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Cancer Epidemiology, Biomarkers & Prevention

Research Article

Risk of Cervical Cancer Associated with Allergies and Polymorphisms in Genes in the Chromosome 5 Cytokine Cluster

Lisa G. Johnson[1], Stephen M. Schwartz[1,2], Mari Malkki[3], Qin Du[3], Effie W. Petersdorf[3], Denise A. Galloway[1,4,5], and Margaret M. Madeleine[1,2]

Abstract

Background: Human papillomavirus is the acknowledged cause of cervical cancer. We hypothesized that allergies, characterized by hyperimmune reaction to common allergens and which have been associated with various cancers, may be related to cervical cancer, and that genetic variation in cytokine genes related to allergies might impact cervical cancer risk.

Methods: We investigated the risk of invasive squamous cell cervical cancer (SCC) associated with self-reported allergies and with variation in allergy-related cytokine genes using data from a case–control study (561 cases, 1,258 controls) conducted in Washington State. Logistic regression models yielded odds ratios (OR) and 95% CI.

Results: Pollen allergy, the most commonly reported allergy, was associated with reduced SCC risk (OR: 0.6; 95% CI: 0.5–0.8). Of 60 tagging single-nucleotide polymorphisms covering eight genes (*CSF2, IL3, IL4, IL13, CSF2RB, IL4R, IL13RA1, IL13RA2*), several were related to pollen allergies among controls: *IL4R* rs3024647 (dominant OR: 1.5; 95% CI: 1.0–2.3; $P = 0.04$), *CSF2RB* rs16997517 (dominant OR: 2.2; 95% CI: 1.0–4.7; $P = 0.04$), and *IL13* rs1800925 (per-allele OR: 1.7; 95% CI: 1.3–2.4; $P = 0.0007$). Two variants were inversely associated with SCC risk: *IL4R* rs3024656 (per-allele OR: 0.8; 95% CI: 0.6–1.0; $P = 0.03$) and *CSF2RB* rs16997517 (dominant OR: 0.4; 95% CI: 0.2–0.9; $P = 0.04$).

Conclusions: Pollen allergies were related to reduced SCC risk. CSF2RB rs16997517 was directly related to pollen allergies in controls and to reduced SCC risk.

Impact: If other studies confirm these results, the mechanism behind allergy-associated immune response associated with SCC risk may be worth exploring in the context of therapeutic or prophylactic vaccines. *Cancer Epidemiol Biomarkers Prev; 20(1); 199–207. ©2011 AACR.*

Introduction

Though cervical carcinoma has become increasingly rare in the developed world due to effective screening programs, it is the second most common malignancy diagnosed among women worldwide (1). There is strong and accepted evidence that cervical cancer is necessarily preceded by persistent infection with oncogenic human papillomavirus (HPV; ref. 2). Given the viral etiology of cervical cancer and the increased risk of anogenital malignancies in immune-suppressed populations such as organ transplant recipients (3–7) and those with HIV, it is likely that conditions related to immunologic dysregulation contribute to a woman's risk of developing cervical cancer.

Allergic symptoms result from an overactive response by the immune system to common environmental allergens and have been associated with a reduced risk of several types of cancer, most notably pancreatic cancer, leukemia, and glioma, and with an increased risk of lung cancer (8–10). No association has been reported between a history of allergies and cervical cancer risk, though 1 study reported a null finding between childhood allergies and cervical cancer in young women in a British cohort (11). There are 2 widely held theories to explain the inverse relationship observed between allergies and most cancer types, either of which could be relevant for cervical cancer etiology. Under the prophylaxis theory, allergies help expel carcinogens, preventing tumors from

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being initiated (12). In the setting of cervical cancer, the immune response related to allergies would act prophylactically to clear oncogenic HPV infection before a persistent infection can be established. The second potential mechanism is tumor immunosurveillance, whereby the heightened immune response in allergy sufferers could target tumor-associated antigens and destroy tumor cells early in progression (13–17).

The biological basis for the most common causes of allergic symptoms is rooted in an abnormal inflammatory response to normally harmless exogenous substances (e.g., pollen). Allergen-specific T-helper type 2 (Th2) cells produce interleukin (IL) 4, IL5, and IL13 that mediate mucus production, eosinophil development, and production of allergen-specific IgE by B cells (18). IgE binds the allergens, which activates the IgE receptor signaling pathway (19). The cytokines resulting from the allergy cascade are coded by genes that are primarily located on chromosome 5, specifically in region 5q31, and include *IL4*, *IL9*, and *IL13* (which stimulate and amplify Th2 response), and *IL3*, *IL5*, and *CSF2* (which promote eosinophil production and activation). A recent review indicates that pollen allergies may confer a Th2-polarized response by initiating migration of activated dendritic cells and recruiting Th2 cells to the site of pollen exposure (20). Because a Th2-polarized response generally produces less effective antitumor response (21), it is worth exploring how variation in the genes for Th2 cytokines may be related to SCC and how that may affect a relationship between SCC and allergic disease. Though it is possible that the Th2 cytokine response in allergic disease is detrimental to immune response to tumors, allergy-related eosinophil stimulation has been shown to have direct tumoricidal effects (22–24).

