Research Article

Cancer Epidemiology, Biomarkers & Prevention

History of Allergy and Atopic Dermatitis in Relation to Squamous Cell and Basal Cell Carcinoma of the Skin

Judy Cheng[1], M. Scot Zens[1], Eric Duell[2], Ann E. Perry[3], M. Shane Chapman[4], and Margaret R. Karagas[1]

Abstract

Background: Little is known about whether history of allergies and atopy is related to the occurrence of keratinocyte cancers. Thus, we evaluated the association between history of allergies and atopy and the incidence of squamous cell carcinoma (SCC) and early onset basal cell carcinoma (BCC).

Methods: As part of a population-based case–control study, interviews were conducted with 1,050 residents of New Hampshire (375 early onset BCC cases and 251 controls, 254 SCC cases and 432 controls). ORs of SCC and early onset BCC and history of allergy and atopic dermatitis were computed using logistic regression, while controlling for potential confounding factors.

Results: An overall inverse association was observed between a history of allergy and early onset BCC [OR, 0.61; 95% confidence interval (CI), 0.38–0.97] but not SCC (OR, 1.18; 95% CI, 0.78–1.79). Among women, we found reduced ORs of both early onset BCC and of SCC in relation to allergy history (early onset BCC OR, 0.53; 95% CI, 0.31–0.92 and SCC OR, 0.59; 95% CI, 0.29–1.19). Among men, we observed no clear association with early onset BCC (OR, 0.87; 95% CI, 0.39–1.99) and an increased risk of SCC (OR, 1.58; 95% CI, 0.93–2.69).

Conclusion: Our findings suggest that allergies and atopy may influence risk of early onset BCC and SCC, and that effects may be gender specific.

Impact: A deeper understanding of the immune mechanisms underlying allergies and atopy may provide new routes of preventing keratinocyte cancers. *Cancer Epidemiol Biomarkers Prev; 24(4); 749–54. ©2015 AACR.*

Introduction

Over the past few decades, there has been considerable debate over whether an atopic or allergic state influences the development of cancer. In theory, tumorigenesis may be enhanced by a hyperactive immune system where random pro-oncogenic mutations are induced from chronic immune stimulation (1). Mediators of the Th2 pathway also may divert tissue immunity away from an antitumor Th1 response (i.e., IgG1, TNFα) and toward an IgE response against allergens, and not tumor antigens through "inappropriate Th2 immune skewing" (2). On the other hand, atopy or allergy could protect against tumorigenesis either by promoting "immune surveillance" or by "prophylaxis" (3–5). The former could occur by heightened detection and elimination of neoplastic cells (3). In the latter, allergic symptoms may have evolved to "prophylactically" expel toxins, micro-organisms, or environmental particles that may contain carcinogens from the body (4, 5). These opposing theories are accompanied by conflicting results in the literature. Many studies have reported inverse associations with allergies (i.e., reactions to bee stings, food, medications; refs. 6–17), some indicated an increased risk (14, 15, 18), and a few found no association at all (19, 20). Similarly, for atopy-related diseases (i.e., asthma, atopic dermatitis), prior studies have found increased risks (14, 18, 21–26), decreased risks (6, 8, 9, 12, 14, 15, 27–30), or no association with cancer risks (1, 20). These disparate results in part may be attributable to differences in definitions of allergy and atopy, types of cancer under investigation, inability to control for potentially confounding factors, or inadequate statistical power.

The possible role of atopic and allergic conditions in the etiology of keratinocyte cancers has been explored only to a limited extent. One cohort study examining squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) as separate outcomes (57 BCC cases, 7 SCC cases) found evidence of an increased risk of both BCC and SCC among those with a history of atopic dermatitis (31). Two further studies of SCC included a nested case–control study among patients with skin cancer that reported higher prediagnostic IgE levels, a marker of type I hypersensitivity reactions or atopic allergy, among those who developed a new primary cutaneous SCC compared with controls who did not (32). Ji and colleagues (24) similarly found a higher risk of SCC among asthmatics compared with nonasthmatics. Other studies, which combined patients with BCC and SCC, reported mixed results, with some positive (24), some negative (6, 15, 30, 33, 34), and some null results (1, 15, 33). Aside from lacking specific histologic information, nearly all studies had limited information on possible modifying factors, such as age at onset, type of allergy,

[1]Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire. [2]Unit of Nutrition, Environment, and Cancer, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain. [3]Department of Pathology, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire. [4]Section of Dermatology, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire.

