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Preventive Therapies for Women at Increased Risk for Breast Cancer

Executive Summary

Purpose

Prevention of breast cancer among women at increased risk for the disease has become a focus of research and is receiving considerable media and public attention. This report evaluates available data on the efficacy, safety, and quality-of-life outcomes of preventive mastectomy for breast cancer and summarizes findings of the American Society of Clinical Oncology (ASCO) in their assessment of two drugs – tamoxifen citrate (Nolvadex®) and raloxifene hydrochloride (Evista®). This assessment refers only to breast cancer in women. Although breast cancer does occur in men, data show that breast cancer occurs approximately 150 times more frequently in women.

Findings and Conclusions

Assessment of Risk

The following factors increase women's risk of breast cancer. Risk increases as the number of factors present increases.

- Increasing in age.
- History of the disease in one or more first- or second-degree relatives, particularly if the cancer occurred prior to menopause and/or occurred in both breasts.
- Results of genetic testing indicate the presence of a genetic mutation that increases susceptibility to breast cancer.
- Menarche prior to age 12 and/or menopause after age 50.
- Having no children or a first child after the age of 30.
- Personal history of a previous breast biopsy, lobular carcinoma in situ, or ductal carcinoma in situ.

Efficacy and Quality of Life

- The necessity and effectiveness of mastectomy and chemopreventive measures in women without a strong family history or genetic susceptibility are not clear. No treatment completely protects women against development of breast cancer and can only reduce the risk of disease. Breast cancers occur after preventive mastectomy and despite tamoxifen or raloxifene treatment.
- In one clinical trial, preventive mastectomy reduced the risk of breast cancer incidence and death by 90% in women at moderate-to-high risk for the disease

due to their strong family history. The surgery improved survival and quality of life in women who have specific genetic mutations that place them at increased risk for the disease. The surgery in women whose genetic status place them at average risk for breast cancer is less efficacious.
- It is not possible to predict which women with risk factors will develop breast cancer. Therefore, preventive mastectomy would not benefit, and could be detrimental to, women who would not have developed breast cancer.
- Findings from clinical trials have shown that chemopreventive agents can reduce breast cancer risk. However, all reductions, regardless of the drug being studied, have been in estrogen receptor (ER)-positive tumors; there has been no difference in the rate of ER-negative tumors.
- No evidence of impact on mortality has been found in any clinical trials of chemopreventive agents.

Ongoing Research

- In addition to continuing analysis of data from clinical trials on preventive mastectomy and chemopreventive agents, a head-to-head trial of tamoxifen and raloxifene is underway. The Prevention Study of Tamoxifen and Raloxifene (STAR) trial is a randomized double-blind study designed to determine whether raloxifene is more or less effective than tamoxifen in reducing the incidence of breast cancer in postmenopausal women and whether any toxicity is associated with either drug. The trial is also designed to evaluate the effect of the drugs on a number of other conditions, including carcinoma in situ, endometrial cancer, heart disease, and fractures of the hip, spine, and wrist; and to determine the drugs' effects on women's quality of life.
- Additional data are needed to determine the optimal roles of surgical and chemopreventive treatments for prevention of breast cancer in women at increased risk for the disease.
- Additional research is needed on methods for early detection of breast cancer, breast cancer risks, and clinical course of the disease in women with a strong family history, genetic susceptibility, or other risk factors. Data from these studies may assist in further refining patient selection criteria.

Recommendations

No therapy can prevent breast cancer with absolute certainty. Preventive mastectomy and drug therapies may reduce the risk of breast cancer in some carefully selected women at high risk for breast cancer. Therefore, the Health Technology Advisory Committee (HTAC) makes the following recommendations:

- Health care providers should continue to stress the importance of regular clinical breast examinations and mammography (appropriate to age and risk status) as well as breast self-examination to all women in their care.
- Prior to starting preventive therapy, individual women must consider the benefits and risks of treatment, including their risk for breast cancer and their susceptibility to potential side effects, in order to arrive at a decision
- Women should be informed about the efficacy of the treatments, their potential risks and effects on quality of life, uncertainties in breast cancer risk estimates, the limitations and implications of genetic testing, insurance issues, and costs of the procedures or drug regimens.

INTRODUCTION

Purpose

Prevention of breast cancer among women at increased risk for the disease has become a focus of research and is receiving considerable media and public attention. This report evaluates available data on the efficacy, safety, and quality-of-life outcomes of preventive mastectomy for breast cancer and summarizes findings of the American Society of Clinical Oncology (ASCO) in their assessment of two drugs – tamoxifen citrate (Nolvadex®) and raloxifene hydrochloride (Evista®). This assessment refers only to breast cancer in women. Although breast cancer does occur in men, data show breast cancer occurs approximately 150 times more frequently in women.[1]

Background

Breast cancer is the most common non-skin cancer in women in the United States and the second most common cause of cancer death in women. In 1996, an estimated 184,300 new cases of breast cancer were diagnosed, and 44,300 deaths due to breast cancer occurred among women in the United States. While breast cancer rates are significant, many women overestimate their risk for the disease. In a study of 145 women between the ages of 40 and 50 with no history of breast cancer, women overestimated their probability of dying of the disease within the next 10 years by more than 20 fold.[2] Another survey of 750 women attending a breast center and 112 women attending a primary care center found that approximately 80% of the women in both settings overestimated their personal lifetime risk by more than 50%. Women attending the breast center included both those who received routine screening and those who were being monitored or being treated for breast abnormalities or cancer.[3,4]

Breast Examinations and Mammography

Appropriate medical check-ups and breast examinations are important whether or not a woman may be at increased risk for breast cancer. However, those women identified at higher than average risk for breast cancer may benefit from more frequent mammograms, breast self-examination, and clinical breast examinations. While mammograms do not prevent the occurrence of cancer, they often detect tumors when they are small and more likely to be treated successfully. Among women between the ages of 50 and 69 at average risk, having a mammogram on a regular basis reduces the risk of dying from breast cancer by 30%. For women in their forties, regular mammography reduces the risk of death due to breast cancer by approximately 17%. Since not all breast cancers are detected by mammography, women should have regular breast examinations by a health care practitioner and conduct self-examinations on a routine basis.[5-8]

Risk Factors

Factors that increase a woman's risk for breast cancer include: age, early menarche or late menopause, having no children or having a first child after age 30, a history of benign breast disease or carcinoma in situ, and a history of breast cancer on either the maternal or paternal side of the family, particularly if the cancers occurred before the affected person(s) reached the age of 50.

Relative Risk and Attributable Risk

Two commonly used terms for describing risk are "relative risk" and "attributable

risk." Attributable risk refers to the proportion of all cases of a disease in the general population that can be attributed to a specific risk factor. Relative risk refers to a ratio comparing the incidence of a disease among individuals with a certain risk factor and the incidence of the disease among individuals without the risk factor.[9] While risk factor analysis cannot predict with certainty which women will and will not develop breast cancer, it can assist in determining whether an individual woman may benefit from preventive therapy or more frequent screening. While the presence of one or more risk factors indicates an increased likelihood that breast cancer may develop, absence of risk factors does not guarantee a woman will not develop cancer.

