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Short Communication

Plasma Omega-3 and Omega-6 Concentrations and Risk of Cutaneous Basal and Squamous Cell Carcinomas in Australian Adults

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Abstract

Laboratory-based evidence suggests that omega-3 and omega-6 polyunsaturated fatty acids may affect skin photocarcinogenesis, but epidemiologic evidence is inconsistent. In 1,191 White Australian adults, we prospectively investigated associations between baseline plasma concentrations of omega-3 and omega-6 fatty acids and cutaneous basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). Relative risks (RR) and 95% confidence intervals (CI) were estimated on the basis of number of histologically confirmed tumors diagnosed during follow-up (1997–2007). Plasma eicosapentaenoic acid (EPA) concentrations and omega-3/-6 ratio showed significant inverse associations with SCC tumors, comparing higher tertiles with the lowest, in age- and sex-adjusted models ($P_{trend} = 0.02$ and 0.03, respectively) which weakened after adjustment for past sun exposure. Associations between EPA and SCC were stronger among participants with a history of skin cancer at baseline ($n = 378$; highest vs. lowest tertile: RR = 0.50; 95% CI, 0.28–0.92; $P_{trend} = 0.01$). Total omega-6 was inversely associated with BCC tumors in multivariate models ($P = 0.04$; highest vs. lowest tertile: RR = 0.71; 95% CI, 0.51–0.99), and more strongly in the subgroup with past skin cancer. Linoleic and linolenic acids were also inversely associated with BCC occurrence in this subgroup. When fatty acids were analyzed as continuous variables, however, there was no evidence of any linear or nonlinear associations. This study provides some support for reduced skin cancer risk with high plasma concentrations of omega-3 and omega-6 fatty acids, but results depended on how fatty acid data were modeled. Further investigation of these associations in larger datasets is needed. *Cancer Epidemiol Biomarkers Prev; 22(10); 1900–5. ©2013 AACR.*

Introduction

Most keratinocytic skin cancers, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are attributable to solar ultraviolet radiation (UVR) exposure (1, 2). UVR-induced carcinogenesis (photocarcinogenesis) occurs by initiation and promotion of skin cancer through inducing DNA damage and modulating immunosuppression (3). Evidence suggests that this process may be modified by dietary factors including polyunsaturated fatty acids (PUFA). In particular, omega-3 and omega-6 PUFA, obtained primarily through dietary intake of fish and plant oils, respectively, are thought to play opposing roles. Experimental studies have shown that although omega-3 PUFA affects early promotional stages by increasing tumor latency and decreasing tumor numbers, omega-6 PUFA has reverse effects (1, 4, 5). Elevated blood concentrations of omega-6 PUFA increase the levels of prostaglandin E2 (PGE-2), an immunoregulator associated with aggressive keratinocytic skin cancer growth (6, 7). Conversely, omega-3 PUFA, particularly eicosapentaenoic acid (EPA), has anti-inflammatory effects in skin post-UVR exposure, reducing sunburn sensitivity and PGE-2 levels (3, 8) and preventing DNA damage (9). Because EPA is in constant competition for metabolism with the omega-6 arachidonic acid, the ratio of omega-3/-6 in circulation plays a key role in determining the overall effect on skin photocarcinogenesis (5).

To date, epidemiologic evidence has mainly focused on dietary intake and has been inconsistent in showing a role of individual PUFA in skin cancer development. An Arizona-based case–control study showed an inverse association of omega-3 intake and odds of SCC (10), and an increased SCC risk with higher serum levels of arachidonic acid (11). We have also previously reported a marginal increase in SCC risk with greater arachidonic acid intake and a decrease in BCC risk with increasing total omega-6 intake (12). However, a study of over 40,000 American male health professionals failed to find a link between omega-3 intake and BCC risk (13), whereas an Italian case–control study found a positive association of

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serum docosapentaenoic acid with melanoma risk only in men (14). The present study aimed to investigate associations between plasma phospholipid levels of omega-3 and omega-6 PUFA, and the development of BCC and SCC.

