The potential of omega-3 fatty acids in the prevention of non-melanoma skin cancer

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Abstract

In toto, there is strong circumstantial evidence from both experimental and clinical studies to support a role for ω-3 FA in the prevention of non-melanoma skin cancer (NMSC). In experimental animal studies there is direct evidence that dietary ω-3 FA inhibits ultraviolet radiation (UVR) carcinogenic expression, with regard to both increased tumor latent period and reduced tumor multiplicity. Equivalent levels of ω-6 FA increase UVR carcinogenic expression. Dietary ω-3 FA dramatically reduces the plasma and cutaneous pro-inflammatory and immunosuppressive PGE2 levels in mice. Dietary ω-6 FA increases prostaglandin E synthase type 2 (PGE2) level. Dietary ω-3 FA significantly reduces the inflammatory response and sustains, or enhances, the delayed type hypersensitivity immune response in mice when compared to an equivalent dietary level of ω-6 FA. Supplementary ω-3 FA significantly increases the UVR-mediated erythema threshold in humans. Supplementary ω-3 FA significantly reduces the level of pro-inflammatory and immunosuppressive PGE2 levels in Ultraviolet B-irradiated human skin.

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1. Introduction

Essential fatty acids (EFA) are those that must be supplied in the diet and, as implied, comprise necessary precursors of a series of highly active chemicals required for normal growth and maintenance of health. The bioactive chemicals produced from EFA are hormones, classified as eicosanoids, and include lipoxins, leukotrienes, prostaglandins, and thromboxanes (Fig. 1). These required substances cannot be synthesized by mammals, but must be produced by oxidation from specific polyunsaturated fatty acids (PUFA), hence, EFA. There are two naturally occurring EFA series. Linoleic (LA) and arachidonic (AA) acids are representative of one, the omega (ω) -6 series, and are so named because the first of their double bonds, as shown, begin at the sixth carbon atom from the methyl end of the carbon chain. Omega-6 EFA are derived from dietary LA.
The other series, the \( \omega-3 \) fatty acids, are characterized by the location of the first double bond at the third carbon from the methyl end of the chain and are represented by eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. These fatty acids are derived from \( \alpha \)-linolenic acid (ALA), found in phytoplankton, the latter being the base of the marine food chain and thus the origin from which high levels of EPA and DHA accumulate in marine fats. The \( \omega-3 \) FA are also found in some plant oils and leaves of vegetables, especially green leafy foods [1].

\[
\text{EICOSAPENTAENOIC ACID} = \text{EPA} \ (20:5, \omega-3)
\]

\[
\text{DOCOSAHEXAENOIC ACID} = \text{DHA} \ (22:6, \omega-3)
\]

Considerable interest has focused upon the potential health benefits of \( \omega-3 \) FA since a series of reports appeared in which high dietary intake of these highly unsaturated FA was specifically associated with low incidence of ischemic heart disease among Greenlandic Eskimos, and inflammatory symptoms, in general [2–5].

In addition, the two series of PUFA are not interconverted in the human body and each leads to active oxidation products that differ in hormonal potency [6], with the \( \omega-3 \) derived products generally being much less active than their \( \omega-6 \) counterparts. Thus, both \( \omega-6 \) and \( \omega-3 \), or more likely their relative levels, can influence the flux of metabolites through the cyclooxygenase and lipoxygenase pathways. Several products of these pathways influence tumor biology. Prostaglandins (PG), particularly of the 2-series derived from \( \omega-6 \) FA, appear to act as tumor promoters, down regulate macrophage tumoricidal activities, and inhibit IL-2 production [7–9]. They promote cellular hyperproliferation and tumor angiogenesis, while suppressing apoptosis [10]. Increased prostaglandin E synthase type 2 (PGE\(_2\)) levels have been associated with aggressive growth patterns of both basal and squamous cell skin carcinomas in humans [11]. Moreover, \( \omega-3 \) FA compete for binding sites on cyclooxygenase and inhibit this enzyme. It has also been suggested that \( \omega-3 \) FA may shunt potential PG precursors through the lipoxygenase pathway, possibly resulting in products that inhibit tumor growth and those that are involved in immunosurveillance [12,13]. However, elevated levels of \( \omega-6 \) FA derived lipoxygenase products associated with cancer promotion have been found in skin cancers, and \( \omega-3 \) FA may also competitively reduce their production [10]. Indeed, the cyclooxygenase and lipoxygenase enzymes are being targeted, via the application of specific inhibitory agents, for chemoprevention of a range of cancers [10,14]. Thus, a rational basis exists for oral \( \omega-3 \) FA supplements to play an important role in the prevention, and/

