

Report

Association between atopic dermatitis and squamous cell carcinoma: a case–control study

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Abstract

Background Conflicting data have been published on whether an association exists between atopic dermatitis (AD) and nonmelanoma skin cancer. This study aimed to determine whether individuals with AD had an increased risk of squamous cell carcinoma (SCC) development.

Methods We conducted a retrospective, case–control study of patients residing in Olmsted County, Minnesota. Cases were selected from patients seen at Mayo Clinic (Rochester, Minnesota) who had an initial SCC diagnosis (either invasive SCC or SCC *in situ*) from January 1, 1996, through December 23, 2010. Age- and sex-matched controls were selected from patients seen at Mayo Clinic with no history of SCC before the case event date.

Results Three hundred ninety-nine individuals with a documented history of SCC were identified and matched with 780 controls who did not have a history of SCC. After adjusting for race, smoking history, ionizing radiation exposure, corticosteroid and cyclosporine use, and non-SCC skin cancers, the odds ratio for SCC development between patients with history of AD versus patients without history of AD was 1.75 (95% CI, 1.05–2.93).

Conclusions Our findings support an increased risk of SCC development in the setting of AD.

Introduction

Limited studies have investigated the association between atopic dermatitis (AD), also termed *eczema*, and squamous cell carcinoma (SCC). A chronic, inflammatory disease, AD causes scaly, pruritic patches and plaques on the skin¹ and affects up to 20% of children and 3% of adults worldwide.² The prevalence of AD has tripled since the 1960s, with new diagnoses of AD occurring at about 11% per year in the United States.³ Alongside the rising incidence of AD, the incidence of nonmelanoma skin cancer (NMSC) is also increasing worldwide.⁴ SCC is the second-most common type of NMSC⁵ and typically manifests on the head and upper limbs as a nonhealing, scaly, erythematous patch.

Research from the past two decades has demonstrated that AD is a disease arising from immunologic dysfunction and may be associated with a loss-of-function mutation in *FLG*, the gene encoding filaggrin, which is elemental in skin barrier function.^{6–8} Skin barrier defects are considered to be a key contributor to the pathogenesis of AD. Treatments for AD target immunologic

dysfunction of the skin, which may increase risk of melanoma and NMSCs.⁹ Corticosteroids, topical immunomodulators and other immunosuppressive agents, and ultraviolet (UV) phototherapy are specific therapeutic options that may increase the risk of skin cancer development. In a 2012 Danish study, SCC appeared on areas normally not exposed to the sun, which raised suspicion that local or systemic immunosuppressants and artificial UV therapy were implicated in the pathogenesis of skin cancer development.¹⁰ Other possible risk factors include smoking¹⁰ and occupations associated with increased UV light exposure.

Previous studies have investigated the possible association between AD and skin cancer. Two Swedish studies, involving 21,000 patients collectively, found an inverse but nonsignificant association between AD and melanoma and no significant correlation between AD and NMSC,^{11,12} but a Danish study showed that AD was positively correlated with NMSC.¹³ A fourth study showed no association between AD and NMSC.¹⁴ A 2012 study from the Danish National Patient Registry that included more than 31,000 patients with AD showed an

increased risk of basal cell carcinoma (BCC) and SCC¹⁰; that study analyzed patients in the inpatient and outpatient settings, allowing a more comprehensive evaluation of the association between AD and skin cancer. As evidenced by the literature, the data regarding the association between AD and skin cancer, particularly NMSC, are conflicting. Because of these inconsistencies, we aimed to determine whether a history of AD increased the risk of developing SCC.

Methods

The Mayo Clinic Institutional Review Board approved this study.

Study design and patient selection

We conducted a retrospective, 1 : 2 matched case-control study. All data were obtained from the Mayo Clinic electronic health records system.

The study population consisted of patients seen in any department at Mayo Clinic (Rochester, Minnesota) from January 1, 1996, through December 23, 2010. All subjects provided research authorization before the start of data abstraction for this retrospective study. Patients were not surveyed for any prospective information.

Selection of cases and controls

Four hundred cases were randomly selected from 5589 patients who were seen at Mayo Clinic and were residents of Olmsted County, Minnesota, when they received an initial diagnosis of invasive SCC or SCC *in situ*. In addition to the health record review and pathology confirmation of the SCC diagnosis, cases were identified using the Hospital International Classification of Diseases Adapted code 01790-65-0.

Eight hundred controls, seen at Mayo Clinic within 1 year of the case's diagnosis, were matched to cases by age and sex. Controls were selected from the population of patients residing in Olmsted County, Minnesota. During chart review, we verified that controls did not have a history of SCC before the case event date.

