

## Mouse Models of Adolescent Obesity and Breast Development

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Increased body weight and adiposity caused by poor diets and sedentary lifestyles have been associated with early onset of menarche in girls - a known risk for breast cancer. Elevated adiposity during puberty may alter breast cancer risk by perturbing breast development, which may have long-term consequences on function and hormonal responsiveness of the adult gland. To investigate the impact of pubertal obesity on breast development, obesity-susceptible C57BL/6 mice and obesity-insusceptible Balb/c mice were fed a high fat diet from weaning (3 wks old) to 7 weeks of age. A set of C57BL/6 mice was also ovariectomized (OVX) to study the effect of obesity on estrogen (E) and/or progesterone (P) regulation of end bud formation and epithelial cell proliferation. The high fat (HF) diet consisted of 60% kcal fat, 20% kcal carbohydrate and 20% kcal protein, whereas the control (C) diet was 10% kcal fat, 70% kcal carbohydrate and 20% kcal protein. C57BL/6 mice fed a HF diet for 4 wks were significantly heavier than C fed mice. Consistent with increased adiposity and mild insulin resistance, C57BL/6 mice fed a HF diet had elevated leptin and insulin levels and diminished glucose tolerance. HF fed C57BL/6 mice had increased breast fat pad and epithelial cell area. The epithelium also appeared have more completely infiltrated the stroma and had less developed end buds compared to controls. Even though the epithelial cells had greater outgrowth, there were fewer progesterone receptor A (PRA) positive duct epithelial cells in HF fed C57/BL6 mice. Ovariectomy led to increased weight gain and leptin levels in both HF and C diet fed C57BL/6 mice. Breast fat pad and epithelial cell area was increased in OVX C57BL/6 mice and this was substantially augmented by HF diet. OVX C57BL/6 mice were refractory for E- and/or P-induced end bud formation. Duct epithelial cells of OVX C57BL/6 mice had markedly reduced numbers of PRA positive cells. Treatment of OVX C57BL/6 mice with E and P, independent of diet, led to a partial recovery of PRA positive cells and duct cell proliferation. Overall this data show that increased body weight during adolescence can result in increased levels of insulin and leptin, breast fat pad and epithelial cell area, and alterations in end bud morphology and hormone responsiveness.