
|                                                       | ≥50 years                         | 0.88    | 1.51     | 1.71 (0.85 to 3.58)  |                       |                        |                        |
| Pulmonary embolus                                      | ≤49 years                         | 0.10    | 0.20     | 2.03 (0.11 to 11.62) |                       |                        |                        |
|                                                       | ≥50 years                         | 0.31    | 1.00     | 3.19 (1.12 to 11.15) |                       |                        |                        |
| Stroke                                                | ≤49 years                         | 0.39    | 0.30     | 0.76 (0.11 to 4.49)  |                       |                        |                        |
|                                                       | ≥50 years                         | 1.26    | 2.20     | 1.73 (0.98 to 3.20)  |                       |                        |                        |
| Fracture (hip, spine, radius)                          | ≤49 years                         | 2.24    | 1.98     | 0.88 (0.46 to 1.68)  |                       |                        |                        |
|                                                       | ≥50 years                         | 7.27    | 5.76     | 0.79 (0.60 to 1.05)  |                       |                        |                        |
| Ischemic heart disease                                | All ages                          | 2.37    | 2.73     | 1.15 (0.81 to 1.64)  |                       |                        |                        |
| All cataracts                                          | All ages                          | 21.72   | 24.82    | 1.14 (1.01 to 1.29)  | 3.10                  | 323                     |
| Cataracts with surgery                                 | All ages                          | 3.00    | 4.72     | 1.57 (1.16 to 2.14)  | 1.72                  | 581                     |
| Breast cancer                                         | All ages                          | 6.76    | 3.43     | 0.51 (0.39 to 0.66)  | −3.33                 | 300                     |
|                                                       | ≤49 years                         | 6.70    | 3.77     | 0.56 (0.37 to 0.85)  | −2.93                 | 341                     |
|                                                       | 50 to 59 years                    | 6.28    | 3.10     | 0.49 (0.29 to 0.81)  | −3.18                 | 314                     |
|                                                       | ≥60 years                         | 7.33    | 3.33     | 0.45 (0.27 to 0.74)  | −4.00                 | 250                     |

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; Risk Ratio, tamoxifen group compared with placebo group; Absolute Rate, difference between groups (placebo minus tamoxifen); NNH, number needed to harm/number need to cause one undesired outcome; NNT, number needed to treat to prevent one undesired outcome.

Adapted from Fisher B, Costantino JP, Wickerham DL, et al. [39]
risk of developing the disease but with fewer adverse events than tamoxifen (see Tables 3 and 4). The raloxifene group developed 168 invasive breast cancers compared with 163 cases in the tamoxifen group (incidence 4.41 per 1,000 versus 4.30 per 1,000; risk ratio 1.02; 95% CI, 0.82 to 1.28). The numbers of invasive breast cancers in both groups of women were statistically equivalent. Based on the risk reduction seen in the BCPT for tamoxifen, both drugs reduced the risk of developing invasive breast cancer by about 50%. While tamoxifen reduced the incidence of LCIS and DCIS, raloxifene did not have an effect on these diagnoses.

It is important to understand that more than half of the women who joined STAR had a hysterectomy before enrollment and, therefore, were not at risk for uterine cancer. While the incidence of uterine cancer among women with an intact uterus at time of study entry was not statistically different in the raloxifene arm (risk ratio = 0.16; 95% CI, 0.09 to 0.29), with or without atypia, compared with the tamoxifen arm. Additionally, 56% more hysterectomies were performed in the tamoxifen group: 244 hysterectomies in the tamoxifen arm compared with 111 in those assigned to raloxifene (risk ratio = 0.44; 95% CI, 0.35 to 0.56). As a result, these differences may potentially obscure the benefits of raloxifene with regard to lower rates of endometrial cancer.

As summarized in Table 4, there were no significant differences in the occurrence of DVT, PE, stroke, transient ischemic attack, fractures (hip, spine, or wrist), or heart attacks among participants in the STAR trial. Combining DVT and PE events together under a “thromboembolic” category yielded a 30% reduction favoring use of raloxifene (risk ratio = 0.70; 95% CI, 0.54 to 0.91). While individually, the rate ratios for DVT and PE did not reach significance, the combined effect is clinically important. Also, it is important to note that women at increased risk of stroke (those with uncontrolled hypertension or uncontrolled diabetes or a history of stroke, transient ischemia attack, or atrial fibrillation).
were not eligible to participate in STAR. Raloxifene resulted in fewer cataracts (risk ratio for raloxifene to tamoxifen = 0.79; 95% CI, 0.68 to 0.92) and cataracts requiring surgery (risk ratio = 0.82; 0.68 to 0.99); PE events appeared to occur less frequently but were of borderline significance (risk ratio = 0.64; 0.41 to 1.00).57

Side effects associated with the use of both drugs were mild to moderate in severity, and quality-of-life measures did not differ.58 The percentage of women who reported vasomotor symptoms during follow up was 4.3% to 6.2% higher among those assigned to tamoxifen than among those assigned to raloxifene. Reports of vaginal discharge, vaginal bleeding, and genital itching or irritation were also higher in the tamoxifen group, ranging from 2.9% to 13% greater than in the raloxifene group. Also higher in the tamoxifen group were reports of difficulty with urinary bladder control (7.5% higher when laughing or crying and 6.6% higher at other times) and reports of leg cramps (8.8% higher). Vaginal dryness and pain with intercourse were higher among women in the raloxifene arm (3.4% and 2.4% higher, respectively). Self-reported weight gain was also higher in the raloxifene group (2.9% higher). Women who participated in the STAR trial to date appear to have had no lasting adverse consequences in terms of symptoms or quality of life as a result of their participation in the trial. There were few differences noted in the resolution of symptoms between users of tamoxifen and raloxifene.59

More recently, results from the Raloxifene Use for the Heart (RUTH) study affirmed the benefit of raloxifene with regard to reduced risk of breast cancer. This trial, designed to focus on heart disease, randomized more than 10,000 postmenopausal women with coronary heart disease or multiple coronary heart disease risk factors to receive either raloxifene 60 mg per day or placebo.50 No differences were found between groups for cardiovascular disease endpoints. Rates of breast cancer (hazard ratio 0.67; 95% CI, 0.47 to 0.96) and vertebral fractures (hazard ratio 0.65, 0.47 to 0.89) were significantly lower in the raloxifene group. Rates of venous thromboembolic events (hazard ratio 1.44; 1.06 to 1.95) and fatal strokes (hazard ratio 1.49; 1.00 to 2.24) were increased among the raloxifene group.50 The larger estimate noted for the number needed to treat (n = 11,111) to prevent one case of breast cancer based on the RUTH trial reflects a study cohort that approximated the general-population risk for developing breast cancer—postmenopausal with a mean age of 67 years at enrollment, either cardiac disease or multiple cardiac risk factors, and women without a prior breast cancer diagnosis. The risk

### TABLE 4 Summary of Selected Adverse Outcomes in the NSABP Breast Cancer Prevention Trial (STAR, P-2) Comparing Tamoxifen Versus Raloxifene (n = 19,747 Subjects)

| Adverse Outcomes* | Annual Rate/1,000 | Risk Ratio (95% CI) | Absolute Rate Difference Per 1,000 (Favors Tamoxifen) | NNT (Favors Raloxifene) |
|-------------------|-------------------|---------------------|--------------------------------------------------------|--------------------------|
| Endometrial cancer | 2.00 1.25         | 0.62 (0.35 to 1.08) | N/A                                                    | N/A                      |
| Deep vein thrombosis | 2.29 1.69     | 0.74 (0.53 to 1.03) | N/A                                                    | N/A                      |
| Stroke             | 1.39 1.33         | 0.96 (0.64 to 1.43) | N/A                                                    | N/A                      |
| Pulmonary embolus  | 1.41 0.90         | 0.64 (0.41 to 1.00) | N/A                                                    | N/A                      |
| Fracture           | 2.73 2.51         | 0.92 (0.68 to 1.22) | N/A                                                    | N/A                      |
| Ischemic heart disease | 3.00 3.29     | 1.10 (0.85 to 1.43) | N/A                                                    | N/A                      |
| Cataracts          | 12.30 9.72        | 0.79 (0.66 to 0.92) | -2.58 ( Favor Tamoxifen)                               | 388                      |
| Cataracts with surgery | 8.03 6.62     | 0.82 (0.68 to 0.99) | -1.41 ( Favor Raloxifene)                              | 709                      |
| Breast cancer      | 4.30 4.41         | 1.02 (0.82 to 1.28) | N/A                                                    | N/A                      |

*Outcomes not stratified by age group since only 9% of the study population was < age 50 years.

