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The Use of Fatty Acids in Malignancies

Key Concepts

1) Fatty acids, which are categorized as w-3, w-6 or w-9, serve as substrates for eicosanoids such as prostaglandins and leukotrienes. They can have anti-inflammatory (w-3), neutral (w-9), or proinflammatory (w-6) effects, depending on the fatty acid substrate. This is of significant importance because inflammation is directly associated with factors such as cancer risk and progression.

2) The role of dietary fat intake in the risk of developing malignancies is controversial, possibly because most studies don't differentiate between the types of fat that are consumed. The effects of a diet where the main source of fat is fish (w-3 fatty acids such as EPA and DHA) is likely very different from a diet where red meat is the main source (w-6 fatty acids such as arachidonic acid), even if both diets contain identical amounts of total fat.

3) Whereas the role of fats in prevention is controversial, studies show that the intake of different fatty acids appears to have an important effect on the level of aggressiveness of the tumors, and the tendency for spread and metastases. W-6 fatty acids such as linoleic and arachidonic acid (found in many vegetable oils, dairy and red meat) tend to promote tumor aggressiveness, whereas w-3 fatty acids have the opposite effect.

4) The role of fatty acids through either diet and/or supplementation should be considered together with the role of substances that act as inhibitors of COX (cyclooxygenase) 1 and 2, and LOX (Lipoxygenase) enzymes.

5) Human studies have shown the potentially beneficial role of specific fatty acid supplementation in cancer cachexia, and in other clinical situations that are associated with significant catabolic and immunosuppressive effects, such as surgery.

6) Due to the effect on the immune system and inflammation, the use of fatty acids such as w-3, usually considered to be beneficial, might have paradoxical negative effects in some clinical situations, where the goal is to intensify immune and inflammatory activity. This might apply to situations where certain monoclonal antibodies or vaccines are used.

7) Studies and mechanistic rationales suggest a positive interaction with chemotherapy and radiation therapy.

The Role of Fats in the Development and Prevention of Human Malignancies

The role of fats in the development of human malignancies has been studied extensively, albeit with some controversial results, particularly in the area of prevention. Fay, et al. (1), performed a meta-analysis of animal experiments, and found that w-6, polyunsaturated fatty acids, and less so, saturated fatty acids, enhance the development of mammary tumors. Hunter, et al. (2), performed a pooled analysis of seven prospective studies looking at the association of breast cancer and fat intake, involving 337,819 women and 4980 cases. They looked at relative risks for saturated, monounsaturated, polyunsaturated and cholesterol intake and found no positive association with the risk of developing breast cancer. Cho, et al. (3), noting that most studies in breast cancer involved postmenopausal women, looked at premenopausal women in a prospective manner. They noted that women in the highest quintile of fat intake had a slightly increased risk of developing breast cancer, which was associated with the intake of animal fat (particularly red meat and high fat dairy foods), but not vegetable fat. They also noted a mildly increased risk associated with saturated fat and cholesterol intake. This is mechanistically plausible because w-6 fatty acids increase aromatase activity, leading to potentially negative effects due to estrogen metabolism.

Whereas the role in prevention isn't clear, possibly due to lack of differentiation in many studies of total fat from individual fatty acid intake, most studies show a relationship between fat intake and the level of aggressiveness, and the tendency for tumors to spread or metastasize (4). There are numerous plausible mechanistic reasons for this, including effects on adhesion molecules, proteolytic enzyme activity, and gap junctional communication (5). Holm, et al. (6), studied the dietary habits of 240 women already diagnosed with breast cancer, 149 of whom were estrogen receptor positive, and 71 who had tumors that were estrogen receptor negative. They found that in women with estrogen receptor positivity, there was a correlation with the tendency to relapse in those women who had a higher total fat, as well as a higher saturated fat intake. A study by Chen, et al. (7), investigated the effect of flaxseed on growth and metastasis in mice with estrogen receptor negative tumors. They noted beneficial effects leading to decreased growth and metastasis formation. This was thought to be partly due to a lowering of insulin growth factor 1, as well as epidermal growth factor receptor receptiveness. In vitro studies by Rose, et al. (8), looking at the tendency to metastasize, found strong suppressive effects of fish oil, as opposed to promoting effects of w-6 fatty acids. A study by Augustsson (9) found that fish intake of greater than 3 times per week decreased the incidence of prostate cancer, particularly those cancers that were metastatic. It was thought that in addition to the fatty acids present, other nutritional factors present in fish, such as Vitamins A and D, which can promote differentiation in cells, could be important.

