Research Article

Cancer Epidemiology, Biomarkers & Prevention

Fat Intake and Risk of Skin Cancer in U.S. Adults

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Abstract

Background: Fat intake has been associated with certain cancers, including colorectal, breast, and prostate cancers. However, literature on dietary fat and skin cancer has been limited.

Methods: We examined the association between fat intake and risk of skin cancer including cutaneous malignant melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) within two prospective studies: the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). Dietary information on total, saturated, monounsaturated, polyunsaturated, omega-6, and omega-3 fat and cholesterol was repeatedly assessed generally every 4 years. Incident cases were identified by self-report. Diagnosis on melanoma and SCC was confirmed by pathologic records.

Results: A total of 794 melanoma, 2,223 SCC, and 17,556 BCC in the NHS (1984–2012) and 736 melanoma, 1,756 SCC, and 13,092 BCC in the HPFS (1986–2012) were documented. Higher polyunsaturated fat intake was associated with risk of SCC [pooled HR for highest vs. lowest quintiles, 1.16; 95% confidence interval (CI), 1.05–1.28; P_{trend}=0.001] and BCC (pooled HR, 1.06; 95% CI, 1.01–1.11; P_{trend}=0.01). Higher omega-6 fat intake was associated with risks of SCC, BCC, and melanoma. Omega-3 fat intake was associated with risk of BCC, but not with SCC or melanoma. No other fats were associated with melanoma risk. The associations were similar in women and men and by other skin cancer risk factors.

Conclusions: Polyunsaturated fat intake was modestly associated with skin cancer risk.

Impact: Further studies are needed to confirm our findings and to identify relevant biological mechanisms. *Cancer Epidemiol Biomarkers Prev; 27(7); 776–82. ©2018 AACR.*

Introduction

Fat intake has been examined in many studies for its association with incident cancer such as colorectal, breast, and prostate cancers (1). A few animal studies showed that high fat intake may promote the development of UV radiation–induced skin cancer (2). In a study with hairless mice, a protective effect of saturated fat intake on UV tumorigenesis was reported compared with polyunsaturated fat (3). In other animal studies, omega-3 fat intake showed increased tumor latent period and decreased tumor multiplicity while omega-6 fat intake showed tumor-promoting effects (4). On the other hand, omega-3 fat has anti-inflammatory function that may protect against UV damage (5–7) and may affect skin cancer risk.

Epidemiologic studies on overall fat intake and skin cancer risk have reported conflicting results and only a few studies used prospective studied designs (8, 9). A few intervention studies found that a low-fat diet reduced the incidence of actinic keratosis, a precursor for skin cancer, (10) and nonmelanoma skin cancer (NMSC) among participants with a history of NMSC (11). In a case–control study, higher fat intake showed lower risk of melanoma and basal cell carcinoma (BCC) and lower risk of squamous cell carcinoma (SCC; ref. 12). However, in European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk study (13), Nambour Skin Cancer Study (14, 15), and Women's Health Initiative Randomized Controlled Dietary Modification Trial (16), no association between fat intake and skin cancer was found. Most of these studies were limited by small sample size ($n < 200$; ref. 8). Few studies evaluated intake of the types of fat in relation to skin cancer (14, 17, 18). Therefore, we aimed to examine the associations between consumption of total and types of fat and risk of skin cancer with prospective data from the Nurses' Health Study (NHS, 1984–2012) and the Health Professionals Follow-up Study (HPFS, 1986–2012).

Materials and Methods

Study population

The NHS was initiated in 1976 with 121,700 U.S. female registered nurses ages 30–55 years and the HPFS was initiated in 1986 with 51,529 U.S. male health professionals ages 40–75 years. Participants of both studies completed questionnaires on their lifestyle and medical history. The participants have been followed biennially with follow-up rate of largely over 90%. The studies were approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health (Boston, MA) and conducted in accordance with the Belmont Report. Participants' responses on the questionnaires were considered as written informed consent. Detailed descriptions of the two cohort studies exist elsewhere (19, 20).

