Published in final edited form as:

Dermatol Surg. 2015 April ; 41(4): 481–486. doi:10.1097/DSS.0000000000000292.

Family History of Skin Cancer Is Associated With Increased Risk of Cutaneous Squamous Cell Carcinoma

Maryam M. Asgari, MD, MPH^{*,†}, E. Margaret Warton, MPH^{*}, and Alice S. Whittemore, PhD[‡]

^{*}Division of Research, Kaiser Permanente Northern California, Oakland, California

[†]Department of Dermatology, University of California, San Francisco, California

[‡]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California

Abstract

BACKGROUND—The contribution of family history to cutaneous squamous cell carcinoma (SCC) risk has not been systematically quantified.

OBJECTIVE—To examine the association between self-reported family history of skin cancer and SCC risk.

METHODS AND MATERIALS—Cases ($n = 415$) with a pathology-verified SCC and 415 age-, gender-, and race-matched controls were identified within a large integrated health care delivery system. Family history and skin cancer risk factors were ascertained by survey. Odds ratios (ORs) for associations of SCC with family history of skin cancer were estimated using conditional logistic regression adjusted for environmental and innate SCC risk factors.

RESULTS—Any known family history of skin cancer was associated with a four-fold higher risk of SCC, adjusting for known environmental and innate SCC risk factors (OR, 4.0; confidence interval [CI]: 2.5–6.5). An unknown family history of skin cancer showed similar risk for SCC (OR, 3.9; CI: 2.4–6.5). In models including skin cancer type, the strongest association was for family history of basal cell carcinoma (OR, 9.8; CI: 2.6–36.8) and for multiple skin cancer types (OR, 10.5; CI: 3.7–29.6).

CONCLUSION—Family history of skin cancer is an important independent risk factor for cutaneous SCCs.

Cutaneous squamous cell carcinoma (SCC) is the second most common malignancy in the United States, afflicting approximately 700,000 Americans annually.¹ Squamous cell carcinomas tend to arise in fair-skinned individuals, and their risk is largely attributed to environmental risk factors, particularly sun-exposure.² There is also a genetic basis for SCC, as evidenced by an increased risk among first-degree relatives of SCC cases,^{3–7} and from hereditary syndromes that are associated with an increased risk of SCCs.⁸

Address correspondence and reprint requests to: Maryam M. Asgari, MD, MPH, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612, or: maryam.m.asgari@kp.org.

The authors have indicated no significant interest with commercial supporters.

The contribution of family history of skin cancer to overall SCC risk has not been systematically examined. Also, there is little known as to whether family history imparts risk because of a heritable propensity to develop skin cancer, innate factors such as pigmentation, or whether the increased risk is due to shared environmental exposures amongst family members such as sun-exposure and sun-protective behaviors. To address this knowledge gap, the authors used data from a case-control study to examine the association between family history of skin cancer and SCC risk adjusting for known environmental and innate SCC risk factors.

Materials and Methods

Study Population

Data were drawn from a case-control study designed to examine the association between nonsteroidal anti-inflammatory drug use and SCCs, as described previously.⁹ The study population consisted of a random sample of 415 adult Kaiser Permanente Northern California (KPNC) members (age, 43–85 years) with a pathology-confirmed SCC diagnosed in 2004 and 415 control subjects with no history of skin cancer matched to cases by year of birth, sex, and self-reported race. Each participant completed a self-administered questionnaire inquiring about demographics and skin cancer risk factors. The questionnaire was modeled on a previous self-administered questionnaire on supplement use and cancer risk,¹⁰ which has shown high test-retest reliability and validity in capturing supplement intake over the past 10 years.¹¹ This study was approved by the Kaiser Foundation Research Institute Institutional Review Board (CN-05MAsga-01-H, approved December 8, 2005) and was conducted according to the Declaration of Helsinki principles.

Family History of Skin Cancer

Subjects provided responses to the question “Have any of your natural parents, brothers, or sisters (not adopted, step, or half) had skin cancer?” (yes, no, not sure). Subjects with positive responses were asked to identify the type(s) of skin cancer, if known (SCC, basal cell carcinoma [BCC], melanoma, not sure).

