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Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention.

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Exposure to estrogens is associated with increased risk of breast and other types of human cancer. Estrogens are converted to metabolites, particularly the catechol estrogen-3,4-quinones (CE-3,4-Q), that can react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone base excision repair of this damage may lead to the mutations that can initiate breast, prostate and other types of cancer. The reaction of CE-3,4-Q with DNA forms the depurinating adducts 4-hydroxyestrone(estradiol) [4-OHE1(E2)-1-N3Ade and 4-OHE1(E2)-1-N7Gua. These two adducts constitute more than 99% of the total DNA adducts formed. Increased levels of these quinones and their reaction with DNA occur when estrogen metabolism is unbalanced. Such an imbalance is the result of overexpression of estrogen activating enzymes and/or deficient expression of the deactivating (protective) enzymes. This unbalanced metabolism has been observed in breast biopsy tissue from women with breast cancer, compared to control women. Recently, the depurinating adduct 4-OHE1(E2)-1-N3Ade has been detected in the urine of prostate cancer patients, but not in urine from healthy men. Mutagenesis by CE-3,4-Q has been approached from two different perspectives: one is mutagenic activity in the lacI reporter gene in Fisher 344 rats and the other is study of the reporter Harvey-ras gene in mouse skin and rat mammary gland. A-->G and G-->A mutations have been observed in the mammary tissue of rats implanted with the CE-3,4-Q precursor, 4-OHE2. Mutations have also been observed in the Harvey-ras gene in mouse skin and rat mammary gland within 6-12 h after treatment with E2-3,4-Q, suggesting that these mutations arise by error-prone base excision repair of the apurinic sites generated by the depurinating adducts. Treatment of MCF-10F cells, which are estrogen receptor-alpha-negative immortalized human breast epithelial cells, with E2, 4-OHE2 or 2-OHE2 induces their neoplastic transformation in vitro, even in the presence of the antiestrogen ICI-182,780. This suggests that transformation is independent of the estrogen receptor. The transformed cells exhibit specific mutations in several genes. Poorly differentiated adenocarcinomas develop when aggressively transformed MCF-10F cells are selected and injected into

severe combined immune depressed (SCID) mice. These results represent the first in vitro/in vivo model of estrogen-induced carcinogenesis in human breast epithelial cells. In other studies, the development of mammary tumors in estrogen receptor-alpha knockout mice expressing the Wnt-1 oncogene (ERKO/Wnt-1) provides direct evidence that estrogens may cause breast cancer through a genotoxic, non-estrogen receptor-alpha-mediated mechanism. In summary, this evidence strongly indicates that estrogens can become endogenous tumor initiators when CE-3,4-Q react with DNA to form specific depurinating adducts. Initiated cells may be promoted by a number of processes, including hormone receptor stimulated proliferation. These results lay the groundwork for assessing risk and preventing disease.