

## Supplementary Online Content

Kim J, Park MK, Li W-Q, Qureshi AA, Cho E. Association of vitamin A intake with cutaneous squamous cell carcinoma risk in the United States. *JAMA Dermatol*. Published online July 31, 2019. doi:10.1001/jamadermatol.2019.1937

**eTable 1.** Baseline characteristics of study participants according to availability of dietary information in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

**eTable 2.** Hazard ratios (HRs; and 95% confidence intervals [CIs]) of SCC by energy-adjusted vitamin A and carotenoid intake in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

**eTable 3.** Pooled multivariable-adjusted hazard ratios (and 95% confidence intervals) of SCC by intake of total vitamin A, total retinol, and carotenoids according to body site of SCC, based on sun exposure in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS)

**eTable 4.** Pooled multivariable hazard ratios (HRs) and 95% confidence intervals [CIs] of SCC using energy-adjusted vitamin A and carotenoid intake excluding those with no physical examination during follow-up in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1.** Baseline characteristics of study participants according to availability of dietary information in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

	Availability of dietary information	
	No Diet	Diet
<b>NHS (women, 1984)</b>		
Number of participants	14,088	75,170
Age (year) <sup>a</sup>	51.0 (7.2)	50.4 (7.2)
Family history of melanoma, %	1.9	2.6
Red/blonde hair, %	16.0	15.8
Painful burn/blisters reaction as a child/adolescent, %	24.5	34.4
Number of blistering sunburns, % of 6+	8.4	7.3
Annual UV flux at residence (x10 <sup>-4</sup> RB count)	188.4 (28.7)	189.0 (29.4)
Number of moles (> 3mm) on arms, % of 6+	4.9	4.6
Body mass index (kg/m <sup>2</sup> )	25.4 (4.9)	25.0 (4.8)
Physical activity level (MET hrs/wk)	14.0 (21.8)	14.1 (20.9)
Smoking, %	27.4	24.4
Postmenopausal status, %	55.7	58.6
Postmenopausal hormones use in postmenopausal women, % <sup>b</sup>	23.6	23.5
<b>HPFS (men, 1986)</b>		
Number of participants	1514	48400
Age (year) <sup>a</sup>	57.0 (10.4)	54.3 (9.9)
Family history of melanoma, %	4.2	3.1
Red/blonde hair, %	14.0	13.9
Painful burn/blisters reaction as a child/adolescent, %	47.9	54.8

Number of blistering sunburns, % of 6+	13.0	13.7
Annual UV flux at residence ( $\times 10^{-4}$ RB count)	192.4 (29.1)	191.8 (27.7)
Number of moles (> 3mm) on arms, % of 6+	5.7	5.4
Body mass index (kg/m <sup>2</sup> )	25.3 (5.6)	24.9 (5.1)
Physical activity level (MET hrs/wk)	22.6 (38.5)	20.9 (29.4)
Smoking, %	9.7	10.0

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

<sup>a</sup>Values are not age-adjusted.

<sup>b</sup>Percentages among postmenopausal women

**eTable 2.** Hazard ratios (HRs; and 95% confidence intervals [CIs]) of SCC by energy-adjusted vitamin A and carotenoid intake in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

	Quintile of intake					P for trend
	Q1	Q2	Q3	Q4	Q5	
<b>Total vitamin A</b>						
<b>NHS</b>						
Median intake, IU/d	6808	9846	12409	15560	21691	
No. of cases/No. of person-years	396/368234	425/369333	437/369348	482/369323	482/368881	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	0.93 (0.81, 1.07)	0.88 (0.77, 1.02)	0.91 (0.79, 1.04)	0.86 (0.75, 0.99)	0.04
<b>HPFS</b>						
Median intake, IU/d	7236	10590	13792	17896	26539	
No. of cases/No. of person-years	298/203564	358/204020	402/203840	384/203660	314/203121	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.02 (0.87, 1.19)	1.07 (0.92, 1.25)	0.97 (0.83, 1.13)	0.80 (0.68, 0.94)	0.0009
<b>Dietary vitamin A</b>						
<b>NHS</b>						
Median intake, IU/d	5821	8104	10005	12333	16764	
No. of cases/No. of person-years	384/368440	444/369166	451/369285	483/369412	460/368816	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.02 (0.89, 1.17)	0.97 (0.85, 1.12)	0.98 (0.86, 1.13)	0.89 (0.77, 1.02)	0.04
<b>HPFS</b>						
Median intake, IU/d	6268	8710	10894	13704	19250	
No. of cases/No. of person-years	300/203762	385/204043	369/204056	395/203616	307/202728	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.13 (0.97, 1.31)	1.03 (0.88, 1.20)	1.06 (0.91, 1.24)	0.83 (0.71, 0.98)	0.003
<b>Total retinol</b>						
<b>NHS</b>						
Median intake, IU/d	1143	2202	3293	4750	7894	
No. of cases/No. of person-years	425/368619	462/369727	477/369608	401/369475	457/367691	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.02 (0.90, 1.17)	1.02 (0.89, 1.16)	0.81 (0.71, 0.93)	0.89 (0.78, 1.02)	0.004
<b>HPFS</b>						
Median intake, IU/d	1240	2300	3611	5667	10163	
No. of cases/No. of person-years	319/203647	359/203960	365/204298	385/203824	328/202475	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	0.99 (0.85, 1.15)	0.95 (0.82, 1.10)	0.97 (0.83, 1.12)	0.86 (0.74, 1.01)	0.05