Fig. 1. Simplified diagram of eicosanoid metabolism. AA is metabolized via lipoxygenase and cyclooxygenase pathways to produce lipoxins, leukotrienes, prostaglandins, and thromboxanes. EPA competes, as a competitive inhibitor to the cyclooxygenase enzyme complex, with AA and produces different oxidation products as shown for the leukotrienes and prostaglandins. The 3-series prostaglandins resulting from EPA oxidation are usually much less active than the 2-series derived from AA. Malondialdehyde (MDA) is a product of prostaglandin and thromboxane metabolism and is commonly used as a measure of lipid peroxidation.
or, modulation of skin cancer expression. Moreover, this dietary approach provides the advantage of a high safety profile, contrasting with that of non-steroidal anti-inflammatory drugs [15]. The purpose of this report is to explore the experimental and clinical evidence suggesting such a preventative role for ω-3 FA in non-melanoma skin cancer (NMSC).

2. Experimental evidence

2.1. Animal studies

2.1.1. Early studies of the influence of dietary fat on carcinogenesis

Although a number of earlier studies had demonstrated that dietary fat could influence the growth of transplanted tumors in animals [reviewed, 16], the first indictment that dietary fat could potentiate carcinogenesis, per se, resulted from the studies of Watson and Mellanby [17] in which dietary fat (12.5–25% butterfat) was shown to enhance coal tar-induced skin tumor formation in mice. It was not long thereafter that the influence of dietary fat on ultraviolet radiation (UVR)-induced carcinogenesis was demonstrated [18]. The fact that dietary fat influences carcinogenesis induced by a physical agent (UVR) implies that this dietary constituent exerts its influence on a basic, underlying facet of cancer development and not merely by altering the nutritional milieu in which the pharmacokinetic action of a chemical carcinogenic agent might be predicated, i.e., transport to target sites, activation/deactivation, binding, etc. Although many of the earlier studies dealt with chemical carcinogenic agents, the results of a few are particularly pertinent to any discussion of the influence of ω-3 FA on carcinogenesis. First, Lavik and Baumann [19] found that diets composed almost entirely of saturated FA would retard chemically induced hepatomas in rats and that the presence of lipid peroxides did not alter the tumor-promoting power of dietary fat. Both oxygenated and UVR-treated samples, while exhibiting a high peroxide number, were relatively inactive in their influence on carcinogenesis. The second interesting observation was that of Haven [20] in 1936, who found that growth rate of rat carcinoma 256 was lower in animals receiving a diet containing cod liver oil (iodine number 145–180) than that of animals fed coconut oil (iodine number 8–9.5). It was suggested that this inhibitory action was related to the presence of long chain FA in cod liver oil. In retrospect, it now seems probable that ω-3 FA were responsible for the inhibitory effect. The importance of these early studies is two-fold in that they pointed to two factors that would only become apparent from later studies—first, the level of lipid peroxidation, as normally measured, may be of less consequence to the carcinogenic process than originally thought and second, there was, even in 1936, a hint that ω-6 and ω-3 FA could have vastly different influence on carcinogenesis, regardless of degree of saturation. With respect to the latter, Carroll et al. [21–23] found that rats fed unsaturated fats developed more mammary tumors than those fed the same levels of saturated fat and that PUFA, especially ω-6 FA, may be tumor promoters. The EFA, LA (ω-6), apparently is required for mammary carcinogenesis in the rat [24].