Materials and Methods

Study population

This was an 11-year prospective cohort study (1997–2007) among White Caucasian adults originally randomly selected using the electoral roll (enrolment is compulsory by law in Australia) from the community in 1986 who participated in a skin cancer prevention field trial, 1992–1996. Details of the sample, trial, and outcomes have been reported elsewhere (15). Briefly, some 1,600 residents of Nambour, Queensland, Australia, took part in a trial evaluating skin cancer prevention using ß-carotene supplements and/or daily application of sunscreen. Participants who provided a blood sample at trial completion in 1996 were included in the present study ($n = 1{,}191$, 73%). Persons with Gorlin syndrome or porokeratosis were ineligible. The study was approved by the Queensland Institute of Medical Research (Brisbane, Australia) ethics committee.

Data collection

Consenting participants provided a 30-mL nonfasting venous blood sample. Samples were processed at collection and stored in 1 mL aliquots at −70°C until analysis. Measurements of plasma phospholipid PUFA were conducted by Flinders Medical Centre, Adelaide, Australia using procedures detailed elsewhere (16). Briefly, plasma was extracted in chloroform: methanol, thin-layer chromatography was used to separate phospholipid fractions, and fatty acid methyl esters were quantified using gas chromatography (Hewlett-Packer 6890, 50-m capillary column). Fatty acid methyl esters were identified on the basis of retention time to authentic lipid standards (GLC-463, Nuchek Prep Inc.) and quantified by comparison with the internal standard using ChemStation software (Agilent).

Demographic variables, phenotypic characteristics, lifestyle habits, sun exposure variables, and presence of medical conditions were obtained via standard interviewer- and self-administered questionnaires. During a physical examination in 1996, height and weight and elastosis of the neck (a measure of long-term sun exposure) were recorded, the latter by dermatologists. A detailed list of variables considered has been described previously (12).

An intensive surveillance system of incident skin cancers in the study population was established during the Nambour trial and continued throughout posttrial follow-up. Questionnaires were mailed twice yearly to the participants for reporting skin cancers. In 2000, a full-body skin examination was conducted by a dermatologist among an unselected proportion of participants, and in 2007, all ongoing participants had full skin examinations by dermatologically trained physicians. Finally, independent pathology laboratories across Queensland provided histology reports for all skin cancers (self-reported or detected during examination). These methods ensured virtually 100% ascertainment of histologically confirmed skin cancers in the population (17).

Statistical analysis

Tumor- and person-based incidence rates of BCC and of SCC were calculated as the number of tumors or people diagnosed between January 01 1997 and December 31 2007, divided by person-years of follow-up and expressed per 100,000 person-years. Tumors and person-years were counted until date of withdrawal from the study, date of death, or December 31 2007, whichever occurred first.

Plasma phospholipid concentrations for each PUFA were classified into ranked thirds based on the entire population at baseline (1996). Relative risks (RR) and 95% confidence intervals (CI) for increasing PUFA concentrations compared with the lowest third were calculated using generalized linear models with negative binomial distribution (tumor-based analyses), and Poisson distribution with a robust error variance (person-based analyses; ref. 18). "Basic" models controlling for age and sex were conducted initially, followed by multivariate models to adjust for confounding. Variables were retained if they changed "basic" risk estimates by more than 10%. Final models included age, sex, trial treatment allocation, and additionally for BCC freckling on the back, and for SCC elastosis of the neck and total number of solar keratoses. To test for a linear trend across tertiles, the median PUFA value in each tertile was modeled as a continuous variable. Subsequent analyses were stratified by personal history of skin cancer, as these individuals are at increased risk of developing subsequent skin cancers (19) and may be more prone to risk modification by dietary factors (12). Skin cancer history was based on tumors identified during examinations and surveys conducted before 1997 (17). Statistical significance was set at $P < 0.05$ (two-tailed). Analyses were conducted using SAS version 9.3. Nonlinear trends were tested by analyzing PUFA variables as continuous variables in natural cubic spline regression using R version 3.0.1.

