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"Fasting-mimicking diet and hormone therapy induce breast cancer regression"

Abstract:
Breast cancer (BC) is the most common malignancy with 1.7 million new diagnoses/year and is responsible for more than 450,000 yearly deaths worldwide. Two thirds of BC express the estrogen receptor (ER) and/or progesterone receptor and are referred to as hormone receptor-positive (HR+) BC. Endocrine therapy (ET) is usually active in these tumors, although drug resistance and side effects limit its benefit. Growth factor signaling through the PI3K/AKT/mammalian target of rapamycin (mTOR) and MAP kinase axes enhances ER activity and is a key mechanism underlying endocrine resistance. Water-only fasting (fasting) or plant-based, low-calorie, carbohydrate- and protein-restricted fasting-mimicking diets (FMDs) reduce circulating growth factors, such as insulin and IGF1. Therefore, we hypothesized that these dietary interventions could be used to enhance the activity of ET and delay the occurrence of resistance. We found that in HR+ BC models, periodic fasting or FMD enhanced tamoxifen and fulvestrant activity by lowering circulating IGF1, insulin, and leptin levels and by blocking AKT-mTOR signaling via EGR1 and PTEN upregulation. When fulvestrant was combined with palbociclib (a cyclin-dependent kinase 4/6 inhibitor), adding periodic FMD cycles promoted long-lasting tumour regressions and reverted acquired resistance to this regime. Moreover, both fasting and FMD prevented tamoxifen-induced endometrial hyperplasia.
Circulating growth factors and adipo-cytokines were also detected in blood samples from 36 patients with HR+ BC, who were enrolled in either one of two clinical trials assessing safety and feasibility of periodic FMD in cancer patients. In these patients receiving ET, FMD cycles caused metabolic changes analogous to those observed in mice, including reduced leptin and IGF1 levels, which were found to remain low for extended periods. In mice, these long-lasting effects were associated with carryover anticancer activity. Overall, our 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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