Types and Sources of Fatty Acids

Fats contain different types of fatty acids, most importantly w-3, 6, and 9. The primary sources of w-3 fatty acids are flax (linseed) oil, and fish. W-3 fatty acids are primarily alpha linolenic (ALA), eicosapentaenoic (EPA), and docasohexanoic (DHA), the latter two coming from fish oils. The main w-6 fatty acids come from vegetable oils (linoleic) and animal fats (arachidonic). The main source of w-9 fatty acids is olive oil (oleic acid). The fatty acids serve as substrates for various eicosanoids, which have numerous effects, including having profound anti, neutral, or proinflammatory actions. As will be discussed in the section on inflammation and malignancies, inflammation can be strongly associated with various aspects of tumor promotion and spread, including effects on angiogenesis, immune function, glucose utilization, and apoptosis. W-3 fatty acids have an anti-inflammatory effect, whereas w-6 fatty acids promote inflammation, by acting as substrate for eicosanoids such as prostaglandins and leukotrienes. Oleic acids, which do not lead to prostaglandin or leukotriene production, are generally neutral in their effect on inflammation. In considering the use of these fatty acids, either through dietary manipulation or supplements, they should be considered in conjunction with inhibitors of inflammation, such as the enzymes COX 1 and 2, and LOX inhibitors (lipoxygenase). Numerous medications (celecoxib, zileuton), and natural substances (curcumin, boswellia) act as inhibitors in these ways.

In addition to acting as substrates for substances related to inflammation, it's important to note that fatty acids get incorporated into the cell membranes. Cell communication, as well as the passage of various substances through the cell membrane into the interior, is effected by the nature of the cell membranes, which is determined largely by the fatty acid content.

Fatty Acids and Tumors

The use of fatty acids has been studied in numerous tumor types, including breast, prostate, esophageal (10), pancreatic (11), and colon (12), with the suggestion of positive results associated with the use of w-3 fatty acids. One perplexing and possibly contradictory study involved a hematological malignancy, mycosis fungoides, in canines (13). They were fed safflower oil which is very high in w-6 fatty acids, and a remission was obtained in 6 of 8 dogs. As well as being unexpected, this does bring up the question if there is a difference in mycosis fungoides or hematological malignancies in general, compared to solid tumors. However, another study in canines, looking at lymphoma, used w-3 fatty acids with positive results (14). A note of caution is raised by Boik (28) regarding the interpretation of studies using fatty acid supplementation. Some studies employ very high doses without supplemental antioxidants, and the positive results obtained are probably due to the generation from unstable fatty acids of reactive oxygen species (ROS), rather than the other actions noted above.

Fatty Acids and Cancer Cachexia

Cancer cachexia is an area where human studies have looked at the use of various supplements, including fatty acids. Whereas feeding of high calorie diets has been the usual practice, considering that cancer cachexia can be viewed as a chronic inflammatory condition, with the presence of elevated levels of proinflammatory cytokines, such as TNF and Il-6 (15), might lead to a change in the high calorie approach. The degree of cachexia is directly correlated with the ratio of w-6/w-3 fatty acids, as well as the incorporation of arachidonic acid (an w-6 fatty acid and a precursor of series 2 proinflammatory prostaglandins) metabolites into the cells (16). In patients with pancreatic cancer, EPA supplementation (12 grams of fish oil, equal to 2 grams of EPA and 1.4 grams of DHA), reversed cachexia (17).

