

Maternal dioxin exposure combined with a diet high in fat increases mammary cancer incidence

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BACKGROUND: Epidemiological studies show that breast cancer risk correlates with total lifetime exposure to estrogens and that early life 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure or diets high in fat can also increase cancer risk.

OBJECTIVES: Because both TCDD and diet impact the estrogen pathway, we examined how TCDD and a high-fat diet (HFD) interact to alter breast cancer susceptibility.

METHODS: At 12.5 days post coitus, we exposed pregnant FVB/NJ female mice to 1 µg/kg of TCDD or vehicle and at parturition randomly assigned dams to a low-fat diet (LFD) or HFD. Female offspring were maintained on the same diets after weaning and exposed to 7,12-dimethyl-benz[a]anthracene (DMBA) at post-natal days (PND) 35, 49 and 63 to initiate mammary tumors. A second cohort of females was treated identically until PND 35 or 49, when mammary gland morphology was examined, or at PND 50, when mammary gland mRNA expression was analyzed.

RESULTS: We found that maternal TCDD exposure doubles mammary tumor incidence only in mice fed HFD. Among mice fed HFD, maternal TCDD exposure caused rapid mammary development with increased *Cyp1b1* and decreased *Comt* expression in mammary tissue. Mammary tumor *Cyp1b1* expression was further increased by maternal TCDD exposure.

CONCLUSIONS: Our data suggest that HFD increases sensitivity to maternal TCDD exposure, resulting in increased breast cancer incidence, by changing estrogen metabolism capability. These results provide a mechanism to explain epidemiological data linking early life TCDD exposure and diets high in fat to increased risk for breast cancer in humans.

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