<b>Dietary retinol</b>						
<b>NHS</b>						
Median intake, IU/d	833	1273	1718	2300	3424	
No. of cases/No. of person-years	463/369144	442/369757	476/369722	447/369449	394/367047	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	0.92 (0.81, 1.05)	0.96 (0.84, 1.09)	0.91 (0.80, 1.04)	0.85 (0.74, 0.98)	0.046
<b>HPFS</b>						
Median intake, IU/d	914	1451	1956	2631	4241	
No. of cases/No. of person-years	314/204457	383/204402	389/203854	371/203380	299/202111	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.14 (0.98, 1.33)	1.14 (0.98, 1.32)	1.05 (0.90, 1.23)	0.92 (0.79, 1.08)	0.08
<b>Carotenoids</b>						
<b>NHS</b>						
Median intake, IU/d	4330	6503	8429	10916	15749	
No. of cases/No. of person-years	364/367910	428/368876	471/369420	476/369432	483/369480	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.02 (0.88, 1.17)	1.04 (0.90, 1.19)	0.99 (0.86, 1.14)	0.94 (0.82, 1.08)	0.21
<b>HPFS</b>						
Median intake, IU/d	4493	6886	9199	12415	18981	
No. of cases/No. of person-years	276/203026	383/203768	398/204033	386/203861	313/203518	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.20 (1.03, 1.40)	1.16 (0.99, 1.36)	1.08 (0.92, 1.26)	0.87 (0.74, 1.03)	0.002
<b>Alpha-carotene</b>						
<b>NHS</b>						
Median intake, µg/d	301	484	656	908	1425	
No. of cases/No. of person-years	403/368183	421/369215	468/369383	479/369574	451/368764	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	0.95 (0.83, 1.09)	1.00 (0.87, 1.14)	0.98 (0.85, 1.12)	0.88 (0.76, 1.01)	0.045
<b>HPFS</b>						
Median intake, µg/d	322	523	721	1047	1727	
No. of cases/No. of person-years	290/203034	367/203770	388/204282	391/204124	320/202994	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.16 (0.99, 1.35)	1.14 (0.97, 1.32)	1.09 (0.93, 1.27)	0.91 (0.77, 1.07)	0.03
<b>Beta-carotene</b>						
<b>NHS</b>						
Median intake, µg/d	2112	3142	4042	5194	7443	
No. of cases/No. of person-years	370/367810	431/368800	432/369269	488/369601	501/369639	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.00 (0.87, 1.15)	0.92 (0.80, 1.06)	0.96 (0.84, 1.10)	0.92 (0.80, 1.06)	0.25
<b>HPFS</b>						

Median intake, µg/d	2259	3458	4580	6066	9195	
No. of cases/No. of person-years	271/203002	387/203766	380/203949	399/203742	319/203746	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.23 (1.05, 1.43)	1.13 (0.96, 1.32)	1.13 (0.97, 1.33)	0.90 (0.76, 1.06)	0.009
<b>Beta-cryptoxanthin</b>						
<b>NHS</b>						
Median intake, µg/d	75	123	167	215	296	
No. of cases/No. of person-years	419/368936	426/369475	457/369692	462/369069	458/367947	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	0.95 (0.83, 1.09)	0.97 (0.85, 1.11)	0.94 (0.82, 1.07)	0.90 (0.78, 1.03)	0.15
<b>HPFS</b>						
Median intake, µg/d	77	135	189	249	357	
No. of cases/No. of person-years	313/203680	364/204165	406/203745	379/203643	294/202973	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.04 (0.89, 1.21)	1.11 (0.96, 1.29)	1.00 (0.86, 1.17)	0.80 (0.68, 0.94)	0.002
<b>Lycopene</b>						
<b>NHS</b>						
Median intake, µg/d	3309	4699	5851	7286	10133	
No. of cases/No. of person-years	494/367868	491/369139	447/369602	406/369546	384/368965	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.03 (0.91, 1.17)	0.96 (0.84, 1.09)	0.89 (0.78, 1.02)	0.87 (0.76, 0.99)	0.008
<b>HPFS</b>						
Median intake, µg/d	3242	5079	6650	8700	12882	
No. of cases/No. of person-years	406/201692	389/203717	347/204059	311/204550	303/204186	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	0.97 (0.84, 1.11)	0.89 (0.77, 1.03)	0.84 (0.72, 0.98)	0.87 (0.75, 1.01)	0.03
<b>Lutein &amp; zeaxanthin</b>						
<b>NHS</b>						
Median intake, µg/d	1333	2024	2614	3325	4787	
No. of cases/No. of person-years	391/368231	421/369020	451/369204	487/369515	472/369148	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	0.93 (0.81, 1.07)	0.94 (0.82, 1.07)	0.96 (0.83, 1.10)	0.90 (0.78, 1.03)	0.19
<b>HPFS</b>						
Median intake, µg/d	1435	2244	2949	3817	5620	
No. of cases/No. of person-years	315/203182	360/203736	392/203806	371/203959	318/203522	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.03 (0.89, 1.20)	1.07 (0.92, 1.25)	1.02 (0.87, 1.18)	0.89 (0.76, 1.04)	0.06

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/adolescent (no experience, no reaction/some redness, burn, or painful burn/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 kg/m<sup>2</sup>), 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 non-skin 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/d), and caffeine intake (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.

