

*Primary Care***REDUCING THE RISK
OF BREAST CANCER**

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RECENT research results suggest that the risk of breast cancer can be reduced. In this review I will focus on chemoprevention, emphasizing evidence from randomized clinical trials, and in addition summarize the evidence regarding preventive strategies involving surgery and lifestyle changes (Table 1).

CHEMOPREVENTION**Tamoxifen and Risk Reduction**

The risk of breast cancer is related to levels of endogenous^{1,2} and exogenous³⁻⁵ hormones. Tamoxifen and raloxifene, which are selective estrogen-receptor modulators, can be used to test the hypothesis that the risk of breast cancer can be reduced by estrogen antagonists.⁶

Tamoxifen is active against advanced breast cancer⁷ and is used as adjuvant therapy for both non-invasive⁸ and invasive^{9,10} breast cancer. According to the analysis of trials of adjuvant therapy conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), treatment with tamoxifen for five years reduced the annual odds of recurrence of breast cancer by 47 percent. Tamoxifen also reduced the annual odds of contralateral breast cancer by 47 percent, regardless of the receptor status of the initial tumor.⁹ Given these findings, a number of groups proposed that tamoxifen might also reduce the risk of breast cancer.¹⁰⁻¹²

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Tamoxifen Prevention Trial, a randomized, placebo-controlled study, evaluated whether 20 mg of tamoxifen daily for five years could reduce the incidence of breast cancer in women at increased risk.¹³ Eligible subjects had a predicted five-year risk

of breast cancer that was equivalent to that of a 60-year-old woman (≥ 1.66 percent). The subjects met the criterion by being at least 60 years old, by having a history of lobular carcinoma in situ, or by being at least 35 years old and having sufficient risk as determined by the Gail model.¹⁴ This model incorporates the ages at menarche and at the first live birth, the number of previous breast biopsies, the presence or absence of atypical hyperplasia, and the number of first-degree relatives with breast cancer.

Among 13,388 women followed for about four years, tamoxifen reduced the overall odds of invasive and noninvasive breast cancer by nearly 50 percent ($P < 0.001$) (Tables 2 and 3).¹³ The effect of tamoxifen was exerted exclusively against receptor-positive tumors. The reduction occurred among women in all age groups, those with a history of lobular carcinoma in situ (56 percent reduction), and those with atypical hyperplasia (86 percent reduction).

In contrast, two European trials did not find tamoxifen protective.^{16,17} The difference in the results may have been related to differences between the U.S. and European trials in the design of the studies and in the populations included (Table 3). The Italian trial¹⁷ had fewer participants than the U.S. trial. Forty-eight percent of the subjects had undergone bilateral oophorectomy, which reduced their risk of breast cancer. Furthermore, compliance in this trial was poor. The British trial¹⁶ involved a younger population with stronger family histories of cancer and, despite its small size, was appropriately powered. Proposed explanations for the lack of effect of tamoxifen in these trials include chance effects in a small sample¹⁹ or the presence of women who, because of family history, may have been at greater risk for tumors not influenced by tamoxifen.²⁰ Although genetic analyses in the British¹⁶ and U.S.¹³ trials are pending, the benefit of tamoxifen in patients with germ-line mutations remains somewhat uncertain.

No trial of tamoxifen has been designed to obtain definitive information on mortality. Since the participants in the NSABP trial were told their treatment assignments and then offered open-label tamoxifen¹³ and since the Italian trial had a high number of dropouts,¹⁷ initial information on the influence of tamoxifen on survival may come from the British trial and an ongoing International Breast Cancer Intervention Study evaluating tamoxifen in a projected 7000 women.²⁰ Neither the optimal duration of therapy nor the duration of benefit from tamoxifen is known. However, there is no evidence that more than five years of therapy results in further benefit.

Tamoxifen has activity against both clinical and sub-

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TABLE 1. POTENTIAL STRATEGIES FOR REDUCING THE RISK OF BREAST CANCER.

