

***In utero* exposure to bisphenol A and mammary gland cancer**

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Epidemiological studies suggest that fluctuating estrogen levels in the fetal environment have long-term consequences regarding the risk of developing breast cancer during adult life. This is supported by laboratory studies showing that perinatal exposure to pharmacological doses of diethylstilbestrol (DES) increased the incidence and decreased the latency period of mammary cancer. We observed that fetal exposure to environmentally relevant doses of the xenoestrogen bisphenol A (BPA), a compound used in the manufacture of polycarbonate plastics and structurally similar to DES, resulted in long-lasting effects in the mouse mammary gland that were manifested during adult life. Of particular interest were: (i) an increase in the number of terminal end buds and terminal ends (the sites where carcinomas are thought to originate), (ii) an increase in ductal density (mammographic density is considered a risk factor) and (iii) an increased sensitivity to estradiol, suggesting enhanced susceptibility for mammary cancer development. Hence, we hypothesize that fetal exposure to low doses of BPA increases the risk of developing mammary cancer.

To explore this hypothesis, we used a Wistar-Furth rat model. Animals were exposed to BPA (2.5, 25, 250 or 1000 μ g/kg/day) or vehicle (50% DMSO) from gestational day 9 to birth using an osmotic pump. We found that fetal BPA exposure caused a 3-fold increase in the incidence of ductal hyperplasias at postnatal day 50 and 95, regardless of the BPA dose. More importantly, carcinoma *in situ* (CIS) were also observed in these animals. Thus, fetal BPA exposure induces the development of preneoplastic and neoplastic lesions in the mammary gland in the absence of any additional treatment aimed at increasing tumor development.

In an ongoing experiment, BPA- and vehicle-treated animals are challenged with a “subcarcinogenic” dose of N-nitrosomethylurea (NMU, 20mg/kg) at 50 days of age to assess whether or not fetal BPA exposure sensitizes the mammary gland to further neoplastic development, which could be manifest by an increased incidence of CIS and palpable tumors.

Our results support the hypothesis that environmental exposure to xenoestrogens during fetal life may contribute to the increased incidence of breast cancer observed over the past five decades.

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