Age is the strongest breast cancer risk factor in the general population.[6] A woman who is under age 40 has a 1 in 217 chance of getting invasive breast cancer. A woman over 70 years of age has a 1 in 14 chance of getting the disease.[10] In Minnesota, nearly 60% of newly diagnosed cases of invasive breast cancer and 70.6% of all deaths due to breast cancer in 1997 were among women age 60 or older.[4]

Familial and Hereditary Breast Cancers

Hereditary breast cancers or a history of breast cancer in women's families also increase the risk for breast cancer. In hereditary breast cancer, susceptibility to the disease is passed from one generation to another through specific mutations in tumor suppressor or other genes. Several tumor suppressor genes have been identified, including *BRCA1*, *BRCA2*, and *P53*. In hereditary breast cancer, multiple members of families are affected throughout multiple generations. This type of cancer susceptibility is inherited as an autosomal dominant trait. An autosomal gene is one that is not associated with the sex chromosomes (x or y). This means genes are inherited by both men and women. The mutations associated with breast cancer are dominant, which means only one gene with the mutation needs to be inherited for the person to have a greater susceptibility to breast cancer.[11] Hereditary breast cancer accounts for 5% to 10% all of breast cancers.[12,13] Hereditary susceptibility to breast cancer is often suspected if a woman has had multiple relatives with breast cancer on either her mother's or father's side of the family, ovarian cancer has occurred in association with breast cancer, the cancer has been bilateral and/or occurred at a young age.[7,14]

In familial breast cancer, the disease occurs in one or more first- or second-degree relative(s) without evidence of autosomal-dominant gene transmission. The risk of developing breast cancer increases for a woman whose mother, sister, or daughter has had the disease. The risk is also increased for a woman who has an aunt or a first cousin with the disease, particularly if it was diagnosed before the age of 40. Current data indicates the increased risk of breast cancer due to familial patterns rarely exceeds 30%.[7,15]

Individual Breast Cancer Risk Assessment

Risk Models

Several strategies have been developed to assess an individual woman's risk for breast cancer. Risk models use mathematical calculations to assess risk based upon a variety of factors. Two such models are the Gail model and the Claus model.

The Gail model[16] is the model most commonly used by clinicians and breast cancer

researchers. The model was used to select participants in randomized trials discussed in this report. The Gail model is a statistical formula based upon data from 243,221 white women who were screened for breast cancer annually for 5 years. In this model, which predicts the risk of cancer until age 80, risk factors for breast cancer include the number of first-degree relatives with breast cancer, the number of previous breast biopsies, the presence of atypical hyperplasia, the age at menarche, and the age at which a woman had her first child. With the model, the relative risk of breast cancer over a specified period of time is based on age intervals from 0–79. Relative risk determined by multiplying calculated relative risk factors and relative risk associated with age. Table 1 lists relative risks for factors from the Gail Model. The Gail model provides useful information for risk assessment, with several limitations. It does not explore family history of the disease beyond first-degree relatives and does not incorporate genetic risk factors. Since the Gail model is based upon data from white women, the model may not be generalizable to women of color.[17,18]

The model developed by Claus et al. determines age-specific risk for breast cancer in women with at least one female relative with breast cancer. This model considers first- and second-degree relatives on the maternal and paternal sides of the family. This data set was based upon 4730 patients between the ages of 20 and 54 with histologically confirmed breast cancer and 4688 control subjects matched by geographic region and age.[19] The model is limited in that it applies only to those women with a known family history of breast cancer and does not estimate risk among women with male relatives who have had breast cancer. As with the Gail model, the Claus model is based on data from white women and may not be generalizable to women of color.

Table 1. Relative Risk Factors of Breast Cancer

Risk Factor	Number of First Degree Relatives with Breast Cancer	Associated Relative Risk
Age at Menarche ≥14 years 12-13 years < 12 years	N/A	nbsp; 1.000 1.099 1.207
Number of Previous Breast Biopsies ***Age < 50 years*** 0 1 ≥2 **≥50 years**		 1.000 1.698 2.882

0 1 ≥2	N/A	 1.000 1.273 1.620
Age at First Live Birth < 20 years	0 1 ≥ 2	1.000 2.607 6.798
20-24 years	0 1 ≥ 2	1.244 2.681 5.775
25-29 years or no children	0 1 ≥2	1.548 2.756 4.907
≥30 years	0 1 ≥ 2	1.927 2.834 4.169

Source: Gail et al.[16]

Genetic Counseling

Genetic counseling may provide useful information to women with a family history of breast cancer regarding their risk for developing the disease. However, women whose level of risk is clear through a routine family history review may not gain additional information from genetic counseling. A genetic counselor or physician will construct a pedigree showing the history of breast and other cancers on both the maternal and paternal sides of a woman's family. The pedigree is analyzed using statistical models to determine the likelihood that a familial pattern of cancer exists. Genetic counseling includes a careful review of the options available to patients with a pattern of cancer in their family. Patients considering genetic counseling should speak with their physician and check with their health plan for coverage of this benefit.

Genetic Testing

Blood tests are available to determine whether specific genetic mutations associated with increased susceptibility to breast cancer are present. A 1997 Health Technology

Advisory Committee (HTAC) evaluation of genetic testing for breast cancer found that although genetic testing for predisposition to breast cancer shows some promise, no conclusions can yet be drawn whether testing will lead to improvements in length or quality of life. There may be psychological benefits for women who test negative for a mutation known to be present in their families. However, negative test results are reassuring only in that they indicate patients do not carry identified genetic mutations that puts them at increased risk for breast cancer. They may carry an as yet unidentified mutation. Further, if negative results give women a false sense of security that leads them to have less frequent medical exams, they may be in greater danger of serious illness than if they had not been tested.[20]

For women who test positive for a mutation, the results may create concerns in addition to the knowledge that they have genetic mutations that increase their risk for breast cancer. Results that suggest a higher risk, but not if or when they will in fact develop breast cancer, may create anxiety in both patients and their families. Those found to carry a mutation may experience fear and guilt that the mutations might have been passed to their children. Relationships with family members may be affected because of these fears. In addition, there is a potential for discrimination if results of genetic tests are made known to the patients' employers or insurance carriers.[20]

Preventive Therapies: Selective Estrogen Receptor Modulators (SERMS)

Estrogens produced within the body and introduced from the environment play a role in development of breast cancer. Growth of breast cancer cells is stimulated by estrogen-dependent secretion of growth factors such as transforming growth factor (TGF)-alpha. Selective estrogen receptor modulators (SERMs) are agents that have both estrogen agonist and antagonist effects. They bind with high affinity to estrogen receptors simulating the effects of estrogen in some tissues but acting like anti-estrogens in other tissues. For example, a SERM may demonstrate anti-estrogen effects in the breast, but have estrogen-like effects on the endometrium, bone metabolism and serum cholesterol. That is, they may stimulate endometrial growth, prevent bone loss, and lower cholesterol levels. In women, the risks of both osteoporotic bone fractures and cardiovascular disease, like the risk for breast cancer, increase with age. Thus, a drug that exerts beneficial effects on the bone and lipids, and that inhibits the growth of abnormal cells in the breasts would be expected to improve the overall health and life expectancy of women.[18,31-33]

Tamoxifen citrate (Nolvadex®), the first clinically available SERM, has been used as adjuvant therapy for over 20 years to reduce the risk of recurrence in women with estrogen receptor (ER)-positive breast cancers and to prevent the occurrence of second primary cancers in the contralateral breast; it was approved by the U.S. Food and Drug Administration (FDA) in 1978 for these indications. The drug increases the production of breast cancer cell growth inhibitory factors, such as TGF-beta, and simultaneously reduces the production of breast cancer cell growth promoters, such as TGF-alpha.

