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Research Article

Serum Omega-3 and Omega-6 Fatty Acids and Cutaneous p53 Expression in an Australian Population

Jolieke C. van der Pols[1], Chunxia Xu[2], Glen M. Boyle[2], Maria C. Hughes[1], Samuel J. Carr[1], Peter G. Parsons[2], and Adèle C. Green[1]

Abstract

Background: There is some evidence from experimental studies that long-chain n-3 and n-6 fatty acids may be able to modify early skin carcinogenesis, but whether this applies in the general population is not known.

Methods: We investigated associations between serum polyunsaturated fatty acid concentrations and p53 expression in normal skin, as a biomarker of early UV-induced carcinogenesis, in an unselected sample of Australian adults. Participants in the Nambour Skin Cancer Prevention Trial provided a dorsal hand punch biopsy which was used for immunohistochemical assessment of p53 immunoreactivity. Cross-sectional associations with serum fatty acid concentrations were analyzed in 139 participants, adjusting for confounding variables including skin phenotype, past sun exposure, and smoking status.

Results: There was an inverse association, showing a dose–response relationship, between total n-3 fatty acid serum concentrations and p53 immunoreactivity in the whole epidermis and the basal layer. This was particularly due to eicosapentanoic acid and docosahexanoic acid concentrations. There was no evidence for increased p53 immunoreactivity in participants with relatively high serum n-6 fatty acid concentrations. The ratio of n-3 to n-6 fatty acid concentrations was not associated with p53 immunoreactivity.

Conclusion: These results add to growing evidence that long-chain fatty acids may be able to modify early skin carcinogenesis.

Impact: The prospect that increased intake of n-3 fatty acids could help prevent skin cancer is attractive.
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Introduction

Exposure to UV radiation, the principal environmental cause of skin cancer (1), causes mutations in the p53 gene, a central component in the mechanisms protecting skin cells from malignant transformations (2). Such mutations are present in the majority of keratinocytic skin cancers (3, 4) resulting in loss of normal ("wild-type") p53 and expression of mutant p53 protein (5), indicating reduced capacity to trigger programmed cell death. Mutant p53 protein may also independently stimulate oncogenesis (6).

There is some evidence that dietary omega-3 polyunsaturated fatty acids (herein termed n-3 fatty acids) have photoprotective effects on the skin, whereas n-6 fatty acids may exacerbate UV-induced carcinogenesis. A series of animal studies showed that supplemental feeding with n-3 fatty acids lengthens the tumor latency period and reduces the number of UV-induced tumors (reviewed in ref. 7). Furthermore, crossover designs of n-3– and n-6–rich diets in animal studies suggested that n-3 fatty acids exert their anticarcinogenic effect during the early UV-initiation phase (7). This is supported by a study of supplementation with the n-3 fatty acid eicosapentaenoic acid (EPA) for 3 months in humans, which showed a reduction in sunburn sensitivity and a reduction in UV-induced p53 expression in the skin (8), indicating that dietary n-3 fatty acids may afford protection against early genotoxic markers. A recent experimental study confirmed the involvement of n-3 and n-6 fatty acid derived prostaglandins in the inflammatory response following sunburn (9).

In contrast, n-6 fatty acids have shown cancer-promoting effects in experimental studies. Feeding studies in rodents have shown that diets containing high levels of n-6 fatty acids enhance UV-induced cancer occurrence (10), and upregulate growth of other tumor types (11). In a case–control study, higher erythrocyte arachidonic acid concentrations increased the risk of cutaneous squamous cell carcinoma (12). In light of these opposing effects of n-3 and n-6 fatty acids on skin carcinogenesis, it may be their relative ratio that influences skin cancer development (7).

Because it is not clear whether findings from these, mostly experimental, studies can be extrapolated to

Authors' Affiliations: [1]Cancer and Population Studies Group and [2]Drug Discovery Laboratory, Queensland Institute of Medical Research, Brisbane, Australia

Corresponding Author: Jolieke C. van der Pols, Cancer and Population Studies, Queensland Institute of Medical Research, Locked Bag 2000, Royal Brisbane Hospital, Brisbane, Queensland 4029, Australia. Phone: 61-7-3845-3591; Fax: 61-7-3845-3503. E-mail: jolieke.vanderpols@qimr.edu.au

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general human populations, we investigated associations between serum polyunsaturated fatty acid concentrations and p53 expression in normal skin, a biomarker of early UV-induced carcinogenesis, in an unselected sample of Australian adults. We previously showed that cutaneous p53 expression in this study population is associated with past UV exposure, and that this may be mitigated by regular sunscreen use (13).