Given the large body of literature reporting a relationship between allergies and cancer coupled with the known importance of immunologic response to HPV infection in cervical neoplasia, we tested the hypothesis that a history of allergies is associated with reduced risk of invasive squamous cell cervical cancer (SCC). We also sought to determine whether common variation in cytokine genes previously reported to be related to allergic response are related to SCC risk.

Methods

Study population and interview data

Case and control recruitment have been described previously (25). Briefly, cases were women diagnosed with invasive squamous cell carcinoma of the cervix (SCC; ICD-O codes 8010–8076) between 1986 and 1998 in the Seattle metropolitan area. Cases were identified through the Cancer Surveillance System, which is part of the Surveillance Epidemiology and End Results (SEER) program (26). Controls were selected using random digit telephone dialing (RDD) and were frequency matched to cases on reference year and age who lived in the same area. Only controls who had an intact uterus at the reference date were included in the study.

All participants completed an in-depth in-person interview that included questions about topics such as number of lifetime sex partners, smoking behaviors, Pap screening habits, medical history, medication use in the 10 years prior to diagnosis, and open-ended questions about allergies: "Have you ever had allergies to anything?" with positive responses followed by "Have you ever had allergies to: foods; pollens/plants/grasses/trees; medications/drugs/immunizations; inhalants/molds/dust/animals/tobacco; other," and the specific types of allergens reported by participants were written down by the interviewer and later coded.

The case response proportion was 63.9%, and the control response proportion was 68.1% (the RDD eligibility screening response, 92.1%, multiplied by the participation proportion, 74.0%). There were 561 cases and 1,258 controls available for the current analysis. Blood was drawn from willing participants (88.6% of cases and 88.3% of controls) and peripheral leukocytes were separated and stored. Study participants completed an in-person informed consent process with a trained interviewer, and all study procedures and materials were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Single-nucleotide polymorphism selection

Single-nucleotide polymorphisms (SNP) were included from genes with functions related to allergy in the cytokine cluster on chromosome 5 and their receptors including *IL13*, *IL13RA1*, *IL13RA2*, *IL4*, *IL4R*, *IL3*, *CSF2*, and *CSF2RB*. Tagging SNPs (tagSNP) were selected to maximize coverage of common variation in the genes including 4,000 base pairs (bp) both 3′ and 5′ of the gene based on r-squared greater than or equal to 0.8, given a minimum-reported minor allele frequency (MAF) in Caucasians of 0.05 using the resequencing data source (HapMap or SeattleSNPs PGA) with the largest number of genotyped polymorphisms among Caucasians for each given gene. Additional SNPs were included that were either of interest based on the previous literature or that were within a coding region and had a reported MAF of at least 0.02. All SNPs genotyped and their characteristics are listed in Supplementary Table 1. Ligand IL3 interacts with coreceptors CSF2RB (also known by aliases *IL3RB* and *IL5RB*) and IL3RA, but genotyping of SNPs in *IL3RA* was not attempted due to its location on the pseudoautosomal portion of the X and Y chromosomes. We also did not attempt to genotype the single tagSNP in *IL5* due to predicted poor performance on the Illumina platform (see in the text later), and thus did not pursue genotyping of tagSNPs in the *IL5* receptor α gene. Additional, redundant tagSNPs were sometimes selected to ensure coverage of areas of the gene that were of interest or to guard against missed coverage due to possible assay failure. None of these redundant SNPs was significantly associated with allergies or SCC in this study.

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Lab methods

DNA was extracted from buffy coats using a manual phenol/chloroform method. The Illumina GoldenGate platform was used to type 1,536 SNPs, of which 72 corresponded to the SNPs from the candidate genes included in this study. Of the 72 SNPs assayed by the GoldenGate platform, 14 failed, which included: 1 SNP of 4 in *CSF2*, 5 SNPs of 19 in *CSF2RB*, 1 SNP of 5 in *IL4*, 6 SNPs of 26 in *IL4R*, and 1 SNP of 6 in *IL13RA1*. We excluded 1 additional SNP that was assayed but had a call frequency below 0.9, which left 57 SNPs that passed on the GoldenGate platform. Call rates for passing SNPs on the GoldenGate platform ranged from 0.977 to 1.00, averaging 0.998. A subset of SNPs ($n = 5$) that had high failure rates on the Illumina platform after a portion of the samples had been genotyped were assayed using a proprietary competitive, allele-specific PCR system (27). Call rates for passing SNPs on this platform ranged from 0.984 to 0.994, averaging 0.989. Two SNPs were passed on both platforms (rs2227282 in *IL4* and rs3024678 in *IL4R*). Because cross-platform concordance was very high for these 2 SNPs (0.994 and 0.999, respectively), results were taken from the Illumina platform and supplemented by results from the Kbioscience platform for those subjects that were missing results data from the Illumina platform.

