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BREAST CANCER

Increased risk with concurrent dietary and EDC exposures

> … maternal exposure to environmentally relevant doses of bisphenol A (BPA) combined with high-fat intake during pregnancy increases the risk of breast cancer in first-generation (F1) offspring

Consumption of a high-fat diet (HFD) and *in utero* exposure to endocrine-disrupting chemicals (EDCs) are both acknowledged risk factors for breast cancer; however, how concurrent dietary and EDC challenges further modulate this risk has been unclear. In new research, Leung *et al.* show that maternal exposure to environmentally relevant doses of bisphenol A (BPA) combined with high-fat intake during pregnancy increases the risk of breast cancer in first-generation (F1) offspring.

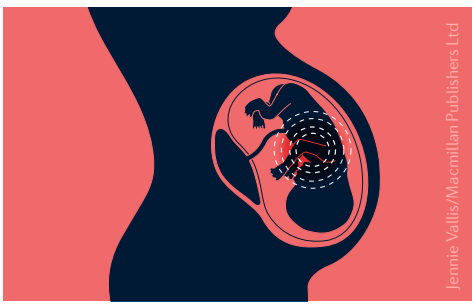
Female (F0) Sprague Dawley rats were fed either a control diet (10% butterfat) or a HFD (39% butterfat; mimicking Western diets) in the absence or presence of BPA (2.5, 25, 250 or 2,500 μg/kg of bodyweight per day) for 2 weeks (acclimatization), during mating and throughout gestation; dams and offspring were subsequently maintained on the control diet without BPA. At postnatal day 50 (PND50), female offspring were treated with either the mammary carcinogen 7,12-dimethylbenz(a) anthracene (DMBA) or corn oil (control) and were palpated weekly to monitor tumour development until PND140.

By the end of the experiment, offspring in the HFD + 25 μg/kg BPA gestational-exposure group who were treated with DMBA had markedly higher tumour incidence (90%) than offspring in the HFD-alone group (45.5%), and a considerably shortened tumour-free survival time. Moreover, this HFD + BPA group had increased numbers of terminal end buds (highly proliferative structures believed to be the target of malignant transformation) as early as PND21. Transcriptomic analysis of epithelia from PND21 mammary glands revealed 504 genes to be differentially regulated by *in utero* HFD + BPA exposure (many of which were cancer related) and evidence of epigenetic regulation by DNA methylation. Crucially, a panel of the seven most differentially regulated HFD + BPA genes (*ALDH1B1*, *ASTL*, *CA7*, *CPLX4*, *KCNV2*, *MAGEE2* and *TUBA3E*) was associated with poor overall survival in The Cancer Genome Atlas breast cancer cohort ($n = 1,082$).

"Our findings show that concurrent exposure to a HFD and BPA (at below the current no-observed-adverse-effect level) during pregnancy modulates developmental morphology and gene expression in the prepubertal mammary gland and increases the incidence of breast cancer in offspring, possibly via epigenetic reprogramming," comments lead investigator Shuk-Mei Ho. Having seen a potential epigenetic effect in F1 offspring, Ho and her team plan to study whether epigenetic memory of the exposure, as well as the associated cancer risk, is maintained in subsequent generations — so-called epigenetic transgenerational inheritance.

David Holmes

ORIGINAL ARTICLE Leung, Y.-K. *et al.* Gestational high-fat diet and bisphenol A exposure heightens mammary cancer risk. *Endocr. Relat. Cancer* http://dx.doi.org/10.1530/ERC-17-0006 (2017)
FURTHER READING Soto, A. M. & Sonnenschein, C. Endocrine disruptors: DDT, endocrine disruption and breast cancer. *Nat. Rev. Endocrinol.* **11**, 507–508 (2015) | Skinner, M. K. Endocrine disruptors in 2015: Epigenetic transgenerational inheritance. *Nat. Rev. Endocrinol.* **12**, 68–70 (2016)



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