
The lack of a relationship between atopic dermatitis and nonmelanoma skin cancers

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Background: Very little has been published on whether a relationship exists between atopic dermatitis (AD) and skin cancer.

Objective: The goal of this study was to investigate whether individuals with AD are more likely than other patients with dermatologic conditions to develop nonmelanoma skin cancer.

Methods: This was a case-control, mailed-survey study.

Results: Of those contacted, 69.8% (3207 of 4591) filled out the survey. Of the control patients, 18.4% (254) had a history of AD as defined by the United Kingdom Working Party diagnosis criteria and composed 13.7% (210) of the cases. The unadjusted odds ratio of AD to nonmelanoma skin cancer was 0.70 (95% confidence interval 0.57-0.85). After fully adjusting for age, sex, ethnicity, and topical steroid use the odds ratio was 0.78 (0.61, 0.98). Using different definitions of AD had little effect on this result.

Conclusions: It does not appear that patients with a history of AD are more likely to develop nonmelanoma skin cancers than other patients with dermatologic conditions. (J Am Acad Dermatol 2004;50:357-62.)

Atopic dermatitis (AD) is a well-described skin condition that may include other systemic manifestations such as asthma, rhinitis, and seasonal allergies.¹⁻⁵ It usually begins in early childhood, and it may be a lifelong affliction.⁵ Clinically, AD has been well described, but the natural history of AD or how it affects adults is not well understood. It has been estimated to afflict between 0.3% and 20% of children, with as many as 50% of affected individuals also being afflicted with asthma or rhinitis.⁵ In adulthood, nonmelanoma skin cancer

(NMSC), such as squamous cell carcinoma and basal cell carcinoma, are very common forms of cancer.^{6,7} These cancers tend to occur in those with light complexions, on sun-exposed areas of the body, and become more prevalent with age.^{6,7}

Because AD and NMSC are both common, it is, therefore, likely that many individuals with histories of AD will develop skin cancers. In general, there has previously been little concern about any potential association between AD and NMSC.^{8,9} However, warnings on the labels for topical compounds that contain tar preparations (a treatment classically used for AD) that describe a potential relationship between tar exposure and cancer have been recently mandated in California (<http://www.psoriasis.org/coaltar.lawsuit.022402.htm>). In addition, 2 new topical agents have become available for the treatment of AD, which are both calcineurin-inhibitor immunosuppressants.^{10,11} Although the use of a topical calcineurin inhibitor (TCI) has never been shown to be related to skin cancer, there is a well-established relationship between the onset of skin cancers and the use of systemic calcineurin inhibitors (eg, cyclosporine and tacrolimus) after whole organ transplantation.¹¹ Furthermore, this concern is listed as part of the *United States Pharmacopeia* precautions to con-

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Abbreviations used:

AD:	atopic dermatitis
CI:	confidence interval
NMSC:	nonmelanoma skin cancer
PICARD:	Pennsylvania integrated clinical and administrative research database
OR:	odds ratio
TCI:	topical calcineurin inhibitor
UKDX:	United Kingdom Working Party diagnostic criteria

sider when prescribing TCIs.¹² It should also be noted that many more agents that modify the immunoregulatory function of the skin will likely be developed for cutaneous inflammatory conditions in the future and, as a result, could be potentially associated with NMSC.

As a result, the level of suspicion and interest in what might have previously been thought to be a chance occurrence of NMSC in a patient with AD is now likely to increase, such that reports of an association between the use of therapies for AD and NMSC may soon begin to appear in the dermatologic literature. Unfortunately, it will not be possible from these reports to interpret if a causal relationship does or does not exist. These findings will be further complicated by the fact that it is now not known if a relationship exists between a patient having a history of AD and the likelihood of a skin cancer developing in that patient.³ Therefore, it would be prudent to document if those who have AD are at an increased risk for the development of NMSC both with respect to the natural history of AD and with respect to the potential that current and future therapies may have on this association. The goal of this study was to investigate whether those with a history of AD were more likely than those with other dermatologic illnesses to develop a NMSC before the widespread use of TCIs.