2.1.2. Influence of dietary PUFA on UVR-induced carcinogenesis

Excessive exposure to solar UVR accounts for approximately 90% of all NMSC in humans [25] and it is surprising that nearly 45 years lapsed from the time that Baumann and Rusch [18] made their seminal observation that dietary fat could influence UVR-carcinogenesis (photocarcinogenesis) before this line of investigation was to again receive attention. A series of studies were begun in 1983 that demonstrated an approximate linear relationship between PUFA (corn or soybean oils which consist of approximately 50% of the ω-6 FA, LA) intake and UVR-carcinogenic expression, with the lowest fat level resulting in a significantly longer tumor latent period and lower tumor multiplicity [26,27]. Regression analysis of data from six experiments clearly demonstrated that tumor latency period decreased and tumor multiplicity increased in an approximate linear manner as the level of corn oil in the diet increased [28].

Reeve et al. [29] found that feeding a diet supplying totally saturated sunflower oil (catalytically hydrogenated) completely abolished the UVR carcinogenic response whereas those animals fed polyunsaturated sunflower oil exhibited 100% tumor incidence, indicating that PUFA was a requirement for UVR carcinogenesis. When the diet of animals receiving the hydrogenated fat was reconstituted to a normal mixed fat diet, large numbers of skin tumors rapidly appeared, suggesting that UVR initiation had not been prevented by lack of PUFA, but that an EFA deficiency held the tumors in abeyance, i.e., at the promotion stage.

2.1.3. The stage of carcinogenesis modified by dietary PUFA

In an effort to delimit the segment along the carcinogenic continuum at which dietary lipid exerts its principal effect, animals were placed on defined isocaloric diets containing low (0.75%, w/w) and high (12%, w/w) levels of corn oil. Immediately after a regimen of UVR and before tumors appeared, diets of some of the groups were crossed to the contravening diet. Analysis of the resulting tumor incidence curves and tumor multiplicity provided confirmation not only that diets containing high levels of ω-6 FA significantly enhance UVR-induced cancer expression, but that the principal enhancement occurred during the post-initiation, or promotion, stage of carcinogenesis [30]. Perhaps more important, crossing from a high fat to a low fat diet, after a cancer-causing dose of UVR had been administered, negated the exacerbating influence of high fat diets. This evidence provided direct experimental evidence that dietary...
modification through a low ω-6 FA intervention could act to ameliorate UVR cancer expression.

It is important to note that in the above study, when ω-3 FA fed animals were crossed to high ω-6 FA after UVR initiation, an exacerbation of UVR carcinogenic expression occurred that was similar to which occurred when crossing from low to high ω-6 FA diets. This was expected. However, crossing from high ω-6 FA to ω-3 FA did not produce the ameliorating effect on tumor multiplicity observed when crossing from high to low ω-6 FA. These results suggest that ω-3 FA either exerts its principal anticarcinogenic effect during the UVR-initiation phase, contrary to the effect of an equivalent level of ω-6 FA, or that promotion events had progressed beyond the point where dietary intervention with ω-3 FA could alter the course of carcinogenic expression. This is an important point when considering the potential of ω-3 FA intervention as a strategy for the prevention of skin cancer.

2.1.4. PUFA modification of photocarcinogenesis and relationship with lipid peroxidation

Some of these studies strongly implied that free-radical-mediated reactions, especially as exemplified by lipid peroxidation [27], played a role in at least part of the carcinogenic response to UVR. Experimentally, the level of UVR-induced cutaneous lipid peroxidation is a direct function of ω-6 FA intake. However, subsequent studies with menhaden oil, a marine oil, indicated that a much more complex response was involved. Menhaden oil is highly unsaturated and is rich in EPA, as well as DHA and other ω-3 FA. EPA has an even higher iodine number (the proportion of unsaturated linkages) than does LA and thus, represents an even more vulnerable target for free radical attack. When animals were fed a diet employing menhaden oil as lipid source, UVR carcinogenic expression was markedly inhibited when compared to animals fed diets with equivalent levels of corn oil [31]. There were no significant differences in UVR transmission through epidermis from corn or menhaden oil fed animals. Thus, the differences in carcinogenic (or acute) responses could not be attributed to UVR dose diminution or reduction in lipid peroxidation.

