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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

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Abstract

Intake of omega-3 and omega-6 fatty acids may modify the risk of basal and squamous cell carcinoma of the skin (BCC and SCC), but population-based evidence is limited and inconsistent. We examined prospectively associations between intake of omega-3 and omega-6 fatty acids estimated from food frequency questionnaires and BCC and SCC incidence among 1322 randomly selected adults in Nambour, Australia. Relative risks (RR) and 95% confidence intervals (CI) were estimated based on histologically confirmed tumors diagnosed between 1997 and 2007. Incidence of BCC was lowest in the middle third of both total omega-6 intake ($RR_{mv.adj}$ = 0.74, 95% CI = 0.56–0.97) and linoleic acid intake ($RR_{mv.adj}$ = 0.75, 95% CI = 0.57–0.99) compared with the lowest third of intake. Evidence for associations with SCC was weak, though persons with arachidonic acid intake in the middle third had a marginally increased risk of SCC ($RR_{mv.adj}$ = 1.42, 95% CI = 1.00–2.02). Consumption of omega-3 fatty acids was not associated with subsequent skin cancer risk. Suggestion that intake of arachidonic acid may be associated with increased SCC incidence and total omega-6 with reduced BCC from our study is still highly uncertain and may be due to chance. These data do not support an association between these fatty acids and risk of BCC or SCC.

INTRODUCTION

The keratinocytic skin cancers basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most commonly occurring cancers in white-skinned populations worldwide.

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Approximately 90% of all keratinocytic skin cancers in humans are attributed to excessive exposure to solar ultraviolet radiation (UVR) (1,2). UVR is a complete carcinogen capable of initiation and promotion of skin cancer and acts in several ways such as by inducing DNA damage and modulating immunosuppression (3).

There is increasing evidence that dietary factors modify carcinogenic processes in the skin and that UVR-induced skin carcinogenesis may be sensitive to the quantity and type of dietary fat ingested. Animal studies have indicated that diets high in omega-6 polyunsaturated fatty acids can reduce the latent period before tumor appearance after UVR exposure, increase the number of tumors, and affect the promotional stage of UV carcinogenesis (4,5). High levels of omega-6 fatty acids are also associated with specific deleterious immune responses such as elevation of prostaglandin E2 levels, an immunoregulator known to exacerbate UVR-carcinogenesis and to be associated with aggressive keratinocytic skin cancer growth in humans (1,6,7). Conversely, omega-3 fatty acids including α-linolenic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), appear to reduce inflammatory effects on skin cells following UVR exposure thereby inhibiting UVR carcinogenesis (1,3,8–11). Further, an inverse dose-response relationship between omega-3 intake and p53 immunoreactivity has been shown such that omega-3 fatty acids appear to prevent DNA damage caused by mutant p53 by influencing the process by which UVR induces mutations in the p53 gene (3,12). Because of the opposing effects of omega-3 and omega-6 fatty acids, the ratio of their intakes may determine the overall effect on skin carcinogenesis (13,14).

Results from previous epidemiological studies of omega-3 and omega-6 fatty acids have been mixed. A decrease in risk of SCC with increased intake of diets with a high omega-3/omega-6 ratio was observed in a population-based case-control study of 792 subjects from southeastern Arizona (14); however a prospective study of more than 40,000 American male health professionals failed to demonstrate a reduction in BCC risk with low dietary fat or high omega-3 fatty acid intake over the 8 yr of follow-up (15).

In the present community-based study we investigated prospectively the association between estimates of dietary intake of omega-3 and omega-6 fatty acids, and the risk of BCC and SCC.

