Dietary pattern in association with squamous cell carcinoma of the skin: a prospective study[1–3]

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ABSTRACT

Background: The role of diet in the development of skin cancer is inconclusive, and the effect of the combined consumption of foods has never been reported.

Objective: We prospectively investigated the association between dietary patterns and cutaneous basal cell (BCC) and squamous cell (SCC) carcinoma.

Design: Principal components analysis of 38 food groups was used to identify dietary patterns in 1360 adults aged 25–75 y who participated in a community-based skin cancer study in Nambour, Australia, between 1992 and 2002. We obtained baseline information about diet, skin color, and sun exposure factors. Multivariate-adjusted relative risks (RRs) for BCC and SCC tumors were estimated by using negative binomial regression modeling.

Results: Two major dietary patterns were identified: a meat and fat pattern and a vegetable and fruit pattern. The meat and fat pattern was positively associated with development of SCC tumors (RR = 1.83; 95% CI: 1.00, 3.37; *P* for trend = 0.05) after adjustment for confounders and even more strongly associated in participants with a skin cancer history (RR = 3.77; 95% CI: 1.65, 8.63; *P* for trend = 0.002) when the third and first tertiles were compared. A higher consumption of the vegetable and fruit dietary pattern appeared to decrease SCC tumor risk by 54% (*P* for trend = 0.02), but this protective effect was mostly explained by the association with green leafy vegetables. There was no association between the dietary patterns and BCC tumors.

Conclusion: A dietary pattern characterized by high meat and fat intakes increases SCC tumor risk, particularly in persons with a skin cancer history. *Am J Clin Nutr* 2007;85:1401–8.

KEY WORDS Dietary patterns, skin cancer, squamous cell carcinoma risk, basal cell carcinoma risk, principal components analysis, food-frequency questionnaire

INTRODUCTION

In the United States, >1 million cases of the skin cancers basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) occur each year (1). Incidence rates are generally increasing in white populations worldwide (2–4), so that the costs of treatment of BCC and SCC tumors exceed the costs of treatment of all other cancers and place a disproportionate burden on health budgets (4–6).

Excessive sun exposure causes skin cancer by mutagenic, immunosuppressive, and oxidative stress–inducing mechanisms (7, 8). Animal studies show that diet—specifically, the intake of lutein (9), vitamin E (10), vitamin C (11), selenium (12), or a combination of these and other antioxidants—can protect against oxidative damage in the skin by directly quenching reactive oxygen species and scavenging free radicals. In addition, dietary n−3 fatty acids can dramatically reduce the plasma cutaneous proinflammatory and immunosuppressive prostaglandin E synthase type 2 (PGE_2) concentration in mice, whereas dietary n−6 fatty acids increase PGE_2 (13). Dietary n−3 fatty acids also can significantly reduce the inflammatory response and enhance the delayed-type hypersensitivity immune response after ultraviolet light exposure in mice when compared with an equivalent dietary amount of n−6 fatty acids (13).

Evidence in humans regarding the association between dietary intake and the risk of developing BCC and SCC tumors suggests a positive relation between fat intake and skin cancers but an inconsistent relation with the other nutrients (14). We previously showed that the consumption of green leafy vegetables and unmodified dairy products can each influence the cumulative incidence of SCC after adjustment for sun exposure in persons with a history of skin cancer (15). A limitation shared by all previous studies, however, is the failure to assess the effects of the combined consumption of nutrients as they naturally occur in foods. Because foods are not consumed in isolation, the study of dietary patterns that capture the complex interactions of nutrients may be a more useful approach to understanding the true relation between diet and cancers of the skin. Therefore, we undertook a novel investigation of the association between empirically determined dietary patterns and the risk of BCC and SCC in which we used data collected in a prospective community-based study in Australia, with adjustments for the sun-exposure histories of participants and other established risk factors for these cancers.

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SUBJECTS AND METHODS

Nambour Study participants

We conducted this 11-y prospective study in 1992 as part of the ongoing Nambour Skin Cancer Study, which began in 1986. For that study, 2095 adults aged 20–69 y were selected at random from the residents of the township of Nambour, a subtropical community in Queensland, Australia, for a baseline study of skin cancer (16). Of this group, 1621 participated in a field trial to assess skin cancer prevention between 1992 and 1996 (17, 18). Detailed descriptions of the community sample, the field trial, and its outcomes were published previously (16–20). In summary, the Nambour Skin Cancer Prevention Trial was a randomized controlled trial with a factorial design that evaluated the effectiveness of daily consumption of β-carotene tablets and the application of sunscreen in preventing skin cancer. At baseline (1992), 1447 trial participants completed a food-frequency questionnaire (FFQ) and questionnaires on complexion type, sun exposure, and other personal characteristics (17).

All participants provided written informed consent. The study was approved by the Ethics Committee of the Queensland Institute of Medical Research.

