JAMA Dermatology | Original Investigation

Association of Vitamin A Intake With Cutaneous Squamous Cell Carcinoma Risk in the United States

Jongwoo Kim, MD, MSc; Min Kyung Park, PhD; Wen-Qing Li, PhD; Abrar A. Qureshi, MD, PhD; Eunyoung Cho, ScD

IMPORTANCE Retinoids are bioactive forms of vitamin A that are essential in the maintenance of epithelial maturation and differentiation. Synthetic retinoids are used in chemoprevention of skin cancer among high-risk populations with potential adverse effects. Epidemiologic data on vitamin A intake and risk of cutaneous squamous cell carcinoma (SCC) are limited.

OBJECTIVE To examine whether vitamin A intake is associated with a reduction in SCC risk.

DESIGN, SETTINGS, AND PARTICIPANTS This cohort study prospectively examined intake of vitamin A and carotenoids and SCC risk in the Nurses' Health Study (1984-2012) and the Health Professionals Follow-up Study (1986-2012). Diet was assessed repeatedly. Incident SCC was confirmed by pathologic reports. Data analysis was performed from June 21, 2017, to December 4, 2018.

EXPOSURES Intakes of vitamin A, retinol, and carotenoids.

MAIN OUTCOMES AND MEASURES Incident SCC. Cox proportional hazards regression models were used to compute cohort-specific hazard ratios (HRs) and 95% CIs. Pooled HRs of the cohort-specific results were calculated.

RESULTS A total of 3978 SCC cases in 75 170 women in the Nurses' Health Study (mean [SD] age, 50.4 [7.2] years) and 48 400 men in the Health Professionals Follow-up Study (mean [SD] age, 54.3 [9.9] years) were documented. Higher total vitamin A was associated with a reduction in SCC risk; with quintile 1 as the reference, the pooled multivariate HRs for the increasing quintiles of vitamin A intake were 0.97 (95% CI, 0.87-1.07) for quintile 2, 0.97 (95% CI, 0.80-1.17) for quintile 3, 0.93 (95% CI, 0.84-1.03) for quintile 4, and 0.83 (95% CI, 0.75-0.93) for quintile 5 ($P < .001$ for trend). Higher intakes of retinol and some carotenoids were also associated with a reduction in SCC risk; the pooled HRs for the highest quintiles of intake compared with the lowest quintiles were 0.88 (95% CI, 0.79-0.97; $P = .001$ for trend) for total retinol, 0.86 (95% CI, 0.76-0.96; $P = .001$ for trend) for beta cryptoxanthin, 0.87 (95% CI, 0.78-0.96; $P < .001$ for trend) for lycopene, and 0.89 (95% CI, 0.81-0.99; $P = .02$ for trend) for lutein and zeaxanthin. The results were generally consistent by sex and other SCC risk factors.

CONCLUSIONS AND RELEVANCE This study suggests that increased intake of dietary vitamin A is associated with decreased risk of incident SCC. Future studies are needed to determine whether vitamin A supplementation has a role in chemoprevention of SCC.

JAMA Dermatol. 2019;155(11):1260-1268. doi:10.1001/jamadermatol.2019.1937
Published online July 31, 2019.

Supplemental content

Author Affiliations: Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, Rhode Island (Kim, Park, Li, Qureshi, Cho); Department of Family Medicine, Sanggye-Paik Hospital, College of Medicine, Inje University, Seoul, South Korea (Kim); Department of Epidemiology, Brown School of Public Health, Providence, Rhode Island (Li, Qureshi, Cho); Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Qureshi, Cho).

Corresponding Author: Eunyoung Cho, ScD, Department of Dermatology, Warren Alpert Medical School of Brown University, 339 Eddy St, Providence, RI 02903 (eunyoung_cho@brown.edu).

Cutaneous squamous cell carcinoma (SCC) is a common skin cancer in populations with fair skin, with an estimated lifetime incidence of 7% to 11% in the United States.[1,2] Squamous cell carcinoma occurs most frequently on body surfaces with the greatest exposure to sunlight, such as the face and head. Prevention and early detection of SCC are critical because of the likelihood of metastasis.[3,4] The most well-established risk factors for SCC are age, skin type, and exposure to sunlight (UV radiation).[5] During the past 20 years, the incidence of SCC has increased potentially because of prolonged life expectancy, greater recreational sun exposure, and other lifestyle changes.[6]

Vitamin A is a term for a large number of related compounds also known as retinoids (eg, retinol, retinal, and retinoic acid).[7] They can be differentiated into 2 groups depending on whether the food source is an animal or a plant. Vitamin A derived from animal-based foods is retinol (also called *preformed vitamin A*), which is a yellow, fat-soluble compound that is the precursor of the most active form of vitamin A (retinoic acid) used in the body. The form of vitamin A found in fruits and vegetables is called *provitamin A carotenoid*, which includes beta carotene, alpha carotene, and beta cryptoxanthin and can be converted into retinol in the body. However, most carotenoids are nonprovitamin A and include lutein, zeaxanthin, and lycopene.[8]

Retinol and its derivatives are essential for growth, differentiation, and maintenance of normal epithelial cell.[9,10] In addition, retinoids bind to nuclear receptors and regulate gene transcription, inducing changes that may ultimately decrease cell growth and help block malignant transformation.[10] Furthermore, retinoids inhibit growth-stimulating signals and induce a multitude of downstream signaling pathways that regulate apoptosis, growth arrest, and cell differentiation in both precancerous and cancerous lesions.[11] Retinoids are considered as chemopreventive agents against cancer sites, including head and neck, breast, and liver.[9] Animal studies[12-15] of UV light–induced skin cancer have provided consistent evidence of the anticancer effect of carotenoids. Collectively, these studies[16,17] suggest a potential role of retinol and its derivatives in the chemoprevention of keratinocyte-derived carcinomas, including SCC.