MATERIALS AND METHODS

The Nambour Trial and Follow-Up Study

We conducted an 11-yr prospective cohort study from 1997 to 2007 among White Caucasian adults who were originally randomly selected using the electoral roll (enrollment is compulsory by law in Australia) from the community in 1986 and who participated in a skin cancer prevention field trial between 1992 and 1996. Detailed descriptions of the community sample, the field trial, and its outcomes have been reported previously (16,17). Briefly, some 1600 residents of Nambour, a township in Queensland, Australia, took part in a trial that evaluated the prevention of skin cancer using ß-carotene supplements and/or daily application of sunscreen. Original study participants from 1986 were eligible for the trial if they attended the 1992 survey, underwent a complete skin examination by a dermatologist with removal of all diagnosed skin cancers, and gave written consent to participate in the trial until 1996 (16,17). Persons with Gorlin's syndrome or porokeratosis were ineligible to participate. Trial participants were eligible for the present study if they had completed a food frequency questionnaire (FFQ). The study was approved by the ethics committee of the Queensland Institute of Medical Research and all participants provided informed written consent.

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Dietary Intake Estimates

Habitual diet during the past 6 mo was assessed using a self-administered, semiquantitative FFQ consisting of 129 food or food group items. These were completed in 1992, 1994, and 1996. The FFQ, originally developed for the U.S. Nurses' Health Study, was adapted for the Australian setting and validated against weighed food records (18). For each food item, a commonly used unit or portion size was specified and participants were asked to estimate how often on average they had eaten the given amount of food over the past 6 mo. The 9 response options ranged from "never" to "4+ times per day." Information on cooking methods; specific types of fats, oils, and margarines used; and frequency of eating breakfast cereals and fried takeaway foods was also collected, as well as detailed information regarding consumption of nutritional supplements.

Average daily intake was calculated by expressing the response to the food item as a proportion of daily use, which was then multiplied by the amount, in grams, of specified portion sizes. Daily intakes of linoleic acid, arachidonic acid, α-linolenic acid, EPA, docosapentaeoic acid (DPA), and DHA were calculated using a comprehensive fatty acid database for Australian foods (19). Total omega-3 fatty acid intake was calculated by summing the intake of α-linolenic acid, EPA, DPA, and DHA (total long chain omega-3′s excluded α-linolenic acid), and total omega-6 fatty acid intake by the sum of linoleic acid and arachidonic acid intake. The ratio of omega-3/omega-6 fatty acids was also calculated. Intake of dietary supplements containing fatty acids or oils was estimated using a supplement database (20). These calculations were compiled for each of the 1992, 1994, and 1996 FFQs and mean nutrient values across the 3 were used in the analysis. Validity of fatty acid intake estimates from the FFQ was evaluated relative to plasma phospholipid measurements and weighed food records. FFQ validity coefficients ranged from 0.45 (arachidonic acid) to 0.63 (total omega-3). Diet-plasma correlations were moderate for total omega-3, α-linolenic acid, EPA, DPA, and DHA (21).

Other Variables

Information on demographic variables, eye color, and hair color was obtained via an interviewer-administered questionnaire (22). Additional standard self-administered questionnaires provided information on education, smoking habits, compliance with the trial treatment supplement, presence of certain medical conditions, and standard skin cancer risk factors such as natural skin color, tanning ability of the skin, and occupational and leisure-time sun exposure (17). During a physical examination in 1996, height and weight were measured and elastosis of the neck was recorded as a measure of long-term sun exposure history.

Determination of Skin Cancer

An intensive surveillance system of incident skin cancers in the study population that was set up during the Nambour trial continued during the complete posttrial follow-up period (1997–2007). Questionnaires were mailed twice-yearly to participants and any reported skin cancers were confirmed through histological reports. In addition in 2000, a full-body skin examination for skin cancer was conducted by a dermatology specialist trainee among an unselected proportion of ongoing study participants, and in 2007 all remaining active participants underwent full-body skin examination. Finally, independent pathology laboratories throughout Queensland provided histology reports for all skin cancers diagnosed among study participants throughout the follow-up period. These methods ensured virtually 100% ascertainment of histologically confirmed skin cancers in the study population (23).

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Outcomes

The two outcomes of analyses were (a) incidence of persons affected by a new BCC or SCC calculated as the number of patients diagnosed from January 1, 1997, to December 31, 2007, divided by the person-yr of follow-up accumulated between these dates and expressed per 100 000 person-yr; and (b) incidence of BCC or SCC tumors during the same person-yr follow-up time as calculated for the person-based analysis. Tumors diagnosed in 1996 were not included in the analyses to exclude disease that already existed during the baseline nutritional assessment. Tumors and person-yr of follow-up were counted until date of withdrawal from the study, date of death, or December 31, 2007, whichever occurred first.