Genotyping was deemed successful for a sample that yielded results for at least for 90% of the passing SNPs, which amounted to 511 controls and 281 cases on the GoldenGate platform, and 521 controls and 271 cases on the Kbioscience platform. Randomly chosen replicate DNA aliquots were included for 7% of subjects, and replicate-pairs with discordant results ranged from 0.0% to 0.7% of the SNP-pairs for each SNP. Hardy–Weinberg equilibrium (HWE) was tested among the Caucasian controls for each SNP, with a threshold of 0.00004 (0.05/1,288, the number of SNPs passing the OPA overall, including those not in this study); however, no SNPs in this analysis had an HWE *P* value below that level. SNPs found to be monomorphic were not considered for further analysis: rs2069616 (expected MAF in Caucasians 0.48) and rs17811365 (expected MAF in Caucasians 0.07).

Tumor tissue was collected from all cases who consented and for whom adequate tissue was available for release (85%). PCR methods were used to amplify HPV DNA extracted from paraffin-embedded tumor tissue using methods previously described (28). Laboratory procedures were performed without the knowledge of patient characteristics. Tissue sections were cut from tumor blocks using strict precautions to prevent intersample HPV DNA contamination; sections from an HPV-negative heart tissue block were cut and tested for HPV as every tenth study sample. HPV DNA-negative results were tested for PCR amplification of a 536- or 268-bp fragment of the human β-globin gene to determine whether any DNA was present and 6.3% of the tumor blocks were β-globin negative. Tissue for genotyping of HPV DNA was not collected from controls.

Statistical analyses

All analyses were performed using the Stata statistical package (StataCorp). We used unconditional logistic regression models to compute odds ratios (OR) and 95%CI to approximate the relative risk of SCC associated with allergy history and with SNPs in *CSF2*, *IL3*, *IL4*, *IL13*, *CSF2RB*, *IL4R*, *IL13RA1*, and *IL13RA2*. We modeled genotypes as log-additive (per-allele) unless there were 5 or fewer homozygous variant carriers. In those instances, we used a dominant model. Specific allergies to the most common groups of allergens were explored: dust, pollens, mold, cats, dogs, bee sting, penicillin, sulfa drugs, and food (subtypes: milk, chocolate, shellfish, wheat, citrus, eggs). We also explored the association between a history of allergy and SNPs in unconditional logistic regression models controlled for age and race. We tested for confounding of the risk estimates by history of Pap testing, smoking, number of lifetime sex partners, reference year, educational attainment, and household income. Variables added to the multivariate baseline model, which included race (modeled dichotomously as white vs. non-white) and age at reference (modeled as a continuous variable), that changed the risk estimates by at least 10% were included as confounders.

We sought to determine whether the association between allergies and SCC was more likely to be due to reporting bias, the effects on HPV infection/persistence, or impact on limiting tumor promotion or progression. Though variables related to socioeconomic status (SES) were not confounders in this analysis, we evaluated models stratified on education, income, and Pap screening, with evidence of heterogeneity possibly reflecting differential reporting of allergy across strata. We used polytomous logistic regression for analyses where case groups defined by FIGO disease stage (stages 1a, 1b, 2+) were compared with controls, and where case groups defined by the type of HPV DNA present in their tumors (HPV16 only, HPV18 only, HPV16 and HPV18) were compared with controls. The polytomous models allowed us to compare relative risk ratios (RRR) between the constrained and the unrestricted forms of the model and to investigate heterogeneity of results across case groups, and using a likelihood ratio test (LRT) *P* value to determine statistical significance at $P < 0.05$. If risk of SCC varies by disease stage, it could indicate that the risk factor either promotes or reduces tumor progression.

The association *P* values for the genotype analyses were corrected for multiple comparisons using a Holm correction on a per gene basis, with a significant threshold of 0.05 (29). Using the Holm correction, results were ordered from lowest *P* value to the highest and then corrected by the number of tests, therefore the significant threshold is specific to each SNP.

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Results

Study population characteristics

Cases were more likely than controls to be non-white (11.4% vs. 7.9%), to have lower educational attainment and household income (Table 1). Consistent with other studies of cervical cancer, the case women reported a greater number of lifetime sex partners compared with controls, an earlier sexual debut, to have been current smokers at reference (41.9% vs. 23.8%), to be parous (82.2% vs. 74.6%), and to have greater parity.