Corresponding Author: Margaret R. Karagas, Geisel School of Medicine at Dartmouth, Norris Cotton Cancer Center, Lebanon, NH 03756. Phone: 603-653-9010; Fax: 603-653-9093; E-mail: Margaret.R.Karagas@dartmouth.edu

doi: 10.1158/1055-9965.EPI-14-1243

Table 1. Selected characteristics of early onset BCC cases and controls and SCC cases and controls

Characteristic	Early onset BCC (*n*, %) (*n* = 375)	Controls for early onset BCC (*n*, %) (*n* = 251)	SCC (*n*, %) (*n* = 254)	Controls for SCC (*n*, %) (*n* = 432)
Age, y				
25–30	14 (3.9)	10 (4.0)	0	10 (2.3)
31–50	350 (96.1)	241 (96.0)	26 (10.2)	241 (55.8)
51–60	—	—	75 (29.5)	61 (14.1)
61–70	—	—	102 (40.2)	89 (20.6)
71–74	—	—	51 (20.1)	31 (7.2)
Gender				
Men	124 (34.1)	91 (36.3)	153 (60.2)	202 (46.8)
Women	240 (65.9)	160 (63.7)	101 (39.8)	230 (53.2)
Smoking status				
Never	207 (57.2)	120 (47.8)	95 (37.4)	181 (41.9)
Former	91 (25.1)	74 (29.5)	119 (46.8)	169 (39.1)
Current	64 (17.7)	57 (22.7)	40 (15.8)	82 (19.0)
Corticosteroid use[a]				
Yes	41 (11.9)	31 (12.9)	34 (13.5)	34 (13.9)
No	305 (88.1)	210 (87.1)	211 (83.7)	211 (86.1)
Immunosuppressant drug use[b]				
Yes	4 (1.1)	2 (0.8)	13 (5.3)	13 (5.3)
No	346 (98.9)	239 (99.2)	232 (94.7)	232 (94.7)
Organ transplantation				
Yes	1 (0.3)	1 (0.4)	9 (3.7)	1 (0.2)
No	341 (99.7)	240 (99.6)	231 (96.3)	405 (99.8)
Ultraviolet radiation therapy				
Yes	17 (4.9)	5 (2.1)	13 (5.3)	14 (3.4)
No	332 (95.1)	237 (97.9)	234 (94.7)	398 (96.6)
Number of lifetime painful sunburns				
0–1	106 (32.1)	108 (45.2)	95 (42.6)	201 (50.0)
2 or more	224 (67.9)	131 (54.8)	128 (57.4)	201 (50.0)
Skin reaction to 1st hour of summer sun				
Tan only	18 (5.0)	30 (12.0)	16 (6.4)	63 (14.7)
Mild sunburn/tan	138 (38.6)	123 (49.2)	136 (54.2)	217 (50.5)
Painful sunburn	170 (47.5)	81 (32.4)	76 (30.3)	123 (28.6)
Blister	32 (8.9)	16 (6.4)	23 (9.2)	27 (6.3)
Solar elastosis				
Absent	3 (1.0)	—	2 (1.0)	—
Minimal	51 (16.8)	—	4 (1.9)	—
Moderate	65 (21.5)	—	27 (12.8)	—
Severe	102 (33.7)	—	142 (67.3)	—
Actinic keratosis				
Yes	0 (0.0)	—	74 (35.2)	—
No	303 (100.0)	—	128 (61.0)	—

NOTE: Missing data: smoking status (2 BCC cases); corticosteroid use (18 BCC cases, 10 BCC controls, 9 SCC cases, 26 SCC controls); immunosuppressant use (14 BCC cases, 10 BCC controls, 9 SCC cases, 27 SCC controls); organ transplantation (1 BCC case, 1 BCC control, 14 SCC cases, 26 SCC controls); ultraviolet radiation therapy (15 BCC cases, 9 BCC controls, 7 SCC cases, 20 SCC controls); painful sunburn history (34 BCC cases, 12 BCC controls, 31 SCC cases, 30 SCC controls); skin reaction to 1st hour of summer sun (6 BCC cases, 1 BCC control, 3 SCC cases, 2 SCC controls); solar elastosis could not be determined from slide material (82 BCC cases, 36 SCC cases); actinic keratosis could not be determined from slide material (8 SCC cases).

[a]Corticosteroid or steroid pills, injections, or inhalers for ≥1 month.

[b]Methotrexate, azathioprine, or cyclosporine.

severity, and use of medications (e.g., NSAIDs, antihistamines, or immunosuppressive drugs). Therefore, we sought to elucidate the role of atopy and allergy in the development of keratinocyte malignancies in a population-based case–control study of invasive SCC and early onset BCC.