2.1.5. PUFA modification of photocarcinogenesis and relationship with acute UVR effects

Other UVR-induced cutaneous responses were also influenced by the ω-3 FA diet. After a 2-week feeding period of 12% (w/w) ω-3 FA, UVR-induced ornithine decarboxylase (ODC) activity and inflammatory responses (erythema and edema) were dramatically inhibited (Table 1). However, the relation of the latter events to carcinogenesis remains highly speculative as low levels (4%, w/w) of ω-3 FA significantly inhibited carcinogenesis while producing no effect upon these acute responses. It may be that inflammation and ODC inhibition on the course of PUVA-tumorigenesis [33]. Whereas ω-3 FA produced a dramatic decrease in inflammatory response and a more rapid repair of PUVA toxicity, there was no inhibition on the course of PUVA-tumorigenesis. There was no significant influence of the ω-3 FA diet on tumor latency but at week 40 of the experiment there was actually a significant increase in tumor multiplicity when compared to animals receiving a ω-6 FA diet. Cutaneous phototoxic reactions to various photosensitizers are mediated by the release of inflammatory agents from dermal mast cells and the generation of AA metabolites, the same mediators that participate in immune responses [34].

Further evidence that inflammation is not necessarily a requisite event for carcinogenesis comes from studies of the influence of ω-3 FA on 8-methoxypsoralen + UVA radiation (PUVA)-induced tumorigenesis [33]. Whereas ω-3 FA produced a dramatic decrease in inflammatory response and a more rapid repair of PUVA toxicity, there was no inhibition on the course of PUVA-tumorigenesis. There was no significant influence of the ω-3 FA diet on tumor latency but at week 40 of the experiment there was actually a significant increase in tumor multiplicity when compared to animals receiving a ω-6 FA diet. Cutaneous phototoxic reactions to various photosensitizers are mediated by the release of inflammatory agents from dermal mast cells and the generation of AA metabolites, the same mediators that participate in immune responses [34].

As PUVA tumorigenesis does not exhibit time-dose reciprocity, i.e., cumulative dose per se is not an accurate index of tumorigenic risk, and because of the dramatic

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**Table 1**

Comparison of the influence of ω-6 and ω-3 FA on UVR-induced carcinogenesis, inflammatory, and immunological responses

<table>
<thead>
<tr>
<th>Dietary lipid</th>
<th>Tumor latency</th>
<th>Tumor multiplicity</th>
<th>Edema</th>
<th>ODC</th>
<th>Inflammatory response</th>
<th>Hapten response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75% ω-6 FA</td>
<td>22.30</td>
<td>1.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0% ω-6 FA</td>
<td>21.2</td>
<td>1.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0% ω-6 FA</td>
<td>20.5</td>
<td>2.10</td>
<td>0.263</td>
<td>2.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.0% ω-6 FA</td>
<td>19.20</td>
<td>2.50</td>
<td>0.269</td>
<td>2.80</td>
<td></td>
<td>40.8</td>
</tr>
<tr>
<td>4.0% ω-3 FA</td>
<td>23.31</td>
<td>0.31</td>
<td>0.109</td>
<td>0.78</td>
<td></td>
<td>29.7</td>
</tr>
<tr>
<td>12.0% ω-3 FA</td>
<td>26.14</td>
<td>0.23</td>
<td>0.070</td>
<td>0.78</td>
<td></td>
<td>21.1</td>
</tr>
</tbody>
</table>

Compilation of data from references [30,31,38].

- **a** Median tumor time (week).
- **b** Number of tumors per animal.
- **c** Measured as double skin fold thickness at 0 and 24 h post-UVR. Reported as change in thickness (mm).
- **d** Ornithine decarboxylase activity 24 h post-UVR (nmol 14CO2/mg protein/h).
- **e** Inflammatory response to dimethyl sulfoxide (DMSO). Increase in footpad thickness (mm × 10^{-2}).
- **f** Net hapten response to dinitrochlorobenzene (DNCB). Total delayed-type hypersensitivity (DTH) minus inflammatory response to DMSO vehicle. Footpad thickness (mm × 10^{-2}).
reduction of PUVA toxicity by ω-3 FA, it was suggested that ω-3 FA supplementation might be used in conjunction with PUVA therapy. By ameliorating PUVA toxicity, more aggressive PUVA therapy might be tolerated, thus taking advantage of the non-reciprocal nature of PUVA tumorigenesis and thereby reduce the risk of skin cancer resulting from PUVA therapy.