Raloxifene hydrochloride (Evista®) also demonstrates anti-estrogenic effects and was investigated as a treatment for breast cancer in the early 1980s. Raloxifene was approved by the FDA on December 10, 1997 for the treatment of osteoporosis in postmenopausal women. In animal and human studies, raloxifene prevents bone loss,

reduces serum cholesterol, and inhibits the development of abnormal cells in the breast; however, unlike tamoxifen, it does not stimulate endometrial growth. Raloxifene is an antagonist of ER-positive mammary tumors and inhibits proliferation in an estrogen-dependent human mammary tumor cell line.[34,35]

Clinical Trial Results

To test the hypothesis that tamoxifen could prevent breast cancer, the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the Breast Cancer Prevention Trial (BCPT), also known as P-1, in 1992. This large, randomized, double-blind, placebo-controlled trial was halted and unblinded in March 1998 when significant differences in breast cancer rates were observed between subjects in the study and control arms of the trial. Data showed that tamoxifen reduced the relative risk of invasive and noninvasive breast cancers by nearly 50% in all age groups. Based on the results of this study, the FDA approved the drug on October 29, 1998 for use as a chemopreventive agent to reduce the incidence of breast cancer in women at high risk for developing the disease.[36]

Study results only showed significant difference between the control and study groups in the rate of ER-positive tumors. No evidence of a significant difference in the rates of ER-negative tumors was found. One prospective endpoint of the P-1 trial was to determine whether tamoxifen had any effect on coronary heart disease (CHD). No benefit in preventing CHD was found in the tamoxifen group.[18,37] Complications of tamoxifen use found in the study include endometrial cancer, stroke, deep vein thrombosis, and pulmonary embolism.[18,36] Among women age 50 or older, strokes occurred nearly twice as frequently in the tamoxifen group.[37]

In the P-1 study, women at increased risk of breast cancer were selected by the presence of one or more of the following factors:

- Being 60 years of age or older.
- Being 35-59 years old with a breast cancer risk of at least 1.66% according to the Gail model (see Table 2).
- Having a history of lobular carcinoma in situ.

Package labeling for tamoxifen includes examples of risk factors that constitute "high risk" for breast cancer. "High risk" is defined as women who are at least 35 years of age with a 5-year predicted risk of breast cancer $\geq$1.66 as calculated by the Gail model. Examples of combinations of factors predicting a 5-year risk $\geq$1.66% are provided in Table 2.

Although the P-1 trial was halted, analysis of data collected during the trial is continuing. At the May 1999 meeting of ASCO, results of a quality-of-life analysis of data from the P-1 trial were presented. Trial subjects were evaluated with four instruments to measure depression, sexual functioning, medical outcomes, and symptoms. No differences in depression or medical outcome were found between the women receiving tamoxifen and those receiving placebos. A greater proportion of women receiving tamoxifen reported having more symptoms, primarily vasomotor and gynecological symptoms, than the placebo group. A greater proportion of the tamoxifen group also reported problems in sexual functioning, although the problems did not appear to affect overall rates of sexual activity.[38]

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was designed to evaluate raloxifene as a treatment for osteoporosis. The trial enrolled 7704 postmenopausal women aged ≤80 years who had osteoporosis and no history of breast or endometrial cancer. However, data from the trial revealed that raloxifene may have a role in preventing breast cancer.

Data on breast cancer incidence from the MORE trial and from a safety database pooled from 9 separate randomized placebo-controlled trials of approximately 12,000 raloxifene-treated women were presented at the annual meeting of ASCO in May 1998. Data indicate that, during a median follow-up of 29 months, the incidence of newly diagnosed breast cancers in the treatment group was reduced by 74% compared with the placebo group; 11 breast cancers (21%) were diagnosed in the raloxifene group versus 21 (82%) in the placebo group. In this study, the risk of ER-positive tumors was reduced by 87%; however, the drug had no effect on the incidence of ER-negative tumors. In contrast to tamoxifen, raloxifene did not increase the incidence of endometrial cancers.[39] Based on this data, the FDA approved a package labeling change for raloxifene that allows the manufacturer to refer to studies showing that the drug is associated with a reduction in breast cancer risk, but women must also be informed that the effectiveness of the drug for this purpose has not been established.[40]

Table 2. Examples of Factors Constituting "High-Risk" for Breast Cancer

Age 35 or older and any of the following combination of factors: • one first-degree relative with a history of breast cancer, 2 or more benign biopsies, and a history of a breast biopsy showing atypical hyperplasia; or • at least 2 first-degree relatives with a history of breast cancer, and a personal history of at least 1 breast biopsy; or • lobular carcinoma in situ.
Age 40 or older and any of the following combination of factors: • one first-degree relative with a history of breast cancer, 2 or more benign biopsies, age at first live birth 25 or older and age at menarche 11 or younger; or • at least 2 first-degree relatives with a history of breast cancer, and age at first live birth 19 or younger; or • one first-degree relative with a history of breast cancer, and a personal history of a breast biopsy showing atypical hyperplasia.
Age 45 or older and any of the following combination of factors: • at least 2 first-degree relatives with a history of breast cancer and age at first live birth 24 years or younger; or • one first-degree relative with a history of breast cancer with a personal history of a benign breast biopsy, age at menarche 11 or less and age at first live birth 20 years or older.

Age 50 or older and any of the following combination of factors: • at least 2 first-degree relatives with a history of breast cancer; or • history of one breast biopsy showing atypical hyperplasia, and age at first live birth 30 years or older and age at menarche 11 or less; or • history of at least two breast biopsies with a history of atypical hyperplasia, and age at first live birth 30 years or older.
Age 55 or older and any of the following combination of factors: • one first-degree relative with a history of breast cancer with a personal history of a benign breast biopsy, and age at menarche 11 years or younger; or • history of at least 2 breast biopsies with a history of atypical hyperplasia, and age at first live birth 20 years or older.
Age 60 or older and: • 5 year predicted risk of breast cancer $ 1.66%, as calculated by the Gail model.

Source: Gail Model Risk Assessment Calculations[16,47]

The MORE trial will continue to assess long-term effects of raloxifene. Data was presented at the May 1999 annual meeting of ASCO that showed, at a median follow-up of 40 months, 22 (0.42%) cases of breast cancer had been confirmed in the raloxifene group and 32 (1.24%) in the placebo group, a 66% decrease in breast cancer cases in the raloxifene group compared with the placebo group. Relative risk for invasive ER-positive cancers was also reduced in the raloxifene group. There was no risk reduction for invasive ER-negative cancer between the two groups.[41]

In June 1999, ASCO published a technology assessment of tamoxifen and raloxifene.[37] Given that an ASCO work group representing a broad spectrum of scientists, physicians, and patients have completed this assessment, HTAC will not present an assessment of what is essentially identical data, but will provide a summary of ASCO's conclusions. The ASCO assessment included references to 102 reports found in a search of the literature with OncoView (which incorporates MEDLINE, Cancer Lit, and selected scientific Internet sites). Data from three randomized clinical trials addressing tamoxifen and two involving raloxifene were reviewed for the assessment, including the MORE and P-1 trials. The conclusions of the ASCO assessment are summarized in Table 3.

