Plasma omega-3 and omega-6 concentrations and risk of cutaneous basal and squamous cell carcinomas in Australian adults

**Running Title:** Omega-3 and omega-6 fatty acids and skin cancer risk

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Abstract

Laboratory-based evidence suggests that omega-3 and omega-6 polyunsaturated fatty acids may affect skin photocarcinogenesis but epidemiological 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 based on number of histologically-confirmed tumours diagnosed during follow-up (1997 to 2007). Plasma eicosapentaenoic acid (EPA) concentrations and omega-3/-6 ratio showed significant inverse associations with SCC tumours, comparing higher tertiles to 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 tumours 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 analysed as continuous variables however, there was no evidence of any linear or non-linear 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 modelled. Further investigation of these associations in larger datasets is needed.
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 while omega-3 PUFA affect early promotional stages by increasing tumour latency and decreasing tumour numbers, omega-6 PUFA have reverse effects (1, 4-5). Elevated blood concentrations of omega-6 PUFA increase 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), have anti-inflammatory effects in skin post-UVR exposure, reducing sunburn sensitivity and PGE-2 levels (3, 8) and preventing DNA damage (9). Since 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, epidemiological evidence has mainly focussed on dietary intake and has been inconsistent in demonstrating 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) while an Italian case-control study found a positive
association of 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.

5 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 1600 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’s syndrome or porokeratosis were ineligible. The study was approved by the Queensland Institute of Medical Research ethics committee.

Data Collection

Consenting participants provided a 30ml non-fasting venous blood sample. Samples were processed at collection and stored in 1ml 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-Packard 6890, 50-m capillary column). Fatty acid methyl esters were identified based on retention time to authentic lipid standards (GLC-463, Nuchek Prep Inc. Elysian, MN) and
quantified by comparison to the internal standard using ChemStation software (Agilent, CA, USA).

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 post-trial follow-up. Questionnaires were mailed twice-yearly to 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

Tumour- and person-based incidence rates of BCC and of SCC were calculated as the number of tumours or people diagnosed between 01 January 1997 and 31 December 2007, divided by person-years of follow-up and expressed per 100,000 person-years. Tumours and person-years were counted until date of withdrawal from the study, date of death or 31 December 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 to the lowest third were
calculated using generalized linear models with negative binomial distribution (tumour-based analyses), and Poisson distribution with a robust error variance (person-based analyses) (18). ‘Basic’ models controlling for age and sex were performed 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 modelled 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 tumours identified during examinations and surveys conducted prior to 1997 (17). Statistical significance was set at p-value <0.05 (two-tailed). Analyses were performed using SAS version 9.3 (Cary, NC, USA). Non-linear trends were tested by analysing PUFA variables as continuous variables in natural cubic spline regression using R version 3.0.1 (Vienna, Austria).

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 tumours were diagnosed in 176 participants during 12,535 person-years of follow-up giving person- and tumour-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 tumours giving a person-based rate of 2,393/100,000 and a tumour-based rate of 5,584/100,000. 398 participants had a personal history of skin cancer.
In age- and sex-adjusted models there was a significant linear decrease in SCC tumour risk with increasing tertiles of plasma EPA concentrations (middle tertile: RR=0.64, 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 tumour risk compared to 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, linoleic acid, arachidonic acid and the individual sums of omega-3 and omega-6 PUFA were not associated with SCC tumours. Among participants with a history of skin cancer, EPA was more strongly associated with reduced occurrence of SCC tumours 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 non-significant inverse associations. For both overall, and subgroup analyses, there was no evidence of linear or non-linear associations between EPA and SCC when EPA was considered as a continuous variable.

After multivariable adjustments, tumour-based incidence of BCC was lower in the highest compared to 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 tumour 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 non-linear associations with BCC occurrence when these fatty acids were considered as continuous variables.
Person-based analyses showed similar patterns to the tumour-based analyses, though risk estimates and trends were generally not statistically significant (results not shown).

