Xenoestrogens, Biotransformation, and Differential Risks for Breast Cancer

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CANCER INITIATION

Until the last decade, epidemiological evidence of an association between sex steroid hormones and breast cancer risk, based on a retrospective study design such as case-control studies, was generally inconsistent. In spite of the lack of evidence, prospective cohort studies conducted in the last 10 years consistently observed that elevated levels of serum estrogens and androgens preceded the occurrence of breast cancer. In a pooled analysis of epidemiological studies of endogenous hormones and breast cancer in different populations, both estrogens and androgens were strongly associated with an increase in breast cancer risk, with evidence of a dose-response relationship.[1] An etiological link has also been specifically demonstrated between sex steroids and breast cancer development in premenopausal women.[2] Thus, exposure to estrogens is a recognized risk factor for breast cancer.

To understand how estrogens can induce breast cancer, we need to begin by considering natural estrogens and xenoestrogens (Fig. 1). The natural, endogenous estrogens are estrone (E_1), estradiol (E_2), and estriol. Contraceptives and hormone replacement therapy formulations include E_1, E_2, the synthetic ethynylestradiol, and the estrogens obtained from mares, equilin and equilenin. Many of these regimens also include progestins, almost always a synthetic progestin in the United States, rather than the natural progesterone itself (Fig. 1). There is a concern that the use of synthetic progestins, rather than natural progesterone, may increase the risk of breast cancer. Some recent data from a study of over 50,000 postmenopausal women in France support this concern (Table 1).[3]

TABLE 1 Breast Cancer Risk in Relation to Hormone Replacement Therapy[3]

54,598 postmenopausal women
948 primary invasive breast cancer in 5.8 years

Group	Relative Risk
HRT users vs nonusers	1.2
Estrogens alone	1.1
Estrogens + progesterone	0.9
Estrogens + synthetic progestins	1.4*

* The risk with estrogens + synthetic progestins was significantly greater than with estrogens + progesterone ($P < .001$).

Estrogens have been considered epigenetic carcinogens that function by stimulating abnormal cell proliferation via estrogen receptor-mediated processes.[4,5] The stimulated cell proliferation could result in increased accumulation of genetic damage, leading to carcinogenesis.[6,7] Compelling evidence has led to a new paradigm of cancer initiation by

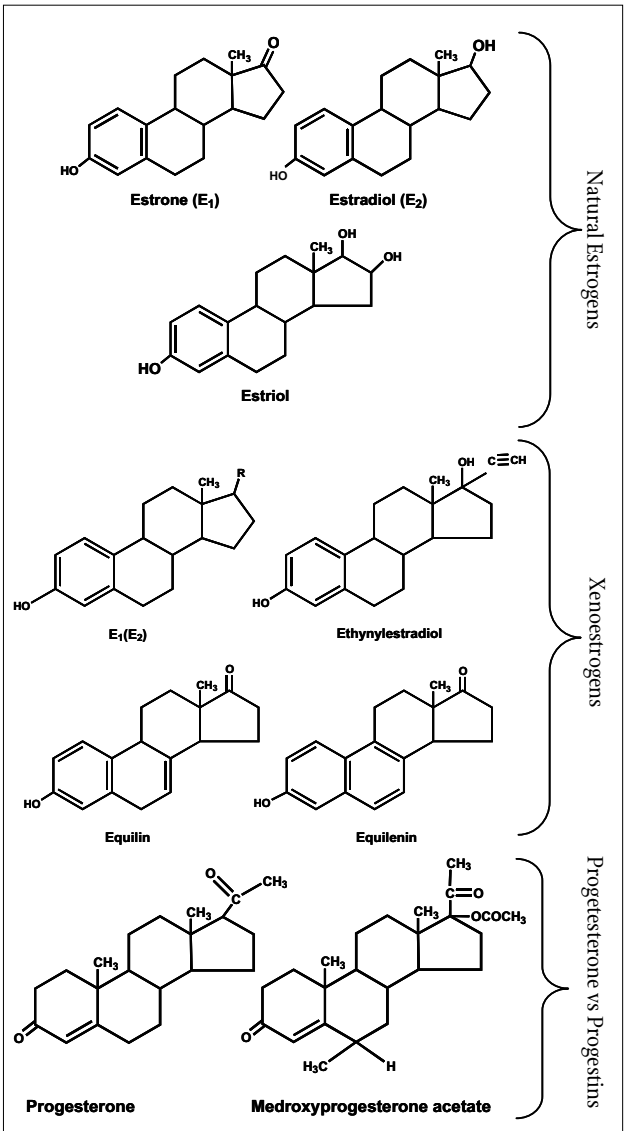

FIGURE 1 Natural estrogens, estrogens in contraceptives and hormone replacement therapy, and progesterone vs progestins.

estrogens. Discovery that specific oxidative metabolites of endogenous estrogens, catechol estrogen-3,4-quinones (CE-3,4-Q), can react with DNA[8-11] led to and has supported the hypothesis that these metabolites can become endogenous chemical carcinogens. Some of the mutations generated by the specific DNA damage can result in the initiation of cancer in breast and other tissues (Fig. 2).[12-15]

Chemical carcinogens, including the estrogens, covalently bind to DNA to form 2 types of adducts: stable ones that remain in the DNA, unless removed by repair, and depurinating ones that are lost from the DNA by destabilization of the glycosyl bond (Fig. 3), generating apurinic sites in the DNA.[16,17] Catechol estrogens (CE) are among the