

Diet and basal cell carcinoma of the skin in a prospective cohort of men¹⁻³

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ABSTRACT

Background: Low intake of fat and high intake of specific vitamins have been hypothesized to reduce risk of basal cell carcinoma of the skin (BCC).

Objective: Our objective was to examine intakes of fat, antioxidant nutrients, retinol, folate, and vitamin D in relation to risk of BCC.

Design: In 1986, diet was assessed by a validated food-frequency questionnaire in 43217 male participants of the Health Professionals Follow-up Study who were 40–75 y of age and free of cancer. During 8 y of follow-up, we ascertained 3190 newly diagnosed cases of BCC.

Results: Total fat consumption was associated with a lower risk of BCC [relative risk (RR): 0.81; 95% CI: 0.72, 0.90 for the highest compared with the lowest quintile of intake; *P* for trend <0.001]. Simultaneous modeling of specific fatty acids suggested that this inverse association was limited to monounsaturated fat (RR: 0.79; 95% CI: 0.65, 0.96; *P* for trend = 0.02); saturated and polyunsaturated fat were not associated with BCC risk. Folate intake was associated with a slightly higher risk of BCC (RR: 1.19; 95% CI: 1.01, 1.40; *P* for trend = 0.11), whereas α -carotene was associated with a slightly lower risk (RR: 0.88; 95% CI: 0.79, 0.99; *P* for trend = 0.01). Intakes of long-chain n-3 fatty acids, retinol, vitamin C, vitamin D, or vitamin E were not materially related to BCC risk.

Conclusions: These findings do not support the hypothesis that diets low in fat or high in specific vitamins lower risk of BCC. *Am J Clin Nutr* 2000;71:135–41.

KEY WORDS Neoplasms, basal cell carcinoma, dietary fat, vitamins, men, skin neoplasms, folate, monounsaturated fat, antioxidants, α -carotene

INTRODUCTION

Nonmelanoma skin cancer is the most common form of malignancy in white populations; the estimated annual incidence in the United States is \approx 1 million (1). An increase in incidence is expected because of the aging of the population and greater exposure to solar ultraviolet radiation from depletion of the ozone layer (2). The 2 primary histologic types of nonmelanoma skin cancer are basal cell carcinoma (BCC) and squamous cell carcinoma. BCC in men is about 4 times as common as squa-

mous cell carcinoma (1). Metastatic spread of BCC is rare, but the malignancy is associated with substantial morbidity and high health-care costs (3).

Although sun exposure is the main established risk factor for BCC, only part of the variation in BCC occurrence is explained by variables related to sun exposure (4, 5). Hence, the possibility remains that other factors, including diet, also influence the development of BCC. Higher intake of total fat, and lower intakes of β -carotene, retinol, vitamin E, vitamin C, vitamin D, and long-chain n-3 fatty acids have been associated with increased squamous cell carcinogenesis in animal studies (6–11). Similar data are not available for BCC because of the lack of an animal model. However, on the basis of a 2-y trial in 101 patients, Black et al (12) suggested that low-fat diets have a protective effect against BCC.

Observational data on the relation between dietary fat or micronutrient intake and risk of BCC are sparse. In a case-control study of 131 BCC patients, an apparent protective effect of multivitamin use was observed (13). In another case-control study of 88 patients, those with nonmelanoma skin cancer had lower intakes of fish and vegetables and lower serum β -carotene concentrations than did control subjects (14). Interpretation of these findings is complicated by the small size of the studies, the possibility of recall and selection biases, and the limited if any assessment of diet. In the prospective Nurses Health Study, intakes of fat, vitamin A, vitamin C, vitamin D, or vitamin E were not materially associated with risk of BCC during 4 y of follow-up (15). However, this study included only women, and for some nutrients,

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a longer follow-up period may be necessary to observe an association with BCC risk. Furthermore, data on folate and specific carotenoids, for which an apparent protective effect has been seen for neoplasms at other sites (16, 17), were not reported. We therefore examined the hypotheses that low intake of dietary fat or high intakes of specific micronutrients decrease risk of BCC in a large prospective study of US men with 8 y of follow-up.