Dietary assessment

The self-administered semiquantitative FFQ adapted from the US Nurses' Health Study FFQ developed by Willett et al (21, 22) was used for the assessment of food intake and dietary supplement use. We have subsequently validated this dietary questionnaire in the Nambour Study population (23–25). Respondents recalled how often, on average, they had consumed a standard serving size of a specific food item in the previous 6 mo for 129 food items; frequency responses ranged from "never" to "≥4 times/d." In addition, we asked about the quantity of sugar habitually added to food or beverages, and the discretionary use of fat was assessed by the frequency with which visible fat from meat, foods fried at home, and fried carry-out foods were consumed. For seasonal fruit and vegetables, participants indicated how often these foods were eaten when in season. To calculate food intake (in g), the reported frequency of intake for each food item was converted to a frequency per day, and that value was multiplied by the standard serving size of each food as specified in the FFQ. Seasonal foods were weighted according to the proportion of the year the food was available. Intakes of the 129 food items and 4 additional fat and sugar items were reclassified into 38 food groups (*see* **Appendix A**). Food items with similar nutrient content were combined (eg, spinach, silver beet, and lettuce were grouped as green leafy vegetables), and foods with unique nutrients (eg, peanut butter, coffee, black tea, and herbal tea) were retained as individual items. For each participant, the average daily intake of each food group was calculated (in g) by summing the intake of the individual foods that made up the food group.

Basal cell carcinoma and squamous cell carcinoma determination

Study participants were followed from the trial baseline in 1992 until the end of 2002 to ascertain all occurrences of BCC and SCC tumors. Full-body skin examinations were conducted in 1992, 1994, and 1996 as part of the trial protocol (18) by dermatologists who assessed sun-induced skin damage—eg, solar elastosis of the neck. Tissue samples from all skin cancers diagnosed clinically underwent biopsy, and the results were confirmed histologically. Between trial surveys, each participant carried a skin cancer treatment card on which his or her doctors recorded all treated skin cancers, and, every 3 mo, participants were followed in study clinics and asked about any skin cancers treated since the last contact. After 1996, when the intervention ceased, information on subsequent skin cancers was collected through questionnaires mailed twice a year to participants. In 2000, participants were offered another full skin examination by a dermatologically trained physician, and tissue samples from suspected skin cancers underwent biopsy for histologic confirmation (26). Finally, independent pathology laboratories throughout southern Queensland provided pathology reports for all skin cancers diagnosed in study participants during the entire follow-up period (1992–2002). These methods ensured virtually 100% ascertainment of histologically diagnosed skin cancers in the study population (26). Information on skin cancer history was based on records of skin cancers identified during skin examinations and surveys conducted between 1986, when the cohort was established, and 1992 (16, 17, 19, 20), on self-reports of any type of skin cancer before 1986 (16), and on pathologic verification of the subset of cancers reported in 1985 and 1986 (19).

Statistical analysis

Intakes of food groups were log transformed to improve normality. Factor analysis (principal components) was conducted using the PCA procedure in STATA software (version 9.0; StataCorp LP, College Station, TX) to derive dietary patterns based on food groups. The retained factors were rotated (varimax rotation) to obtain an orthogonal solution. The first 2 factors were retained on the basis of the point at which the scree plot levels off, eigenvalue >1, and interpretability. Factor scores were produced by using the SCORE option in the STATA software. Tertiles were created from factor scores for further analysis.

Study outcomes were the risks of BCC and of SCC tumors calculated as the numbers of BCC tumors and SCC tumors diagnosed after the baseline 1992 skin examination survey through to 31 December 2002 divided by the person-years of follow-up accumulated between these dates and expressed per 100 000 person-years. Person-years of follow-up (computed from baseline in 1992 until date of withdrawal from study, date of death, or end of follow-up, whichever came first) were log transformed and used as offset.

The first model adjusted for the confounding effect of age (continuous), sex (male or female), and total energy intake in kJ/d (continuous). The expanded model further adjusted for skin color (fair, medium, or olive), burn-tan propensity of the skin on first summer exposure to sun for 1 h (always burn, burn and tan, or tan only), degree of solar elastosis of the neck (none, mild-to-moderate, or severe), history of skin cancer before 1992 (yes or no), smoking (pack-years smoked: none, ≤7, >7–20, or >20), dietary supplement use (yes or no), and trial treatment allocation group (sunscreen treatment: yes or no; β-carotene treatment: yes or no). Confounding covariates were included in the regression model if they changed the risk estimates by >10%.

The distributions of demographic characteristics and potential risk factors were compared for tertiles of each dietary pattern score by using one-factor analysis of variance for means and a chi-square test for proportions. Adjusted relative risks (RRs) and 95% CIs were estimated across tertiles of dietary patterns by using a generalized linear model with negative binomial distribution. The negative binomial distribution has been recommended for analyzing nonnegative integer data with variance greater than the mean (27), and it provided the best fit for our tumor-count data.