METHODS

Study design

This was a case-control study. Patients were selected as described below. We asked them to participate after receiving permission from their attending dermatologist. All patients were contacted by mail. All data were obtained from them using a self-administered questionnaire written in English. The survey was conducted in a manner consistent with the Dillman¹³ tailored design method.

Study population and patient selection

Patients were selected on the basis of knowledge of their outcome (ie, NMSC or no NMSC) and then queried for information about their exposures. The

study population consisted of patients seen by the dermatology practices of the department of dermatology at University of Pennsylvania School of Medicine, Philadelphia, between 1998 and 2001. All patients were identified using the Pennsylvania integrated clinical and administrative research database (PICARD) of the University of Pennsylvania health system. This database contains information on all of the outpatients seen in the outpatient practices of that health system, which includes the dermatology attending staff of the school of medicine of the University of Pennsylvania.

Selection of cases. Our potential cases were randomly selected from the PICARD database on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification* codes consistent with a NMSC (173.0, 173.1, 173.2, 173.3, 173.4, 173.5, 173.6, 173.7, 173.8, and 173.9), which are the codes used in the dermatology practice studied. We also evaluated patients' self-reporting of skin cancer.¹⁴ Because we evaluated patients seen between 1998 and 2001, it was possible that a patient had a history of a skin cancer that was not reported by the database. Therefore, a patient was classified as having a skin cancer either if they were identified by PICARD as having a skin cancer or if, after they were selected from PICARD as a control patient, they responded on their survey form that they had a skin cancer before 1998, which was the date that PICARD began to accrue patient information. All cases found to have a history consistent with HIV disease or use of oral immunosuppressives (ie, azathioprine, cyclosporine, cyclophosphamide, methotrexate, and systemic tacrolimus) were excluded from analyses.

Selection of control patients. When selecting the control group for a case-control study, it is important to select the control patients in an unbiased manner as if they were from the same population of patients who would have been included as a case in the study had they developed disease.¹⁵ Finding the correct base or referent population from which to select the control patients is always a challenge and was especially challenging for this study. Furthermore, to assure unbiased ascertainment, selection of the cases and control patients must not depend on individual exposure status. Unfortunately, because patients may be referred to a dermatologist for the treatment and diagnosis of skin cancer and dermatitis, a natural population referent group does not exist. It is for this reason that we selected multiple control groups with the understanding that our primary exposure should not be unreasonably associated (positively or negatively) with the selected control groups. Furthermore, by having more than 1 control group we would be able to demonstrate

more convincingly an unbiased association or lack of association between our primary exposure and the case groups. Therefore, we randomly sampled as control patients from the PICARD database patients seen at the institution during the same time period as the cases with the following specific cutaneous diagnoses: warts, seborrheic keratosis, acne rosacea, and dermatophyte infection. Patients who had a PICARD diagnosis of skin cancer were excluded from the control group. We a priori determined that if the frequency of AD in any of our control groups differed by more than 10%, then that control subgroup (eg, warts, dermatophyte) would be excluded from the control population. Finally, as noted above, any control patient who indicated having a skin cancer on his or her survey form and was chart confirmed was ultimately classified as a case.

Exposure and confounders

The primary exposure variable was a history of AD. Because this disease is not clearly defined in the dermatologic literature and there is not expert agreement, we evaluated several possible markers for this diagnosis: the United Kingdom Working Party diagnostic criteria (UKDX) for AD, which has been validated for use by mail survey; and patients' self-reported history of AD, eczema, chronic dermatitis, or asthma.^{1,16} Because the UKDX has been used in mail surveys, this was considered our primary exposure variable.¹⁶

In addition, many potential confounding variables were evaluated. A confounder is an exposure variable that is related to the exposure of interest and the outcome. The presence of a confounder can result in error in the estimate of the association of the exposure of interest with the outcome. Potential confounders included questionnaire-derived patient characteristics and exposures or history of illnesses such as age, skin type, ethnicity, family history of skin cancer, history of herpes or varicella infection, history of smoking, alcohol use, coffee use, radiation exposure, history of sunburn and tanning-booth use, history of diabetes, history of hypertension, history of rheumatoid arthritis, history of lupus, occupational dermatitis, and recent and past use of medications, including use of topical steroids, oral steroids, and tar products. Confounders that were selected for use in our adjusted models included those that either changed the unadjusted association between our markers for AD and skin cancer by more than 10% or were deemed by the study team to be clinically relevant.¹⁷ Many of the measured potential confounders were not found to be of clinical or statistical interest and are, therefore, not reported.

