

## Chapter 4: Estrogens as Endogenous Genotoxic Agents—DNA Adducts and Mutations

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Estrogens induce tumors in laboratory animals and have been associated with breast and uterine cancers in humans. In relation to the role of estrogens in the induction of cancer, we examine formation of DNA adducts by reactive electrophilic estrogen metabolites, formation of reactive oxygen species by estrogens and the resulting indirect DNA damage by these oxidants, and, finally, genomic and gene mutations induced by estrogens. Quinone intermediates derived by oxidation of the catechol estrogens 4-hydroxyestradiol or 4-hydroxyestrone may react with purine bases of DNA to form depurinating adducts that generate highly mutagenic apurinic sites. In contrast, quinones of 2-hydroxylated estrogens produce less harmful, stable DNA adducts. The catechol estrogen metabolites may also generate potentially mutagenic oxygen radicals by metabolic redox cycling or other mechanisms. Several types of indirect DNA damage are caused by estrogen-induced oxidants, such as oxidized DNA bases, DNA strand breakage, and adduct formation by reactive aldehydes derived from lipid hydroperoxides. Estradiol and the synthetic estrogen diethylstilbestrol also induce numerical and structural chromosomal aberrations and several types of gene mutations in cells in culture and *in vivo*. In conclusion, estrogens, including the natural hormones estradiol and estrone, must be considered genotoxic carcinogens on the basis of the evidence outlined in this chapter.