Chemoprevention
Tamoxifen
Raloxifene
Prophylactic surgery
Bilateral mastectomy
Bilateral oophorectomy
Lifestyle changes
Reduction in fat intake
Increase in exercise
Weight loss
Reduction in alcohol intake

TABLE 2. EFFECTS OF TAMOXIFEN AND RALOXIFENE ON THE RISK OF BREAST CANCER IN VARIOUS GROUPS OF PATIENTS.*

DRUG AND OUTCOME	DRUG	PLACEBO	RR (95% CI)
	no. of cancers/ 1000 woman-yr		
Tamoxifen (NSABP)†			
All invasive breast cancers	3.4	6.8	0.51 (0.39–0.66)
Receptor status			
Positive	1.6	5.0	0.31 (0.22–0.45)
Negative	1.5	1.2	1.22 (0.74–2.03)
Patient characteristics			
History of LCIS	5.7	13.0	0.44 (0.16–1.06)
History of atypical hyperplasia	1.4	10.1	0.14 (0.03–0.47)
No. of first-degree relatives with breast cancer			
0	3.0	6.4	0.46 (0.24–0.84)
1	3.0	6.0	0.51 (0.35–0.73)
2	4.8	8.7	0.55 (0.30–0.97)
≥3	7.0	13.7	0.51 (0.15–1.55)
Raloxifene (MORE)‡			
All invasive breast cancers	0.9	3.6	0.24 (0.13–0.44)
Receptor status			
Positive	0.3	2.7	0.10 (0.04–0.24)
Negative	0.5	0.5	0.88 (0.26–3.00)

*RR denotes relative risk, CI confidence interval, NSABP National Surgical Adjuvant Breast and Bowel Project, LCIS lobular carcinoma in situ, and MORE Multiple Outcomes of Raloxifene Evaluation.

†The tamoxifen results are based on 264 invasive breast cancers reported in the NSABP Tamoxifen Prevention Trial.¹³

‡The raloxifene results are based on 40 invasive breast cancers reported in the MORE trial.¹⁵ The MORE trial, primarily a study of osteoporosis, did not assess breast-cancer risk at entry.

clinical breast cancer in a wide range of clinical settings. Taken together with the strongly positive results of the appropriately powered NSABP Tamoxifen Prevention Trial, these data support the recent approval by the Food and Drug Administration (FDA) of tamoxifen for the reduction of breast-cancer risk in women at increased risk for this disease. At present there is insufficient evidence to determine whether tamoxifen provides overall benefit in terms of health or survival.²¹

Side Effects of Tamoxifen

Tamoxifen is generally well tolerated, with a well-defined toxicity profile based on many years of clinical use, but it can in rare instances cause life-threatening endometrial cancer and vascular events.^{7,13,22} Symptoms of estrogen deficiency (hot flashes, vaginal discharge, and, in some cases, sexual dissatisfaction) increase in about 5 to 20 percent of women given tamoxifen. These are the most frequent adverse effects of tamoxifen and are somewhat more common in premenopausal women.^{7,13,23} The incidence of vascular events is increased; such events occur in about 1 percent of women taking tamoxifen. Thromboembolic events are about three times as frequent and strokes are twice as frequent as in women not taking tamoxifen, with the absolute risk of both conditions increasing substantially with age.^{13,22}

Tamoxifen increases the risk of uterine disease. The drug increases the risk of endometrial cancer by a factor of three or four in postmenopausal women, but substantially less in premenopausal women.¹³ Previous use of estrogen and obesity both increase the risk of endometrial cancer associated with tamoxifen use.²⁴ The rate of death from endometrial cancer is increased by about 1 to 2 per 1000 among postmenopausal women who have a uterus and are treated with tamoxifen.⁹ Benign ovarian cysts have also been observed in women taking tamoxifen.²⁵ Women receiving tamoxifen should have a careful gynecologic history taken and should undergo annual pelvic examinations and evaluation for abnormal vaginal discharge or bleeding. Routine ultrasonography or endometrial biopsy is not recommended.²⁶

Tamoxifen maintains bone density in postmenopausal women.²⁷ In premenopausal women, however, tamoxifen may result in bone loss.²⁸ The NSABP Tamoxifen Prevention Trial, which enrolled mostly postmenopausal women, was the only prospective evaluation of the influence of tamoxifen on fracture. The study found a moderate reduction in the risk of fracture among women taking tamoxifen.¹³