Materials and Methods

Study population

Study participants were randomly selected from those taking part in the Nambour Skin Cancer Prevention Trial carried out between 1992 and 1996. Full details have been reported elsewhere (14, 15). In summary, the trial participants were randomly chosen residents of Nambour, a township in southeast Queensland, Australia (latitude 26° S). In a 2 × 2 factorial design, individuals were randomized independently to daily sunscreen application Sun Protection Factor 15+ sunscreen to head, neck, arms, and hands or usual, discretionary sunscreen use, and β-carotene or placebo supplementation.

During a clinic visit for the trial in 1996, 162 randomly selected participants were invited to provide a 2-mm punch biopsy from the back of the left hand, which was fixed in formalin and stored in paraffin. Participants also completed a questionnaire which asked about typical time spent outdoors, use of sunscreen on different parts of the body including the hands, and smoking behavior. History of skin cancer treated by a doctor before the trial, skin color, and propensity to sunburn were recorded in the baseline questionnaire of the trial.

All participants provided written informed consent, the Declaration of Helsinki was followed, and the Queensland Institute of Medical Research Ethics Committee approved the study.

Immunohistochemical staining

Using immunohistochemistry, mutant p53 protein in skin tissue sections was made visible microscopically through binding with a color-labeled, protein-specific antibody. Wild-type p53 protein has a very short half-life (5 to 20 minutes) and is not readily detectable by immunohistochemistry, whereas mutated p53 gene encodes a protein with a substantially prolonged half-life (5 to 24 hours) indicated by p53 immunoreactivity (16–18).

Expression of the p53 protein in the paraffin-embedded skin sections was investigated by the DO-7 monoclonal antibody (Novocastra Laboratories) at 1:50 dilution. The immunohistochemical staining method, using microwave antigen retrieval, has been described previously (19). All slides were counterstained with hematoxylin and examined at ×400 magnification by investigator C. X. who was blinded to subject identity. For each subject, a negative control section was examined to monitor the staining quality based on the level of nonspecific background staining. The intensity of the counterstain and maintenance of tissue architecture were also considered for the staining quality. Sections considered of poor quality were discarded or replaced with spare slides cut from the same tissue block. Only brown-red nuclear staining epidermal cells, including keratinocytes and melanocytes, were interpreted as p53-positive cells. The total number of epidermal cells and p53-positive epidermal cells was counted in the whole section. Furthermore, the total number of basal cells (epidermal cells attached to the dermal–epidermal junction) and p53-positive basal cells was also counted separately in the whole section. Three randomly selected sections were counted twice for reproducibility analysis.

We assessed p53 immunoreactivity in two ways: by the proportion (percent) of p53-positive cells in the whole epidermis (the number of p53-positive cells in the whole section divided by the total number of epidermal cells in the whole section) and by the proportion (percent) of p53-positive cells in the basal layer (the number of p53-positive cells in the basal layer divided by the total number of basal cells in the whole section). Mutations of the p53 gene occur in cells that are located in both the outer and basal layers of the epidermis (20). It remains unclear whether the location of p53-damaged cells within the epidermis is associated with skin cancer risk, but mutations in the more differentiated outer layers of the skin are thought to be less detrimental than mutations in the basal, stem-cell rich layer of the epidermis.

Plasma phospholipid fatty acids

Nonfasting venous blood samples of 30 mL were collected by standard venipuncture techniques performed by experienced phlebotomists in 1996. Only participants who had consumed a light breakfast (e.g., toast or cereal, no cooked breakfast) provided a blood sample. Blood samples were processed at the time of collection and serum samples were stored in approximately 1 mL aliquots at −70°C until analysis. Measurements of plasma phospholipids fatty acids were conducted by Flinders Medical Centre (Adelaide, Australia) using procedures described in detail previously (21). Briefly, plasma was extracted in chloroform: methanol and stored at −70°C before fatty acids analysis. The total lipid extract from the plasma fractions was fractionated by thin-layer chromatography and the phospholipids fractions retained. Fatty acid methyl esters were separated and quantified with gas chromatography (Hewlett-Packerd 6890 with a 50-m capillary column).

