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Risk of Squamous Cell Carcinoma of the Skin in Relation to IgE: A Nested Case-Control Study

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Abstract

Background—Individuals diagnosed with non-melanoma skin cancer have a high risk of developing a second skin cancer diagnosis. We assessed whether a marker of immune function related to atopic allergy, IgE, was associated with diagnosis of subsequent squamous cell carcinoma (SCC) of the skin in patients with a previous skin cancer enrolled in a skin cancer prevention trial.

Methods—One hundred twelve cases with a repeat skin cancer diagnosis were compared to 227 controls, matched on age, sex, and study center. Total, respiratory, and food-specific IgE were measured in the baseline or year one (prior to diagnosis) sera samples for each subject.

Results—IgE levels were higher in cases with a second SCC than controls (comparing the highest quartile to the lowest, $OR_{total\ IgE}=1.44$; 95% CI:0.73–2.85; $OR_{respiratory\ IgE}=2.43$; 95% CI:1.16–5.06; $OR_{food\ IgE}=2.53$; 95% CI:1.19–5.35). The association between respiratory IgE and subsequent skin cancer was strongest among individuals with a tendency to sunburn ($OR_{respiratory\ IgE}=3.82$; 95% CI: 1.05–13.88) compared with those with a tendency to tan ($OR_{respiratory\ IgE}=0.95$; 95% CI:0.20–4.76). Among 25 subjects with repeat IgE measurements taken over several years, IgE levels were remarkably stable (interclass coefficient = 0.90 for total IgE).

Conclusions—These results indicate that allergy or allergy-associated IgE may be indicative of an immune phenotype that enhances risk of SCC, possibly via immune-associate inflammatory mediators.

Impact—Our results indicate that controlling allergy and IgE levels may be a new avenue of skin cancer prevention in susceptible populations, and implicate immune mechanisms in skin carcinogenesis.

Introduction

Squamous cell carcinoma (SCC) is the most common skin cancer apart from basal cell carcinoma (BCC), but with few recognized risk factors besides ultraviolet (UV) radiation. The skin is a major site of type I hypersensitivity reactions (atopic allergy), which may be related to risk of skin cancer. Two opposing mechanisms whereby allergy may affect cancer risk include enhanced immunosurveillance (leading to risk reduction) or increased inflammation (resulting in increased risk). Allergy and certain allergic conditions have been associated with reduced risk of certain cancers including pancreas, blood, and brain (1, 2). However, other cancers show increased risk with allergies, notably lung, with prostate and breast cancers having no relationship to allergies and asthma (1, 2). Skin cancers, including melanoma and non-melanoma histologies, demonstrated differing relationships with allergies in various case-control and cohort studies (3–8). This lack of clarity may be attributable to various forms of information bias including surveillance bias (cohort studies), varying or indeterminate definitions of allergy, and subject selection bias, which may explain part of the conflicting results (3–8). The largest and most recent study of atopic dermatitis and cancer risk indicated an increased risk of all types of skin cancers among individuals with atopic dermatitis (an allergic pathology of the skin) but it was unclear whether the disease, or immune suppressive treatments for the disease, was the cause for the increase (9).

Here, we examined whether markers of atopic allergy, total and specific IgE, are associated with SCC occurrence in a unique cohort study of subjects with a prior diagnosis of skin cancer (10, 11). We also determined the stability of IgE markers in repeat measurements from the same subjects, and whether skin cancer diagnosis impacts IgE levels (comparing pre- and post-diagnosis sera). Our results indicate that risk of SCC associated with atopic allergy may be modified by sun sensitivity, and that IgE phenotype is quite stable over time and unaffected by SCC diagnosis.