Results

Average age (SD) of the 1,191 study participants was 54.0 (12.8) years and 55% were female. Over the 11-year study period, 337 histologically confirmed new SCC tumors were diagnosed in 176 participants during 12,535 person-years of follow-up giving person- and tumor-based incidence rates of 1,404/100,000 and 2,688/100,000, respectively. During the same follow-up, 300 people developed 700 histologically confirmed new BCC tumors giving a person-based rate of 2,393/100,000, and a tumor-based rate of 5,584/100,000. Three hundred and ninety-eight participants had a personal history of skin cancer.

In age- and sex-adjusted models, there was a significant linear decrease in SCC tumor risk with increasing tertiles of plasma EPA concentrations (middle tertile: RR = 0.64;

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95% CI, = 0.42–0.97; highest tertile: RR = 0.58; 95% CI, 0.38–0.88; $P_{trend} = 0.02$; Table 1). Associations with omega-3/-6 ratio were similar: participants in the highest tertile had significantly reduced SCC tumor risk compared with those in the lowest (RR = 0.61; 95% CI, 0.39–0.95; $P_{trend} = 0.03$). In the multivariate models, these inverse trends were maintained though did not reach statistical significance. Linolenic acid, docosahexaenoic acid (DHA), linoleic acid, arachidonic acid, and the individual sums of omega-3 and omega-6 PUFA were not associated with SCC tumors. Among participants with a history of skin cancer, EPA was more strongly associated with reduced occurrence of SCC tumors after full confounder adjustment (Table 1), but based on the point estimates of EPA tertiles, there was no clear dose–response relationship (middle vs. lowest tertile: RR = 0.41; 95% CI, 0.19–0.91; highest vs. lowest tertile: RR = 0.50; 95% CI, 0.28–0.92; $P_{trend} = 0.01$). Omega-3/-6 ratio showed similar, though

Table 1. RR and 95% CIs for SCC by tertiles of plasma omega-3 and omega-6 concentrations, tumor-based analysis in all participants of the Nambour Skin Cancer Study, and in those with a personal history of skin cancer, 1997–2007

