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Authors

Chung, Heekyung
Sears, Dorothy D
Webster, Nicholas J
[et al.](#)

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(152319_1) - Omega-3 fatty acids reduce mammary tumor growth in a mouse model of postmenopausal breast cancer

Heekyung Chung, Dorothy D. Sears, Nicholas J. Webster, Jerrold M. Olefsky, Lesley G. Ellies.

University of California, San Diego, CA.

Obesity is a risk factor for postmenopausal breast cancer. Inflammation, hyperinsulinemia, insulin resistance and altered levels of adipokines have been proposed as possible links between obesity and tumor progression. Furthermore, the composition of fats in the diet can influence inflammation and epidemiological studies have shown that an increase in fish oil (omega-3 fatty acids; ω -3 FAs) intake is associated with a reduction in breast cancer incidence in humans. Several mechanisms have been proposed for the anticancer effect of ω -3 FAs such as suppression of neoplastic transformation, cell proliferation or angiogenesis, or an increase in apoptosis. To study the effects of ω -3 FA on mammary tumor growth in a mouse model of postmenopausal obesity, ovariectomized C57BL/6 mice were fed either a high fat diet (HFD, 60% kcal from fat) or an isocaloric HFD containing 30% ω -3 FA replacement [wt/wt, 24% docosahexaenoic acid (DHA), 6% eicosapentanoic acid (EPA)]. Fourteen weeks after starting HFDs, mice received orthotopic mammary fat pad injections of Py230 cells derived from a spontaneous polyomavirus middle T antigen (PyVmT) mammary tumor. Mammary tumor growth, inflammatory cytokine expression in perigonadal fat and the mammary fat pads and tumors, and apoptosis and cell proliferation in the tumors were determined at 22 weeks following initiation of the HFDs. There was no difference in body weights between mice fed a HFD with or without ω -3 FA, but ω -3 FA-fed mice had a significantly reduced mammary tumor burden (33%) compared to counterpart HFD-fed mice. The ω -3 FA-fed mice showed decreased expression of macrophages and inflammatory cytokines such as CD11c, TNF- α and iNOS in perigonadal fat. However, surprisingly the ω -3 FA-fed mice showed increased macrophage and inflammatory cytokine expression: CD11c, TNF- α , IL-1 β and IL-6 in the mammary fat pads implanted with tumor cells, suggesting that the anti-inflammatory effect of ω -3 FAs may be modulated by implanted tumor cells. No difference was observed in the expression of macrophage marker and inflammatory cytokines in mammary tumors between mice fed a HFD with or without ω -3 FA. Immunohistochemical staining of mammary tumors revealed a high degree of variability in cell proliferation and apoptosis between tumors and no significant differences were observed. To examine whether ω -3 FAs may act directly on Py230 tumor cells to reduce mammary tumor growth, we tested the effects of ω -3 FA on cell growth, apoptosis and signaling in Py230 cells *in vitro*. DHA significantly inhibited Py230 cell growth in a dose-dependent manner. In addition, DHA inhibited TNF- α -induced cell growth and blocked NF- κ B signaling activated by TNF- α in Py230 cells. Furthermore, DHA increased the activities

of caspases 3 and 7 and induced apoptosis in Py230 cells. Our results suggest that ω -3 FAs may suppress mammary tumor growth by directly inhibiting the growth of mammary tumor cells via induction of apoptosis. Further analysis of the signaling pathways involved may identify new therapeutic targets for postmenopausal women with breast cancer.

Category: Other

Keywords: omega-3 fatty acids; obesity; a mouse model of postmenopausal breast cancer

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