Environmental Risk Factors for Squamous Cell Carcinoma

Subjects also answered questions concerning environmental factors known to influence SCC risk including history of severe lifetime sunburns, regular (at least once-a-week) peak-time sun-exposure (yes/no), occupational sun-exposure (yes/no), tanning bed use (yes/no), high-risk exposures, including ultraviolet light treatment, burn scar, nonhealing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no), and smoking (current vs former/never). Subjects reporting regular peak-time sun-exposure also reported the average number of hours of exposure per week and the use of sunscreen and sun-protective clothing (never/rarely vs much/ most of the time).

Innate Risk Factors for Squamous Cell Carcinoma

Subjects self-reported information on hair color (black/brown, light brown, red/blond), eye color (brown, green/hazel, blue/gray), and Fitzpatrick skin Type (I, II, III, IV+).

Statistical Analysis

The authors used conditional logistic regression analysis of matched case–control pairs to estimate odds ratios (ORs) and Wald 95% confidence intervals (CI) related to family history, adjusted for environmental and innate risk factors. All statistical analyses were performed using SAS, version 9.3, (SAS Institute Inc., Cary, NC).

Results

The average age of participants at index date was 72.5 ± 8.6 years, and the majority were male (61.9%). Regarding environmental risk factors for SCC, cases were more likely than controls to have had >2 sunburns, to have had routine peak sun-exposure, to use sunscreen only or sunscreen plus protective clothing when exposed to peak sun, to have had higher daily average hours of exposure, to have had high-risk exposures, and to be current smokers. Cases and controls were similar with respect to occupational sun-exposure and tanning bed use. Regarding innate risk factors for SCC, cases were more likely to have lighter hair and eye color and skin type (Table 1).

In unadjusted models examining family history of skin cancer, those with any known family history of skin cancer were at substantially increased risk of SCC (OR, 4.2; CI: 2.8–6.3, compared with those with no family history of skin cancer). Subjects reporting an unknown family history of skin cancer were at similarly increased risk of SCC compared with those with no family history of skin cancer (OR, 4.3; CI: 2.8–6.7).

In models adjusted for environmental risk factors (sunburns, peak sun, high-risk exposures, and smoking), the four-fold higher risk of SCC among those with a known and unknown family history of skin cancer (as compared with those with no history) persisted, with little change in the point estimate of risk (Figure 1). The point estimates did not change substantially in models that adjusted for both environmental and innate variables (eye color, hair color, and skin type). Further examination of the impact of familial history of skin cancer type (Figure 2) indicated that although there was increased risk with family history of SCC only (OR, adjusted 3.4; CI: 1.0–11.6) and melanoma only (OR, 5.6; CI: 1.6–19.7), the highest magnitude of risk was associated with family history of BCC (OR, 9.8; CI: 2.6–36.8) or multiple types of skin cancer (OR, 10.5; CI: 2.7–29.6). Examining interactions of hair color and skin type with family history yielded no significant findings.

Discussion

The authors report that family history of skin cancer is strongly associated with SCC risk, independent of known environmental and innate risk factors. Although SCC risk was strongest among individuals with a family history of BCC or multiple skin cancer types, their findings suggest that any self-report of positive family history of skin cancer, regardless of type, places individuals at a greater risk of SCC. Adjusting for environmental or innate SCC risk factors did not appreciably alter ORs. This finding further emphasizes the importance of family history of skin cancer, which has been noted by the US Preventative Services Task Force as an important risk factor in determining whether to screen adults for skin cancer.¹²

Numerous studies have suggested a heritable component to SCCs.^{3–7} A large Swedish registry-based population study reported that individuals with at least 1 relative affected with SCC had a 2- to 3-fold increased SCC risk relative to risk in the general population,³ but this study did not include data on known SCC risk factors. Previous case–control studies have also reported an increased risk of SCC with positive family history of skin cancer (ORs, 1.9–2.8).^{5–7} Although some of these studies employed multivariate models to adjust for known risk factors,^{6,7} no previous studies have examined the impact of types of familial skin cancer on SCC risk. Their findings suggest that compared with no history of skin cancer, both known family history and unknown family history were independently associated with increased SCC risk. In other words, people who are unaware of their family history are at similar risk to those who report a known family history of skin cancer when compared with those who do not have a history of skin cancer. It should be noted that the majority of their participants were aware of their family history ($n = 682$), whereas only 148 subjects (18% of subjects) were unaware of their family history of skin cancer. Regarding the subtype of skin cancer, there was increased risk with family history of SCC and melanoma, the highest magnitude of risk was associated with family history of BCC and multiple types of skin cancer.