	All participants ($n = 1,191$) Tertiles of plasma phospholipid concentrations				Participants with previous skin cancers ($n = 398$) Tertiles of plasma phospholipid concentrations			
Fatty acids	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P_{trend}[a]**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P_{trend}[a]**
Sum of omega-3, μg/mL[b]	*<48.56*	*48.56–63.20*	*>63.20*		*<48.56*	*48.56–63.20*	*>63.20*	
Sum of tumors, *n*	*86*	*131*	*120*		*70*	*103*	*90*	
Basic RR (95% CI)[c]	1.00	0.92 (0.59–1.42)	0.71 (0.45–1.11)	0.11	1.00	0.86 (0.51–1.44)	0.63 (0.38–1.07)	0.07
Multivariate RR (95% CI)[d]	1.00	1.01 (0.67–1.54)	0.82 (0.53–1.27)	0.31	1.00	0.88 (0.53–1.47)	0.66 (0.39–1.11)	0.10
Linolenic acid (18:3), μg/mL	*<1.67*	*1.67–2.53*	*>2.53*		*<1.67*	*1.67–2.53*	*>2.53*	
Sum of tumors, *n*	*106*	*117*	*114*		*82*	*90*	*91*	
Basic RR (95% CI)[c]	1.00	1.06 (0.70–1.61)	1.00 (0.66–1.51)	0.95	1.00	0.82 (0.50–1.34)	0.93 (0.57–1.51)	0.86
Multivariate RR (95% CI)[d]	1.00	0.96 (0.64–1.43)	0.94 (0.62–1.40)	0.76	1.00	0.84 (0.52–1.36)	1.00 (0.62–1.63)	0.89
EPA (20:5), μg/mL	*<9.24*	*9.24–13.28*	*>13.28*		*<9.24*	*9.24–13.28*	*>13.28*	
Sum of tumors, *n*	*124*	*90*	*123*		*101*	*70*	*92*	
Basic RR (95% CI)[c]	1.00	0.64 (0.42–0.97)	0.58 (0.38–0.88)	0.02	1.00	0.59 (0.36–0.97)	0.52 (0.32–0.84)	0.01
Multivariate RR (95% CI)[d]	1.00	0.70 (0.47–1.06)	0.67 (0.45–1.01)	0.08	1.00	0.41 (0.19–0.91)	0.50 (0.28–0.92)	0.01
DHA (C22:6), μg/mL	*<36.42*	*36.42–47.68*	*>47.68*		*<36.42*	*36.42–47.68*	*>47.68*	
Sum of tumors, *n*	*99*	*103*	*135*		*76*	*83*	*104*	
Basic RR (95% CI)[c]	1.00	0.71 (0.46–1.11)	0.75 (0.49–1.16)	0.27	1.00	0.72 (0.43–1.22)	0.69 (0.41–1.14)	0.19
Multivariate RR (95% CI)[d]	1.00	0.73 (0.48–1.11)	0.83 (0.55–1.26)	0.51	1.00	0.87 (0.51–1.49)	0.99 (0.59–1.65)	0.18
Sum of omega-6, μg/mL[e]	*<348.9*	*348.90–408.01*	*>408.03*		*<348.9*	*348.90–408.01*	*>408.03*	
Sum of tumors, *n*	*146*	*86*	*105*		*126*	*56*	*81*	
Basic RR (95% CI)[c]	1.00	0.83 (0.54–1.27)	0.94 (0.62–1.42)	0.81	1.00	0.68 (0.41–1.13)	0.76 (0.48–1.21)	0.27
Multivariate RR (95% CI)[d]	1.00	0.81 (0.54–1.22)	0.96 (0.65–1.42)	0.89	1.00	0.66 (0.40–1.09)	0.77 (0.48–1.22)	0.29
Linoleic acid (C18:2), μg/mL	*<228.23*	*228.23–273.44*	*>273.44*		*<228.23*	*228.23–273.44*	*>273.44*	
Sum of tumors, *n*	*143*	*103*	*91*		*115*	*86*	*62*	
Basic RR (95% CI)[c]	1.00	1.03 (0.68–1.56)	0.85 (0.56–1.29)	0.44	1.00	0.98 (0.60–1.58)	0.65 (0.40–1.06)	0.09
Multivariate RR (95% CI)[d]	1.00	0.95 (0.64–1.41)	0.91 (0.61–1.36)	0.65	1.00	0.98 (0.61–1.59)	0.67 (0.41–1.10)	0.12
AA (C20:4), μg/mL	*<113.45*	*113.45–139.72*	*>139.72*		*<113.45*	*113.45–139.72*	*>139.72*	
Sum of tumors, *n*	*126*	*98*	*113*		*109*	*72*	*82*	
Basic RR (95% CI)[c]	1.00	0.89 (0.59–1.36)	1.05 (0.70–1.58)	0.76	1.00	0.79 (0.49–1.29)	0.89 (0.55–1.42)	0.65
Multivariate RR (95% CI)[d]	1.00	1.17 (0.78–1.76)	1.15 (0.77–1.71)	0.52	1.00	0.79 (0.49–1.28)	0.87 (0.55–1.39)	0.59
Omega-3/omega-6 ratio	*<0.13*	*0.13–0.16*	*>0.16*		*<0.13*	*0.13–0.16*	*>0.16*	
Sum of tumors, *n*	*94*	*114*	*129*		*75*	*90*	*98*	
Basic RR (95% CI)[c]	1.00	0.76 (0.49–1.16)	0.61 (0.39–0.95)	0.03	1.00	0.83 (0.50–1.39)	0.63 (0.38–1.06)	0.07
Multivariate RR (95% CI)[d]	1.00	0.81 (0.54–1.22)	0.67 (0.44–1.03)	0.07	1.00	0.81 (0.49–1.33)	0.64 (0.38–1.06)	0.08

[a]All *P* values from two-sided tests.

[b]Sum of omega-3: linolenic acid, EPA, DHA.

[c]Basic RR adjusted for age, sex.

[d]Multivariate RR adjusted for age, sex, elastosis of neck, total solar keratoses, treatment allocation.