Data Analysis

For the linear modeling, intake estimates of dietary fatty acids were adjusted for total energy intake using the nutrient residual method as described by Willet (24). Distributions of dietary intake were identified as skewed and variables were log-transformed to improve normality prior to calculation of the residuals. Dietary intakes were classified into ranked thirds. For tumor-based analyses, relative risks (RR) and 95% confidence intervals (CI) for increasing levels of dietary intake compared to the lowest third were derived using generalized linear models with negative binomial distribution and person-years of follow up as offset (25). RR and 95% CI for person-based analysis were estimated by generalized linear models specifying Poisson distribution with a robust error variance (26).

We first applied models controlling for age and sex (“basic” models). We also assessed the multivariate adjusted model, which considered the confounding effects of tanning ability (always burn, burn then tan, only tan), skin color (fair, medium/olive), eye color (blue/grey, hazel/green, light brown, dark brown), hair color (blonde, light brown, ginger/auburn, dark brown/black), mean daily energy intake, supplement use (yes/no), freckling of the back (none, few, many), elastoses of the neck (none, mild, moderate, severe), total number of solar keratoses (0, 1–10, 11–50, >50), pack-yr of smoking (nonsmoker, 0 to 7, >7 to 20 pack-yr), body mass index (BMI), randomized treatment allocation, lifetime number of painful sunburns (0, 1–10, >10), weekday and weekend hours spent outdoors (<1, 1–4, 5–8, 9–12), habitual sunscreen use on face, hands, and other body parts independent from treatment allocation (less than or more than 50% of the time), use of nonsteroidal antiinflammatory drugs (yes/no), and previous history of skin cancer before 1997 (yes/no). Among these, the factors that changed the relative risk estimates of the basic model by ≥10% were considered significant confounders of the model (27) in the context of findings of previous studies on diet and skin cancer. Adjustment variables included in the final multivariate models were age, sex, freckling on the back, elastosis of the neck, and trial treatment allocation for BCC models, and age, sex, elastosis of the neck, total number solar keratoses, and trial treatment allocation for SCC models.

People with a history of skin cancer have an increased risk of developing subsequent skin cancers (28,29) and may be more prone to risk modification by dietary factors. Thus the above analyses were repeated using stratification for previous history of skin cancers prior to 1997. Information on skin cancer history was based on skin cancers identified during skin examinations and surveys conducted in the participants prior to 1996 (16,22,30,31). Analyses stratified by sex were also performed. Statistical significance was set at P value <0.05 (2-tailed). The statistical analyses of the data were carried out using SAS version 9.2 (SAS, Cary, NC).

RESULTS

Of the 1621 original Nambour trial participants, 1334 completed at least one FFQ and consented to be followed-up. Two persons died soon after and 4 participants were excluded because they did not indicate consumption frequencies for 10% or more of the FFQ food items or they reported energy intakes outside the normal ranges (24). A further 6 persons were excluded because they were not of white Caucasian ethnicity, leaving 1322 people for study. No significant difference was found between the subjects in the present study and the 1621 trial participants in terms of randomized treatment allocation, age, sex, education, occupation, smoking status, use of dietary supplements, and skin cancer factors. Participants who had any incident skin cancer during follow-up were more likely to be male, older, have mainly outdoors occupations, have elastosis of the neck, have freckling on the back, and have a previous history of skin cancer (Table 1). In addition, persons affected by SCC were also more likely to have fair skin color and to always sunburn on acute sun exposure.

