In North America and Europe, breast cancer accounts for over 25% of all new cancer diagnoses in women, and approximately 1 in 8 women will be diagnosed with breast cancer in their lifetime (1-3). Despite ongoing advances in screening, prevention, diagnosis, and treatment, breast cancer remains the second leading cause of cancer-related death in women, and one of the most expensive to treat (4). Relapse and metastasis remain high despite treatment with surgery and chemotherapy (5). Treatment itself carries risks. The side effects of chemotherapy include dose-limiting toxicity to the cardiac, immune, and nervous systems (6). Improving treatment...
without increasing toxic side effects is crucial to successful outcomes and long-term health.

**Omega-3 Fatty Acids and Breast Cancer**

Fish oil and high dietary consumption of fatty fish has consistently been associated with reduced incidence of breast cancer (7, 8). Fish oil is a rich source of omega-3 long chain polyunsaturated fatty acids (LCPUFA), predominantly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The majority of omega-3 LCPUFA in the diet is alpha-linolenic acid (ALA). EPA and DHA can be synthesized in the body from ALA, and EPA itself is a precursor of DHA. However, endogenous synthesis is very low and the only way to significantly increase these LCPUFA is to directly consume them. Consequently, the primary dietary sources of EPA and DHA are fatty cold water fish, supplements, or foods fortified with DHA/EPA. There is a growing evidence that EPA and DHA have distinct but overlapping physiological effects (9) and this might also apply to anti-cancer functions.

Breast cancer is divided into subtypes based on the expression of estrogen receptor (ER), progesterone receptor (PR), and the human epidermal group factor receptor 2 (HER2). The three main types of breast cancer are i) ER+/PR+ (also referred to as hormone sensitive), ii) HER2+, and iii) triple negative breast cancer, which does not express ER, PR, or HER2 (10). Treatment depends on several factors including
subtype and extent of disease, and can include a combination of surgery, radiation, and systemic therapy (11). Systemic therapy includes hormone therapy, targeted therapies, and chemotherapy. Hormone therapy, including treatment with the anti-estrogen drug tamoxifen, is indicated for patients with ER+/PR+ tumors. HER2+ tumors are treated with Herceptin (trastuzumab), a targeted therapy that binds and inhibits the HER2 receptor. Chemotherapy with cytotoxic agents is indicated for triple-negative breast cancer and advanced disease. There is convincing experimental evidence that incubating the different subtypes of human breast cancer cells with DHA alone or in combination with EPA decreases the survival of tumor cells (12). Similarly, when rodents with mammary tumors are fed a combination of EPA and DHA or DHA alone, tumor growth is decreased (13). This anti-cancer effect is specific to cancer cells, as the growth of normal mammary cells is not negatively altered by DHA and EPA (14).

**DHA and Breast Cancer Treatment**

**Reducing side effects of treatment**

Cytotoxic agents are toxic to cells, inhibiting growth. Unfortunately, cytotoxic agents are rarely specific to cancer cells. Consequently, chemotherapy in cancer treatment is often limited by dose-limiting toxicity or side effects. Side effects of chemotherapy include short-term side effects like fatigue, hair loss, and pain. Other side effects including cardiotoxicity and nerve damage can result in long-term health problems. DHA may ameliorate the side effects of some chemotherapeutic agents. Taxane drugs are commonly used to treat breast cancer, as well as ovarian, lung, and other solid tumors. These drugs inhibit cell proliferation. Treatment with some taxane drugs are limited by neurotoxicity, termed peripheral neuropathy, characterized by
numbness, tingling, and pain in the hands and feet (15). In a small randomized control trial, omega-3 LCPUFA supplementation (640 mg/day gelatin capsule, 54% DHA, 10% EPA) decreased the incidence of peripheral neuropathy in breast cancer patients being treated with the taxane drug paclitaxel (16). Other clinical trials report that supplementation with omega-3 LCPUFA (0.6g-8.6 g/day) increased the ability of patients to tolerate a variety of different chemotherapeutic drugs in a range of cancers, including lung cancer, pancreatic cancer, and colorectal cancer (17). In these patients, supplementation with DHA was associated with decreased weight loss, improved quality of life, and reduced anemia (17).