Materials and Methods

Study Participants

Our study sample was derived from a multicenter, randomized trial designed to test the capacity for oral β -carotene supplementation in preventing nonmelanoma skin cancer (11). Of the 5,232 potentially eligible participants (<85 years old, and having 1 or more SCC or BCC removed prior to enrollment), 1,805 enrolled. Participants completed a questionnaire upon enrollment, and at 4 month intervals as described previously (11); blood samples were obtained at each of these visits. Of the participants, 132 contracted SCC during the 3–5 year follow up period. These “cases” were matched to 264 “controls” who did not have cancer during the follow-up period and were randomly selected on the basis of age, gender, and study center (10). For both cases and controls, the earliest serum sample was utilized for case/control comparisons in order to minimize potential disease effects on IgE levels. Additionally, pre-post diagnosis sera were analyzed from 25 cases to determine whether SCC diagnosis impacted sera measurements. Finally, sera from 25 controls with 5 or more repeat blood draws were analyzed to test the variability of IgE over time. Skin type was classified by an examining dermatologist in 4 categories, from type I (always burns) to type IV (never burns) as described previously (11). For the current analysis, subjects were grouped into two categories (burn and tan); burn include types 1 and 2, tan includes types 3 and 4: 1=Always burns easily and severely, tans little or none and peels; 2=Usually burns easily and severely, tans minimally or lightly, also peels; 3=Burns moderately and tans about average; 4=Burns minimally, tans easily, and above average with each exposure, exhibits immediate pigment darkening reaction.

IgE measurements

An attempt was made to analyze the “first draw” sera available for cohort participants (baseline or next annual blood draw prior to the reference date). Total IgE was assessed using Phadia Diagnostics ImmunoCAP assay (Portage, MI) as previously described (12). Briefly, 40 uL of serum were incubated on the mix of allergens or anti-IgE antibodies bound to solid-phase ImmunoCAP. Incubations with enzyme-labeled antibodies against the heavy chain (constant) for total IgE were followed by incubations of developer and stop solutions, and measurements were made on a UniCAP 100. IgE was analyzed as a continuous variable, and also as a categorical variable using quartiles (based on the levels in controls).

Statistical Analysis

For case-control analyses, all three of the IgE measurements (total, respiratory, and food IgE) were categorized into quartiles based on the control distribution. The lowest quartile for IgE (a cutoff of 12.3 kU/L for total IgE, 98 kU/L for respiratory (Phadiatop), and 17 kU/L for food) was used as a reference, and odds ratios for matched pairs were calculated using conditional logistic regression for the three higher quartiles with adjustment for age (continuous), sex and smoking status (never, former, current). OR for stratified analyses were calculated using unconditional regression, and interaction between skin type and IgE variables was evaluated using Wald test. Spline curves were constructed to portray the proportion of cases falling within different levels of IgE, separately for “burn” and “tan” subjects. A loess curve represents the nonparametric trend of SCC risk with increasing IgE. In this analysis, measurements of IgE, data were natural log-transformed to approximate a normal distribution [$\ln(\text{IgE}+1)$].

To assess reliability of IgE measures, we applied a paired t-test to compare transformed IgE values from pre- and post diagnosis sera; data were transformed back to get geometric mean as well as 95% CI. Finally, we calculated interclass coefficients (ICC) for 25 subjects with over 5 repeat measurements. Interclass coefficients were calculated as

$$\frac{\sigma_a^2}{\sigma_a^2 + \sigma_e^2}.$$

Results

This nested case-control study has been described previously in detail (11). One hundred and twelve cases and 227 controls had available serum for IgE analysis. Three cases and 36 controls lacked a matched pair and therefore were excluded from the conditional logistic regression analysis. Cases with SCC were more likely to have a sun sensitive phenotype than controls and a higher rate of smoking than controls (Table 1). The distribution of blood draw season was similar between the groups and therefore not considered as a potential confounder in the analysis. Total IgE levels were an order of magnitude higher than food and respiratory IgE, indicating that most IgE content in sera was not captured in the “specific” panels [for all subjects, median (Interquartile Range (IQR)) total, respiratory, and food IgE values were 34.3 (89.7), 0.13 (0.27) and 0.04 (0.07) kU/L respectively].

