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### **Does breast cancer start in the womb?**

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Recent data have suggested that perturbations in the fetal environment may predispose individuals to disease and/or organ dysfunction, which become apparent in adulthood. This new emphasis on the fetal origins of adult diseases has prompted scientists to hypothesize that fetal exposure to environmental estrogens may be an underlying cause of the increased incidence of uterine leiomyoma, testicular cancer and breast cancer observed in European and US populations over the last 50 years. Humans are routinely exposed to bisphenol-A (BPA), an estrogenic compound that leaches from dental materials, food and beverage containers and other plastic consumer products. In CD-1 mice, prenatal exposure to environmentally relevant levels (25 and 250 ng BPA/kg body weight/day) from gestational day (GD) 9 to postnatal day (PND) 2 accelerated the development of the fetal mammary gland (examined at GD18) and induced alterations of the mammary gland architecture which manifested during puberty and adulthood, long after the period of exposure ended. In these mice, BPA increased the number of terminal end buds at PND 30 and terminal ends at PND 180 and increased lateral branching of the ducts at PND 120. Just as significant, BPA exposed mice showed an enhanced sensitivity to estradiol when ovariectomized at PND 25. All these parameters are associated with an increased risk for developing breast cancer.

But...does prenatal exposure to BPA induce mammary gland neoplasia? To answer this question, we chose a rat model because it more closely mimics the human disease regarding hormone factors and histopathology than the available mouse models. Wistar/Furth dams were implanted with osmotic pumps delivering 0, 2.5, 25, 250 and 1000 $\mu$ g BPA/kg body weight/day; exposing offspring from GD 9 to PND 1. Mammary glands were examined during early adulthood (PND50 and PND 95). BPA induced the development of ductal hyperplasias at all doses tested and carcinoma in situ at the two highest

doses tested. These highly proliferative lesions were found to have an increased number of estrogen receptor- $\alpha$  positive cells. Thus, fetal BPA exposure is sufficient to induce the development of preneoplastic and neoplastic lesions in the mammary gland in the absence of any additional treatment aimed at increasing tumour development.

Women prenatally exposed to diethylstilbestrol are now reaching the age at which breast cancer is commonly diagnosed. Emerging epidemiological data are revealing an increased incidence of breast cancer in this population. Hence, animal experiments and epidemiological data strengthen the hypothesis that exposure to xenoestrogens, including BPA, during early development may be an underlying cause of the increased incidence of breast cancer observed over the last 50 years.