The STAR Trial

In addition to continued assessment of participants in the MORE trial and data analysis from the P-1 trial, a head-to-head trial of tamoxifen and raloxifene is underway. The Prevention Study of Tamoxifen and Raloxifene (STAR) trial will enroll 22,000 postmenopausal women who are at increased risk for breast cancer but have not had breast cancer or prophylactic mastectomy and have no clinical signs of cancer at time of enrollment.[42] The STAR trial, also known as P-2, will include women who participated in the placebo arm of the P-1 trial. This has raised controversy since some researchers believe that including women from the P-1 study will deter efforts to determine the long-term efficacy and safety of tamoxifen. If these

women are switched to tamoxifen in the P-2 trial, they will essentially be lost to follow-up.[43]

A randomized double blind study, the STAR trial is designed to:

- determine whether raloxifene is more or less effective than tamoxifen in reducing the incidence of breast cancer in postmenopausal women;
- determine the effect of tamoxifen and raloxifene regimens on women's quality of life;
- evaluate the effect of tamoxifen and raloxifene on a number of other conditions including carcinoma in situ, endometrial cancer, heart disease, and fractures of the hip, spine, and wrist; and
- evaluate any toxicity that may be associated with either of the two drugs.[42]

In one arm of the trial, subjects will receive oral tamoxifen plus placebo daily for 5 years. In the second arm, subjects will receive oral raloxifene plus placebo daily for 5 years. Subjects will be followed every 3 months for 5 years, then annually for 2 years, with a quality-of-life assessment included in the trial data. A total of 400 centers in the United States and Canada are taking part in the study. As of August 1999, twenty centers in Minnesota are participating in the study, including 14 centers in the greater Twin Cities area and one center each in Waconia, Litchfield, Duluth, St. Cloud, Willmar, and Rochester.

Table 3. Conclusions of the ASCO Assessment on Breast Cancer Risk Reduction Strategies: Tamoxifen and Raloxifene*

Tamoxifen For women with a defined 5-year projected risk of breast cancer of $ 1.66%, tamoxifen (at 20 mg/d for up to 5 years) may be offered to reduce their risk.
Consideration of tamoxifen use is appropriate if the primary goal of therapy is to lower the risk of breast cancer, rather than focus on other health-related issues.
There is currently insufficient evidence to determine whether tamoxifen provides overall health benefit or increases breast cancer-specific or overall survival.
In all circumstances, tamoxifen use should be discussed as part of an informed decision-making process with careful consideration of risks, benefits, and alternatives.
Raloxifene It is premature to recommend raloxifene use to lower the risk of developing breast cancer outside of a clinical trial setting.
On the basis of available information, use of raloxifene should currently be reserved for its approved indication to prevent bone loss in postmenopausal women.
Conclusions regarding raloxifene are limited to use in postmenopausal women. There are no current published data on raloxifene in premenopausal women.

Other Issues Conclusions are based on single-agent use of the drugs. At the present time, the effect of using tamoxifen or raloxifene with other medications (such as hormone replacement therapy) or using tamoxifen and raloxifene in combination or sequentially has not been adequately studied or has not been studied at all.
The continuing active support for placebo-controlled trials in women receiving preventive interventions highlights the current uncertainty concerning the absolute risk level at which to recommend a potential preventive therapy, especially when influence on net health benefit remains to be determined.
Breast cancer risk reduction is a rapidly evolving area. Indeed, current maturing data in planned studies may affect the conclusions of the (ASCO) Working Group in the short term. This technology assessment represents an ongoing process with existing plans to monitor and review data and to update recommendations in a timely matter.

** The conclusions presented in this table apply only to the use of tamoxifen and raloxifene in reduction of risk for breast cancer. They do not apply to use of these drugs for other indications, such as use of raloxifene in hormone replacement therapy.*

Source: Cheblowski et al.[37]

Preventive Therapies: Mastectomy

The surgical procedure for preventive mastectomy is either a total (also called simple) or subcutaneous mastectomy. In a simple mastectomy, virtually all breast tissue and an overlying layer of skin including the nipple and areola are removed. Total mastectomy has become the surgery of choice since it removes more tissue than subcutaneous mastectomy. In a subcutaneous mastectomy, the nipple and areola are preserved because some breast tissue must remain to promote revascularization of the areola and nipple. Approximately 75% to 95% of the total amount of breast tissue is removed by this procedure.[7,15,21] There are questions about the significance of leaving behind 5% to 10% of breast tissue in women who are at high risk for breast cancer. Due to a lack of follow-up data, the incidence of breast cancer following subcutaneous mastectomy is unknown.[14,15,17]

Neither subcutaneous nor total mastectomy can completely remove all breast tissue since it is widely distributed over the chest wall and axilla as well as in the abdomen, and the risk of breast cancer is not completely eliminated. Breast cancer has been reported to occur in residual mammary tissue or preserved tissue in the nipple or areola. In one study, breast cancer either developed in the residual breast tissue or as bone metastases in 1.1% of the patients.[5,7]

Many women choose to undergo breast reconstruction after mastectomy. In one type of reconstructive surgery, the shape of the breast is re-created by an implant placed under the skin and chest muscles. A breast can also be reconstructed by using skin, fat, and muscle from the patient's abdomen or back. The nipple and areola may also be reconstructed using skin from the upper inner thigh. Following the surgery, there may be limitations on arm movement and exercise. Possible complications of reconstructive surgery include infection, migration of the implant, contracture,

collection of fluid in the tissue, and bleeding. The extent to which health plans cover reconstructive surgery varies. Patients should check with their insurer prior to deciding on whether to have a preventive mastectomy.[7,22]

Study Limitations

The efficacy of preventive mastectomy has been difficult to evaluate due to limitations in methodology and study design.[5,7,21,23]

- There is lack of data from randomized controlled trials employing well-defined patient inclusion criteria. Existing studies employed various selection criteria, used different surgical techniques, and lacked adequate or specific follow-up data.
- Methodological limitations of early studies hampered efforts to estimate the cumulative risk of breast cancer after surgery.
- While reported reductions in the risk of subsequent breast cancer have been as high as 97%, the initial level of risk for the study subjects varied since the women did not all have a similar indication for surgery.
- Many of the studies were performed before genetic testing was available. Thus, the risk of post mastectomy breast cancer in women carrying specific mutations may be underestimated.
- Studies included heterogenous groups of patients with various conditions ranging from benign breast disease to atypical hyperplasia. Breast cancer rates after preventive mastectomy have been reported to range from 1% to 19%; however, the true rate of breast cancer after the surgery may be higher since these studies included women who were at average and indeterminate risk for the disease in addition to those at high risk. The percentage of women with an inherited susceptibility is not known.