Strengths of this study include a large sample size ($n = 830$) and thorough measurement of known innate and environmental SCC risk factors, such as skin type and sun-exposure history, through self-report. An additional strength is the KPNC setting that is a large integrated health care delivery system and allows comprehensive capture of all pathology specimens, thereby minimizing misclassification of case–control assignment.

There are some potential limitations to this study, including the possibility of recall bias, selection bias, unmeasured confounding variables, and limitations of generalizability. Recall bias is a potential problem for self-reported variables, and it is possible that cases were more likely than controls to recall relatives with skin cancer. Recall bias in subjective reports of familial cancer is a known phenomenon, as illustrated by twin studies in which 1 member of a pair of twins had suffered cancer that demonstrate differential recall of family history amongst cancer survivors.¹³ Interestingly, cases were not only more likely to report positive family history of skin cancer, but also to report unknown family history of skin cancer, suggesting that any recall bias may have manifested as cases recalling positive family history or being unsure about their family history. There may also be residual unmeasured confounding variables such as exposure to photosensitizing medications, which may be prescribed for certain conditions that cluster in families (e. g., Plaquenil treatment for autoimmune disorders), and thus may be associated with both family history and SCC risk. Alternatively, it may be that subjects who do not know their family history come from familial backgrounds that may have engaged in unmeasured environmental exposures, which may have led to increased exposure to SCC risk factors. However, their analysis took into account most known risk factors for SCC and the likelihood that an unmeasured confounding variable would explain the magnitude of the risk is small. The generalizability of their study may be limited because the authors only studied the KPNC members, although previous studies have shown that the KPNC membership is highly representative of the surrounding region except for the tail ends of the income distribution.¹⁴

In this case-control study, the authors show that family history is an important independent risk factor for cutaneous SCCs. Family history may represent a shared genetic propensity to develop SCC independent of genetic influences on skin pigmentation. Future studies, such as genome-wide association studies, may help identify genetic determinants of cutaneous SCCs. Clinicians should inquire about family history of skin cancer when ascertaining risk factors for skin cancer.

Acknowledgments

Supported by the National Cancer Institute of Arthritis Musculoskeletal and Skin Diseases (K23 AR 051037 to M.M.A.).

