

## **Pubertal Exposure to High Fat Diet Alters Mouse Mammary Gland Development and Estrogen Responsiveness**

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Increased obesity rates in the United States are associated with health risks. It is possible that obesity or increased adiposity in girls during puberty, an important period of breast development and a window of exposure sensitivity, may influence breast development and cancer risk. To investigate the impact of pubertal obesity on mammary gland development, obesity-susceptible C57BL/6 mice and obesity-resistant BALB/c mice were fed a high fat diet (HFD) (60% kcal fat) or control diet (CD) (12% kcal fat) from weaning (3 wks old) to 7 weeks of age. Only pubertal C57BL/6 mice fed the HFD had a significant increase in body weight compared with CD fed mice. Pubertal HFD-fed C57BL/6 mice had reduced mammary growth as evidenced by reduced numbers of terminal end buds (TEBs), stunted ductal elongation, and reduced epithelial cell proliferation. Weight loss initiated by switching C57BL/6 mice from HFD to CD restored TEBs and ductal elongation. In contrast, BALB/c mice HFD had a modest weight gain, exhibited increased mammary epithelial cell proliferation and increased susceptibility to carcinogen-induced mammary cancer. Importantly, HFD had no effect on the mammary glands of adult C57BL/6 or BALB/c mice, indicating that the effects of diet and adiposity were specific to the pubertal period of development. Pubertal HFD-fed C57BL/6 mice showed a decreased mammary gland response to estrogen (E) compared to CD-fed mice and decreased production of amphiregulin, an E-induced mammary growth factor. In summary, dietary fat and adiposity had a profound strain-specific effect on mammary gland development during puberty and also affected subsequent susceptibility to mammary cancer.

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