The effect of tamoxifen on coronary heart disease remains controversial. Tamoxifen decreases the serum levels of total cholesterol by 13 percent and those of low-density lipoprotein cholesterol by 19 percent.²⁹ However, retrospective analyses of trials of tamoxifen as adjuvant therapy for breast cancer found only a small reduction in the incidence of cardiac events.²¹ According to the most recent EBCTCG overview of trials of adjuvant tamoxifen therapy,⁹ which included data on 1775 deaths, mortality from causes other than breast cancer was not influenced by tamoxifen. In the only randomized study that prospectively monitored cardiac events, tamoxifen had no effect on coronary heart disease.¹³ These results are similar to those of the Heart and Estrogen/Progestin Replacement Study (HERS).³⁰ This study found that despite the favorable changes in serum lipids, the incidence of

TABLE 3. RESULTS OF RANDOMIZED CHEMOPREVENTION TRIALS TO REDUCE THE RISK OF BREAST CANCER.*

DRUG AND TRIAL	CRITERIA FOR ELIGIBILITY AND BREAST-CANCER RISK	NO. OF WOMEN ENROLLED	NO. OF BREAST CANCERS†	DRUG	PLACEBO	RR
				no. of cancers/ 1000 woman-yr		
Tamoxifen NSABP	Increased risk according to Gail model No concurrent HRT	13,388	368	3.4	6.8	0.50‡
United Kingdom	Increased risk according to family history Concurrent HRT in 26%	2,471	70	4.7	5.0	0.94
Italy	Increased risk not required Oophorectomy in 48% Concurrent HRT allowed	5,408	41	2.1	2.3	0.92
Raloxifene MORE§	Increased risk not required Osteoporosis required No concurrent HRT	7,705	54	1.5	4.3	0.35‡
Fenretinide Fenretinide investigators	Stage I breast cancer or DCIS No concurrent HRT or tamoxifen End point of contralateral breast cancer	2,972	136	5.5	5.9	0.92

*Data on tamoxifen were from Fisher et al.,¹³ Powles et al.,¹⁶ and Veronesi et al.¹⁷ Data on raloxifene were from Cummings et al.¹⁵ Data on fenretinide were from Veronesi et al.¹⁸ RR denotes relative risk, NSABP National Surgical Adjuvant Breast and Bowel Project, HRT hormone-replacement therapy, MORE Multiple Outcomes of Raloxifene Evaluation, and DCIS ductal carcinoma in situ.

†Breast cancers include invasive and noninvasive cancers.

‡The value is significantly different from placebo ($P < 0.001$).

§Women were randomly assigned to raloxifene at one of two dose levels or to the placebo group.

new cardiac events in postmenopausal women with prior heart disease was not reduced by a hormonal intervention that increased vascular events. The potential interaction between vascular and cardiac events raises questions regarding the beneficial effect of any hormonal therapy on the risk of cardiac disease.

Ophthalmologic toxic effects have only rarely been associated with tamoxifen.³¹ However, a statistically significant but small increase in the risk of cataract has been reported (relative risk, 1.14).¹³

Tamoxifen does not increase depression or decrease mental function, as measured by screening questionnaires.^{13,23} However, because estrogen has a potential role in supporting cognition,³² and because neuropsychological testing has revealed cognitive impairment in women receiving chemotherapy combined with tamoxifen,³³ the long-term effects of tamoxifen on mental function will require assessment by sensitive methods.

Using information from a variety of sources, Gail and colleagues²² devised tables to estimate the net benefit–risk indexes of the use of tamoxifen to reduce the risk of breast cancer in different groups of

women. This method incorporates calculations of a woman's breast-cancer risk, age, presence or absence of a uterus, and race as major variables. This approach has met with some controversy, related largely to its reliance on the imputed effects of tamoxifen in various ethnic groups.³⁴ This concern was recently partially addressed by a report of the effects of tamoxifen in black women.³⁵ Use of these tables suggests that tamoxifen is most beneficial in younger women at higher risk and in women without a uterus. Also, the estimated benefit–risk index of tamoxifen is lower in blacks than in whites, because blacks have a higher underlying risk of vascular disease and a lower risk of osteoporosis (Table 4).²²

Raloxifene and Risk Reduction

Raloxifene, a selective estrogen-receptor modulator that acts as both an agonist and an antagonist to estrogen, has been approved by the FDA for the prevention and treatment of osteoporosis in postmenopausal women.^{36,37} In preclinical studies, raloxifene has both prevented new mammary cancers and inhibited the growth of existing mammary cancers.³⁸

TABLE 4. EXAMPLES OF PROJECTED NET BENEFIT–RISK INDEXES FOR TAMOXIFEN USE ACCORDING TO BREAST-CANCER RISK, AGE, RACE, AND WHETHER THE WOMAN HAS A UTERUS.