Efficacy

The efficacy and quality of life associated with mastectomy are somewhat dependent upon the underlying reasons why the surgery is performed. An individual's decision to have preventive surgery is complex, and possible benefits, such as reducing the risk of developing breast cancer, increased life expectancy, and decreased anxiety, must be weighed against the risks of surgery and its potential effects on a woman's self-image, sexuality, and psychological well-being. In addition, since it is not possible to predict which women with *BRCA*mutations will develop breast cancer, the surgery would not benefit, and could be detrimental to, an unknown number of women who would not have developed breast cancer. This assessment discusses three scenarios under which mastectomy may be performed in an effort to prevent breast cancer: women whose genetic mutation status is unknown, women who are known to have genetic susceptibility, and women with lobular or ductal carcinoma in situ. This assessment does not address preventive mastectomy for women with abnormal breast histology or unilateral breast cancer as there are no large, well-designed clinical trials on the efficacy of this scenario.

Preventive Mastectomy in Women of Unknown Genetic Status

To evaluate the efficacy of preventive mastectomy in women of unknown genetic status who had a family history of breast cancer, Hartmann et al.[17] performed a retrospective study of the subsequent incidence of breast cancer and the risk of death in 639 women with a family history of breast cancer who underwent preventive mastectomy at the Mayo Clinic between 1960 to 1993. The women were divided into

two groups, based on their degree of breast cancer risk. (See Appendix I)

The expected numbers of breast cancers in the two risk groups were predicted by the Gail model for moderate-risk women. In high-risk women, expected numbers were based upon the incidence of breast cancer among a control group of 403 of their sisters who had not had preventive mastectomy. Findings of the study include:[17]

- At a median follow-up time of 14 years, 156 (38.7%) of the probands' sisters developed breast cancer, compared with 3 (1.4%) of the probands, a reduction of 94.3%.
- In the moderate-risk group, 4 women were diagnosed with breast cancer compared with 37.4 expected cases. The reduction in the risk of breast cancer was 89.5% ($P<0.001$) after preventive mastectomy.
- There were no deaths due to breast cancer in this group, and the predicted number of deaths was 10.4. Thus, the risk of death due to breast cancer was reduced by 100% (95% CI, 70% to 100%).

Hartmann et al.[17] attempted to correct for possible biases that could have resulted in the overestimation of the efficacy of preventive mastectomy by: including only data on control women whose breast cancer developed after their respective proband's surgery; and using Weinberg's method for adjusting disease rates within families selected since they had multiple cases of the disease being examined.

The efficacy of preventive mastectomy for reducing the risk of death due to breast cancer may have been overestimated since the estimates of death rates obtained from the SEER program pertain to women in the general population. Assuming that women at high risk for breast cancer undergo more frequent screening, breast cancers in women at usual risk may be diagnosed at later stages, and, therefore, they may have a higher risk of dying of the disease. Since the study began before the widespread adoption of *BRCA* gene mutation testing, the effects of this gene mutation on patient outcome could not be evaluated. Perhaps most significant to patients is the fact that preventive mastectomy is an unnecessary and potentially detrimental procedure in a women whose breast cancer risk has been overestimated. In the Hartmann et al. study, for example, 621 women underwent preventive mastectomy when they probably would have survived without the surgery. This finding raises serious questions about the impact that fear of breast cancer has on women, particularly those who perceive themselves to be at increased risk due to family history.[23]

Preventive Mastectomy in Women Known to Have Genetic Susceptibility to Breast Cancer

Two decision analyses[24,25] evaluated the outcome after preventive mastectomy and preventive oophorectomy in women with *BRCA1* and *BRCA2* mutations. Both studies used the Markov model. Markov model of prognosis assume that a patient is always in one of a finite number of discrete health states, called Markov states. For example, in these two studies, the states might be good health, breast cancer, ovarian cancer, and death. All events of interest are represented as transitions from one state to another. The use of Markov models potentially may permit the development of decision models that more faithfully represent clinical problems and can be useful when a decision problem involves a risk that is ongoing or continuous over time.[26]

In one of the decision analyses, Schrag et al.[24] compared the outcomes of preventive

mastectomy and preventive oophorectomy in women at increased risk with outcomes in women who had no preventive surgery. Due to the lack of well-designed studies on the efficacy of preventive mastectomy, the efficacy was estimated to be 85% based on consultations with experienced clinicians. The researchers constructed hypothetical cohorts of women, defined according to age and cancer risk, who were evaluated annually for the development of new breast and ovarian cancers, cancer progression, and death. Nine strategies that included both immediate surgery and surgery after a 10-year delay were considered. The researchers modeled a range of values for the risks associated with *BRCA1* and *BRCA2* mutations. Preventive mastectomy provided significant gains in life expectancy, depending upon the cumulative risk of breast cancer, particularly among younger women. In comparison, the gains in life expectancy associated with treatment of breast cancer are 0.9 and 1.4 years for patients who receive adjuvant chemotherapy for node-negative disease and node-positive disease, respectively.[24]

Birkmeyer and Welch[27] argued that Schrag et al.[24] overestimated the benefits of preventive surgery and genetic testing for the *BRCA1* and *BRCA2* gene mutations on life expectancy. The authors stated that: Schrag and colleagues ignored the effects of surgery on quality of life, including immediate effects related to postoperative recovery and long-term effects of surgery on body image; the timing of risks and benefits were not accounted for in the decision analysis model, so that patients who are risk-averse would place less value on years of life gained, which happens in the future, than on the immediate risks of morbidity and mortality related to surgery; and the gain in life expectancy would only apply to women who were already aware that they were gene mutation carriers so that the health care policy required to achieve this gain would have to include genetic testing. In order to detect the mutation in the few numbers in which it occurs, many women would have to be tested with resultant false-negative and false-positive diagnoses.[27]

In the second decision analysis, Grann et al.[25] evaluated the effects of preventive mastectomy and oophorectomy in women with *BRCA1* and *BRCA2* mutations. The women were followed for 50 years from age 30 to age 80. For each of four alternative health strategies, including surveillance, mastectomy alone, oophorectomy alone, and mastectomy and oophorectomy combined, the annual age-dependent probabilities that a woman would develop breast cancer, develop ovarian cancer, die from any cause, or remain well were determined.

For women who had preventive mastectomy at age 30 and were followed to age 80, the surgery, compared with surveillance alone, improved survival by 2.8 and 3.4 years for low- and high-risk women, respectively. The improvements in survival were slightly lower than those determined by Schrag et al.[24] (i.e., 2.9 and 5.3 years added to life expectancy). For women who had preventive mastectomy and oophorectomy, the surgeries improved survival by 3.3 to 6.0 years. Preventive oophorectomy improved survival by 0.4 years and 2.6 years in the low- and high-risk groups, respectively. Combined oophorectomy and mastectomy improved survival by 3.3 years and 6.0 years in the low- and high-risk groups, respectively. As in the study by Schrag and colleagues, the improvements in survival were dependent upon the estimated risk of developing breast (and/or ovarian) cancer.[25]

The slight differences found in the improvement in survival between the two decision analyses could be attributed to differences in assumptions made regarding the efficacy of the surgery and in the lengths of patient follow-up. However, in both

studies, the degree of improvement in survival following preventive mastectomy was highly dependent upon the level of breast cancer risk. The findings from these studies apply only to women who carry *BRCA* gene mutations and, as such, are not generalizable to other populations. Since the results of both studies were based on certain assumptions, their findings must be interpreted with caution as there is the possibility that the assumptions were not entirely correct, and that altering the assumptions may alter the findings.