References

1. Skin Cancer Facts. Skin Cancer Foundation; Available from: <http://www.skincancer.org/Skin-Cancer-Facts/>. Accessed June 5, 2011.
2. Preston DS, Stern RS. Nonmelanoma cancers of the skin. *N Engl J Med*. 1992; 327:1649–62. [PubMed: 1435901]
3. Hussain SK, Sundquist J, Hemminki K. The effect of having an affected parent or sibling on invasive and in situ skin cancer risk in Sweden. *J Invest Dermatol*. 2009; 129:2142–7. [PubMed: 19242514]
4. Hemminki K, Zhang H, Czene K. Familial invasive and in situ squamous cell carcinoma of the skin. *Br J Cancer*. 2003; 88:1375–80. [PubMed: 12778064]
5. Hogan DJ, Lane PR, Gran L, Wong D. Risk factors for squamous cell carcinoma of the skin in Saskatchewan, Canada. *J Dermatol Sci*. 1990; 1:97–101. [PubMed: 2100549]
6. Ferreira FR, Nascimento LF, Rotta O. Risk factors for nonmelanoma skin cancer in Taubaté, São Paulo, Brazil: a case-control study. *Rev Assoc Med Bras*. 2011; 57:424–30. [PubMed: 21876926]
7. Wang LE, Xiong P, Strom SS, Goldberg LH, et al. In vitro sensitivity to ultraviolet B light and skin cancer risk: a case-control analysis. *J Natl Cancer Inst*. 2005; 97:1822–31. [PubMed: 16368944]
8. Goudie DR, D'Alessandro M, Merriman B, Lee H, et al. Multiple self-healing squamous epithelioma is caused by a disease-specific spectrum of mutations in TGFBR1. *Nat Genet*. 2011; 43:365–9. [PubMed: 21358634]
9. Asgari MM, Chren MM, Warton EM, Friedman GD, et al. Association between nonsteroidal anti-inflammatory drug use and cutaneous squamous cell carcinoma. *Arch Dermatol*. 2010; 146:388–95. [PubMed: 20157019]
10. White E, Patterson RE, Kristal AR, Thornquist M, et al. VITamins and Lifestyle cohort study: study design and characteristics of supplement users. *Am J Epidemiol*. 2004; 159:83–93. [PubMed: 14693663]
11. Satia-Abouta J, Patterson RE, King IB, Stratton KL, et al. Reliability and validity of self-report of vitamin and mineral supplement use in the vitamins and lifestyle study. *Am J Epidemiol*. 2003; 157:944–54. [PubMed: 12746248]
12. Wolff, T., Tai, E., Miller, T. Screening for skin cancer: an update of the evidence for the US Preventive services task force. Rockville, Maryland: Agency for Healthcare Research and Quality; 2009. Evidence synthesis No. 67. AHRQ Publication No. 09-05128-EF-1 Available at: <http://www.uspreventiveservicestaskforce.org/uspstf09/skincancer/skincanrs.htm>. Accessed January 8, 2014.
13. Floderus B, Barlow L, Mack TM. Recall bias in subjective reports of familial cancer. *Epidemiology*. 1990; 1:318–21. [PubMed: 2083311]
14. Gordon, N. Internal Division of Research report. Oakland, CA: Kaiser Permanente Division of Research; 2012. Similarity of the adult kaiser permanente membership in northern California to the insured and general population in northern California: statistics from the 2009 California Health Interview Survey. Available at: http://www.dor.kaiser.org/external/chis_non_kp_2009/ Accessed March 1, 2014.

Figure 1.
Adjusted models for the association of SCC risk with family history of skin cancer.

¹Adjusted for history of sunburns, peak sun exposure and protective behaviors, average # hours/day peak sun exposure, high-risk exposures, and current cigarette smoking

² Adjusted for all environmental variables as well as hair color, eye color and skin type

* p = 0.05

Figure 2.
Adjusted models for the association of SCC risk with family history of skin cancer by skin cancer type.