Assessment of fat intake and other dietary intake

A validated food-frequency questionnaire (FFQ) including about 130 food items have been used for the assessment of

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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dietary intake in the study participants (21). The first collection of dietary information with this FFQ started in 1984 in the NHS and the information was updated every 4 years since 1986. For HPFS, dietary information has been collected every 4 years since 1986. This study included the data from the FFQs administered in 1984, 1986, 1990, 1994, 1998, 2002, 2006, and 2010 for the NHS and 1986, 1990, 1994, 1998, 2002, 2006, and 2010 for the HPFS. Participants were asked how often on average they had consumed a given unit or one portion size of each food item in the FFQ during the previous year, with nine frequency responses ranging from "never or less than once per month" to "6 or more times per day." Nutrient intake including energy and fatty acids of participants were calculated by multiplying the consumption frequency of each food item with nutrient database prepared for specified amount of the food item. The nutrient database was based on the Harvard University Food Composition Database derived from the U.S. Department of Agriculture (USDA) sources (22) and supplemented with information from manufacturers. Previous studies have demonstrated reasonable levels of reproducibility and validity of the FFQ for ranking individuals by consumption of nutrients and foods (23–25). The fatty acid intake measured by the FFQ has also been validated in NHS showing moderate-to-strong correlations between dietary intakes and plasma biomarkers (Spearman partial correlation coefficients, 0.21–0.56; ref. 26).

Assessment of covariates

By sending the questionnaires to participants biennially, we collected information on anthropometric and lifestyle factors such as height, weight, physical activity and smoking status for NHS and HPFS, and menopausal status and postmenopausal hormone use for NHS. Major skin cancer–related factors (27, 28) were also collected, including family history of melanoma (in parents or siblings); natural hair color; number of moles on arms; skin reaction to sun exposure as a child/adolescent; number of severe or blistering sunburns; and cumulative UV flux at residence since baseline.

Assessment of melanoma, SCC, and BCC cases

Participants had reported new diagnosis of melanoma, SCC, and BCC biennially since 1984 for NHS and 1986 for HPFS. Participants who reported melanoma or SCC were asked for permission to review their medical and pathologic reports. These reports were reviewed by physicians to confirm the diagnoses. The proportions of reviewed cases with medical and pathologic reports were 67% for melanoma and 60% for SCC in NHS, and 76% for melanoma and 71% for SCC in HPFS. Only confirmed invasive cases of melanoma and SCC were used in the current study. For BCC, self-reported cases were used. The self-reported cases of BCC demonstrated about 90% of agreement with histopathology records in the previous validation studies for both cohorts (17, 29, 30).

Statistical analysis

The participants who did not have information on fat intake were excluded in the analysis. We also excluded the participants who had baseline history of melanoma for the analysis of melanoma, SCC for the analysis of SCC, and BCC for the analysis of BCC. As skin cancer among nonwhite participants was rare (28), nonwhite participants were excluded. At baseline, included participants were 75,311 women and 48,516 men for melanoma analysis, 75,189 women and 48,400 men for SCC analysis, and 73,564 women and 48,550 men for BCC analysis.

Person-year of follow-up was calculated from the return month of baseline questionnaire to the first diagnosis of melanoma, SCC or BCC, date of death, loss to follow-up, or the end of follow-up (June 2012 for NHS and January 2012 for HPFS), whichever came first.

We used cumulative average of fat intake during the follow-up period examined to better estimate long-term dietary intake and to minimize within-person variation. For example, intake in 1986 was used for 1986–1990 follow-up and the average of 1986 and 1990 intake was used for 1990–1994 follow-up and so on in HPFS (31). Percentages of energy contributed by each fat intake were calculated to examine the effect of each type of fat on skin cancer comparing with other energy contributing nutrients such as protein and carbohydrate. Total and each type of fat intakes were categorized into quintiles with the lowest quintile as a reference.

Cox proportional hazard models were used to estimate the age-adjusted and multivariable-adjusted HRs of fat intake on skin cancer with 95% confidence intervals (CI). The assumption of proportion hazards was satisfied. We stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle to control for confounding by age or calendar year, or any possible two-way interactions between these two time scales. We adjusted for possible confounding lifestyle factors (32, 33) and risk factors of skin cancer (27, 28) for multivariable model 1: body mass index (BMI; <18.5, 18.5–24.9, 25–29.9, 30–34.9, and $\geq$35), physical activity (metabolic-equivalents hours/week, quintiles), smoking status (never, past with < 10, 10–19, 20–39, $\geq$40 pack year, unknown cigarettes/day, current), personal history of nonskin cancer (yes vs. no), total energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, and $\geq$20.0 gram/day), caffeine intake (quintiles), citrus intake (quintiles), family history of melanoma (yes vs. no), natural hair color (red, blonde, light brown, dark brown, and black), number of arm moles (0, 1–2, 3–5, and $\geq$6), sunburn susceptibility as a child/adolescent (no experience, no reaction/some redness, burn, and painful burn/blisters), number of lifetime blistering sunburns (0, 1–2, 3–5, and $\geq$6), and cumulative UV flux since baseline ($\times 10^{-4}$ Robertson–Berger units: an estimate of amount of UV radiation reaching Earth's surface of residence within 1 year, quintiles). We also adjusted for incident SCC and BCC for the analyses of melanoma, incident melanoma and BCC for the analyses of SCC, and incident melanoma and SCC for the analyses of BCC. Menopausal status (yes vs. no) and postmenopausal hormone use (no vs. current) were additionally adjusted for NHS. For multivariable model 2, we adjusted for the same covariates as multivariable model 1 and other types of fats simultaneously. In this model, saturated, polyunsaturated, monounsaturated fats, and cholesterol were included in one model. For the analysis of omega-6 and omega-3 fats, the two fats were included in one model simultaneously in addition to saturated and monounsaturated fats and cholesterol. All covariates except for family history of melanoma, natural hair color, and sunburn susceptibility as a child/adolescent were updated whenever new data were available during follow-up. The Anderson–Gill data structure (34) was used for efficient management of time-varying covariates, with a new dataset created for every questionnaire cycle at which a participant was at risk and covariates set to their values at the time the questionnaire was returned.