Clinical trials have tested the effect of systemic retinoids on development of nonmelanoma skin cancer (NMSC), including SCC, among high-risk populations, and some of them found the synthetic retinoids effective.[16] On the basis of these findings, synthetic retinoids are used to prevent NMSC among high-risk populations. For example, in the case of oral acitretin (one of the synthetic retinoids), daily doses ranging from 10 to 20 mg are recommended.[18] However, these retinoids also have significant adverse effects, including hypercholesterolemia, hypertriglyceridemia, increased liver dysfunction, joint and muscle pain, dry lip and mouth, hair loss, and headache.[19-21]

Epidemiologic studies of the association between vitamin A or carotenoid intake and SCC risk have been limited and often inconsistent. A previous prospective study[22] based on the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HFPS) found no association between retinol intake and SCC incidence. However, the duration of follow-up in that study was only 14 years in women and 10 years in men, which may not have been long enough to capture the benefit of vitamin A, given the slow-growing nature of SCC.[23] Therefore, using longer follow-up and a larger sample size, we reevaluated the association between SCC risk and intakes of vitamin A, retinol, and carotenoids based on data from the NHS (1984-2012) and the HFPS (1986-2012).

Key Points

Question Is vitamin A intake associated with reduced cutaneous squamous cell carcinoma risk?

Findings In this cohort study of 48 400 US men and 75 170 US women, during a follow-up period of more than 26 years, higher total vitamin A intake was associated with a reduction in cutaneous squamous cell carcinoma risk.

Meaning This study found an inverse association between intake of vitamin A and carotenoids and risk of cutaneous squamous cell carcinoma, supporting the protective role of vitamin A against squamous cell carcinoma development.

Methods

Study Population

This cohort study used data from the NHS, which was established in 1976 with 121 700 US female registered nurses aged 30 to 55 years, and the HPFS, which was established in 1986 with 51 529 US male health professionals aged 40 to 75 years. Participants in both cohorts completed a questionnaire on their medical history and lifestyle and have been followed up biennially, with follow-up rates generally exceeding 90%. Detailed descriptions of the 2 cohort studies can be found elsewhere.[5,22] The present study was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health. We considered the participants' completion and return of the self-administered questionnaires to be written informed consent. All data were deidentified.

We excluded participants who did not report diet and those who had a history of cancer (including melanoma and SCC) at baseline. Owing to the small number of cases and low risk of SCC in nonwhite populations, we included only participants of white ancestry. Dietary information was available from most participants (84% in the NHS and 97% in the HPFS) (eTable 1 in the Supplement). Participants with vs without dietary information were generally similar in terms of basic lifestyle factors and skin cancer risk factors. However, those with dietary information tended to have experience with painful burn or blister reactions at a younger age (eTable 1 in the Supplement). Finally, 75 170 women and 48 400 men remained for analysis. Person-years of follow-up were calculated starting with the month in which the baseline questionnaire was returned to the first diagnosis of SCC, date of death, unavailability for follow-up, or the end of follow-up (June 2012 for the NHS and January 2012 for the HPFS), whichever came first.

Because dietary intake may prevent skin carcinogenesis during an extended period, we used cumulative means of vitamin A and carotenoid intakes during the follow-up period as a time-varying exposure measure to better estimate long-term dietary

intake and to minimize within-person variation.[24,25] For example, intake in 1986 was used for 1986-1990 follow-up, and the mean of 1986 and 1990 intake was used for 1990-1994 follow-up and so on. We also evaluated baseline intake and the most recent intake as a time-varying variable. Data analysis was performed from June 21, 2017, to December 4, 2018.

Assessment of Vitamin A and Carotenoid Intake

Information on diet has been collected using a validated food frequency questionnaire (FFQ) of approximately 130 food items[26] since 1984 in the NHS and 1986 in the HPFS. The FFQ has been repeated almost every 4 years. Cohort members were asked how often on average they had consumed a given unit (or 1 serving size) of each food item in the FFQ during the previous year, with 9 possible responses that ranged from never or less than once per month to 6 or more times per day. Nutrient intakes were calculated by multiplying the consumption frequency of each food item by its nutrient content, and the contributions from all foods were summed. Nutrient contents of foods were obtained from a nutrient database prepared for a specified amount of the food item, based on the Harvard University Food Composition Database, in turn derived from the US Department of Agriculture sources and supplemented with information from manufacturers. Carotenoid contents were assessed based on the US Department of Agriculture and National Cancer Institute databases.[27,28] Detailed information on use of supplemental multivitamins and individual vitamins was also collected. Total vitamin A was the sum of retinol and carotenoids according to their vitamin A activity. Validation studies[29,30] among the cohort participants have demonstrated good reproducibility and validity of the FFQ for ranking individuals by consumption of nutrients. Correlation coefficients between FFQ and diet records were 0.79 for vitamin A in the NHS.[22] For the HPFS, the correlation between participants' baseline FFQ and the mean of two 1-week diet records for carotenoid intake was 0.64.[30]