ESTIMATED 5-YR RISK OF BREAST CANCER (%)	AGE GROUP (YR)	RACE	UTERUS	NET BENEFIT–RISK INDEX*
6	60–69	White	No	+198
3	60–69	White	No	+31
3	60–69	White	Yes	–175
3	60–69	Black	Yes	–358
6	50–59	White	No	+269
3	50–59	White	No	+102
3	50–59	White	Yes	–18
3	50–59	Black	No	–78
6	40–49	White	Yes	+318
3	40–49	White	No	+151
3	40–49	White	Yes	+135
3	40–49	Black	Yes	+76

*The net benefit–risk index is based on the projected number of life-threatening events (invasive breast cancer, endometrial cancer, pulmonary embolus, stroke, and hip fracture), plus half the projected number of severe events (noninvasive breast cancer and deep-vein thrombosis) in 10,000 women receiving tamoxifen in each class.²²

However, the limited clinical experience³⁹ with raloxifene in clinical cancer management is insufficient to support its use for any breast-cancer treatment.

The effect of raloxifene on the risk of breast cancer has been monitored in several ongoing placebo-controlled trials directed at osteoporosis and other end points. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial randomly assigned 7705 postmenopausal women with existing osteoporosis (a marker of low breast-cancer risk⁴⁰) to receive 60 or 120 mg of raloxifene per day or placebo. After 40 months of follow-up, raloxifene was found to have reduced the annual odds of breast cancer by 65 percent (on the basis of 58 events) and reduced the risk of invasive breast cancer by 76 percent ($P < 0.001$).¹⁵ A partially overlapping meta-analysis of nine randomized trials of raloxifene (including the MORE trial), which involved 10,575 patients, found a somewhat smaller (54 percent) reduction in the risk of invasive and noninvasive breast cancer.⁴¹ Like tamoxifen, raloxifene influences only receptor-positive cancers (Table 2).

There is less evidence supporting the use of raloxifene to reduce the risk of breast cancer than there is supporting the use of tamoxifen (Table 3). The use of raloxifene for this indication remains investigational.²¹ The ongoing Study of Tamoxifen and Raloxifene (STAR) trial will evaluate whether raloxifene is effective in reducing the risk of breast cancer and will provide comparative information on the side effects of tamoxifen and raloxifene.

Side Effects of Raloxifene

Raloxifene is, in general, well tolerated at the dose of 60 mg per day approved for the prevention of os-

teoporosis.^{36,37} Because raloxifene was only recently approved, its side-effect profile is based on a relatively short period of use and its influence on other disease processes such as coronary heart disease has not yet been defined.⁴²

Raloxifene does not treat the symptoms of estrogen deficiency and causes a small increase in the frequency of hot flashes. Raloxifene increases the frequency of vascular events, including pulmonary embolism and deep-vein thrombosis, by a factor of about three.^{15,37} At present, the use of raloxifene is limited to postmenopausal women.

Raloxifene is anticipated to have little effect on the risk of endometrial cancer on the basis of preclinical observations, including its low estrogenic activity in the rat uterus.⁴² In clinical trials, raloxifene has not increased endometrial thickness in postmenopausal women,^{36,43} and no increase in the risk of endometrial cancer has been seen in early analyses of data from ongoing trials.¹⁵

Raloxifene decreases total cholesterol levels by 6 percent and low-density lipoprotein cholesterol levels by 12 percent but does not increase high-density lipoprotein cholesterol levels.⁴⁴ Trials are in progress to define the relations between raloxifene and clinical heart disease.

Fenretinide and Risk Reduction

The retinoid fenretinide, or *N*-(4-hydroxyphenyl)-retinamide, which was effective in preclinical prevention models, failed to reduce the risk of contralateral breast cancers in a randomized trial enrolling 2972 patients with early-stage breast cancer (Table 3).¹⁸ In a post hoc analysis, fenretinide reduced the rate of contralateral breast cancers in premenopausal women, but any use of this agent for breast-cancer risk reduction requires further study.