[e]Sum of omega-6: linoleic acid, AA.

Abbreviation: AA, arachidonic acid.

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nonsignificant inverse associations. For both overall and subgroup analyses, there was no evidence of linear or nonlinear associations between EPA and SCC when EPA was considered as a continuous variable.

After multivariable adjustments, tumor-based incidence of BCC was lower in the highest compared with the lowest tertile of total omega-6 concentrations (RR = 0.71; 95% CI, 0.51–0.99; Table 2), and the linear trend across tertiles was significant ($P_{trend} = 0.04$). Linoleic acid showed a similar though not statistically significant inverse association with BCC. Among those with a history of skin cancer, BCC tumor incidence was significantly lower after full confounder adjustment for total omega-6, linoleic acid, and linolenic acid, though no dose–response relationships were apparent. There was no evidence of linear or nonlinear associations with BCC occurrence when these fatty acids were considered as continuous variables.

Table 2. RR and 95% CI for BCC by tertiles of plasma omega-3 and omega-6 concentrations, tumor-based analysis in all participants of the Nambour Skin Cancer Study, and in those with a personal history of skin cancer, 1997–2007

	All participants ($n = 1,191$) Tertiles of plasma phospholipid concentrations				Participants with previous skin cancers ($n = 398$) Tertiles of plasma phospholipid concentrations			
Fatty acids	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P_{trend}[a]**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P_{trend}[a]**
Sum of omega-3, μg/mL[b]	*<48.56*	*48.56–63.20*	*>63.20*		*<48.56*	*48.56–63.20*	*>63.20*	
Sum of tumors, *n*	*208*	*244*	*248*		*155*	*174*	*179*	
Basic RR (95% CI)[c]	1.00	0.96 (0.68–1.34)	0.90 (0.63–1.29)	0.57	1.00	0.86 (0.56–1.31)	0.83 (0.53–1.28)	0.38
Multivariate RR (95% CI)[d]	1.00	0.94 (0.67–1.33)	0.92 (0.64–1.31)	0.64	1.00	0.81 (0.53–1.25)	0.79 (0.51–1.22)	0.33
Linolenic acid (18:3), μg/mL	*<1.67*	*1.67–2.53*	*>2.53*		*<1.67*	*1.67–2.53*	*>2.53*	
Sum of tumors, *n*	*242*	*274*	*184*		*177*	*210*	*121*	
Basic RR (95% CI)[c]	1.00	1.00 (0.72–1.37)	0.78 (0.55–1.09)	0.13	1.00	0.92 (0.62–1.36)	0.91 (0.62–1.35)	0.02