Allergies and SCC

Approximately, 60% of controls and 53% of cases reported at least 1 allergy, and history of any allergy was associated with reduced risk of SCC (OR: 0.7; 95% CI: 0.6–0.9; Table 2). Allergies to any airborne agent (any of mold, dust, or pollen) was associated with a 40% reduced risk of SCC (OR: 0.6; 95% CI: 0.5–0.7). Pollen was the most commonly reported allergen (31.6% of controls, 20.9% of cases) and was associated with reduced risk of SCC (OR: 0.6; 95% CI: 0.5–0.8). Adjustment for other types of allergies did not affect the risk estimates for pollen allergy. When further exploring the risk of SCC associated with any type of allergies, there was no reduction in risk for those with allergies that did not include pollen (OR for any allergies other than pollen relative to those with no history of allergies: 1.0; 95% CI: 0.8–1.2; data not shown). Among pollen types, allergies to tree pollen was associated with the greatest reduction in risk of SCC (OR: 0.3; 95% CI: 0.2–0.6). Antihistamine use was neither a confounder nor an effect modifier of the relationship between pollen allergies and SCC risk (data not shown). Though allergies to dust, mold, and pollen were associated with reduction in risk of SCC, the risk estimates for dust and mold were no longer significant after adjustment for pollen allergies (respectively OR: 0.8; 95% CI: 0.6–1.2; OR: 0.8; 95% CI: 0.5–1.4; data not shown). Allergy to any type of foods was reported by 14.7% of controls and 10.9% of cases and was associated with reduced risk of SCC (OR: 0.7; 95% CI: 0.5–0.9). Allergy to wheat was rare in controls (1.7%) but was reported by only 1 case (0.2%), resulting in a significantly reduced risk of SCC (OR: 0.1; 95% CI: 0.0–0.8). Allergy to cats was associated with a 40% reduction in disease risk (OR: 0.6; 95% CI: 0.4–1.0; $P < 0.05$) and allergy to dogs was associated with a 50% reduction in disease risk that was not statistically significant (OR: 0.5; 95% CI: 0.3–1.0), and neither result was significant after adjustment for pollen allergies (OR: 0.8; 95% CI: 0.5–1.2; OR: 0.7; 95% CI: 0.4–1.3, respectively).

To explore whether the inverse association between SCC and pollen allergy was potentially related to tumor promotion or progression rather than on HPV infection or persistence, we looked at the associations with disease by stage. We hypothesized that if the allergy association was a marker for response to a tumor antigen that higher stage cancers would be more strongly associated with pollen allergy. There was a significant difference in the risk estimates by stage, with a stronger inverse association for stage 2+ invasive SCC (12.7% of these cases reported pollen allergy; RRR: 0.3; 95% CI: 0.2–0.5) than for micro-invasive (stage 1a) SCC (RRR: 0.7; 95% CI: 0.5–0.9; LRT P compared with stage 2+ = 0.01) or stage 1b SCC (RRR: 0.6; 95% CI: 0.4–0.9; LRT P compared with stage 2+ = 0.04) associated with pollen allergies. This difference

Table 1. Characteristics of cervical squamous cell carcinoma cases and controls, Seattle metropolitan area, 1986–1998

Characteristic	Controls (n = 1,258) n (%)	Cases (n = 561) n (%)
Reference age, y		
18–39	420 (33.4)	181 (32.3)
40–59	398 (31.6)	168 (29.9)
60–74	440 (35.0)	212 (37.8)
Race		
Caucasian	1158 (92.1)	497 (88.6)
African-American	31 (2.5)	24 (4.3)
Asian	45 (3.6)	21 (3.7)
Other	24 (1.9)	19 (3.4)
Highest educational attainment		
Some high school or less	65 (5.2)	82 (14.6)
High-school graduate	301 (23.9)	186 (33.2)
Some college/technical school	442 (35.1)	197 (35.1)
College graduate	295 (23.4)	63 (11.2)
Postgraduate education	155 (12.3)	33 (5.9)
Household income		
<$15,000	148 (11.9)	158 (28.5)
$15,000–30,000	360 (29.0)	161 (29.0)
$30,000–45,000	264 (21.3)	107 (19.3)
>$45,000	469 (37.8)	129 (23.2)
refused/unknown	17	6
Lifetime number of sex partners		
0	15	0
1	382 (30.9)	62 (11.1)
2 to 4	348 (28.1)	191 (34.1)
5 to 14	374 (30.2)	212 (37.9)
15+	133 (10.8)	95 (17.0)
Age at first intercourse, y		
Up to 17	316 (25.2)	221 (39.5)
18–19	482 (38.5)	239 (42.7)
20+	455 (36.3)	100 (17.9)
refused/unknown	5	1
Cigarette smoking at reference date		
Never	657 (52.2)	185 (33.0)
Former	302 (24.0)	141 (25.1)
Current	299 (23.8)	235 (41.9)
Parity		
0	319 (25.4)	100 (17.8)
1	213 (16.9)	99 (17.6)
2	374 (29.7)	152 (27.1)
3+	352 (28.0)	210 (37.4)

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Table 2. Association of cervical squamous cell carcinoma with self-reported history of allergies, Seattle metropolitan area, 1986–1998