Materials and Methods

Study population

Subjects comprised participants in the New Hampshire Skin Cancer Study, an ongoing population-based case–control study of keratinocyte cancers obtained through an active surveillance network of dermatology, dermatopathology, and pathology clinics across New Hampshire. The study design has been previously described (35–37). To be eligible, subjects were required to be residents of New Hampshire, speak English, have a listed telephone number, and be between 25 and 74 years old at skin cancer diagnosis. In a small percentage of these cases (<1%), the diagnosing physicians refused to allow us to contact the subject and these subjects were excluded. The present study of allergy and atopy included incident cases of invasive SCC and early onset BCC (at or before age 50 years) diagnosed from July 2001 to June 2002. Controls were selected from files of New Hampshire residents provided by the New Hampshire Department of Transportation (for individuals <65 years old) and the Center for Medicaid and Medicare services (for individuals ≥65 years old). A shared control group was frequency-matched to the combined distribution of SCC and BCC cases based on gender and age strata of 24 to 35, 36 to 45, 46 to 50, 51 to 59, 60 to 64, 65 to 69, and 70 to 74 years old. Reference dates for controls were assigned matched

dates to the diagnosis dates of the cases. Of the 821 cases and 662 controls confirmed eligible, 618 (75%) cases and 432 (65%) controls were interviewed. Informed consent was obtained from participants in compliance with the Committee for Protection of Human Subjects at Dartmouth College in Hanover, New Hampshire.

Interview and pathology review

Structured personal interviews were conducted at the participants' homes. To minimize reporting bias, neither interviewers nor subjects were made aware of the hypotheses of the study, and interviewers were masked to participant's case–control status. Questions addressed aspects of each subject's lifestyle and personal history, including socioeconomic status, family and medical history, pigmentary characteristics, and skin sensitivity to sunlight. To assess sun exposure, interviewers used a standardized questionnaire modified from a previous study (38) and validated in our study population (36). Questions included information about amount of time spent outdoors from 9 a.m. to 5 p.m. during work and nonwork days, as well as lifetime number of painful sunburns.

We further asked participants if they were "ever allergic" to animals or animal dander, plants (i.e., trees, grass, weeds, or pollen), food (i.e., eggs, dairy, seafood, shellfish, berries, peanuts, wheat, or soy), insect stings (i.e., bees, hornets, wasps, yellow jackets, spiders, scorpions, bugs), molds, and house dust. For positive responses, we asked at what age they developed the allergy and at what age they last had an allergic reaction. In addition, we asked participants if a physician ever diagnosed them with eczema (atopic dermatitis) and if so, at what age they were diagnosed.

For cases, we requested the diagnostic specimens (slides and paraffin-embedded tumor tissue) from the original pathology laboratory. Slides underwent a standardized re-review of the histopathologic diagnosis by a board-certified dermatopathologist, who documented the presence in adjacent normal skin of actinic keratoses (presence or absence) and solar elastosis (absent, mild, moderate, or severe; ref. 36).

Method of analysis

We calculated the ORs and 95% confidence intervals (CI) for invasive SCC and early onset BCC associated with any allergy, specific types of allergies (animal, insect sting, food, plant, mold, and dust), and eczema with adjustment for age, gender, and skin reaction to the first hour of sunlight during the summer (blister, painful sunburn followed by peeling, mild sunburn followed by tanning, tanning with no sunburn). We further evaluated the potential confounding effects of race, education level (less than college, college, graduate school), family history of keratinocyte cancer, number of hours spent outdoors recreationally (i.e., during nonworking days), number of hours spent outdoors from 9 a.m. to 5 p.m. during the summer, number of lifetime painful sunburns, smoking status (never, former, current), number of moles (on the back), number of freckles (on the face, arms, shoulder), grams of alcohol consumed per month (beer, wine, liquor, and alcohol total), coffee consumption, tea consumption, tanning lamp use, history of ultraviolet radiation therapy, history of radiation therapy, and use of immunosuppressive medications, oral corticosteroids, and NSAIDs and included factors that changed the ORs by more than 10% (39). To assess the effects of severity, we calculated the ORs and 95% CIs for SCC and early onset BCC in relation to number of allergies (1 or >1 vs. none). We further examined age of onset of allergy (<20 years vs. $\geq$20 years), duration of allergy (<20 years vs. $\geq$20 years), and age of onset of eczema (<10 years vs. $\geq$10 years). As there is evidence that the incidence of atopic diseases and sensitization rates to environmental allergens vary by gender (40, 41), we examined for the presence of effect modification by stratifying by gender. All analyses were conducted with the statistical software SAS version 9.3.

Results

In total, 375 early onset BCC cases and 251 controls, and 254 SCC cases and 432 controls were available for analysis. Early onset BCC cases were more likely to have a sun-sensitive phenotype and a history of two or more lifetime painful sunburns as compared with controls. SCC cases were more likely to have had an organ transplant and to have taken immunosuppressant medications (i.e., methotrexate, azathioprine, cyclosporine) and less likely to have a tendency to tan as compared with controls. The prevalence of other characteristics was roughly similar between cases and controls (Table 1).