Statistical analysis

Participants were divided into thirds, ranked according to their plasma fatty acid concentration. Group differences in p53 immunoreactivity were tested by ANOVA for an unbalanced design (PROC GLM in SAS) for which the p53 immunoreactivity outcome variables were $\log_e$ transformed to achieve a normal distribution. We first applied a basic adjustment for age and sex. In the multivariable model we also adjusted for the confounding effects of skin color, propensity to sunburn,

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β-carotene allocation during the trial, and reported use of sunscreen on the hands. Variables which were also investigated as confounders but did not change the estimates of p53 immunoreactivity include smoking status, skin cancer history before or during the trial (including self-reported history of skin cancer before the trial or incident skin cancer during the trial), time spent outdoors on weekend days during the past 6 months, time spent outdoors on weekdays during the past 6 months, and sunscreen allocation during the trial

All tests were 2-sided and a significance level of $P < 0.05$ was used. All analyses were carried out by SAS version 9.1.3 (SAS Institute, Inc.).

Results

Of the 162 invited participants, 147 (91%) provided a skin sample by punch biopsy. Immunohistochemical staining of p53 was successfully carried out in 139 (95%) of these samples. The intraclass correlation coefficient for the sections that were counted twice for reproducibility analysis was 0.98. The p53 immunoreactivity of both the whole epidermis and the basal layer was significantly higher among men than women, and among participants who had spent more time outdoors on weekdays and weekend days during the past 6 months (Table 1).

Table 1. General subject characteristics by p53 immunoreactivity of the skin; Nambour Skin Cancer Prevention Trial, 1996

Subject characteristic	Number of subjects	% p53-positive cells in the whole epidermis, median (25% percentile, 75% percentile)	% p53-positive cells in the basal layer of the epidermis, median (25% percentile, 75% percentile)
Sex			
Male	78	8[a] (4, 22)	10[a] (5, 22)
Female	61	5[a] (2, 13)	7[a] (2, 11)
Age group, y			
30–39	73	7 (3, 21)	9 (4, 20)
40–49	18	9 (4, 13)	9 (5, 20)
50–59	22	11 (3, 25)	10 (5, 28)
60–69	19	6 (1, 11)	6 (2, 12)
≥70	7	4 (3, 9)	4 (4, 8)
Skin color			
Fair	80	9 (4, 20)	9 (4, 21)
Medium	52	6 (3, 15)	8 (4, 13)
Olive	7	3 (3, 16)	6 (2, 12)
Propensity to sunburn			
Always burn	34	7 (2, 17)	7 (4, 17)
Burn then tan	96	7 (3, 16)	9 (4, 17)
Only tan	9	9 (4, 34)	9 (6, 25)
Cigarette smoking			
Current smoker	20	8 (2, 33)	9 (3, 50)
Former smoker	43	7 (4, 18)	13 (7, 33)
Never smoker	76	7 (2, 15)	9 (4, 20)
Time spent outdoors on a typical week day during the past 6 months, h			
<1	53	7[b] (3, 13)	8[a] (4, 12)
2–4	50	5[b] (2, 12)	7[a] (2, 12)
5–8	30	11[b] (6, 36)	16[a] (6, 34)
9–12	5	22[b] (9, 42)	24[a] (14, 50)
Time spent outdoors on a typical weekend day during the past 6 months, h			
<1	21	4[b] (2, 13)	5[b] (3, 11)
2–4	84	6[b] (3, 14)	8[b] (3, 14)
5–8	32	16[b] (6, 30)	17[b] (7, 39)
9–12	1	9[b]	14[b]
Skin cancer history before or during the trial			
No	111	7 (3, 19)	9 (4, 20)
Yes	28	7 (3, 13)	8 (4, 15)

[a] $P < 0.01$ for group differences.
[b] $P < 0.05$ for group differences.

