

Breast Cancer Prevention: A Review of Current Evidence

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Abstract

The National Cancer Institute has created a breast cancer risk assessment tool that quickly estimates a woman's individualized absolute risk of developing breast cancer. Understanding the magnitude of risk is important because recent data show that breast cancer incidence may be reduced. All women may improve their overall health and thus perhaps minimize breast cancer risk by maintaining a healthy weight, avoiding cigarettes, limiting alcohol consumption, getting regular exercise, and avoiding non-diagnostic ionizing radiation. Nevertheless, no lifestyle modifications have yet been proven to prevent or definitively lower the risk of breast cancer. In addition, women whose personal breast cancer risk is high may consider reducing risk by pharmacologic or surgical means. In such women, a five-year course of tamoxifen reduced the risk of invasive breast cancer by 49%; women with lobular carcinoma in situ or atypical hyperplasia experienced even greater risk reductions. Because of the potential for vascular and endometrial side effects, women who are candidates for a preventive course of tamoxifen must be counseled regarding its relative risks and benefits. Prophylactic mastectomy offers at least a 90% reduction in the risk of breast cancer, but the physical and psychologi-

cal changes involved in such a procedure make it a difficult choice for many women. Breast cancer risk assessment and appropriate counseling are becoming standard components of breast cancer screening and overall health maintenance. (CA Cancer J Clin 2000;50:156-170.)

Breast cancer is the most common cancer among women in the Western world. In 2000, it is estimated that there will be more than 41,000 deaths from breast cancer in the US alone.¹ While there is no certain means of preventing breast cancer, all women may limit their risk factors for breast cancer, and women at high risk for the disease may be candidates for medical or surgical preventive measures. Reviewing available evidence on breast cancer prevention is important now because of the new choices available to healthy women.

Reproductive Risk Factors

MENARCHE & MENOPAUSE

Most breast cancer risk factors relate to gynecological or endocrinological events in a woman's life.²⁻⁸ Age at menarche is related to a woman's chance of developing breast cancer: Compared with women who experience menarche at age 16, girls who experience menarche two to five years earlier have a 10% to 30% greater risk of developing breast cancer later in life. A similar observation has been made for the timing of events at the other end of the reproductive spectrum, the age at menopause. The average age at menopause in the US is slightly older than 51 years. If we use women who experience menopause between the ages of 45

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and 55 years as the referent group, women who experience menopause at age 55 or older have a 50% higher risk of subsequently developing breast cancer, and women who cease menstruating at age 45 or younger have a 30% lower risk of subsequently developing breast cancer.

These data, along with the observations about the age at menarche, indicate that one way of expressing the risk of breast cancer in relation to gynecological events is simply to count the number of ovulatory menstrual cycles that a woman experiences in her lifetime. Early menarche and late menopause lead to an increased total lifetime number of menstrual cycles and a corresponding 30% to 50% increase in breast cancer risk. Conversely, late menarche and early menopause lead to a reduction in breast cancer risk of similar magnitude. Consistent with this observation is the fact that oophorectomy before the age of menopause (especially before the age of 40) lowers the risk of breast cancer by approximately two thirds.⁹

ENDOGENOUS ESTROGEN LEVELS

It is tempting to say that the explanation for these observations is the level of circulating estrogen to which a woman is exposed in her lifetime. In an adult woman, the predominant circulating estrogen is estradiol, and most of this is bound to sex hormone binding globulin (SHBG). A smaller proportion is bound to albumin. Between menarche and menopause, a woman is exposed to higher static levels of circulating estradiol (bound to either SHBG or albumin as well as freely circulating). Cell proliferation is low during the follicular phase of the menstrual cycle and does not increase with the preovulatory peak in estradiol.⁶ Following ovulation, progesterone stimulates cell proliferation to three times the follicular rates. If fertilization and pregnancy do not occur, progesterone levels fall, breast cell division decreases, and apoptosis follows.⁷ (During pregnancy, circulating

levels of both estrogen and progesterone remain elevated. In animal models, progesterone is a potent mitogen to breast cells, possibly making them more susceptible to the effects of breast carcinogens. During the second half of pregnancy, however, cell differentiation occurs in the breast and proliferation decreases.)