Multivariate RR (95% CI)[d]	1.00	0.95 (0.69–1.31)	0.77 (0.55–1.08)	0.13	1.00	0.62 (0.41–0.84)	0.61 (0.40–0.92)	0.02
EPA (20:5), μg/mL	*<9.24*	*9.24–13.28*	*>13.28*		*<9.24*	*9.24–13.28*	*>13.28*	
Sum of tumors, *n*	*197*	*285*	*218*		*146*	*212*	*150*	
Basic RR (95% CI)[c]	1.00	1.25 (0.90–1.74)	0.88 (0.62–1.24)	0.30	1.00	1.23 (0.82–1.83)	3.24 (1.86–5.64)	0.18
Multivariate RR (95% CI)[d]	1.00	1.19 (0.86–1.66)	0.86 (0.61–1.22)	0.27	1.00	0.80 (0.53–1.22)	0.89 (0.47–1.71)	0.15
DHA (C22:6), μg/mL	*<36.42*	*36.42–47.68*	*>47.68*		*<36.42*	*36.42–47.68*	*>47.68*	
Sum of tumors, *n*	*210*	*242*	*248*		*151*	*174*	*183*	
Basic RR (95% CI)[c]	1.00	1.00 (0.71–1.40)	0.95 (0.67–1.36)	0.77	1.00	0.96 (0.63–1.47)	1.07 (0.74–1.55)	0.63
Multivariate RR (95% CI)[d]	1.00	0.97 (0.69–1.36)	0.96 (0.67–1.36)	0.81	1.00	0.90 (0.59–1.39)	0.69 (0.44–1.09)	0.57
Sum of omega-6, μg/mL[e]	*<348.9*	*348.90–408.01*	*>408.03*		*<348.9*	*348.90–408.01*	*>408.03*	
Sum of tumors, *n*	*289*	*228*	*183*		*225*	*157*	*126*	
Basic RR (95% CI)[c]	1.00	0.92 (0.66–1.26)	0.72 (0.52–1.00)	0.05	1.00	0.96 (0.64–1.42)	0.96 (0.64–1.43)	0.01
Multivariate RR (95% CI)[d]	1.00	0.94 (0.68–1.29)	0.71 (0.51–0.99)	0.04	1.00	0.60 (0.41–0.89)	0.59 (0.39–0.88)	0.01
Linoleic acid (C18:2), μg/mL	*<228.23*	*228.23–273.44*	*>273.44*		*<228.23*	*228.23–273.44*	*>273.44*	
Sum of tumors, *n*	*263*	*263*	*174*		*206*	*185*	*117*	
Basic RR (95% CI)[c]	1.00	1.14 (0.82–1.56)	0.74 (0.53–1.03)	0.08	1.00	0.99 (0.67–1.46)	0.98 (0.66–1.44)	0.009
Multivariate RR (95% CI)[d]	1.00	1.17 (0.85–1.61)	0.72 (0.52–1.02)	0.06	1.00	0.58 (0.39–0.87)	0.54 (0.35–0.82)	0.005
AA (C20:4), μg/mL	*<113.45*	*113.45–139.72*	*>139.72*		*<113.45*	*113.45–139.72*	*>139.72*	
Sum of tumors, *n*	*252*	*264*	*184*		*194*	*188*	*126*	
Basic RR (95% CI)[c]	1.00	1.19 (0.86–1.64)	0.79 (0.57–1.11)	0.13	1.00	1.20 (0.81–1.77)	1.20 (0.81–1.78)	0.18
Multivariate RR (95% CI)[d]	1.00	1.19 (0.86–1.64)	0.80 (0.57–1.11)	0.14	1.00	0.77 (0.52–1.15)	0.76 (0.51–1.14)	0.27
Omega-3/omega-6 ratio	*<0.13*	*0.13–0.16*	*>0.16*		*<0.13*	*0.13–0.16*	*>0.16*	
Sum of tumors, *n*	*211*	*219*	*270*		*143*	*162*	*203*	
Basic RR (95% CI)[c]	1.00	0.84 (0.60–1.18)	0.95 (0.67–1.34)	0.87	1.00	1.10 (0.73–1.68)	1.10 (0.71–1.68)	0.51
Multivariate RR (95% CI)[d]	1.00	0.86 (0.61–1.21)	0.93 (0.66–1.31)	0.76	1.00	1.15 (0.77–1.74)	1.15 (0.76–1.74)	0.51