Table 1. Baseline characteristics of study participants according to quintile of total fat intake in the NHS and HPFS

	Quintile of total fat intake (% of energy intake)				
	Q1	Q2	Q3	Q4	Q5
NHS (women, 1984)					
Total fat intake (% of energy intake), mean (SD)	26.6 (3.0)	31.8 (0.9)	34.7 (0.8)	37.6 (0.9)	42.6 (3.1)
Number of participants	15,079	15,020	15,092	15,057	15,063
Age, years, mean (SD)	51.8 (7.1)	50.7 (7.2)	50.1 (7.2)	49.7 (7.1)	49.4 (7.1)
Family history of melanoma, %	2.5	2.6	2.5	2.6	2.6
Red/blonde hair, %	15.8	15.7	15.6	15.7	15.8
Painful burn/blisters reaction as a child/adolescent, %	34.7	33.9	35.1	34.6	33.8
6+ of blistering sunburns, %	6.6	7.0	7.7	7.4	8.0
6+ of moles, %	4.1	4.8	4.8	4.6	4.8
BMI (kg/m^2), mean (SD)	24.3 (4.3)	24.7 (4.4)	25.1 (4.7)	25.3 (4.9)	25.8 (5.2)
Physical activity level (MET hr/wk), mean (SD)	17.6 (25.6)	15.2 (21.3)	13.6 (19.4)	12.4 (18.3)	11.7 (18.8)
Alcohol intake (g/d), mean (SD)	10.4 (16.0)	7.8 (11.7)	6.5 (9.9)	5.6 (8.6)	4.3 (7.3)
Smoking, %	24.2	22.6	22.6	24.6	28.8
Menopause status, %	59.1	58.1	57.8	58.3	58.2
Postmenopausal hormones use in postmenopausal women, %	24.5	23.9	23.3	23.1	23.0
Total citrus intake (serving/d), mean (SD)	1.1 (0.9)	1.0 (0.8)	0.9 (0.7)	0.8 (0.6)	0.6 (0.6)
Caffeine intake (mg/d), mean (SD)	281.4 (221.7)	303.7 (224.0)	322.4 (229.5)	342.2 (236.4)	366.4 (248.7)
Total energy intake (kcal/d), mean (SD)	1,675.8 (517.3)	1,746.3 (519.5)	1,775.7 (526.4)	1,782.7 (534.4)	1,745.3 (546.3)
HPFS (men, 1986)					
Total fat intake (% of energy intake), mean (SD)	23.0 (3.3)	28.9 (1.1)	32.2 (0.9)	35.3 (1.0)	40.6 (3.3)
Number of participants	9,703	9,703	9,704	9,703	9,703
Age, years, mean (SD)	55.4 (10.0)	54.6 (10.0)	54.0 (9.8)	53.5 (9.7)	53.9 (9.5)
Family history of melanoma, %	2.7	2.8	3.3	3.1	3.4
Red/blonde hair, %	13.3	13.6	14.0	14.5	14.4
Painful burn/blisters reaction as a child/adolescent, %	54.1	55.1	54.9	55.7	54.7
6+ of blistering sunburns, %	12.6	13.7	13.9	13.7	14.7
6+ of moles, %	5.1	5.4	5.6	5.2	5.6
BMI (kg/m^2), mean (SD)	24.3 (4.7)	24.7 (5.0)	25.0 (5.0)	25.2 (5.2)	25.5 (5.2)
Physical activity level (MET hr/wk), mean (SD)	27.2 (34.8)	22.6 (32.1)	20.3 (28.1)	18.6 (27.8)	16.1 (21.8)
Alcohol intake (g/d), mean (SD)	15.9 (21.4)	13.7 (17.4)	12.0 (15.0)	10.2 (13.5)	7.8 (10.9)
Current smoking, %	6.6	8.5	9.8	10.9	14.1
Total citrus intake (serving/d), mean (SD)	1.3 (1.2)	1.1 (0.9)	0.9 (0.8)	0.8 (0.7)	0.7 (0.6)
Caffeine intake (mg/d), mean (SD)	173.6 (201.3)	210.6 (212.8)	227.6 (220.5)	248.4 (232.9)	281.1 (250.7)
Total energy intake (kcal/d), mean (SD)	1,884.1 (591.3)	1,938.1 (580.7)	2,007.1 (603.0)	2,052.7 (629.2)	2,068.6 (660.7)