**Discussion**

In this prospective study of associations between plasma phospholipid PUFA and keratinocytic skin cancer risk there was a reduction in risk of SCC tumours in persons with relatively high EPA concentrations and omega-3/-6 ratio, and a decrease in BCC tumour 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 modelled as continuous variables.

Our findings with regards to SCC are consistent with those of Hakim et al. 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) (20). Evidence of EPA’s protective potential in skin has also been demonstrated 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 tumour 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 two 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 non-linear associations when PUFA were 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 to other populations (22), consequently the range of individual PUFA values in the first two tertiles was narrow, thus limiting the distribution of PUFA levels being compared.

To our knowledge this is the first prospective epidemiological 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/tumours 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.

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Table 1. Relative risks (RR) and 95% confidence intervals (CI) for SCC by tertiles of plasma omega-3 and omega-6 concentrations, tumour-based analysis in all participants of the Nambour Skin Cancer Study, and in those with a personal history of skin cancer, 1997-2007

| Fatty acids | Sum of omega-3, µg/ml | Tertile 1 | Tertile 2 | Tertile 3 | p trend | Sum of tumours, n | Tertile 1 | Tertile 2 | Tertile 3 | p trend |
|-------------|-----------------------|----------|----------|----------|---------|------------------|----------|----------|----------|---------|
|             |                       | <48.56   | 48.56-63.20 | >63.20   |         | 86               | 131      | 120      |         | 1.01    |
|             |                       | 1.00     | 0.92 (0.59-1.42) | 0.71 (0.45-1.11) | 0.11    | 70               | 103      | 90       | 0.94 (0.62-1.40) | 0.76    | 0.07    |
|             |                       | 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 |<1.67 | 1.67-2.53 | >2.53 | 0.86 |
| EPA (20:5), µg/ml | <9.24 | 9.24-13.28 | >13.28 | <9.24 | 9.24-13.28 | >13.28 |<9.24 | 9.24-13.28 | >13.28 | 0.01 |
| DHA (C22:6), µg/ml | <36.42 | 36.42-47.68 | >47.68 | <36.42 | 36.42-47.68 | >47.68 |<36.42 | 36.42-47.68 | >47.68 | 0.18 |
| Sum of omega-6, µg/ml | <348.9 | 348.90-408.01 | >408.03 | <348.9 | 348.90-408.01 | >408.03 |<348.9 | 348.90-408.01 | >408.03 | 0.27 |

Data on March 19, 2020. © 2013 American Association for Cancer Research. cebp.aacrjournals.org Downloaded from aacrjournals.org on March 19, 2020.
|                 | <228.23 | 228.23-273.44 | >273.44 | <228.23 | 228.23-273.44 | >273.44 |
|----------------|----------|---------------|---------|----------|---------------|---------|
| **Linoleic acid (C18:2), µg/ml** |          |               |         |          |               |         |
| Sum of tumours, n | 143      | 103           | 91      | 115      | 86            | 62      |
| Basic RR (95% CI)<sup>c</sup> | 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)<sup>d</sup> | 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 |
| **Sum of tumours, n** | 126      | 98            | 113     | 109      | 72            | 82      |
| **Basic RR (95% CI)<sup>c</sup>** | 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)<sup>d</sup>** | 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 |
| **AA (C20:4), µg/ml** |          |               |         |          |               |         |
| Sum of tumours, n | 94       | 114           | 129     | 75       | 90            | 98      |
| Basic RR (95% CI)<sup>c</sup> | 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)<sup>d</sup> | 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 |