Linear trends were assessed by assigning ordinal numbers ranging from 1 to 3 (for lowest to highest tertile, respectively) for each participant's consumption level and modeled as a continuous variable. Stratification on the presence or absence of a history of skin cancer before 1992 was performed, on the basis of a priori knowledge that people with a history of skin cancer have a greater risk of subsequent skin cancers (18, 28, 29) and may be more susceptible to risk modification by dietary intake (15). Tests for interaction were performed by including a product term between history of any skin cancer (binary variable; yes or no) and the dietary pattern scores (continuous variable). Analyses were performed separately for each dietary pattern. All statistical analyses were performed in STATA software (version 9.0), and P values were based on 2-sided statistical tests.

RESULTS

Of 1447 study participants who completed the FFQ in 1992, 53 were missing ≥10% food-consumption frequencies, whereas 34 participants reported energy intakes outside the recommended normal ranges (22). These subjects were excluded from the study, which left 1360 participants (577 M, 783 F) in the final analysis.

During the 11-y follow-up period, 664 histologically confirmed BCC tumors were diagnosed in 267 participants and 235 histologically confirmed SCC tumors were diagnosed in 127 participants. The overall crude incidence rates among participants without a history of skin cancer were 2000 BCC tumors and 775 SCC tumors per 100 000 person-years; the corresponding rates in those with a prior of skin cancer were >6 times as high: 13 936 BCC and 4744 SCC tumors, respectively, per 100 000 person-years.

Two major dietary patterns were identified and labeled the meat and fat and the vegetable and fruit dietary patterns on the basis of food groups with high factor loadings (**Table 1**). The meat and fat dietary pattern featured high consumption of red meats, processed meats, discretionary fat, processed grains, snacks, sweet drinks, and high-fat dairy products, whereas the vegetable and fruit dietary pattern was characterized by high consumption of vegetables, fruit, unprocessed grains, fish, and low-fat dairy products.

On average, participants who more often followed the meat and fat dietary pattern (highest tertile) compared with less often (lowest tertile) were more likely to be men and <50 y old, to be smokers, and to engage in outdoor occupations and leisure activities but less likely to have photo damage of the skin of the neck or to report a history of skin cancer. That same group also was more likely to report high intakes of total energy, total fat, total saturated fat, and alcohol and less likely to use supplements (**Table 2**). In contrast, participants who more often followed the vegetable and fruit diet (highest tertile) compared with less often (lowest tertile) were more likely to be women, >50 y old, and to be highly educated and more likely to have professional jobs. That same group also was more likely to report a history of skin cancer and less likely to have mainly outdoor occupation. They were more likely to use dietary supplements and to report higher intakes of total energy, total fat, β-carotene, and vitamin C and a lower intake of alcohol (Table 2)

The meat and fat dietary pattern was not associated with BCC tumor risk, but, after adjustment for skin color, sun exposure factors, and other potential confounders, RRs of SCC tumors from the lowest to the highest tertile of the dietary pattern score were 1.0, 1.02, and 1.83 (95% CI: 1.00, 3.37; P for trend = 0.05) (**Table 3**). The vegetable and fruit dietary pattern was not associated with either BCC or SCC tumor risk among participants overall (Table 3).

TABLE 1
Pearson correlation coefficients for the relation between food intake and factors representing dietary patterns in 1360 participants of the Nambour Skin Cancer Study, 1992–2002[1]

Foods or food groups	Vegetable and fruit dietary pattern	Meat and fat dietary pattern
Green leafy vegetables	0.65	—[2]
Fruit[3]	0.57	−0.17
Cruciferous vegetables	0.56	—
Red or yellow vegetables	0.55	—
Vitamin C– and vitamin A–containing fruit	0.56	−0.18
Tuna, sardines	0.47	—
Whole-meal bread	0.45	−0.20
Vegetables[4]	0.45	0.20
Rice	0.45	—
Legumes	0.42	—
Salad dressing	0.40	—
Reduced-fat dairy products	0.37	−0.38
Pasta	0.31	0.16
Breakfast cereal	0.30	—
Fish and seafood[5]	0.31	0.21
Cereal products[6]	0.28	—
Poultry	0.26	0.34
Peanut butter	0.21	—
Nuts	0.21	—
Juice	0.19	0.20
Red wine	0.17	0.21
Black tea	0.10	0.16
Herbal tea	0.29	−0.31
Processed meat	—	0.66
Red meat only	—	0.66
Discretionary fat[7]	−0.21	0.54
White bread	−0.33	0.48
Sweet drinks and artificially sweetened drinks	—	0.48
Beer	—	0.47
Potato	—	0.46
Snacks	—	0.43
High-fat dairy products	—	0.45
Egg	—	0.39
Cakes and sugars	—	0.39
Butter and margarine	—	0.38
Alcohol other than beer and wine	—	0.27
White wine	—	—
Coffee	—	0.19
Variance explained (%)	10.1	9.8

[1] With the orthogonal rotation used, correlation coefficients are identical to the factor-loading matrix.
[2] Loadings with absolute values <0.15 (all such).
[3] Other than vitamin A– or vitamin C–containing fruit.
[4] Other than yellow, green leafy, and cruciferous vegetables.
[5] Fish other than tuna, sardines, salmon, and other oily fish.
[6] Other than whole-meal bread, white bread, and breakfast cereal.
[7] Habitual consumption of visible fat on meat, fried food at home, and fried carry-out foods.