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Table 2. Serum fatty acids by p53 immunoreactivity expressed as proportion of p53-positive cells in the whole epidermis (mean and 95% CI) by tertile group of serum fatty acids; Nambour Skin Cancer Prevention Trial, Australia

Fatty acid	Tertile 1	Tertile 2	Tertile 3	*P*[a]
Total n-3[b], μg/mL	36.7 (20.7–43.6)	50.2 (43.8–55.8)	67.1 (55.9–112.2)	
% Basic[c]	10.6 (7.0–16.1)	7.6 (5.2–10.9)	5.5 (3.9–7.8)	0.03
% Multivariable[d]	14.0 (8.0–24.5)	8.1 (4.8–13.6)	6.1 (3.9–9.6)	0.006
ALA, μg/mL	1.2 (0.5–1.5)	1.8 (1.5–2.2)	2.9 (2.2–5.2)	
% Basic	7.1 (4.7–10.7)	6.5 (4.4–9.4)	7.7 (5.3–11.1)	0.78
% Multivariable	7.2 (4.1–12.6)	7.0 (4.1–11.9)	8.2 (5.0–13.3)	0.83
EPA, μg/mL	6.5 (2.7–8.0)	10.1 (8.1–12.2)	14.8 (12.3–32.6)	
% Basic	9.4 (6.2–14.4)	7.8 (5.3–11.5)	5.7 (4.0–8.2)	0.15
% Multivariable	11.2 (6.6–19.3)	7.8 (4.7–12.8)	6.0 (3.6–10.0)	0.06
DHA, μg/mL	26.7 (16.0–31.7)	37.7 (32.0–42.1)	52.1 (42.2–77.4)	
% Basic	9.2 (6.1–14.0)	6.7 (4.6–9.7)	6.4 (4.5–9.2)	0.27
% Multivariable	13.3 (7.2–22.6)	7.4 (4.5–12.2)	6.8 (4.2–10.8)	0.03
Total n-6, μg/mL	305.5 (187.1–331.1)	361.7 (331.6–387.3)	426.6 (389.4–573.7)	
% Basic	7.1 (4.9–10.4)	9.4 (6.4–13.7)	5.4 (3.7–7.8)	0.07
% Multivariable	8.8 (5.4–14.6)	9.7 (5.6–16.8)	5.6 (3.4–9.3)	0.08
LA, μg/mL	194.3 (122.8–212.7)	240.3 (214.1–264.2)	290.2 (267.2–413.4)	
% Basic	7.2 (4.9–10.6)	9.6 (6.4–14.3)	5.6 (3.9–8.0)	0.09
% Multivariable	8.8 (5.3–14.6)	9.5 (5.4–16.6)	6.2 (3.8–10.2)	0.22
AA, μg/mL	98.3 (54.8–114.7)	124.4 (115.3–132.2)	148.1 (134.1–181.8)	
% Basic	7.6 (5.2–11.1)	8.2 (5.2–12.1)	5.8 (4.0–8.5)	0.32
% Multivariable	9.0 (5.4–15.0)	8.8 (5.3–14.7)	5.9 (3.6–9.7)	0.16
Ratio n-3/n-6	0.10 (0.08–0.13)	0.14 (0.13–0.15)	0.18 (0.15–0.38)	
% Basic	7.8 (5.2–12.1)	7.7 (5.2–11.4)	6.4 (4.5–9.0)	0.64
% Multivariable	9.6 (5.4–16.9)	7.8 (4.7–12.9)	6.8 (4.1–11.1)	0.41

Abbreviations: AA, arachidonic acid; ALA, alpha-linolenic acid; LA, linoleic acid.

[a]From ANOVA for unbalanced design, type III sum of squares.

[b]Median (minimum–maximum), all such values.

[c]Proportion of p53-positive cells (mean and 95% CI) adjusted for age and sex.

[d]Proportion of p53-positive cells (mean and 95% CI) adjusted for age, sex, skin color, propensity to sunburn, β-carotene allocation during the trial, and use of sunscreen on the hands.

There was an inverse association, showing a dose–response relationship, between total n-3 fatty acid serum concentrations and p53 immunoreactivity in the whole epidermis and the basal layer. Participants in the highest group of total plasma n-3 fatty acid concentrations had lowest p53 immunoreactivity in both the whole epidermis (Table 2) and the basal layer (Table 3). After adjustment for confounding variables, those in the highest group of total plasma n-3 fatty acid had on average 6.1% (95% CI, 3.9–9.6) p53 immunoreactivity in the whole epidermis compared with 14.0% (95% CI, 8.0–24.5) in participants in the lowest group of total plasma n-3 fatty acid ($P = 0.006$). This inverse trend was also seen for individual long-chain n-3 fatty acids, with lowest p53 immunoreactivity in participants in the highest compared with lowest groups of EPA ($P = 0.06$) and docosahexaenoic acid (DHA; $P = 0.03$) serum concentrations (Table 2). p53 immunoreactivity of the basal layer showed similar associations, although only statistically significant for total n-3 fatty acids and DHA (Table 3).