Both decision analyses have inherent limitations. The studies are not controlled clinical trials but rather are theoretical models based upon a number of assumptions regarding the efficacy of the surgery, the biological similarity of the study subjects' breast cancers to cancers in women who do not carry *BRCA* gene mutations, the cumulative risk of breast cancer in mutation carriers, and the survivability of breast cancer. In addition, the models do not account for comorbid conditions that may affect life expectancy. Finally, the generalizability of the study results is unclear as they apply only to very specific conditions that may not exist in the clinical setting.

In the Grann et al.[25] analysis, only high-risk women derived measurable health benefits from preventive mastectomy and oophorectomy combined (1.9 QALYs) or oophorectomy (0.5 QALYs) compared with surveillance in analyses that adjusted for differences in individual preferences (age, sex, self-perceived health status, and occupation). Minimal or negative QALYs were observed in the low-risk women; quality-of-life adjustment markedly reduced the potential benefits of prophylaxis. The negative effects of adjustment for quality of life may have been due to the fact that the women in this model had surgery at age 30 and were estimated to live for up to 50 years longer with this lower utility for quality of life. Alternatively, the quality-of-life ratings, measured by community-based preferences, may have been excessively low and did not take into consideration the reduction in anxiety that women with a family history of breast cancer may experience after the surgery.[25]

If the assumptions made by Grann et al.[25] are accepted, preventive mastectomy confers survival benefits to women at high risk for breast cancer. This information may help individual women weigh the risks and disability of surgery against the benefits of longer survival after surgery. Factors that were not assessed but that may influence an individual's decision to have preventive surgery include cultural and religious beliefs, and prior experience with illness and death.

Lobular Carcinoma In Situ (LCIS) and Ductal Carcinoma In Situ (DCIS)

Women who have abnormal epithelial proliferative changes and cellular atypia demonstrated on breast biopsy are at increased risk for breast cancer. The presence of atypical hyperplasia or LCIS is associated with a 5-fold increased risk of breast cancer. Women with atypical hyperplasia of the breast who have a first-degree relative with breast cancer have a risk of breast cancer 11 times greater than women without these proliferative changes. Preventive mastectomy may be recommended for these women. The increased risk for breast cancer is lower (1.5 to 2 fold for women with moderate hyperplasia without atypia, or for papillomatosis with fibrovascular core).[7,15]

Preventive mastectomy may be recommended for women with LCIS since the risk of developing breast cancer, particularly ductal carcinoma, was estimated to be as high as 15%, 27%, and 35% at 10, 15, and 20 years, respectively, after diagnosis for women with histologically confirmed LCIS. A 4% incidence of ductal carcinoma has

also been reported in mastectomy specimens from patients operated on for LCIS. While preventive mastectomy was performed in the past for DCIS, based on survival data, lumpectomy with radiotherapy was found to be as effective as mastectomy and is now recommended for treating women with nonmulticentric DCIS in the absence of other breast cancer risk factors.[15]

Safety and Quality of Life

Like all surgeries, preventive mastectomy has risks and benefits that must be weighed for the individual patient. While it may remove some of the anxiety about developing breast cancer in the future, despite breast reconstruction, the procedure can be disfiguring, thereby affecting the woman's self-image, her femininity and sexuality, and her psychological well-being. Postoperative complications may include increased anxiety, mood impairment, tension, depression, anger, guilt, denial, and sexual problems.[5,7,24,28]

Hartmann and colleagues presented data regarding long-term satisfaction and psychological and social function among women with bilateral preventive mastectomy at the 1999 annual meeting of ASCO. In this study, questionnaires were sent to 609 women with a family history of breast cancer who received a bilateral preventive mastectomy at the Mayo Clinic between 1960 and 1993. Ninety-four percent responded. At a median follow-up of 14 years, 69% of the women were satisfied or very satisfied with their mastectomy, with 19% dissatisfied or very dissatisfied. The strongest positive change, reported by 74% of the responders, was a diminished level of anxiety about developing breast cancer. In contrast, 25% of responders noted decreased feelings of femininity. Stress was increased in 14% of responders.[29]

Among 370 women who were part of the National Preventive Mastectomy Registry and who underwent bilateral preventive mastectomy, 21 (5%) expressed regrets about the procedure within a median follow-up of 14.6 years (mean, 14.8 years; range, 0.2 to 5.1 years); 95% of the women expressed satisfaction with their surgery. Regrets were more frequent when a physician had initiated the discussion about the surgery compared with when the patient initiated the discussion (19 of 255, 7.5% versus 2 of 108, 1.9%; $P < 0.05$).[30] No deaths following preventive mastectomy were reported in the literature reviewed.

Costs and Cost-effectiveness

Screening Mammography

Charges for screening mammograms average $50 to $100. Most states have laws requiring insurance companies to pay for all or part of the charges. Effective January 1, 1998, Medicare pays for one annual screening mammogram for women who qualify for Medicare benefits.[6]

Preventive Mastectomy and Breast Reconstruction

Grann et al.[25] estimated the charges of preventive mastectomy, in 1995 dollars, based on Medicare payments for 1995 from the Health Care Financing Administration (HCFA) as a proxy for these charges. These figures were supplemented with data from data on Part B payments to physicians in Connecticut. The charges included those for surgical procedures (mastectomy, breast surgery with reconstruction, oophorectomy, gynecologic surgery, and treatment of metastatic cancer). Indirect

costs such as loss of wages or losses related to other medical conditions were excluded from this analysis. A summary of the analysis is provided in Table 4.

The analysis found that preventive mastectomy is cost-effective for years of life saved when compared with surveillance. The model was based on women who tested positive for *BRCA1* or *BRCA2* and used a base of 30 years of age to calculate the improved survival rate for those having a prophylactic mastectomy. Based on calculations with future costs and years of survival discounted at a rate of 3%, with a follow-up period of up to 50 years, preventive mastectomy resulted in a cost per year of life saved of $1271 for women with an 85% risk of developing breast cancer, of $336 for women with a 56% risk of developing breast cancer, and of $961 for women with a 40% risk of developing the disease, compared with surveillance. The cost per life-year varies according to the annual risk of death due to all causes, the decade of age in which the patient was diagnosed and the time from diagnosis. The cost per life-year estimates are therefore sensitive to mortality and morbidity associated costs for the three risk groups. In comparison, the incremental cost of bone marrow transplantation is $28,600 per year of life saved.[25]

Selective Estrogen Receptor Modulators

Currently, the average wholesale price (AWP) for a month's supply (30 tablets) for 20 mg of tamoxifen is approximately $101.80. If used for a 5-year period at the 1999 AWP, tamoxifen's 5-year cost would be an estimated $6100. The current AWP for a month's supply (30 tablets) for 60 mg of raloxifene is approximately $60.94. If used for a 5-year period at the 1999 AWP, raloxifene's 5-year cost would be an estimated $3700.[44] No cost-effectiveness analyses on tamoxifen or raloxifene for breast cancer prevention were found in searches of the medical literature.