SUBJECTS AND METHODS

Study population

The Health Professionals Follow-up Study started in 1986 when 51 529 male health professionals completed a questionnaire on medical history and known and suspected risk factors for cancer and other major illnesses (18). The study population included US dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists who were 40–75 y of age in 1986. Biennial follow-up questionnaires are sent to the entire cohort to document new diagnoses of disease and to update exposure information. We collected information about age, height, weight, natural hair color, major ancestry, frequency of routine physical examinations, cigarette smoking habits, and state of residence. The cohort was 1.7% Asian and 1.0% African American. Because exposure or reporting of exposure may be affected by a diagnosis of cancer, we excluded men who reported any cancer (including squamous cell carcinoma or a previous BCC) at baseline and at the beginning of each 2-y time period. We also excluded men with improperly completed dietary questionnaires (≥ 70 items blank or reported intake of > 17.6 or < 3.35 kJ/d) (18). After exclusions, 43 217 men remained in the study population at baseline. This investigation was approved by the Harvard School of Public Health Human Subjects Committee.

Dietary assessment

A detailed description of the 131-item semiquantitative food-frequency questionnaire used in this study and documentation of its reproducibility and validity have been published elsewhere (19, 20). Briefly, for each food, a commonly used unit or portion size was specified and participants were asked to indicate for each food how often, on average, they had consumed the amount specified during the past year. Nine multiple choice responses were possible, ranging from “never or less than once a month” to “6 or more times/d”. We also inquired about the brand and type of breakfast cereal eaten; the brand, dose, duration, and frequency of multivitamin use; the dose and duration of use of individual vitamin supplements; and the types of fat commonly used for cooking and at the table. The questionnaire also contained an open-ended section for foods that were not listed. We computed nutrient intakes by multiplying the consumption frequency of each unit of food by the nutrient content in the specified portion. Values for the nutrient amounts in foods were obtained from the Harvard University Food Composition Database, derived from US Department of Agriculture sources (21) and supplemented with information from manufacturers. We used a variable for “carotene” that represents vitamin A activity from carotenoid sources, as well as variables for specific carotenoids (α -carotene, β -carotene, lycopene, zeaxanthin and lutein, and β -cryptoxanthin).

In 1986, we evaluated the validity of the nutrient consumption measured by the food-frequency questionnaire in a sample of 127 men from the Boston area (19) who completed

2 detailed 1-wk diet records. The Pearson correlation coefficients between questionnaire and dietary record estimates of energy-adjusted nutrients (adjusted for week-to-week variation in the diet records) were 0.67 for total fat, 0.75 for saturated fat, 0.68 for monounsaturated fat, 0.75 for retinol, 0.64 for carotene, 0.77 for folate, 0.92 for vitamin C, and 0.92 for vitamin E. The correlation was appreciably lower for polyunsaturated fat ($r = 0.37$). However, correlations between the proportion of polyunsaturated fat in adipose tissue and estimates of intake from the questionnaire (Spearman $r = 0.50$) and from diet records ($r = 0.47$) were very similar. This suggests that these 2 dietary assessment methods have similar validity in the measurement of long-term polyunsaturated fat intake and that measurement error in the dietary record contributed to the low correlation between questionnaire and dietary record estimates (22). The validity for vitamin D could not be assessed directly because this information was not available from the diet record database, but vitamin D intake assessed by a similar questionnaire correlated significantly with plasma calcidiol (Pearson $r = 0.34$, $P < 0.01$) in a study of 139 men and women (23).

Identification of basal cell carcinoma

On the questionnaires mailed to all study participants in 1988, 1990, 1992, and 1994, men were asked whether BCC had been diagnosed during the previous 2 y. After repeated mailings, the follow-up rate to these questionnaires averaged 94%. Deaths were reported by family members, coworkers, postal authorities, or were identified through systematic searches of the National Death Index. To assess the validity (positive predictive value) of self-report of BCC in this study population, we requested permission to obtain medical records from a sample of 109 participants who had reported a diagnosis of BCC. For 19 men, no records were obtained: 13 did not return the request form, 1 could not be contacted, and 5 did not give us permission to review the record. Of the remaining 90 men, 9 denied the diagnosis, 5 self-reports were not confirmed by medical records, and 76 self-reports were confirmed by medical records (84% of potentially confirmable self-reports). Furthermore, consistent with other data, incidence of self-reported BCC in this cohort was strongly associated with hair color, ancestry, and region of residence (5), indicating the validity of this endpoint.