In the 10-yr follow-up period a total of 325 participants with 746 histologically confirmed new BCC tumors were diagnosed in during 13 903 person-yr of follow-up. This gave a BCC person-based incidence rate of 2,338/100,000 and a tumor-based incidence rate of 5,366/100,000 person-yr. One hundred ninety-six participants with 368 histologically confirmed new SCC tumors were diagnosed during the same follow-up giving an SCC person-based incidence rate of 1,409/100,000 and a tumor-based incidence rate of 2,646/100,000. Among the 1322 participants, 429 (32%) had a prior history of skin cancer before 1997.

From the person-based analyses after multi-variable adjustments, incidence of BCC was lower in persons in the middle thirds of both total omega-6 intake ($RR_{mv.adj}$ = 0.74, 95% CI = 0.56–0.97) and linoleic acid intake ($RR_{mv.adj}$ = 0.75, 95% CI = 0.57–0.99) compared to those in the lowest but not the highest third of intake (Table 2). BCC incidence was lowest in participants with intake of arachidonic acid in the highest third ($RR_{mv.adj}$ = 0.78, 95% CI = 0.59–1.03) but this was not statistically significant. None of the other fatty acids studied were associated with BCC incidence.

In the person-based analyses there was little evidence for associations between omega-3 and omega-6 fatty acids and SCC incidence, though arachidonic acid intake in the middle compared to the lowest third showed a small increase of borderline significance in incidence of SCC ($RR_{mv.adj.}$ = 1.42, 95% CI = 1.00–2.02) (Table 3).

Results from the tumor-based analyses were generally similar to those of the person-based analyses. Incidence of BCC tumors was similarly marginally inversely related to the middle third of total omega-6 intake ($RR_{mv.adj}$ = 0.73, 95% CI = 0.53–1.00), but the association of the middle third of linoleic acid intake was attenuated (full results not shown). None of the other fatty acids were associated with tumor-based BCC incidence. The borderline association seen for SCC in the person-based analyses was also seen in the tumor-based analyses. SCC tumour-based incidence was high in those in the top third of arachidonic acid intake ($RR_{mv.adj}$ = 1.44, 95% CI = 0.97–2.14), but even higher in the middle third ($RR_{mv.adj}$ = 1.68, 95% CI = 1.14–2.46; p for trend = 0.08).

We repeated analyses stratified by previous history of skin cancer and by sex, but there were no significant interactions between these variables and omega-3 and omega-6 fatty acids and nor were there major differences in risk estimates between the stratified and unstratified results (not shown).

DISCUSSION

Our findings in this prospective study of omega-3 and omega-6 fatty acid consumption did not provide consistent evidence of associations with BCC or SCC risk. We observed that although incidence of BCC was lower for intermediate intakes of omega-6 fatty acids, in particular linoleic acid, compared to lowest but not highest thirds of intake, intermediate intakes of arachidonic acid showed a marginal increased risk of SCC. Tumor-based analyses also suggested that medium to high arachidonic acid intakes were associated with increased incidence of SCC tumors.

Our results are consistent with a case-control study among adults 30 years of age and older in southeast Arizona, which showed a significantly higher risk of SCC with greater arachidonic acid concentrations in red blood cell membranes (32) but not for arachidonic acid intake (14). The red blood cell data from the population-based study in Arizona, however, adds to evidence from mouse-model studies that have demonstrated a role of omega-6 fatty acids in enhancing carcinogenesis and have correlated dietary omega-6 intake with keratinocytic cancers (32,33).

Risk estimates for BCC associated with intake of arachidonic acid tended to be in the opposite direction to those for SCC, with weak protective associations for BCC and suggestions of increased risk for SCC, though the lack of a consistent pattern of associations indicates that these may be chance findings. These findings for BCC contrast with our hypothesis, which was based on the mostly animal evidence available. There is also a lack of consistency between these results and those of van Dam and colleagues, which failed to find an association between polyunsaturated fatty acids and BCC risk (15). Though theirs too was a prospective study with energy- and sun exposure-adjusted results, the study was limited by the restriction to male participants only, and by the small number of BCC cases observed (15). Interestingly, in the same Nambour study participants we have previously noted that a meat and fat diet pattern was associated with an increased risk of SCC tumors (34). As red meats such as beef and lamb are the predominant source of arachidonic acid in this population, our results, although marginally significant, are in agreement with these earlier findings. It remains unclear, however, why omega-6 fatty acids might affect BCC and SCC carcinogenesis differently. A different role for polyunsaturated fatty acids in these cancers would be plausible given that BCC and SCC are 2 quite separate entities with different aetiologies. Dietary factors may influence these skin cancers in diverse ways, as we have previously observed for food groups (35,36).