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study population except for age and number of participants.
Abbreviation: MET, metabolic-equivalents.

We conducted trend tests with median values of each quintile of fat as a continuous variable. Pooled HRs were calculated with the results of separated analyses for the HPFS and the NHS using a random effects model. To examine interactions between the risk of skin cancer and sun exposure–related variables, we conducted stratified analyses by body locations of tumors, number of moles, childhood reaction to sun, and annual UV flux at residence. We also conducted stratified analyses by BMI and diagnostic year of skin cancers. Sensitive analyses with history of physical examination and other types of skin cancer were conducted as well. Spearman correlation coefficients were calculated to examine correlations between different fats.

All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc.) with two-sided *P* values at the significance level of 0.05.

Results

The characteristics of participants at baseline in NHS and HPFS were presented in Table 1 according to total fat intake. Participants with higher intake of total fat intake were more likely to have higher BMI, lower physical activity, lower alcohol intake, lower citrus intake and higher caffeine intake in both men and women, and more likely to be current smokers in men. The characteristics of participants at baseline in NHS and HPFS according to cholesterol, omega-6, and omega-3 fats intakes were also presented in Supplementary Table S1–S3.

Because some fats may be highly correlated, we evaluated the correlation coefficients among the fats. In both women and men, we found high correlations (correlation coefficients of over 0.6) between total fat and saturated and monounsaturated fats, between saturated fat and monounsaturated fat, and between polyunsaturated fat and omega-6 fat. Cholesterol intake was not highly correlated with any other type of fat.

A total of 794 melanoma, 2,223 SCC, and 17,556 BCC cases in the NHS (1984–2012); and 736 melanoma, 1,756 SCC, and 13,092 BCC cases in the HPFS (1986–2012) were documented during the follow-up. We found no association between either total fat or any type of fat intake and melanoma risk except for omega-6 fat (Table 2). The pooled multivariate HR for the highest quintile of total fat intake was 1.05 (CI, 0.88–1.25) compared with the lowest quintile. Higher intake of omega-6 fat was associated with risk of melanoma (pooled multivariate HR, 1.20; 95% CI, 1.02–1.41; P_{trend}=0.03) although the association was attenuated and no longer significant after adjusting for other types of fat simultaneously.

For SCC, although total fat intake was not associated with the risk, polyunsaturated fat intake was associated with SCC risk (pooled multivariate HR, 1.16; 95% CI, 1.05–1.28; $P_{trend} = 0.001$; Table 3). Among types of polyunsaturated fats, higher intake of omega-6 fat was associated with SCC risk. We also

Table 2. Pooled multivariable HRs and 95% CIs of melanoma by fat intake in the NHS and HPFS