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; P-2, Study of Tamoxifen and Raloxifene ("STAR") for the Prevention of Breast Cancer; CI, confidence interval; Risk Ratio, raloxifene group compared with tamoxifen group; Absolute Rate Difference Between Groups, raloxifene minus tamoxifen; NNT, number needed to treat to prevent one undesired outcome.

Adapted from Vogel VG, Costantino JP, Wickerham DL, et al.57
of breast cancer among study participants was low (15 cases of breast cancer per 1,000 over 5 years, or 3/1,000 per year, in the placebo group).

Raloxifene recently received 2 FDA indications for breast cancer risk reduction among postmenopausal women: those with osteoporosis and those with an increased risk of developing breast cancer. The approved indication for use of raloxifene for breast cancer risk reduction does not include women at general population risk.

Use of SERMs in Clinical Practice

Tamoxifen has been approved by the FDA since 1998 for breast cancer risk reduction. Despite the significant reduction in breast cancer risk conferred by tamoxifen, it has not been widely accepted in the primary care community, and utilization has only been limited. This is likely due to a myriad of factors, including the risks of tamoxifen therapy, as well as the relative unfamiliarity of the drug among primary care practitioners. Primary care clinicians have generally been unenthusiastic about tamoxifen for chemoprevention given its original use by oncologists in breast cancer treatment, combined with concerns about serious adverse events. As a result, many women who were at increased risk of developing breast cancer were not considered to be candidates for tamoxifen chemoprevention therapy and were not offered risk-reduction therapy.

The recent addition of raloxifene as another FDA-approved breast cancer risk-reduction agent will likely contribute to the expanded use of breast cancer chemoprevention in general medical practice since raloxifene is already familiar to primary care clinicians in the treatment of osteoporosis.

While tamoxifen is the only agent approved to reduce breast cancer risk in premenopausal women at increased risk of breast cancer, postmenopausal women now have 2 options: tamoxifen or raloxifene. For many postmenopausal women, the benefits of raloxifene outweigh its risks in a way that is not achieved with tamoxifen. For example, the STAR trial observed a 30% reduction in thromboembolic events for raloxifene compared with use of tamoxifen. As with any medication, raloxifene is not appropriate for all women. A risk/benefit profile based on breast cancer risk, as well as family and medical history, should be performed to determine which option is best for any given woman. A significant component of the risk/benefit assessment is the patient’s therapeutic goals. Through a shared decision-making process, the patient and the clinician can ascertain which SERM is most appropriate for her.

Although raloxifene is equivalent to tamoxifen in reducing invasive breast cancer risk, it does not have the benefits for preventing noninvasive breast cancers. While raloxifene is the only one to have an FDA indication for the management of osteoporosis, it is important to remember that the osteoporotic fractures in STAR were equivalent for both tamoxifen and raloxifene. Thus, the decision to use raloxifene is not solely predicated on the osteoporosis benefit. Risks, in general, are fewer with raloxifene. However, scenarios can be envisioned in which a woman, appropriately counseled, might elect tamoxifen over raloxifene. For example, a woman who has had a hysterectomy and, therefore, is no longer at risk of endometrial cancer might perceive that the benefit in preventing both invasive and noninvasive breast cancer with tamoxifen outweighs the differences in risks between the 2 agents.

For breast cancer risk reduction, the goal is 5 years of risk-reduction therapy. After 5 years of therapy, tamoxifen should be discontinued. There are no data indicating additional benefit with continued therapy. Additionally, follow-up data from the International Breast Cancer Intervention Study has shown that the benefit of breast cancer risk reduction appears to persist for 10 years, but most side effects disappear after discontinuation of tamoxifen. Use of raloxifene beyond 5 years of therapy would, at this time, be based on osteoporosis treatment factors as no data yet exist to suggest further breast cancer risk reduction with continued use, although this possibility cannot be excluded.

The paradigm for breast cancer management has expanded to include the reality of breast cancer prevention. Modeling by Freedman et al compared the number of women in the United States...
who would be eligible for tamoxifen with the number of women who would benefit from tamoxifen chemoprevention.64 While there are limitations to their analysis, results suggest that approximately 2.5 million American women aged 35 to 70 years could benefit from chemopreventive therapy with tamoxifen. Acknowledging that the benefits of tamoxifen therapy do not outweigh the risks for all women, this estimate represents only 25% of women in that age range who are considered at increased risk for breast cancer. The opportunity exists for a significant impact of these drugs on the incidence of breast cancer.

**Aromatase Inhibitors**

Aromatase inhibitors (AIs), including anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara), lower circulating estrogen levels by blocking the conversion of androgens to estrogens catalyzed by the enzyme aromatase.

AIs have proven effective in breast cancer treatment among postmenopausal women with hormone-sensitive tumors. In the adjuvant setting, third-generation AIs (anastrozole, letrozole, and exemestane) have been found in numerous studies to be superior to tamoxifen.65–69 Clinical trial data from 3 studies show that AIs decrease the incidence of contralateral breast cancers by 37% to 55%.68,70,71 The safety profile for AIs appears relatively favorable compared with tamoxifen. The principle toxicity of AIs is accelerated bone resorption. AIs are generally well tolerated, with the primary side effects being musculoskeletal and joint discomfort.

Prospective studies are underway to investigate the role of AIs as potential breast cancer chemoprevention agents. The International Breast Cancer Intervention–II launched in 2003 in the United Kingdom will randomize 6,000 postmenopausal women at increased risk of breast cancer to anastrozole or placebo. A parallel trial is comparing anastrozole to tamoxifen among 4,000 women diagnosed with hormone receptor-positive DCIS; women will receive treatment for 5 years.72,73 The National Cancer Institute of Canada (NCIC) Clinical Trials Group designed a three-arm trial, called MAP-3 (Mammary Prevention trial #3, also referred to as the ExCel trial), to compare breast cancer incidence in three groups: exemestane alone, exemestane plus celecoxib, and placebo among 5,100 postmenopausal women at increased risk. Exemestane was to be given for 5 years while celecoxib was to be administered for 3 years. It was hypothesized that the addition of celecoxib to exemestane would prevent both hormone receptor-negative as well as hormone receptor-positive breast cancers. Shortly after the MAP-3/ExCel trial opened in late 2004, data from colorectal adenoma prevention trials using the cyclooxygenase-2 (COX–2) inhibitors rofecoxib74 and celecoxib75 noted an increased risk of cardiovascular events with these agents. As a result, the MAP-3/ExCel trial was modified into a two-arm trial comparing exemestane with placebo among 4,560 subjects.