Exposure and confounders

The primary exposure variable was a history of AD. The inclusion criteria were *atopic dermatitis* and *eczema*, as diagnosed by a dermatologist or another provider; alternatively, a history of the condition could be self-reported to the provider, even without current evidence of dermatitis on examination. All diagnoses of AD preceded the SCC diagnosis. Other potential conditions such as nummular eczema, hand dermatitis, ear dermatitis, and contact dermatitis were also included because their risk factors and morphology are similar to those of AD.

Potential confounders included race, history of skin cancer, history of smoking, exposure to medical ionizing radiation (imaging or radiotherapy), and history of corticosteroid and other immunosuppressant use. Patients whose race could not

be determined by chart review were categorized as "Unknown."

Method of analysis

Patient characteristics for cases and controls were summarized and compared with the Pearson χ^2 test or Fisher's exact test. Odds ratios were used to test for associations and were calculated using conditional logistic regression to account for the matched design. Randomized case selection and statistical analyses were completed using SAS software version 9.4 (SAS Institute Inc).

Results

Four hundred cases and 800 controls initially were selected. Twenty controls declined research authorization and were excluded. For one case, both matched controls were excluded, and therefore the case was also excluded. In total, the study included 399 individuals with a documented history of SCC and 780 matched controls who did not have a history of SCC (Table 1). Compared with controls, a greater percentage of cases had a history of AD (8% vs. 5%; $P = 0.04$), history of smoking (37.1% vs. 31.2%; $P = 0.04$), prior phototherapy (2.3% vs. 0.5%; $P = 0.01$), cyclosporine use (1.3% vs. 0.1%; $P = 0.02$), and non-SCC skin cancer (26.8% vs. 10.0%; $P < 0.001$).

As noted in Table 2, after adjusting for race, smoking history, exposure to ionizing radiation, corticosteroid use, cyclosporine use, and history of non-SCC skin cancers, we identified a statistically significant association between SCC and AD (adjusted odds ratio, 1.75; 95% CI, 1.05–2.93). To account for other dermatitides that share similar risk factors and morphologic characteristics as AD, we performed a separate analysis to measure the association of SCC with AD, nummular eczema, hand dermatitis, ear dermatitis, and contact dermatitis (Table 3) and observed a positive association (adjusted odds ratio, 1.72; 95% CI, 1.21–2.46).

When examining the possibility of surveillance bias, we noted that patients with SCC had more dermatologic visits than patients without SCC. However, we included patients with diagnoses from nondermatologist providers and those who self-reported AD if they had it in their younger years. We also noted that patients with SCC also had more non-SCC cancers, which increased dermatologic care. When we analyzed patients with non-SCC cancers versus those without, the AD status was 7% versus 5.9%; we concluded that AD did not appear to be associated with non-SCC cancers.

Discussion

Our findings demonstrate that the odds of SCC development are greater in patients with a history of AD. This finding has also been supported by previous studies.^{10,12,13} Our study

Table 1 Characteristics of controls and cases

Characteristic	Controls (n = 780)	Cases (n = 399)	P value
Age, years			
Mean (SD)	69.6 (13.5)	69.5 (13.5)	
Median (IQR)	72 (61, 79)	72 (61, 79)	
Female sex, No. (%)	361 (46.3)	186 (46.6)	
Race, No. (%) ^a			
White	709 (90.9)	387 (97.0)	<0.001
Nonwhite	49 (6.3)	4 (1.0)	
Unknown	22 (2.8)	8 (2.0)	
Atopic dermatitis, No. (%) ^a	40 (5.1)	32 (8.0)	0.0497
Smoking history, No. (%) ^a	243 (31.2)	148 (37.1)	0.04
Corticosteroids, No. (%) ^a	170 (21.8)	94 (23.6)	0.49
Antibiotics, No. (%) ^a	157 (20.1)	115 (28.8)	<0.001
Antihistamines, No. (%) ^a	165 (21.2)	84 (21.1)	0.97
Tacrolimus, No. (%) ^b	2 (0.3)	3 (0.8)	0.34
Pimecrolimus, No. (%) ^b	0 (0)	1 (0.3)	0.34
UV phototherapy, No. (%) ^b	4 (0.5)	9 (2.3)	0.01
Cyclosporine, No. (%) ^b	1 (0.1)	5 (1.3)	0.02
Azathioprine, No. (%) ^b	4 (0.5)	5 (1.3)	0.18
Methotrexate, No. (%) ^b	5 (0.6)	6 (1.5)	0.20
Mycophenolate mofetil, No. (%) ^b	4 (0.5)	5 (1.3)	0.18
History of ionizing radiation, No. (%) ^a	609 (78.1)	283 (70.9)	0.007
Family history of skin cancer, No. (%) ^a	75 (9.6)	41 (10.3)	0.72
Personal history of non-squamous cell skin cancer, No. (%) ^a	78 (10.0)	107 (26.8)	<0.001
Basal cell carcinoma	73 (9.4)	101 (25.3)	
Melanoma	9 (1.2)	6 (1.5)	

IQR, interquartile range; UV, ultraviolet.