There was an elevated OR of SCC among those in the highest versus lowest quartiles of total IgE levels, adjusted for smoking status, gender, and age, but associations were not statistically significant, and there was no evidence of a trend (Table 2). Positive associations were apparent for the upper quartile of IgE for both the respiratory and food specific markers ($\text{OR}_{\text{respiratory}} = 2.43$; 95% CI: 1.16–5.06, and $\text{OR}_{\text{food}} = 2.53$; 95% CI: 1.19–5.35).

When subjects were stratified by skin type, respiratory elevated IgE was largely associated with SCC among those with sun “burn” phenotype (OR = 3.82; 95% CI: 1.1–13.9, Table 2), and not for the “tan” phenotype (OR = 0.95, 95% CI: 0.2–4.8, Table 2). We explored the relationship of SCC and IgE further by constructing smoothened spline curves stratified by skin type. For all three IgE measurements, among those with a tendency to sun burn, risk increased with higher IgE levels, whereas among those with a tendency to tan, the trend was in the opposite direction (Figure 1). To understand the stability of IgE measurements over time, we tested IgE from the earliest available time point for 24 SCC cases, and again after their SCC diagnosis (approximately one to two years prior to diagnosis; minimum number of days between pre and post is 265, maximum 729 days; and range is 464 days.). IgE were highly similar between the two time periods (Table 3), indicating that IgE measurements are particularly stable and insensitive to SCC and its treatments. In repeat sera samples measured from 25 individuals (with at least 4 successive measurements over 2–8 years), we found a high degree of stability (Interclass coefficients of 0.90 for total IgE, 0.78 for respiratory IgE, and 0.89 for food IgE).

Discussion

The current study indicated that a marker of atopic allergy, specific IgE to respiratory and food allergens, identifies a population with increased risk to SCC among persons with prior skin cancer. Furthermore, this increased risk is confined to individuals with fair skin, *ie.*, those with a “burn” phenotype as determined by a dermatologist. Furthermore, IgE was found to be a highly stable biomarker over time and insensitive to diagnosis of cancer.

Allergy and allergic conditions are related to the etiology of several cancers, including pancreas, lymphoma, brain, and lung. While the skin is a primary target organ for allergic pathology [*e.g.*, atopic dermatitis (AD), eczema], little literature exists assessing the relationship of allergy and allergy biomarkers to skin cancers. The association of allergy to melanoma is equivocal: one study suggested marked reduction in melanoma in asthma patients in a health registry dataset (4), another cohort study indicated an increased melanoma risk in male hayfever patients (8), and a case-control study found a marked reduction in risk (5). Non-melanoma skin cancers were examined far less, possibly due to their lack of capture in most central cancer registries; results have been mixed. A twin study suggested an increased risk of skin cancer with atopic eczema, but was non-significant due to low power (13). A large cohort study found no relationship between non-melanoma skin cancer and allergy (6), while a case control study saw a slight inverse relationship (7). An inverse association also was observed in a study assessing potential effects of AD treatment on nonmelanoma skin cancer risk, using controls that had other types of dermatitis besides AD (14). Two recent large cohort studies demonstrated clear age-dependent increased risk of non-melanoma skin cancer with atopic dermatitis (9, 15). These cohorts may suffer from surveillance bias as atopic dermatitis patients will be subjected to frequent cutaneous examination by their physicians or their increased cancer risk could be confounded by immunosuppressive therapies for dermatitis (for example, glucocorticoid or light therapy) rather than dermatitis pathology itself (9, 15). Our current study may suffer less from detection bias as all participants were actively screened for subsequent cancer on an annual basis. However, as individuals in the highest quartile of IgEs are most likely to be those participants who are under treatment for allergies there may have been some treatment bias. In support of a true association is that the increased risk was largely confined to fair-skinned individuals, and skin type should not affect intention to obtain treatments for allergy. Additional studies on immunologic conditions that may affect skin cancer risk should incorporate biological markers to help clarify relationships as we have done here.