Statistical analysis

Analyses adjusted for age and energy intake were based on incidence rates of BCC by using person-months of follow-up. Men contributed follow-up time from the date of return of the 1986 questionnaire until BCC was diagnosed, the subject died from any cause, or 31 December 1993, whichever came first. Relative risks (RRs) were calculated by dividing the incidence rate of BCC among men in each category of intake by the rate in the lowest category. To reduce extraneous variation or confounding due to variation in body size, physical activity, and metabolic efficiency, as well as over- or underreporting, we adjusted nutrient intake for total energy intake by using the residual method (20). Nutrient intakes from supplemental sources were not adjusted for energy intake. The Mantel-Haenzel estimator (24) was used to adjust for age (across 5-y categories) and total energy intake; linear trends were tested with the Breslow and Day statistic (25).

To adjust for other potential confounding variables, a pooled logistic regression approach using 2-y follow-up intervals asymp-

totally equivalent to a proportional hazards analysis, was used to calculate odds ratios to estimate RRs (26). The model contained terms for age (5-y categories), quintiles of body mass index, smoking habits (never smoked, former smoker, or current smoker of 1–14, 15–24, or >24 cigarettes/d), major ancestry (northern European, southern European, or other ancestry), natural hair color (red, blond, light brown, dark brown, or black), sun exposure according to region of residence (high, medium, or low), routine physical examinations (in 1, 2, 3, or all of the 2-y periods), and quintiles of total energy intake. Additional models also included intake of other nutrients in quintiles. In the multivariate logistic analyses, we tested for linear trends by assigning each participant the median value for the category and modeling this value as a continuous variable. For men who did not report data for a given covariate, missing values were included as indicator variables in the multivariate models. Information about cigarette smoking and body mass index was updated in each 2-y time period of the analysis. All reported *P* values are for two-sided tests.

To evaluate the possibility of detection bias, we conducted a separate analysis excluding all men at the beginning of each 2-y period who neither had a routine physical examination in that period nor in any of the following 2-y periods. We also performed an analysis restricted to white men.

RESULTS

During 308071 person-years of follow-up from 1986 through 1994, 3190 incident cases of BCC were reported. Characteristics of the study population according to quintile of selected nutrient intakes are shown in **Table 1**. Cigarette smoking and frequency of routine physical examinations differed among quintiles of nutrient intake. For smoking and frequency of physical examinations, associations with saturated fat were similar to those for total and monounsaturated fat, whereas associations with carotene, vitamin C, vitamin E, polyunsaturated fat, and retinol were similar to those with folic acid and vitamin D. Furthermore, intake of long-chain *n*–3 fatty acids (from fish, including eicosapentaenoic acid and docosahexaenoic acid) was associated with ancestry, and men with high intakes of folate, vitamin C, carotene, and vitamin E were more likely to live in a region with high solar radiation.

In the analyses with adjustment for age and energy intake, a higher total fat intake was associated with a lower risk of BCC (RR for the highest compared with the lowest quintile of intake: 0.80; *P* for trend < 0.0001) (**Table 2**). Adjustment for ancestry, 2-y follow-up period, body mass index, cigarette smoking, hair color, frequency of routine physical examinations, and region of residence did not appreciably change the associations between dietary fat and BCC risk (Table 2). When saturated fat, monounsaturated fat (predominantly oleic acid), polyunsaturated fat (predominantly linoleic acid), and long-chain *n*–3 fatty acids were included in the multivariate model simultaneously, only monounsaturated fat (RR for highest quintile: 0.79; 95% CI: 0.65, 0.96) and long-chain *n*–3 fatty acids (RR: 1.13; 95% CI: 1.01, 1.27) were significantly associated with BCC risk. However, after exclusion of nonwhite men, the association between long-chain *n*–3 fatty acids and risk of BCC was weakened (multivariate RR with allowance for other fats: 1.09; 95% CI: 0.97, 1.23); for other nutrients, results remained essentially the same after exclusion of nonwhite men. Monounsaturated fat was strongly correlated with saturated fat ($r = 0.77$), and less so with polyunsaturated fat ($r = 0.50$) and long-chain *n*–3 fatty acids ($r = -0.21$) (all $P < 0.0001$). Including dietary cholesterol, *trans* fatty acids, or folate in the multivariate models with monounsaturated fat did not appreciably change the results. Furthermore, a highly significant negative trend with higher intakes of monounsaturated fat was observed across deciles of intake (multivariate RR: 0.76; 95% CI: 0.65, 0.89 for the highest compared with the lowest decile; *P* for trend < 0.0001). To investigate whether a long-term effect of dietary fat on BCC existed, we conducted an analysis relating the 1986 diet to incidence of BCC between 1990 and 1994. The results remained essentially the same.