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TABLE 2
Baseline characteristics of 1360 participants according to tertiles of dietary pattern score: the Nambour Skin Cancer Study, 1992–2002

	Meat and fat dietary pattern				Vegetable and fruit dietary pattern			
Variables	Tertile 1 (lowest)	Tertile 2	Tertile 3 (highest)	*P* for trend[1]	Tertile 1 (lowest)	Tertile 2	Tertile 3 (highest)	*P* for trend[1]
Subjects (*n*)	454	453	453		454	453	453	
Age (y)[2]	53 ± 12[3]	50 ± 13	45 ± 12	< 0.01	48 ± 13	50 ± 13	52 ± 12	< 0.01
Women (%)[2]	75	62	36	< 0.01	50	58	64	< 0.01
Schooling (y)[2]	15 ± 2	15 ± 1	16 ± 1	0.05	15 ± 1	15 ± 1	16 ± 2	0.01
Professional occupation (%)[4]	28	30	30	NS	23	30	35	< 0.001
Dietary supplement use (%)[2]	50	37	24	< 0.01	29	37	46	< 0.01
Nonsmoker (%)[5]	67	58	48	< 0.01	54	59	60	NS
Sun exposure history								
Occupation mainly outdoors (%)[5]	14	17	23	< 0.01	23	16	15	NS
Leisure activity mainly outdoors (%)[2]	36	39	47	< 0.01	39	39	44	0.03
Severe elastosis of neck (%)[4]	36	31	26	0.01	33	32	28	NS
Reported skin cancer before 1992 (%)[2]	31	26	21	0.01	21	28	30	0.02
Sun sensitivity								
Skin color (%)				NS				NS
Fair	56	58	53		55	56	55	
Medium	37	36	40		37	37	39	
Olive	7	6	7		8	6	6	
Tanning ability of skin								
Always burn (%)	23	22	17	NS	20	19	22	NS
Daily intakes								
Total energy (MJ)[2]	7.2 ± 2	8.7 ± 2	10.7 ± 2	< 0.01	8.0 ± 2	8.9 ± 2	9.7 ± 2	< 0.01
Total fat (g)[2]	57 ± 19	77 ± 19	100 ± 24	< 0.01	73 ± 26	79 ± 28	83 ± 27	< 0.01
Total saturated fat (g)[5]	22 ± 8	32 ± 9	42 ± 12	< 0.01	31 ± 13	33 ± 13	33 ± 12	NS
Alcohol (g)[2]	3 ± 6	7 ± 11	15 ± 18	< 0.01	10 ± 16	8 ± 13	7 ± 13	0.02
β-Carotene (μg)[4]	9471 ± 5934	9098 ± 5212	8881 ± 4192	NS	6177 ± 3574	9186 ± 4119	12094 ± 573	< 0.01
Vitamin C (mg)[4]	196 ± 106	200 ± 105	206 ± 95	NS	141 ± 79	194 ± 78	268 ± 105	< 0.01
Fiber (g)[4]	30 ± 13	29 ± 11	29 ± 10	NS	21 ± 7	29 ± 8	38 ± 12	< 0.01

[1] All statistical tests were 2-sided. ANOVA was used for comparison of means, and chi-square statistic was used to compare proportions.
[2] $P < 0.05$ or $P < 0.01$ for both dietary patterns (tertile 3 compared with tertile 1).
[3] $\bar{x} \pm$ SD (all such values).
[4] $P < 0.01$ for vegetable and fruit dietary pattern only (tertile 3 compared with tertile 1).
[5] $P < 0.01$ for meat and fat dietary pattern only (tertile 3 compared with tertile 1).

Formal testing revealed no significant interaction between the 2 dietary patterns ($P = 0.77$). However, there were a significant ($P = 0.04$) interaction between the meat and fat pattern and a history of skin cancer and a nonsignificant ($P = 0.11$) interaction between the vegetable and fruit pattern and history of skin cancer in relation to SCC tumor risk. After stratification by skin cancer history, there was no evidence of an association between the meat and fat dietary pattern and a risk of developing SCC tumors in the 930 participants without a history of skin cancer (**Table 4**). In contrast, in the 341 participants with a history of skin cancer, the RR of developing SCC tumors, from the lowest to the highest tertile of the meat and fat dietary pattern score, was 1.0, 1.88, and 3.77 (95% CI: 1.65, 8.63; *P* for trend = 0.002; Table 4). For those without a history of skin cancer, there was no evidence of an association between the vegetable and fruit dietary pattern and a risk of developing SCC tumors (data not shown). However, for those with a history of skin cancer, the RR of developing SCC tumors from the lowest to the highest tertile of the vegetable and fruit dietary pattern score was 1.0, 0.76, and 0.46, respectively (95% CI: 0.23, 0.91; *P* for trend = 0.02) after multivariate adjustment, despite the lack of a significant interaction between the vegetable and fruit dietary pattern and skin cancer history. No significant association was found between dietary patterns and BCC tumor risk in participants with a history of skin cancer (data not shown).

