

Selective Estrogens and Breast Tissue

Based on a presentation by Ronald L. Young, MD



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Presentation Summary

Because of the possible link between postmenopausal estrogen replacement and breast cancer risk, there is mounting interest in finding preventive strategies that would provide the skeletal and cardiovascular benefits of estrogen without its deleterious effects on the breast and uterus. Certain selective estrogen receptor modulators (SERMs) may provide such a strategy. Tamoxifen, toremifene, and raloxifene are three clinically available SERMs that have been studied for their effects on breast tissue.

Tamoxifen has been used extensively for breast cancer treatment and recently was approved for breast cancer prevention in women at high risk for the disease. In the Breast Cancer Prevention Trial, tamoxifen reduced the risk of invasive and noninvasive breast cancers by approximately 50% in healthy women at high risk for breast cancer. However, not all studies confirm these findings, perhaps because of differences in study design and population. One concern about the long-term use of tamoxifen is its estrogenic effect

on the uterus. Toremifene, approved for treatment of metastatic breast cancer in postmenopausal women who have tumors that are either estrogen receptor (ER) positive or of unknown receptor status, is a closely related chemical analog of tamoxifen. Raloxifene is currently approved in the United States for the prevention of postmenopausal osteoporosis. In pooled safety data from placebo-controlled osteoporosis studies, raloxifene reduced breast cancer risk by more than 50%; long-term observation continues. The first direct comparison of tamoxifen and raloxifene, the Study of Tamoxifen and Raloxifene (STAR), is scheduled to begin this year.

The results from early breast cancer prevention trials are promising, suggesting that both tamoxifen and raloxifene are effective in reducing breast cancer risk. However, their long-term preventive effects are unknown. If the benefits of these agents outweigh their risks, the use of certain SERMs could substantially reduce the incidence of breast cancer, osteoporosis, and cardiovascular disease.

Breast cancer is a major health concern among American women. According to a 1995 Gallup survey, 40% of women believed that breast cancer was the leading

cause of death in women.¹ In reality, women in the United States have a greater chance of dying of heart disease. One in 2 women will die of heart disease,² and 1 in 28 will die of

breast cancer.³ However, breast cancer was the second major cause of cancer mortality, accounting for 43,900 deaths and 17% of all cancer deaths among women in 1997.^{4,5} Only lung cancer exceeded breast cancer in estimated mortality, accounting for 25% of all cancer deaths in American women.⁵

Breast cancer is also associated with substantial morbidity. Invasive breast cancer is estimated to develop in 1 of 8 women in the United States, resulting in a 12.6% lifetime risk for developing breast cancer.³ In 1997, the breast was estimated to be the leading site of new cancer cases for US women, accounting for an estimated 30% of newly diagnosed cancers and 180,200 new cancer cases.⁵

Risk Factors for Breast Cancer

Widely accepted breast cancer risk factors include family history⁶ and age (Figure 1).⁷ Proliferative breast disease also increases risk.^{8,9} In addition, endocrine history, including early age at menarche^{10,11} and late age (55 or older) at natural menopause,¹² may also play a role in breast cancer. Inconsistent data have been reported regarding whether parity or having the first live birth at age 30 or later puts a woman at greater risk for breast cancer.^{11,13,14} Other possible risk factors include adult weight gain, alcohol use, and sedentary lifestyle.^{10,15-19} In addition, higher bone mineral density measurements in older women have been associated with increased breast cancer risk.²⁰

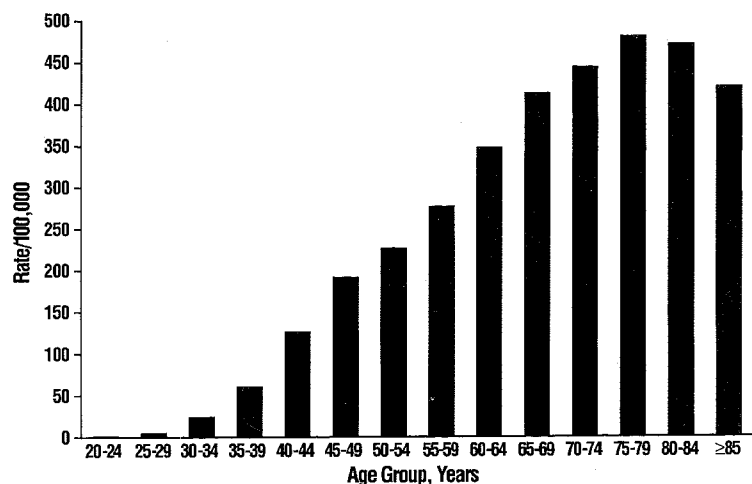
Many of these risk factors form the basis of the Gail model,²¹ which has been used to calculate predicted breast cancer risk when enrolling patients in studies, including the Breast Cancer Prevention Trial (P-1) initiated by the National Surgical Adjuvant Breast and Bowel Project.²² However, a substantial proportion of breast cancer cases cannot be explained by risk factors.²³