PREGNANCY

Pregnancy at a young age, especially before the age of 20, markedly reduces the incidence of subsequent breast cancer. Conversely, both nulliparity and age older than 30 at first live birth are associated with nearly a doubling of the risk of subsequent breast cancer. Pregnancies not ending in the birth of a viable fetus do not confer reduction in the risk of breast cancer.⁸⁻⁹

A Model for Risk Assessment

Gail and colleagues at the National Cancer Institute have developed a statistical model¹⁰ to assess a woman's individualized absolute risk of developing breast cancer (i.e., the chance that a woman with specific risk factors at a given age will develop breast cancer in a specified future time period). The risk factors used in the model are listed in Table 1. Women are considered to have a "high" risk for breast cancer when their risk is equal to or greater than that of the average 60-year-old woman.¹⁰

While this model is very useful in assessing individual risk of breast cancer in most American women, it has not been validated in all population subsets, including women younger than 20 years of age, patients who already have cancer, minority group women, and those who had recently lived outside the US. Validation has been demonstrated only in women undergoing regular mammographic screening. The model was also developed before genetic testing for breast cancer was common, so the accuracy of the assessment in women with ge-

Table 1
Factors Used in the National Cancer Institute's
Model to Determine the Risk of Breast Cancer^{10, 19}

- | | |
|--|---|
| <ul style="list-style-type: none"> • Current age • Race • Age at menarche • Age at first live birth (or nulliparity) | <ul style="list-style-type: none"> • Number of breast biopsies • Atypical hyperplasia • Number of first-degree relatives with breast cancer (ie, mother, sisters, daughters) |
|--|---|

netic predisposition is not known.¹¹⁻¹³ This model has been validated, however, in a recent prospective study of women who were at risk of developing breast cancer.¹⁴

Approaches to Breast Cancer Prevention

Breast cancer can spread insidiously. At diagnosis, 5% to 15% of patients have metastatic disease and almost 40% more have had regional spread of the disease.¹⁵ Further, among those with only local tumors at diagnosis, 24% to 30% will experience relapse.¹⁶ As treatment is sometimes unsuccessful or may be started too late, preventing cancer is preferable. Further, preventing breast cancer with safe, well-tolerated drugs is clearly preferable to treatment with radiation and cytotoxic chemicals that have significant, and often distressing, side effects.

Currently, two approaches have been proven to decrease breast cancer incidence: Prophylactic mastectomy and preventive therapy with tamoxifen. Surgery provides the greater risk reduction, but because of its severe physiologic and psychological consequences, it is considered only in very high-risk cases. Pharmacologic breast cancer prevention has been associated with side effects (including increased risk of endometrial cancer) but has been shown to improve the lipid profile,¹⁷ preserve bone mineral density,¹⁸

Table 2
Lifestyle Modifications
Recommended for All Women

- | |
|--|
| <ul style="list-style-type: none"> • Weight control • No cigarette smoking • Decreased alcohol consumption • Exercise • Avoidance of non-diagnostic, ionizing radiation |
|--|

and decrease the incidence of bone fractures to the hip, radius, and spine.¹⁹ Risks of both approaches must therefore be weighed carefully against potential benefits in the reduction of breast cancer risk.

Risk reduction should be considered throughout a woman's life. Women with low-to-normal risk should consider lifestyle modifications and vigilant surveillance (Table 2). Although these lifestyle choices have not been proven to prevent breast cancer, they are generally associated with good health and generally believed to offer some protection against cancer. Women may consider preventive pharmacologic therapy when increased breast cancer risk is noted. In some cases, prophylactic bilateral mastectomy may be an appropriate option; in others, pharmacological options may be more suitable. Women who have been successfully

treated for breast cancer should consider, together with their practitioners, how best to prevent recurrence.

Current Evidence on Primary Cancer Prevention

CHEMOPREVENTION

Tamoxifen

Tamoxifen has historically been used to treat rather than prevent breast cancer. Several treatment trials, though, reported a decrease in the incidence of cancers in the contralateral breast (i.e., prevention of new primary cancers).²⁰⁻²² Notably, the National Surgical Adjuvant Breast and Bowel Project (NSABP), which enrolled 2,644 breast cancer patients in its B-14 trial, reported that tamoxifen use decreased the incidence of new breast cancers. At trial entry, all patients had been diagnosed with node-negative breast cancer and estrogen-receptor (ER)-positive tumors. This randomized, double-blind, placebo-controlled trial tested the use of tamoxifen 10 mg twice per day for five years. After four years of follow-up, 29 cancers of the opposite breast (2.2%) were reported in the placebo group while only 13 cases were reported in the tamoxifen group (1%, $p = 0.0089$).²³⁻²⁴

In addition, a meta-analysis performed by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) analyzing 55 prospective treatment trials found that women who had received tamoxifen for five years had a 47% reduction in new primary breast cancers occurring in the 10 years after treatment initiation ($p < 0.00001$). Interestingly, this reduction in new primary cancers occurred regardless of whether the patient's initial tumor had been ER-positive or -negative.²⁵

Because of the NSABP finding that tamoxifen reduced the incidence of contralateral disease in breast cancer patients and because of early EBCTCG data showing a 39% reduction in the incidence

of contralateral breast tumors when tamoxifen was given,²⁶ the NSABP designed a study, the Breast Cancer Prevention Trial (BCPT), to assess the efficacy of tamoxifen for the prevention of breast cancer in women at increased risk of the disease.