In the analyses with adjustment for age and energy intake, intake of retinol, folate, vitamin C, and vitamin D were positively associated with risk of BCC (**Table 3**). After multivariate adjustment, the associations were somewhat attenuated: the RRs for the highest compared with the lowest quintile were 1.12 for retinol (*P* for trend = 0.03), 1.03 for carotene (*P* for trend = 0.99), 1.22 for folate (*P* for trend = 0.004), 1.19 for vitamin C (*P* for trend = 0.005), 1.20 for vitamin D (*P* for trend = 0.03), and 1.10

TABLE 1
Characteristics of the participants according to quintiles 1 (Q1) and 5 (Q5) of nutrient intake¹

	Folate		Vitamin D		Total fat		Monounsaturated fat		Long-chain <i>n</i> –3 fatty acid	
	Q1, 244 (67–284)	Q5, 840 (661–4092)	Q1, 98 (0–139)	Q5, 752 (560–3702)	Q1, 24.4 (6.8–27.5)	Q5, 40.5 (37.8–70.3)	Q1, 8.9 (2.2–10.2)	Q5, 15.9 (14.7–39.2)	Q1, 0.07 (0.01–0.11)	Q5, 0.58 (0.44–8.00)
Age (y)	53	55	52	56	55	54	55	54	53	55
Ancestry										
Northern European (%)	68	69	65	69	67	70	67	70	74	63
Southern European (%)	25	26	28	25	26	25	26	25	22	30
Nonwhite (%)	6.4	5.2	7.2	5.3	7.7	4.6	7.2	5.0	4.5	7.3
Physical examination (%) ²	75	81	77	81	80	76	80	76	77	81
Current smoker (%)	16	8.3	13	8.5	6.9	14	6.8	14	12	8.1
Body mass index (kg/m ²)	26	25	26	25	25	26	25	26	26	26
Red hair color (%)	2.6	2.3	2.0	2.3	2.2	2.5	2.3	2.4	2.6	2.3
High-sun region (%) ³	32	36	34	34	34	34	34	34	31	32

¹Standardized for age to the total cohort used for analysis for 43217 men free of cancer at baseline. For each nutrient the median and lower and upper boundary of the quintile is given; units are µg/d for folate, IU/d for vitamin D, % of energy for total and monounsaturated fat, and g/d for long-chain *n*–3 fatty acid.

²Those who had at least one routine physical examination during the study period.

³Relatively high mean annual solar radiation.

TABLE 2

Relative risk (RR) and 95% CI of basal cell carcinoma of the skin according to energy-adjusted dietary fat intake