	Q1	Q2	Q3	Q4	Q5	P_{trend}
Total fat						
HR1[a] (95% CI)	1.00 (referent)	1.04 (0.83–1.30)	0.99 (0.84–1.16)	1.00 (0.73–1.38)	1.05 (0.88–1.25)	0.80
Saturated fat						
HR1[a] (95% CI)	1.00 (referent)	1.01 (0.81–1.27)	1.02 (0.82–1.28)	0.94 (0.79–1.11)	0.96 (0.80–1.14)	0.36
HR2[b] (95% CI)	1.00 (referent)	0.98 (0.76–1.25)	0.97 (0.78–1.22)	0.87 (0.69–1.08)	0.88 (0.68–1.12)	0.13
Monounsaturated fat						
HR1[a] (95% CI)	1.00 (referent)	1.02 (0.87–1.19)	0.95 (0.81–1.12)	1.07 (0.84–1.35)	1.02 (0.86–1.21)	0.81
HR2[b] (95% CI)	1.00 (referent)	0.99 (0.83–1.18)	0.91 (0.74–1.13)	1.04 (0.82–1.31)	0.98 (0.75–1.28)	0.92
Cholesterol						
HR1[a] (95% CI)	1.00 (referent)	1.00 (0.85–1.17)	1.05 (0.89–1.23)	1.18 (1.00–1.38)	1.03 (0.87–1.22)	0.30
HR2[b] (95% CI)	1.00 (referent)	1.02 (0.86–1.20)	1.09 (0.92–1.28)	1.23 (1.04–1.46)	1.09 (0.90–1.31)	0.13
Polyunsaturated fat						
HR1[a] (95% CI)	1.00 (referent)	1.08 (0.76–1.53)	1.11 (0.91–1.35)	1.17 (1.00–1.38)	1.15 (0.95–1.40)	0.05
HR2[b] (95% CI)	1.00 (referent)	1.09 (0.74–1.59)	1.12 (0.88–1.42)	1.19 (0.99–1.42)	1.17 (0.94–1.45)	0.08
Omega-6 fat						
HR1[a] (95% CI)	1.00 (referent)	1.04 (0.74–1.47)	1.09 (0.92–1.30)	1.08 (0.79–1.47)	1.20 (1.02–1.41)	0.03
HR2[b] (95% CI)	1.00 (referent)	1.04 (0.71–1.54)	1.10 (0.85–1.41)	1.07 (0.69–1.63)	1.18 (0.95–1.46)	0.18
Omega-3 fat						
HR1[a] (95% CI)	1.00 (referent)	1.05 (0.88–1.26)	0.99 (0.84–1.18)	1.17 (0.99–1.37)	1.16 (0.99–1.37)	0.03
HR2[b] (95% CI)	1.00 (referent)	1.03 (0.87–1.22)	0.96 (0.80–1.14)	1.10 (0.92–1.32)	1.06 (0.87–1.28)	0.54

NOTE: The multivariate-adjusted HRs from each cohort were pooled using random effects model.

[a]Multivariable model 1 was jointly stratified by age in months and calendar year of the questionnaire cycle and adjusted for family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child/adolescent, number of lifetime blistering sunburns, cumulative UV flux since baseline, BMI, physical activity, smoking status, incident SCC, incident BCC, personal history of non-skin cancer, intakes of total energy, alcohol, caffeine, and citrus fruits. Among women analyses were additionally adjusted for menopausal status and postmenopausal hormone use.

[b]Multivariable model 2 was adjusted for the same covariates as multivariable model 1 and for other fats in quintiles simultaneously. Saturated, polyunsaturated, and monounsaturated fats and cholesterol were adjusted for each other. Omega-6 fat and omega-3 fat were adjusted for each other, as well as adjustment for saturated, monounsaturated fats, and for cholesterol.

found that cholesterol intake was associated with lower risk of SCC.

Intake of polyunsaturated fat was associated with higher BCC risk (pooled multivariate HR 1.06; 95% CI, 1.01–1.11; $P_{trend} = 0.01$; Table 4). We found that intake of both omega-6 fat and omega-3 fat was associated with BCC risk (pooled multivariate HR 1.08; 95% CI, 1.02–1.14; P_{trend}=0.01 for omega-6 fat; pooled multivariate HR 1.09; 95% CI, 1.04–1.13; $P_{trend} < 0.0001$ for omega-3 fat). Intake of monounsaturated fat was associated with lower BCC risk.

The association between fat intake and skin cancer was largely similar in men and women (Supplementary Tables S4–S6).

Table 3. Pooled multivariable HRs and 95% CIs of SCC by fat intake in the NHS and HPFS