**Increasing sensitization to cytotoxic drugs**

There is increasing evidence that pre-treatment with DHA can increase the sensitivity of breast cancer cells to chemotherapy drugs. Doxorubicin, a drug that interferes with DNA replication, is commonly used in breast cancer treatment. In breast cancer cell lines, pre-incubation of cells with DHA followed by treatment with doxorubicin increases the effectiveness of this drug (14). A similar effect is seen in vivo in mice implanted with human breast tumors. Dietary supplementation with fish oil increased the effectiveness of doxorubicin, resulting in a greater reduction in tumor size compared to mice fed the control diet (18).

Similar results were seen when human breast cancer cells were treated with DHA and taxane drugs, commonly used as first line therapy in breast cancer (19). This increased sensitivity to taxanes has been confirmed in a rat model of breast cancer. Rats treated with a carcinogen to induce mammary tumors were fed either a control diet, or a diet rich in omega-3 LCPUFA (1% EPA, 2.5% DHA), and treated with
docetaxel, a widely used taxane drug. Tumors in rats fed a DHA rich diet had a significantly greater reduction in size compared to rats fed control diet (20). Thus, not only was DHA able to decrease side effects of taxanes, it may also improve the effectiveness of these drugs.

**Increasing sensitization to hormonal and targeted therapy**

In addition to sensitization to cytotoxic drugs, omega-3 LPCUFA may also be beneficial for hormone and targeted therapy in breast cancer. Tamoxifen is a hormone treatment used in ER+/PR+ breast cancer. It binds to ERα, preventing activation of this receptor by estrogen. This in turn prevents the activation of estrogen responsive genes including genes involved in proliferation, and other genes that can enhance tumor growth (21). In rats treated with a carcinogen to induce mammary tumors, a diet high in n-3 LCPUFA in combination with tamoxifen increased the regression of pre-cancerous growths compared to tamoxifen alone (22).

Herceptin is a monoclonal antibody that specifically recognizes and binds to the HER2 receptor, which is imbedded in the cell membrane. When HER2 is overexpressed or mutated, as it is in some breast cancers, it can signal to cells to proliferate (23). While HER2 is expressed by many cells in the body, a subset of breast cancer patients have tumors that overexpress this protein. When these patients are treated with Herceptin, the breast cancer cells that specifically overexpress this protein are targeted. Binding of Herceptin to HER2 on breast cancer cells inhibits proliferation (24). Recent studies have observed that when breast cancer cells expressing HER2 were treated with Herceptin, incubation with DHA increased cell death, and reduced growth compared to cells treated with Herceptin alone (25, 26).
Possible explanations as to how DHA and EPA can improve breast cancer treatment

The exact way that omega-3 LCPUFA inhibit breast cancer growth is not completely clear but there is evidence for several different possible paths. Incubating breast cancer cells with DHA and EPA reduces cell proliferation, and induces cell death (12). This anti-cancer effect is specific to malignant cells, as normal breast cells are not sensitive to similar concentrations of EPA or DHA (14). EPA and DHA are fatty acids that incorporate into the membrane. This results in a number of changes. Firstly, the membrane is more susceptible to oxidative damage. Tumors are not well equipped to repair this damage and it leads to a suicide-like death called apoptosis. Secondly, changes in the amount of EPA and DHA in the membrane can alter permeability to other molecules, perhaps even chemotherapy drugs. It also changes the amount, location and function of receptors and signals in the membrane that regulate growth and death of the tumor cells (27, 28). DHA has also been demonstrated to decrease the migration of breast cancer cells, and metastasis in mouse models of breast cancer (29-31). This could be due to changes in the cell membrane due to incorporation of DHA and EPA and/or changes in expression of proteins that promote metastasis. There is also evidence that DHA may eliminate breast cancer ‘stem’ or initiating cells. These are the cells within a tumor that are widely believed to be responsible for treatment resistance, cancer relapse and metastasis. Treatment of breast cancer cells with DHA can decrease the number of these cancer stem cells (32, 33).
DHA and other omega-3 LCPUFA have well established roles in the immune system (34). During development, these LCPUFA play essential roles in the proper establishment of the immune system. Omega-3 LCPUFA, specifically DHA and EPA can be metabolized to give rise to anti-inflammatory signaling molecules that mediate and reduce the inflammatory response (34). Omega-3 LCPUFA have been demonstrated to reduce inflammation and improve the ability of the immune system to recognize and target cancer cells in a variety of cancer models (35). In lung, colorectal, and pancreatic cancer, dietary DHA has been demonstrated to downregulate inflammation, and may improve anti-cancer immune targeting (36). This has not been well studied in breast cancer, but preliminary evidence suggests that DHA can alter the inflammatory response within mammary tumors (13), resulting in improved response to, and ability to tolerate, current treatment.