There was an inverse association between total serum n-6 fatty acids and p53 immunoreactivity of the whole

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Table 3. Serum fatty acids by p53 immunoreactivity expressed as proportion of p53-positive cells in the basal layer of the epidermis (mean and 95% CI) by tertile group of serum fatty acids; Nambour Skin Cancer Prevention Trial, Australia Prevention Trial, Australia

Fatty acid	Tertile 1	Tertile 2	Tertile 3	*P*[a]
Total n-3[b], μg/mL	36.7 (20.7–43.6)	50.2 (43.8–55.8)	67.1 (55.9–112.2)	
% Basic[c]	11.2 (7.3–17.1)	7.7 (5.3–11.3)	5.8 (4.1–8.3)	0.04
% Multivariable[d]	13.0 (7.4–22.7)	7.4 (4.4–12.5)	5.8 (3.7–9.2)	0.008
ALA, μg/mL	1.2 (0.5–1.5)	1.8 (1.5–2.2)	2.9 (2.2–5.2)	
% Basic	6.8 (4.5–10.3)	6.6 (4.5–9.6)	8.8 (6.0–12.8)	0.44
% Multivariable	6.1 (3.5–10.7)	6.4 (3.8–10.9)	8.1 (4.9–13.2)	0.53
EPA, μg/mL	6.5 (2.7–8.0)	10.1 (8.1–12.2)	14.8 (12.3–32.6)	
% Basic	8.7 (5.7–13.4)	8.4 (5.7–12.5)	6.3 (4.3–9)	0.38
% Multivariable	9.3 (5.3–16.0)	7.7 (4.6–12.8)	5.8 (3.5–9.6)	0.21
DHA, μg/mL	26.7 (16.0–31.7)	37.7 (32.0–42.1)	52.1 (42.2–77.4)	
% Basic	10.6 (7.0–16.1)	6.5 (4.5–9.5)	6.8 (4.8–9.7)	0.08
% Multivariable	13.0 (7.4–23.0)	6.5 (4.0–10.7)	6.5 (4.0–10.4)	0.009
Total n-6, μg/mL	305.5 (187.1–331.1)	361.7 (331.6–387.3)	426.6 (389.4–573.7)	
% Basic	7.3 (5.0–10.8)	9.3 (6.3–13.8)	6.0 (4.1–8.8)	0.20
% Multivariable	8.2 (5.0–13.6)	8.5 (4.9–14.8)	5.6 (3.3–9.2)	0.19
LA, μg/mL	194.3 (122.8–212.7)	240.3 (214.1–264.2)	290.2 (267.2–413.4)	
% Basic	7.4 (5.0–10.9)	9.6 (6.4–14.4)	6.2 (4.3–9.0)	0.23
% Multivariable	8.1 (4.8–13.6)	7.8 (4.4–13.8)	6.2 (3.8–10.2)	0.54
AA, μg/mL	98.3 (54.8–114.7)	124.4 (115.3–132.2)	148.1 (134.1–181.8)	
% Basic	7.9 (5.4–11.5)	8.7 (5.9–12.9)	6.2 (4.2–9.0)	0.33
% Multivariable	8.4 (5.0–14.0)	8.4 (5.0–14.1)	5.5 (3.3–9.0)	0.15
Ratio n-3/n-6	0.10 (0.08–0.13)	0.14 (0.13–0.15)	0.18 (0.15–0.38)	
% Basic	8.4 (5.5–12.9)	8.0 (5.4–11.8)	6.7 (4.7–9.5)	0.62
% Multivariable	9.1 (5.1–16.1)	7.2 (4.3–12.0)	6.4 (3.9–10.6)	0.41

Abbreviations: AA, arachidonic acid; ALA, alpha-linolenic acid; LA, linoleic acid.

[a]From ANOVA for unbalanced design, type III sum of squares.

[b]Median (minimum–maximum), all such values.

[c]Proportion of p53-positive cells (mean and 95% CI) adjusted for age and sex.

[d]Proportion of p53-positive cells (mean and 95% CI) adjusted for age, sex, skin color, propensity to sunburn, β-carotene allocation during the trial, and use of sunscreen on the hands.

epidermis though this was of borderline statistical significance ($P = 0.08$; Table 2) and not seen in the basal layer. Assessment of individual n-6 fatty acids showed no associations with p53 immunoreactivity.