Variable	Quintile of fat intake					P for trend
	1	2	3	4	5	
Total fat (% of energy)	24.4 ¹	29.5	32.8	35.8	40.5	—
Cases/person-years	725/59 902	628/61 278	666/62 083	601/62 240	570/62 569	—
Age-adjusted RR ²	1.0	0.88	0.93	0.85	0.80	<0.0001
Multivariate RR and 95% CI ³	1.0	0.88 (0.79, 0.98)	0.93 (0.84, 1.04)	0.86 (0.77, 0.96)	0.81 (0.72, 0.90)	0.0003
Saturated fat (% of energy)	7.6 ¹	9.7	11.1	12.5	14.7	—
Cases/person-years	695/59 384	693/61 502	622/61 782	620/62 458	560/62 945	—
Age-adjusted RR ²	1.0	1.00	0.91	0.93	0.84	<0.0005
Multivariate RR ³	1.0	1.00	0.92	0.94	0.85	0.003
Multivariate RR with fats and 95% CI ⁴	1.0	1.06 (0.94, 1.20)	1.01 (0.88, 1.17)	1.08 (0.92, 1.26)	1.03 (0.87, 1.23)	0.74
Monounsaturated fat (% of energy)	8.9 ¹	11.1	12.5	13.8	15.9	—
Cases/person-years	715/60 321	631/61 528	684/61 776	596/62 303	564/62 142	—
Age-adjusted RR ²	1.0	0.90	0.98	0.85	0.80	<0.0001
Multivariate RR ³	1.0	0.90	0.98	0.86	0.81	0.0002
Multivariate RR with fats and 95% CI ⁴	1.0	0.89 (0.78, 1.01)	0.97 (0.83, 1.12)	0.84 (0.71, 0.99)	0.79 (0.65, 0.96)	0.02
Polyunsaturated fat (% of energy)	4.2 ¹	5.2	5.9	6.6	8.0	—
Cases/person-years	652/60 242	630/62 442	637/61 935	614/62 035	657/61 416	—
Age-adjusted RR ²	1.0	0.97	1.00	0.96	1.03	0.70
Multivariate RR ³	1.0	0.95	0.97	0.92	0.98	0.73
Multivariate RR with fats and 95% CI ⁴	1.0	0.97 (0.87, 1.09)	1.00 (0.89, 1.13)	0.97 (0.86, 1.10)	1.07 (0.94, 1.22)	0.30
Long-chain n-3 fatty acids (g/d)	0.07 ¹	0.15	0.24	0.34	0.58	—
Cases/person-years	604/63 581	590/62 641	644/61 641	642/60 495	710/59 712	—
Age-adjusted RR ²	1.0	0.98	1.07	1.07	1.14	0.003
Multivariate RR ³	1.0	0.98	1.06	1.07	1.18	0.0005
Multivariate RR with fats and 95% CI ⁴	1.0	0.97 (0.86, 1.09)	1.04 (0.93, 1.17)	1.05 (0.93, 1.18)	1.13 (1.01, 1.27)	0.008

¹Median.²Adjusted for age and energy intake by stratification.³Multivariate logistic regression analysis with control for age (in 5-y categories), 2-y follow-up periods, major ancestry (north European, south European, or nonwhite), energy intake (in quintile groups), BMI (in quintile groups), hair color (red, blond, light brown, dark brown, or black), frequency of routine physical examinations (in 1, 2, 3, or all of the periods), cigarette smoking (never smoked, formerly smoked, or currently smoking ≤ 15 , 15–24, or ≥ 25 cigarettes/d), mean annual solar radiation in region of residence (high, medium, or low).⁴Monounsaturated fat, saturated fat, polyunsaturated fat, and long-chain n-3 fatty acids (all in quintile groups) were included in the multivariate model simultaneously.

for vitamin E (P for trend = 0.61). When retinol, carotene, folate, vitamin C, vitamin D, and vitamin E were included simultaneously in the multivariate model, only folate and vitamin C remained associated with BCC risk. However, the association with vitamin C disappeared after exclusion of men without a routine physical examination (RR: 0.98; 95% CI: 0.83, 1.17 for the highest quintile), suggesting that health consciousness may explain this association. When we included individually specific carotenoids in the multivariate model with other micronutrients (instead of the carotene variable reflecting vitamin A activity from all carotenoids), we observed a significant inverse association for α -carotene but not for the other carotenoids (β -carotene, lycopene, zeaxanthin and lutein, and β -cryptoxanthin). RRs for quintiles 2, 3, 4, and 5 of α -carotene intake as compared with the lowest quintile were 0.97, 1.00, 0.91, and 0.88 (95% CI: 0.79, 0.99), respectively (P for trend = 0.01). The RR for the third quintile of folate intake was 1.21 (95% CI: 1.06, 1.38), as compared with the lowest quintile; no further increase in risk was observed for higher quintiles of folate intake (P for trend = 0.11). Pearson correlations with folate intake were 0.72 for vitamin D, 0.61 for retinol, 0.49 for vitamin C, 0.39 for vitamin E, and 0.24 for carotene (all $P < 0.0001$). The association between folate and BCC risk remained significant after adjustment for monounsaturated or total fat.