An inverse association was observed for early onset BCC and history of any allergy (OR, 0.61; 95% CI, 0.38–0.97), animal

Table 2. ORs of early onset BCC and SCC in relation to history of allergy and type of allergy

	Early onset BCC			SCC		
Variable	Cases *n* (%) = 375	Controls *n* (%) = 251	Adjusted OR[a] (95% CI)	Cases *n* (%) = 254	Controls *n* (%) = 432	Adjusted OR[b] (95% CI)
No allergies	166 (47.4)	98 (47.4)	1.00 (Ref)	125 (51.0)	192 (47.2)	1.00 (Ref)
Any allergy	184 (52.6)	143 (59.3)	0.61 (0.38–0.97)	129 (49.0)	215 (52.8)	1.18 (0.78–1.79)
Type of allergy						
Animal	69 (19.9)	71 (29.6)	0.39 (0.23–0.67)	38 (15.6)	82 (20.3)	1.41 (0.81–2.47)
Insect sting	33 (9.5)	27 (11.3)	1.13 (0.56–2.26)	34 (13.9)	44 (10.9)	1.44 (0.74–2.81)
Food	44 (12.6)	26 (10.8)	1.14 (0.53–2.28)	29 (11.9)	36 (8.9)	1.65 (0.83–3.27)
Plant	130 (37.8)	103 (42.9)	0.66 (0.42–1.05)	75 (30.9)	151 (37.3)	1.02 (0.66–1.59)
Mold	49 (14.6)	43 (18.3)	0.48 (0.23–0.91)	16 (6.8)	55 (13.9)	0.64 (0.30–1.38)
Dust	69 (19.9)	56 (23.4)	0.56 (0.33–0.95)	32 (13.3)	69 (17.2)	1.02 (0.55–1.89)
No eczema	295 (85.3)	213 (88.4)	1.00 (Ref)	213 (86.9)	367 (90.2)	1.00 (Ref)
Eczema	51 (14.7)	28 (11.6)	1.52 (0.77–3.01)	32 (13.1)	40 (9.8)	1.83 (0.97–3.45)

NOTE: *P* values are <0.05 if 95% CI does not include value of 1.

[a]Adjusted for sex, age, skin reaction to first hour of sunlight in the summer, and wine consumed per month (in grams).

[b]Adjusted for sex, age, skin reaction to first hour of sunlight in the summer, number of lifetime painful sunburns, and alcohol consumed per month (in grams).

Table 3. Association between type of allergy, eczema, number of allergies, age at onset and duration of allergy, and risk of early onset BCC and SCC stratified by gender