Method of analysis

The initial analyses were exploratory and descriptive, characterizing the case and control groups by our exposure definitions of dermatitis, and characterizing the confounders. Next, each exposure definition and confounder was analyzed comparing each case group with each control group using chi-square, exact tests, or univariate logistic regression. Finally, adjusted associations were estimated by multivariable logistic regression. Modeling was conducted using each definition of AD and any of the confounders that either changed the unadjusted association between AD and skin cancer by more than 10% or were clinically associated with skin cancer. In all cases, odds ratio (OR) was reported with 95% confidence interval (CI).

Several sensitivity analyses were also performed. These included altering the patient's classification of case and control status solely on the basis of PICARD classification and solely on the patient's survey response, exclusion of all control patients who reported a skin cancer, evaluation of interactions between the confounding variables and the exposure variable, removal of the acne rosacea group from the control group because the frequency of AD came closest in this group to being more than 10% different from the other control patients (see above selection of control patients), alternate definitions of AD, and variance adjustment for physician-based clustering.

RESULTS

In all, 4591 individuals were successfully contacted. Of these, 69.8% (3207) filled out and returned the survey. Of those who responded, 296 were excluded because they revealed that they had a solid organ transplant. Survey response rates were similar whether the patient had a prior diagnosis of skin cancer, acne rosacea, dermatophyte infection, seborrheic keratoses, or wart. Overall, 1378 patients were classified as control patients and 1533 patients were classified as cases; 18.4% (254) of the control patients had a history of AD as defined by the UKDX, as did 13.7% (210) of the cases (Table I). In general, those in the control group were more likely to have a history of AD on the basis of any of our definitions of AD, to be female, to be nonwhite, to have never had blistering sunburn, and to use topical skin therapies associated with AD (Table I). In total, 70.2% of our cases were identified by PICARD with the remainder of the case patients being those who reported developing a skin cancer before 1998. There was some variability with respect to age, sex, and ethnicity between our control and case groups (Table I). Within the control group, none of the

Table I. The frequency of various characteristics in the control and case groups

Characteristic	Control group (N = 1378)	Case group (N = 1533)
Age (y)	60.1 (59.5, 60.6)	66.4 (65.8, 66.8) [‡]
Sex (male)	39.9%	51.3% [‡]
Ethnicity (white)	87.9%	99.3% [‡]
History of UKDX	18.4%	13.7% [‡]
History of asthma	12.8%	10.3% [‡]
History of atopic dermatitis	8.6%	6.6% [‡]
History of eczema	16.5%	12.9% [‡]
Recent topical corticosteroid use	14.8%	10.5% [*]
Recent inhaler use	8.1%	8.4% [*]
Use of any topical agent	79.4%	68.6% [‡]
Use of tar preparations	11.1%	8.6% [*]
Insurance	98.3%	98.6%
Severe childhood sunburns	40.2%	56.3% [‡]
Cigarettes (never used)	48.4%	45.6%

UKDX, United Kingdom Working Party diagnostic criteria

Univariate *P* values: * $<.05$, [‡] $<.001$, [‡] $<.0001$.

Age is reported as a mean with 95% confidence intervals. For all other characteristics, the percentage of those with the characteristic either in the case or control group is reported.

subgroups (eg, acne rosacea, warts) varied by more than an absolute 10% for the prevalence of a history of AD on the basis of the UKDX criteria or our other markers of AD (Table II). As a result, all additional analyses are reported comparing the control group as a whole, consisting of all of the patients in Table II, with the skin cancer group (case group).