We investigated the association of folate from dietary and supplemental sources (individual folate and multivitamin supplements) with BCC risk. Only 2.7% of the participants (1182 men) reported use of specific folate supplements, but 41.3% (17 861 men) used multivitamin supplements. Among men not using any supplemental folate, the multivariate RRs for quintiles 2–5 of dietary folate as compared with the lowest quintile were 1.15, 1.20, 1.29, and 1.31 (95% CI: 1.12, 1.54), respectively (P for trend = 0.0004). The medians of dietary folate intake for quintiles 1–5 were 232, 292, 340, 395, and 495 $\mu\text{g}/\text{d}$. Use of supplemental folate was associated with an increased risk of BCC only in the category with a supplemental intake $> 600 \mu\text{g}/\text{d}$ (multivariate RR: 1.22; 95% CI: 1.05, 1.42) relative to men with no supplemental intake of folate. As compared with nonusers of multivitamins, the multivariate RRs for past multivitamin use and weekly use of < 5 , 6–9, and > 9 multivitamin pills were 1.04, 1.03, 1.08, and 1.34 (95% CI: 1.16, 1.55), respectively. Consumption of vegetables was not significantly associated with BCC risk (multivariate RR: 1.06; 95% CI: 0.95, 1.20, for > 5 servings/d compared with < 2 servings/d), nor was fruit consumption (multivariate RR: 1.09; 95% CI: 0.95, 1.25, for > 4 compared with < 1 serving/d).

In the analysis relating the micronutrient intake in 1986 to BCC occurrence between 1990 and 1994, intake of folate and

TABLE 3

Relative risk (RR) and 95% CI of basal cell carcinoma of the skin according to energy-adjusted intake of specific micronutrients

Variable	Quintile of micronutrient intake					P for trend
	1	2	3	4	5	
Retinol, (IU/d) ¹	1053 ²	1929	3073	6199	12533	—
Cases/person-years	574/64025	592/62613	664/61430	652/60510	708/59492	—
Age-adjusted RR ³	1.0	1.01	1.09	1.09	1.17	0.006
Multivariate RR ⁴	1.0	0.99	1.07	1.03	1.12	0.03
Multivariate RR with micronutrients and 95% CI ⁵	1.0	0.92 (0.81, 1.04)	0.94 (0.82, 1.07)	0.91 (0.79, 1.05)	0.99 (0.84, 1.16)	0.55
Carotene (IU/d) ⁶	3726 ²	5729	7746	1192	18440	—
Cases/person-years	560/64131	635/62190	630/61379	712/61019	653/59352	—
Age-adjusted RR ³	1.0	1.11	1.07	1.17	1.06	0.72
Multivariate RR ⁴	1.0	1.10	1.05	1.15	1.03	0.99
Multivariate RR with micronutrients and 95% CI ⁵	1.0	1.07 (0.96, 1.21)	1.00 (0.89, 1.13)	1.08 (0.96, 1.21)	0.94 (0.83, 1.06)	0.12
Folate (μg/d)	244 ²	317	388	517	840	—
Cases/person-years	522/64116	597/62129	682/61113	689/61075	700/59637	—
Age-adjusted RR ³	1.0	1.12	1.28	1.29	1.29	<0.0001
Multivariate RR ⁴	1.0	1.09	1.24	1.25	1.22	0.004
Multivariate RR with micronutrients and 95% CI ⁵	1.0	1.08 (0.95, 1.23)	1.21 (1.06, 1.38)	1.22 (1.06, 1.41)	1.19 (1.01, 1.40)	0.11
Vitamin C (mg/d)	95 ²	156	228	402	1164	—
Cases/person-years	543/63629	619/62237	652/61275	659/61101	717/59829	—
Age-adjusted RR ³	1.0	1.07	1.13	1.14	1.27	<0.0001
Multivariate RR ⁴	1.0	1.05	1.11	1.11	1.19	0.005
Multivariate RR with micronutrients and 95% CI ⁵	1.0	0.97 (0.85, 1.10)	1.00 (0.88, 1.14)	1.02 (0.89, 1.16)	1.12 (0.96, 1.29)	0.04
Vitamin D (IU/d)	98 ²	174	263	429	752	—
Cases/person-years	511/64675	620/62213	671/61231	685/60850	703/59102	—
Age-adjusted RR ³	1.0	1.19	1.24	1.24	1.28	0.002
Multivariate RR ⁴	1.0	1.16	1.21	1.22	1.20	0.03
Multivariate RR with micronutrients and 95% CI ⁵	1.0	1.15 (1.02, 1.30)	1.18 (1.04, 1.35)	1.17 (1.02, 1.34)	1.10 (0.94, 1.30)	0.63
Vitamin E (IU/d)	7.6 ²	10.2	13.3	28.9	416.6	—
Cases/person-years	555/63769	603/63325	656/61123	682/60707	694/59147	—
Age-adjusted RR ³	1.0	1.07	1.13	1.20	1.15	0.26
Multivariate RR ⁴	1.0	1.04	1.11	1.13	1.10	0.61
Multivariate RR with micronutrients and 95% CI ⁵	1.0	1.02 (0.90, 1.15)	1.05 (0.93, 1.19)	1.01 (0.87, 1.17)	0.94 (0.81, 1.09)	0.14