2.1.6. PUFA modification of photocarcinogenesis and relationship with immunosuppression

Earlier studies had suggested that the promotion stage of carcinogenesis might be modulated immunologically. Indeed, the systemic alteration induced by UVR that suppresses an animal’s ability to reject highly antigenic UVR-induced tumor transplants occurs during the chemical-promotion stage of carcinogenesis [35]. Further, the studies that reported that UVR carcinogenesis could be inhibited by feeding mice an EFA (ω-6 FA) deficient diet [29], led to the suggestion that lack of eicosanoid precursors, as occurs in EFA deficiency, might prevent UVR induction of the immune suppressed state and, thus, account for the protection from UVR-initiated tumor outgrowth [36]. Indeed, it has been shown that suppressor T-cell function is PGE2 dependent and that UVR-induced suppression of contact hypersensitivity (CH), an immune response that may share pathways with tumor transplant rejection, is abrogated by treatment with an inhibitor of PG synthesis [37]. Subsequently, it was shown that plasma PGE2 levels were directly related to the level of ω-6 FA intake, with the highest PGE2 level occurring with the highest level of ω-6 FA that, in turn, induced the greatest exacerbation of UVR-carcinogenic expression [38]. Dietary ω-3 FA reduced the plasma PGE2 level below that exhibited by the lowest level of ω-6 FA intake, even when supplemental LA was added to the diet. The latter reflects the effective competitive nature, as a substrate analogue, to block synthesis of 2-series of PG through the cyclooxygenase pathway. Perhaps more importantly, dietary EPA provides dramatic protection against UVR-induced immunosuppression [39].

Just as with CH, delayed type hypersensitivity (DTH) is also regulated by T-cell function and shares common paths with immunologic tumor rejection [40]. DTH is significantly suppressed in animals fed high levels of ω-6 FA compared with those fed low levels of ω-6 FA or comparable levels of ω-3 FA [38,41]. In support of a dietary fat and immune function relationship, the ability of an animal to reject a transplanted tumor was found to be related to the level of ω-6 FA intake. Animals receiving low dietary ω-6 FA exhibited a tumor rejection time that was comparable to that of non-irradiated animals, whereas the rejection time for animals fed high levels of ω-6 FA was three-times longer, and occurred at a time when high ω-6 FA had been shown to exacerbate primary tumor expression [41]. Subsequent T-lymphocyte transfer studies, in which lymphocytes from animals receiving high ω-6 FA and a cancer-initiating dose of UVR were transferred to animals receiving the same UVR regimen but a low ω-6 FA diet, resulted in a significant reduction of the tumor latent period [42].

2.2. Conclusions from experimental data

The following conclusions can be drawn from the above data:

- Dietary ω-6 FA exacerbates UVR carcinogenic expression, both with respect to a shorter tumor latent period and increased tumor multiplicity. Exacerbation is linearly related to the log of ω-6 FA intake over the range of 0.75–4% (w/w) and plateaus with maximum effect at 12% (w/w).
- Dietary ω-3 FA inhibits UVR carcinogenic expression with respect to both tumor parameters, i.e., ω-3 FA lengthens the tumor latent period and reduces tumor multiplicity.
- The principal effect of ω-6 FA on carcinogenic expression is manifested during the post-initiation, or promotion, stage of UVR-carcinogenesis.
- The influence of ω-3 FA on carcinogenic expression is manifested across the carcinogenic continuum and is apparently induced during the pre-experimental feeding run-in period before UVR is administered.
- Pro-inflammatory and immunosuppressive PGE2 levels increase linearly with the log of the concentration of dietary ω-6 FA intake.
- Pro-inflammatory and immunosuppressive PGE2 levels are dramatically reduced by dietary ω-3 FA intake. A two–three-fold reduction in plasma PGE2 level occurs in ω-3 FA fed animals, compared to an equivalent level of ω-6 FA intake, even when ω-3 FA diets are supplemented with a level of ω-6 FA adequate to meet the minimum dietary LA requirement.
- Dietary ω-6 FA suppresses the immunologic responses involved in tumor transplant rejection and the immunologic pathway(s) manifested in DTH.
- Dietary ω-3 FA does not suppress, but sustains, the DTH response.