Table 4. Charges for Health Strategies

HEALTH STRATEGY	PROCEDURE	BASE CASE[1]	HIGH COST[2]
Surveillance	Initial[3]	$ 1700	$ 1700
	Follow-up examination and tests per year	$ 677	$ 1353
Mastectomy	Initial[4]	$ 7726	$ 15,600
	Follow-up examination and tests per year	$ 607	$ 1232
Mastectomy and Oophorectomy	Initial[5]	$ 12,537	$ 21,800
	Follow-up examination and tests per year	$ 332	$ 732

1 Base case charges are derived from HCFA.

2 High cost is derived from fee-for-service and managed care.

3 Initial charges include genetic testing and counseling; mammogram and Pap smear every 12 months; gynecologic examination, ultrasound, and CA-125 testing every 6 months; and physical examination every 3 months.

4Initial charges include bilateral mastectomy with reconstruction; genetic testing and counseling; mammogram and Pap smear every 12 months; gynecologic examination, ultrasound, and CA-125 testing every 6 months; and physical examination every 3 months.

5Initial charges include bilateral mastectomy with reconstruction; oophorectomy with laparoscopy; genetic testing and counseling; mammogram and Pap smear every 12 months; gynecologic examination, ultrasound, and CA-125 testing every 6 months; and physical examination every 3 months.

Source: Grann et al.[25]

Statements of Professional Organizations

There is disagreement within the medical community about treatment protocols for women at increased risk for breast cancer. Some clinicians recommend preventive mastectomy, while others recommend close surveillance such as monthly breast self-examination with regular clinical breast examination and screening mammography. Some physicians are concerned that women who undergo preventive mastectomy will be lulled into a false sense of security since the surgery cannot guarantee that the patient will never develop the disease.[45] Professional organizations, including the NCI, National Human Genome Research Institute, and the Society of Surgical Oncology, have issued consensus statements on one or more aspects of breast cancer prevention for women at increased risk for the disease.

National Cancer Institute (NCI)

In a statement on breast cancer screening and prevention published in January 1999, the NCI stated that intervention to reduce the risk of cancer should be offered to individuals who test positive for a cancer susceptibility gene. These interventions include screening, preventive surgery, or chemoprevention. The NCI statement cautioned that the efficacy of such procedures are unknown for both patients carrying gene mutations and for individuals in the general population. Additional statements by the NCI regarding preventive therapy include the following:

- Preventive mastectomy does not completely eliminate the risk of breast cancer, and it is unknown to what extent it reduces the incidence and mortality due to breast cancer. It is also unclear if mammography reduces the risk of breast cancer in high-risk women under the age of 50 years.
- The NCI recommends that women who are 40 years of age or older undergo screening mammograms every 1 to 2 years and that women who are at increased risk should ask their physicians about when to begin screening and how often they should be screened.[6]
- While tamoxifen reduces breast cancer risk in women at increased risk, data are not yet available regarding the efficacy in women at high risk who carry specific gene mutations.[46]
- In a Physician Data Query (PDQ) statement on breast cancer prevention published in November 1998, the NCI stated that decisions to use tamoxifen as

a breast cancer chemopreventive agent must be individualized since in some women the risks of therapy outweigh the benefits due to increased risks of endometrial cancer and vascular events in women aged 50 years or older.[8]

National Human Genome Research Institute (NHGRI)
A task force convened by the Cancer Genetics Consortium (CGSC) and organized by the NHGRI (one of the National Institutes of Health) issued a Consensus Statement in 1997 regarding recommendations for follow-up care of women with an inherited predisposition to cancer.[5] The provisional recommendation, based on expert opinion only, states that the evidence is insufficient to recommend for or against preventive bilateral mastectomy for the purpose of reducing breast cancer risk. The NHGRI recommends that women be counseled about this option but should be warned that breast cancer has been documented to occur after the surgery, and that its efficacy in reducing the risk of disease is uncertain.

The recommendation was developed for individuals known to carry *BRCA*1 or *BRCA2* gene mutations as well as those whose mutation status is unknown but who are very likely to be mutations carriers, i.e., women from families in which a *BRCA1* or *BRCA2* gene mutation is known to be present or in which an autosomal dominant predisposition to early-onset breast or ovarian cancer has been identified. It does not apply to the majority of individuals with a family history of breast cancer who do not meet these criteria and whose cancer risks are estimated to be much lower than those for mutation carriers.[5]

For female carriers of *BRCA1* and *BRCA2* gene mutations, the task force recommended monthly breast self-examination beginning by age 18 to 21 years with training and education in the proper technique, annual or semiannual clinical breast examination by a health professional beginning at age 25 to 35 years, and annual mammography beginning at age 25 to 35 years. Individuals should be counseled that the risks and benefits of screening mammography before the age of 50 years have not been established and that the benefits for women aged 50 years and older are based on data from women at average risk for breast cancer. While the efficacy of screening mammography has not been specifically determined in women who carry gene mutations, due to their increased risks for the disease (20-fold over the general population), it is believed that regular screening would be beneficial.[5]

Society of Surgical Oncology (SSO)
Prior to the advent of testing for *BRCA* gene mutations, the SSO developed a position statement on selection criteria for patients for whom preventive mastectomy may be considered. Indications for patients with no prior history of breast cancer included:[7,15]

- Atypical ductal or lobular hyperplasia.
- Family history of a relative with premenopausal bilateral breast cancer.
- Dense, nodular breasts in association with atypical hyperplasia, and either of the aforementioned conditions.

Indications for women with unilateral breast cancer included:

- Diffuse microcalcifications, particularly when DCIS has been diagnosed in the ipsilateral breast.
- LCIS.

- Large, difficult-to-evaluate breasts in the presence of LCIS, or risk factors such as atypical hyperplasia, family history in a first-degree relative, or young age at diagnosis (< 40 years).

The SSO position on preventive mastectomy for women with a prior diagnosis of breast cancer does not take into account the issue of survival after the initial diagnosis of breast cancer. The risk of death due to metastasis of lymph node-positive and lymph node-negative breast cancer is greater than the risk of developing a second primary breast cancer.[7]

Assessment of Risk

The following factors increase women's risk of breast cancer. Risk increases as the number of factors present increases:

- Increasing in age.
- History of the disease in one or more first- or second-degree relatives, particularly if the cancer occurred prior to menopause, and/or occurred in both breasts.
- Results of genetic testing indicate the presence of a genetic mutation that increases susceptibility to breast cancer.
- Menarche prior to age 12 and/or menopause after age 50.
- Having no children or a first child after the age of 30.
- Personal history of a previous breast biopsy, lobular carcinoma in situ, or ductal carcinoma in situ.

Efficacy and Quality of Life

- The necessity and effectiveness of mastectomy and chemopreventive measures in women without a strong family history or genetic susceptibility are not clear. No treatment completely protects women against development of breast cancer and can only reduce the risk of disease. Breast cancers occur after preventive mastectomy, and despite tamoxifen or raloxifene treatment.
- In one clinical trial, preventive mastectomy reduced the risk of breast cancer incidence and death by 90% in women at moderate-to-high risk for the disease due to their strong family history. The surgery improved survival and quality of life in women who have specific genetic mutations that place them at increased risk for the disease. The surgery in women whose genetic status place them at average risk for breast cancer is less efficacious.
- It is not possible to predict which women with risk factors will develop breast cancer. Therefore, preventive mastectomy would not benefit, and could be detrimental to, women who would not have developed breast cancer.
- Findings from clinical trials have shown that chemopreventive agents can reduce breast cancer risk. However, all reductions, regardless of the drug being studied, have been in estrogen receptor (ER)-positive tumors; there has been no difference in the rate of ER-negative tumors.
- No evidence of impact on mortality has been found in any clinical trials of chemopreventive agents.

