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Omega-3 Fatty Acids and Cancer Prevention

Homer S. Black*

Department of Dermatology, Baylor College of Medicine, Houston, Texas 77030, USA

***Corresponding author:** Homer S. Black, Department of Dermatology, Baylor College of Medicine, Houston, Texas 77030, USA, Tel: 832-741-1052; E-mail: hblack@bcm.edu

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Introduction

A recent review has summarized the evidence that omega-3 fatty acids (FA) have potential in reducing the risk for a common form of cancer [1]. This editorial is a synopsis of that review covering the historical interest in the potential health benefits of omega-3 FA; the mechanistic rationale for such beneficial effect; and the experimental and clinical evidence that omega-3 supplementation could play an important role in cancer prevention.

Omega-3 fatty acids (FA) are one of two classes (Omega-3 and Omega-6) of essential fatty acids (EFA). They are both considered essential as they cannot be interconverted by the human body and the precursors, linoleic acid and linolenic acid for omega-6 and omega-3 FA respectively, must be provided in the diet [2]. Interest in the health benefits of omega-3 FA arose from earlier observations that Greenlandic West Coast Eskimos, whose lipid diet consisted mainly of marine oils, rich in omega-3 FA, exhibited low incidence of ischemic heart disease and general inflammatory symptoms [3-5]. Results from randomized clinical trials regarding the relation of omega-3 FA on cardiovascular disease (CVD) have remained controversial although observational studies have generally shown that higher levels of omega-3 FA intake was associated with lower risk for CVD outcomes [6-9]. Whereas the primary interest has been on cardiovascular disease, studies of other inflammatory diseases have included diabetes, inflammatory bowel disease, arthritis, and asthma [10,11]. A recent study reports that supplementation of omega-3 FA in the third trimester of pregnancy reduced the absolute risk of wheeze and asthma in offspring by about one-third [12].

Inflammatory mechanisms appear to be common to the above noted diseases as well as to carcinogenesis. Indeed, inflammatory processes are involved in initiation, promotion, and progression stages of cancer [13]. Herein, lays a rationale for potential involvement of omega-3 FA in reduction of cancer risk. These two series of FA, omega-6 and omega-3, compete for active enzyme sites in the cyclooxygenase (COX) and lipoxygenase (LOX) pathways and thus influence the oxidative metabolites passing through these pathways [2]. The omega-6 FA metabolites are of greater hormonal potency than those of the omega-3 FA. Some of these metabolites are known to influence tumor biology. As an example, prostaglandin E2 (PGE2), derived from the omega-6 FA metabolism through the COX pathway, acts as a tumor promoter and has been associated with aggressive growth patterns in both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in humans [14]. Contrarily, omega-3 FA, competing with omega-6 FA, inhibit the production of PGE2 and results in formation of the less potent PGE3. Omega-3 FA may also shunt potential prostaglandin precursors through the LOX pathway resulting in intermediates that inhibit tumor growth and that are involved in immune surveillance [15]. Based upon the influence of dietary lipids on the COX and LOX pathways, and their differential bioactive intermediates, a strong rationale is provided for the potential of omega-3 FA in cancer prevention. Consequently, this potential has been examined in several types of cancers. Although studies on the effects of omega-3 FA on CVD have generally been positive, the studies on human cancers have been equivocal. Some cohort and case control studies, but not all, have shown that women that have a higher intake of omega-3 FA intake, compared to omega-6 FA, have a lower incidence of breast cancer. However, among 43 risk ratios calculated across 19 cohorts for 11 different types of cancer and five different ways to assess omega-3 FA consumption, only four were significant and it was concluded that omega-3 FA did not reduce overall cancer risk [16-19]. Similar ambiguities occur with respect to prostate cancer [20,21].

The American Cancer Society estimates that over 3.5 million new cases of skin cancer will occur this year in the U.S. [22]. In regard to this most common cancer, a considerable body of experimental and clinical evidence, albeit circumstantial at this point, exists that omega-3 FA supplementation could reduce the incidence of this most frequently occurring cancer. This evidence has been reviewed [1] and is herein summarized:

Experimental animal studies

- Increasing dietary levels of omega-6 FA exacerbates ultraviolet radiation (UVR)–induced carcinogenic expression whereas omega-3 FA dramatically inhibits UVR carcinogenic expression with regard to both tumor latency and multiplicity [23, 24].
- Pro-inflammatory and immunosuppressive PGE2 levels are increased linearly as dietary omega-6 FA levels are increased whereas PGE2 levels are dramatically reduced by dietary omega-3 FA consumption [25].
- Dietary omega-6 FA suppresses the immunologic responses involved in tumor transplant rejection and the immunologic pathways involved in delayed type hypersensitivity (DTH) and contact hypersensitivity (CHS), whereas omega-3 FA inhibits the UVR induced suppression of DTH and CHS [25-27].

Human clinical and cell culture studies

- Omega-3 FA supplementation significantly increases the erythema (an inflammatory response) threshold to UVR [28, 29].
- Omega-3 FA modulate a number of cytokines and eicosanoids, including PGE2, that mediate immune and inflammatory responses [30-34].
- Omega-3 FA inhibit specific genotoxic markers of UVR-induced DNA damage, including UVR-induced cutaneous p53 [35].
- Omega-3 FA abrogate UVR-induced immunosuppression of cell mediated immunity assessed as nickel CHS [34].

Indeed, these data are overwhelming suggestive that omega-3 FA supplementation could result in a significant reduction in human skin cancer incidence. It has been suggested that the most direct evidence for the positive potential of omega-3 FA in this preventive role is through intervention trials in populations with high, and known risk for non-melanoma skin cancer with a study design similar to that in which reduction of total dietary fat intake was shown to reduce cancer risk [36-38]. It is probable that omega-3 FA supplementation could have beneficial effects on a range of other inflammatory diseases.

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