^a χ^2 test.^bFisher exact test.**Table 2** Odds of squamous cell carcinoma comparing patients with and without atopic dermatitis

Type	Odds ratio (95% CI)
Unadjusted	1.56 (0.97–2.51)
Adjusted	1.75 (1.05–2.93)

population was mostly composed of white, elderly patients who have elevated risk of skin cancer development.¹⁵ Medications such as topical and systemic corticosteroids, antihistamines, and various immunosuppressants did not increase risk of SCC development; the exception was the immunosuppressant cyclosporine, which was significantly associated with increased SCC risk. The inability to measure the differences in effect of corticosteroids and antihistamines on SCC risk may be due to their ubiquitous use, broad scope, and ready availability.

As previously discussed, filaggrin is a key protein in skin barrier function, and skin barrier defects are associated with AD

Table 3 Odds of squamous cell carcinoma comparing patients with and without atopic dermatitis, nummular eczema, hand dermatitis, ear dermatitis, and contact dermatitis

Type	Odds ratio (95% CI)
Unadjusted	1.71 (1.23–2.37)
Adjusted	1.72 (1.21–2.46)

pathogenesis. In addition, filaggrin is degraded to trans-urocanic acid, a chromophore that provides protection from UV radiation. In one study, individuals with mutations in the filaggrin gene also had an increased risk of SCC.¹⁶ Another case-control study showed no elevated risk of BCC in *FLG* mutation carriers,¹⁷ but the study had low statistical power. Further studies are needed to assess the association between filaggrin deficiency and risk of NMSCs.

Studies have shown that actinic keratoses, the most common precursor to SCC, may be associated with AD. In a Danish questionnaire study, a significant association was identified between filaggrin mutation and actinic keratosis in patients with AD. Thirteen of 20 patients (65%) had a history of actinic keratosis and AD. Patients with homozygote or compound heterozygote mutations had an actinic keratosis prevalence of 16.7% versus 2.2%.¹⁸ Yet a Dutch study showed no association between AD and actinic keratosis and actually showed that a lower proportion of patients with AD had actinic keratosis compared with those without AD.¹⁹ In our study, we did not specifically examine actinic keratosis; however, we did observe a statistically significant positive association between AD and SCC.

We acknowledge several limitations to our study. As with all retrospective studies, our observations were limited to the details documented in the health record and could have been affected by human error in the data abstraction process. We were unable to determine the reliability of provider coding for AD and so included other dermatitis diagnoses such as nummular eczema, hand dermatitis, ear dermatitis, and contact dermatitis. Furthermore, most of the eczema diagnoses were made using *International Classification of Diseases*, ninth revision coding, which has poor predictive value with regard to the outpatient setting.²⁰ The time-frame of first diagnosis of AD to SCC development was difficult to ascertain because of inconsistent documentation. Patients often self-reported AD to their provider without specifying the date of diagnosis, and it is possible that a patient may have had an earlier diagnosis of SCC that was not documented in the medical record. Clinical assessment and documentation of AD can be difficult because dermatologic manifestations of AD resemble other closely related skin conditions and thus may lead to inaccurate diagnoses; in contrast, SCC diagnoses are less variable, and a pathology report is considered conclusive. Not every patient in our study had a final clinical diagnosis of AD rendered by a dermatologist. Our analysis of time from AD to SCC development

was also limited because the duration of follow-up for the cases and controls was fixed. Also, our retrospective study design did not allow us to accurately ascertain the initial date of onset of AD in many patients; therefore, we were unable to perform statistical analyses assessing the interval between AD and SCC. Moreover, data regarding the location of SCC and the location of AD cutaneous manifestations were not collected; therefore, we were unable to assess whether the development of SCC preferentially occurred within areas of previous inflammation of AD skin lesions. Medication dosing, frequency, and route of administration (i.e., topical or systemic) were not captured during data abstraction. Finally, we were unable to quantify how much sun exposure patients received, or which body areas typically received sunlight exposure, and thus were unable to account for this risk factor in our calculation of the odds ratio between AD and SCC.