The BCPT, also known as the P-1 trial, included 13,388 women who had been determined to be at high risk for breast cancer based on a modified version of the Gail model for estimating breast cancer risk.^{13,19} Patients were randomly assigned to receive either 20 mg/day of tamoxifen ($n = 6,681$) or placebo ($n = 6,707$) for five years. After a median follow-up time of 54.6 months, the risk of invasive breast cancer in patients receiving tamoxifen was reduced by 49% ($p < 0.00001$). Tamoxifen reduced the cumulative incidence of cancer from 43.4 cases per 1,000 women in the placebo group to 22.0 cases per 1,000 in the treatment group (Table 3). The relative breast cancer risk was reduced by 44% in women 49 years or younger; 51% in women 50 to 59 years, and 55% in women age 60 and older. Women with atypical hyperplasia experienced an 86% risk reduction. Tamoxifen also reduced the risk of noninvasive breast cancer by 50% ($p < 0.002$). Although tamoxifen did not affect the incidence of ER-negative tumors, it decreased the incidence of ER-positive tumors by 69% compared with the placebo group.¹⁹

Other long-term effects of tamoxifen were noted in this study. Endometrial stage I cancers were more common in the tamoxifen group, with a tamoxifen-to-placebo risk ratio of 2.53; risk was greatest in women 50 years of age or older. Moreover, the rates of stroke (risk ratio 1.59, CI 0.93-2.77), pulmonary embolism (risk ratio 3.01, CI 1.15-9.27), and deep-vein thrombosis (risk ratio 1.60, CI 0.91-2.86) were elevated in the tamoxifen group, particularly among those 50 years or older. Tamoxifen was also associated with several beneficial effects, including a

Table 3
Breast Cancer Risk Reduction with Tamoxifen Among
Various Subsets of Healthy Women

| Subset | Relative Risk Reduction (%) | p Value |
|---|-----------------------------|---------|
| Overall Incidence of Invasive Breast Cancer | 49 | 0.00001 |
| <u>Age Group</u> | | |
| < 49 | 44 | |
| 50-59 | 51 | |
| ≥ 60 | 55 | |
| Lobular Carcinoma In Situ | 56 | |
| Atypical Hyperplasia | 86 | |
| Overall Incidence of Non-invasive Breast Cancer | 50 | 0.002 |
| Incidence of ER-Positive Tumors | 69 | |
| Incidence of ER-Negative Tumors | 0 | |

ER = estrogen receptor.
 Adapted from Fisher B et al,¹⁹ with permission.

reduction in hip (45%), radius (Colles', 39%), and spine (26%) fractures probably associated with the maintenance of bone mineral density.¹⁹

In contrast to the findings of the P-1 trial, two preliminary reports from European trials did not confirm a significant preventive effect with tamoxifen. An interim analysis of a study conducted at the Royal Marsden Hospital reported, after a median of 70 months of follow-up, that the overall frequency of breast cancer was approximately the same for patients on tamoxifen (34/1238) as for patients receiving placebo (36/1233, $p=0.80$). This study population differed from that of the NSABP prevention trial in that patients qualified for the study strictly on the basis of a family history of breast cancer. The British study enrolled healthy women with either two first-degree relatives with breast cancer; one affected relative plus a history of benign biopsy; or one first-degree relative who developed breast can-

cer before the age of 50 or who developed cancer in both breasts. Unlike the P-1 trial, hormone replacement therapy (HRT) was also allowed, and 26% of patients used it during the study. In fact, this study found that the use of HRT at randomization was a prognostic factor for increased relative risk of breast cancer (relative risk 1.9, $p<0.04$ compared with women not receiving HRT). The inclusion criteria of the Royal Marsden study may also have selected for patients with increased breast cancer risk due to oncogenes (which are often associated with progesterone-receptor negative tumors). This study is ongoing, and later results may clarify outcome differences between this trial and the P-1 study.²⁷

