Breast Cancer Chemoprevention: A Review of Selective Estrogen Receptor Modulators

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In the United States, breast cancer is the most common cancer diagnosis among women (American Cancer Society, 2005). The risk for breast cancer development increases with age, with the highest incidence occurring from age 75–79 (American Cancer Society, 2003). An estimated 211,240 cases of invasive breast cancer and 58,490 cases of in situ breast cancer will be diagnosed in 2005, and an estimated 40,410 deaths from breast cancer are projected to occur in women in 2005 (American Cancer Society, 2005).

Breast cancer chemoprevention plays an important role for women at high risk for development of the disease. Chemoprevention is the delay or reversal of cancer by the use of pharmacologic agents that inhibit its development (Torrisi, Decensi, Formelli, Camerini, & De Palo, 2001). Selective estrogen receptor modulators (SERMs) have antiestrogen and estrogen-like effects. Tamoxifen and raloxifene are first- and second-generation SERMs, respectively. These SERMs have improved side-effect profiles and are approved for use for breast cancer prevention in women at high risk. The continued development of SERMs with improved side-effect profiles is needed. Oncology nurses play a pivotal role in helping patients to understand the current status of breast cancer prevention as well as the future direction of research.

The Physiology of Estrogen Effects on Breast Tissue

Breast cancer is the most common cancer diagnosis among women in the United States. Chemoprevention plays an important role for women at high risk for developing breast cancer. The use of selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene has demonstrated mixed results in breast cancer prevention clinical trials. In the United States, tamoxifen is approved for use for breast cancer prevention in women at high risk. The continued development of SERMs with improved side-effect profiles is needed. Oncology nurses play a pivotal role in helping patients to understand the current status of breast cancer prevention as well as the future direction of research.

The development of breast cancer is complex, involving a multitude of factors. Discussing all factors involved in breast cancer development is beyond the scope of this article, but the influence of estrogen on breast tissue and the role of estrogen in breast cancer development will be highlighted.

Estrogens are steroid hormones that are produced in the ovaries, adrenal glands, and placenta during pregnancy. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH act on the ovaries to produce estrogen in the form of estradiol and estrone. These estrogens bind with estrogen receptors in target tissues of the breast, uterus, brain, bone, liver, and heart. Estrogen receptors are molecules inside the cell to which only estrogens or closely related molecules can bind; however, not all cells contain receptors specific for estrogen. Once an estrogen has combined with a receptor in a cell, the shape of the receptor changes to combine with the DNA sites inside the target tissue. The DNA stimulates gene activation and production of RNA, which, in turn, stimulates the synthesis of protein. This protein produces changes in the cell according to tissue type and underlying conditions. The cycle is completed when high levels of estrogen in the blood send negative feedback to the hypothalamus to suppress the release of GnRH (Huether & McCance, 2004).

Estrogen released from the ovaries during adolescence stimulates the growth of the ductal system in breast tissue, which is not developed fully until pregnancy in preparation for lactation (Vanney, Kribs, & Gergor, 2004). Prolonged exposure to high levels of estrogen may cause changes in cell proliferation from normal growth to hyperplasia to neoplasia with DNA mutations and uncontrolled cell proliferation (Clemens & Goss, 2001) (see Figure 1). Women may be at increased risk for breast cancer from prolonged exposure to estrogen such as with early menarche before age 12, first full-term pregnancy after age 30, late menopause after age 55, or recent long-term use of postmenopausal hormone replacement therapy (HRT) (American Cancer Society, 2003; Clemens & Goss; Fabian & Kimler, 2002).

Most cases of breast cancer develop from the ductal epithelium and may be classified as invasive or noninvasive. Invasive breast cancers have broken through the basement membrane of the ducts or lobules into the fatty tissue of the breast (Huether & McCance, 2004). About 70%–80% of all breast cancers are termed estrogen receptor positive (ER+) if they express the ER protein α. These ER+ breast cancers are more likely to respond to hormonal therapy such as SERMs. Breast cancers that do not express the ER protein α are termed estrogen receptor negative (ER−).

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Breast Cancer Risk-Assessment Models

Several risk-assessment models can be used to determine a woman’s risk for developing breast cancer. The Claus model used data from the Cancer and Steroid Hormone study to calculate the cumulative risk of breast cancer with information about the family history of breast cancer and the ages at onset for first- and second-degree relatives with breast cancer (Claus, Risch, & Thompson, 1990). For women with a strong family history of breast cancer, the Claus model tends to be more helpful for determining risk (Claus, 2001).