	Women			Men		
	Cases *n* (%)	Controls *n* (%)		Cases *n* (%)	Controls *n* (%)	
Early onset BCC	240	160	OR (95% CI)[a]	124	91	OR (95% CI)[a]
No allergies	112 (47.9)	60 (39.2)	1.00 (Ref)	54 (46.6)	38 (43.2)	1.00 (Ref)
Any allergy	122 (52.1)	93 (60.8)	0.53 (0.31–0.92)	62 (53.5)	50 (56.8)	0.87 (0.39–1.99)
Type of allergy						
Animal	52 (22.5)	50 (32.9)	0.35 (0.18–0.67)	17 (14.7)	21 (23.9)	0.39 (0.14–1.11)
Insect sting	23 (10.0)	17 (11.3)	1.07 (0.43–2.64)	10 (8.6)	10 (11.4)	1.57 (0.28–8.86)
Food	30 (12.9)	18 (11.8)	1.07 (0.45–2.57)	14 (12.2)	8 (9.1)	1.51 (0.43–5.34)
Plant	84 (36.5)	70 (46.1)	0.48 (0.27–0.87)	46 (40.4)	33 (37.5)	0.96 (0.42–2.23)
Mold	42 (18.7)	36 (24.3)	0.39 (0.19–0.80)	7 (6.31)	7 (8.1)	0.53 (0.07–4.12)
Dust	54 (23.4)	44 (29.0)	0.50 (0.27–0.96)	15 (13.0)	12 (13.8)	0.45 (0.14–1.41)
Number of allergies						
0	112 (47.9)	60 (39.2)	1.00 (Ref)	54 (46.6)	38 (43.2)	1.00 (Ref)
1	44 (18.8)	30 (19.6)	0.74 (0.33–1.67)	31 (26.7)	29 (33.0)	0.73 (0.28–1.90)
>1	78 (33.3)	63 (41.2)	0.42 (0.22–0.80)	31 (26.7)	21 (23.9)	1.09 (0.39–3.04)
Age of onset of allergy, y						
<20	71 (38.8)	56 (48.3)	0.48 (0.25–0.93)	34 (38.6)	33 (46.5)	0.73 (0.28–1.87)
≥20	51 (31.3)	37 (38.1)	0.52 (0.24–1.12)	28 (34.2)	17 (30.9)	1.17 (0.37–3.66)
Duration of allergy						
<20 years	48 (30.0)	37 (38.1)	0.64 (0.30–1.35)	26 (32.5)	20 (34.5)	0.85 (0.28–2.61)
≥20 years	74 (39.8)	56 (48.3)	0.42 (0.21–0.84)	36 (40.0)	30 (44.1)	0.90 (0.34–2.34)
No eczema	194 (84.0)	133 (86.9)	1.00 (Ref)	101 (87.8)	80 (90.9)	1.00 (Ref)
Eczema	37 (15.7)	20 (12.5)	1.59 (0.66–3.80)	14 (11.5)	8 (8.8)	2.02 (0.61–6.72)
Age of onset of eczema, y						
<10	11 (5.2)	8 (5.4)	1.07 (0.28–4.11)	3 (2.7)	2 (2.4)	2.27 (0.17–29.47)
≥10	26 (11.8)	12 (8.3)	2.00 (0.66–6.05)	11 (9.8)	6 (7.0)	2.06 (0.55–7.74)
SCC	101	230	OR (95% CI)[b]	153	202	OR (95% CI)[b]
No allergies	51 (52.6)	95 (43.8)	1.00 (Ref)	74 (50.0)	97 (51.0)	1.00 (Ref)
Any allergy	46 (47.4)	122 (56.2)	0.59 (0.29–1.19)	74 (50.0)	93 (49.0)	1.58 (0.93–2.69)
Type of allergy						
Animal	10 (10.4)	56 (25.9)	0.43 (0.15–1.20)	28 (19.1)	26 (13.8)	2.71 (1.30–5.65)
Insect sting	16 (16.5)	27 (12.6)	0.97 (0.36–2.62)	18 (12.2)	17 (9.0)	1.78 (0.70–4.51)
Food	11 (11.6)	21 (9.7)	1.07 (0.36–3.15)	18 (12.2)	15 (7.9)	2.36(0.93–5.98)
Plant	26 (27.4)	89 (41.2)	0.46 (0.21–1.02)	49 (33.1)	62 (32.8)	1.48 (0.85–2.58)
Mold	5 (5.5)	42 (19.9)	0.22 (0.05–1.07)	11 (7.6)	13 (7.0)	1.60 (0.59–4.36)
Dust	16 (16.7)	51 (23.7)	0.79 (0.30–2.08)	16 (11.0)	18 (9.6)	1.27 (0.54–3.01)
Number of allergies						
0	51 (52.6)	95 (43.8)	1.00 (Ref)	74 (50.0)	97 (51.1)	1.00 (Ref)
1	22 (22.7)	44 (20.3)	0.74 (0.32–1.70)	39 (26.4)	61 (32.1)	1.22 (0.67–2.25)
>1	24 (24.7)	78 (35.9)	0.45 (0.18–1.13)	35 (23.7)	32 (16.8)	2.40 (1.18–4.91)
Age of onset of allergy, y						
<20	12 (19.1)	68 (41.7)	0.35 (0.12–0.98)	40 (35.1)	52 (34.9)	1.54 (0.80–2.96)
≥20	34 (40.0)	54 (36.2)	0.80 (0.37–1.75)	34 (31.5)	41 (29.7)	1.67 (0.86–3.25)
Duration of allergy						
<20 years	22 (30.1)	50 (34.5)	0.82 (0.36–1.88)	30 (28.9)	44 (31.2)	1.19 (0.59–2.38)
≥20 years	24 (32.0)	72 (43.1)	0.44 (0.18–1.07)	44 (37.3)	49 (33.6)	2.05 (1.09–3.87)
No eczema	85 (84.2)	188 (81.7)	1.00 (Ref)	128 (86.5)	179 (94.2)	1.00 (Ref)
Eczema	12 (11.9)	29 (12.6)	0.95 (0.35–2.57)	20 (13.3)	11 (5.5)	3.50 (1.39–8.82)
Age of onset of eczema, y						
<10	5 (5.3)	11 (5.2)	0.86 (0.15–4.83)	5 (3.7)	3 (1.6)	2.43 (0.44–13.51)
≥10	7 (7.6)	18 (8.7)	1.01 (0.32–3.14)	15 (10.5)	8 (4.3)	3.84 (1.33–11.15)

NOTE: *P* values are <0.05 if 95% CI does not include value of 1.

[a]Adjusted for age, skin reaction to first hour of sunlight in the summer, and wine consumed per month (in grams).