**eTable 3.** Pooled multivariable-adjusted hazard ratios<sup>a</sup> (and 95% confidence intervals) of SCC by intake of total vitamin A, total retinol, and carotenoids according to body site of SCC, based on sun exposure in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS)

	Quintile of intake					P trend
	Q1	Q2	Q3	Q4	Q5	
<b>Total vitamin A</b>						
<b>Higher exposure sites<sup>b</sup> (n=3469)</b>	1 (referent)	0.93 (0.78, 1.10)	0.94 (0.79, 1.12)	0.90 (0.80, 1.01)	0.83 (0.74, 0.93)	0.002
<b>Lower exposure sites<sup>b</sup> (n=547)</b>	1 (referent)	1.11 (0.84, 1.48)	0.93 (0.70, 1.25)	1.11 (0.83, 1.47)	0.82 (0.61, 1.11)	0.1
<b>Total retinol</b>						
<b>Higher exposure sites<sup>b</sup> (n=3469)</b>	1 (referent)	1.01 (0.90, 1.13)	0.99 (0.89, 1.10)	0.86 (0.69, 1.08)	0.86 (0.77, 0.96)	0.0003
<b>Lower exposure sites<sup>b</sup> (n=547)</b>	1 (referent)	0.99 (0.75, 1.31)	0.90 (0.68, 1.19)	0.90 (0.68, 1.19)	0.95 (0.72, 1.25)	0.56
<b>Carotenoids</b>						
<b>Higher exposure sites<sup>b</sup> (n=3469)</b>	1 (referent)	1.11 (0.92, 1.34)	1.10 (0.96, 1.27)	1.04 (0.92, 1.16)	0.93 (0.83, 1.05)	0.02
<b>Lower exposure sites<sup>b</sup> (n=547)</b>	1 (referent)	1.20 (0.90, 1.60)	1.10 (0.82, 1.48)	1.04 (0.77, 1.40)	0.92 (0.56, 1.50)	0.32

<sup>a</sup>Multivariate model was adjusted for age (continuous, years), 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, body mass index, physical activity, smoking status, incident SCC, incident BCC, personal history of non-skin cancer, intakes of total energy, alcohol, and caffeine. Among women analyses were additionally adjusted for menopausal status and postmenopausal hormone use. Pooled HRs of cohort-specific results were calculated using a random-effects model.

<sup>b</sup> Higher exposure sites included scalp, forehead, cheeks, nose, face, ears, neck, upper arm, elbow, forearm, hand, finger, lower leg, ankle, and foot. Lower exposure sites included trunk, shoulder, hip, upper and lower back, abdomen, thigh, and buttock.



**eTable 4.** Pooled multivariable hazard ratios<sup>a</sup> (HRs) and 95% confidence intervals [CIs] of SCC using energy-adjusted vitamin A and carotenoid intake excluding those with no physical examination during follow-up in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

	Quintile of intake					P for trend
	Q1	Q2	Q3	Q4	Q5	
<b>Total vitamin A</b>						
HR (95% CI)	1.00 (referent)	0.97 (0.88, 1.08)	0.98 (0.80, 1.19)	0.93 (0.84, 1.03)	0.84 (0.76, 0.93)	0.0001
<b>Total retinol</b>						
HR (95% CI)	1.00 (referent)	0.99 (0.90, 1.10)	0.98 (0.89, 1.08)	0.88 (0.76, 1.03)	0.88 (0.79, 0.97)	0.002
<b>Carotenoids</b>						
HR (95% CI)	1.00 (referent)	1.11 (0.90, 1.36)	1.08 (0.97, 1.20)	1.03 (0.93, 1.15)	0.91 (0.81, 1.01)	0.03

<sup>a</sup>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  $\geq 6$ ), sunburn susceptibility as a child/adolescent (no experience, no reaction/some redness, burn, or painful burn/blisters), number of lifetime blistering sunburns (0, 1-2, 3-5, or  $\geq 6$ ), cumulative UV flux since baseline quintiles), body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9,  $\geq 35$  kg/m<sup>2</sup>), physical activity (quintiles), smoking status (never, past with <10, 10-19, 20-39,  $\geq 40$ , or unknown pack-years, current), personal history of basal cell carcinoma, melanoma, or non-skin 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,  $\geq 20.0$  g/d), and caffeine intake (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.