While total IgE is a good indicator of an atopic individual, the Phadia-designed specific allergen panels are diagnostics for clinically-relevant allergies. Our current results indicate that these specific allergies more closely define the “allergic immune phenotype” that impacts risk of skin cancer. Risk ratios were larger and associated with dose-related trends in risk with the specific panels (respiratory and food). In our prior studies on brain cancer, total IgE was a predictor of risk but self-reported respiratory and food allergies, as well as the numbers of reported allergies, were more consistently and strongly inversely associated with risk than total IgE (12, 16).

It is likely that the specific allergy pathologies themselves underlie risk rather than simply the presence of IgE. For skin cancer, this result is consistent with the theory that increased inflammation induced by allergic dermatitis, caused by specific allergens that induce disease pathology, may promote skin cancer occurrence. Type I hypersensitivity reactions are associated with increased oxygen radicals, recruitment of granulocytes with inflammatory mediators, and subsequent tissue damage and tissue remodeling. This pathology could promote skin cancer, much the way that allergic asthma promotes lung cancer [fourteen studies reviewed in (17)]. Our study population already had skin cancer, indicating that immune immunosurveillance systems had already failed once. It is not surprising that immunosurveillance mechanisms have failed a second time in these individuals (11). Whether such effects occur among those without a prior history of skin cancer remains to be elucidated.

The effect of elevated serum IgE on risk of skin cancer clearly differed by skin type – those who sunburn easily exhibited an increased risk related to higher IgE, whereas those with a tendency to tan demonstrated a reduced risk but not statistically significantly so (Table 2 and Figure 1). There are known pathophysiologic and etiologic skin cancer differences between tan and burn skin type individuals in populations worldwide (18). Darker skinned individuals, who exhibit the tan skin phenotype, are more likely to have an etiology of SCC involving burn scars or chronic infection, and a more aggressive phenotype (19). This suggests that some of the difference in associations with IgE and subsequent risk of skin cancer by skin type may be accounted for by differences in the disease phenotypes, with solar-associated skin cancer being more susceptible to the impact of allergy/IgE. Whether allergy and IgE levels might be related to skin type is more difficult to discern. Skin color is associated with several physical parameters of skin, including lipid content, permeability, and the number of cell layers (20), however, it is unclear if these differences affect allergies. Many allergy studies have found significant effects of socioeconomic and environmental factors on allergy separately from skin type, such as income, gender, house pets, and family history of atopic disease. Skin type may be confounded with one or more of these factors in the current study as well as many other allergy studies. Thus, while we accounted for some of the major risk factors for SCC occurrence, we cannot completely rule out the possibility of residual confounding.

While IgE is an immunoglobulin with a very short half-life in serum (about 48 hours), an IgE-related allergen reaction from a specific acute challenge (*eg.*, bee venom) can result in an elevated level of IgE for several years (21, 22). Our current data indicate that an IgE phenotype may be highly stable in individuals irrespective of allergen challenge – total IgE and perhaps more significantly, specific allergen IgEs are extremely stable for several years and over repeat measurements in different seasons, and insensitive to change in the presence of a new cancer. Very little information on longitudinal testing of IgE exists. Thus, the current result provides strong rationale for considering IgE as a stable biomarker of immune response in longitudinal studies rather than simply a transient and environmentally/seasonally labile marker. IgE as a marker could be effectively utilized in skin cancer case-control studies in which blood samples are collected after diagnosis.

In conclusion, allergy and allergy-associated IgE may impact risk of subsequent skin cancer among persons who have had a prior skin cancer. Respiratory allergy-related IgE is associated with a nearly 4-fold increased risk of skin cancer among persons with a sun sensitive skin type. Our findings raise the possibility that efforts to control allergy and IgE levels may be a new avenue of skin cancer prevention in susceptible populations.

