Prospective study evaluating personal history of rosacea and risk of cutaneous squamous cell carcinoma among women in the US

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Keywords

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Inflammation and ultraviolet (UV) exposure play important roles in cutaneous squamous cell carcinoma (cSCC) development and rosacea.[1–3] We evaluated the relationship between personal history of rosacea with risks of cSCC by body site in the Nurses' Health Study II (NHSII), focusing on the head and neck region given rosacea's primary presentation in the central face.

Study participants completed biennial questionnaires that gathered medical history, including clinician-diagnosed cSCC and rosacea. Our study consisted of 90,249 white participants with no skin cancer history at baseline followed for 20 years (1991–2011) (MendeleySupplement1). Cox proportional hazard models were applied to estimate associations between history of rosacea and cSCC risk. Multivariate models were adjusted for age and other skin cancer risk factors.

During the follow-up, 577 cSCC cases were documented and confirmed by pathology reports. Baseline characteristics of study participants according to history of rosacea are

described in Table 1. Rosacea was associated with statistically significant increased cSCC risk; relative risks (RR) and 95% confidence intervals were 1.40 (1.02, 1.93) (Table 2). When cSCCs were grouped by head and neck (HN) vs. non-head and neck (non-HN) sites, there was a significantly increased risk of HN cSCC (RR= 1.71[1.09, 2.69]), but no significant associations with non-HN cSCC (RR=1.21[0.78, 1.90]; p for difference=0.29). When comparing face versus non-face HN cSCCs, rosacea was associated with an increased non-face HN cSCC risk, but not with face HN cSCC (p for difference=0.32). Associations did not differ by sunscreen usage and UV exposure (MendeleySupplementaryTable1). cSCC in regions of typical rosacea outbreaks (forehead/nose/cheeks/periocular/chin) in patients with no rosacea history comprised 72.8% of total HN cSCC versus 75.0% in those with rosacea history.

This was the first study evaluating associations between rosacea history and cSCC body site. The innate immune system has a role in rosacea pathogenesis. One important player is cathelicidin peptides, which have modified functions in rosacea, including modulating leukocyte chemotaxis and angiogenesis, in contrast to their typical antibiotic function in healthy skin. LL-37, a common cathelicidin in rosacea, is also upregulated in cSCC.[4,5] Rosacea's inflammatory nature may also play a part as inflammation has a significant role in cSCC development.[3] Inflammation may lead to immunologic and neurovascular changes in the region that promote cSCC development. Meanwhile, patients with rosacea are advised to decrease sun exposure and many common topical rosacea treatments have anti-inflammatory effects.[1] Study strengths include its prospective design, long follow-up time, ability to control for several skin cancer risk factors, and accurate ascertainment of cSCCs and tumor location. Limitations include an exclusively white female health professional cohort and lack of skin phenotype, rosacea severity and subtype, and tumor staging information. Certain datapoints (e.g.sunscreen use) were only assessed once. Questionnaires included self-reported information and there may be unaccounted confounders. Number of participants with rosacea and cSCC were also small in body site analyses, limiting statistical power to detect differences of associations by body site.

These findings may support head and neck cSCC screening in rosacea patients. Further studies are warranted to confirm these associations and to determine underlying mechanisms.

Acknowledgements:

Abbreviation and acronym list:

CI	Confidence interval
cSCC	Cutaneous squamous cell carcinoma
HN	Head and neck
NHSII	Nurses' Health Study II
Non-HN	Non-head and neck
RI	Rhode Island
RR	Relative risks
UV	Ultraviolet

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Table 1.

Age-standardized baseline characteristics of study participants according to history of rosacea in the Nurses'
Health Study II, 1991

Characteristics [a]	Rosacea	
	No	Yes
No. of participants	89,163	1,086
Age, mean (SD), y [b]	36.1 (4.7)	37.6 (4.1)
Family history of melanoma, %	4.4	5.2
Current smoker, %	11.9	9.2
Past smoker, %	22.7	26.5
Pack years, for ever smokers	11.8 (8.6)	10.4 (7.8)
Alcohol intake, mean (SD), g/d	3.2 (6.1)	2.9 (5.3)
Body mass index, mean (SD), kg/m^2	24.6 (5.3)	25.0 (5.9)
Physical activity, metabolic equivalent hours per week (SD)	20.7 (26.5)	18.8 (22.5)
Annual erythemal UV exposure at residence, mean (SD), mW/m^2	185.6 (23.6)	184.4 (23.3)
Hair color, %		
Light brown	30.4	33.5
Dark brown/black	39.9	36.7
Blonde	16.5	18.6
Red	3.9	4.2
Missing	9.3	7.0
Skin reaction to sun, %		
Burn reaction to the sun	24.1	25.3
Blistering burn reaction to the sun	24.0	30.2
Number of severe or blistering sunburns from ages 15–20, %		
None	32.8	30.3
1 – 2	39.7	35.5
3 – 4	17.2	19.8
5 +	10.0	13.6
Missing	0.3	0.8
Number of moles on the legs (>3 mm), %		
None	45.7	43.2
1 – 2	18.8	18.5
3 – 4	10.2	10.9
5 +	21.8	24.1
Missing	3.5	3.3
Physical exam, %	89.6	93.1
Use of sunscreen during the past summer [**], %		
0% to 50% of time	31.8	27.7

Characteristics [a]	Rosacea	
	No	Yes
75% of time	28.2	30.3
100% of time	20.6	26.7
Missing	19.4	15.3

[**] Value is from 1993

[a] Data are presented as means (SD) or medians (Q25, Q75) for continuous variables, by percentage for categorical variables, and are standardized to the age distribution of the study population, unless otherwise indicated.

[b] Values are not age adjusted.

Table 2.

Relative risks (95% CIs) of cutaneous squamous cell carcinoma (cSCC) in relation to history of rosacea in the Nurses' Health Study II

	Number Of cSCC (Rosacea/No Rosacea)	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)[a]
Overall	42/535	1.52 (1.10,2.08)	1.40 (1.02,1.93)
By location [b]			
Non-head and neck	21/291	1.32 (0.85–2.06)	1.21 (0.78–1.90)
Head and neck	21/240	1.81 (1.15–2.84)	1.71 (1.09–2.69)[c]
Face	15/184	1.71 (1.01–2.91)	1.61 (0.94–2.74)
Head and neck, not face	6/44	2.69 (1.14–6.37)	2.71 (1.13–6.46)[d]

[a] Multivariate models were adjusted for age (continuous), family history of melanoma, smoking status (never; past with <10, 10–20, 20–40, >40, or unknown pack-years; current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, 20.0 g/day), body mass index (<18.5, 18.5–24.9, 25–29.9, 30–34.9, 35, kg/cm^2), quintiles of UV exposure at residence, history of severe or blistering sunburns (0, 1–2, 3–5, or 6), number of moles on the extremity (0,1–2, 3–4, or 5), skin reaction to sun exposure (not burn or blister, burn, blister), natural hair color (red/blonde, light brown, dark brown, or black), annual physical exam(yes or no) and sunscreen use during past summer (0–50%, 75% and 100%)

[b] There was missing data that did not allow for precise determination of face vs. non-face location for all cSCC.

[c] $p = 0.29$ for head and neck vs. non-head and neck SCC

[d] $p = 0.32$ for face vs. head and neck, not face SCC