FASTING-MIMICKING DIET AND HORMONE THERAPY INDUCE BREAST CANCER REGRESSION (2020)

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Abstract	Approximately 75% of all breast cancers express the oestrogen and/or progesterone receptors. Endocrine therapy is usually effective in these hormone-receptor-positive tumours, but primary and acquired resistance limits its long-term benefit1,2. Here we show that in mouse models of hormone-receptor-positive breast cancer, periodic fasting or a fasting-mimicking diet3-5 enhances the activity of the endocrine therapeutics tamoxifen and fulvestrant by lowering circulating IGF1, insulin and leptin and by inhibiting AKT-mTOR signalling via upregulation of EGR1 and PTEN. When fulvestrant is combined with palbociclib (a cyclin-dependent kinase 4/6 inhibitor), adding periodic cycles of a fasting-mimicking diet promotes long-lasting tumour regression and reverts acquired resistance to drug treatment. Moreover, both fasting and a

fasting-mimicking diet prevent tamoxifen-induced endometrial hyperplasia. In patients with hormone-receptor-positive breast cancer receiving oestrogen therapy, cycles of a fasting-mimicking diet cause metabolic changes analogous to those observed in mice, including reduced levels of insulin, leptin and IGF1, with the last two remaining low for extended periods. In mice, these long-lasting effects are associated with long-term anti-cancer activity. These results support further clinical studies of a fasting-mimicking diet as an adjuvant to oestrogen therapy in hormone-receptor-positive breast cancer.

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