Patients with a history of AD (on the basis of our 5 markers for AD) were less likely to develop a skin cancer than those without such a history. As can be noted in Table III, the unadjusted ORs varied from about 0.70 to 0.87 and, with the exception of the nonspecific diagnosis of dermatitis, all cases revealed a statistically significant (as measured by *P* value and 95% CI) decreased odds of having a history of AD in those with a skin cancer as compared with those without. After adjustment, the ORs varied between 0.78 and 1.00 and were generally no longer statistically significant. Interestingly, although the statistical "protective" association was removed in the fully adjusted analysis (confounders: age, sex, topical steroid use, and ethnicity), a trend persisted of ORs being less than 1.0. None of the other variables listed on Table I, or listed under exposure and confounders above and not reported, altered the ORs of association of our definitions of AD by more than 10% and, therefore, did not qualify by our definition of confounder.

Multiple additional analyses were performed. First, we evaluated the presence of interactions between our definitions of AD and age and sex, and did not find any. Second, we conducted several sensitivity analyses. These sensitivity analyses are described in the "Methods" section. Briefly: altering our definition of AD to evaluate only the individuals with more severe active disease (as defined by having a survey response consistent with the UKDX for AD in addition to a current history of asthma and topical corticosteroid use); excluding from our control group those subgroups (seborrheic keratosis and acne rosacea) that had the highest and lowest prevalence of AD as per the UKDX criteria (seborrheic keratoses or acne rosacea); and changing our definition of a case (as outlined above) did not substantially change the lack of association between definitions of AD and skin cancer.

DISCUSSION

It does not appear that the odds of patients having a history of AD were greater in our case group (patients with NMSC) than those in our control group (patients with general dermatologic illness and a history of warts, seborrheic keratosis, acne rosacea, dermatophyte infection, or a combination of these). Furthermore, the lack of association between those with AD and NMSC persisted when we conducted several sensitivity analyses including sensitivity analyses of those with AD who were current users of therapy. In fact, our unadjusted analyses appeared to show an unexpected protective association between AD and skin cancer. However, the statistical significance of this effect diminished when our multivariable analysis controlled for confounders that included disparities between the case and control groups of age, sex, topical steroid use, and ethnicity. Although it might be tempting to interpret the persistent ORs of less than 1.0 as a protective trend, because the underlying hypothesis of this study was that those with NMSC would have increased odds of having AD, this study was not designed to demonstrate a protective effect and, with our current sample size, after adjustment the precision (ie, 95% CI) of the estimate effect included or closely approximated 1.0.¹⁸ Therefore, we can only safely conclude that there is no association between a history of AD and NMSC.

As should have been expected, individuals who were more likely to have been sunburned, were older, had a fair complexion, and were male were all more likely to have had a NMSC. These findings have been frequently reported.⁷ However, we were not able to independently associate the use of a topical compound like tar or corticosteroid with

Table II. The frequency and number of control patients who fulfill one of our definitions for atopic dermatitis

Diagnosis	UKDX	History of atopic dermatitis	History of eczema	History of asthma	History of dermatitis
Acne rosacea	22.8% 90	11.4% 45	18.3% 72	13.2% 52	25.6% 101
Dermatophyte	18.0% 62	9.8% 32	18.6% 61	12.8% 42	19.3% 63
Seborrheic keratoses	15.7% 49	6.7% 21	13.4% 42	12.2% 38	12.5% 39
Wart	15.4% 53	6.1% 21	15.4% 53	13.0% 45	12.5% 43