AIs are not FDA approved for breast cancer prevention. Current clinical practice does not support a role for AIs in the primary chemoprevention of breast cancer.72,73

**Other Pharmacotherapy for Breast Cancer Risk Reduction**

Regular use of aspirin and other nonsteroidal anti-inflammatory agents has been reported to decrease the risk of breast cancer in a few studies,76,77 but this has not been supported in other studies.78 More recently, a publication based on the Women’s Health Study reported no difference in breast cancer incidence with use of 100 mg of aspirin on alternative days after 10 years of follow up.79

**Other Chemopreventive Agents Under Investigation**

Important priorities for breast cancer prevention are to develop a variety of new prevention agents that have fewer side effects, that are compatible with postmenopausal HT, and that are effective in preventing hormone-negative breast cancers.

To develop new drugs in a short period and at reasonable cost, more efficient clinical testing models are being developed for Phase I and II prevention trials. These models use potentially reversible morphological and molecular biomarker targets that will enhance short-term risk prediction, improve the probability of response by matching the biomarker profile in precancerous tissue to agents in the appropriate drug
class, and assess response in a preliminary fashion before completion of a randomized trial. Tyrosine kinase inhibitors, retinoids, rexinoids, vitamin D analogs, green tea derivatives, nonsteroidal anti-inflammatory drugs, both selective (eg, COX-2 inhibitors) and nonselective (eg, aspirin and ibuprofen) cyclooxygenase inhibitors, statins, soy/isoflavones, and gonadotropin-releasing hormone agonist regimens combined with low-dose HT as well as statins are undergoing active investigation in premenopausal and postmenopausal women.

**STRATEGIES FOR BREAST CANCER RISK REDUCTION—THE INFLUENCE OF POSTMENOPAUSAL HORMONE USE**

A meta-analysis consisting of 51 studies examining the relationship between breast cancer risk and use of postmenopausal HT reported an increased risk among women who ever used HT for at least 5 years (RR 1.35; 95% CI, 1.21 to 1.49), and risk increased with duration of use. However, women who had discontinued use more than 5 years previously did not demonstrate any excess risk. Also, among current users of HT or those who discontinued use within the last 4 years, the RR of breast cancer was 1.023 (95% CI, 1.01 to 1.046); however, risk was not elevated among former users of HT who had discontinued use more than 5 years previously.

Participants in the Women’s Health Initiative (WHI) aged 50 to 79 years at time of enrollment were randomized to either estrogen (conjugated equine estrogen, 0.625 mg daily) and progesterone (medroxyprogesterone acetate, 2.5 mg daily) or placebo for a mean of 5.6 years when the intervention was terminated and then were observed for a mean of 2.4 years. While breast cancer risk was not elevated over the 2.4 years of observation (HR = 1.27; 95% CI, 0.91 to 1.78), when examined across the overall 8-year study window, a 27% increase in breast cancer risk was observed among those in the active hormone-intervention arm (HR = 1.27; 95% CI, 1.06 to 1.51).

WHI participants randomized to the estrogen–only arm exhibited a borderline significant reduction in breast cancer risk (HR = 0.77; 95% CI, 0.59 to 1.01). In contrast, a paper based on the Nurses’ Health Study (NHS) reported that longer duration of use of unopposed estrogen was associated with increased risk of breast cancer (P-trend, P < .001); however, risk increased only among those with 20+ years of unopposed estrogen use.

These results are generally consistent with an earlier report based on the NHS, which concluded that 10 years of postmenopausal estrogen increased the risk of breast cancer by about 23% (RR = 1.23; 95% CI, 1.06 to 1.72) and that 10 years of postmenopausal combined HT (estrogen + progesterone) increased the risk of breast cancer by 67% (RR = 1.67; 95% CI, 1.18 to 2.36).

In summary, the current evidence suggests that combination postmenopausal hormone use (with estrogen + progesterone) increases breast cancer risk, even within 5 years of use. In contrast, estrogen alone increases breast cancer risk more modestly, although no increase is seen until 10 to 15 years of use. For estrogen alone, excess risk declines rapidly after stopping; however, further follow up of the WHI cohort is needed to understand whether this is similar for use of estrogen plus progesterone.

**STRATEGIES FOR BREAST CANCER RISK REDUCTION—THE INFLUENCE OF DIET/NUTRITION**

Links between adult diet and risk of breast cancer have been extensively investigated, but many topics remain controversial. Because it is difficult to randomize large numbers of women to specific diets and maintain good long-term compliance, we necessarily rely on evidence from large, well-conducted cohort and case-control studies to draw inferences about causal relationships. The long latency of breast cancer makes evaluation of diet during early life, a period when environmental exposures may play a strong role, a further methodologic challenge.

The large body of literature on nutrition and breast cancer has been recently reviewed and summarized. An international panel of the World Cancer Research Fund and American Institute for Cancer Research concluded that there is convincing evidence that alcohol intake raises the risk of breast cancer at all ages, while...
Body fatness increases the risk of breast cancer after menopause. Taller height is related to elevated risk of breast cancer, possibly because it is a marker for genetic, environmental, hormonal, and nutritional factors affecting growth, and body fatness is probably related to a decreased risk of premenopausal breast cancer. The panel found limited evidence and drew no firm conclusions on the role of individual foods and nutrients on overall breast cancer risk.

**Dietary Fat**

Whether dietary fat is a risk factor for breast cancer has been a topic of extensive investigation. The hypothesis originated from ecological and case-control studies showing a positive association between higher total fat intake and breast cancer. Potential mechanisms include an influence on steroid hormone levels or higher energy density affecting other established risk factors, such as weight gain or age at menarche. However, evidence from large, prospective cohort studies has been largely unsupportive, and clinical trials have not supported a strong association with total fat. Two meta-analyses of cohort studies showed non-significant increased rates of 6% and 11%, respectively, among women consuming higher levels of total fat, and a pooled analysis of cohort studies showed a reduced risk of 0.96 (0.86 to 1.08) per 25 gram increase. A nonsignificant decrease in breast cancer risk was observed in the WHI trial (RR = 0.91; 95% CI, 0.83 to 1.02 comparing low- to high-fat groups). Furthermore, in a recent prospective study of 188,736 postmenopausal women with 3,501 cases of invasive breast cancer, a small increase in risk was seen among women with the highest intake of dietary fat. The World Cancer Research Fund/American Institute for Cancer Research panel concluded that there is only limited or suggestive evidence that total fat may increase the risk of breast cancer after menopause. Considering the results of more than 70 studies on this topic, any effect of dietary fat during midlife on risk of breast cancer is likely to be small if it exists at all.

**Carbohydrate**

Carbohydrates and carbohydrate quality could influence breast cancer risk by affecting circulating insulin levels, insulin resistance, insulin-like growth factors, and sex hormone bioavailability. However, the 12 prospective cohort studies to date have not shown consistent associations between total carbohydrate, glycemic index, glycemic load, and breast cancer risk, and most results have been null.

