Journal of the National Cancer Institute Monographs, No. 27, 67-73, 2000

Chapter 3: Endogenous Estrogens as Carcinogens Through Metabolic Activation

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A common thread linking the main risks for developing breast cancer in women is cumulative, excessive exposure to estrogen. The standard paradigm to account for this association focuses on increased cell proliferation caused by estrogen through estrogen receptor-mediated signal transduction accompanied by increased probability for mutation to occur during DNA synthesis. This chapter provides an overview of the mounting evidence, provided from cell culture and whole animal experimental studies, in support of a role for the oxidative metabolites of estrogen, in particular, the catechol estrogens, in the development of estrogen carcinogenesis. This provides a paradigm for how estrogens may contribute to the development of human breast cancer. The chapters that follow will fill in the details. Evidence shows that the catechols themselves are signaling molecules that work through the estrogen receptor. In addition, upon further oxidation, the catechols can give rise to reactive quinones capable of forming direct adducts with glutathione and purines in DNA and of redox cycling to generate reactive oxygen species that can cause oxidative damage. Estradiol and estrone, as well as their 4-hydroxy catechols, are carcinogenic in the Syrian golden hamster kidney, and ethinyl estradiol is a strong promoter of hepatocarcinogenesis in the rat. Increased oxidative DNA damage has been detected in target tissues after estrogen treatment in both animal model systems. Furthermore, several recent molecular epidemiologic studies have found that a polymorphism associated with a low-activity form of catechol-*O*-methyltransferase, an enzyme involved in the inactivation of catechol estrogens, is associated with an increased risk for developing breast cancer. The increased risk is observed in certain women, although the studies are not consistent on which subgroup of women (e.g., premenopausal or postmenopausal) is at increased risk, and one study detected no increased risk. Reasons for such discrepancies are discussed in light of factors, such as genetic polymorphisms and environmental/lifestyle susceptibility factors, which control the tissue-specific balance within cells among the estrogen metabolites. It is concluded that such factors will have to be identified through additional mechanistic studies and that, as they are identified, they can be incorporated into future molecular epidemiologic studies designed to determine their actual impact on cancer risk in human populations.