[b]Adjusted for age, skin reaction to first hour of sunlight in the summer, number of lifetime painful sunburns, and alcohol consumed per month (in grams).

allergy (OR, 0.39; 95% CI, 0.23–0.67), mold allergy (OR, 0.48; 95% CI, 0.23–0.91), or dust allergy (OR, 0.56; 95% CI, 0.33–0.95; Table 2). No clear associations were found with insect sting allergy, food allergy, or plant allergy, and for eczema, a weak positive association was observed that lacked statistical precision. For SCC, associations tended to be positive, but with wide confidence intervals that did not exclude the possibility of a chance association (Table 2).

For women, an inverse association with allergy was found for early onset BCC (OR, 0.53; 95% CI, 0.31–0.92). An inverse relationship was also observed for SCC (OR, 0.59; 95% CI, 0.29–1.19), but the association lacked statistical precision. Women with more allergies, an allergy beginning before age 20 years, or of more than 20 years duration had a lower risk of early onset BCC and SCC. Among men, a slightly decreased risk of early onset BCC (OR, 0.87; 95% CI, 0.39–1.99) was observed but with wide CIs. In contrast, an elevated OR was observed for SCC in men with eczema (OR, 3.50; 95% CI, 1.33–11.15) and to a lesser extent allergies (OR, 1.58; 95% CI, 0.93–2.69). Allergy at a younger age and of long duration was also

associated with a slightly decreased risk of early onset BCC, and long duration and a greater number of allergies was associated with an increased risk of SCC among men (Table 3). We did not detect any clear patterns of risk by age of onset of eczema (Table 3).

Discussion

Overall, we observed a reduced risk of early onset BCC associated with history of allergies, particularly among women, and, with limited statistical precision, a positive trend in risk of SCC among men. Our trend toward an increased risk of SCC associated with allergy is consistent with the two previous studies examining SCC specifically (24, 32). For example, a longitudinal cohort study from Sweden found a positive association with SCC and asthma (standardized incidence ratio, 1.33; 95% CI, 1.19–1.48; ref. 24). A more recent nested case–control study using IgE as a biologic marker for atopic allergy observed an elevated risk of SCC in relation to higher IgE levels (32). Notably, the latter study had a high proportion of men, and in our study, the positive association with SCC was largely confined to men.

There is evidence to support the role of IgE in mediating the immune response to neoplasia (42). For instance, allergic donor peripheral blood mononuclear cells exhibit decreased tumor killing capacity in the presence of tumor antigen–specific IgE. This suggests that occupancy of IgE receptors by allergen-specific IgE may deter binding of tumor antigen–specific IgE and subsequent tumor-eradicating functions (2, 42). Type I hypersensitivity responses are also associated with recruitment of inflammatory mediators, increased oxygen radicals, and tissue remodeling. These changes could promote tumorigenesis in a mechanism similar to how asthma may increase the risk for lung cancer (32, 43).

Our results differed for BCC and SCC tumors, and between men and women. Although the mechanisms are uncertain, proteins, like galectin-3, important for the development of Th2 responses to epicutaneously introduced antigens, are downregulated in keratinocyte tumors compared with the non-neoplastic epidermis (44) and appear to be differentially expressed in BCC and SCC tumors (45). With respect to gender differences, hormones are known to influence allergic phenotype and biomarkers of atopy. In particular, estrogen can skew the immune response toward allergy and promote antigen-specific IgE production (40). Skin reactivity to inhalant allergens and serum IgE levels are higher in males than females at younger ages, and then reverses later in life (41). Responses to allergens on skin tests further vary with the menstrual cycle, with a heightened reaction during ovulation when estrogen levels peak (46). Mechanistically, estrogens can affect each step of the allergic sensitization process (antigen presentation, Th2 polarization, isotype switching to IgE, and mast cell degranulation) through ERα, ERβ, and G-protein–coupled receptor 30 (GPCR 30; ref. 47). Nonetheless, further studies are needed to confirm or refute our findings.

In our data, having allergy symptoms at a young age (<20 years old), long duration of allergy (>20 years), and multiple types of allergies were each associated with a reduced risk of early onset BCC among both men and women, albeit with limited statistical precision. Wiemels and colleagues (48) reported that early onset of respiratory allergy (≤12 years old) was associated with higher IgE levels compared with later onset disease. For pancreatic cancer, Holly and colleagues (13) similarly found reduced risks of pancreatic cancer with increasing number of allergies and severity of allergic symptoms. Examining risks for various cancers, Hwang and colleagues (34) found that individuals with more than one atopic disease had lower cancer risks compared with those with only one.