	Q1	Q2	Q3	Q4	Q5	P_{trend}
Total fat						
HR1[a] (95% CI)	1.00 (referent)	0.92 (0.83–1.03)	1.07 (0.94–1.21)	1.02 (0.92–1.13)	1.03 (0.92–1.15)	0.20
Saturated fat						
HR1[a] (95% CI)	1.00 (referent)	1.07 (0.97–1.17)	1.04 (0.94–1.15)	1.07 (0.96–1.19)	0.98 (0.88–1.09)	0.99
HR2[b] (95% CI)	1.00 (referent)	1.13 (1.01–1.25)	1.13 (1.00–1.27)	1.18 (1.03–1.34)	1.11 (0.96–1.30)	0.11
Monounsaturated fat						
HR1[a] (95% CI)	1.00 (referent)	0.96 (0.87–1.07)	1.01 (0.92–1.12)	0.97 (0.88–1.08)	1.02 (0.92–1.13)	0.63
HR2[b] (95% CI)	1.00 (referent)	0.90 (0.80–1.02)	0.92 (0.81–1.04)	0.87 (0.75–1.00)	0.91 (0.77–1.07)	0.37
Cholesterol						
HR1[a] (95% CI)	1.00 (referent)	0.96 (0.88–1.06)	0.93 (0.85–1.03)	0.96 (0.87–1.05)	0.82 (0.73–0.93)	0.002
HR2[b] (95% CI)	1.00 (referent)	0.94 (0.86–1.04)	0.91 (0.83–1.01)	0.92 (0.83–1.03)	0.80 (0.67–0.94)	0.001
Polyunsaturated fat						
HR1[a] (95% CI)	1.00 (referent)	1.04 (0.94–1.15)	1.08 (0.97–1.19)	1.09 (0.99–1.21)	1.16 (1.05–1.28)	0.001
HR2[b] (95% CI)	1.00 (referent)	1.06 (0.96–1.18)	1.11 (1.00–1.24)	1.13 (1.01–1.27)	1.20 (1.07–1.36)	0.001
Omega-6 fat						
HR1[a] (95% CI)	1.00 (referent)	1.02 (0.88–1.17)	1.08 (0.97–1.19)	1.11 (1.00–1.23)	1.18 (1.06–1.30)	0.0001
HR2[b] (95% CI)	1.00 (referent)	1.04 (0.89–1.21)	1.11 (1.00–1.25)	1.16 (1.03–1.31)	1.23 (1.08–1.41)	0.0005
Omega-3 fat						
HR1[a] (95% CI)	1.00 (referent)	0.99 (0.90–1.10)	1.04 (0.94–1.15)	1.02 (0.93–1.13)	1.04 (0.94–1.15)	0.36
HR2[b] (95% CI)	1.00 (referent)	0.98 (0.88–1.08)	1.01 (0.91–1.12)	0.98 (0.88–1.09)	0.97 (0.87–1.10)	0.78

NOTE: The multivariate-adjusted HRs from each cohort were pooled using random effects model.

[a]Multivariable model 1 was jointly stratified by age in months and calendar year of the questionnaire cycle and adjusted for family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child/adolescent, number of lifetime blistering sunburns, cumulative UV flux since baseline, BMI, physical activity, smoking status, incident melanoma, incident BCC, personal history of non-skin cancer, intakes of total energy, alcohol, caffeine, and citrus fruits. Among women analyses were additionally adjusted for menopausal status and postmenopausal hormone use.

[b]Multivariable model 2 was adjusted for the same covariates as multivariable model 1 and for other fats in quintiles simultaneously. Saturated, polyunsaturated, and monounsaturated fats and cholesterol were adjusted for each other. Omega-6 fat and omega-3 fat were adjusted for each other, as well as adjustment for saturated, monounsaturated fats, and for cholesterol.

Table 4. Pooled multivariable HRs and 95% CIs of BCC by fat intake in the NHS and HPFS

	Q1	Q2	Q3	Q4	Q5	P_{trend}
Total fat						
HR1[a] (95% CI)	1.00 (referent)	0.99 (0.96–1.03)	0.96 (0.89–1.03)	0.97 (0.89–1.05)	0.94 (0.86–1.03)	0.20
Saturated fat						
HR1[a] (95% CI)	1.00 (referent)	1.01 (0.97–1.04)	0.98 (0.95–1.02)	0.96 (0.93–1.00)	0.90 (0.79–1.01)	0.04
HR2[b] (95% CI)	1.00 (referent)	1.01 (0.97–1.06)	0.99 (0.95–1.04)	0.98 (0.93–1.03)	0.92 (0.79–1.08)	0.29
Monounsaturated fat						
HR1[a] (95% CI)	1.00 (referent)	0.96 (0.93–1.00)	0.98 (0.92–1.06)	0.95 (0.89–1.02)	0.92 (0.87–0.98)	0.02
HR2[b] (95% CI)	1.00 (referent)	0.94 (0.89–0.99)	0.96 (0.88–1.03)	0.93 (0.89–0.98)	0.90 (0.85–0.96)	0.002
Cholesterol						
HR1[a] (95% CI)	1.00 (referent)	1.04 (0.99–1.10)	1.00 (0.97–1.04)	1.02 (0.98–1.06)	0.97 (0.93–1.01)	0.03
HR2[b] (95% CI)	1.00 (referent)	1.06 (0.99–1.13)	1.03 (0.99–1.06)	1.06 (0.97–1.16)	1.02 (0.96–1.10)	0.65
Polyunsaturated fat						
HR1[a] (95% CI)	1.00 (referent)	1.00 (0.96–1.03)	1.03 (0.99–1.07)	1.04 (1.01–1.08)	1.06 (1.01–1.11)	0.01
HR2[b] (95% CI)	1.00 (referent)	1.01 (0.97–1.05)	1.05 (1.00–1.10)	1.08 (1.04–1.12)	1.11 (1.06–1.16)	0.0002
Omega-6 fat						
HR1[a] (95% CI)	1.00 (referent)	1.03 (0.99–1.07)	1.03 (1.00–1.07)	1.03 (1.00–1.07)	1.08 (1.02–1.14)	0.01
HR2[b] (95% CI)	1.00 (referent)	1.03 (1.00–1.07)	1.04 (1.00–1.08)	1.05 (1.00–1.09)	1.11 (1.05–1.16)	0.0003
Omega-3 fat						
HR1[a] (95% CI)	1.00 (referent)	1.02 (0.97–1.08)	1.04 (1.00–1.08)	1.08 (1.04–1.12)	1.09 (1.04–1.13)	<.0001
HR2[b] (95% CI)	1.00 (referent)	1.01 (0.95–1.07)	1.02 (0.98–1.06)	1.04 (1.00–1.09)	1.04 (0.98–1.09)	0.07