**Red Meat**

Several hypotheses exist to explain consumption of red meat could induce carcinogenesis: its highly bioavailable iron content, growth-promoting hormones used in animal production, carcinogenic heterocyclic amines formed in cooking, and its specific fatty acid content may all contribute. A meta-analysis of case-control and cohort studies showed a modest association of red meat intake with breast cancer incidence (RR = 1.17; 95% CI, 1.06 to 1.29), but no association was noted in a pooled analysis of prospective studies. More recent reports from 2 large prospective cohorts noted an elevated risk with higher red meat consumption. In an analysis of the NHS II (n = 1,021 cases that were largely premenopausal), a positive association between red meat and breast cancer risk was seen, especially for ER- and progesterone receptor-positive cancers (RR = 1.97; 95% CI, 1.35 to 2.88), comparing more than 1.5 servings per day to 3 or fewer servings per week. In the UK Women’s cohort study (n = 678 cases), an increased risk of breast cancer was observed among women with high red meat intake, with a 12% increase (95% CI, 3% to 22%) in risk per 50 gram increment of meat each day. A study of postmenopausal Danish women (n = 378 cases) showed an elevated risk of breast cancer in those women consuming red meat and processed meat (RR = 1.15; 95% CI, 1.01 to 1.31 and RR = 1.23; 95% CI, 1.04 to 1.45, respectively, per 25 grams per day). This association was confined to women genetically susceptible to carcinogenic aromatic amines due to polymorphisms in N-acetyl transferase.

**Fruits and Vegetables**

The antioxidant and fiber content of fruits and vegetables has been hypothesized to protect...
from breast cancer. A pooled analysis from 8 prospective cohorts including 7,377 cases found no significant association (for highest versus lowest quartiles, vegetables: RR = 0.96 [95% CI, 0.89 to 1.04] and fruits: RR = 0.93 [95% CI, 0.86 to 1.00]). A more recent large prospective study from Europe (N = 3,659 cases) found lack of association for both fruits and vegetables. Furthermore, no reduction in breast cancer recurrence or mortality was noted in the Women’s Health Eating and Living trial in which over 3,000 women with early-stage breast cancer were randomized to a diet very high in vegetables, fruits, and fiber and low in fat.99

**Micronutrients**

The relationship between breast cancer and micronutrients, including folic acid, vitamins, and carotenoids, has been investigated in large prospective studies using questionnaires and biomarkers of intake. Two recent meta-analyses noted a possible protective effect of folic acid, especially among women who drink alcohol.100,101 Vitamin D intake has been inversely related to breast cancer in the NHS102; moreover, high serum levels of dietary vitamin D were inversely related to risk of breast cancer in a dose-dependent manner.103 Caffeine was not linked to breast cancer in a large prospective study of Swedish women.104 Although some studies have shown significant protective effects of high serum carotenoid levels,105 studies of dietary intake of carotenoids remain inconclusive.

**Soy and Phytoestrogens**

Phytoestrogens present in soy are structurally and functionally similar to estrogen and have hence received significant attention as potential dietary modifiers of breast cancer risk. A meta-analysis of published studies on soy intake and breast cancer noted a significant protective effect of high soy intake on risk of breast cancer.106 Data on phytoestrogen intake and breast cancer incidence and recurrence have recently been reviewed in this journal.107 The authors concluded that although studies on adult intake are inconsistent, intake during early childhood or adolescence may be protective.

**Alcohol**

Alcohol consumption consistently predicts higher breast cancer rates in epidemiologic and animal studies. The effects of alcohol may be mediated by direct carcinogenic effects of metabolites such as acetaldehyde or oxygen radicals. Other hypothesized mechanisms include increased solubility of carcinogens, interference with folate or estrogen metabolism, or nutrient deficiencies associated with high alcohol use. A meta-analysis of cohort studies showed a 10% increase in breast cancer risk for every 10 grams of alcohol consumed each day and a similar magnitude of association was noted in 2 pooled analyses.108,109 A dose–response relationship without a threshold effect has been observed, such that even one drink per day predicts modestly elevated breast cancer risk.110,111 Menopausal status and type of alcoholic drink do not seem to modify this association. However, an interaction between folate and alcohol intake suggests that an adequate folate intake (most commonly achieved by taking a multiple vitamin) seems to reduce or eliminate the excess risk due to alcohol consumption.100,112,113

**Early-life Nutritional Exposures**

Plausible biologic explanations support evidence that exposures in early life may be particularly important in predicting later breast cancer risk. Breast tissue develops during puberty, although terminal differentiation of the end buds is attained during lactation after first pregnancy. This window of undifferentiated cell division appears to result in a period of susceptibility and increased sensitivity to environmental risk factors. Data from animal studies suggest that mammary tissue is especially sensitive to carcinogenic exposures that occur after menarche and before first pregnancy.114,115 Ecologic studies also highlight the importance of time of exposure in predicting breast cancer risk in humans.116–119 Moreover, nutrition in early life can affect height and age at menarche, which are established breast cancer risk factors. Therefore, the relationship
between the diets of children and adolescents and subsequent risk for breast cancer have been of particular scientific interest.

Case-control studies of diet in adolescence have reported decreased risk for cancer with diets high in fat from dairy foods, milk, and vitamin D, an increased risk with frequent consumption of meat with visible fat, and a marginally significant relation with high-fat meats. Using dietary data collected after the diagnosis of breast cancer, consumption of vegetable fat and vitamin E was inversely associated with breast cancer in the NHS-II, which used a validated food-frequency questionnaire to assess the diet of 45,947 nurses while they were in high school. This study also showed a positive association between the consumption of foods with a high glycemic index and the incidence of breast cancer. High soy and phytoestrogen consumption in adolescence are related to lower breast cancer rates in several case-control studies.

Body Size/Body Mass Index

Compelling evidence supports a higher risk of postmenopausal breast cancer among overweight and obese women. However, women with higher body mass index (BMI) are at lower risk for breast cancer before menopause. Because breast cancer is much more common after menopause, the beneficial effect of body fatness on premenopausal cancer is outweighed by its detrimental role on postmenopausal cancer. Also, it is likely that overweight premenopausal women do not experience lower breast cancer mortality than lean women because tumors are diagnosed at later stages in women with fatter breasts. Weight gain during adulthood and abdominal fatness are also associated with higher risk of postmenopausal breast cancer.

The associations between foods/nutrients and breast cancer risks among females stratified by menopausal status are summarized in Table 5.

Postmenopausal Breast Cancer

Possible mechanisms through which excess body fat could contribute to the initiation and progression of breast cancer include influence on steroid hormone levels and inflammatory responses. The aromatization of adrenal androgens in adipose tissue generates estrogens, and circulating estrogen levels are much higher in obese postmenopausal women compared with leaner women. Moreover, sex hormone-binding globulin levels are lower in overweight women, resulting in more bioavailable estrogen in their circulation. Because plasma estrogens are known to contribute to breast cancer, higher concentrations after menopause are likely to increase the chance of developing this disease.

A pooled analysis of prospective cohort studies including over 4,300 cases and 337,000 participants showed significantly increased breast cancer risk among fatter women. Participants with a BMI of 28 kg/m² or higher were 26% more likely to develop postmenopausal breast cancer compared with lean women (95% CI, 9% to 46%). Weight gain during adult life significantly increases risk for breast cancer after menopause, and an estimated 15% of breast cancers within the NHS are attributed to weight gain in adulthood. Excess body fat and weight gain are stronger risk factors for postmenopausal breast cancer among women who do not use postmenopausal HT. In a recent prospective study including over 2,000 cases that examined weight gain at multiple time points throughout adulthood, weight gain of 20 to 29 kg was associated with a 56% higher risk of breast cancer, and weight gain of 40 to 49 kg was associated with a doubling in risk of breast cancer compared with maintaining a stable weight among HT nonusers. One explanation is that high circulating hormone levels caused by exogenous estrogens could mask the effects of estrogens produced by excess fat tissue. Because HT use is declining, the relative contribution of obesity could become even more pronounced in the future.