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Figure 1.

Lowess-smoothed proportion of cases to controls over varying levels of IgE. IgE levels were natural log-transformed. Cases are positioned along the top of each panel at their measured IgE level, with controls positioned along the bottom. Individuals with tan phenotype are red dots, with burn phenotype as blue dots. The lowess line for each phenotype is indicated separately on each panel. **A.** Total IgE; **B.** Respiratory IgE; and **C.** food IgE. For panel C, outliers above 0.3 kU/L were removed.

Table 1

Distribution of selected characteristics among participants in the squamous cell carcinoma, nested case-control study.

Characteristic	SCC Cases (N=112)		Controls (N=227)		P-value
	No.	%	No.	%	
Age					
<65	33	29.46	72	31.72	0.905
65~69	35	31.25	71	31.28	
70 and above	44	39.29	84	37.00	
Gender					
Women	13	11.61	28	12.33	1.000
Men	99	88.39	199	87.67	
Smoking status					
Never	28	25.00	91	40.09	0.010
Former	62	55.36	110	48.46	
Current	22	19.64	26	11.45	
Skin type					
Tan	41	36.61	117	51.77	0.011
Burn	71	63.39	109	48.23	
Season					
Winter	29	25.89	75	33.04	0.388
Spring	36	32.14	57	25.11	
Summer	23	20.54	41	18.06	
Fall	24	21.43	54	23.79	

* One control did not have information on skin type

Table 2

Odds ratios between quartile categories of IgE using the lowest quartile among controls as reference:
Squamous cell carcinoma, nested case-control study.

Outcome	n (% [*])		Odds Ratio (95% CI) [†]
	Control (N=227)	Case (N=112)	
Overall			
Total IgE			
<=12.3 kU/L	45 (62.5)	27 (37.5)	1.00 (reference)
12.31~34.3 kU/L	50 (68.49)	23 (31.51)	0.79 (0.39, 1.62)
34.31~102 kU/L	49 (72.06)	19 (27.94)	0.55 (0.27, 1.12)
>102 kU/L	47 (54.02)	40 (45.98)	1.44 (0.73, 2.85)
ln(Total IgE)			1.08 (0.92, 1.26)
Specific - Respiratory			
<=0.09758 kU/L	52 (72.22)	20 (27.78)	1.0 (reference)
0.09759~0.1312 kU/L	46 (69.7)	20 (30.3)	1.16 (0.51, 2.66)
0.1313~0.3693 kU//L	49 (63.64)	28 (36.36)	1.47 (0.67, 3.20)
>0.3693 kU/L	44 (51.76)	41 (48.24)	2.42 (1.16, 5.06)
ln(Specific - Respiratory)			1.40 (1.07, 1.84)
Specific - Food			
<=0.01748 kU/L	49 (71.01)	20 (28.99)	1.00 (reference)
0.01749~0.03515 kU/L	47 (74.6)	16 (25.4)	0.90 (0.39, 2.07)
0.03516~0.08875 kU/L	47 (58.02)	34 (41.98)	1.87 (0.90, 3.91)
>0.08875 kU/L	48 (55.17)	39 (44.83)	2.53 (1.19, 5.35)
ln(Specific - Food)			1.27 (0.36, 4.54)