The Italian Tamoxifen Prevention Study recruited hysterectomized women (as they had no risk of endometrial cancer). Women did not need to have any risk factors for breast cancer to enter the trial. In this study, 5,408 women were

randomized to receive either tamoxifen 20 mg/day or placebo for five years. The study was terminated early due to a high drop-out rate. After a median follow-up period of 46 months, the frequency of breast cancer was the same in the tamoxifen and placebo groups (22 and 19 cases, respectively). HRT was used by 14% of women during the trial. The investigators noted increased rates of thrombophlebitis, phlebothrombosis, or embolus ($p=0.0053$) in women taking tamoxifen, as well as more self reports of hypertriglyceridemia ($p=0.0013$). They concluded that "in this preliminary analysis of low power, in this cohort of women at low-to-normal risk of breast cancer, the postulated protective effects of tamoxifen are not yet apparent."²⁸

Several differences between this study and the P-1 trial—i.e., the smaller sample size, the use of HRT, recruitment by advertising, hysterectomy as an entry criterion, the low proportion of patients who completed therapy, the small number of breast cancer events occurring in the placebo group, and, most seriously, the fact that most of the population had normal or lower-than-average breast cancer risk—may explain the different study results. Because oophorectomy is known to lower the risk of breast cancer, it is doubtful that the addition of tamoxifen in this already low-risk group could have any additional benefits. At this time, women with low or normal risk for breast cancer are not appropriate candidates for therapies that reduce breast cancer risk.

Tamoxifen is approved in the US for reduction of breast cancer risk in women at high risk for the disease, based on the results of the NSABP P-1 trial, which had the largest sample size, greatest statistical power, and greatest number of new breast cancer cases of any study conducted to date. Only women at increased risk based on NCI criteria¹³ should consider tamoxifen for risk reduction, and they should receive therapy for five years. Factors used to identify women at increased risk are

shown in Table 1. The relative benefit of tamoxifen in women on HRT and in those with specific breast cancer genotypes remains to be determined.

Small invasive breast cancer; ER-negative tumors; or a Remote diagnosis of breast cancer: Consensus opinion suggests that adjuvant therapy with tamoxifen is not indicated for women with invasive breast tumors smaller than 1 cm in size with negative axillary lymph nodes.²⁵ However, that consensus opinion was based on studies of tamoxifen as treatment for primary cancer rather than as a preventive agent against a second new breast cancer. Because the risk of a contralateral, second invasive breast malignancy approaches 20% during the remaining years of life in a woman diagnosed with a first breast cancer at the age of 40 (and is similar to the risk of women in the P-1 trial), the use of tamoxifen for risk reduction may be a reasonable option, particularly for younger women.

To date, no studies examining this question are available, but a review of data from several NSABP treatment trials and from other trials showed that tamoxifen reduces the incidence of contralateral second primary breast cancers by roughly the same proportion as observed for primary breast malignancies in P-1.²⁹ Thus, preventive use of tamoxifen for women with small, node-negative invasive breast cancers may be justified, even where there is doubt about its use as adjuvant therapy.

It is not known whether some breast cancers arise without expressing estrogen receptors at any point in their genesis or whether all invasive breast cancers pass through a developmental phase in which they produce ER protein. The data from the P-1 trial indicate that the breast cancers arising among women taking placebo were more likely to express estrogen receptors than were those tumors arising in women taking tamoxifen. This suggests that tamoxifen suppressed those develop-

ing lesions that expressed estrogen receptors but had little or no effect on tumors that did not express estrogen receptors. An alternative explanation is that there are breast tumors that arise without expressing estrogen receptors at any time in their natural history. If the latter hypothesis is true, and if subsequent breast cancers in women whose first cancer did not express estrogen receptors are also ER-negative, tamoxifen would offer them little benefit. Alternatively, if all breast tumors pass through a phase of ER expression, then tamoxifen may offer benefit even to those women whose first primary breast cancer was ER-negative. Although more basic and clinical research is necessary to resolve this question, a meta-analysis of the effects of tamoxifen²⁵ revealed that "...the proportional reduction in contralateral breast cancer appeared to be about the same size in women with ER-poor tumors ($29 \pm 15\%$) as in other women ($30 \pm 6\%$)."

Another group of women for whom there is no definitive answer about the prophylactic use of tamoxifen are cancer-free women who were diagnosed with breast cancer five or more years previously ("remote diagnosis") and who were not treated with adjuvant tamoxifen. Data from several NSABP protocols are available to estimate the subsequent risk of breast cancer in women who survived disease-free for five years following an initial diagnosis of invasive breast cancer and who had not received adjuvant tamoxifen.²⁹ The subsequent five-year cumulative risk of contralateral invasive breast cancer was 3.4%, which is close to the 3.3% risk for invasive breast cancer in the placebo arm of the P-1 trial; the cumulative risk of all invasive breast cancer in such women was 14.4%.