[a]All *P* values from two-sided tests.
[b]Sum of omega-3: linolenic acid, EPA, DHA.
[c]Basic RR adjusted for age, sex.
[d]Multivariate RR adjusted for age, sex, freckling on back, treatment allocation.
[e]Sum of omega-6: linoleic acid, AA.
Abbreviation: AA, arachidonic acid.

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Person-based analyses showed similar patterns to the tumor-based analyses, though risk estimates and trends were generally not statistically significant (results not shown).

Discussion

In this prospective study of associations between plasma phospolipid PUFA and keratinocytic skin cancer risk, there was a reduction in risk of SCC tumors in persons with relatively high EPA concentrations and omega-3/-6 ratio, and a decrease in BCC tumor risk with greater total omega-6, linoleic acid, and linolenic acid concentrations. These inverse associations were particularly evident in people with a history of skin cancer, and were independent of other risk factors. However, they were only apparent when participants were grouped into tertiles of plasma PUFA levels, and not when PUFA were modeled as continuous variables.

Our findings with regards to SCC are consistent with those of Hakim and colleagues who noted an inverse trend between the ratio of omega-3/-6 intake and SCC risk (10), but are at odds with our past observations that intake of omega-3 PUFA was not associated with developing SCC (12). Previous analyses in the Nambour Study population showed a lower rate of acquisition of actinic keratoses (precancerous cutaneous lesions) among the highest consumers of oily fish (high in EPA content; ref. 20). Evidence of EPA's protective potential in skin has also been shown in human supplementation studies (3, 8). Although our findings did not show a clear dose–response relationship, collectively the evidence suggests that moderate omega-3 intake may sustain circulating and target tissue levels to influence early stages of photocarcinogenesis. With respect to omega-6 PUFA, our study failed to confirm earlier findings that higher serum arachidonic acid levels increase SCC risk (11).

The observed inverse associations of linoleic acid and total omega-6 concentrations with BCC in our study are consistent with our previous findings on dietary intake of PUFA in relation to skin cancer (12), but they are contrary to hypotheses generated from animal studies which indicate omega-6 PUFA increase carcinogenesis (1, 5, 7). Furthermore, the lower BCC tumor incidence with greater linolenic acid levels among persons with a history of skin cancer is a novel finding not previously reported (12, 13). BCC and SCC each have a distinct biology and epidemiology (21) so it is not unexpected that dietary factors have different associations with these 2 different skin cancer types, yet it remains unclear why the direction of associations for BCC and omega-6 were opposite to that expected.

The lack of linear or nonlinear associations when PUFA was considered as continuous variables means that caution is needed in interpreting the associations reported from the tertile comparisons. It suggests that no simple dose–response relationship exists for any of the PUFA explored and that further analyses across a wide range of plasma PUFA levels are needed in larger datasets to confirm optimal circulating concentrations. PUFA levels in our study were relatively low compared with other populations (22), consequently the range of individual PUFA values in the first 2 tertiles was narrow, thus limiting the distribution of PUFA levels being compared.

To our knowledge, this is the first prospective epidemiologic study to report inverse associations between plasma omega-3 and omega-6 PUFA and BCC and SCC incidence. Study strengths include the prospective design and rigorous data collection on potential confounders. Our analyses are based on histologically confirmed BCC and SCC data identified through a comprehensive surveillance system, thus participant misclassification was unlikely. However, the study may have lacked statistical power to detect associations due to a relatively small numbers of cases/tumors in some PUFA tertiles.

In conclusion, our findings generally agree with the notion that omega-3 and omega-6 PUFA may reduce incidence of keratinocytic skin cancers, particularly in high-risk groups. Further prospective studies among larger and diverse populations are warranted to substantiate our findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.C. van der Pols
Development of methodology: A.C. Green, J.C. van der Pols
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.C. Hughes, A.C. Green
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.C. Wallingford, M.C. Hughes, J.C. van der Pols
Writing, review, and/or revision of the manuscript: S.C. Wallingford, M. C. Hughes, A.C. Green, J.C. van der Pols
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.C. Hughes, A.C. Green
Study supervision: J.C. van der Pols

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References

1. Black HS, Rhodes LE. The potential of omega-3 fatty acids in the prevention of non-melanoma skin cancer. Cancer Detect Prev 2006;30:224–32.

2. Lucas RM, McMichael AJ, Armstrong BK, Smith WT. Estimating the global disease burden due to ultraviolet radiation exposure. Int J Epidemiol 2008;37:654–67.