**Clinical evidence to support omega-3 LCPUFA supplementation in breast cancer patients**

A small phase II clinical trial was published in 2009 that examined the potential beneficial effect of DHA in combination with chemotherapy. In this trial, 25 patients with advanced, metastatic breast cancer were given DHA supplements in the form of capsules containing DHA-enriched triglyceride oil (1.8g/day total DHA), taken three times daily with meals. DHA supplementation started 7-10 days before beginning chemotherapy with a combination of cytotoxic drugs, and then continued with DHA supplementation for five months of chemotherapy (37). While all patients were given
the same amount of DHA, incorporation of DHA after a one week loading period was highly variable between patients, as measured by the amount of DHA incorporated into plasma phospholipids. Importantly, patients with high incorporation of DHA had significantly better response to chemotherapy than patients who had lower levels of DHA incorporation. In patients with high DHA incorporation, overall survival was 34 months, compared to 18 months in patients with low DHA incorporation. A similar study examining the potential benefit of DHA in combination with chemotherapy in advanced non-small cell lung cancer observed an increased response rate in patients receiving fish oil supplements containing DHA (38).

These results are supported by findings from a small prospective study of patients with non-metastatic, invasive breast cancer. In this study, the fatty acid content of breast adipose tissue obtained during biopsies was analyzed for fatty acid content. Increased DHA correlated with increased response to chemotherapy and the study determined that DHA was an independent predictive factor of sensitivity of the tumor to treatment (39).

While these results are promising, additional work is necessary for inclusion of supplementation with DHA into the current treatment for breast cancer and other cancers. Of note, while patients who had high incorporation of DHA had improved response to chemotherapy, presently, there is no way to predict which patients will have high DHA incorporation. The phase II clinical trial contained only a small number of patients with advanced breast cancer. DHA supplementation in patients with early breast cancer, and patients undergoing treatment with hormone and targeted therapy remains to be examined. Nonetheless, the pre-clinical evidence suggests that DHA has the potential to help all breast cancer patients
who undergo chemotherapy.

Conclusions

There is considerable interest by the public and patients for advice on nutritional interventions to treat cancer. Breast cancer patients have very high rates of reported use of nutritional supplements after diagnosis, with studies reporting 45-85% of breast cancer patients reporting supplement use (40-42). The anti-tumor effects of the nutrient DHA in preclinical models is well established and a number of potential ways to explain this effect have been identified. This anti-cancer effect is supported by human studies that observe decreased incidence of breast cancer with increased intake of fish oil containing omega-3 LCPUFA. Omega-3 LCPUFA, and specifically DHA, have been demonstrated to sensitize breast cancer cells to current treatment, without harming normal cells. This is supported by preliminary studies in advanced breast cancer patients undergoing chemotherapy. Current chemotherapy is limited by dose-limiting toxicity. Improving current treatments while sparing non-cancerous cells is essential to improving patient outcome. Using omega-3 LCPUFA to improve current breast cancer treatment provides a promising avenue of investigation and a new market for supplements and functional foods.

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