The decision to use tamoxifen for risk reduction in these patients must be informed by an assessment of the duration and quality of life remaining, the risks as well as potential benefits of tamoxifen, and the presence of competing morbidity

that may weigh against the use of tamoxifen. For example, tamoxifen may be appropriate in a 50-year-old woman who is otherwise healthy, but less suitable for a 68-year-old woman with a history of cataracts and deep vein thrombosis.

BRCA1/2 Mutation Carriers: Both prospective and retrospective genetic epidemiologic studies have demonstrated that women who carry mutations in either BRCA1 or BRCA2 genes are at very high risk of developing both breast and ovarian cancers.³⁰⁻³² The use of tamoxifen for the reduction of breast cancer risk is now approved in the US, and the results of the P-1 trial are encouraging, especially because all age groups derived benefit. Critics of the trial argued at its inception that an antiestrogen could not reduce risk in premenopausal women due to their endogenous high-estrogen environment. The empirical observation of reduced breast cancer incidence among younger women in the trial raises interesting questions about the mechanisms of action of tamoxifen and similar antiestrogens.

It is not yet known whether antiestrogens, or any chemoprevention drug, can prevent the development of malignancy in women with heritable risk. It does appear, however, that BRCA1 acts, in part, as a tumor suppressor gene. This is suggested by the observation that reduction in BRCA1 expression *in vitro* results in accelerated growth of breast and ovarian cell lines while overexpression of BRCA1 results in inhibited growth.³³⁻³⁴ The murine homologue of BRCA1 is expressed at highest levels in rapidly proliferating cells such as the breast during puberty and pregnancy, and expression of BRCA1 is regulated in a cell cycle-dependent fashion, with peak mRNA protein produced at the G1/S transition. BRCA1 also serves as a substrate for certain cyclin-dependent kinases.

It is known, too, that estradiol induces BRCA1 through an increase in DNA synthesis, suggesting that BRCA1

may serve as a negative modulator of estradiol-induced growth.³⁵ The kinetics and magnitude of this induction are different from the estradiol gene pS2 in that *de novo* protein synthesis is required, but resemble the growth induced by either insulin-like growth factor 1 or epidermal growth factor. BRCA1 genomic fragments near the 5' end fail to respond to estradiol when transfected into breast cancer cell lines.

Like BRCA1, BRCA2 expression in the breast is induced during puberty and pregnancy, as well as following treatment with estradiol and progesterone. In multiple fetal and adult tissues, the temporal expression of BRCA2 mRNA is indistinguishable from BRCA1^{33, 36} and it appears that both BRCA1 and BRCA2 expression may be regulated by similar pathways. Expression of both genes is differentially regulated by hormones during the development of specific target tissues, but the up-regulation of mRNA expression in the breast by ovarian steroid hormones is greater for BRCA1 than for BRCA2.

Together, these data suggest that in women who carry mutations in either BRCA1 or BRCA2 genes that predispose to the development of malignancy, the absence of the negative regulatory role of intact BRCA1 and BRCA2 molecules may still be abrogated by the negative modulation of estradiol and other estrogens by selective estrogen response modulators such as tamoxifen and raloxifene. Additional clinical and laboratory studies will address this fascinating preventive hypothesis.

Women with either BRCA1 or BRCA2 mutations would appear to be ideal candidates for the use of tamoxifen as primary prevention of breast cancer, but there are no data yet available that relate directly to them. While the mechanisms whereby tamoxifen might prevent breast cancer in BRCA1/2 mutation carriers are not fully understood, there is no reason to suppose *a priori* that tamoxifen

would necessarily be less effective in mutation carriers, other than the observation that BRCA1 carriers are more likely to develop ER-negative tumors.³⁸⁻⁴¹ Additional laboratory modeling of the effects of tamoxifen *in vitro* is necessary to address this question, as are prospective data from primary prevention trials that administer tamoxifen to women who carry mutations. Until these studies are completed, the use of tamoxifen in such women should be accompanied by disclosure beforehand that tamoxifen may not be effective.