Other anticachectic agents of interest are those that protect the gastrointestinal lining, such as glutamine, as well as various antioxidants, such as high doses of Vit E, n-acetyl cysteine (18), and melatonin (19,20). Cancer cachexia is also associated, partly through a state of insulin resistance, with inefficient glucose uptake by normal cells, and excessive, partly anaerobic, use of glucose by tumor cells. W-6 fatty acids promote insulin resistance, whereas w-3 fatty acids reduce insulin resistance.(21, 22, 23). The use of fatty acids has also been studied in relationship to surgery (24), with beneficial results. This is probably related to the catabolic and immunosuppressive effects of surgery.

Interaction of Fatty Acids with Chemotherapy and Radiation Therapy

There are a few studies addressing the question of the interaction of fish oils with chemotherapy and radiation therapy (25, 26, 27). These suggest a positive interaction. Various mechanisms are suggested to explain this including improved delivery of drugs to the tumor through effects on normalizing the blood circulation (26). There is also an interesting perspective raised through the fact the use of high doses of fatty acids, without accompanying antioxidants, leads to an increase in ROS. Indeed, as mentioned above, many studies note beneficial tumor cell cytotoxicity effects of high doses of fatty acids precisely because of the production of ROS. As various chemotherapeutic and radiotherapeutic regimens kill cells through the production of ROS, combining these modalities with high doses of fatty acids might be worthwhile to study.

The improved delivery of drugs seen with fatty acids mentioned above has also been considered with antiangiogenesis agents. There are investigations addressing this same phenomenom by combining antiangiogenesis drugs with chemotherapy. Many chemotherapeutic regimens lead to a counterproductive, reflex elevation in inflammatory markers, such as COX 2 and NFkB, which work to limit the initial beneficial effects of chemotherapy. The use of fish oil supplements, as well as other anti-inflammatory substances, works against this limiting effect.

Negative Effects

Although in general it appears that increasing the use of w-3 fatty acids and decreasing w-6 fatty acids and saturated fats is beneficial, there are some potential unexpected negative effects to consider. Fatty acids, either through the diet or through supplements, have important effects on the immune system. They also have important effects on the inflammatory pathways, which are the tools the immune system employs to function. Although the study results are mixed, supplementation of fatty acids, especially w-6 but also w-3, tends to inhibit macrophage and lymphocyte proliferation and actions, such as T and NK cell activation (28). Supplementation of w-3 fatty acids will also decrease many inflammatory activities through its effects on prostaglandins and NFkB. There are certain clinical situations where this can be potentially deleterious. An example is when immune therapies, such as monoclonal antibodies or vaccines, are employed. These therapies activate the body's innate immune activities to attack the tumor cells. If these are inhibited, as could potentially happen with fatty acid supplementation, the efficacy of these treatments could be decreased. This important issue is discussed in more detail, though without a definitive conclusion, by Boik (29).

Another area of potential concern is combining very high doses of fatty acid supplementation with high doses of antioxidants. Many animal studies have employed extremely high doses of fatty acids (30), and the mode of action in these studies has been through the generation of reaction oxidation species (ROS). Antioxidants can block these actions, and certain studies have suggested this. However, the doses of fish oils recommended here and generally used probably work through their other effects, such as decreasing inflammation, rather than the generation of ROS. In this scenario, antioxidants and fatty acid supplementation probably work synergistically.

Dosages of fish oils or EPA/DHA are discussed in detail by Boik (30), extrapolating from animal and human studies. The recommended range is from 6-21 grams/day, assuming a synergistic effect being obtained when this is part of a multisupplement program, which is usually the case.

Conclusion

In conclusion, fatty acids have been studied in prevention, in combined use with chemotherapy and radiation therapy, as adjuvants in cancer cachexia, for their role in limiting aggressiveness and spread, and for their uses related to inflammation, estrogen and insulin metabolism. There is significant evidence and rationale to suggest the use of moderate to high doses of fish oil or DHA/EPA in most situations. One area of caution is using fish oils in combination with treatments that require significant activation of the body's immune system, such as with some monoclonal antibodies and vaccines.

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