Losing weight after menopause can reduce circulating estrogens and increase sex hormone-binding globulin, making weight loss a plausible target for risk reduction, especially for women who are not using postmenopausal HT. The effect of weight loss on reducing postmenopausal cancer risk has been examined in prospective observational studies. In one of the largest studies able to assess long-term weight change, which included 4,393 cases of invasive
breast cancer, women who lost 10 kg or more after menopause and maintained this weight loss halved their risk for breast cancer (RR = 0.43; 95% CI, 0.21 to 0.86), a result that was particularly clear among women not using postmenopausal hormones. Additionally, results from the Iowa Women’s Study suggest that maintaining weight in adulthood, as opposed to the usual pattern of gaining weight, is protective for postmenopausal cancer.

### TABLE 5  Summary of Associations Between Foods/Nutrients and Breast Cancer Risk Among Females, by Menopausal Status

| Food or Nutrient          | Effect Among Premenopausal Women | Effect Among Postmenopausal Women | Level of Evidence Based Upon Selected References |
|---------------------------|----------------------------------|----------------------------------|-------------------------------------------------|
| Alcohol                   | 5% to 10% increase in risk per 10 grams of alcohol per day | 5% to 10% increase in risk per 10 grams of alcohol per day | Pooled analysis of 6 prospective studies^{87,103} |
| Total fat                 | No association                   | Equivocal findings              | Observational cohort, Nurses’ Health Study^{131}; randomized study, Women’s Health Initiative, pooled analysis of 8 studies: observational cohort, AARP Diet and Health Study^{97–99} |
| Type of fat               | Inconsistent associations overall; trend of increased risk with increased animal fat intake | Weak positive association for saturated fat intake; mixed results for unsaturated fats | Observational cohort, Nurses’ Health Study^{131}; pooled analysis of 8 studies: observational cohort, AARP Diet and Health Study^{97–99} |
| Total carbohydrate        | No association                   | No association                  | Observational cohort, Nurses’ Health Study^{132} |
| Carbohydrate quality (glycemic index and glycemic load) | No association                   | No association                  | Observational cohorts, Cancer Prevention Study II, Nurses’ Health Study and Women’s Health Study^{132–134} |
| Fiber                     | No association                   | No association                  | Observational cohort, Nurses’ Health Study^{132} |
| Red meat                  | Inconsistent association overall; increased risk with increased meat consumption may be restricted to hormone-sensitive breast malignancies | Inconsistent association overall | Observational cohort, Nurses’ Health Study and UK Women’s Health Study; pooled analysis of 8 prospective studies^{85–97} |
| Dairy/milk                | No association                   | No association                  | Pooled analysis of 8 prospective studies; observational cohort, Nurses’ Health Study^{95,102} |
| Fruits and vegetables     | No association                   | No association                  | Pooled analysis of 8 prospective studies^{15} |
| Soy/phytoestrogens        | ~30% reduced risk among those reported highest intakes | ~20% to 25% reduced risk among those reporting the highest intakes | Meta-analysis; review^{106,107} |
| Caffeine                  | No association                   | No association                  | Observation cohort, Swedish Mammography Screening^{105} |
| Vitamin D                 | Reduced risk among women with high serum vitamin D | Possible reduced risk among women with high plasma vitamin D | Observational cohort, Nurses’ Health Study^{102,103} |
| Vitamins E, A, and C      | Weak association for decreased risk with increased intake, which may be modified among women with a family history of breast cancer | No association | Observational cohort, Nurses’ Health Study; reviews^{84,136,137} |
| Folic acid                | No association, but increased intake may moderate risk of excess alcohol consumption | No association, but increased intake may reduce excess breast cancer risk due to alcohol consumption | Observational cohort, Nurses’ Health Study^{103,113} |
| Carotenoids               | Trend favoring risk reduction among highest quintiles of carotenoid consumption; may be variable by carotenoid class | Trend favoring risk reduction among highest quintiles of carotenoid consumption and serum carotenoid levels; may be variable by carotenoid class | Observational cohort, Nurses’ Health Study^{98,100,112} |

Micronutrients, specifically carotenoids, exhibit a great deal of interindividual variation in their absorption, metabolism, and excretion.^{86,103}
Premenopausal Breast Cancer

Contrary to the findings for postmenopausal cancer, overweight women seem to have a lower risk for breast cancer before menopause.\textsuperscript{142,147} In a pooled analysis of cohort studies, the risk of premenopausal breast cancer was lower by 14\% for every 5 kg/m\textsuperscript{2} increase in BMI.\textsuperscript{142} Although exact mechanisms are not clear, one hypothesis is that obesity can cause anovulation and, in the extreme, reduced hormonal cycling and reduced total hormone exposure. Another hypothesis is that obesity in early life may induce earlier breast differentiation, reducing the period of carcinogenic susceptibility. Finally, serum insulin-like growth factor 1, which is higher in women who were leaner in childhood and adolescence, may increase premenopausal breast cancer risk.\textsuperscript{151}

In summary, breast cancer represents a heterogeneous disease, and diet may interact with a variety of other genetic and environmental factors to impact risk. The study of nutrigenomics and future studies of breast cancer classified according to different subtypes of this disease may provide additional avenues for prevention through diet. To date, there is sufficient evidence to conclude that weight gain and body fatness in adulthood are risk factors for postmenopausal breast cancer. Additionally, alcohol, even at moderate levels, increases breast cancer risk, although some of the detrimental effects may be reduced by sufficient folate intake. Therefore, women may reduce their risk of cancer by maintaining a healthy body weight and reducing alcohol consumption. Women who drink should take sufficient folate through diet or supplements. Although much is already known about the dietary predictors of breast cancer, promising areas for future research include the effects of red meat, phytoestrogens, and micronutrients, with particular attention to exposures in childhood and early adult life.

STRATEGIES FOR BREAST CANCER RISK REDUCTION—SURGERY

Surgical options for women judged to be at substantially increased risk of breast cancer include prophylactic mastectomy and prophylactic salpingo-oophorectomy. This approach is limited to women at markedly increased risk based on the presence of known or suspect genetic mutations (\textit{BRCA1}, \textit{BRCA2}, p53, PTEN) and/or a family history of breast and/or ovarian cancers among first- and second-degree relatives.\textsuperscript{13} Among women at moderate and high risk, bilateral risk-reduction mastectomy can reduce breast cancer risk by 89.5\% to 100\% (95\% CI, 41\% to 100\%).\textsuperscript{152,153} Women with \textit{BRCA1}/2 mutations reduced their risk of breast cancer by 53\% (HR = 0.47; 95\% CI, 0.29 to 0.72) and their risk of ovarian cancer by 96\% (HR = 0.04; 95\% CI, 0.01 to 0.16) after undergoing an elective bilateral salpingo-oophorectomy compared with women of similar risk who did not complete this risk-reduction procedure.\textsuperscript{154} However, this surgical procedure may impact negatively on quality of life by inducing menopausal symptoms and increasing the risk of osteoporosis. Use of bilateral salpingo-oophorectomy as a breast cancer risk-reduction strategy should be limited to women with \textit{BRCA1}/2 mutations,\textsuperscript{155} although further surgical indications have been offered.\textsuperscript{156} For women wishing to contemplate risk-reduction surgery, presurgical evaluations at comprehensive cancer centers are recommended. These evaluations include consultations with a genetics professional (including genetic testing) and a psychologist to assure that patients fully understand the magnitude of risk and the breadth of potential harms and benefits.\textsuperscript{155}

The impact of either reduction mammoplasty or augmentation mammoplasty on breast cancer risk remains under study. These procedures remain appropriate for cosmetic reasons or to relieve the discomfort of macromastia but should not be undertaken specifically for breast cancer risk reduction.