Future studies should examine BCC and SCC development in patients with AD. More expansive studies looking at all cases of SCC and BCC at a single institution and determining the prevalence of AD before any NMSC diagnosis would be highly beneficial. Because AD is often first diagnosed in childhood, perhaps prospective studies in the pediatric population, with long-term follow-up, may capture more accurate statistical data, although such a study would be time and cost intensive. It is also prudent to note that visits to any health-care provider may increase the likelihood of skin cancer detection, and the probability of detection may be further increased if the provider is a dermatologist. Future studies may help address this potential confounding variable. More studies assessing the effects of topical therapy on risk of skin cancer development would be beneficial because many patients with atopy use topical corticosteroids and topical calcineurin inhibitors for treatment and symptomatic relief.

Our finding of an association between a history of AD and SCC has clinical implications. As we continue to gather more data on this possible relationship, we can begin to counsel patients with AD on the importance of skin examinations and sunscreen use at a young age. Ideally, awareness should increase among other health-care providers who frequently see patients with AD. This concise case-control study may be of value to future studies investigating the possible association between AD and skin cancer development.

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References

- 1 Darsow U, Raap U, Stander S. Atopic dermatitis. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and Treatment*. Boca Raton: CRC Press, 2014: 19–31.
- 2 Garnacho-Saucedo G, Salido-Vallejo R, Moreno-Gimenez JC. Atopic dermatitis: update and proposed management algorithm. *Actas Dermosifiliogr* 2013; **104**: 4–16.
- 3 Eichenfield LF, Ellis CN, Mancini AJ, et al. Atopic dermatitis: epidemiology and pathogenesis update. *Semin Cutan Med Surg* 2012; **31**: S3–S5.
- 4 Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer: the role of sunlight. *Adv Exp Med Biol* 2008; **624**: 89–103.
- 5 Sapijaszko M, Zloty D, Bourcier M, et al.; Canadian Non-melanoma Skin Cancer Guidelines Committee. Non-melanoma skin cancer in Canada chapter 5: management of squamous cell carcinoma. *J Cutan Med Surg* 2015; **19**: 249–259. Errata in: *J Cutan Med Surg*. 2015; **19**: 604.
- 6 van den Bogaard EH, Bergboer JG, Vonk-Bergers M, et al. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. *J Clin Invest* 2013; **123**: 917–927.
- 7 Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–446.
- 8 Irwin McLean WH, Irvine AD. Heritable filaggrin disorders: the paradigm of atopic dermatitis. *J Invest Dermatol* 2012; **132**: E20–E21.
- 9 Maughan WZ, Muller SA, Perry HO, et al. Incidence of skin cancers in patients with atopic dermatitis treated with ocal tar: a 25-year follow-up study. *J Am Acad Dermatol* 1980; **3**: 612–615.
- 10 Jensen AO, Svaerke C, Kormendine Farkas D, et al. Atopic dermatitis and risk of skin cancer: a Danish nationwide cohort study (1977–2006). *Am J Clin Dermatol* 2012; **13**: 29–36.
- 11 Synnerstad I, Fredrikson M, Ternesten-Bratel A, et al. Low risk of melanoma in patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2008; **22**: 1423–1428.
- 12 Hagstromer L, Ye W, Nyren O, et al. Incidence of cancer among patients with atopic dermatitis. *Arch Dermatol* 2005; **141**: 1123–1127.
- 13 Olesen AB, Engholm G, Storm HH, et al. The risk of cancer among patients previously hospitalized for atopic dermatitis. *J Invest Dermatol* 2005; **125**: 445–449.
- 14 Ming ME, Levy R, Hoffstad O, et al. The lack of a relationship between atopic dermatitis and nonmelanoma skin cancers. *J Am Acad Dermatol* 2004; **50**: 357–362.
- 15 Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br J Dermatol* 2002; **146**: 1–6.
- 16 Kaae J, Szecsi PB, Meldgaard M, et al. Individuals with complete filaggrin deficiency may have an increased risk of squamous cell carcinoma. *Br J Dermatol* 2014; **170**: 1380–1381.
- 17 Kaae J, Thyssen JP, Johansen JD, et al. Filaggrin gene mutations and risk of basal cell carcinoma. *Br J Dermatol* 2013; **169**: 1162–1164.
- 18 Heede NG, Thyssen JP, Thuesen BH, et al. Health-related quality of life in adult dermatitis patients stratified by filaggrin genotype. *Contact Dermatitis* 2017; **76**: 167–177.
- 19 Hajdarbegovic E, Blom H, Verkouteren JA, et al. Atopic dermatitis is not associated with actinic keratosis: cross-sectional results from the Rotterdam study. *Br J Dermatol* 2016; **175**: 89–94.
- 20 Hsu DY, Dalal P, Sable KA, et al. Validation of International Classification of Disease Ninth Revision codes for atopic dermatitis. *Allergy* 2017; **72**: 1091–1095.