Breast Cancer Risk and Estrogen

The potential role of estrogen replacement therapy (ERT) or estrogen plus progestin (hormone replacement therapy [HRT]) as a risk factor for breast cancer is a topic of great interest and controversy. The long-term use of HRT is a relatively recent development prompted by the finding that unopposed estrogen increases the risk of endometrial cancer.²⁴ HRT is now considered the standard therapy for women with intact uteri who take estrogen. Because the number of women using HRT has only recently increased, the epidemiologic data are insufficient to assess the impact of long-term progestin use on breast cancer risk.

The relationship between breast cancer risk and use of estrogen (including ERT and HRT) was investigated by the Collaborative Group on Hormonal Factors in Breast Cancer, which reanalyzed the results from 51

Figure 1. Breast Cancer Incidence Among US Women by Age—1986 to 1990*



*Rates are per 100,000 and age-adjusted to the 1970 US standard population. Source: Links between hormone replacement therapy and neoplasia by B. S. Hulka in *Fertil Steril* 1994;62[suppl 2]:170S. Copyright 1994. Elsevier Science

studies including more than 160,000 women in 21 countries. This composite reanalysis represented approximately 90% of the worldwide epidemiologic evidence on estrogen use and breast cancer.²⁵ In this analysis, the annual risk of breast cancer increased 2.8% with each year of delayed menopause among women who never used estrogen. Among women who used estrogen for less than 5 years before breast cancer diagnosis, risk increased 2.3% with each year of estrogen use. After 5 or more years of estrogen use, the risk for breast cancer increased 35%. When estrogen therapy was stopped, it took at least 5 years for the risk level to return to that of women who never used estrogen.

A meta-analysis that reviewed epidemiologic studies as well as reports on cell proliferation and endogenous hormone levels also supports a causal relationship between use of estrogen (including ERT and HRT) and breast cancer incidence in postmenopausal women.²⁴ The analysis found growing evidence that higher blood levels of estrogens increase breast cancer risk, with up to a fourfold increase in risk for women who had the highest compared with those who had the lowest estradiol levels. It also found that the annual increase in breast cancer risk with estrogen use is comparable to that associated with a 1-year delay in menopause.

The potential for developing breast cancer is an overwhelming issue for many postmenopausal women, and there is evidence that breast cancer may be an estrogen-related disease. Thus, patients and clinicians are looking for preventive strategies that will help provide postmenopausal women with long-term protection against breast cancer, bone loss, and heart disease without estrogen's negative effects on the breast and uterus. Selective estrogen receptor modulators (SERMs) are newer agents that are estrogenic in some tissues, such as bone and lipid pathways, and

antiestrogenic in other tissues, such as the breast.²⁶ Tamoxifen, toremifene, and raloxifene are three SERMs that appear to act as estrogen antagonists in breast tissue and thus may provide some of the answers sought by women and care providers regarding long-term therapy options after menopause.

Effects of SERMs on Breast Tissue

Tamoxifen. Tamoxifen, one of the first clinically available compounds with a SERM profile, has been used worldwide for more than 20 years for the treatment of advanced breast cancer in postmenopausal women. Tamoxifen has repeatedly been shown to prolong the overall survival of breast cancer patients.²⁷

Tamoxifen (20 to 40 mg/day) is approved for treatment of metastatic breast cancer in men and women and for adjuvant therapy for axillary node-negative or node-positive breast cancer in postmenopausal women. The standard duration of tamoxifen therapy for breast cancer treatment is 5 years, as recommended by the National Cancer Institute.²⁸ In 1998, tamoxifen (20 mg/day) was also approved for the prevention of breast cancer in healthy women at high risk for the disease.²⁹ Currently, there are no guidelines about duration of tamoxifen use for breast cancer prevention. However, the manufacturer recommends a 5-year course of tamoxifen therapy for breast cancer prevention.