The Gail model used data from the Breast Cancer Detection Demonstration Project to calculate risk of breast cancer development over five years and over a lifetime. The model is based on risk factors such as a mother and the number of sisters with breast cancer, number of benign breast biopsies, age at first live birth, age at menarche, and current age (Gail et al., 1989). The model has been modified and used as the breast cancer risk-assessment tool for the National Surgical Adjuvant Breast and Bowel Project P1 Study (NSABP-P1). The tool is most useful for women without a significant family history of breast cancer (Claus, 2001) and is available on the National Cancer Institute’s Web site at http://bcrca.nci.nih.gov/brc.

For most women younger than 60, multiple risk factors are needed to be classified as high risk by the Gail model. “High risk is defined as women at least 35 years of age with a five-year predicted risk of breast cancer greater than or equal to 1.67%, as calculated by the Gail model” (U.S. Food and Drug Administration, 1998, p. 13).

Dependent on the age group as defined by the Gail model, examples of the high-risk factors include one or more combinations of these factors: one or more first-degree relatives with breast cancer; breast biopsy-confirmed atypical hyperplasia, DCIS, or LCIS; age 25 or older at first live birth; or age 11 or younger at onset of menarche (U.S. Food and Drug Administration, 1998).

History of Selective Estrogen Receptor Modulators

During the initial development of chemoprevention protocols, tamoxifen was considered as a chemopreventive agent because of many factors. First, tamoxifen has antiestrogen effects and prevents the development of rat mammary tumors. Second, tamoxifen reduces the development of contralateral breast cancer in women receiving adjuvant therapy for breast cancer. Lastly, tamoxifen has low symptomatic toxicity (Cuzick et al., 2002; Fisher et al., 1998; Powles et al., 1998; Rutqvist et al., 1991; Veronesi et al., 1998). Because researchers believed that estrogen was a promoter of breast cancer development, they theorized that the risk of breast cancer development might be decreased by the use of an antiestrogen such as tamoxifen (Cuzick et al.; Fisher et al., 1998; Rutqvist et al.; Veronesi et al.).

Tamoxifen, formally considered an antiestrogen, now is considered to be a SERM that has antiestrogen and estrogen-like effects (see Figure 2). Tamoxifen produces its antiestrogen effect on breast tissue by competing with estradiol for binding to estrogen receptors, thus preventing cell replication (U.S. Food and Drug Administration, 1998). The usual dosage for tamoxifen is 20 mg daily for five years. The adverse effects associated with use of tamoxifen include increased risk for cataract formation, cataract surgery, endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis. Frequently reported side effects include increased hot flashes, vaginal discharge, and reduced sexual functioning (Fisher et al., 1998).

In the early 1990s, two European research groups and one North American research group initiated clinical trials to examine the use of tamoxifen as a chemopreventive agent. In each trial, women were randomized to receive tamoxifen 20 mg or placebo by mouth daily for five to eight years dependent on the design of the research group. Results of the European research groups, the Royal Mardsen trial (RMT) and Italian trial (IAT), revealed no significant influence on the rate of breast cancer development (Powles et al., 1998; Veronesi et al., 1998), whereas the North American research group (NSABP-P1)
showed a 49% decrease in breast cancer incidence and a 69% decrease in ER+ breast cancer. The differences in the results can be explained partially by the facts that the European trials were smaller (RMT = 2,494, IAT = 5,408, and NSABP-P1 = 13,388), women from the RMT study had a strong family history of breast cancer and were allowed to use HRT (Powles et al.), women from the IAT study were post-hysterectomy and also were allowed to use HRT (Veronesi et al.), women from the NSABP-P1 study were not allowed to use HRT, and eligibility for participation in NSABP-P1 was based on risk factors such as a history of LCIS, age of 35–59 years with a 1.66% risk of breast cancer development in the next five years, or age 60 years or older (Powles et al, Fisher et al., 1998). The data from the NSABP-P1 study showed that women participating in the study who were 50 years of age and older demonstrated a higher incidence for thromboembolic events and development of endometrial cancer. Tamoxifen can improve lipid profiles but failed to show a significant decrease in the development of cardiovascular disease. Also, a lower number of bone fractures of the hip, radius, and spine were observed but were insignificantly related to the ability of tamoxifen to affect osteoporosis positively. Based on the results of the NSABP-P1 study, tamoxifen was approved in October 1998 for use in breast cancer prevention for women at high risk (U.S. Food and Drug Administration, 1998).

Raloxifene is a second-generation SERM used in treatment for osteoporosis in postmenopausal women. With a daily oral dosage of 60 mg, raloxifene blocks cell replication by binding to estrogen receptors in the breast and endometrium. Raloxifene produces estrogen-like effects on bone and antiestrogen effects on breast and uterine tissues. Like tamoxifen, raloxifene increases the risk for pulmonary embolism, deep vein thrombosis, and hot flashes but not endometrial cancer. Raloxifene decreases low-density lipoprotein cholesterol, does not alter high-density lipoprotein cholesterol (Fabian & Kimler, 2002), and increases bone density, thereby decreasing the incidence of vertebral fractures (Johnell, Cauley, Kulkarni, Wong, & Stock, 2004).