NOTE: The multivariate-adjusted HRs from each cohort were pooled using random effects model.

[a]Multivariable model 1 was jointly stratified by age in months and calendar year of the questionnaire cycle and adjusted for family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child/adolescent, number of lifetime blistering sunburns, cumulative UV flux since baseline, BMI, physical activity, smoking status, incident melanoma, incident SCC, personal history of non-skin cancer, intakes of total energy, alcohol, caffeine, and citrus fruits. Among women analyses were additionally adjusted for menopausal status and postmenopausal hormone use.

[b]Multivariable model 2 was adjusted for the same covariates as multivariable model 1 and for other fats in quintiles simultaneously. Saturated, polyunsaturated, and monounsaturated fats and cholesterol were adjusted for each other. Omega-6 fat and omega-3 fat were adjusted for each other, as well as adjustment for saturated, monounsaturated fats, and for cholesterol.

The results were also similar when other types of fats were adjusted simultaneously. The associations between fat intake and melanoma and SCC were similar by body location of the tumor (head/neck/extremities vs. trunk) based on sun exposure pattern.

We further examined the associations between intake of trans fat and marine omega-3 fat [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] and risk of skin cancer. Trans fat intake was not associated with any type of skin cancer. The association between marine omega-3 fat intake (EPA + DHA) and risk of skin cancer were similar to the association of total omega-3 fat intake that was associated with higher risk of BCC. Intake of individual omega-6 fat (linoleic acid and arachidonic acid) was not associated with risk of skin cancer.

When we conducted stratified analyses with sun exposure–related variables such as number of moles (with moles vs. with no mole), childhood reaction to sun (no reaction vs. burn or blister), and annual UV flux at residence (below median vs. above median), the associations were similar. We found similar associations in a stratified analysis by BMI (below median vs. above median). When we evaluated the associations by year of diagnosis using approximate median year of 2004, the results were not materially different by the year.

In the analyses among participants with history of physical examination, the results remained essentially unchanged. When we excluded SCC cases in the analysis of BCC and BCC cases in the analysis of SCC, the results also remained similar.

Discussion

Using the data from two large prospective studies of women and men in the United States, we found no association of fat intake with melanoma except for omega-6 fat intake. For SCC, we found higher risk associated with higher intake of polyunsaturated fat and omega-6 fat. Higher intake of cholesterol was associated with lower risk of SCC. For BCC, we found that higher intake of polyunsaturated fat, omega-6 fat, and omega-3 fat was each associated with higher risk. On the other hand, higher intake of monounsaturated fat was associated with lower risk of BCC.

Few studies have examined fat intake and risk of melanoma. A case–control study in Australia with 105 melanoma cases showed lower risk of melanoma with high fat intake (OR, 0.61; 95% CI, 0.40–0.92; $P_{trend} = 0.02$; ref. 12). On the other hand, in the Women's Health Initiative randomized controlled dietary modification trial, low-fat diet intervention over 8 years of follow-up did not affect incidence of melanoma ($n = 114$; HR, 1.04; 95% CI, 0.82–1.32; ref. 16), which was consistent with our study of total fat intake. No previous study evaluated individual types of fat in relation to melanoma risk.