Assessment of Covariates

Information on anthropometric and lifestyle factors, such as height, weight, physical activity, and smoking status for the NHS and HPFS participants and menopausal status and postmenopausal hormone use for the NHS participants, was collected using biennial questionnaires. Information on skin cancer risk factors was also collected,[31,32] including family history of melanoma (in parents or siblings), natural hair color, number of moles (>3 mm) on arms, skin reaction to sun exposure as a child or adolescent, number of severe or blistering sunburns, and cumulative UV flux at residence from baseline.

Assessment of SCC Cases

Cohort participants were asked to report new diagnoses of SCC biennially since 1984 for the NHS and 1986 for the HPFS. To confirm SCC diagnoses, physicians blinded to participants' dietary intake reviewed medical and pathological records.

Statistical Analysis

Cox proportional hazards regression models were used to assess the hazard ratios (HRs) and 95% CIs of SCC associated with intakes of total and dietary vitamin A, total and dietary retinol, carotenoids, and individual carotenoids, including alpha carotene, beta carotene, beta cryptoxanthin, lycopene, and lutein and zeaxanthin. Energy-adjusted vitamin A and carotenoid intake was calculated using a regression-residual method to minimize variation attributable to energy intake and its related measurement error.[33] All nutrient values were classified into quintiles. Multivariate analyses adjusted for age, body mass index, physical activity, smoking status, personal history of basal cell carcinoma and melanoma along with nonskin cancer (the cancers documented during follow-up), total energy intake, alcohol intake, family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child or adolescent, number of lifetime blistering sunburns, and cumulative UV flux since baseline.[34,35] Menopausal status and postmenopausal hormone use were additionally adjusted for in the NHS. Trend tests were conducted by assigning median values for each category of nutrient and analyzing this value as a continuous variable.

We performed study-specific analyses and then calculated pooled HRs using a random effects model. *P* values for heterogeneity were calculated using Q statistics.[36] We conducted stratified analyses according to risk factors for SCC, including annual UV flux at residence (below vs above median value), childhood reaction to sun exposure (no reaction vs burn or blistered), presence of arm moles (no vs yes), number of severe sunburns (≤5 vs >5), family history of melanoma (no vs yes), and natural hair color (dark brown or black vs red, blonde, or light brown). We also performed an analysis by body site of SCC. Finally, we performed a sensitivity analysis excluding those with no physical examination during follow-up. All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc) with 2-sided $P < .05$ considered to be statistically significant.

Results

A total of 3978 SCC cases in 75 170 women in the NHS (mean [SD] age, 50.4 [7.2] years) and 48 400 men in the HPFS (mean [SD] age, 54.3 [9.9] years) were documented. **Table 1** gives age-adjusted baseline characteristics of the study population according to total vitamin A intake. Participants with higher intake of total vitamin A tended to be older and to have higher levels of physical activity. They were also less likely to smoke and to consume alcohol and caffeine. Among women, participants with a higher intake of total vitamin A were more likely to use postmenopausal hormones. Other characteristics, including phenotypic traits and sun exposure–related factors, were similar by total vitamin A intake.

We documented 2222 SCC cases in the NHS during 26 years of follow-up and 1756 SCC cases in the HPFS during 28 years of follow-up (eTable 2 in the Supplement). The medians of total vitamin A intake were 6808 IU/d in the first quintile and 21 691 IU/d in the fifth quintile for women and 7236 IU/d in the first quintile and 26 539 IU/d in the fifth quintile for men (eTable 2 in the Supplement). A larger proportion of the intake was derived from diet (median dietary vitamin A intake for fifth quintile, 16 764 IU/d in the NHS and 19 250 IU/d in the HPFS) than

Table 1. Baseline Characteristics of Study Participants According to Quintile of Energy-Adjusted Total Vitamin A Intake in the NHS and HPFS[a]