A possible explanation for the associations seen in middle thirds of intake may be the existence of a U-shaped (linoleic acid and total omega-6 fatty acids and BCC) or inverse U-shaped (arachidonic acid and SCC) relationship. U-shaped relationships where disease risk differs at high and low doses of exposure (37) have been identified in nutritional epidemiology studies; for example, between intake of alcohol and cardiovascular disease (38). Only 1 study has reported such a relation in fatty acid nutrition, for the association between fish and omega-3 consumption and heart failure (39). Though theoretically U-shaped associations are possible in the context of our study, they are difficult to prove given the low-to-moderate fatty acid intake levels we observed and, because of the number of observations, we were restricted to an analysis of 3 intake categories only. Further, there has been no previous indication of U-shaped relations between omega-3 and -6 fatty acids and cancer.

To the best of our knowledge this is the first longitudinal study to describe associations between dietary intake of individual omega-3 and omega-6 fatty acids and subsequent keratinocytic skin cancer risk in both sexes. A major strength of this study is its prospective

nature, and our ability to fully assess potential confounding given the extensive and rigorous data collections in this study population. Estimations of intakes of omega-3 and omega-6 fatty acids by FFQ were previously evaluated in a validation study of our study population using weighed food records and plasma phospholipid fatty acids, which had shown adequate estimation of the fatty acids considered in this study (21). As a result, the degree of misclassification in fatty acid intake levels is expected to be low, though if present may have diluted risk estimates to some extent. Our study is based on analyses of histologically confirmed BCC and SCC identified through a comprehensive surveillance system, thus it is unlikely that study participants were misclassified through missed cases or misdiagnosis. Given the large number of group comparisons, chance findings may have occurred in our study and the study may have lacked power to detect associations or dose-response relationships if they did indeed exist due to relatively small numbers of participants with a BCC or SCC in each level of intake of a specific fatty acid.

In summary, though our results suggest that moderate intakes of arachidonic acid may be associated with increased SCC and omega-6 fatty acids with reduced BCC, this study did not provide strong support for associations of omega-3 and omega-6 fatty acid intake with human skin carcinogenesis. Replicated analyses in larger study populations are needed to support or refute our findings, in particular with regard to the generally weak associations observed.

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TABLE 1

Baseline characteristics by skin cancer status of 1322 participants of the Nambour Skin Cancer Study, 1997–2007