Raloxifene

Several other pharmacologic agents that act on reproductive hormones, including raloxifene, are being examined for breast cancer risk reduction. In a trial designed to assess the effect of raloxifene on the prevention of bone fractures, 7,705 postmenopausal women were treated with raloxifene (60 or 120 mg/day) or placebo (in a 2:1 ratio) for two years. After a median of 40 months of follow-up, invasive breast cancer had been confirmed in 13 women given raloxifene and 27 women given placebo. The relative risk of breast cancer was 0.24 in the raloxifene group.⁴²

The significance of this finding is being examined in the Study of Tamoxifen and Raloxifene (STAR) trial, a new study currently enrolling participants. This trial tests the risk reduction purported for tamoxifen and raloxifene in a randomized, controlled manner, with breast cancer incidence as the primary end point. This is the first breast cancer prevention trial to incorporate an active agent (tamoxifen instead of placebo) as the standard of care.

Other antiestrogens may also be useful in preventing breast cancer; toremifene citrate and droloxifene, for instance, have activity similar to that of tamoxifen in certain populations; however, no clinical research has yet been published regarding risk reduction with these agents.

Other chemoprevention strategies are in early stages of development. One controlled pilot study enrolled women with a breast cancer risk at least five times that of the normal population, randomly assigning them to receive either placebo or a luteinizing hormone-releasing hormone (LHRH) agonist. Women receiving the LHRH agonist showed reduced breast cell proliferation, which has been hypothesized to be related to breast cancer risk.^{43,44} Use of LHRH agonists could potentially provide both contraception and breast cancer risk reduction in high-risk, premenopausal women, provided proof of clinical efficacy is documented.

Another approach to breast cancer prevention is the use of retinoids, derivatives of vitamin A.^{45,46} No large-scale studies on use of these compounds for prevention have been reported, however. As with raloxifene, their use should be restricted to well-controlled clinical trials until their efficacy has been proven.

SURGICAL RISK REDUCTION

Bilateral prophylactic mastectomy is the most certain means of reducing breast cancer risk. Nevertheless, because breast tissue is widely distributed over the entire anterolateral portion of the chest wall and axilla, no mastectomy can remove all existing mammary tissue. One retrospective study examined women with a family history of breast cancer who underwent bilateral mastectomy at the Mayo Clinic between 1960 and 1993. Women were classified as having either moderate or high risk for breast cancer. The median duration of follow-up was 14 years.⁴⁷ In the moderate risk group (n=425), breast cancer incidence was compared with that predicted by the Gail model.¹⁰ In the high-risk group (n=214), breast cancer incidence was compared with that of 403 sisters who had not had mastectomies. In the moderate-risk group, four cases of breast cancer occurred where the Gail model predicted 37.4 without surgery (risk reduction, 89.5%, $p<0.001$). In the

high-risk group, three women (1.4%) developed breast cancer after surgery, compared with 38 sisters who developed breast cancer after the time of the sibling's surgery. [Note: An additional 115 sisters had breast cancer diagnosed before their sibling's mastectomy.] Prophylactic mastectomy was therefore associated with a reduction in the incidence of breast cancer of at least 90%.⁴⁷

Prophylactic mastectomy has been described as a "disfiguring and potentially psychologically damaging operation."⁴⁸ As such, it should be considered carefully, particularly as less invasive therapies become available. Possible indications for prophylactic mastectomy include a strong family or personal history of breast cancer, multiple previous breast biopsies, unreliable results on physical examination because of nodular disease, findings of dense breast tissue on mammography, mastodynia, and cancerphobia.⁴⁷

LIFESTYLE MODIFICATIONS

Many lifestyle modifications that may affect breast cancer risk are recommended for all women, as part of a healthy lifestyle (Table 2). Some lifestyle choices affect reproductive hormone levels, which may influence breast cancer risk. It should be noted, however, that no lifestyle modifications have been proven to prevent or definitively lower the risk of breast cancer. Controlled studies of the impact of lifestyle changes on breast cancer incidence either cannot or have not been done. At best, research has shown that groups of women with certain characteristics have lower incidences of breast cancer than groups without those characteristics. Some of the factors for which evidence suggests a link to breast cancer risk are discussed below.

Diet

The potential link between a high-fat ("Western") diet and the incidence of breast cancer has been examined in several observational studies. A meta-analy-

sis of case-control studies,⁴⁹ as well as several international comparisons,⁵⁰⁻⁵² have suggested that high total dietary fat intake or consumption of certain types of dietary fat might increase the risk for breast cancer. Cohort studies, however, have found no link between breast cancer and dietary fat.⁵³⁻⁵⁵

Most recently, a long-term cohort study following 88,795 women for 14 years compared breast cancer incidence among two groups of women that differed in fat intake: Those in whom 30.1% to 35% of total calories were from dietary fat compared with those in whom fat intake was 20% or less of total calories. The relative risk of breast cancer for those eating less fat was 1.15 compared with women with higher fat diets. Researchers found no evidence that lower intake of total fat or of specific types of fat helped reduce risk of breast cancer.⁵⁶

Although current data do not support specific dietary guidelines for reducing breast cancer risk, the American Cancer Society still recommends that women maintain a healthy weight and limit intake of high-fat foods, particularly those from animal sources, as part of a healthy lifestyle.