Allergy history	Controls (n = 1,258) n (%)	SCC Cases (n = 561) n (%)	OR[a]	(95% CI)
Any allergy	750 (59.6)	299 (53.3)	**0.7**	**(0.6–0.9)**
Airborne allergies	445 (35.4)	134 (23.9)	**0.6**	**(0.5–0.7)**
Pollen	397 (31.6)	117 (20.9)	**0.6**	**(0.5–0.8)**
Grasses	115 (9.1)	25 (4.5)	**0.6**	**(0.3–0.8)**
Trees	77 (6.1)	12 (2.1)	**0.3**	**(0.2–0.6)**
Ragweed	14 (1.1)	3 (0.5)	0.6	(0.2–2.0)
Dust	177 (14.1)	50 (8.9)	**0.6**	**(0.4–0.9)**
Mold	112 (8.9)	29 (5.2)	**0.6**	**(0.4–0.9)**
Antibiotic allergies	244 (19.4)	96 (17.1)	0.9	(0.7–1.1)
Penicillin	129 (10.3)	58 (10.3)	1.1	(0.8–1.5)
Sulfa drugs	107 (8.5)	40 (7.1)	0.8	(0.5–1.2)
Food allergies	185 (14.7)	61 (10.9)	**0.7**	**(0.5–0.9)**
Milk	40 (3.2)	13 (2.3)	0.7	(0.4–1.4)
Chocolate	23 (1.8)	6 (1.1)	0.6	(0.2–1.5)
Shellfish	21 (1.7)	6 (1.1)	0.6	(0.2–1.6)
Wheat	21 (1.7)	1 (0.2)	**0.1**	**(0.0–0.8)**
Citrus fruit	18 (1.4)	8 (1.4)	0.9	(0.4–2.1)
Eggs	14 (1.1)	3 (0.5)	0.5	(0.1–1.7)
Animal allergies[b]	181 (14.4)	56 (10.0)	**0.7**	**(0.5–1.0)**
Cats	129 (10.3)	35 (6.2)	**0.6**	**(0.4–1.0)**
Dogs	57 (4.5)	13 (2.3)	0.5	(0.3–1.0)
Bee sting	27 (2.1)	12 (2.1)	0.9	(0.5–1.9)

[a]Adjusted for age at reference date, smoking (never, former, current), number of lifetime sex partners.
[b]Includes allergies to cats, dogs, horses, cows, rabbits, bee stings, and responses of "other" or "all animals."

between microinvasive and stage 2+ persisted when adjusted for Pap-screening interval (LRT $P = 0.03$).

There was also a significant difference in the risk of SCC that was positive for HPV16 DNA containing tumors (HPV16+ SCC) relative to SCC that contained HPV18 DNA (HPV18+ SCC) associated with pollen allergies (LRT P for difference = 0.02). Pollen allergies were associated with a reduced risk of HPV16+ SCC (OR: 0.6; 95% CI: 0.4–0.8, data not shown), and 20.7% of the 285 HPV16+ SCC cases reported pollen allergens. A stronger reduced risk of HPV18+ SCC (OR: 0.2; 95% CI: 0.1–0.5) was reported and only 7.3% of the 41 SCC cases with HPV18+ SCC reported pollen allergies. Cases with both HPV16 and HPV18 detected in their tumor (n = 26) were similar to controls with 30.8% reporting pollen allergies (OR: 1.0; 95% CI: 0.4–2.3).

We next assessed the relationship between allergies and surrogates of SES and other common SCC risk factors among controls. We were concerned that the association between allergies and cervical cancer was potentially driven by demographic differences between cases and controls. Pollen allergies were not associated with lifetime number of sex partners ($\chi^2P = 0.9$), smoking ($\chi^2P = 0.6$), household income ($\chi^2P = 0.3$), or recency of Pap screening ($\chi^2P = 0.2$) in the controls. There was a borderline association between pollen allergies and educational attainment: those controls reporting pollen allergies were somewhat more likely to have at least a college degree than those without (41% vs. 33%, respectively; $\chi^2P = 0.06$). There was a nonsignificant difference in the association between pollen allergies and SCC across groups defined by educational attainment. The relative risk of SCC associated with pollen allergies was similar for those with a high school diploma or less (OR: 0.7; 95% CI: 0.4–1.0; $P < 0.05$) and those with some college or technical school (OR: 0.7; 95% CI: 0.5–1.1), but slightly lower among women with a college degree or more (OR: 0.4; 95% CI: 0.3–0.7; LRT P for difference in ORs = 0.2; data not shown). This nonsignificant difference in the risk estimates for SCC was due to a lower proportion of pollen

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allergies reported by those controls with less educational attainment (28.1% compared with 36.2% among those controls with at least a college degree), whereas the proportion of cases reporting a history of pollen allergies was similar in each stratum (20.1% compared with 20.8%). There was no difference in the risk of SCC associated with history of pollen allergies across groups defined by household income or interval since last Pap screening, with ORs ranging from 0.6 to 0.7 in each stratum.