UKDX, United Kingdom Working Party diagnostic criteria

NMSC. For example, the unadjusted ORs of a patient with NMSC as compared with a control patient of having used a topical tar preparation was 0.76 (0.60, 0.95). The adjusted OR varied between 0.84 to 0.92 depending on the definition of AD (95% CIs always included 1.0 and *P* values were always < .05). A similar effect was noted for those who used topical steroids, which was one of our confounders. The unadjusted odds of a patient with NMSC as compared with a control patient of having used a topical steroid was 0.76 (0.61, 0.96) and when adjusted the OR varied between 0.66 to 0.76 depending on the definition of AD (95% CIs never included 1.0 and *P* values were always < .001). In other words, the odds of being a user of topical steroids were about 30% less in those with a NMSC as compared with those without a NMSC. This effect was not expected, is very small, and because of the small size of association is likely to be biased. Furthermore, we do not have any information on total dose, duration of use, frequency of use, or site of use. Finally, the goal of this study was to evaluate the association of AD and NMSC. Our initial study hypothesis was that those with AD, likely a result of treatments that they had received, were likely to be at an increased risk of NMSC. Therefore, using strict epidemiologic and statistical criteria, at best this association should be viewed as a hypothesis-generating result.

As with all observational studies, there are many limitations to our study. First, this was a case-control study. It is possible that our case and control patients were not selected from the same population of patients. In other words, the likelihood of finding a case among the population of patients selected as a control group was not the same as being selected as a case from our source population.¹⁵ We think that this form of selection bias is unlikely because the frequency of AD was similar among our control groups and within the range expected from larger population-based studies. In addition, a sensitivity

Table III. Unadjusted and full adjusted odds ratios reported with 95% confidence interval of the odds of a patient with nonmelanoma skin cancer as compared with a patient with general dermatologic illness of having a history of atopic dermatitis

Variable	Unadjusted odds ratio (95% CI)	Fully adjusted odds ratio (95% CI)*
UKDX	.70 (.57, .85)	.78 (.61, .98)
History of atopic dermatitis	.75 (.57, .99)	.92 (.68, 1.26)
History of eczema	.75 (.61, .93)	.85 (.67, 1.08)
History of dermatitis	.87 (.72, 1.06)	1.00 (.80, 1.26)
History of asthma	.78 (.62, .98)	.95 (.73, 1.24)

CI, Confidence interval; UKDX, United Kingdom Working Party diagnostic criteria

*Simultaneously adjusted for by age, sex, topical steroid use, and ethnicity.

analysis that used only those patients who were not listed in PICARD as having a skin cancer diagnosis between 1998 and 2001 and then determining case and control status by patient self-report resulted in similar findings. Second, it might be possible that our definition of case status is in error. However, in a separate study we have demonstrated the validity of ascertaining whether a patient has a NMSC both by using PICARD and by patient self-report, and both methods work well.¹⁴ It is possible that patients are unable to accurately report that they have AD. It is for this reason that we used multiple definitions for this exposure. Again, in all cases our measures of association were similar. Third, we were not able to collect information about the duration or intensity of AD. It is, therefore, possible that the association between NMSC and those with more extensive AD may differ from what we report. However, it is important to note that an exposure-related effect would need to be substantially different from the lack of effect noted in this study because, as a trend,

this study may have shown that those with AD may be less likely to develop a NMSC. Finally, it is possible that those with AD are more likely to modify their health behaviors, such as sun exposure, cigarette use, and many that we could not measure, which are ultimately responsible for the lack of association that we noted.

In conclusion, it does not appear that patients with a history of AD are more likely to develop NMSCs than other patients with dermatologic conditions. However, we may have noted a trend in that those with AD were slightly less likely to develop NMSCs. Although within the design and statistical limitations of this study, we are limited to calling this a statistically significant trend. However, a small protective effect and an increased risk with respect to other cancers in association with AD have been previously report.¹⁹⁻²¹ Nevertheless, it is important that future studies realize that those with AD may be at a decreased risk of developing NMSC. This is especially important for future studies evaluating the risk of NMSCs in patients with AD in that the appropriate comparison group would likely not be those with general dermatologic conditions as used for our study (who may be more prone to develop NMSC) but other patients with AD. The use of TCIs will increase in the future and other new agents that will likely modify the immunoregulation of the skin. It is likely that they will be used on individuals who develop a NMSC by random chance and, perhaps, even on individuals predisposed to develop skin cancers.²² It is, therefore, very important that before it is decided that TCIs or any new therapy are associated with the development of NMSC that clinicians carefully determine if this association is by chance or indeed related to the use of the topical therapy.

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