Tamoxifen has been used as a treatment for breast cancer over the past 2 decades in worldwide randomized trials.³⁰ A meta-analysis of trials involving 30,000 women who received adjuvant tamoxifen therapy for a median of 2 years found that tamoxifen reduced the annual rates of breast cancer recurrence and death by 25% and 17%, respectively. Tamoxifen also reduced the risk of developing contralateral breast cancer by 39%. The benefits of tamoxifen

were more pronounced in women age 50 years or older; but the population of women under age 50 was smaller, and the effects of tamoxifen were less clear. The reduction in breast cancer recurrence chiefly occurred during the first 4 years of tamoxifen therapy; these gains were neither increased nor decreased during the next 5 years. However, the reduction in mortality was significant both before and after 4 years, providing a cumulative difference in survival that was larger at 10 years than at 5 years.

Tamoxifen's effect in reducing the incidence of new contralateral primary tumors was also observed in a randomized study of 1846 postmenopausal breast cancer patients who received either adjuvant tamoxifen therapy for 2 or 5 years after surgery or no adjuvant endocrine therapy.³¹ A significant reduction of contralateral breast cancer was seen in the tamoxifen group compared with the control group after a median follow-up of 7 years (range, 3 to 13 years) ($P = 0.03$). At 10 years, the cumulative incidence of contralateral breast cancer was 5% and 8% for the tamoxifen and control groups, respectively. Tamoxifen therapy was most beneficial during the first 1 to 2 years, although a continued risk reduction was seen during the entire follow-up period.

The efficacy of tamoxifen in breast cancer prevention was evaluated in the P-1 trial initiated by the National Surgical Adjuvant Breast and Bowel Project.²² This was a double-blind, randomized, placebo-controlled trial designed to determine whether 5 years of tamoxifen therapy (20 mg/day) would reduce the incidence of invasive breast cancer in women at high risk for the disease.

The study involved 13,388 women at 131 centers. Women were considered at high risk for breast cancer based on Gail's probability algorithm, which includes age, family history of breast cancer, nulliparity or age at

first live birth, multiple breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche.²¹ Eligible women were 60 years old or older, were 35 to 59 years old with a 5-year predicted breast cancer risk of at least 1.66%, or had a history of lobular carcinoma in situ. Nearly 30% of

The P-1 trial results are the first randomized, clinical trial data to support the hypothesis that breast cancer can be prevented in an at-risk female population.

women were 60 years of age or older, and approximately 76% had first-degree relatives with breast cancer. The women were assigned to receive either tamoxifen ($n = 6681$) or placebo ($n = 6707$) for 5 years. The mean time in the study for participants who were included in the analysis was 47.7 months, and the median follow-up was 54.6 months. Because the findings provided strong evidence of a reduction in breast cancer risk with tamoxifen therapy, the trial was stopped prematurely and the results were released.

The P-1 trial results are the first randomized, clinical trial data to support the hypothesis that breast cancer can be prevented in an at-risk female population. Tamoxifen reduced the risk of invasive and noninvasive breast cancer by 49% and 50%, respectively. The annual rate of estrogen receptor (ER)-positive tumors was reduced by 69% with tamoxifen, but there was no significant reduction in the occurrence of ER-negative tumors.

Other data from the trial showed that tamoxifen was effective in preventing invasive breast cancers in all risk category subgroups (age, history

of lobular carcinoma in situ, history of atypical hyperplasia, 5-year predicted cancer risk, and family history). The reduction in the incidence of invasive breast cancer ranged from 44% among women 49 years or younger at the time of randomization to 55% among those 60 years or older at the time of randomization (Figure 2).

One ongoing concern about the long-term use of tamoxifen is its estrogenic effect on the uterus, which was reflected in the results of this trial. The risk for developing invasive endometrial cancer was 2.53 times greater for tamoxifen-treated women than for those receiving placebo, with the increased risk occurring predominantly in women who were 50 years old or older. Annual rates of endometrial cancer per 1000 patients were 2.30 and 0.91 for the tamoxifen and placebo groups, respectively.

Not all studies confirm that tamoxifen significantly reduces breast cancer incidence. The effects of tamox-