It is clear that a major mode of action of dietary fat on UVR-carcinogenic expression occurs by modulation of immune pathways; that this modulation appears to be closely related to differential influence of ω-6 and ω-3 FA on immuno-active and inflammatory products of the eicosanoid pathways; and that these effects are manifested at a time when the host animal is being immuno-compromised by UVR. The experimental evidence from animal studies strongly suggests that ω-3 FA intake could have a beneficial influence on NMSC occurrence and provides the rationale upon which clinical studies with this EFA have been undertaken.

2.3. Human studies

2.3.1. Epidemiologic studies of fat intake and NMSC

An international study had found an association of dietary fat intake with skin cancer incidence but the
controlled study have recently been reviewed [56]. However, unlike the experimental animal studies that have clearly demonstrated a strong influence of dietary fat upon UVR carcinogenesis, epidemiologic studies have failed to provide consistent evidence for a link between any type of dietary fat and skin cancer occurrence [44–48]. Recent examination of a selected number of such studies have found that, overall, the evidence suggests a positive relationship between fat intake and BCC and SCC incidence [49]. However, the authors point to the limitations of the existing observational studies and call for further well-designed and implemented studies to clarify the role of diet in skin cancer. Indeed, these types of studies are fraught with methodological difficulties that are primarily related to the complex nature of the human diet in a free-living population and difficulties in measuring food intake and analyzing dietary information (especially those involving dietary history questionnaires that rely on the study subjects’ recall over long periods of time), although some methodology has even involved “self-diagnoses” of a specific skin cancer type, i.e., BCC [47].

2.3.2. Intervention study of fat intake and NMSC

Some of the limitations of observational studies of diet and cancer can be circumvented by randomized intervention designs, whereby direct answers to the question of dietary impact upon cancer incidence can be obtained [50]. The results of such a study, a randomized clinical intervention trial that directly addressed whether dietary lipid could influence the occurrence of NMSC, were reported in a series of papers beginning in 1994 [16,51–55]. This study provided clear evidence that a large decrease in the percentage of calories taken as fat reduced the occurrence of pre-malignant actinic keratoses and NMSC in patients who had experienced one, but not more than two, previous skin cancers and suggested that implementation of a low-fat diet could play an important role in the clinical management of this highly prevalent form of cancer. The dietary parameters involved only a reduction in the calories consumed as fat, while maintaining total calorie intake and body weight, the latter two being potentially confounding variables that could cloud the trial outcome. An effort was made to maintain the polyunsaturated/saturated fat (P/S) ratio and there were no significant increases in ω-3 FA intake. The parameters of the experimental design of this tightly controlled study have recently been reviewed [56]. Another prospective study of a cohort of men, in which higher total fat intake was associated with a lower risk of BCC, found that higher intake of ω-3 FA was significantly associated with a lower BCC risk, although the association weakened when non-white males were excluded. The authors concluded that ω-3 FA was not materially related to BCC risk [47]. A further, population-based case control study, showed a consistent tendency toward a lower risk of SCC with higher intakes of ω-3 FA [58]. These investigators also found a tendency toward decreased risk of SCC with increased intake of diets with high ω-3 to ω-6 FA ratios.