PROPHYLACTIC SURGERY

Bilateral Mastectomy

Prophylactic mastectomy has been long considered a potential approach to reducing the risk of breast cancer.^{45,46} In a recent retrospective cohort analysis of 639 women with an increased risk of breast cancer, bilateral mastectomy reduced the calculated odds of breast cancer and associated mortality by about 90 percent.⁴⁷ Recently, a similar reduction in risk was observed in women with *BRCA1* or *BRCA2* mutations.⁴⁸ Sources of bias that may have led to an overestimation of benefit have been noted,^{49,50} especially with respect to survival, since the potential influence of close surveillance and new detection strategies⁵¹ was not considered.

Although most women who have undergone prophylactic mastectomy do not regret having undergone the procedure, 5 to 20 percent report at least some dissatisfaction,^{52,53} often in relation to breast numbness and absence of nipple sensation. Total mas-

tectomy, with removal of the nipple and areola and reconstruction, leaves less residual breast tissue than subcutaneous mastectomy, which preserves the nipple. Because subcutaneous mastectomy does not maintain nipple sensation and skin-sparing total mastectomy with nipple reconstruction may have equivalent cosmetic results, total mastectomy is the recommended procedure.^{45,47}

Prophylactic mastectomy is a reasonable option only for women identified as being at very high risk for breast cancer who are willing to consider its long-term implications. An irreversible procedure not uncommonly associated with dissatisfaction on the part of patients requires extremely careful discussion of the risks and benefits.

Bilateral Oophorectomy

According to observational studies, bilateral oophorectomy performed before menopause reduces the odds of breast cancer by 22 to 50 percent.^{54,55} However, in the EBCTCG overview analysis of trials of adjuvant breast-cancer therapy, oophorectomy was not associated with a significant reduction in the risk of contralateral breast cancer.⁵⁶ In women identified from registry data bases as carriers of the *BRCA1* mutation, bilateral oophorectomy was associated with a nearly 50 percent reduction in the calculated risk of breast cancer.⁵⁷ As in at least one prior report,⁵⁵ hormone-replacement therapy did not eliminate the reduction in breast-cancer risk that was associated with oophorectomy.⁵⁷ Thus, in women with *BRCA1* or *BRCA2* mutations who are at increased risk for ovarian cancer, observational studies suggest that surgical oophorectomy may reduce the risk of ovarian cancer by about 50 percent as well.⁵⁸ Although further study is required, bilateral oophorectomy may prove to be an option for premenopausal women at high risk for breast cancer who have decided not to have children or not to have more children.

Future Approaches

The use of gonadotropin-releasing hormone agonists that reduce estradiol to postmenopausal levels could have effects similar to those of oophorectomy.^{54,55} Combination therapy with a gonadotropin-releasing hormone agonist and low-dose estrogen was well tolerated and reduced mammographic breast density⁵⁹ (a marker of breast-cancer risk⁶⁰). The effectiveness of tamoxifen combined with a gonadotropin-releasing hormone agonist as adjuvant therapy for breast cancer⁶¹ and as therapy for advanced breast cancer⁶² suggests that other combinations may be worthy as well. Also under evaluation as a method to reduce the risk of breast cancer are combination therapy with tamoxifen and fenretinide⁶³ and monotherapy with novel selective estrogen-receptor modulators (such as EM-652⁶⁴ and LY353381⁶⁵) and aromatase inhibitors.⁶⁶

LIFESTYLE AND RISK REDUCTION

Increased dietary fat intake,^{67,68} body weight,⁶⁹ and alcohol intake⁷⁰ and decreased exercise⁷¹ have been associated with increased breast-cancer risk in preclinical and observational studies. Although it is not without controversy,^{72,73} the current evidence on dietary fat and breast-cancer risk has been judged sufficient to support ongoing full-scale outcome studies targeting primary⁷⁴ or secondary^{75,76} breast-cancer prevention. The feasibility of maintaining such dietary change for several years has been established, and reduced estrogen levels in postmenopausal women^{77,78} and decreased density on mammographic scans⁷⁹ have been observed after reductions in fat intake. In the largest ongoing clinical trial of dietary change, conducted by the Women's Health Initiative, more than 47,000 postmenopausal women who were initially free of breast cancer have been randomly assigned to a control group or a dietary-modification group. The goals of dietary modification are to reduce fat intake and to increase the intake of fruits and vegetables. The major study end points include overall survival and the occurrence of breast cancer, and the results are anticipated in about five years.⁷⁴ There are no ongoing outcome studies of the effect of weight reduction or exercise on breast-cancer risk.