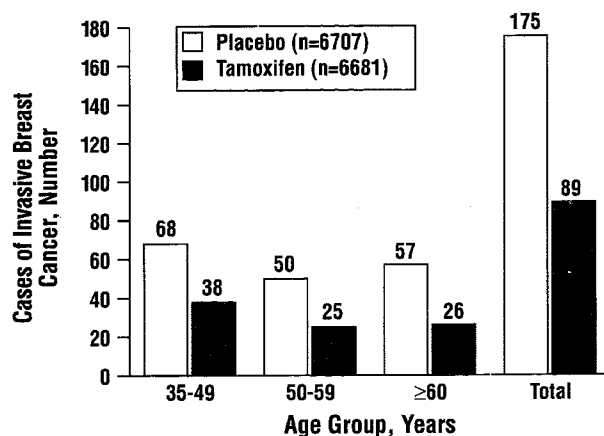
ifen (20 mg/day) versus placebo on breast cancer incidence did not differ significantly in a British trial³² of 2471 women ages 30 to 70 years or in an Italian trial³³ of 5048 women ages 35 to 70 years. However, the results of these randomized, double-blind studies may be difficult to compare because of differences in design and study population (Table). Unlike the P-1 trial, the British and Italian studies permitted HRT use. In the British trial, an increased risk of breast cancer was seen in women who were receiving HRT when they entered the study compared with women who were not, while participants who started HRT during the trial had a reduced risk of breast cancer.³² Breast cancer incidence also was reduced among tamoxifen-treated women who used HRT during the Italian trial. Breast cancer occurred in 8 of 390 women in the placebo group who used HRT and in 1 of 362 women in the tamoxifen group who also used HRT.³³

Additional information regarding the use of tamoxifen in the prevention of breast cancer is still needed. Because of the short follow-up of the P-1 trial, it is unclear whether the preventive effects of tamoxifen will be sustained in the long term. The overall risk-benefit profile of tamoxifen as a preventive agent is also unclear.

Toremifene. Toremifene is an analog of tamoxifen that differs from it chemically by one chlorine atom.³⁴ The recommended dosage is 60 mg/day. It is approved for first-line treatment of metastatic breast cancer in postmenopausal women who have tumors that are either ER positive or of unknown receptor status.³⁵ Toremifene is not yet indicated for adjuvant use because long-term data are not available.

Clinical experience with toremifene includes a 3-year, international Phase III trial involving 648 postmenopausal women with metastatic breast cancer (receptor status ER positive or

Figure 2. Cases of Invasive Breast Cancer in the Breast Cancer Prevention Trial (P-1)



Source: See reference 22.

unknown).³⁶ The patients were randomized to receive toremifene (60 or 200 mg/day) or tamoxifen (20 mg/day). There were no significant differences in response rates to toremifene and tamoxifen. In addition, median times to disease progression and overall participant survival were not significantly different. Although preclinical and Phase II data showed a possible dose-response effect for toremifene, no such effect was observed in this trial. Adverse events and quality-of-life assessments were also similar for the three treatment arms. This study demonstrated that toremifene is similar to its parent compound in efficacy and toxicity.

Because of insufficient long-term clinical data on toremifene, the effects of this agent on bone mineral density, frequency of cardiac events, and endometrial cancer risk cannot yet be assessed.³⁴ However, toremifene and tamoxifen exhibit comparable estrogenic activity in the uterus, producing similar increases in endometrial thickness among postmenopausal breast cancer patients.³⁷

Raloxifene. Raloxifene was originally studied for its potential use as an antiestrogenic therapy for breast cancer.²⁶ However, the majority of

clinical research on this compound has subsequently focused on its skeletal effects. Findings from these studies led to its approval in the United States for prevention of postmenopausal osteoporosis, with a recommended dosage of 60 mg/day. While this is currently its only approved use in the United States, preclinical and clinical studies have examined the effects of raloxifene on breast tissue, and the results are promising.

Laboratory experiments demonstrate that raloxifene reduced the incidence of mammary tumors in rats, either alone or in combination with 9-*cis*-retinoic acid (9cRA). 9cRA is a compound that prevents carcinogen-induced mammary tumors.³⁸ These results obtained with raloxifene and 9cRA were comparable to those of a similar study of tamoxifen and 9cRA.³⁹ Another preclinical study demonstrated that raloxifene inhibits proliferation of the MCF-7 breast cancer cell line with and without exogenous estrogen.⁴⁰ In contrast, tamoxifen stimulated rather than antagonized MCF-7 proliferation without exogenous estrogen. Raloxifene also was shown to inhibit human breast tumors as xenografts in nude mice.⁴¹

Table. Breast Cancer Incidence With Tamoxifen Versus Placebo in Three Trials

Trial	Sample Size	Risk	HRT Use	Median Follow-up (months)	Breast Cancers per 1000 Woman-Years	
					Placebo	Tamoxifen
Breast Cancer Prevention Trial ²²	13,338	High (multifactorial)	No	55	6.6	3.6*
British trial ³²	2471	High (positive family history)	Yes	70	5.0	4.7
Italian trial ³³	5048	Low/normal	Yes	46	2.3	2.1

**P* < 0.01.

The first data regarding the effects of raloxifene on breast cancer have emerged from the Multiple Outcomes of Raloxifene Evaluation (MORE) study, an ongoing worldwide trial developed to assess the effects of raloxifene on fracture, breast cancer, and endometrial cancer incidence.⁴² This randomized, double-blind study involved 7704 older postmenopausal women up to 80 years old (mean age, 67 years) who had osteoporosis and no history of breast or endometrial cancer. Participants received raloxifene (60 or 120 mg/day) or placebo for 2 years.