Obesity

Obesity has been associated with an increased risk of breast cancer in postmenopausal women,⁵⁷⁻⁵⁸ which may occur because fat stores provide an important source of hormone substrates in postmenopausal women. This association is complex, though, and may change with age⁵⁹ or fat distribution.⁶⁰ It has not been shown clinically that reducing body weight can lower breast cancer risk, but this topic deserves further study.

Smoking

Cigarette smoking has been shown to increase the risk of lung and other types of cancer and to increase the risk of heart disease. Smoking affects overall health

and may increase risk for breast cancer, but no controlled trials have thus far established a definite link between smoking and breast cancer.⁶¹⁻⁶²

Alcohol Consumption

Alcohol consumption, like dietary fat intake, has been a controversial topic in breast cancer research. There are several mechanisms by which ethanol may increase the risk of breast cancer. It may (1) induce increased levels of circulating estrogen; (2) stimulate hepatic metabolism of carcinogens such as acetaldehyde; (3) facilitate transport of carcinogens into breast tissue; (4) stimulate pituitary production of prolactin; (5) modulate cell membrane integrity with an effect on carcinogenesis; (6) aid production of cytotoxic protein products; (7) impair immune surveillance; (8) interfere with DNA repair; (9) promote production of toxic congeners; (10) increase exposure to toxic oxidants; and/or (11) reduce intake and bioavailability of protective nutrients. Few of these mechanisms have been studied, however, either in experimental animals or humans. Alcohol consumption has, however, been linked to higher serum estrogen levels: Women with consistently high estradiol levels have a significantly higher average alcohol intake (92.8 g/wk) than those with consistently lower estradiol levels (alcohol intake, 31.6 g/wk).⁶³

In a pooled analysis of cohort studies, risk of breast cancer increased linearly with increasing alcohol intakes less than 60 g/d (reported by 99% of participants). The pooled multivariate relative risk for an increment of 10 g/d of alcohol (about 0.75 to 1 drink) was 1.09. The multivariate-adjusted relative risk for total alcohol intakes of 30 to less than 60 g/d (about two to five drinks) versus non-drinkers was 1.41 (95% CI, 1.18-1.69). Moderate or high amounts of alcohol consumption have been associated with increased breast cancer incidence.⁶⁴

In a case-control study conducted in

Italy, the odds ratio (OR) for breast cancer, adjusted only for age, was 1.31 (95% CI 1.13-1.53) when drinkers were compared with nondrinkers, and the trend in risk was significantly associated with the daily level of alcohol consumption ($X^2=12.28$, $p<0.0005$). The association was apparently stronger in premenopausal women (OR=1.80 where alcohol consumption was greater than 27.60 g/d). If causal, this association could explain 12% (95% CI, 5-19%) of breast cancers, thus representing a major avoidable risk factor for breast cancer.⁶⁵

By contrast, one notable long-term study of cardiovascular risk factors and heart disease, the Framingham study, performed a subanalysis of breast cancer patients that showed an inverse correlation between alcohol consumption and breast cancer. This may have been due to reporting methods or due to the subjects' alcohol consumption patterns.⁶⁶⁻⁶⁷ Whether reducing alcohol consumption will reduce breast cancer risk is an important subject for future study.

Exercise

Exercise may reduce breast cancer risk, but no biologic mechanism has been determined. Exercise enhances immune function, is associated with lower body fat, and affects hormonal levels, all of which may affect breast cancer.⁶⁸⁻⁶⁹ Confounding factors make it difficult to assess this relationship, because women who exercise regularly are also likely to smoke less, drink less, have different menstrual and reproductive patterns, and consume different diets than sedentary women.⁷⁰ Most studies report a decreased risk of breast cancer with increasing amounts of physical activity,⁷⁰⁻⁸⁰ though a few studies found no such association.⁸¹⁻⁸⁴ The Framingham study, started in 1948 to study cardiovascular risk factors, unexpectedly associated physical activity with increased breast cancer risk,⁸⁵ but this may have resulted from the selection of the population or the cohort, or from the measure of

physical activity.