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3. Rhodes LE, Shahbakhti H, Azurdia RM, Moison RMW, Steenwinkel M-JST, Homburg MI, et al. Effect of eicosapentaenoic acid, an omega-3 polyunsaturated fatty acid, on UVR-related cancer risk in humans. An assessment of early genotoxic markers. Carcinogenesis 2003;24:919–25.
4. Reeve VE, Bosnic M, Boehm-Wilcox C. Dependence of photocarcinogenesis and photoimmunosuppression in the hairless mouse on dietary polyunsaturated fat. Cancer Lett 1996;108:271–9.
5. Black HS, Thornby JI, Gerguis J, Lenger W. Influence of dietary omega-6, -3 fatty acid sources on the intiation and promotion stages of photocarcinogenesis. Photochem Photobiol 1992;56:195–9.
6. Fischer MA, Black HS. Modification of membrane composition, eicosanoid metabolism, and immunoresponsiveness by dietary omega-3 and omega-6 fatty acid sources, modulators of ultraviolet-carcinogenesis. Photochem Photobiol 1991;54:381–7.
7. Vanderveen EE, Grekin RC, Swanson NA, Kragballe K. Arachidonic acid metabolites in cutaneous carcinomas: evidence suggesting that elevated levels of prostaglandins in basal cell carcinomas are associated with an aggressive growth pattern. Arch Dermatol 1986;122:407–12.
8. Shahbakhti H, Watson REB, Azurdia RM, Ferreira CZ, Garmyn M, Rhodes LE. Influence of eicosapentaenoic acid, an omega-3 fatty acid, on ultraviolet-B generation of prostaglandin-E2 and proinflammatory cytokines interleukin-1β, tumor necrosis factor-α, interleukin-6 and interleukin-8 in human skin *in vivo*. Photochem Photobiol 2004;80:231–5.
9. van der Pols JC, Xu C, Boyle GM, Hughes MC, Carr SJ, Parsons PG, et al. Serum omega-3 and omega-6 fatty acids and cutaneous p53 expression in an Australian population. Cancer Epidemiol Biomarkers Prev 2011;20:530–6.
10. Hakim IA, Harris RB, Ritenbaugh C. Fat intake and risk of squamous cell arcinoma of the skin. Nutr Cancer 2000;36:155–62.
11. Harris RB, Foote JA, Hakim IA, Bronson DL, Alberts DS. Fatty acid composition of red blood cell membranes and risk of squamous cell carcinoma of the skin. Cancer Epidemiol Biomarkers Prev 2005;14:906–12.
12. Wallingford SC, van As JA, Hughes MC, Ibiebele TI, Green AC, van der Pols JC. Intake of omega-3 and omega-6 fatty acids and risk of basal and squamous cell carcinomas of the skin: a longitudinal community-based study in Australian adults. Nutr Cancer 2012;64:982–90.
13. van Dam RM, Huang Z, Giovannucci E, Rimm EB, Hunter DJ, Colditz GA, et al. Diet and basal cell carcinoma of the skin in a prospective cohort of men. Am J Clin Nutr 2000;71:135–41.
14. Vinceti M, Malagoli C, Iacuzio L, Crespi CM, Sieri S, Krogh V, et al. Serum fatty acids and risk of cutaneous melanoma: a population-based case-control study. Dermatol Res Pract 2013;2013:659394.
15. Green AI, Battistutta D, Hart V, Leslie D, Marks G, Williams G, et al. The Nambour Skin Cancer and Actinic Eye Disease Prevention Trial: design and baseline characteristics of participants. Control Clin Trials 1994;15:512–22.
16. Mantzioris E, Cleland LG, Gibson RA, Neumann MA, Demasi M, James MJ. Biochemical effects of a diet containing foods enriched with n-3 fatty acids. Am J Clin Nutr 2000;72:42–8.
17. Valery PC, Neale R, Williams G, Pandeya N, Siller G, Green A. The effect of skin examination surveys on the incidence of basal cell carcinoma in a Queensland community sample: a 10-year longitudinal study. J Investig Dermatol Symp Proc 2004;9:148–51.
18. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702–6.
19. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524–30.
20. Hughes MCB, Williams GM, Fourtanier A, Green AC. Food intake, dietary patterns, and actinic keratoses of the skin: a longitudinal study. Am J Clin Nutr 2009;89:1246–55.
21. van der Pols JC. Skin cancer epidemiology. In: Dummer R, Pittelkow MR, Iwatsuki K, Green A, Elwan NM, editors. Skin cancer–a world-wide perspective. Heidelberg: Springer-Verlag; 2010. p. 3–12.
22. Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, et al. Dietary fish intake and plasma phospholipid n–3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer–Norfolk United Kingdom cohort. Am J Clin Nutr 2006;84:1330–9.

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