

## **Isoflavone exposure during adolescence modulates estrogen sensitivity of the mammary gland as a function of dose and time window of exposure**

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The effects of isoflavones (ISO) on the female breast are controversially discussed. There is evidence that ISO-rich Asian diet decreases the incidence of hormone related cancer and postmenopausal disorders. Whether chronic exposure to ISO over all critical periods of mammary gland development modulates its estrogen sensitivity was tested in a dose-dependent animal study. From in utero stages, through weaning and adolescence into adulthood female Wistar rats were exposed to different diets enriched with varying concentrations of the soy extract Novasoy650®: ISO-depleted diet (IDD), IRD50 (50 mg ISO/kg diet) and IRD400 (400 mg ISO/kg diet). Rats were ovariectomized (OVX) at day 80 and treated with 4 µg/kg BW E2 or vehicle for 3 days after 2 weeks of hormonal decline. Intact animals served as control. In a second trial adult female rats were exposed to IRD400 directly after OVX for 2 weeks and then treated with E2 as described above.

Uterine wet weight (UWW), PCNA expression (proliferation marker) and expression of progesterone receptor (PR) in the mammary gland were determined. IRD dose dependently induced earlier puberty onset. IRD400, but not IRD50, decreased estrus cycle length and prolonged the estrus phase. Treatment of OVX animals with E2 significantly increased UWW in all groups. Chronic exposure to IRD400, but not IRD50, resulted in a reduced proliferative response (60% decreased PCNA expression) and decreased PR protein expression of 55% in the mammary gland within the E2 groups compared to IDD. In contrast, in animals grown up ISO free but exposed to ISO for 14 days prior E2 treatment, IRD400 led to an increased expression of PCNA of 40% in mammary gland in both OVX and E2 compared to IDD. In summary our data demonstrate a dose-dependent biological activity of ISO exposure. Furthermore, the results provide evidence that the time window of exposure is a crucial determinant of whether dietary ISO have protective or adverse effect on breast cancer development.