

## Chapter 5: Tissue-Specific Synthesis and Oxidative Metabolism of Estrogens

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Estrogen exposure represents the major known risk factor for development of breast cancer in women and is implicated in the development of prostate cancer in men. Human breast tissue has been shown to be a site of oxidative metabolism of estrogen due to the presence of specific cytochrome P450 enzymes. The oxidative metabolism of 17 $\beta$ -estradiol ( $E_2$ ) to  $E_2$ -3,4-quinone metabolites by an  $E_2$ -4-hydroxylase in breast tissue provides a rational hypothesis to explain the mammary carcinogenic effects of estrogen in women because this metabolite is directly genotoxic and can undergo redox cycling to form genotoxic reactive oxygen species. In this chapter, evidence in support of this hypothesis and of the role of P4501B1 as the 4-hydroxylase expressed in human breast tissue is reviewed. However, the plausibility of this hypothesis has been questioned on the grounds that insufficient  $E_2$  is present in breast tissue to be converted to biologically significant amounts of metabolite. This critique is based on the assumption that plasma and tissue  $E_2$  levels are concordant. However, breast cancer tissue  $E_2$  levels are 10-fold to 50-fold higher in postmenopausal women than predicted from plasma levels. Consequently, factors must be present to alter breast tissue  $E_2$  levels independently of plasma concentrations. One such factor may be the local production of  $E_2$  in breast tissue through the enzyme aromatase, and the evidence supporting the expression of aromatase in breast tissue is also reviewed in this chapter. If correct, mutations or environmental factors enhancing aromatase activity might result in high tissue concentrations of  $E_2$  that would likely be sufficient to serve as substrates for CYP1B1, given its high affinity for  $E_2$ . This concept, if verified experimentally, would provide plausibility to the hypothesis that sufficient  $E_2$  may be present in tissue for formation of catechol metabolites that are estrogenic and which, upon further oxidative metabolism, form genotoxic species at levels that may contribute to estrogen carcinogenesis.