The Multiple Outcomes of Raloxifene Evaluation trial was designed to test whether three years of raloxifene reduced the risk of bone fracture in postmenopausal women with osteoporosis (Cummings et al., 1999). An objective of the trial was to determine whether raloxifene decreased the development of breast cancer. Evaluation of the trial after three years revealed that the risk of invasive breast cancer development decreased by 76% among postmenopausal women with osteoporosis taking raloxifene, and a 90% decrease in ER+ breast cancer was observed. Evaluation of the safety of raloxifene versus tamoxifen in the prevention of breast cancer is ongoing.

The NSABP initiated the Study of Tamoxifen and Raloxifene (STAR) trial in 1999; it is designed to evaluate whether tamoxifen or raloxifene is superior in the prevention of breast cancer in high-risk, postmenopausal women. Women participating in STAR must have a 1.7% risk of breast cancer development in the next five years (NSABP, 2000). Researchers anticipate results by 2006 (NSABP, 2004). The use of aromatase inhibitors, which block the synthesis of estrogens from androgens, in women with early-stage ER+ breast cancer has been found to reduce the risk of breast cancer recurrence after the use of tamoxifen for three years. The role of aromatase inhibitors in breast cancer prevention is currently under study (Ingle, 2005).

**Future Direction of Selective Estrogen Receptor Modulators**

Arzoxifene is a third-generation SERM that acts as an estrogen antagonist in breast and uterine tissue and an estrogen agonist to maintain bone density and lower serum cholesterol. During in vitro and in vivo testing, arzoxifene was shown to be a highly effective chemopreventive agent superior to raloxifene (Suh et al., 2001). The drug still is in the research phase, supported by the National Cancer Institute, and researchers want to determine how well arzoxifene reverses or halts breast hyperplasia and atypical breast hyperplasia in women at high risk for breast cancer development.

**Conclusion**

The use of SERMs for the prevention of ER+ breast cancer has changed markedly since their inception. Tamoxifen, which has been used for treatment of ER+ breast cancer for more than 20 years, is approved for use in breast cancer prevention for women at high risk. Even though this is a considerable landmark for cancer prevention, women considering therapy with tamoxifen for breast cancer prevention should not initiate treatment without weighing the benefits of treatment and the risks of adverse effects.

The most significant results of the studies show that tamoxifen substantially reduces the incidence of ER+ breast cancer in women at high risk for disease development (Fisher et al., 1998), but it seldom is active in preventing ER− breast cancer (Keen & Davidson, 2003).

A second concept derived from the NSABP-P1 study is the understanding that prevention does not necessarily mean permanent prevention, only the reduction of invasive breast cancer over the study period. The length of prevention after treatment with tamoxifen was not incorporated into the design of the study but would assist practitioners with recommendations for patients’ treatment.

The results of the STAR trial, anticipated in 2006, will determine whether raloxifene has an improved side-effect profile (i.e., no increased risk of endometrial cancer). The results also will indicate whether raloxifene has a role in primary prevention of breast cancer (NSABP, 2004). As the generations of SERMs continue to undergo metamorphosis, the hope is to develop drugs with minimal adverse effects that can be used by the majority of women at high risk.

Oncology nurses play a pivotal role in helping patients to understand the current status of breast cancer prevention as well as the future direction of research. When nurses care for women taking SERMs, they should assess them for adverse effects and instruct them to report symptoms of pulmonary embolus (shortness of breath, sudden unexplained tachycardia at rest, anxiety, and hypoxia), deep vein thrombosis (tenderness and swelling in one extremity), and hot flashes and provide solid documentation of their teaching and observations.

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**Rapid Recap**

**Breast Cancer Chemoprevention: A Review of Selective Estrogen Receptor Modulators**

- Breast cancer is the most common cancer diagnosis among women in the United States.

- Since its inception in the early 1990s, breast cancer chemoprevention with selective estrogen receptor modifiers (SERMs) has undergone many changes, with approval of the first drug used for breast cancer prevention, modification of SERMs to minimize side effects, and comparison of standard therapy to potentially safer therapy.

- When nurses care for women taking SERMs, they should assess for symptoms of pulmonary embolus (shortness of breath, sudden unexplained tachycardia at rest, anxiety, and hypoxia), deep vein thrombosis (tenderness and swelling in one extremity), and hot flushes.

- Women considering treatment for breast cancer prevention should be made aware of current open trials and should not initiate standard therapy without weighing the benefits of treatment and the risks of adverse effects.