Ongoing Research

- In addition to continuing analysis of data from clinical trials on preventive mastectomy and chemopreventive agents, a head-to-head trial of tamoxifen and raloxifene is underway. The Prevention Study of Tamoxifen and Raloxifene

(STAR) trial is a randomized double-blind study designed to determine whether raloxifene is more or less effective than tamoxifen in reducing the incidence ofbreast cancer in postmenopausal women and whether any toxicity is associated with either drug. The trial is also designed to evaluate the effect of the drugs on a number of other conditions, including carcinoma in situ, endometrial cancer, heart disease, and fractures of the hip, spine, and wrist; and to determine the drugs' effects on women's quality of life.
- Additional data are needed to determine the optimal roles of surgical and chemopreventive treatments for prevention of breast cancer in women at increased risk for the disease.
- Additional research is needed on methods for early detection of breast cancer, breast cancer risks, and clinical course of the disease in women with a strong family history, genetic susceptibility, or other risk factors. Data from these studies may assist in further refining patient selection criteria.

Recommendations

No therapy can prevent breast cancer with absolute certainty. Preventive mastectomy and drug therapies may reduce the risk of breast cancer in some carefully selected women at high risk for breast cancer. Therefore, the Health Technology Advisory Committee (HTAC) makes the following recommendations:

- Health care providers should continue to stress the importance of regular clinical breast examinations and mammography (appropriate to age and risk status) as well as breast self-examination to all women in their care.
- Prior to starting preventive therapy, individual women must consider the benefits and risks of treatment, including their risk for breast cancer and their susceptibility to potential side effects, in order to arrive at a decision.
- Women should be informed about the efficacy of the treatments, their potential risks and effects on quality of life, uncertainties in breast cancer risk estimates, the limitations and implications of genetic testing, insurance issues, and costs of the procedures or drug regimens.

Appendix I: Breast Cancer Risk Factor Groups from Hartmann et al study[17]

The high-risk group

The high-risk group consisted of 214 women, whose family history included: one or more relatives with breast cancer, and a family history of ovarian cancer, bilateral breast cancer, or breast cancer in males. High-risk women also met at least one of the following criteria:

- Two or more first-degree relatives with breast cancer.
- One first-degree relative and two or more second-degree or third-degree relatives with breast cancer.
- One first-degree relative with breast cancer before the age of 45 years \ and one other relative with breast cancer.
- One first-degree relative with breast cancer and one or more relatives with ovarian cancer.
- Two second-degree or third-degree relatives with breast cancer and one or more with ovarian cancer.
- One second-degree or third-degree relative with breast cancer and two or more

with ovarian cancer.
- Three or more second-degree or third-degree relatives with breast cancer.
- One first-degree relative with bilateral breast cancer.

The moderate-risk group
The moderate-risk group consisted of 425 women who did not meet the high-risk criteria, but 268 had at least one affected first-degree relative, aunts, cousins, or both with breast cancer, or family histories of breast cancer affecting fewer second-degree or third-degree relatives.[17]

Appendix II: National Cancer Institute (NCI): Guidelines for Preventive Mastectomy

In statements published in 1997 and 1999, The National Cancer Institute (NCI) stated that:

Preventive mastectomy may be considered for the following conditions:[45,46]

- Women who have had one breast removed due to cancer to avoid the development of cancer in the contralateral breast.
- Members of families with hereditary breast cancer syndromes, including breast cancer syndromes and breast-ovarian cancer syndromes who test positive for *BRCA1* and/or *BRCA2* gene mutations.
- Strong family history of breast cancer, especially if several close relatives developed the disease before age 50.
- Prior treatment for LCIS, a condition that increases the risk of cancer in the same breast or contralateral breast.
- Carefully selected women with breast calcifications or very dense breast tissue that makes diagnosing breast abnormalities difficult.

Appendix III: Public Comment

The following statement was submitted to HTAC during the public comment period on this assessment. The workgroup and full Committee review each statement and incorporate into the report as the Committee deemed appropriate.

From: "jane korn" To: brenda.holden@health.state.mn.us Copies to: jane.korn@health.state.mn.us Subject: HTAC Report Comments Date sent: Tue, 31 Aug 1999 14:39:05 PDT

I finished reviewing the HTAC document on "Preventive Therapies for Women at Increased Risk for Breast Cancer" and wanted to get you my comments in a timely way. I have been mostly out of the office this month on vacation.

Let me first compliment the exhaustive and informative review that has been put together. It really is a useful summary of the literature to date. I do, however, have a few comments.

1. In noticed in the Executive Summary, Assessment of Risk Section, that you list

(on line 15, page 1) that being age 60 or older increases a woman's risk of breast cancer. Actually, while this was the age used in the Gail model to enroll women in the Tamoxifen trial, it is a little misleading the way it is stated here and it does not agree with the information in the RISK FACTOR section on page 4. I would suggest editing that to say "increasing age" rather than chose a specific age for the summary statement.

2. In the Executive Summary, Recommendations Section, line 28, I would change the wording "regular medical examinations" to regular clinical breast examinations", otherwise the need for CBE is completely lost.
3. On page 4, under Relative and Attributable Risk, while this is good information, I was bothered by the fact that in the paragraph beginning on Line 18, women in their 40's 70+ and 60 are mentioned, yet information pertaining to women in their 50's is absent. To aid primary care physicians, you might consider adding decade-specific risk information for women in the 5th, 6th, 7th and 8th decade for example, and frame it in terms of "Risk over the next x years". Many people use the cumulative risk factor data as well. ACS has a nice compilation of that information and I believe it would be useful for primary care physicians to have that information when they speak with women.
4. On page 7, under Genetic Counseling, I would mention the fact that genetic counselors verify cancer diagnoses in families. To my understanding, this is a very important part of what they do (and time consuming as well) and it is notably lacking in the summary.
5. The PREVENTIVE THERAPIES: MASTECTOMY section is a very detailed literature review and I thought at times a bit too detailed. The Section "Study Limitations" on page 8 seems misplaced at the beginning, or else the title seems wrong. It would appear that the information in this relates to efficacy, which is the following section.
6. As a general comment, I would have preferred to see the information on Tamoxifen and Raloxifene first, since it pertains to more women than Preventive Mastectomy.
7. In the title for Table 2,page 16, I would elaborate more on the origin of this information and what is being used for, i.e. to determine women who might benefit from the use of Tamoxifen.
8. On page 17, lines 32 and 33, I was confused when you state that one arm was tamoxifen plus placebo (and raloxifene plus placebo). Isn't it really tamoxifen versus placebo?
9. In the COSTS AND COST EFFECTIVENESS section on page 19, I was struck by the lack of any statement about the cost effectiveness of mammography (since some does exist) or any statement about the presence or lack of data about cost effectiveness of mammography in women at elevated risk.
10. In Appendix I, it looked like a heading was missing somewhere for the Section beginning on line 21, since it currently is "under" Patient Selection Criteria for the Hartmann study.

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