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid

<sup>a</sup> All p-values from two-sided tests
<sup>b</sup> Sum of omega-3: linolenic acid, EPA, DHA
<sup>c</sup> Basic RR adjusted for age, sex
<sup>d</sup> Multivariate RR adjusted for age, sex, elastosis of neck, total solar keratoses, treatment allocation
<sup>e</sup> Sum of omega-6: linoleic acid, AA
Table 2. Relative risks (RR) and 95% confidence intervals (CI) for BCC by tertiles of plasma omega-3 and omega-6 concentrations, tumour-based analysis in all participants of the Nambour Skin Cancer Study, and in those with a personal history of skin cancer, 1997-2007

| Fatty acids | All participants (n=1,191) | Participants with previous skin cancers (n=398) |
|-------------|-----------------------------|-----------------------------------------------|
|             | Tertiles of plasma phospholipid concentrations | Tertiles of plasma phospholipid concentrations | p trend | Tertiles of plasma phospholipid concentrations | Tertiles of plasma phospholipid concentrations | p trend |
|             | Tertile 1 | Tertile 2 | Tertile 3 | Basic RR (95% CI) | Tertile 1 | Tertile 2 | Tertile 3 | Multivariate RR (95% CI) | Tertile 1 | Tertile 2 | Tertile 3 | Multivariate RR (95% CI) |
| **Sum of omega-3, µg/ml** | <48.56 | 48.56-63.20 | >63.20 | 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 |
| Sum of tumours, n | 208 | 244 | 248 | 155 | 174 | 179 | 0.05 |
| Basic RR (95% CI) | 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 |
| Multivariate RR (95% CI) | 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 |
| **Linolenic acid (18:3), µg/ml** | <1.67 | 1.67-2.53 | >2.53 | 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 |
| Sum of tumours, n | 242 | 274 | 184 | 177 | 210 | 121 | 0.02 |
| Basic RR (95% CI) | 1.00 | 1.00 (0.69-1.33) | 0.92 (0.64-1.31) | 0.64 | 1.00 | 0.81 (0.53-1.25) | 0.79 (0.51-1.22) | 0.33 |
| Multivariate RR (95% CI) | 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 | 1.00 | 1.00 (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 |
| Sum of tumours, n | 197 | 285 | 218 | 146 | 212 | 150 | 0.15 |
| Basic RR (95% CI) | 1.00 | 1.00 (0.69-1.31) | 0.96 (0.67-1.36) | 0.81 | 1.00 | 0.90 (0.59-1.39) | 0.69 (0.44-1.09) | 0.57 |
| Multivariate RR (95% CI) | 1.00 | 1.00 (0.69-1.31) | 0.96 (0.67-1.36) | 0.81 | 1.00 | 0.90 (0.59-1.39) | 0.69 (0.44-1.09) | 0.57 |
| **DHA (C22:6), µg/ml** | <36.42 | 36.42-47.68 | >47.68 | 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 |
| Sum of tumours, n | 210 | 242 | 248 | 151 | 174 | 183 | 0.57 |
| Basic RR (95% CI) | 1.00 | 1.00 (0.69-1.31) | 0.96 (0.67-1.36) | 0.81 | 1.00 | 0.90 (0.59-1.39) | 0.69 (0.44-1.09) | 0.57 |
| Multivariate RR (95% CI) | 1.00 | 1.00 (0.69-1.31) | 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** | <348.9 | 348.90-408.01 | >408.03 | 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 |
| Sum of tumours, n | 289 | 228 | 183 | 225 | 157 | 126 | 0.01 |
| Basic RR (95% CI) | 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) | 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 |
| Linoleic acid (C18:2), µg/ml | <228.23 | 228.23-273.44 | >273.44 | <228.23 | 228.23-273.44 | >273.44 |
|-----------------------------|---------|----------------|--------|---------|----------------|--------|
| Sum of tumours, n           | 263     | 263            | 174    | 206     | 185            | 117    |
| Basic RR (95% CI)
|                           | 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)
|                           | 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 tumours, n | 252     | 264            | 184    | 194     | 188            | 126    |
| Basic RR (95% CI)
|                           | 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)
|                           | 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 tumours, n     | 211   | 219      | 270   | 143   | 162      | 203   |
| Basic RR (95% CI)
|                           | 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)
|                           | 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 |

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid

* All p-values from two-sided tests
* Sum of omega-3: linolenic acid, EPA, DHA
* Basic RR adjusted for age, sex
* Multivariate RR adjusted for age, sex, freckling on back, treatment allocation
* Sum of omega-6: linoleic acid, AA
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