TABLE 1

Environmental, Innate, and Family History Risk Factors Among Cases and Controls

Risk Factors for SCC	SCC (n = 415)	Controls (n = 415)	Crude OR (95% CI)
Environmental			
Lifetime sunburns (% > 2 severe sunburns)	263 (63.5)	184 (44.7)	2.1 (1.6–2.8)
Occupational peak sun-exposure [*] (% yes)	96 (23.2)	85 (20.6)	1.2 (0.9–1.8)
Routine peak sun-exposure [†] (% yes)	311 (75.1)	281 (68.2)	1.4 (1.0–1.9)
Peak sun-exposure and sun-protection [‡]			
No peak sun-exposure	103 (24.9)	131 (31.8)	1.0 (Ref)
Yes peak sun: sunscreen only	58 (14.0)	27 (6.6)	3.0 (1.7–5.3)
Yes peak sun: protective clothing only	59 (14.3)	79 (19.2)	1.0 (0.63–1.5)
Yes peak sun: sunscreen and protective clothing	77 (18.6)	40 (9.7)	2.4 (1.5–3.9)
Yes peak sun: no sunscreen or protective clothing	117 (28.3)	135 (32.8)	1.1 (0.8–1.6)
Average no. h/wk peak sun-exposure [‡]			
<1	103 (24.9)	132 (31.8)	1.0 (Ref)
1–2	47 (11.3)	29 (7.0)	2.1 (1.2–3.6)
3–5	92 (22.2)	113 (27.2)	1.1 (0.7–1.6)
6–10	82 (19.8)	71 (17.1)	1.5 (1.0–2.3)
>10	91 (21.9)	70 (16.9)	1.8 (1.2–2.8)
Tanning bed use (% yes)	49 (11.8)	36 (8.7)	1.4 (0.9–2.3)
High-risk exposure [§] (% yes)	177 (42.7)	150 (36.1)	1.3 (1.0–1.7)
Cigarette smoking (% current)	29 (7.0)	16 (3.9)	2.1 (1.0–4.1)
Innate (pigmentation)			
Hair color			
Black/dark brown	122 (29.4)	169 (40.7)	1.0 (Ref)
Light brown	191 (46.0)	178 (42.8)	1.5 (1.1–2.1)
Red/blond	102 (24.6)	67 (16.1)	2.2 (1.5–3.3)
Eye color [¶]			
Brown	91 (21.9)	137 (33.0)	1.0 (Ref)
Green/hazel	132 (31.8)	111 (26.8)	1.7 (1.2–2.5)
Blue/gray	191 (46.0)	165 (39.8)	1.7 (1.2–2.3)
Fitzpatrick skin type [#]			
I	58 (14.0)	20 (4.8)	1.0 (Ref)
II	76 (18.3)	40 (9.6)	0.6 (0.3–1.2)
III	244 (58.8)	253 (61.0)	0.3 (0.2–0.6)
IV	36 (8.7)	90 (21.7)	0.1 (0.1–2.7)
Missing	1 (0.2)	12 (2.9)	0.0 (0.0–0.3)
Family history			
No family history of skin cancer	171 (41.2)	315 (75.9)	1.0 (Ref)
Yes	137 (33.0)	59 (14.2)	4.2 (2.8–6.3)

Risk Factors for SCC	SCC (n = 415)	Controls (n = 415)	Crude OR (95% CI)
Unknown family history of skin cancer	107 (25.8)	41 (9.9)	4.3 (2.8–6.7)
No family history of skin cancer	171 (41.2)	315 (75.9)	1.0 (Ref)
Yes: SCC only	12 (2.9)	5 (1.2)	3.3 (1.1–9.8)
Yes: BCC only	26 (6.3)	4 (1.0)	13.0 (3.8–44.8)
Yes: melanoma only	14 (3.4)	6 (1.4)	5.0 (1.7–14.6)
Yes: multiple skin cancer types	39 (9.4)	6 (1.4)	11.1 (4.5–27.4)
Yes: unknown type	46 (11.1)	38 (9.2)	2.3 (1.4–3.8)
Unknown family history of skin cancer	107 (25.8)	41 (9.9)	4.4 (2.8–6.9)

* At least 2 h/d of sun-exposure between 10 AM and 4 PM for primary occupation.

† At least 2 h/d once-a-week of sun-exposure between 10 AM and 4 PM in the past 10 years. Survey question asked “Over the past 10 years, did you regularly (at least once-a-week) spend at least 2 hours outdoor between 10 AM and 4 PM?” (yes/no). Those who answered “yes” were queried further about their average number of hours, sunscreen use, and protective clothing. Four respondents were missing information on either sunscreen or protective clothing use. Values were imputed based on responses to other sun-exposure questions for modeling purposes. Those who answered no ($n = 103$ cases and $n = 133$ controls) were not queried further.

‡ Much/most of the time.

§ Includes UV light treatment ($n = 50$), burn scar ($n = 49$), nonhealing ulcers ($n = 40$), radiation treatment ($n = 101$), arsenic exposure ($n = 10$), and exposure to industrial chemicals ($n = 184$).

|| One control had missing hair color (excluded from model).

¶ One case and 2 controls had missing eye color (excluded from models).

Skin type defined as response to the following question: “Which of the following describes your skin’s reaction after exposure to 1 hour of mid-day sun for the first time in the summer?” with responses categorized as follows: painful or blistering sunburn with no tan (Type I), painful or blistering sunburn followed by a light tan (Type II), mild sunburn followed by a moderate tan (Type III), no sunburn followed by a deep tan (Type IV).