

Vitamin D Suppresses Leptin Stimulation of Cancer Growth through microRNA.

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Abstract

Obesity is a pandemic and major risk factor for cancers. The reduction of obesity would have been an effective strategy for cancer prevention, but the reality is that worldwide obesity has kept increasing for decades, remaining a major avoidable cancer risk secondary only to smoke. The present studies suggest that vitamin D may be an effective agent to reduce obesity-associated cancer risks in women. Molecular analyses showed that leptin increased human telomerase reverse transcriptase (hTERT) mRNA expression and cell growth through estrogen receptor- α (ER α) activation in ovarian cancer cells, which was suppressed by 1 α ,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]. The suppression was compromised when miR-498 induction by the hormone was depleted with microRNA (miRNA) sponges. In mice, high-fat diet (HFD) stimulation of ovarian tumor growth was remarkably suppressed by 1,25(OH)₂D₃ analogue EB1089, which was also compromised by miR-498 sponges. EB1089 did not alter HFD-induced increase in serum leptin levels but increased miR-498 and decreased the diet-induced hTERT expression in tumors. Quantitative RT-PCR analyses revealed an inverse correlation between hTERT mRNA and miR-498 in response to 1,25(OH)₂D₃ in estrogen-sensitive ovarian, endometrial, and breast cancers. The studies suggest that miR-498-mediated hTERT downregulation is a key event mediating the anti-leptin activity of 1,25(OH)₂D₃ in estrogen-sensitive tumors in women. *Cancer Res*; 74(21); 1-11. ©2014 AACR.

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PMID:

25252917

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