There are several limitations to this study that need to be kept in mind. First, our case–control study had the potential for selection bias, which we attempted to minimize by choosing cases and controls from a geographically defined U.S. population. Second, patients with allergies or atopy may visit dermatologists more often, leading to a higher probability of detecting skin cancer. The presence of this bias is not strongly suggested by our data, especially as inverse associations with allergies were detected especially among women. Third, we investigated atopic dermatitis as clinically defined eczema, as we did not have data on components of the Hanifin and Rajka criteria, which are used in clinical practice (49). We attempted to refine the definition of eczema by stratifying by age of eczema diagnosis whereby a younger age of onset is more consistent with true atopic dermatitis. However, no clear associations emerged. Accuracy of self-report remains an issue for which we tried to improve by asking participants about allergy symptoms, medication use, age at onset, and duration.

In conclusion, our findings of specific histologic types of keratinocyte cancers in the general population of the United States raise the possibility of a reduced risk of early onset BCC and SCC among women with allergies, and of an increased SCC risk among men. Our results, like others, suggest that the association between cancer and allergy is complex and may depend on the type of allergy, specific allergens, and further may be specific to type of cancer and by gender.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.S. Chapman, M.R. Karagas
Development of methodology: M.S. Chapman, M.R. Karagas
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.S. Zens, A.E. Perry, M.R. Karagas
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Cheng, M.S. Zens, M.S. Chapman, M.R. Karagas
Writing, review, and/or revision of the manuscript: J. Cheng, M.S. Zens, E. Duell, M.S. Chapman, M.R. Karagas
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.R. Karagas
Study supervision: M.R. Karagas

Acknowledgments

The authors thank the physicians comprising the New Hampshire Skin Cancer Study Group and the New Hampshire Society of Dermatology.

Grant Support

This work was in part supported by grant R01CA57494 awarded to M.R. Karagas from the NIH, NCI.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 4, 2014; revised January 6, 2015; accepted January 30, 2015; published OnlineFirst February 10, 2015.