In terms of SCC, several studies evaluated the risk in relation to total fat intake. A small intervention study including 76 patients with a history of NMSC found that two years of low-fat diet reduced the incidence of actinic keratosis (10). Another intervention study of 101 participants with a history of NMSC found lower incidence of NMSC in the low-fat diet group after 2 years of intervention (11). However, other studies including case–control studies (12, 18), cohort studies (14, 15), and an intervention study (16) found no association between fat intake and the risk of SCC. On the other hand, Ibiebele and colleagues found increased risk of SCC with total fat intake in participants with a skin cancer history in an Australian cohort study (15). Only one case–control study has examined the associations of individual fatty acids with risk of SCC, which found nonsignificant inverse association with omega-3 fat intake (18). Our findings on polyunsaturated, omega-6 fat, and cholesterol intake are new and need to be replicated in other studies.

For BCC, EPIC-Norfolk study, a cohort study in England, found no association with total fat intake (13). A case–control study in

Australia found lower risk of BCC in high-fat intake group (OR, 0.60; 95% CI, 0.39–0.91; $P_{trend} = 0.02$; ref. 12). Nambour Skin Cancer Study, a cohort study in Australia, found no association between risk of BCC and fat intake (15). The Nambour study, on the other hand, found lower risk of BCC in the middle tertile of omega-6 intake suggesting a U-shaped relationship with BCC (14). However, our findings were different from these studies. In a previous evaluation of HPFS with shorter follow-up ($n = 3,190$), BCC risk was inversely associated with total fat and monounsaturated fat intakes and positively associated with omega-3 fat intake (17). After 18 years of extended follow-up, our study confirmed this association. In a pooled analysis with NHS, we additionally discovered a positive association with polyunsaturated fat and omega-6 fat.

Because fat intake is associated with BMI, some of the associations we observed might be due to the association with BMI. However, we adjusted for BMI in multivariate analysis. There was additionally no effect modification by BMI.

In our study, the positive association with intake of polyunsaturated fat, especially omega-6 fat was consistent across the three types of skin cancer. In a few animal studies, tumor promoting effects of omega-6 fat on UVR-induced carcinogenesis were found (4, 35), which may support our findings. The animal studies showed that proinflammatory and immunosuppressive prostaglandin E synthase type 2 levels that are associated with aggressive growth patterns of NMSC, increased linearly with the concentration of omega-6 fat intake. The studies also found tumor-suppressing effects of omega-3 fat on UVR-carcinogenic expression (35), which is contrary to what we found about omega-3 fat. The investigators reported that plasma level of prostaglandin E synthase type 2 was dramatically reduced in omega-3 fat-fed animals, compared with an equivalent amount of omega-6 fat-fed animals.

The strengths of our study include large sample size, repeated dietary assessment, and use of cumulative averaged dietary intake to reduce measurement error, confirmed cases of melanoma and SCC with information on body site of tumor, and extensive information on skin cancer–related covariates. We also have several study limitations. The participants of the cohorts were health professionals who were knowledgeable on healthy lifestyle and diet. This might limit the generalizability of our study results to general populations. Use of self-reported dietary assessment method may cause exposure misclassification, although this is likely to be nondifferential and may attenuate the true associations even though we used a validated FFQ. Although we adjusted for some highly correlated fats simultaneously in the multivariable models, we could not completely tease out the effect of individual fats if they shared food sources. We also lacked information on some potential sources of confounding such as sun protective behaviors, particularly later in life. The self-reported BCC cases we used in this study might cause misclassification although the validity of self-reported cases of BCC was high (17, 29, 30). Finally, because we evaluated multiple types of fat, some of the associations we found might be due to chance and need to be confirmed in other populations.

In conclusion, there was no association between total fat intake and risk of skin cancer in the two prospective studies. However, we found that higher intake of polyunsaturated fat, especially omega-6 fat, was associated with higher risk of skin cancer. In addition, higher intake of cholesterol was associated with lower risk of SCC. Higher intake of monounsaturated fat was associated with lower risk of BCC. Because there have been few experimental and epidemiologic studies of fat intake and skin cancer, our findings on certain types of fat and skin cancer need to be replicated and may motivate future studies.

Disclosure of Potential Conflicts of Interest

A.A. Qureshi is a consultant/advisory board member for AbbVie, Amgen, CDC, Janssen, Merck, Novartis, Pfizer, Regeneron, and Sanofi. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these data.

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Development of methodology: M.K. Park, E. Cho
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Cho
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.K. Park, W.-Q. Li
Writing, review, and/or revision of the manuscript: M.K. Park, W.-Q. Li, A.A. Qureshi, E. Cho
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.K. Park
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