2.3.4. Dietary ω-3 FA photoprotection studies in humans

Whereas the latter study was suggestive that ω-3 FA could influence NMSC risk, a number of human studies have provided a physiologic rationale to support such a hypothesis. Encouraged by the results obtained in animal studies, a short-term supplementation study of mixed ω-3 FA was conducted in humans [59]. Twenty-six subjects were randomized into two groups, one receiving 4 g/day of mixed EPA (2.8 g) and DHA (1.2 g), the other group, the control, received a gelatin placebo. Assessments of the erythemal threshold to UVR (minimal erythema dose, MED) were made at 0 time, 2 and 4 weeks. Cholesterol, triglycerides, and PGE2 levels were also determined at the respective time intervals. There were no significant effects on any of the measured parameters seen after 2-week supplementation. However, at 4 week there was a small, but significant increase in the MED (the equivalent of a sun protection factor, SPF, of 1.15) and the triglyceride levels had decreased by 40 mg/dl. Based upon the age-adjusted cancer incidence/UV exposure plots of Sayre [28], even an SPF of the magnitude reported, if provided over a lifetime, could reduce skin cancer incidence by as much as 30%. Subsequently, a second study involving 15 patients was undertaken to examine the effect of ω-3 FA supplementation upon susceptibility to UBV-induced erythema and epidermal lipid peroxidation [60]. The subjects were given 3 g of mixed ω-3 FA (1.8 g EPA; 1.2 g DHA) per day, administered in five capsules taken twice daily, over a 3–6 month period. The MED to UBV rose progressively with increasing time of ω-3 FA supplementation, until it had more than doubled at 6 months. This increase in MED was accompanied by a pronounced increase in epidermal ω-3 FA composition and a rise in cutaneous susceptibility to lipid peroxidation. The MED returned to baseline 2.5 months after cessation of ω-3 FA supplementation. Omega-3 FA supplementation that led to decreased sensitivity to UBV was accompanied by a significantly increased threshold to UVA-provocation of a photosensitivity condition, polymorphic light eruption. Another photosensitivity disorder, hydroa vacciniforme, was also partially ameliorated with mixed ω-3 FA supplementation [61].
2.3.5. Relationship between anti-inflammatory and chemoprotective properties of ω-3 FA

An increase in SPF, based on erythema, does not, of course, assure that other manifestations of UVR damage, particularly those associated with cancer, have not occurred. There now exists a rather diverse group of agents, both steroidal and non-steroidal, that demonstrate apparent photoprotection by ameliorating the inflammatory response to UVR, i.e., erythema, while other effects of UVR are unaffected [62,63]. On the other hand, a specific cyclooxygenase-2 inhibitor has been shown to be an effective protectant in mice to UVR-carcinogenesis and an inhibitor of PGE2 induction, while exhibiting no overt reduction in inflammation [64]. Certainly it can be seen in Table 1 that inflammatory response (edema) is not detected in mice at 4% level of ω-3 FA intake, a level that does, however, have a significant inhibitory effect upon tumor expression. In addition, as UVR transmission through epidermis of mice receiving equivalent levels of ω-6 and ω-3 FA is not significantly different, this is further indication that ω-3 FA influences the SPF, not by physical absorption of UVR or diminution of UVR dose, but rather by differential cycling of precursors through the lipoxygenase and cyclooxygenase pathways. Upstream events may also play a role, since EPA inhibits arachidonic acid-induced activation of NFκB, transcription factor responsible for inducing the synthesis of a range of inflammatory mediators [65].

Omega-3 FA has, indeed, been shown to modulate a number of cytokines and prostaglandins that mediate inflammatory and immune responses. When normal human keratinocytes were cultured in the presence of EPA and then irradiated, tumor necrosis factor-α (TNF-α) and interleukin 1α (IL-1α) secretion was induced [66]. Moreover, LA, an ω-6 FA, did not result in higher TNF-α or IL-1α levels in non-irradiated or UVB-irradiated keratinocytes. The ω-3 FA treatment resulted in a higher level of lipid peroxidation and reduced PGE2 and IL-6 levels. The increased levels of TNF-α and IL-1α could be expected to have pronounced stimulatory effects on cellular immune function. Subsequent studies with cultured keratinocytes revealed that ω-3 FA, both EPA and DHA, inhibited IL-8, a chemokine pivotal to UBV-induced skin inflammation, which also exhibits pro-carcinogenic properties. TNF-α induces IL-8 secretion and this induction is also inhibited by ω-3 FA [67]. However, in a double-blind, randomized study of 28 patients, receiving 4 g/day of 95% of ethyl esters of EPA or oleic acid for 3 months, there was no evidence that reduction of the sunburn response in healthy skin in vivo by EPA was mediated by the pro-inflammatory cytokines IL-18, TNF-α, IL-6 or IL-8. The authors noted that this was not an exhaustive study of the effects of EPA on cutaneous cytokines, since other time-points after UVR and mRNA, as opposed to protein expression, remain to be examined. There was, however, a pronounced and significant reduction in levels of the pro-inflammatory and immunosuppressive mediator PGE2 in UVB-irradiated skin after EPA supplementation [68].