Genetic risk of pollen allergies among controls and risk of SCC

Cases and controls who were genotyped were largely similar to the participants in the parent study overall. Controls who were genotyped were similar to controls who were not genotyped, other than being more likely to have had more than 1 sex partner (73.7% vs. 65.9%), to have had Pap screening in the 3 years prior to reference (89.2% vs. 83.2%), and to be slightly younger at reference (mean 41.1 years vs. 44.2 years; data not shown). Cases who were genotyped were similar to cases who were not genotyped, other than being more likely to have had Pap screening in the 3 years prior to diagnosis (57.7% vs. 51.1%).

Among Caucasian controls, there was strong linkage disequilibrium between several SNPs in our data (see Supplementary Fig. 1). Table 3 presents the results of the genotype analysis for SNPs that had a significant association (before correction) with either pollen allergies or cervical cancer. Not all of these results remained significant after correction for multiple comparisons and corrected P values for these are noted in Table 3 and in the text later. The full genotype association results for the SNPs typed for the candidate genes in this study are presented in Supplementary Table 2. Controls who carried a rare nonsynonymous coding SNP in *CSF2RB* (rs16997517) more commonly reported pollen allergies than those without the variant (OR: 2.2; 95% CI: 1.0–4.7; corrected $P < 0.05$; Table 3). There was also a significant log-additive association between *IL13* promoter SNP rs1800925 and pollen allergies among the controls (per-allele OR: 1.7; 95% CI: 1.3–2.4; corrected $P = 0.0007$), which remained statistically significant after correcting for multiple comparisons. In addition, 2 SNPs in *IL4R* were also related to allergy among controls. There was an increase in the reported history of pollen allergy among controls who were heterozygous for a rare nonsynonymous coding SNP in *IL4R* (rs1805016, OR: 1.8; 95% CI: 1.0–3.3; corrected P value $= 0.07$), relative to those controls who did not carry the variant allele. Controls who carried a rare intronic SNP in *IL4R* also reported a modestly higher rate of pollen allergies (rs3024647, OR: 1.5; 95% CI: 1.0–2.3; $P < 0.05$).

The *CSF2RB* nonsynonymous coding SNP associated with pollen allergies in the controls (rs16997517) was also associated with reduced risk of SCC (OR: 0.4; 95% CI: 0.2–0.9; corrected $P = 0.03$). Two intronic SNPs were also associated with reduced risk of SCC (*CSFRB2* rs6000488, OR: 0.7; 95% CI: 0.5–1.0; corrected $P = 0.09$, and *IL4R* rs3024656, OR: 0.8; 95% CI: 0.6–1.0; corrected $P < 0.05$), though not with pollen allergies. There was no detectable effect modification between pollen allergies and the SNPs with respect to cervical cancer risk as the size of the study population was not adequately powered to pursue a formal statistical test for interaction.

Discussion

We found that a history of any allergies was related to a reduced risk of SCC (OR: 0.7; 95% CI: 0.6–0.9); the association was principally due to reduced risk of SCC associated with pollen allergies (OR: 0.6; 95% CI: 0.5–0.8). Although there was a strong log-additive association between the minor allele for rs1800925 (*IL13* promoter SNP previously reported to be associated with atopy; refs. 30, 31) and pollen allergies among controls (OR: 1.7; 95% CI: 1.3–2.4; $P = 0.0007$), this SNP was not related to risk of SCC. Interestingly, a rare nonsynonymous coding SNP in *CSF2RB*, rs16997517, was related to both increased reportage of pollen allergies in controls and decreased risk of SCC. If there is a link between reduced risk of cervical cancer and allergies, there may be an important link that remains to be uncovered between cervical cancer and immune response.

The association between SCC and pollen allergies did not appear to be due to confounding by socioeconomic status (SES) or other characteristics commonly associated with SCC, nor was there appreciable effect modification by these factors. This study had extensive information on demographic characteristics to address this potential source of confounding. We were also able to partially address whether the hyperimmune response related to allergy might lead to increased tumor surveillance. Possibly in support of this hypothesis, the risk of more advanced stage disease (stage 2+, OR: 0.3; 95% CI: 0.2–0.5) associated with pollen allergies was found to be lower than risk for stage 1a or 1b cervical cancer (microinvasive, OR: 0.7; 95% CI: 0.5–0.9; stage 1b, OR: 0.6; 95% CI: 0.4–0.9), even after adjustment for recency of Pap screening. These results should be cautiously interpreted as the stage distribution of our case group is affected by several factors including participants who died prior to recruitment who may have had higher stage disease at diagnosis. It is possible that women with early stage disease may have been more likely to participate than those with later stage disease. The stage distribution may also have been affected by differences in Pap screening that we were not able to capture in our analytic variables.