Characteristic	Quintile of Total Vitamin A Intake				
	1	2	3	4	5
NHS (Women, 1984)					
No. of participants	15 036	15 032	15 031	15 037	15 034
Age, mean (SD), y[b]	48.4 (7.0)	49.9 (7.1)	50.4 (7.1)	51.1 (7.1)	52.0 (7.0)
Family history of melanoma	406 (2.7)	376 (2.5)	376 (2.5)	376 (2.5)	406 (2.7)
Red or blonde hair	2182 (15.6)	2190 (15.6)	2132 (15.2)	2236 (15.9)	2312 (16.5)
Painful burn or blister reactions as a child or adolescent	5428 (34.9)	5125 (34.1)	5231 (34.8)	5143 (34.2)	5111 (34.0)
≥6 Blistering sunburns	1003 (7.7)	961 (7.4)	942 (7.3)	929 (7.2)	890 (7.0)
Annual UV flux at residence (× 10^{-4} red blood cell count)	187 (28)	187 (28)	188 (28)	190 (30)	193 (32)
≥6 Moles (>3 mm) on arms	524 (4.1)	610 (4.7)	634 (4.9)	623 (4.8)	613 (4.7)
BMI, mean (SD)	25.2 (5.0)	25.2 (4.8)	25.1 (4.8)	24.9 (4.7)	24.6 (4.5)
Physical activity level, mean (SD), MET hours per week	10.6 (19.0)	12.5 (18.7)	13.7 (20.4)	15.4 (21.7)	18.4 (25.1)
Alcohol intake, g per day, mean (SD)	8.0 (13.3)	7.3 (11.9)	7.1 (11.3)	6.6 (10.5)	5.8 (9.2)
Smoking	4472 (31.8)	3960 (26.4)	3525 (23.5)	3195 (21.3)	2877 (19.2)
Menopause status	8560 (58.1)	8485 (57.7)	8589 (58.5)	8557 (58.4)	8584 (58.7)
Postmenopausal hormones use in postmenopausal women[c]	1420 (19.8)	1719 (21.1)	2063 (23.9)	2299 (25.3)	2574 (26.5)
Caffeine intake, mean (SD), mg/d	355 (241)	335 (234)	326 (232)	312 (230)	288 (228)
Total energy intake, mean (SD), kcal/d	1695 (532)	1752 (526)	1789 (535)	1776 (526)	1705 (526)
HPFS (Men, 1986)					
No. of participants	9678	9684	9678	9680	9680
Age, mean (SD), y	51.5 (9.4)	53.6 (9.7)	54.3 (9.8)	55.5 (9.8)	56.4 (9.9)
Family history of melanoma	149 (3.0)	133 (2.7)	164 (3.3)	149 (2.9)	166 (3.3)
Red or blonde hair	1054 (14.2)	1107 (14.7)	984 (13.2)	1038 (13.9)	1013 (13.8)
Painful burn or blister reactions as a child or adolescent	5352 (55.3)	5326 (55.0)	349 (55.6)	5266 (54.4)	5179 (53.5)
≥6 blistering sunburns	1018 (13.4)	1089 (14.3)	1051 (13.8)	1068 (14.1)	958 (12.8)
Annual UV flux at residence (× 10^{-4} red blood count)	191 (27)	191 (27)	192 (27)	192 (28)	194 (29)
≥6 Moles (>3 mm) on arms	311 (5.0)	348 (5.4)	349 (5.5)	356 (5.6)	344 (5.5)
BMI, mean (SD)	25.2 (5.1)	25.1 (4.9)	24.9 (5.1)	24.9 (5.1)	24.6 (5.1)
Physical activity level, mean (SD), MET h/wk,	16.7 (22.8)	19.5 (26.0)	21.0 (29.6)	22.6 (31.8)	25.1 (35.2)
Alcohol intake, mean (SD), g/d	15.2 (19.9)	12.3 (16.3)	11.9 (15.9)	11.0 (14.9)	9.7 (13.8)
Smoking	1303 (14.0)	949 (10.2)	927 (10.0)	783 (8.4)	695 (7.5)
Caffeine intake, mg/d	265 (240)	240 (229)	232 (226)	215 (220)	188 (211)
Total energy intake, kcal/d	1955 (618)	1980 (609)	2038 (628)	2012 (617)	1955 (610)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HPFS, Health Professionals Follow-up Study; MET, metabolic equivalents; NHS, Nurses' Health Study.

[a] Data are presented as number (percentage) of cases and are standardized to the age distribution of the study population unless otherwise indicated.

[b] Values are not age adjusted.

[c] Percentages among postmenopausal women.

from supplements. In addition, a larger proportion of dietary vitamin A was derived from carotenoids (vegetable sources) than from retinol (animal sources). We evaluated the risk of SCC associated with vitamin A or carotenoid intake and did not find significant heterogeneity in the association by sex. Higher total vitamin A level was associated with a reduction in SCC risk; with quintile 1 as the reference, the pooled multivariate HRs for the increasing quintiles of vitamin A intake were 1.00, 0.97 (95% CI, 0.87-1.07) for quintile 2, 0.97 (95% CI, 7 0.80-1.17) for quintile 3, 0.93 (95% CI, 0.84-1.03) for quintile 4, and 0.83 8 (95% CI, 0.75-0.93) for quintile 5 ($P < .001$ for trend). The pooled analysis of NHS and HPFS data also found that higher intakes of total retinol and some individual carotenoids were significantly associated with decreased risk of SCC (**Table 2**, **Table 3**, and **Figure**). The pooled HRs of SCC for the highest quintiles of intake compared with the lowest quintiles were 0.88 (95% CI, 0.79-0.97; $P = .001$ for trend) for total retinol, 0.86 (95% CI, 0.76-0.96; $P = .001$ for trend) for beta

Table 2. Pooled Multivariable HRs (95% CIs) of Squamous Cell Carcinoma by Energy-Adjusted Vitamin A and Carotenoid Intake in the Nurses' Health Study and Health Professionals Follow-up Study[a]