2.3.6. Influence of dietary ω-3 FA on early genotoxic markers in humans

The same supplementation regimen, i.e., 4 g EPA/day for 3 months, produced an eight-fold increase of the ω-3 FA in skin, thus demonstrating its bioavailability. In this study a number of early genotoxic markers were examined [69]. Not only did the ω-3 FA, EPA, protect against the clinical sunburn response, but also against UVR-induced p53 expression in skin, considered to be a biomarker of DNA damage. There was no evidence of an effect of EPA on direct UVR-induced damage, e.g., cyclobutane thymine dimer formation, nor upon basal oxidative damage to DNA. However, there was significant protection by EPA against UVR-induced single strand breaks. It is conceivable that protection to acute UVR-induced genotoxic responses, i.e., sunburn, UVR-induced cutaneous p53, and strand breaks in ex vivo UVR-treated peripheral blood lymphocytes, might predict a long-term reduction in skin cancer in humans. The investigators speculated that these effects may indicate ω-3 FA protection against UVR-induced free-radical mediated mutagenesis. Possible mechanisms include preferential damage of these unstable fatty acids by free radical attack [60] and a reduction in reactive species generated during AA metabolism [70]. Supplementary ω-3 FA not only inhibits the sunburn reaction, but inhibits other genotoxic markers of DNA damage, i.e., UVR-induced cutaneous p53 expression and single strand breaks in ex vivo UVR-treated peripheral blood lymphocytes.

2.4. Future considerations

It seems unlikely that observational studies, using current methodology and experimental design, will provide a clear answer to the question of whether ω-3 FA can reduce NMSC occurrence. However, because of the promising evidence provided from animal studies; the provocative results from photosensitivity studies; the influence of ω-3 FA on cyclooxygenase and lipoxygenase products; and upon cancer biomarkers in humans, it is important that the potential of ω-3 FA as a preventive agent to NMSC be fully explored. This might best be achieved through direct intervention trials in populations with high, and known, risk for NMSC—much in the manner that reduction in the percentage of calories consumed as fat has been shown to influence NMSC occurrence in skin cancer patients [51,52].

There are several questions that must be considered in designing such a study. First, in animal studies in which ω-3 FA were shown to inhibit cutaneous carcinogenesis, the dietary FA, either ω-6 or ω-3, were the sole sources of lipid. This will not be the case in human diets. The relative ratios of ω-6/ω-3 FA in the human diet will determine response. Indeed, it has been shown in a population-based case control study that SCC risk is increased when the AA level of red blood cell membrane is highest [71]. It has already been demonstrated that cutaneous ω-3 FA composition increases eight-fold and that PGE2 levels are significantly reduced in
humans after 3 months of supplementation with 4 g ω-3 FA/day. These responses should be indexed to some easily determined parameter such as red blood cell membrane ω-6/ω-3 FA ratio that can be frequently monitored. In addition, frequent dietary assessment of ω-6/ω-3 FA intake should be monitored, as an increase in ω-6 FA will diminish any beneficial effect of ω-3 FA.

Even in such a tightly controlled study there are other concerns. The results from animal studies suggest that ω-3 FA exerts its anti-carcinogenic effect during initiation, contrary to the effect of an equivalent level of ω-6 FA, or that events in ω-6 to ω-3 FA crossover had already progressed beyond the point where dietary intervention with ω-3 FA could alter the course of carcinogenic expression. Because of the long latent period of human NMSC, in any short-term intervention trial of cancer patients, as suggested above, it is assumed that most NMSC arise from previously transformed (initiated) cells and outgrowth of tumors is related to post-initiation, or promotion, events. Others have reported that ω-3 FA operates at both initiation and promotion stages, the latter related to ω-3 FA modulation of PG synthesis [72]. In the case of NMSC, ω-3 FA influence on initiation could be related to effects on acute biomarkers as previously reported and this would cause under-reporting of any long-term benefits derived from ω-3 FA in skin cancer patients in an intervention trial. Nevertheless, in as much as tumor outgrowth is related to the action of immunomodulatory eicosanoids, a medium-term study of cancer patients should provide a definitive answer to the question of whether ω-3 FA can ameliorate NMSC expression.

References