STRATEGIES FOR BREAST CANCER RISK REDUCTION—SUMMARY

Risk-reduction strategies for women at general population risk of developing breast cancer are focused primarily on lifestyle modifications. Aside from following general dietary recommendations for healthy eating, there is no clear evidence that specific dietary components can effectively reduce breast cancer risk.
While all patients should be advised to moderate their alcohol use, in particular, women judged to be at moderate or high risk should be counseled to moderate their alcohol intake or even to avoid alcohol. A meta-analysis based on data from 53 studies concluded that alcohol increased the RR of breast cancer by 7.1% (95% CI, 5.5% to 8.7%) for each daily serving of alcohol consumed. Results from this meta-analysis suggest that about 4% of all breast cancers in developed countries may be attributable to alcohol consumption.

Although prescribing patterns for postmenopausal HT have changed dramatically as a result of recent reports from the WHI, use of HT for the management of menopausal symptoms had been a common practice. A large retrospective study determined that use of HT was associated with an increase of about 10% in the risk of developing breast cancers for each 5 years of use, which suggests that brief use of HT may be considered for postmenopausal symptom management after weighing individual risks and benefits. While current evidence suggests that the use of combination postmenopausal HT consisting of estrogen plus progestin increases breast cancer risk even if used for short intervals (eg, 5 years), use of estrogen alone increases breast cancer risk more modestly, without an increase in breast cancer risk until 10 to 15 years of use. Also, breast cancer risk declines rapidly after discontinuing use of estrogen-only HT.

Patients should be counseled on the importance of maintaining a healthy body weight, since gaining over 20 pounds during adulthood has been reported to result in an increased risk of breast cancer. Data from the WHI Observational Study revealed that among never users of HT, baseline BMI in excess of 31 resulted in a doubling of the risk for postmenopausal breast cancer. The impact of weight gain is more apparent for hormone receptor-positive breast cancers.

A recent report based on data from the NHS reported that a weight gain of more than 25 kg since age 18 years was associated with a 50% increased risk of invasive breast cancer (RR, 1.45; 95% CI, 1.27 to 1.66), while women who gained over 10 kg since menopause had an increased risk of breast cancer (RR, 1.18; 95% CI, 1.03 to 1.35).

Physical activity and obesity are closely related through many factors that may independently or jointly influence breast cancer risk (eg, estrogen levels, body-fat distribution, insulin levels, insulin-like growth hormone, and mammographic density). Although observational studies provide evidence that higher levels of physical activity result in lower rates of breast cancer, some researchers have argued that intervention trials are needed to better define this relationship, even though the feasibility of maintaining compliance for a sufficiently long time is doubtful. Moreover, regular physical activity is an important weight-control strategy. All persons, regardless of gender, should be encouraged to engage in at least 30 minutes of moderate-to-vigorous intensity physical activity on at least 5 days per week.

Use of pharmacotherapy for breast cancer risk reduction should be individualized to each patient based on their medical history, family history, quantified estimate of developing breast cancer, and patient preferences. Clinicians are strongly encouraged to engage patients in a thorough discussion of risks and benefits as part of shared decision-making process. Clinicians should be aware of potential drug-drug interactions with tamoxifen. While serotonin reuptake inhibitors are known to decrease the formation of the active metabolite of tamoxifen (endoxifen), the clinical impact of this is unclear. Citalopram and venlafaxine are not known to disrupt tamoxifen metabolism.

The P-1 and STAR trials, as well as the MORE, CORE, and RUTH studies, all enrolled a limited proportion of non-Whites, and findings from those trials may be difficult to generalize to other population subgroups. While racial/ethnic factors impact screening, from a practical perspective, the issue of limited minority enrollment is relatively minor since breast cancer risk factors are generally similar across racial/ethnic groups, with biologic differences in breast cancer more related to differences in hormone-receptor status among racial/ethnic groups. These clinical trials also excluded other groups of women at increased risk of developing breast cancer, such as patients with a prior...
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history of chest wall irradiation. Both the P-1 and STAR trials included women with atypical hyperplasia; in fact, these studies represent the largest prospective studies on the management of women with atypical hyperplasia.155

Women who opt to take pharmacotherapy to achieve breast cancer risk reduction, as well as those participating in clinical trials of breast cancer prevention, should understand the importance of adhering to surveillance recommendations for the prompt detection of breast cancer, as well as the need to seek medical evaluation for specific symptoms of adverse events, such as abnormal vaginal bleeding and vision problems.

Patients being considered for breast cancer chemoprevention should be counseled regarding modifiable lifestyle factors as an initial approach to risk reduction. Qualitative and quantitative approaches to risk assessment should be used to identify women at increased risk of breast cancer for whom genetics consultation, individualized surveillance, and/or chemoprevention may be appropriate. Women interested in breast cancer chemoprevention are urged to consider participating in clinical trials.

REFERENCES

1. National Cancer Institute, US National Institutes of Health. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 17 Regs Limited-Use, Nov 2006 Sub (1973–2004 varying), Linked to County Attributes, Total US, 1969–2004 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.

2. American Cancer Society. Cancer Facts & Figures 2008. Atlanta, GA: American Cancer Society; 2008.

3. National Cancer Institute, US National Institutes of Health. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). Smigal C, Jemal A, Ward E, et al. Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin 2006;56:168–183.

4. American Cancer Society. Breast Cancer Facts and Figures 2005–2006. Atlanta, GA: American Cancer Society; 2005.

5. American Cancer Society. Breast Cancer Facts and Figures 2008–2009. Atlanta, GA: American Cancer Society; 2008.

6. National Cancer Institute, US National Institutes of Health. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). DevCan Database: SEER, 17 Incidence and Mortality, 2000–2003, with Kaposi Sarcoma and Mesothelioma. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission.

7. National Cancer Institute, US National Institutes of Health. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). DevCan Database: SEER, 17 Incidence and Mortality, 2000–2003, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission.

8. National Center for Health Statistics. Health, United States, 2006 with Chartbook on Trends in the Health of Americans. Hyattsville, MD: National Center for Health Statistics; 2006.

9. Centers for Disease Control and Prevention. Use of mammograms among women aged > or = 40 years—United States, 2000–2005. MMWR. Morb Mortal Wkly Rep 2007;56:49–51.

10. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2008: a review of current American Cancer Society guidelines and cancer screening issues. CA Cancer J Clin 2008;58:161–179.

11. Salow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75–89.

12. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397–2406.

13. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Available at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed July 18, 2008.

14. Nelson HD, Huffman LH, Fu R, Harris EL. Genetic risk assessment and BRCA1 mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2005;143:362–379.

15. Singletary SE. Rating the risk factors for breast cancer. Ann Surg 2003;237:474–482.

16. Levy-Lahad E, Friedman E. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br J Cancer 2007;96:11–15.

17. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187–195.

18. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005;97:1248–1347.

19. Urwin G, Ma H, Wu AH, et al. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev 2003;12:332–338.

20. Monnikhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. Epidemiology 2007;18:137–157.

21. Whittemore AS, Gong G, John EM, et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol Biomarkers Prev 2004;13:2078–2083.

22. Nusbaum R, Vogel KJ, Ready K. Susceptibility to breast cancer: hereditary syndromes and low penetrance genes. Breast Dis 2006;27:21–50.

23. Bhatia S, Robinson LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin’s disease. N Engl J Med 1996;334:745–751.

24. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin’s disease. J Natl Cancer Inst 1993;85:25–31.

25. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465–475.

26. Children’s Oncology Group. Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Bethesda, MD: Children’s Oncology Group; 2006.

27. Gal MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81:1879–1886.

28. Gal MH, Costantino JP, Pee D, et al. Projecting individualized absolute invasive breast cancer risk in African American women. J Natl Cancer Inst 2007;99:1782–1792.

29. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet 1991;48:232–242.

30. van Asperen CJ, Jonker MA, Jacobi CE, et al. Risk estimation for healthy women from breast cancer families: new insights and new strategies. Cancer Epidemiol Biomarkers Prev 2004;13:87–93.

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

32. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 2006;98:1215–1226.
33. Barlow WE, White E, Ballard-Barbash R, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. J Natl Cancer Inst 2006;98:1204–1214.

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

35. Evans DG, Howell A. Breast cancer risk-assessment models. Breast Cancer Res 2007;9:213.

36. Jordan VC. Selective estrogen receptor modulation: a personal perspective. Cancer Res 2001;61:5683–5687.

37. Fisher B, Redmond C. New perspective on the contralateral breast: a marker for assessing tamoxifen as a preventive agent. J Natl Cancer Inst 1991;83:1278–1280.

38. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451–1467.

39. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P–1 Study. J Natl Cancer Inst 1998;90:1371–1388.

40. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–1662.

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

42. Veronesi U, Maisonneuve P, Rotmensch N, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 2001;93:727–737.

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

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

45. Powles T, Eeles R, Tidy A, et al. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 2007;99:283–290.

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

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

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

49. Day R, Ganz PA, Costantino JP, et al. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999;17:2659–2669.

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

51. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. Breast Cancer Res Treat 2001;65:125–134.

52. Cumming SR, Eckert S, Krause KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189–2197.

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

54. Lamb CA, Helguero LA, Fabris V, et al. Differential effects of raloxifene, tamoxifen and fulvestrant on a murine mammary carcinoma. Breast Cancer Res Treat 2003;79:25–35.

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

56. Sporn MB, Dowsett SA, Mershon J, Bryant HU. Role of raloxifene in breast cancer prevention in postmenopausal women: clinical evidence and potential mechanisms of action. Clin Ther 2004;26:830–840.

57. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2727–2741.

58. Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2742–2751.

59. Ganz PA, Gotay CC. Use of patient-reported outcomes in phase III cancer treatment trials: lessons learned and future directions. J Clin Oncol 2007;25:5063–5069.

60. Kaplan CP, Haas JS, Perez-Stable EJ, et al. Factors affecting breast cancer risk reduction practices among California physicians. Prev Med 2005;41:7–15.

61. Bevers TB.Raloxifene and the prevention of breast cancer: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2131–2139.

62. Cuzick J. Aromatase inhibitors for breast cancer prevention. J Clin Oncol 2005;23:1636–1643.

63. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793–1802.

64. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–62.

65. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–1092.

66. Baum M, Budzar AJ, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359:2131–2139.

67. Cuzick J. Aromatase inhibitors for breast cancer prevention. J Clin Oncol 2005;23:1636–1643.

68. Goss PE, Strasser-Weippl K. Prevention strategies with aromatase inhibitors. Clin Cancer Res 2004;10:3725–3798.

69. Breslaur RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092–1102.

70. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1092–1102.

71. Moores N, Grubber JM, Millikan RC, Newman B. Association between non-steroidal anti-inflammatory drugs (NSAIDs) and invasive breast cancer and carcinoma in situ of the breast. Cancer Causes Control 2003;14:915–922.