Component	HR (95% CI) by Quintile of Intake					*P* Value for Trend
	1	2	3	4	5	
Total vitamin A	1 [Reference]	0.97 (0.87-1.07)	0.97 (0.80-1.17)	0.93 (0.84-1.03)	0.83 (0.75-0.93)	<.001
Dietary vitamin A	1 [Reference]	1.07 (0.96-1.18)	1.00 (0.90-1.11)	1.02 (0.92-1.13)	0.86 (0.78-0.96)	<.001
Total retinol	1 [Reference]	1.01 (0.91-1.11)	0.99 (0.89-1.09)	0.88 (0.74-1.05)	0.88 (0.79-0.97)	.001
Dietary retinol	1 [Reference]	1.02 (0.83-1.26)	1.04 (0.88-1.23)	0.97 (0.84-1.12)	0.88 (0.79-0.98)	.009
Carotenoids	1 [Reference]	1.10 (0.94-1.30)	1.09 (0.98-1.22)	1.03 (0.93-1.14)	0.91 (0.82-1.01)	.007

Abbreviation: HR, hazard ratio.

[a] Multivariate model was adjusted for age (continuous, years); family history of melanoma; natural hair color (red, blonde, light brown, dark brown, or black); number of arm moles (0,1-2, 3-5, or ≥6); sunburn susceptibility as a child or adolescent (no experience, no reaction or some redness, burn, or painful burn or blisters); number of lifetime blistering sunburns (0, 1-2, 3-5, or ≥6); cumulative UV flux since baseline quintiles); body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35 [calculated as weight in kilograms divided by height in meters squared]); physical activity (quintiles); smoking status (never, past with <10, 10-19, 20-39, ≥40, or unknown pack-years, current); personal history of basal cell carcinoma, melanoma, or nonskin cancer (yes vs no); total energy intake (quintiles); and intakes of total energy, alcohol (0, 0.1-4.9, 5.0-9.9, 10.0-19.9, ≥20.0 g per day), and caffeine (quintiles.) Among women, analyses were additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (no vs current). Pooled hazards ratios of cohort-specific results were calculated using a random-effects model.

Table 3. Pooled Multivariable Hazard Ratios (95% CIs) of Squamous Cell Carcinoma by Energy-Adjusted Individual Carotenoid Intake in the Nurses' Health Study and Health Professionals Follow-up Study[a]

Component	HR (95% CI) by Quintile of Intake					*P* Value for Trend
	1	2	3	4	5	
Alpha carotene	1 [Reference]	1.05 (0.87-1.27)	1.06 (0.93-1.20)	1.02 (0.92-1.14)	0.89 (0.80-0.99)	.003
Beta carotene	1 [Reference]	1.10 (0.90-1.35)	1.01 (0.83-1.24)	1.04 (0.88-1.22)	0.91 (0.82-1.02)	.006
Beta cryptoxanthin	1 [Reference]	0.99 (0.89-1.09)	1.03 (0.90-1.19)	0.96 (0.87-1.07)	0.86 (0.76-0.96)	.001
Lycopene	1 [Reference]	1.00 (0.91-1.10)	0.93 (0.84-1.02)	0.87 (0.79-0.96)	0.87 (0.78-0.96)	<.001
Lutein and zeaxanthin	1 [Reference]	0.98 (0.88-1.08)	1.00 (0.87-1.14)	0.98 (0.89-1.09)	0.89 (0.81-0.99)	.02

Abbreviation: HR, hazard ratio.

[a] Multivariate model was adjusted for age (continuous, years); family history of melanoma; natural hair color (red, blonde, light brown, dark brown, or black); number of arm moles (0,1-2, 3-5, or ≥6); sunburn susceptibility as a child or adolescent (no experience, no reaction or some redness, burn, or painful burn or blisters); number of lifetime blistering sunburns (0, 1-2, 3-5, or ≥6); cumulative UV flux since baseline quintiles); body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35 [calculated as weight in kilograms divided by height in meters squared]); physical activity (quintiles); smoking status (never, past with <10, 10-19, 20-39, ≥40, or unknown pack-years, current); personal history of basal cell carcinoma, melanoma, or nonskin cancer (yes vs no); total energy intake (quintiles); and intakes of total energy, alcohol (0, 0.1-4.9, 5.0-9.9, 10.0-19.9, ≥20.0 g per day), and caffeine (quintiles.) Among women analyses were additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (no vs current). Pooled hazards ratios of cohort-specific results were calculated using a random-effects model.

cryptoxanthin, 0.87 (95% CI, 0.78-0.96; *P* < .001 for trend) for lycopene, and 0.89 (95% CI, 0.81-0.99; *P* = .02 for trend) for lutein and zeaxanthin. In the NHS, higher intakes of retinol and lycopene were significantly associated with a lower risk of SCC (eTable 2 in the Supplement). For other nutrient intakes, we found no significant associations with SCC risk in women, although the directions of the associations were consistently inverse. In the HPFS, higher intakes of total vitamin A and carotenoids were significantly associated with a lower risk of SCC. Among types of individual carotenoids, we also found significantly lower SCC risk in the highest quintiles of alpha carotene, beta carotene, beta cryptoxanthin, and lutein and zeaxanthin intakes compared with the lowest quintiles (Table 3). However, none of the *P* values for heterogeneity by study (sex) for top vs bottom quintiles were significant.