In a secondary analysis in the subgroup with a skin cancer history ($n = 341$), we examined the possibility that significant associations observed between the dietary patterns and SCC tumor risk could have been driven by the diet of a small number of participants with many incident SCC tumors during the follow-up period; we did this by excluding 12 participants who had developed 5–7 SCC tumors during the follow-up period. There was no material difference in the results obtained. As an additional check, we performed a multiple regression analysis using the number of persons affected by SCC (person-based incidence) as outcome by using a generalized linear model and specifying Poisson distribution with a robust error variance (30). The results obtained (data not shown) were very similar to those presented for the tumor-based analysis.

Given our previous observations (15), we explored the possibility that any particular food group played a predominant role in the observed associations. From the meat and fat dietary pattern, we selected processed meat, red meat, discretionary fat, high-fat dairy, white bread, sweetened drinks, beer, potato, and snacks; from the vegetable and fruit dietary pattern, we selected green leafy, cruciferous, red and yellow, and other vegetables; vitamin C– or vitamin A–containing fruit; other fruit; oily fish; and whole-grain bread. These food groups had contributed substantially to the dietary patterns (Table 1). The multivariate-adjusted RR of developing SCC tumors from the lowest to the highest tertile

TABLE 3
Relative risks (RR) (and 95% CIs) of basal cell carcinoma and squamous cell carcinoma across tertiles of the 2 dietary patterns for 1271 participants in the Nambour Skin Cancer Study, 1992–2002[1]

	Meat and fat dietary pattern				Vegetable and fruit dietary pattern			
Cancer type	Tertile 1	Tertile 2	Tertile 3	*P* for trend[2]	Tertile 1	Tertile 2	Tertile 3	*P* for trend[2]
Basal cell carcinoma								
Subjects (*n*)	419	421	431		414	432	425	
Tumors (no.)	217	263	184		189	221	254	
Person-years of follow-up (y)	4164	4318	4460		4195	4407	4340	
Model 1[3]	1.00	1.00 (0.68, 1.46)	0.90 (0.57, 1.44)	NS	1.00	1.12 (0.77, 1.63)	1.36 (0.93, 2.00)	NS
Model 2[4]	1.00	1.27 (0.88, 1.82)	1.31 (0.85, 2.04)	NS	1.00	0.93 (0.65, 1.34)	1.14 (0.79, 1.65)	NS
Squamous cell carcinoma								
Subjects (*n*)	419	421	431		414	432	425	
Tumors (*n*)	72	88	75		76	84	75	
Person-years of follow-up (y)	4164	4318	4460		4195	4407	4340	
Model 1[3]	1.00	1.07 (0.64, 1.79)	1.59 (0.87, 2.91)	NS	1.00	1.04 (0.63, 1.73)	0.95 (0.56, 1.62)	NS
Model 2[4]	1.00	1.02 (0.61, 1.72)	1.83 (1.00, 3.37)	0.05	1.00	1.07 (0.64, 1.78)	0.83 (0.47, 1.44)	NS

[1] Total number of subjects may vary because of missing covariates. RRs were obtained by using a generalized linear model with negative binomial distribution.
[2] All statistical tests were 2-sided.
[3] Adjusted for age (continuous), sex (male or female), and total energy intake (continuous).
[4] Multivariate model, adjusted for age, sex, total energy, skin color (fair, medium, or olive), burn-tan propensity of the skin (always burn, burn and tan, or tan only), elastosis of the neck (none, mild to moderate, or severe), history of skin cancer (yes or no), smoking status (nonsmoker, smoked up to 7 pack-years, smoked > 7–20 pack-years, or smoked > 20 pack-years), dietary supplement use (yes or no), and trial treatment allocation: sunscreen (yes or no) or β-carotene treatment (yes or no) group.

of high fat dairy food group was 1.0, 1.84, and 2.38 (95% CI: 1.20, 4.73; *P* for trend = 0.02) and that from the lowest to the highest tertile of green leafy vegetable food group was 1.0, 0.82, and 0.51 (95% CI: 0.26, 0.99; *P* for trend = 0.05). No other food groups had significant associations with SCC tumor risk (**Table 5**).

We further performed a likelihood ratio statistic comparing models to affirm that the meat and fat and the vegetable and fruit dietary patterns had effects beyond the predominant effects of the high-fat dairy and green leafy vegetables food groups. After adjustment for age, sex, total energy intake, burn-tan propensity of the skin, and solar elastosis of the neck in a first model that included the high-fat dairy food group as main effect, high-fat dairy was significantly associated with SCC tumors (RR = 2.20; 95% CI: 1.12, 4.33; *P* = 0.02 when the third tertile was compared with the first tertile). After adjustment for the same confounders in a second model that included the meat and fat dietary pattern as main effect, the meat and fat pattern also was strongly associated with SCC tumor risk (RR = 3.83; 95% CI: 1.70, 8.63; *P* = 0.001 when the third tertile was compared with the first tertile. After including both the meat and fat dietary pattern and the

