

# 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 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 (Torrissi, 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 been reviewed in clinical trials as chemopreventive agents with mixed results. Careful consideration should be given before initiating therapy for breast cancer prevention by weighing the benefits of treatment and the risks of adverse effects for women at high risk who are considering treatment.

## The Physiology of Estrogen Effects on Breast Tissue

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

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.

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 (Varney, Kriebs, & Geger, 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 (Clemons & 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; Clemons & 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  $\alpha$ . These ER+ breast cancers are more likely to respond to hormonal therapy such as SERMs. Breast cancers that do not express the ER protein  $\alpha$  are termed estrogen

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