With regard to intake of supplemental vitamin A, the median of the daily dose for the highest quintiles was 8125 IU/d for women and 11 754 IU/d for men. A higher intake of vitamin A from supplements was not significantly associated with a decreased risk of SCC (pooled HR for the highest quintile, 0.94; 95% CI, 0.85-1.03; *P* = .07 for trend).

Stratified analyses by risk factors of SCC, including annual UV flux, childhood reaction to sun, number of moles, numbers of severe sunburns, family history of melanoma, and natural hair color, revealed consistent inverse associations between total vitamin A intake and SCC (**Table 4**). The associations appeared to be more apparent among those with higher annual UV flux at residence, those who had a higher sunburn susceptibility, those with no family history of melanoma, and those with arm moles. Similar stratified analyses of retinol and carotenoid intake found a generally similar pattern of associations. Baseline intake of vitamin A was also similarly inversely associated with SCC (pooled HR for the highest quintile, 0.83; 95% CI, 0.75-0.93; *P* = .54). Most recent vitamin A intake was not significantly associated with SCC (pooled HR for the highest quintile, 0.91; 95% CI, 0.82-1.01; *P* = .71).

In an analysis by body site of SCC (higher vs lower sun exposure sites), there was a significant inverse association between total vitamin A intake and SCC risk at body sites with higher sun exposure (pooled HR for the highest quintile, 0.83; 95% CI, 0.74-0.93) (eTable 3 in the Supplement). Finally, in a

sensitivity analysis excluding those who did not undergo a physical examination, no substantial differences in associations were found (eTable 4 in the Supplement).

Discussion

In this large prospective study of US women and men, we found that higher intake of total vitamin A, retinol, and several individual carotenoids, including beta cryptoxanthin, lycopene, and lutein and zeaxanthin, was associated with lower risk of SCC. The results were generally consistent between men and women. The inverse associations appeared to be more prominent among those with moles and those with burn or blistering sunburn reaction as children or adolescents.

The populations were well nourished with vitamin A. The US Recommended Dietary Allowance (RDA) of vitamin A is 3000 IU in the form of retinol for adult men and 2331 IU for adult women.[37] The medians of the lowest quintiles of total vitamin A intake were higher than the RDA, and those of the highest quintiles were several times higher than the RDA in each cohort. Large proportions of vitamin A were contributed by food, especially carotenoids (vegetable sources).

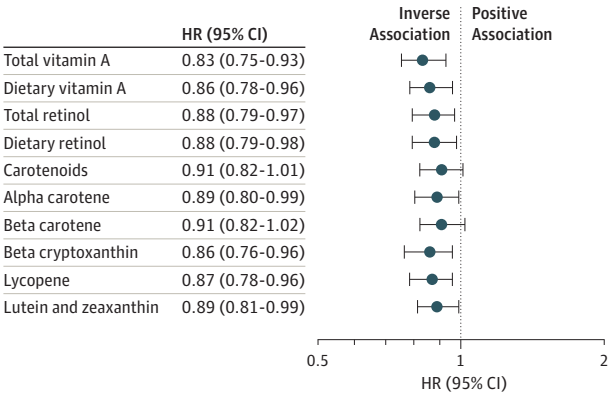
The potential mechanisms underlying the association of vitamin A with the development of cutaneous SCC are well supported by experimental studies.[9,10,38] Retinoids are essential for the maintenance of epithelial differentiation[9,10] and decrease cellular proliferation, enhance normal differentiation of cells, and reduce the formation of a tumor mass of undifferentiated cells.[38]

However, only 1 epidemiologic study,[22] to our knowledge, has examined the associations between vitamin A intake and SCC risk. Examination of that association in the NHS and HPFS with a follow-up 14 years or more (611 of SCC cases) reported nonsignificant inverse associations between intake of retinol and some carotenoids and risk of SCC (comparing the highest with the lowest quintile: relative risk [RR], 0.85 [95% CI, 0.67-1.09] for retinol; RR, 0.92 [95% CI, 0.72-1.19] for alpha carotene; and RR, 0.98 [95% CI, 0.72-1.33] for lutein and zeaxanthin).[22] On the basis of an additional 16 years of follow-up and a larger number of SCC cases (n = 3978), we found significant inverse associations based on trend between SCC and these nutrients. Regarding serum levels of vitamin A, no significant associations were found between levels of beta carotene and retinol and the risk of subsequent SCC in 2 studies.[39,40]

There have been some clinical trials of synthetic retinoids, which have a higher potency than dietary vitamin A. A small randomized clinical trial (n = 70) among individuals with a history of skin cancer found no effect of oral retinol supplementation (25 mg per day of acitretin for 2 years) on NMSC risk.[41] Conversely, in a secondary prevention trial with 25 000 IU/d of retinol supplementation for 5 years among patients with multiple actinic keratosis and NMSC (n = 2297), the risk of first new diagnosis of SCC (n = 249) was reduced (HR, 0.74; 95% CI, 0.56-0.99; P = .04).[16] Two other small trials[19,20] among renal transplant recipients, a high-risk population for SCC development, found that acitretin reduced the risk of SCC. However, adverse effects of systemic acitretin were reported.[19,20] On the basis of these findings, synthetic retinoids are used in chemoprevention of SCC in high-risk patients and are not recommended for the general population.[9,21,42] With respect to topical retinoids, the Veterans Affairs Topical Tretinoin Chemoprevention Trial in high-risk patients found that high-dose topical tretinoin was ineffective at reducing the risk of NMSC.[43]