We also saw that there was variability in the risk of SCC associated with pollen allergies by the type of HPV present in the tumor, with a greater reduced risk of HPV18+ disease than HPV16+ disease. Thus, it is possible that allergies are acting to reduce the exposure to persistent HPV infection in a type-specific manner, supporting a prophylaxis mechanism of reduced cancer risk associated with allergies.

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Table 3. TagSNPs in candidate allergy-related genes associated with either history of pollen allergies among controls or with cervical SCC at $P < 0.05$, Seattle metropolitan area, 1986–1998

	Controls						SCC Cases			
	No pollen allergy		Pollen allergy		Risk of allergy among controls		SCC		SCC risk relative to all controls	
SNPs	*n*	(%)	*n*	(%)	OR[a]	(95% CI)	*n*	(%)	OR[a]	(95% CI)
CSF2RB										
rs16997517[b]										
GG	322	(95.8)	159	(91.4)	ref		274	(97.5)	ref	
AG	14	(4.2)	15	(8.6)	**2.2**	**(1.0–4.7)**	5	(1.8)	**0.4**	**(0.2–0.9)**
AA	0	(0.0)	0	(0.0)		$P = 0.039$[d]	2	(0.7)		$P = 0.035$[d]
rs6000488[b]										
GG	263	(78.3)	134	(77.0)	ref		237	(84.3)	ref	
AG	69	(20.5)	36	(20.7)	1.2	(0.6–2.5)	38	(13.5)	**0.7**	**(0.5–1.0)**
AA	4	(1.2)	4	(2.3)			6	(2.1)		$P = 0.037$
IL13										
rs1800925										
GG	236	(70.0)	97	(55.7)	ref		177	(63.2)		
AG	92	(27.3)	65	(37.4)	**1.7**	**(1.3–2.4)**	89	(31.8)	1.1	(0.8–1.4)
AA	9	(2.7)	12	(6.9)		$P = 0.0007$[d]	14	(5.0)		
IL4R										
rs1805016[b,c]										
AA	312	(92.3)	156	(86.7)	ref		240	(89.6)	ref	
AC	26	(7.7)	24	(13.3)	**1.8**	**(1.0–3.3)**	26	(9.7)	1.0	(0.6–1.6)
CC	0	(0.0)	0	(0.0)		$P = 0.045$	2	(0.7)		
rs3024647[b]										
AA	250	(74.2)	114	(65.5)	ref		201	(71.5)	ref	
AG	77	(22.8)	56	(32.2)	**1.5**	**(1.0–2.3)**	70	(24.9)	1.0	(0.7–1.3)
GG	10	(3.0)	4	(2.3)		$P = 0.041$[d]	10	(3.6)		
rs3024656										
GG	148	(43.9)	83	(47.7)	ref		155	(55.2)	ref	
AG	154	(45.7)	76	(43.7)	0.9	(0.7–1.2)	105	(37.4)	**0.8**	**(0.6–1.0)**
AA	35	(10.4)	15	(8.6)			21	(7.5)		$P = 0.033$[d]

[a] Models are log-additive modeling of the genotypes, adjusted for race (white, non-white) and age (linear). The risk estimates presented are the per-allele ORs.
[b] Dominant modeling used due to one or more cells with less than 5 participants.
[c] Genotyped on Kbioscience platform.
[d] Result significant after Holm correction.

Interpretation of our results is limited by several factors. Our response proportions, though good for epidemiologic studies of cervical cancer, were somewhat low at 64% and 68% for cases and controls, respectively. If the interviewed participants differed on allergy status from those who were not interviewed, our estimates could be hampered by response bias, though this would likely be nondifferential based on case–control status; so, the bias would likely be toward the null. In addition, because our data on allergy history were obtained by self-report, it is possible that reporting bias affected our results. However, differential reporting of allergies seems unlikely, as allergy reporting was unrelated to most of the cofactors that we explored. Also, it is reassuring that the prevalence of allergies in our questionnaire was similar to prevalence estimates found in other studies. The prevalence of allergies was reported from the NHANES III study, which reported a 40%-positive skin prick test for "outdoor" allergens, including 26.2% positive for allergy to short ragweed, 18.1% positive for Bermuda grass, and 13.2% positive for white oak (32).

Our genetic analyses are limited to the extent that several SNPs of potential importance failed genotyping and by the limited number of genes related to allergy. Specifically, not

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having data for *IL5*, part of the chromosome 5q31 cluster, limits our ability to examine the impact of genes in that region on allergy and SCC.