The association between changes in lifestyle and the risk of breast cancer currently rests on inferences from observational studies and preclinical evidence. However, it has been reasonably proposed that the threshold should be lower for the use of interventions that call for a return to the "evolutionary norm," such as reducing animal-fat and alcohol intake and exercising more, than for interventions involving drugs or surgery.⁸⁰

Phytoestrogens are plant-derived compounds with estrogen agonist and antagonist effects that have been linked to a low risk of breast cancer in some observational reports.⁸¹ Ongoing studies have yet to determine whether phytoestrogens influence the risk of breast cancer or are safe to use in women with diagnosed breast cancer.^{5,82}

ENVIRONMENTAL FACTORS

There is increasing public concern about and scientific interest in the potential contribution of environmental factors, such as exposure to organochlorines⁸³ and electromagnetic radiation,⁸⁴ to the risk of breast cancer. Whether such factors have an influence on breast cancer is currently unresolved because of limited and inconsistent evidence, but further studies are warranted. Detailed discussion of this important issue is beyond the scope of the current review.

CONCLUSIONS

There is controversy over the use of the term "prevention," as opposed to "risk reduction," since prevention implies complete protection from breast

cancer. Given current evidence, “risk reduction” is the most acceptable term to describe the goals of the available interventions.

A technology assessment by the American Society of Clinical Oncology recently reviewed the use of tamoxifen and raloxifene to reduce the risk of breast cancer.²¹ The report recommended that women at increased risk for breast cancer (defined as a risk of at least 1.7 percent over five years) “may be offered tamoxifen (20 mg/d) to reduce their risk” after an informed decision-making process, with careful consideration of risks and benefits.²¹ Because the overall benefits to health and survival have not been established, the decision to use tamoxifen for risk reduction depends on an individual woman’s perception of her breast-cancer risk and her reaction to this risk. On the basis of current information, the routine use of raloxifene should be reserved for its approved indication, the prevention or treatment of bone loss in postmenopausal women.²¹

The identification of appropriate candidates for tamoxifen therapy requires assessment of breast-cancer risk, estimation of the risks and benefits of tamoxifen, and informed decision making, with full participation by the patient.^{21,22,85} A recent comprehensive review outlines methods for the assessment of breast-cancer risk.⁸⁶ Risk–benefit indexes for general tamoxifen use for breast-cancer risk reduction can be estimated from published tables that incorporate breast-cancer risk, age, race, and the presence or absence of a uterus.²² This projection is then adjusted by considering individual risk factors for endometrial cancer, stroke, vascular events, and fractures such as obesity, smoking, and hypertension. Although there is hope for future improvement,⁸⁷ the inexact nature of the current process should be recognized,³⁴ and the information should be discussed in the context of a patient’s individual concerns and circumstances.⁸⁸ Efforts are under way to develop methods of conveying this complex medical and numerical information.^{88,89}

The use of tamoxifen in combination with raloxifene or other hormonal agents (such as estrogen), or the sequential use of such agents, has not been well studied and should be avoided in clinical practice.

Observational results suggest that prophylactic surgery, including bilateral mastectomy or bilateral oophorectomy, reduces breast-cancer risk, although there have been no prospective clinical trials of these procedures. Prophylactic surgery is a reasonable approach only in women at substantial risk for breast cancer who are willing to accept its irreversible consequences. Lifestyle change is a prudent approach to reducing the risk of breast cancer but is currently supported only by observational studies and preclinical evidence.

Risk reduction in women at greatly increased risk for breast cancer because of germ-line mutations remains a dilemma.⁸⁶ The use of tamoxifen in women

with *BRCA1* or *BRCA2* mutations is currently based on inference, since current studies have yet to identify a sufficient number of women with mutations to evaluate efficacy. Observational studies suggest that prophylactic mastectomy⁴⁶ and oophorectomy⁵⁷ are beneficial in women with *BRCA1* and *BRCA2* mutations. Although published decision analyses compare predicted outcomes of various interventions,^{90,91} their value is limited by the uncertainty surrounding the estimates of the magnitude of the reduction in risk associated with the interventions. Further studies in this important population are critically needed.

The era of risk reduction with respect to breast cancer has arrived. Although many questions remain, current evidence is sufficient to support the informed application of selected interventions in women at risk for this disease.

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