With respect to carotenoids, some (including alpha carotene, beta carotene, and beta cryptoxanthin) can convert to retinol and contribute to the effect of vitamin A on the skin.[44] Carotenoids might also help prevent SCC by acting as antioxidants to block UV-induced free radicals from damaging the skin.[45] Among carotenoids, the association between beta carotene and SCC has been studied most extensively.[23] A meta-analysis of randomized clinical trials reported no association of beta carotene supplementation with the incidence of SCC (RR, 0.99; 95% CI, 0.86-1.14).[46] In our study, beta carotene intake was also not associated with reduced SCC risk. Few studies have examined the associations between the intake of other individual carotenoids besides beta carotene and SCC risk. A previous evaluation[22] of these carotenoids and SCC in the NHS and HPFS found no significant association. With extended follow-up, we found an inverse association between intakes of beta cryptoxanthin, lycopene, and lutein and zeaxanthin and

Figure. Forest Plot of Pooled Multivariable Hazard Ratios (HRs) and 95% CIs of Squamous Cell Carcinoma by Energy-Adjusted Vitamin A and Carotenoid Intake (Quintile 5 vs Quintile 1) in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)



The multivariate model was adjusted for age (continuous, years); family history of melanoma; natural hair color (red, blonde, light brown, dark brown, or black); number of arm moles (0,1-2, 3-5, or ≥6); sunburn susceptibility as a child or adolescent (no experience, no reaction or some redness, burn, or painful burn or blisters); number of lifetime blistering sunburns (0, 1-2, 3-5, or ≥6); cumulative UV flux since baseline quintiles; body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35 [calculated as weight in kilograms divided by height in meters squared]); physical activity (quintiles); smoking status (never, past with <10, 10-19, 20-39, ≥40, or unknown pack-years, current); personal history of basal cell carcinoma, melanoma, or nonskin cancer (yes vs no); total energy intake (quintiles); and intakes of total energy, alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-19.9, ≥20.0 g per day), and caffeine (quintiles). Among women, analyses were additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (no vs current). Pooled HRs of cohort-specific results were calculated using a random-effects model. Error bars indicate 95% CIs.

Table 4. Pooled Multivariable-Adjusted HRs (95% CIs) of Squamous Cell Carcinoma by Energy-Adjusted Total Vitamin A Intake Stratified by Squamous Cell Carcinoma Risk Factors in the Nurses' Health Study and Health Professionals Follow-up Study[a]

Componant	No.	HR (95% CI) Quintile of Total Vitamin A Intake					*P* Value for Trend
		1	2	3	4	5	
Annual UV flux							
Below median value	1777	1 [Reference]	1.05 (0.75-1.47)	1.02 (0.83-1.26)	0.99 (0.84-1.16)	0.89 (0.76-1.05)	.053
Above median value	2118	1 [Reference]	0.91 (0.79-1.05)	0.93 (0.77-1.12)	0.88 (0.77-1.02)	0.79 (0.69-0.92)	.001
Childhood reaction to sun							
None or redness only	1388	1 [Reference]	0.96 (0.80-1.15)	0.94 (0.75-1.17)	0.96 (0.80-1.14)	0.93 (0.78-1.11)	.40
Burn or blistered (n = 2318)	2318	1 [Reference]	1.00 (0.87-1.14)	0.99 (0.87-1.13)	0.95 (0.83-1.09)	0.80 (0.69-0.92)	<.001
Moles (>3 mm) on arms							
No	1264	1 [Reference]	0.86 (0.67-1.09)	0.91 (0.74-1.13)	0.79 (0.66-0.96)	0.91 (0.75-1.10)	.57
Yes	2053	1 [Reference]	1.00 (0.87-1.15)	0.94 (0.80-1.10)	0.96 (0.83-1.11)	0.77 (0.66-0.89)	<.001
No. of severe sunburns							
≤5	934	1 [Reference]	0.88 (0.71-1.09)	0.92 (0.64-1.31)	0.95 (0.76-1.18)	0.87 (0.71-1.09)	.31
>5	2622	1 [Reference]	1.02 (0.90-1.16)	0.98 (0.86-1.12)	0.95 (0.84-1.09)	0.86 (0.75-0.98)	.002
Family history of melanoma							
No	3582	1 [Reference]	0.96 (0.86-1.07)	0.98 (0.79-1.22)	0.90 (0.80-1.02)	0.82 (0.73-0.92)	<.001
Yes	396	1 [Reference]	1.04 (0.73-1.49)	0.85 (0.59-1.22)	1.23 (0.88-1.72)	0.92 (0.48-1.76)	.92
Natural hair color							
Dark brown or black	1530	1 [Reference]	0.98 (0.82-1.16)	1.00 (0.85-1.18)	1.05 (0.85-1.29)	0.88 (0.73-1.04)	.13
Red, blonde, or light brown	2074	1 [Reference]	1.02 (0.85-1.22)	0.95 (0.77-1.17)	0.92 (0.73-1.17)	0.86 (0.74-1.00)	.007

Abbreviation: HR, hazard ratio.