References

1. Eriksson NE, Mikoczy Z, Hagmar L. Cancer incidence in 13811 patients skin tested for allergy. J Investig Allergol Clin Immunol 2005;15:161–6.
2. Josephs DH, Spicer JF, Corrigan CJ, Gould HJ, Karagiannis SN. Epidemiological associations of allergy, IgE and cancer. Clin Exp Allergy 2013; 43:1110–23.
3. Lindelof B, Granath F, Tengvall-Linder M, Ekbom A. Allergy and cancer. Allergy 2005;60:1116–20.
4. Sherman PW, Holland E, Sherman JS. Allergies: their role in cancer prevention. Q Rev Biol 2008;83:339–62.
5. Hsiao JR, Ou CY, Lo HI, Huang CC, Lee WT, Huang JS, et al. Allergies and risk of head and neck cancer: an original study plus meta-analysis. PLoS One 2013;8:1–11.
6. Fisherman EW. Does the allergic diathesis influence malignancy. J Allergy 1960;31:74–8.
7. Johnson KJ. Relation of cancer to allergy. J Lancet 1966;86:5–11.
8. Mackay WD. Incidence of allergic disorders and cancer. Br J Cancer 1966;20:434–7.
9. Gabriel R, Dudley BM, Alexander WD. Lung cancer and allergy. Br J Clin Pract 1972;26:202–4.
10. Meers PD. Allergy and cancer. Lancet 1973;1:884–5.
11. Rozencwaig R. Allergies - protective against cancer but predisposing to heart-disease. Postgrad Med 1982;72:42.
12. Hughes WF, Raitz RL. Comparison of cancer occurrence in allergic and non-allergic populations. Ann Allergy 1979;43:163–4.
13. Holly EA, Eberle CA, Bracci PM. Prior history of allergies and pancreatic cancer in the San Francisco Bay Area. Am J Epidemiol 2003;158:432–41.
14. Mills PK, Beeson WL, Fraser GE, Phillips RL. Allergy and cancer - organ site-specific results from the Adventist Health Study. Am J Epidemiol 1992;136:287–95.
15. Vena JE, Bona JR, Byers TE, Middleton E, Swanson MK, Graham S. Allergy-related diseases and cancer: an inverse association. Am J Epidemiol 1985;122:66–74.
16. Cotterchio M, Lowcock E, Hudson TJ, Greenwood C, Gallinger S. Association between allergies and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2014;23:469–80.
17. Olson SH, Hsu M, Satagopan JM, Maisonneuve P, Silverman DT, Lucenteforte E, et al. Allergies and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Case-Control Consortium. Am J Epidemiol 2013; 178:691–700.
18. McWhorter WP. Allergy and risk of cancer - a prospective study using NHANES I follow-up data. Cancer 1988;62:451–5.
19. McKee WD, Arnold CA, Perlman MD. A double-blind study of comparative incidence of malignancy and allergy. J Allergy 1967;39:294–301.
20. Shapiro S, Heinonen OP, Siskind V. Cancer and allergy. Cancer 1971;28: 396–400.
21. Robinette CD, Fraumeni JF. Asthma and subsequent mortality in World War II veterans. J Chronic Dis 1978;31:619–24.
22. Hagstromer L, Ye WM, Nyren O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. Arch Dermatol 2005;141:1123–7.
23. Talbot-Smith A, Fritschi L, Divitini ML, Mallon DFJ, Knuiman MW. Allergy, atopy, and cancer: a prospective study of the 1981 Busselton cohort. Am J Epidemiol 2003;157:606–12.
24. Ji J, Shu X, Li X, Sundquist K, Sundquist J, Hemminki K. Cancer risk in hospitalised asthma patients. Br J Cancer 2009;100:829–33.
25. Olesen AB, Engholm G, Storm HH, Thestrup-Pedersen K. The risk of cancer among patients previously hospitalized for atopic dermatitis. J Invest Dermatol 2005;125:445–9.
26. Arana A, Wentworth CE, Fernandez-Vidaurre C, Schlienger RG, Conde E, Arellano FM. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. Br J Dermatol 2010;163: 1036–43.
27. Alderson M. Mortality from malignant disease in patients with asthma. Lancet 1974;2:1475–7.
28. Cockcroft DW, Klein GJ, Donevan RE, Copland GM. Is there a negative correlation between malignancy and respiratory atopy. Ann Allergy 1979;43:345–7.
29. Ford RM. Primary lung cancer and asthma. Ann Allergy 1978;40:240–2.
30. Kallen B, Gunnarskog J, Conradson TB. Cancer risk in asthmatic subjects selected from hospital discharge registry. Eur Respir J 1993;6:694–7.
31. Jensen AO, Svaerke C, Farkas DK, Olesen AB, Kragballe K, Sorensen HT. Atopic dermatitis and risk of skin cancer: a Danish Nationwide Cohort Study (1977–2006). Am J Clin Dermatol 2012;13:29–36.
32. Wiemels JL, Wiencke JK, Li ZZ, Ramos C, Nelson HH, Karagas MR. Risk of squamous cell carcinoma of the skin in relation to IgE: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2011;20:2377–83.
33. Ming ME, Levy R, Hoffstad O, Filip J, Abrams BB, Fernandez C, et al. The lack of a relationship between atopic dermatitis and nonmelanoma skin cancers. J Am Acad Dermatol 2004;50:357–62.
34. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC, et al. Cancer risk in patients with allergic rhinitis, asthma and atopic dermatitis: a nationwide cohort study in Taiwan. Int J Cancer 2012;130:1160–7.
35. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. Int J Cancer 1999;81:555–9.
36. Karagas MR, Zens MS, Nelson HH, Mabuchi K, Perry AE, Stukel TA, et al. Measures of cumulative exposure from a standardized sun exposure history questionnaire: a comparison with histologic assessment of solar skin damage. Am J Epidemiol 2007;165:719–26.
37. Karagas MR, Waterboer T, Li Z, Nelson HH, Michael KM, Bavinck JNB, et al. Genus β human papillomaviruses and incidence of basal cell and squamous cell carcinomas of skin: population based case-control study. Br Med J 2010;341:290–9.
38. Kricker A, Armstrong BK, English DR, Heenan PJ. Pigmentary and cutaneous risk-factors for non-melanocytic skin-cancer - a case-control study. Int J Cancer 1991;48:650–62.
39. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993;138:923–36.
40. Bonds RS, Midoro-Horiuti T. Estrogen effects in allergy and asthma. Curr Opin Allergy Clin Immunol 2013;13:92–9.
41. Osman M. Therapeutic implications of sex differences in asthma and atopy. Arch Dis Child 2003;88:587–90.
42. Karagiannis SN, Wang Q, East N, Burke F, Riffard S, Bracher MG, et al. Activity of human monocytes in IgE antibody-dependent surveillance and killing of ovarian tumor cells. Eur J Immunol 2003;33:1030–40.
43. Santillan AA, Camargo CA Jr, Colditz GA. A meta-analysis of asthma and risk of lung cancer (United States). Cancer Causes Control 2003;14: 327–34.
44. Larsen L, Chen H-Y, Saegusa J, Liu F-T. Galectin-3 and the skin. J Dermatol Sci 2011;64:85–91.
45. Kapucuoglu N, Basak PY, Bircan S, Sert S, Akkaya VB. Immunohistochemical galectin-3 expression in non-melanoma skin cancers. Pathol Res Pract 2009;205:97–103.
46. Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I. Influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen. Clin Exp Allergy 1995;25:461–6.
47. Chalubinski M, Kowalski ML. Endocrine disrupters–potential modulators of the immune system and allergic response. Allergy 2006;61:1326–35.
48. Wiemels JL, Wiencke JK, Patoka J, Moghadassi M, Chew T, McMillan A, et al. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. Cancer Res 2004;64:8468–73.
49. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980:44–7.