72. Swede H, Mirand AL, Menezes RJ, Moysich KB. Association of regular aspirin use and breast cancer risk. Oncology 2005;68:40–47.
78. Egan KM, Stampfer MJ, Giovannucci E, et al. Prospective study of regular aspirin use and the risk of breast cancer. J Natl Cancer Inst 1996;88:988–993.
79. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:47–55.
80. Fabian CJ. Breast cancer chemoprevention: beyond tamoxifen. Breast Cancer Res 2001;3:99–103.
81. Howell A, Sims AH, Ong KR, et al. Mechanisms of Disease: prediction and prevention of breast cancer—cellular and molecular interactions. Nat Clin Pract Oncol 2005;2:635–646.
82. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1997;350:1047–1059.
83. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progesterin. JAMA 2008;299:1036–1045.
84. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–1712.
85. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med 2006;166:2253–2259.
86. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol 2000;152:950–964.
87. World Cancer Research Fund and American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. 2007. Washington, DC: World Cancer Research Fund and American Institute for Cancer Research; 2007.
88. Michels KB, Mohlajee AP, Roset-Bahmanyar A. Coffee, tea, and caffeine consumption and breast cancer risk. J Natl Cancer Inst 2007;99:64–76.
89. Lewis SJ, Harbord RM, Harris R, Smith GD. Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. J Natl Cancer Inst 2006;98:1607–1622.
90. Shin MH, Holmes MD, Hankinson SE, et al. Intake of dairy products, calcium, and vitamin D and risk of breast cancer. J Natl Cancer Inst 2004;96:1139–1146.
91. Bertone-Johnson ER, Chen WY, Holick MF, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1991–1997.
92. Michels KB, Holmberg L, Bergqvist L, Wolk A. Coffee, tea, and caffeine consumption and breast cancer incidence in a cohort of Swedish women. Ann Epidemiol 2002;12:21–26.
93. Lundback AC, Kipnis V, Chang SC, et al. Dietary fat and postmenopausal invasive breast cancer in the National Institutes of Health-AARP Diet and Health Study cohort. J Natl Cancer Inst 2007;99:451–462.
94. Sieri S, Pala V, Brighenti F, et al. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. Am J Clin Nutr 2007;86:1160–1166.
95. Masoro SM, Smith-Warner SA, Spiegelman D, et al. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. Int J Epidemiol 2002;31:78–85.
96. Cho E, Chen WY, Hunter DJ, et al. Red meat intake and risk of breast cancer among premenopausal women. Arch Intern Med 2006;166:153–160.
97. Taylor EE, Burley VJ, Greenwood DG, Cade JE. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. Br J Cancer 2007;96:1139–1146.
98. Eggerb R, Olsen A, Attrup H, et al. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. Eur J Cancer Prev 2008;17:39–47.
99. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 2007;298:289–298.
100. Larson SC, Giovannucci E, Wolk A. Folate and risk of breast cancer: a meta-analysis. J Natl Cancer Inst 2007;99:64–76.
101. Lewis SJ, Harbord RM, Harris R, Smith GD. Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. J Natl Cancer Inst 2006;98:1607–1622.
102. Shim MH, Holmes MD, Hankinson SE, et al. Intake of dairy products, calcium, and vitamin D and risk of breast cancer. J Natl Cancer Inst 2004;96:1139–1146.
103. Bertone-Johnson ER, Chen WY, Holick MF, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1991–1997.
104. Michels KB, Holmberg L, Bergqvist L, Wolk A. Coffee, tea, and caffeine consumption and breast cancer incidence in a cohort of Swedish women. Ann Epidemiol 2002;12:21–26.
105. Tamimi RM, Hankinson SE, Campos H, et al. Plasma carotenoids, retinol, and tocopherol and risk of breast cancer. Ann Epidemiol 2002;12:21–26.
106. Trock BJ, Hilakivi-Clarke L, Clarke R, Meta-analysis of soy intake and breast cancer risk. J Natl Cancer Inst 2006;98:459–471.
107. Duffy C, Perez K, Partridge A. Implications of phytoestrogen intake for breast cancer. CA Cancer J Clin 2007;57:260–277.
108. Smith-Warner SA, Spiegelman D, Yuwan SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279:535–540.
109. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 38,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234–1245.
110. Chen WY, Willett WC, Rosner B, Colditz GA. Moderate alcohol consumption and breast cancer [abstract]. J Clin Oncol 2005;23(suppl):7s. Abstract 515.
111. Zhang SM, Lee IM, Manson JE, et al. Alcohol consumption and breast cancer risk in the Women's Health Study. Am J Epidemiol 2007;165:667–676.
112. Zhang SM, Willett WC, Selhub J, et al. Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. J Natl Cancer Inst 2003;95:373–380.
113. Zhang S, Hunter DJ, Hankinson SE, et al. A prospective study of folate intake and the risk of breast cancer. JAMA 1999;281:1632–1637.
114. Russo J, Tay I, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat 1982;2:5–73.
115. Ariazi JL, Haag JD, Lindstrom MJ, Gould MN. Mammary glands of sexually immature rats are more susceptible than those of mature rats to the carcinogenic, lethal, and mutagenic effects of N-nitroso-N-methylurea. Mol Carcinog 2005;43:155–164.
116. Land CE. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. JAMA 1998;274:402–407.
117. Land CE, Tokunaga M, Koyama K, et al. Incidence of female breast cancer among atomic bomb survivors. Hiroshima and Nagasaki, 1950–1990. Radiat Res 2003;160:707–717.
118. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian American women. J Natl Cancer Inst 1993;85:1819–1827.
119. Treit S, Gaard M. Lifestyle changes during adolescence and risk of breast cancer: an ecologic study of the effect of World War II in Norway. Cancer Causes Control 1996;7:507–512.
120. Pryor M, Slattery ML, Robson LM, Egger M. Adolescent diet and breast cancer in Utah. Cancer Res 1989;49:2161–2167.
121. Knight JA, Lesosky M, Barnett H, et al. Vitamin D and reduced risk of breast cancer: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2007;16:422–429.
122. Bissonnette TG, Coldman AJ, Elwood JM, et al. Childhood and recent eating patterns and risk of breast cancer. Cancer Detect Prev 1989;4:47–58.
123. Potischman N, Weis HA, Swanson CA, et al. Diet during adolescence and risk of breast cancer among young women. J Natl Cancer Inst 1998;90:226–233.
124. Maruth SS, Feskahin D, Rockett HR, et al. Validation of adolescent diet recalled by adults. Epidemiology 2006;17:226–229.
125. Maruth SS, Feskahin D, Colditz GA, et al. Adult recall of adolescent diet: reproducibility and comparison with maternal reporting. Am J Epidemiol 2005;161:89–97.
126. Frazier AL, Li L, Cho E, et al. Adolescent diet and risk of breast cancer. Cancer Causes Control 2004;15:73–82.
127. Wu AH, Wan P, Hankin J, et al. Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. Carcinogenesis 2002;23:1491–1496.
128. Shu XO, Jin F, Da Q, et al. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomarkers Prev 2001;10:483–488.
129. Thanas J, Cotterchio M, Boucher BA, et al. Adolescent dietary phytoestrogen intake and breast cancer risk (Canada). Cancer Causes Control 2006;17:1253–1261.
130. Treili S. Height and weight in relation to breast cancer morbidity and mortality. A prospective study of 570,000 women in Norway. Int J Cancer 1989;44:23–30.
131. Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079–1085.
132. Holmes MD, Liu S, Hankinson SE, et al. Dietary carbohydrates, fiber, and breast cancer risk. Am J Epidemiol 2004;159:732–739.
133. Higgimbotham S, Zhang ZF, Lee IM, et al. Dietary glycemic load and breast cancer risk in the Women's Health Study. Cancer Epidemiol Biomarkers Prev 2004;13:65–70.
134. Jonas CR, McCullough ML, Teras LR, et al. Dietary glycemic index, glycemic load, and risk of incident breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2003;12:573–577.
135. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA 2001;285:769–776.
136. Holmes MD, Willett WC. Does diet affect breast cancer risk? Breast Cancer Res 2004;6:170–178.
137. Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. J Natl Cancer Inst 1999;91:547–556.
138. Hankinson SE, Willett WC, Manson JE, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995;87:1297–1302.
139. Newcomb PA, Klein R, Klein BE, et al. Association of dietary and lifestyle factors with sex hormones in postmenopausal women. Epidemiology 1995;6:318–321.
140. Thomas HV, Reeves GK, Key TJ. Endogenous estrogen and postmenopausal breast cancer: a quantitative review. Cancer Causes Control 1997;8:922–928.
141. Key TJ, Verkasalo PK. Endogenous hormones and the aetiology of breast cancer. Breast Cancer Res 1999;1:18:1–21.
142. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000;152:514–527.
143. Radimer KL, Ballard-Barbash R, Miller JS, et al. Weight change and the risk of late-onset breast cancer in the original Framingham cohort. Nutr Cancer 2004;49:7–13.
144. Ahu J, Schatzkin A, Lacey JV Jr, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. Arch Intern Med 2007;167:2091–2102.
145. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). Int J Cancer 2004;111:762–771.
146. Eliassen AH, Tworker SS, Mantzoros CS, et al. Circulating insulin and c-peptide levels and risk of breast cancer among predominately premenopausal women. Cancer Epidemiol Biomarkers Prev 2007;16:161–164.
147. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997;278:1407–1411.
148. Enriori CL, Orsini W, del Carmen Cremona M, et al. Decrease of circulating level of SHBG in postmenopausal obese women as a risk factor in breast cancer: reversible effect of weight loss. Gynecol Oncol 1986;23:77–86.
149. de Ward F, Poortman J, de Pedro-Alvarez Ferrero M, Baanders-van Halewijn EA. Weight reduction and oestrogen excretion in obese postmenopausal women. Maturitas 1982;4:155–162.
150. Harvie M, Howell A, Vierkant RA, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2005;14:656–661.
151. Schernhammer ES, Tworkor SS, Eliassen AH, et al. Body shape throughout life and correlations with IGFB and GH. Endocr Relat Cancer 2007;14:721–732.
152. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340:77–84.
153. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 2001;93:1633–1637.
154. Rebeck TR, Lynch HT, Neuhasson SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616–1622.
155. Breast Cancer Risk Reduction 2007. Jenkinson, PA: National Comprehensive Cancer Network; 2007. Available at http://www.nccn.org/professionals/physician_gls/PDF/breast_risk.pdf. Accessed on August 24, 2008.
156. Guillem JG, Wood WC, Moley JF, et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. J Clin Oncol 2006;24:8462–8466.
157. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progesterin. J Natl Cancer Inst 2000;92:328–332.
158. Feigelson HS, Patel AV, Teras LR, et al. Adult weight gain and histopathologic characteristics of breast cancer among postmenopausal women. Cancer 2006;107:12–21.
159. Feigelson HS, Jonas CR, Teras LR, et al. Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. Cancer Epidemiol Biomarkers Prev 2004;13:220–224.
160. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 2002;13:741–751.
161. Eliassen AH, Colditz GA, Rosner B, et al. Adult weight change and risk of postmenopausal breast cancer. JAMA 2006;296:193–201.
162. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 2002;132(suppl):3456S–3464S.
163. Irwin ML. Randomized controlled trials of physical activity and breast cancer prevention. Exerc Sport Sci Rev 2006;34:182–193.