[a] Multivariate model was adjusted for age (continuous, years); family history of melanoma; natural hair color (red, blonde, light brown, dark brown, or black); number of arm moles (0,1-2, 3-5, or ≥6); sunburn susceptibility as a child or adolescent (no experience, no reaction or some redness, burn, or painful burn or blisters); number of lifetime blistering sunburns (0, 1-2, 3-5, or ≥6); cumulative UV flux since baseline quintiles); body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35 [calculated as weight in kilograms divided by height in meters squared]); physical activity (quintiles); smoking status (never, past with <10, 10-19, 20-39, ≥40, or unknown pack-years, current); personal history of basal cell carcinoma, melanoma, or nonskin cancer (yes vs no); total energy intake (quintiles); and intakes of total energy, alcohol (0, 0.1-4.9, 5.0-9.9, 10.0-19.9, ≥20.0 g per day), and caffeine (quintiles.) Among women analyses were additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (no vs current). Pooled hazards ratios of cohort-specific results were calculated using a random-effects model.

SCC risk. Another study[23] evaluating serum α-carotene, beta carotene, and lycopene levels and SCC found no association.

Because synthetic retinoids used in chemoprevention of SCC in high-risk populations have adverse effects,[19,20] dietary vitamin A could be explored as an alternative prevention strategy in the high-risk and general populations. However, individuals at a high risk of skin cancer may be more likely to develop subsequent skin cancers at faster rates. Whether dietary vitamin A would still be effective in this case needs to be explored because our data were not based on high-risk populations. Future studies are needed to determine whether vitamin A supplementation has a role in chemoprevention of SCC. Future studies should also consider vitamin A with nicotinamide, another nutrient identified to be effective in chemoprevention of SCC in a phase 3 clinical trial,[47,48] as natural chemopreventive agents. In the trial of participants with a history of NMSC, nicotinamide supplementation reduced the rate of new SCC by 30%. In our observational study, higher vitamin A intake was associated with a 17% reduction in SCC risk. Whether nicotinamide works with vitamin A in cell differentiation in carcinogenesis remains unclear. An experimental study[49] found that nicotinamide modulated the effect of vitamin A on the expression of cell surface antigens, as well as functional differentiation markers and cell cycle arrest of human myeloblastic leukemia cells. Finally, although high vitamin A intake may be effective in chemoprevention of skin cancer, high intake of vitamin A, especially the preformed vitamin A (from animal foods, fortified foods, and dietary supplements), may have some adverse health effects, such as potentially increased risk of osteoporosis and hip fracture.[50] More research is needed to understand the appropriate level of vitamin A intake for maximum health benefits. Therefore, risks and benefits of high vitamin A intake should be considered individually.

Strengths and Limitations

Strengths of this study include its prospective design and use of histologically confirmed SCC. The cohorts also offered a large sample size, repeated dietary data, and extensive information on skin cancer-related factors. Limitations of our study include the homogeneity of the study population, mostly well-educated, white health care professionals. Such lack of diversity in demographics may limit the generalizability of our findings. However, the variation of vitamin A intake was good. In addition, skin cancer is not common in nonwhite individuals. Although we controlled for major factors associated with SCC risk, we could not rule out residual confounding. For example, exposure to UV radiation, a primary risk factor for SCC, is difficult to measure accurately. Dietary assessment with the FFQ could introduce some misclassification of vitamin A intake. However, multiple dietary

assessments were used to reduce measurement error. Furthermore, given that individuals with higher vitamin A intake tended to have healthier behaviors, including higher physical activity levels and lower prevalences of smoking and alcohol intake, than those with lower intake, they might also adopt better sun protective behaviors, such as use of sun protective clothing or sunscreen or avoidance of midday sun, which we did not measure.

Conclusions

We found an inverse association between intake of vitamin A and carotenoids and risk of cutaneous SCC, supporting the protective role of vitamin A against SCC development. Our data further support the contention that supplemental and dietary vitamin A may be beneficial in preventing SCC.

ARTICLE INFORMATION

Accepted for Publication: April 22, 2019.

Published Online: July 31, 2019. doi:10.1001/jamadermatol.2019.1937

Author Contributions: Dr Cho had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Park, Qureshi, Cho.
Acquisition, analysis, or interpretation of data: Kim, Park, Li, Cho.
Drafting of the manuscript: Kim, Park.
Critical revision of the manuscript for important intellectual content: Park, Li, Qureshi, Cho.
Statistical analysis: Kim, Park.
Obtained funding: Cho.
Administrative, technical, or material support: Park, Li, Qureshi, Cho.
Supervision: Qureshi, Cho.

Conflict of Interest Disclosures: Dr Qureshi reported serving as a consultant for AbbVie, Amgen, the Centers for Disease Control and Prevention, Janssen, Merck, Novartis, and Pfizer and as a compensated investigator for Amgen, Regeneron, and Sanofi. No other disclosures were reported.

Funding/Support: This study was supported by grants CA186107, CA87969, CA167552, and CA198216 from the National Institutes of Health and a grant from Research Year of Inje University (South Korea) in 2016-2017. Dr Li is supported by a Research Career Development Award from the Dermatology Foundation.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Additional Contributions: We thank the participants and staff of the Nurses' Health Study and Health Professionals Follow-up Study for their valuable contributions as well as the state cancer registries from the following states for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

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