Characteristics	Basal cell carcinoma			Squamous cell carcinoma		
	Present (*n* = 318) *n* (%)	Absent (*n* = 1004) *n* (%)	*P* value*	Present (*n* = 191) *n* (%)	Absent (*n* = 1131) *n* (%)	*P* value*
Sex						
Male	159 (50)	421 (42)	0.01	100 (52)	480 (42)	0.01
Female	159 (50)	583 (58)		91 (48)	651 (58)	
Age (mean ± SD)	60 ± 12	52 ± 13	<0.0001	6 3± 11	52 ± 13	<0.0001
Occupation (in/outdoors)						
Mainly outdoors	73 (23)	173 (17)	0.002	47 (25)	199 (18)	0.02
Both	130 (41)	359 (36)		75 (39)	414 (37)	
Mainly indoors	115 (36)	471 (47)		69 (36)	517 (46)	
Pack-years smoked						
Life-long non-smoker	178 (56)	562 (56)	0.77	93 (49)	647 (57)	0.05
≤7 pack-years smoked	52 (16)	168 (17)		32 (17)	188 (17)	
7–20 pack-years smoked	32 (10)	117 (12)		23 (12)	126 (11)	
≥20 pack-years smoked	56 (18)	157 (16)		43 (23)	170 (15)	
Skin color						
Fair	191 (60)	544 (54)	0.05	123 (64)	612 (54)	0.01
Medium	114 (36)	385 (38)		62 (32)	437 (39)	
Olive/black/brown	13 (4)	74 (8)		6 (3)	81 (7)	
Skin type						
Always burn	78 (25)	195 (19)	0.06	67 (35)	206 (18)	<0.0001
Burn/tan	216 (68)	701 (70)		110 (58)	807 (71)	
Only tan	24 (8)	107 (11)		14 (7)	117 (10)	
Painful sunburns						
Never	48 (16)	144 (15)	0.25	28 (16)	164 (15)	0.92
Once	181 (60)	592 (63)		114 (64)	659 (62)	
2–5 Burns	43 (14)	144 (15)		25 (14)	162 (15)	
>5 Burns	31 (10)	64 (7)		12 (7)	83 (8)	
Elastosis of the neck						
None	17 (6)	191 (20)	<0.0001	4 (2)	204 (19)	<0.0001
Mild/moderate	151 (51)	539 (58)		76 (43)	614 (58)	
Severe	127 (43)	207 (22)		96 (55)	238 (23)	
Freckling on the back						
None	39 (13)	199 (21)	0.0001	19 (11)	219 (21)	0.0003
Mild	115 (40)	417 (44)		70 (40)	462 (44)	
Moderate	86 (30)	228 (24)		50 (29)	264 (25)	
Severe	51 (18)	95 (10)		34 (20)	112 (11)	
History of skin cancer						

Characteristics	Basal cell carcinoma			Squamous cell carcinoma		
	Present (*n* = 318) *n* (%)	Absent (*n* = 1004) *n* (%)	*P* value*	Present (*n* = 191) *n* (%)	Absent (*n* = 1131) *n* (%)	*P* value*
Yes	198 (62)	231 (23)	<0.0001	132 (69)	297 (27)	<0.0001
No	120 (38)	773 (77)		59 (31)	834 (74)	

**P* value from chi-square test (categorical data) or ANOVA (continuous data); significance $p < 0.05$.

TABLE 2

Relative risks (RR) and 95% confidence intervals (95% CI) for **basal cell carcinoma** by ranked thirds of dietary intake of omega-3 and omega-6 fatty acids from food frequency questionnaire, person-based analysis in 1322 participants of the Nambour Skin Cancer Study, 1997–2007