¹IU retinol = 0.30 μg retinol equivalents.²Median.³Adjusted for age and energy intake by stratification.⁴Multivariate logistic regression analysis with control for age (in 5-y categories), 2-y follow-up periods, major ancestry (north European, south European, or nonwhite), energy intake (in quintile groups), BMI (in quintile groups), hair color (red, blond, light brown, dark brown, or black), frequency of routine physical examinations (in 1, 2, 3, or all of the periods), cigarette smoking (never smoked, formerly smoked, or currently smoking ≤15, 15–24, or ≥25 cigarettes/d), mean annual solar radiation in region of residence (high, medium, or low).⁵Retinol, carotene, folate, vitamin C, vitamin D, and vitamin E (all in quintile groups) were included in the multivariate model simultaneously.⁶Carotene represents vitamin A activity from carotenoids, mainly α-carotene and β-carotene; IU β-carotene = 0.10 μg retinol equivalents.

vitamin D tended to be positively associated with risk of BCC. However, the tests for trend were not significant (multivariate RR for folate with other micronutrients: 1.35; 95% CI: 1.08, 1.70 for the highest compared with the lowest quintile; *P* for trend = 0.10) (for vitamin D: RR = 1.26; 95% CI: 1.00, 1.59; *P* for trend = 0.13). Carotene intake was significantly associated with risk of BCC (RR: 0.81; 95% CI: 0.68, 0.96; *P* for trend = 0.03). This inverse association was due to an association of α-carotene (RR: 0.86; 95% CI: 0.74, 1.01; *P* for trend = 0.06) and β-carotene (RR: 0.81; 95% CI: 0.68, 0.96; *P* for trend = 0.03) with risk of BCC.

DISCUSSION

Our findings in a study of 43217 men with 8 y of follow-up do not support the hypotheses that low intake of fat or high intakes of long-chain n–3 fatty acids, retinol, carotene, folate, or the vitamins C, D, or E decrease risk of BCC. By contrast, high

intake of monounsaturated fat and low intake of folate were associated with a small decrease in BCC risk. After adjustment for other micronutrients, we observed a weak inverse association between α-carotene intake and BCC risk.

Because the exposure variables and occurrence of disease were assessed by self-reports, the possible effect of misclassification has to be considered. The validity of the self-reports of BCC when compared with medical records in this study of health professionals was reasonably good. The comparison of the self-reports of BCC with medical records indicated that self-report of BCC is a valid measure in this medically knowledgeable population. Diet was assessed before the diagnosis of BCC and errors in recall should thus be nondifferential between cases and non-cases. Thus, misclassification would have attenuated rather than exaggerated the true association. In general, nutrient intakes assessed by the questionnaire were strongly correlated with the estimates from diet records. Even with some inevitable error in measuring dietary intake and assessing outcome, it seems

unlikely that in a study of this size substantial associations would have been missed. The high rate of follow-up in this study reduced the potential bias from loss to follow-up.

We considered the possibility of detection bias. Men with a diet low in total fat (and low in saturated and monounsaturated fat) and high in specific vitamins seemed to be somewhat more health conscious: they smoked less and had routine physical examinations more often. Because BCC is a slow-growing, asymptomatic tumor, the malignancy may be detected earlier in health-conscious men; this could have resulted in elevated observed RRs of BCC for nutrients associated with a so-called health-conscious diet. In general, however, adjustment for smoking and frequency of routine physical examinations and exclusion of men with no routine physical examinations did not substantially change the results. Only the weak positive association between vitamin C intake and BCC risk disappeared, suggesting that health consciousness may explain this association.

