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Effects of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Breast Cancer

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Shapiro, Lisa

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## Epidemiology

The incidence of breast cancer differs widely across industrialized nations. For example, breast cancer incidence in the United States is five-fold greater than in Japan (1). Less dramatic differences can also be seen in the neighboring countries of Spain and France where annual breast cancer rates differ by 50% (86 and 129 per 100,000, respectively) (1). Known risk factors for breast cancer include age at menarche, age of first child, known genetic mutations, and hormonal factors. However, all the known risk factors cannot explain differences in breast cancer incidence across populations. Therefore, diet, which varies greatly between different countries, has been given a lot of attention. In particular, the differences may be attributed to different patterns of dietary fat intake. Women in North America and Europe consume high-fat diets containing large amounts of omega-6 polyunsaturated fatty acids, primarily linoleic acid, which is found in corn and safflower oils. In contrast, in Japan the diet is low-fat and contains a higher proportion of omega-3 polyunsaturated fatty acids, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish oil (2). Likewise, epidemiological studies have shown that the diet of Greenland Eskimos contains an almost equal amount of total fat as the diet of women in Denmark. However, breast cancer incidence is much lower in the Eskimos. This difference may be attributable to the higher content of omega-3 fatty acids such as EPA known to be present in marine fats, and a lower content of omega-6 fatty acids such as linoleic acid in the Eskimos diet compared to the Denmark diet (3). There is experimental evidence that omega-6 fatty acid metabolites promote breast cancer tumor growth and invasion, whereas omega-3 fatty acids inhibit tumor growth and metastasis. The western diet is high in omega-6 fatty acids, specifically linoleic acid. The average American consumes 10-20 g/day of linoleic acid, which accounts for 85% of the total polyunsaturated fat intake (2).

In addition to breast cancer risk, it has been suggested that a high fat diet may adversely effect the recurrence rate after surgical removal of a primary breast cancer. One study reported that Japanese breast cancer patients, who consume a low-fat diet, are more likely than Caucasian patients to have localized disease at diagnosis and more likely to have a better prognosis with regard to tumor pathological staging. The high fat diet of American women was associated with reduced survival, and high omega-6 fatty acid intakes were associated with a more advanced disease stage at diagnosis (4). These finding could have potential adjuvant treatment implications.

Two large epidemiological studies addressed the question of the effects of omega-3 and omega-6 fatty acids on breast cancer incidence and found conflicting results. Simonsen, et al studied the polyunsaturated fatty acid content of gluteal adipose tissue of women with and without breast cancer in five centers in different European countries: the Netherlands, Northern Ireland, Switzerland, Germany, and Spain. They found that the ratio of omega-3 to omega-6 fatty acids was inversely associated with breast cancer in four of the five centers (1). This finding supports experimental research that will be described below. Holmes, et al conducted a 14 year follow-up on 88,795 women who were cancer free in 1980. These women were part of the Nurses' Health Study, and they received questionnaires every 2 years and food frequency questionnaires in 1980, 1984, 1986 and 1990. A total of 2956 women developed breast cancer during the study. The investigators found no increased risk with omega-6 fatty acid intake, and actually found a positive risk associated with the omega-3 fatty acids found in fish oil (5). These findings directly

oppose much of the experimental findings. Inaccuracy or bias of the food frequency questionnaire may partially account for their results.

### Basic Research

An abundance of research exists on the relationship between polyunsaturated fats and breast cancer. Over fifty years ago, Tannenbaum, et al noted that increased dietary fat promoted mammary carcinogenesis in mice (6). In 1978, the type of dietary fat was narrowed down when Carroll and Hopkins observed that omega-6 polyunsaturated fatty acid diets promoted tumorigenesis to a much greater extent than equivalent saturated fat diets. Rats fed a 20% corn oil diet high in omega-6 fatty acids developed nearly twice the number of breast cancers as did rats on a 20% saturated fat diet. They also found that a small amount of omega-6 fatty acids added to a high saturated fat diet could induce breast cancers to the same extent as a 20% corn oil diet (6). In 1985, Jurkowski and Cave conducted experiments comparing the two essential polyunsaturated fatty acids, omega-6 and omega-3 fatty acids. They found that rats fed a 20% corn oil diet (omega-6) had the shortest tumor latency period and the highest tumor incidence, and that rats fed a 20% menhaden oil diet (omega-3) had the longest tumor latent period and the lowest tumor incidence (6). Omega-3 and omega-6 fatty acids also play a role in tumor growth rates and ability of the tumor to metastasize. Senzaki, et al conducted an experiment to evaluate different dietary fat diets on rats inoculated with the KPL-1 human breast carcinoma cell line that has a propensity to metastasize to axillary lymph nodes. They found that a diet high in the omega-3 fatty acid, EPA produced a reduction in tumor cell growth and metastasis, whereas the diet high in linoleic acid (omega-6) had an enhancing effect on growth and invasion (3).