TABLE 4
Relative risks (RRs) (and 95% CIs) of squamous cell carcinoma in participants with and without a history of skin cancer across tertiles of meat and fat dietary pattern in the Nambour Skin Cancer Study, 1992–2002[1]

	History of skin cancer (*n* = 341)				No history of skin cancer (*n* = 930)			
Cancer type	Tertile 1	Tertile 2	Tertile 3	*P* for trend[2]	Tertile 1	Tertile 2	Tertile 3	*P* for trend[2]
Squamous cell carcinoma								
Subjects (*n*)	137	113	91		282	308	340	
Tumors (no.)	45	69	47		27	19	28	
Person-years of follow-up (y)	1325	1156	914		951	601	790	
Model 1[3]	1.00	1.60 (0.85–3.02)	2.78 (1.26, 6.13)	0.01	1.00	0.65 (0.28, 1.51)	0.90 (0.36, 2.27)	NS
Model 2[4]	1.00	1.88 (0.97, 3.63)	3.77 (1.65, 8.63)	0.002	1.00	0.56 (0.23, 1.37)	0.87 (0.32, 2.34)	NS

[1] Total number of subjects may vary because of missing covariates. RRs were obtained by using a generalized linear model with negative binomial distribution. Interaction between meat and fat dietary pattern and history of skin cancer (*P* = 0.04).
[2] All statistical tests were 2-sided.
[3] Adjusted for age (continuous), sex (male or female), and total energy intake (continuous).
[4] Multivariate model, adjusted for age, sex, total energy, skin color (fair, medium, or olive), burn-tan propensity of the skin (always burn, burn and tan, or tan only), elastosis of the neck (none, mild to moderate, or severe), smoking status (nonsmoker, smoked ≥7 pack-years, smoked >7–20 pack-years, or smoked >20 pack-years), dietary supplement use (yes or no), and trial treatment allocation: sunscreen (yes or no) or β-carotene treatment (yes or no) group.

TABLE 5
Relative risk (RR) (and 95% CIs) of squamous cell carcinoma in 341 participants with a history of skin cancer across tertiles of the 2 dietary patterns and their respective high-factor-loading food groups in the Nambour Skin Cancer Study, 1992–2002[1]

	History of skin cancer			
Dietary patterns and high-factor-loading food groups	Tertile 1	Tertile 2	Tertile 3	*P* for trend[2]
Meat and fat dietary pattern	1.00	1.89 (1.00, 3.65)	4.12 (1.78, 9.45)	0.001
High-fat dairy food group	1.00	1.84 (0.96, 3.55)	2.38 (1.20, 4.73)	0.02
Processed-meat food group	1.00	1.07 (0.58, 1.98)	1.13 (0.56, 2.29)	NS
Red-meat food group	1.00	1.00 (0.54, 1.87)	1.02 (0.49, 2.15)	NS
Discretionary fat food group	1.00	1.36 (0.67, 2.79)	1.52 (0.81, 2.87)	NS
White-bread food group	1.00	1.11 (0.55, 2.25)	1.68 (0.91, 3.09)	NS
Sweetened drinks food group	1.00	1.52 (0.82, 2.80)	1.22 (0.64, 2.32)	NS
Beer only	1.00	1.72 (0.86, 3.42)	1.18 (0.56, 2.47)	NS
Potato food group	1.00	0.94 (0.46, 1.89)	1.28 (0.63, 2.60)	NS
Snacks food group	1.00	0.97 (0.44, 2.12)	1.19 (0.53, 2.67)	NS
Vegetable and fruit dietary pattern	1.00	0.74 (0.40, 1.37)	0.44 (0.22, 0.89)	0.02
Green leafy vegetables food group	1.00	0.82 (0.43, 1.56)	0.51 (0.26, 0.99)	0.05
Cruciferous vegetables food group	1.00	1.34 (0.73, 2.46)	0.67 (0.34, 1.31)	NS
Red and yellow vegetables food group	1.00	1.89 (0.98, 3.64)	0.98 (0.50, 1.94)	NS
Other vegetables food group	1.00	1.01 (0.55, 1.87)	0.84 (0.42, 1.67)	NS
Vitamin A– or vitamin C–containing fruit food group	1.00	0.96 (0.49, 1.91)	0.79 (0.41, 1.49)	NS
Other fruit food group	1.00	1.46 (0.74, 2.89)	0.63 (0.30, 1.31)	NS
Tuna, salmon, and sardines (oily fish) food group	1.00	0.75 (0.39, 1.44)	0.78 (0.43, 1.40)	NS
Whole-meal bread food group	1.00	0.74 (0.41, 1.33)	0.91 (0.40, 2.08)	NS

[1] Total number of subjects may vary because of missing covariates. RRs were obtained by using a generalized linear model with negative binomial distribution. Risk estimates were adjusted for age, sex, total energy, skin color (fair, medium, or olive), burn-tan propensity of the skin (always burn, burn and tan, or tan only), elastosis of the neck (none, mild to moderate, or severe), smoking status (nonsmoker, smoked ≥7 pack-years, smoked >7–20 pack-years, or smoked >20 pack-years), dietary supplement use (yes or no), and trial treatment allocation: sunscreen (yes or no) or β-carotene treatment (yes or no) group.
[2] All statistical tests were 2-sided.