	Ranked thirds of intake			
Fatty acids	**Low** ***n*** **= 440**	**Middle** ***n*** **= 441**	**High** ***n*** **= 441**	***P*** **for trend**[a]
Sum of omega-3, g/day[b]	<0.90	0.90–1.10	>1.10	
Number of cases, *n*	109	99	117	
Basic RR (95% CI)[c]	1.00	0.89 (0.68–1.17)	0.94 (0.72–1.23)	0.67
Multivariate RR (95% CI)[d]	1.00	0.89 (0.68–1.18)	0.91 (0.70–1.19)	0.49
Sum of long-chain omega-3, g/day[e]	<0.16	0.16–0.26	>0.26	
Number of cases, *n*	10.4	110	104	
Basic RR (95% CI)	1.00	1.01 (0.77–1.32)	0.89 (0.67–1.17)	0.38
Multivariate RR (95% CI)	1.00	1.02 (0.77–1.33)	0.88 (0.67–1.16)	0.35
α-Linolenic acid (18:3), g/day	<0.68	0.68–0.83	>0.83	
Number of cases, *n*	112	99	114	
Basic RR (95% CI)	1.00	0.87 (0.67–1.14)	0.96 (0.74–1.25)	0.79
Multivariate RR (95% CI)	1.00	0.86 (0.66–1.14)	0.93 (0.71–1.21)	0.59
EPA (20:5), g/day	<0.05	0.05–0.09	>0.09	
Number of cases, *n*	103	115	107	
Basic RR (95% CI)	1.00	1.07 (0.82–1.40)	0.92 (0.70–1.21)	0.54
Multivariate RR (95% CI)	1.00	1.07 (0.82–1.40)	0.91 (0.69–1.20)	0.50
DPA (22:5), g/day	<0.03	0.03–0.05	>0.05	
Number of cases, *n*	102	122	94	
Basic RR (95% CI)	1.00	1.12 (0.86–1.45)	0.81 (0.61–1.07)	0.13
Multivariate RR (95% CI)	1.00	1.11 (0.85–1.44)	0.79 (0.59–1.04)	0.10
DHA (C22:6), g/day	<0.07	0.07–0.13	>0.13	
Number of cases, *n*	100	119	106	
Basic RR (95% CI)	1.00	1.18 (0.90–1.54)	0.97 (0.73–1.28)	0.78
Multivariate RR (95% CI)	1.00	1.17 (0.90–1.53)	0.96 (0.72–1.26)	0.73
Sum of omega-6, g/day[f]	<7.17	7.17–8.91	>8.91	
Number of cases, *n*	118	92	115	
Basic RR (95% CI)	1.00	0.74 (0.56–0.97)*	0.88 (0.68–1.15)	0.37
Multivariate RR (95% CI)	1.00	0.74 (0.56–0.97)*	0.86 (0.66–1.12)	0.28
Linoleic acid (C18:2), g/day	<7.06	7.06–8.80	>8.80	
Number of cases, *n*	117	93	115	
Basic RR (95% CI)	1.00	0.76 (0.58–1.00)	0.89 (0.69–1.16)	0.41
Multivariate RR (95% CI)	1.00	0.75 (0.57–0.99)*	0.86 (0.67–1.14)	0.32
AA (C20:4), g/day	<0.07	0.07–0.10	>0.10	
Number of cases, *n*	113	122	90	

Fatty acids	Ranked thirds of intake			
	Low ***n*** **= 440**	**Middle** ***n*** **= 441**	**High** ***n*** **= 441**	***P*** **for trend**[a]
Basic RR (95% CI)	1.00	1.10 (0.85–1.43)	0.90 (0.60–1.05)	0.12
Multivariate RR (95% CI)	1.00	1.08 (0.84–1.40)	0.78 (0.59–1.03)	0.09
Omega-3/omega-6 ratio	<0.11	0.11–0.14	>0.14	
Number of cases, *n*	115	98	112	
Basic RR (95% CI)	1.00	0.88 (0.67–1.16)	0.94 (0.72–1.22)	0.65
Multivariate RR (95% CI)	1.00	0.91 (0.69–1.19)	0.94 (0.72–1.22)	0.65

[a] All *P* values from 2-sided tests.

[b] Sum of omega-3: α-linolenic acid, eicosapentaenoic acid (EPA), docosapentaeoic acid (DPA), docosahexaenoic acid (DHA).

[c] RR_{basic} adjusted for age and sex.

[d] $RR_{mv.adj}$ adjusted for age, sex, freckling on back, elastosis of neck, treatment allocation.

[e] Sum of long-chain omega-3: EPA, DPA, DHA.

[f] Sum of omega-6: linoleic acid, arachidonic acid (AA).

[*] $P < 0.05$.

TABLE 3

Relative risks (RR) and 95% confidence intervals (95% CI) for squamous cell carcinoma by ranked thirds of dietary intake of omega-3 and omega-6 fatty acids from FFQ, person-based analysis in 1322 participants of the Nambour Skin Cancer Study, 1997–2007