Thune and colleagues reported on the largest prospective cohort organized specifically to study the association between exercise and breast cancer risk. They found that greater leisure-time activity was associated with a 37% reduction in relative risk of breast cancer ($p=0.04$ for women who exercised regularly versus sedentary women), even after adjustments for age and body-mass index. Risk reduction was greatest in premenopausal women, particularly those younger than 45 years. The lowest breast cancer risk was found in lean women who exercised more than four hours per week (relative risk, 0.28, CI, 0.11-0.70).⁸⁰

In a recent prospective study of women between 30 and 55 years of age, notable for 16 years of follow-up, women who reported engaging in moderate or vigorous physical activity for seven or more hours per week had a relative risk of breast cancer of 0.82 (95% CI, 0.70-0.97) compared with women who reported less than one hour of such exercise per week. The exercise dose-response trend was statistically significant ($p=0.004$).⁸⁶ Higher levels of physical activity probably afford modest protection against breast cancer.

Hormone Use

Breast cancer risk is decreased when reproductive hormone levels are altered through surgery or when tamoxifen competes with natural estrogens. It seems logical that other factors involving reproductive hormones might also affect breast cancer risk. Risks associated with the use of oral contraceptives are not well defined, though a recent meta-analysis found that current users of oral contraceptives had a higher relative risk of breast cancer (1.24, $p<0.00001$) than women who had never used oral contraceptives. A slightly elevated risk of breast cancer persisted for up to 10 years after cessation of oral contraceptives, but the risk was not significantly greater be-

yond that time. Notably, though, tumors diagnosed in women who were using or had used oral contraceptives were generally less advanced clinically than those diagnosed in women who had never used oral contraceptives (relative risk of tumors spread beyond the breast, 0.88, $p=0.002$).⁸⁷

Use of HRT is associated with an increased risk of invasive breast cancer. A prospective cohort study of 37,105 women found that, compared to women who had never used HRT, women who had used HRT for five or fewer years had a relative risk for breast cancer of 1.81, and women who had used HRT for more than five years had a relative risk for breast cancer of 2.65. Women currently receiving HRT for menopause have a significantly increased breast cancer risk (relative risk compared to nonusers, 1.36),⁸⁸ and this risk may rise in women who use HRT beyond five years.⁸⁹ Further, women entering menopause may sometimes receive concomitant oral contraceptives and HRT, which was shown in one study to triple the risk of breast cancer compared with that in women who did not use either agent.⁹⁰ Nevertheless, HRT has been shown to improve cardiovascular measures and increase bone density, along with relieving menopausal symptoms. In patients with a strong history of cardiovascular disease, benefits of HRT may outweigh increased risk of breast cancer.⁹¹ The decision to use HRT or oral contraceptives should include an assessment of risks and benefits in each individual.

Radiation Exposure

Relatively low doses of radiation (less than 0.2 Gy) have been associated with an increased incidence of solid tumors such as breast cancer.⁹²⁻⁹⁴ Women who have undergone chest wall irradiation therapy—as treatment for Hodgkin's disease, for example—during childhood or adolescence have a significantly increased

risk for breast cancer. It is important to note, however, that the very low doses of radiation associated with screening mammography do not increase the risk of breast cancer appreciably in individual women.

Conclusions

To date, only two options have been proven to reduce the risk of breast cancer in high-risk patients: Bilateral prophylactic mastectomy and tamoxifen therapy. While mastectomy may have a role in preventing breast cancer in some patients, it is associated with dramatic physical and psychological effects. Many healthy, high-risk women will choose pharmacologic means of preventing breast cancer, when such means are appropriate. Tamoxifen has been shown to significantly reduce the risk of breast cancer in females who are at high risk for developing the disease. Women may have elevated risk due to family history of breast cancer, hormonal factors such as early menarche or delayed age at first parturition, unusual breast tissue associated with biopsy, or advanced age. In such women, five years of tamoxifen therapy (along with increased cancer vigilance) should be considered for breast cancer risk reduction. Use of tamoxifen for risk reduction of breast cancer should be weighed against the potential risks of long-term drug usage.

All women, regardless of risk group, should be encouraged to adopt a healthy lifestyle, with moderate exercise, limited fat and alcohol intake, no smoking, and maintenance of healthy body weight. The decision to use tamoxifen versus HRT should involve consideration of many factors in addition to breast cancer risk, such as family history of cardiovascular disease, risk for osteoporosis, and quality of life issues pertaining to menopausal symptoms. **CA**

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