high-fat dairy food group as main effects in a third model and after adjustment for the same confounders, a significant association was no longer observed between high-fat dairy and SCC tumor risk (RR = 1.66; 95% CI: 0.82, 3.33; $P = 0.16$ when the third tertile was compared with the first tertile of the high-fat dairy food group), but a significant association between the meat and fat dietary pattern and SCC tumor risk remained (RR = 3.29; 95% CI: 1.41, 7.67; $P = 0.01$ when the third tertile was compared with the first tertile of the meat and fat pattern).

Similarly, after adjustment for the confounders in a first model that included the green leafy vegetables food group as a main effect, green leafy vegetables were associated, although not significantly, with SCC tumor risk (RR = 0.55; 95% CI: 0.29, 1.04; $P = 0.07$ when the third tertile was compared with the first tertile). After adjustment for the same confounders in a second model that included the vegetable and fruit dietary pattern as a main effect, the result showed that the vegetable and fruit dietary pattern had a significant effect on SCC tumor risk (RR = 0.45; 95% CI: 0.23, 0.87; $P = 0.02$ when the third tertile was compared with the first tertile). After adjustment for the same confounders and inclusion of both the vegetable and fruit dietary pattern and the green leafy vegetables food group as main effects in a third model, the vegetable and fruit dietary pattern was no longer significantly associated with SCC tumor risk (RR = 0.52; 95% CI: 0.24, 1.14; $P = 0.10$ when the third tertile was compared with the first tertile); the green leafy vegetables food group remained nonsignificantly associated with SCC tumor risk (RR = 0.73; 95% CI: 0.35, 1.53; $P = 0.40$).

In addition, because of the difference in the composition of tea, we reanalyzed the data after separating tea into 2 separate groups (black tea and herbal tea groups). The risk estimates from the analyses did not differ appreciably from the original results.

DISCUSSION

In the present prospective study, we showed that a diet characterized by high meat and fat intakes significantly increases SCC tumor risk after adjustment for the effects of sun exposure. This is particularly so in persons with a skin cancer history. Indeed, the association between dietary patterns and skin cancer risk differed markedly according to whether a person had previously had skin cancer. Those previously unaffected showed little evidence of an association, whereas, in those with a skin cancer history, the risk of developing subsequent SCC tumors was more than tripled with high intake from the meat and fat dietary pattern.

Our previous study showed an increased SCC tumor risk with increasing consumption of high-fat dairy foods in people with a history of skin cancer (15). The present study extends this finding to show that a meat and fat dietary pattern has an effect on the development of subsequent SCC tumors beyond the effect of the high-fat dairy food group alone. This additional effect can be attributed to the combined effect of other components of the pattern—namely, processed meat, discretionary fat, and white bread—for which a linear association with SCC tumor risks was observed. Intervention studies have shown that low dietary fat intakes reduce the risk of skin cancer incidence (31). However, not all fats have a positive association with SCC tumor risk. Hakim et al (32) reported a reduced SCC risk in those whose diets featured a high ratio of n−3 to n−6 fatty acid and a consistent tendency for a lower risk of SCC with higher intakes of n−3 fatty acids. Moreover, diets rich in n−6 fatty acids have been reported to enhance carcinogenesis (33). Free radical–initiated lipid peroxidation, which yields unsaturated hydroperoxides and fatty acid radicals, has been reported to underlie this mechanism (33), and a combination of PGE_2 and nitric oxide has also been hypothesized to play a role in ultraviolet B–induced erythema formation (33, 34).

Our previous study of the association between food groups and SCC tumor risk in participants with a history of skin cancer also found a lower risk with high intakes of green leafy vegetables (15). The present study confirms this finding by showing a 54% reduction in SCC tumor risk in participants with greater intake of the vegetable and fruit dietary pattern. This study showed that the vegetable and fruit dietary pattern does not have a significant effect on the development of subsequent SCC tumors beyond the effect of the green leafy vegetables food group alone. The green leafy vegetables food group was the only component of the vegetable and fruit pattern for which a significant linear association with SCC tumor risk was observed.

In a case-control study, Kune et al (35) reported protective effects of vegetables, fish, and legumes on the risk of BCC and SCC combined. In a population-based case-control study, Hakim et al (36) found an inverse association between the consumption of hot black tea and SCC risk. Therefore, given the involvement of oxidative damage in skin carcinogenesis (11), our results add to the evidence that the consumption of leafy green vegetables that contain antioxidants and a variety of vitamins, minerals, and other bioactive substances such as polyphenols may underlie the apparently protective effect of the vegetable and fruit dietary pattern in persons who are susceptible to skin cancer (15, 35, 36).