We may not have observed the hypothesized associations if the BCC that appeared clinically during follow-up was already present at the start of the study period in the form of small undetectable tumors. However, the analyses excluding the first 4 y of follow-up confirmed the results observed for the whole study period.


We observed a 20% higher risk of BCC for the third quintile of folate intake (median: 388 $\mu\text{g}/\text{d}$) as compared with the lowest quintile (median: 244 $\mu\text{g}/\text{d}$); higher intake did not further increase BCC risk. To our knowledge, no data on the relation between folate intake and BCC has been reported before. Our finding that a low intake of folate was associated with a reduced risk of BCC was unexpected and needs to be confirmed. We did not observe an inverse association of β -carotene for the first 4 y of follow-up, which is consistent with results of a 5-y placebo-controlled randomized trial of β -carotene supplementation and nonmelanoma skin cancer in 1805 patients (27). However, in the analyses that excluded the first 4 y of follow-up, β -carotene was weakly and inversely associated with BCC risk. Thus, it may be useful to examine whether a long-term effect exists for β -carotene after additional years of follow-up.

We observed no protective effect for retinol, carotene, or vitamins C, D, or E. This is consistent with the findings of Hunter et al (15) in the Nurses Health Study. In other observational studies, BCC risk was not significantly associated with serum concentrations of retinol (28), β -carotene (28, 29), lycopene (28), α -tocopherol (28, 30), or dietary vitamin A (31), but the number of BCC cases in these studies was low ($n < 60$). Although high-dose oral isotretinoin (2 mg \cdot kg body $\text{wt}^{-1} \cdot \text{d}^{-1}$) was effective in preventing skin cancer in a trial of 5 patients with xeroderma pigmentosum (32), in large randomized trials with lower doses of isotretinoin or retinol no reduction in BCC risk was observed (33, 34). In contrast with our findings, Wei et al (13) reported an inverse association between multivitamin use and risk of BCC. However, recall and selection bias resulting from the case-control design and the low participation rates (15.8% for cases, 14.2% for controls) may explain this observation.

We observed an inverse association between monounsaturated fat consumption and BCC risk. Saturated and polyunsaturated fat were not associated with BCC risk after adjustment for monounsaturated fat intake. Hunter et al (15) also observed no increase in risk of BCC in participants with high fat intakes; for monounsaturated fat the RR was 0.88 (95% CI: 0.70, 1.13; P for trend = 0.22). Furthermore, that study showed an inverse linear

trend of BCC risk with monounsaturated fat intake (P for trend = 0.02) in the group of women at high risk of BCC (according to sun-related factors).

The present results for total fat conflict with findings from a 2-y dietary intervention study reported by Black et al (12). In that trial, 101 skin cancer patients were randomly assigned either to a control group in which no change in dietary habits was introduced (average fat intake was 38% of energy) or to a group that attended weekly classes to reduce fat consumption. In the last 8 mo of the study period, the average number of nonmelanoma skin cancers in the intervention group was significantly lower than that in the control group. Within the intervention group, the number of patients developing skin cancer was significantly reduced over the course of the study (8 patients developed skin cancer in the first 8-mo period, 1 in the last 8-mo period). However, in a more appropriate analysis, the difference in the number of patients with new skin cancers between the intervention and the control group in the last 8-mo period was not significant (1 case in the intervention group compared with 6 in the control group). The percentage of energy consumed as fat in the intervention group (mean: 21% of energy) was similar to that in the lowest decile of fat intake in our study (median: 21.7% of energy), for which we did not observe a decreased risk of BCC (RR: 1.22; 95% CI: 1.04, 1.43 as compared with the highest decile of fat intake). However, in contrast with our study, which only included men without previous BCC, this trial studied the recurrence of skin cancer. In addition, limitations of this trial could account for the difference in results: the intervention was not blinded, the number of cases was very small, and comparison of skin cancer occurrence in the first and last 8 mo of intervention is not a valid test of the effects of fat reduction.

We cannot exclude effects of dietary factors beyond the range of intake in our population, at earlier periods in life, or in populations with different susceptibilities. However, our results do not suggest that a diet low in fat or high in specific nutrients substantially reduces risk of BCC in men during an 8-y period. 

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