Other studies do not agree with the hypothesis that omega-6 fatty acids promote breast cancer and omega-3 fatty acids inhibit tumor growth. The above mentioned Nurses' Health Cohort Study conducted by Holmes (5) found opposing results. Sasaki, et al conducted a study exploring the effects of varying the omega-3/omega-6 fatty acid ratio in rats induced with a carcinogen. They found that an increase in the ratio not only did not suppress carcinogenesis, but actually promoted tumor development (7).

### Possible Biochemical Mechanisms

Omega-3 and omega-6 polyunsaturated fatty acids are essential fatty acids that cannot be made by the body, so they must be consumed through the diet. Diets containing large quantities of omega-6 fatty acids, primarily linoleic acid, are associated with increased breast cancer promotion and a more aggressive and invasive phenotype. It is important to note that these dietary lipids do not induce carcinogenesis, but rather influence breast cancer tumor development by affecting biochemical events that occur after initiation of a cancerous cell (6). Addition of omega-3 fatty acids to the diet can block the promoting effects of omega-6 fatty acids. Therefore, omega-3 fatty acids have a protective role in breast cancer. The best understood mechanism involves the regulation of eicosanoid metabolism. Both omega-3 and omega-6 fatty acids give rise to metabolites such as prostaglandins, leukotrienes, and thromboxanes, which are collectively called eicosanoids (1). Eicosanoids are members of a family of autoacids and they exert hormone-like actions close to their sites of synthesis (4). The omega-6 fatty acid, linoleic acid can be converted to arachidonic acid which is the parent compound for several eicosanoids (1). Arachidonic acid is released from membrane phospholipid by stimuli such as growth factors and is further metabolized by the cyclooxygenase pathway into the series-2 eicosanoid,

prostaglandin E2, or through the lipoxygenase pathway into leukotrienes B4 and C4 (2). Tumor cells produce large amounts of arachidonic acid-derived eicosanoids like prostaglandin E2, which may have immunosuppressive properties that promote tumor growth (1). Omega-3 fatty acids inhibit the conversion of linoleic acid into arachidonic acid. Also, omega-3 fatty acids directly compete with arachidonic acid for incorporation into cell membranes. They also compete for the same enzyme pathways as arachidonic acid. Fish oil which is high in omega-3 fatty acids, specifically EPA and DHA, can compete as substrates for the cyclooxygenase and lipoxygenase pathways and produce prostaglandin E3 and 5 series leukotrienes which are not harmful to the cell (2). Therefore, omega-3 fatty acids inhibit tumor development by competitive inhibition of arachidonic acid metabolism, as well as by the unique effects of omega-3 fatty acid-derived metabolites. Omega-3 fatty acids achieve their anticancer effects by competitive inhibition of omega-6 fatty acid metabolism, which suggests that it is not the total amount of omega-3 fatty acids, but the balance of omega-3 and omega-6 fatty acids that is important (2). Therefore, one can compensate for a high omega-6 fatty acid diet by eating larger amounts of omega-3 fatty acids.

Other possible mechanisms of omega-3 fatty acid protection include reduction of circulating estrogen levels associated with high fish oil intake, modification of hepatic phase I and phase II detoxification systems affecting carcinogen detoxification and/or activation, and lipid peroxidation products of these fatty acids producing direct cytotoxic effects (1). Omega-3 and omega-6 fatty acids do not appear to affect BRCA1 gene expression in normal breast epithelial cells or breast cancer cell lines, nor do they seem to interact directly with estrogen receptors (8).

### Implications for Treatment/Prevention

As the biochemical mechanism of omega-3 and omega-6 fatty acid metabolism is further elucidated, there is promise for clinical applications to both reduce breast cancer risk in the general population as well as to provide treatment for the breast cancer patient. As the epidemiological evidence shows, populations with diets high in fish and seafood and low in corn and safflower oil have reduced breast cancer incidence. Therefore, efforts to increase the omega-3/omega-6 fatty acid ratio in one's diet can potentially reduce breast cancer risk. Having three to four servings of fish a week and substituting olive oil for corn oil, combined with exercise and a balanced diet could be a standard recommendation for breast cancer prevention. Also, it is possible that the ratio of omega-3/omega-6 fatty acids could be used as a screening tool to assess breast cancer risk (2).