After a median follow-up of 29 months, interim results demonstrated that raloxifene markedly reduced the risk of newly diagnosed invasive breast cancer. Breast cancer was diagnosed in 11 women (0.21%) receiving raloxifene and 21 women (0.82%) receiving placebo. No significant difference was seen in risk reduction between the two raloxifene dosage groups.⁴²

Pooled safety data from placebo-controlled osteoporosis studies, which included approximately 14,800 patient-years of cumulative exposure to raloxifene and approximately 6750 patient-years of cumulative exposure to placebo, also suggest a profound reduction in the risk of developing breast cancer with raloxifene use.⁴³ A total of 49 newly diagnosed breast cancer cases were reported. Raloxifene (median overall exposure, 28 months) was associated with a 58% reduction in breast cancer risk. Raloxifene significantly reduced the incidence of both newly diagnosed ER-positive tumors ($P < 0.001$) and progesterone receptor-positive tumors ($P = 0.028$), without affecting the incidence rate of ER- or progesterone receptor-negative tumors.

Additional pooled data collected from ongoing osteoporosis studies continue to demonstrate that raloxifene reduces breast cancer risk.⁴⁴ At a median of 33 months of overall

exposure, which includes approximately 16,900 patient-years of cumulative exposure to raloxifene and 8130 patient-years of cumulative exposure to placebo, raloxifene reduced breast cancer risk by 54%. The incidence of newly diagnosed breast cancer was 1.7 per 1000 patient-years in the raloxifene group and 3.7 per 1000 patient-years in the placebo group. Moreover, raloxifene reduced the risk of ER-positive tumors by 70% (relative risk: 0.30; confidence interval: 0.14, 0.64) but did not affect ER-negative tumor risk. Long-term follow-up will continue.

While these results are encouraging, some questions regarding raloxifene's effect on breast tissue remain unanswered. Will the breast cancer preventive effects of raloxifene be sustained over a longer follow-up period? Is raloxifene effective in preventing various breast cancer tumors (ie, ductal carcinoma in situ, ER-positive tumors, and ER-negative tumors)? The optimal duration of raloxifene treatment for breast cancer prevention is also unknown at this time. Finally, further data are needed to assess the potential benefits of raloxifene in light of any long-term risks.⁴⁵

STAR

The Study of Tamoxifen and Raloxifene (STAR) is both the first direct comparison of tamoxifen and raloxifene and the first study designed specifically to assess raloxifene's effect on human breast tissue. STAR, which is scheduled to begin this year, is the second major breast cancer prevention trial initiated by the National Surgical Adjuvant Breast and Bowel Project. This randomized, double-blind study will include 22,000 postmenopausal women ages 35 years and older who are at increased risk for breast cancer. The use of tamoxifen (20 mg/day) and raloxifene (60 mg/day) for at least 7 years will be evaluated, providing additional data that will further eluci-

date the role of these two SERMs in the prevention of breast cancer in younger as well as older women.

Breast Pain and Tenderness

Unlike ERT and HRT, tamoxifen, toremifene, and raloxifene have not been associated with breast pain or tenderness.^{29,35,45} The absence of these side effects may improve long-term adherence as well as overall quality of life among women who use SERM therapy. In addition, tamoxifen has been used to treat cyclical and noncyclical breast pain, although it is not indicated for these conditions.^{46,47}

Conclusion

The results from early breast cancer prevention trials are promising, suggesting that both tamoxifen and raloxifene are effective in reducing the risk of breast cancer. However, the long-term effects of these preventive measures are unknown, and it is not clear whether these strategies are effective against ER-negative cancers. Only long-term, controlled clinical trials will provide the data necessary to determine if the preventive benefits of these agents outweigh their risks. As with all pharmacologic agents, the risks associated with long-term therapy should be well understood before initiating long-term therapy.

If these compounds prove effective for long-term breast cancer prevention, they could substantially reduce the incidence of breast cancer. Thus, the mortality and morbidity associated with one of the most common cancers among American women also would be significantly reduced. In addition, women who are greatly concerned about their risk of breast cancer or the increased risk of breast cancer related to estrogen use may be more likely to accept and adhere to long-term SERM therapy as part of an overall strategy to prevent breast cancer, osteoporosis, and, possibly, cardiovascular disease.

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