We did not find an association between dietary patterns and BCC tumor risk in persons with or without a prior history of skin cancer; this lack of association may reflect the distinctly different pathogenesis of BCC and SCC tumors (8, 37, 38). In a randomized, double-blind, controlled trial, Moon et al (39) reported the role of retinol in preventing SCC but not BCC. In a nested case-control study, McNaughton et al (40) found no association between BCC and carotenoids (except lutein), vitamin E, or selenium, as measured by serum biomarkers or dietary intake.

The strengths of our study include its population-based prospective design, the high rate of follow-up (94% of the participants who completed an FFQ in 1992 were still in the study in 2002), and the availability of information on sun exposure and other related factors in this study population, the effect of which we were able to take into account in our analyses. The study was based on histologically confirmed BCC and SCC tumors, which were ascertained through an extensive surveillance system comprising dermatologic examinations, questionnaires, doctors' records, and independent reports from pathology laboratories. We thus consider misclassification of participants through misdiagnosis or missed diagnosis of these skin cancers unlikely.

As for limitations of the present study, factor analysis was used and is an empirical technique: the method used to select the number of components is subjective. However, we performed analysis with 3 components, and results from the third component, which featured high consumption of beverages, did not improve the results. Our dietary patterns explained 20% (10% for the meat and fat pattern and 10% for the vegetable and fruit pattern) of the total variance, which is similar to that reported by other authors (41) but which suggests the potential existence of other patterns. We acknowledge that dietary intake would inevitably be measured with error, and this undoubtedly would result in some misclassification. However, the FFQ from which the dietary patterns were derived has shown reasonably good validity when compared with food records and serum carotenoids in our validation studies (23–25), and our derived dietary patterns resembled the Western and Prudent dietary patterns identified first by Slattery et al (42) and subsequently reported by Hu et al (43). We found no evidence of a role of dietary patterns in the primary or secondary prevention of BCC.

In conclusion, we have shown that high intake of a meat and fat dietary pattern increases the risk of developing SCC tumors of the skin, especially in persons who have a skin cancer history. These results do not, however, presume causality. Further research is needed to confirm these findings in other populations, because the relation between skin cancers and dietary patterns is likely to vary by ethnic group and perhaps also by geographic location.

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Appendix A

Food groupings used in dietary pattern analyses in the Nambour Skin Cancer Study, 1992– 2002

Food groups	Food items and food preparations
Rice	Brown rice, white rice
Pasta	Spaghetti, macaroni, other pastas
Cereal products	Crispbread, crackers, rye
Whole-meal bread	Whole-meal or mixed-grain bread or toast
White bread	White bread or toast
Breakfast cereal	Cooked oatmeal, cold breakfast cereal
Reduced-fat dairy products	Skim milk, low-fat milk, low-fat yogurt, cottage or ricotta cheese
High-fat dairy products	Whole milk, cream, ice cream, yogurt, other cheese, custard
Potato	Potato; boiled, mashed, baked
Egg	Egg; boiled, poached, fried, scrambled
Tuna or sardines (oily fish)	Tuna, salmon, sardines
Other fish and seafoods	Other fish (eg, fried, baked; prawns, crabs, scallops)
Red meat	Beef, pork, lamb as main dish; ham, beef, pork in sandwich; hamburger patty; liver, beef, pork, or lamb as mixed dish; minced in tomato sauce; other mince-meat dishes; meat pie
Poultry	Chicken with or without skin
Processed meat	Sausage, bacon, sausage rolls, processed meat, hot dogs or saveloy
Legumes	Baked beans, soybeans, other beans or lentils
Nuts	All types
Peanut butter	Peanut butter
Cruciferous vegetables	Broccoli, cauliflower, cabbage, Brussels sprouts, coleslaw
Red and yellow vegetables	Pumpkin, sweet potato, carrots, tomatoes
Green leafy vegetables	Spinach, silverbeet, spring onions, lettuce
Other vegetables	Peas, green beans, sweet corn, eggplant, mushrooms, celery, bean sprouts
Sweet drinks and artificially sweetened drinks[1]	Coke, Pepsi, other soft drinks, cordial, low-calorie colas, other low-calorie soft drinks
Juice	Orange juice, pineapple juice, grape juice, tomato juice, carrot juice, other juice
Vitamin A– or vitamin C–containing fruit	Strawberries, other fresh berries, cantaloupe, mango, pawpaw, orange, grapefruit
Other fruit	Peaches, grapes, pineapples, watermelon, apples, pear, bananas, prunes, dried fruit, canned fruit
Beer	All types
White wine	All types
Red wine	All types
All other alcoholic beverages	Champagne, sherry or port, spirits
Cakes and sugars	Chocolates, hard candy, jam, cakes
Snacks	Potato chips, corn chips, etc
Herbal tea	Herbal tea
Black tea	Black tea
Coffee	Coffee
Fat spreads	Butter, margarine
Discretionary fat	Visible fat on meat, food fried at home, fried carry-out foods
Salad dressing	Oil-and-vinegar dressing, mayonnaise

[1] Coke; Coca-Cola Co, Atlanta, GA; Pepsi; PepsiCo, Purchase, NY.