The ratio of plasma n-3 to n-6 fatty acids concentrations was not associated with p53 immunoreactivity of the epidermis.

Discussion

In this unselected community-based sample of Australian adults there was an inverse association, showing a dose–response relationship, between total n-3 fatty acid serum concentrations and p53 immunoreactivity. Persons in the highest group of serum n-3 fatty acid concentrations, in particular EPA and DHA, had lower p53 immunoreactivity both in the whole epidermis and the basal, stem-cell rich layer of the epidermis. There was no evidence for increased p53 immunoreactivity in participants with relatively high serum n-6 fatty acid concentrations. The ratio of n-3 to n-6 fatty acid concentrations was not associated with p53 immunoreactivity.

These findings corroborate those of Rhodes and colleagues, who showed that p53 expression was significantly

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reduced in persons who took an EPA supplement for 3 months compared with a control supplement (8), and other previous experimental work (reviewed in ref. 7).

The p53 protein detected through immunohistochemical staining represents stabilized and probably mostly mutant rather than wild-type p53 protein, due to its increased half-life which makes it immunohistochemically detectable. The inverse association between n-3 fatty acids and p53 expression in this and other studies thus suggests that n-3 fatty acids may influence the process by which UV exposure causes mutations in the p53 gene, resulting in a lower expression of mutant p53 protein. The mechanism that could underlie such an effect remains unclear but it has been suggested that n-3 fatty acids, which are relatively unstable and readily oxidized (22), may act as a buffer to protect other structures from UV-induced damage (23). Different mechanisms such as through altered inflammatory response due to metabolic competition between n-3 and n-6 fatty acids are also possible.

On the basis of the literature, we had hypothesized that higher concentrations of n-6 fatty acids would be associated with increased p53 immunoreactivity, because p53 immunoreactivity is an early marker of UV-induced carcinogenesis and n-6 fatty acids have been associated with increased tumor growth (10, 11) and increased risk of squamous cell carcinoma of the skin (12). However, our results did not suggest such an association; on the contrary they showed that p53 immunoreactivity was lowest in participants with highest total serum n-6 fatty acid concentrations, although the group differences were of borderline statistical significance ($P = 0.08$). The association between n-6 fatty acids and skin carcinogenesis is mainly hypothesized to be due to mediation by arachidonic acid of the inflammatory and immune responses to UV damage, through its role in production of eicosanoids such as prostaglandins, thromboxanes, and leukotrienes (24). This hypothesized underlying pathway may be less relevant to increases in mutant p53 protein levels, which were detected in our immunohistochemical study. Sacrificial oxidation to protect other structures, as hypothesized for n-3 fatty acids (as discussed earlier in the text), may be a possible explanation for this inverse relationship but evidence for an underlying protective mechanism is needed.

The prospect that long-chain n-3 fatty acids are able to modify early skin cancer carcinogenesis is attractive, because these fatty acids are of dietary origin, in particular from oily fish such as salmon and sardines, and diet is readily modifiable. However, evidence from dietary studies of the association between n-3 or n-6 fatty acid intake or biochemical status of these fatty acids and skin cancer risk is very limited to date. A large, prospective study in male U.S. health professionals suggested a small but statistically significant positive association between intake of long-chain n-3 fatty acids and risk of basal cell carcinoma, but personal-level past UV exposure could not be accounted for in that study (25). Erythrocyte long-chain n-3 fatty acids were not associated with squamous cell carcinoma risk in a case–control study in Arizona, but concentrations of the n-6 fatty acid AA were associated with increased squamous cell carcinoma risk in that study (12). More evidence from studies that are designed to assess specific intake of long-chain fatty acids or biomarkers of these and skin cancer risk is needed.

In conclusion, we have shown an inverse association between serum n-3 fatty acid concentrations, in particular EPA and DHA, and p53 immunoreactivity in the epidermis in a community-based sample of unselected adults. These results add to the growing evidence that long-chain fatty acids may be able to modify early skin carcinogenesis. The prospect that increased intake of n-3 fatty acids, in particular through increased consumption of oily fish, could have skin cancer preventive effects is attractive. More evidence from well-designed observational studies is needed, and human clinical trials to test this proposition are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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