For women who develop breast cancer, dietary intervention with increased omega-3 fatty acids and decreased omega-6 fatty acids may help improve prognosis. Combining these dietary changes with pharmacological agents that inhibit the cyclooxygenase or lipoxygenase pathways, which are responsible for the carcinogenic omega-6 metabolites, may enhance the efficacy of the treatment (9). Rose, et al studied the use of omega-3 fatty acids on disease progression after surgical excision of breast cancer tumors in nude mice. They used omega-3 fatty acids as both neoadjuvant (pre-surgical) and adjuvant (post-surgical) treatment. They found that the omega-3 fatty acids, EPA and DHA were effective in inhibiting lung metastases and could be a potential clinical intervention (10).

If dietary intervention could help improve the prognosis of breast cancer patients, then the efficacy of dietary changes must be measured. Bagga, et al conducted a study to determine if

short-term dietary intervention could change omega-3/omega-6 ratios in plasma and adipose tissue (breast and gluteal). Twenty-five women with high-risk localized breast cancer adopted a low-fat diet (less than 15% of total calories) and took fish oil supplements for a three-month period. They found that plasma levels of omega-6 fatty acids decreased, plasma omega-3 fatty acid levels increased three-fold, and the plasma omega-3/omega-6 ratio increased four-fold. The omega-3/omega-6 ratio in breast adipose tissue increased from .05 to .07. Furthermore, more dramatic changes were noted in breast adipose tissue compared to gluteal adipose tissue, suggesting a distinct microenvironment in the breast (2). Interestingly, total omega-6 content of adipose tissue did not change reflecting long-term storage of this prevalent polyunsaturated fat. Studies show that it takes approximately three years to decrease omega-6 fatty acid levels in adipose tissue (2). However, the short-term increases in omega-3 fatty acids can help offset the omega-6 stores by increasing the omega-3/omega-6 ratio.

### Conclusion

Breast cancer is a terrible disease that kills thousands upon thousands of women each year. Breast cancer is multi-factorial, and research into the genetic basis of the disease as well as development of novel new therapies continues at a frenetic pace. As the search for a "cure" continues, it is promising that simple dietary changes may help reduce breast cancer risk or even improve the prognosis of women who currently suffer from this devastating disease. Much research remains to be done, but until a definitive answer on the question of omega-3/omega-6 fatty acids is reached, it cannot hurt to eat a few extra servings of fish each week.

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### REFERENCES

1. Simonsen N, van't Veer P, Strain JJ, et al. Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC study. *Am J Epidemiol.* 1998;147:342-352.
2. Bagga D, Capone S, Wang H, et al. Dietary Modulation of omega-3/omega-6 polyunsaturated fatty acid ratios in patients with breast cancer. *J Natl Cancer Inst.* 1997;89:1123-1131.
3. Senzaki H, Iwamoto S, Ogura E, et al. Dietary effects of fatty acids on growth and metastasis of kpl-1 human breast cancer cells in vivo and in vitro. *Anticancer Res.* 1998;18:1621-1628.
4. Rose DP, Connolly JM. Dietary fat and breast cancer metastasis by human tumor xenografts. *Breast Cancer Res Treat.* 1997;46:225-237.
5. Holmes HD, Hunter DJ, Colditz GA, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. *JAMA.* 1999;281:914-920.
6. Cave WT. Omega-3 polyunsaturated fatty acids in rodent models of breast cancer. *Breast Cancer Res Treat.* 1997;46:239-246.

7. Sasaki T, Kobayashi Y, Shimizu J, et al. Effects of dietary n-3-to-n-6 polyunsaturated fatty acid ratio on mammary carcinogenesis in rats. *Nutr Cancer*. 1998;30:137-143.
8. Bernard-Gallon DJ, Maurizis J, Rio PG, et al. Effects of monounsaturated and polyunsaturated fatty acids (omega-3 and omega-6) on brca1 protein expression in breast cancer cell lines (correspondence). *J Natl Cancer Inst*. 1998;90:1234-1235.
9. Rose DP, Connolly JM, Liu XH. Fatty acid regulation of breast cancer cell growth and invasion. *Advances in Experimental Medicine and Biology*. 1997;422:47-55.
10. Rose DP, Connolly JM, Coleman M. Effect of omega-3 fatty acids on the progression of metastases after surgical excision of human breast cancer cell solid tumors growing in nude mice. *Clin Cancer Res*. 1996;2:1751-1756.

#### Additional Readings

Siguel EN. Re: Dietary Modulation of omega-3/omega-6 polyunsaturated fatty acid ratios in patients with breast cancer. *J Natl Cancer Inst*. 1998;90:629-631.