Outcome	n (% [*])		Odds Ratio (95% CI) [†]
	Control (N=117)	Case (N=41)	
Tan (Skin type 3 or 4)			
Total IgE			
<=12.3 kU/L	33 (75)	11 (25)	1.00 (reference)
12.31~34.3 kU/L	24 (64.86)	13 (35.14)	1.59 (0.59, 4.24)
34.31~102 kU/L	26 (76.47)	8 (23.53)	0.93 (0.32, 2.71)
>102 kU/L	34 (79.07)	9 (20.93)	0.90 (0.32, 2.53)
ln(Total IgE)			0.96 (0.76, 1.23)
Specific - Respiratory			
<=0.09758 kU/L	27 (69.23)	12 (30.77)	1.00 (reference)
0.09759~0.1312 kU/L	30 (83.33)	6 (16.67)	0.43 (0.14, 1.32)
0.1313~0.3693 kU//L	29 (69.05)	13 (30.95)	1.00 (0.38, 2.65)
>0.3693 kU/L	31 (75.61)	10 (24.39)	0.80 (0.29, 2.19)
ln(Specific - Respiratory)			1.15 (0.75, 1.78)
Specific - Food			
<=0.01748 kU/L	30 (75)	10 (25)	1.00 (reference)
0.01749~0.03515 kU/L	29 (82.86)	6 (17.14)	0.73 (0.23, 2.36)

Outcome	n (%*)		Odds Ratio (95% CI) [†]
	Control (N=117)	Case (N=41)	
0.03516~0.08875 kU/L	26 (65)	14 (35)	1.89 (0.69, 5.18)
>0.08875 kU/L	32 (74.42)	11 (25.58)	1.28 (0.46, 3.57)
ln(Specific - Food)			0.86 (0.13, 5.51)

Outcome	n (% [‡])		Odds Ratio (95% CI) [§]
	Control (N=109)	Case (N=71)	
Burn (Skin type 1 or 2)			
Total IgE			
<=12.3 kU/L	23 (58.97)	16 (41.03)	1.00 (reference)
12.31~34.3 kU/L	33 (73.33)	12 (26.67)	0.45 (0.18, 1.16)
34.31~102 kU/L	31 (72.09)	12 (27.91)	0.51 (0.20, 1.30)
>102 kU/L	22 (41.51)	31 (58.49)	1.71 (0.72, 4.08)
ln(Total IgE)			1.21 (0.98, 1.48)
Specific - Respiratory			
<=0.09758 kU/L	30 (78.95)	8 (21.05)	1.00 (reference)
0.09759~0.1312 kU/L	26 (61.9)	16 (38.1)	2.35 (0.85, 6.49)
0.1313~0.3693 kU//L	28 (63.64)	16 (36.36)	2.01 (0.73, 5.53)
>0.3693 kU/L	25 (44.64)	31 (55.36)	4.96 (1.89, 13.00)
ln(Specific - Respiratory)			1.89 (1.26, 2.83)
Specific - Food			
<=0.01748 kU/L	27 (69.23)	12 (30.77)	1.00 (reference)
0.01749~0.03515 kU/L	28 (71.79)	11 (28.21)	0.94 (0.34, 2.55)
0.03516~0.08875 kU/L	30 (60)	20 (40)	1.47 (0.60, 3.62)
>0.08875 kU/L	24 (46.15)	28 (53.85)	2.76 (1.13, 6.73)
ln(Specific - Food)			4.13 (0.51, 33.66)

* row percentage. Observations without complete case-control match (36 control and 3 cases) were excluded from analysis

[†] Odds ratio and p-values were derived from conditional logistic regression adjusted by gender, smoking status and age

[‡] row percentage. Observation with missing skin type (one in control group) was excluded from analysis

[§] Odds ratio and p-values were derived from unconditional logistic regression adjusted by gender, smoking status and age

Table 3

Comparison of IgE levels before and after diagnosis of squamous skin cell carcinoma among 24 subjects with paired data

Outcome	Geometric Mean (95% CI)		p-value *
	Pre	Post	
Total IgE (kU/L)	45.85 (23.68, 88.77)	45.34 (23.41, 87.81)	0.93
Specific - Phadiatope (kU/L)	1.52 (1.13, 2.03)	1.56 (1.13, 2.16)	0.28
Specific - Food (kU/L)	1.10 (1.05, 1.16)	1.11 (1.05, 1.17)	0.71

* P value from paired T-test of transformed data (see Methods)