	Ranked thirds of intake			
Fatty acids	**Low** ***n*** **= 440**	**Middle** ***n*** **= 441**	**High** ***n*** **= 441**	***P*** **for trend**[a]
Sum of omega-3, g/day[b]	<0.90	0.90–1.10	>1.10	
Number of cases, *n*	60	58	78	
Basic RR (95% CI)[c]	1.00	0.93 (0.65–1.34)	1.00 (0.71–1.40)	0.98
Multivariate RR (95% CI)[d]	1.00	0.94 (0.65–1.36)	1.03 (0.72–1.46)	0.88
Sum of long-chain omega-3, g/day[e]				
Number of cases, *n*	67	51	73	
Basic RR (95% CI)	1.00	0.69 (0.48–0.99)*	0.86 (0.61–1.20)	0.41
Multivariate RR (95% CI)	1.00	0.77 (0.53–1.13)	0.97 (0.69–1.38)	0.90
α-Linolenic acid (18:3), g /day	<0.68	0.68–0.83	>0.83	
Number of cases, *n*	65	62	69	
Basic RR (95% CI)	1.00	0.93 (0.65–1.31)	0.94 (0.67–1.32)	0.73
Multivariate RR (95% CI)	1.00	0.95 (0.66–1.36)	0.87 (0.61–1.24)	0.44
EPA (20:5), g/day	<0.05	0.05–0.09	>0.09	
Number of cases, *n*	67	56	73	
Basic RR (95% CI)	1.00	0.73 (0.51–1.05)	0.83 (0.59–1.15)	0.29
Multivariate RR (95% CI)	1.00	0.77 (0.53–1.11)	0.93 (0.66–1.32)	0.72
DPA (22:5), g/day	<0.03	0.03–0.05	>0.05	
Number of cases, *n*	59	61	71	
Basic RR (95% CI)	1.00	0.92 (0.64–1.32)	0.96 (0.68–1.36)	0.83
Multivariate RR (95% CI)	1.00	0.91 (0.62–1.31)	1.03 (0.72–1.47)	0.86
DHA (C22:6), g/day	<0.07	0.07–0.13	>0.13	
Number of cases, *n*	67	55	74	
Basic RR (95% CI)	1.00	0.77 (0.54–1.10)	0.89 (0.63–1.24)	0.51
Multivariate RR (95% CI)	1.00	0.83 (0.57–1.20)	0.95 (0.67–1.34)	0.80
Sum of omega-6, g/day[f]	<7.17	7.17–8.91	>8.91	
Number of cases, *n*	63	64	69	
Basic RR (95% CI)	1.00	0.92 (0.65–1.31)	0.91 (0.65–1.28)	0.60
Multivariate RR (95% CI)	1.00	0.89 (0.62–1.27)	0.92 (0.64–1.31)	0.65
Linoleic acid (C18:2), g/day	<7.06	7.06–8.80	>8.80	
Number of cases, *n*	63	63	70	
Basic RR (95% CI)	1.00	0.91 (0.64–1.29)	0.92 (0.66–1.30)	0.66
Multivariate RR (95% CI)	1.00	0.89 (0.62–1.27)	0.94 (0.66–1.35)	0.76
AA (C20:4), g/day	<0.07	0.07–0.10	>0.10	
Number of cases, *n*	56	79	61	
Basic RR (95% CI)	1.00	1.47 (1.04–2.07)*	1.08 (0.75–1.56)	0.69

Fatty acids	Ranked thirds of intake			
	Low ***n*** **= 440**	**Middle** ***n*** **= 441**	**High** ***n*** **= 441**	***P*** **for trend**[a]
Multivariate RR (95% CI)	1.00	1.42 (1.00–2.02)	1.18 (0.81–1.72)	0.39
Omega-3/omega-6 ratio	<0.11	0.11–0.14	>0.14	
Number of cases, *n*	60	57	79	
Basic RR (95% CI)	1.00	0.99 (0.69–1.43)	1.20 (0.86–1.68)	0.28
Multivariate RR (95% CI)	1.00	1.05 (0.72–1.53)	1.22 (0.86–1.73)	0.25

[a] All *P* values from 2-sided tests.

[b] Sum of omega-3: α-linolenic acid, eicosapentaenoic acid (EPA), docosapentaeoic acid (DPA), docosahexaenoic acid (DHA).

[c] RR_{basic} adjusted for age and sex.

[d] $RR_{mv.adj}$ adjusted for age, sex, elastosis of neck, total solar keratoses, treatment allocation.

[e] Sum of long-chain omega-3: EPA, DPA, DHA.

[f] Sum of omega-6: linoleic acid, arachidonic acid (AA).

[*] *P* value < 0.05.