Wang and Diegpin, Turner, and Merrill noted in their reviews that atopy was associated with a reduced risk for cancers at several sites, including pancreatic cancer, leukemia, and brain tumors and an increased risk of increased risk of lung cancer (8–10). One published study has explored the relationship between atopy and cervical cancer. Montgomery et al. (11) reported no association between hay fever in childhood and cervical cancer using 2 British cohorts (the National Child Development Study and the 1970 British Cohort Study cohorts), OR: 1.04 (95% CI: 0.50–2.17). The cohorts followed all persons born during April 3 to 9, 1958, and March 5 to 11, 1970, to ages 42 and 30 years, respectively, which led to a younger study population relative than that reported on here (average diagnosis age in the current study population was 43 years). The cohorts also collected information on hay fever only at age 16, missing those who developed allergies in adulthood and captured cervical cancer only by self-report, possibly including women who self-reported cancer but had *in situ* disease. A Swedish study reported by Ivansson et al., found that women who reported that their sons had allergies were at reduced risk of both *in situ* (OR: 0.84; 95% CI: 0.81–0.86) and invasive (OR: 0.80; 95% CI 0.71–0.92) cervical cancer (33). Though the latter study suggests that a genetic predisposition to allergies may be associated with reduced risk of cervical disease, it is difficult to draw conclusions based on the association between allergy in sons and cervical disease in mothers.

Previous reports have shown a relationship between the variant allele at *IL13* promoter SNP rs1800925 and atopy (30, 31) corresponding to the strong increased association between this SNP and allergy history among controls in this study. However, the association between allergy and cervical cancer was not found to be directly mediated by this SNP or any of the other variants in the 5q31 cluster that we studied. We did find an inverse relationship between SCC and rare coding SNP *CSF2RB* rs16997517, which was also related to an increased history of allergies (among controls). It is also possible that variations in other genes involved in allergic disease that were not measured in our study could contribute to both an increase in the risk of pollen allergy and decrease in the risk of cervical cancer.

There are 2 theoretical biological mechanisms by which allergies could be influencing reduced risk of cervical cancer: prophylaxis against exposure to the primary carcinogen involved in cervical cancer, persistent infection with oncogenic HPV through a hyperimmune response; or the destruction of malignant cells via tumor immunosurveillance shortly after initiation or early in progression (34). We hypothesized that if women with allergies had increased tumor immunosurveillance due to generalized hyperimmunity, allergy history would have a stronger inverse relationship to higher stage disease than lower stage cancer because a longer time to tumor development increases the chances for tumors to be detected at a lower stage. Our data showed a significantly greater reduction in risk of later stage disease (FIGO stage 2+, OR: 0.3) than for earlier stage disease (FIGO stage 1a or 1b, ORs: 0.7 and 0.6, respectively). An alternative hypothesis based on the data in this study might be that a lower risk of advanced stage at diagnosis could indicate that those with pollen allergies who do develop invasive SCC may have had a less rapid disease progression, perhaps due to hyperstimulation of the immune system. Similarly, if there is conformational homology between HPV epitopes or cervical cancer tumor antigens and pollen fragments recognized by the immune system, there could be efficient elimination of HPV infection before the virus can establish a persistent infection. It is difficult to assess which mechanism may be dominant in the relationship between cervical cancer and pollen allergies, but either or both together could have a role. Given the localized allergic response is specific to mucous membranes, possibly including the cervix, the role of the localized immune response in efficient elimination of HPV either through nonspecific humoral response or some correlated Th1 response is possible (35, 36); alternatively, even the recruitment of eosinophils may then have a tumoricidal effect (22–24).

As with many other types of cancer, we found that the risk of cervical cancer is reduced in persons with allergies. This is the first study to report this association and it needs to be confirmed in other populations. Further genetic characterization of allergy-related phenotypes may uncover shared genetic pathways and exploration of possible biological mechanisms mediating this relationship may be warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Table 1. Characteristics of tag SNPs genotyped for CSF2, IL3, IL4, IL13, CSF2RB, IL4R, IL13RA1, and IL13RA2.

Gene	SNP	Chromosomal location	SNP context	Alleles (Maj/Min), amino acid	Control MAF	Genotyping platform
CSF2	rs2069616	5:131435976	5' flanking	G	**0.00***	OPA
CSF2	rs25882	5:131439359	nonsynon	A/G, I117T	0.20	OPA
CSF2	rs27438	5:131441154	3' flanking	G/A	0.20	OPA
IL3	rs181781	5:131423014	5' flanking	G/A	0.10	OPA
IL3	rs2069803	5:131428332	3' flanking	A/G	0.41	OPA
IL3	rs31481	5:131425101	intronic	G/A	0.16	OPA
IL3	rs40401	5:131424377	nonsynon	G/A, P27S	0.21	OPA
IL4	rs2070874	5:132037609	5'-UTR	G/A	0.14	OPA
IL4	rs2227282	5:132041078	intronic	C/G	0.26	BOTH
IL4	rs2243248	5:132036543	5' flanking	A/C	0.08	OPA
IL4	rs2243263	5:132041198	intronic	C/G	0.11	OPA
IL13	rs1800925	5: 132070708	promoter	A/G	0.19	OPA
IL13	rs20541	5: 132023863	nonsynon	G/A, Q144R	0.20	OPA
IL13	rs2243204	5: 132027393	3' flanking	A/G	0.10	OPA
IL13	rs848	5: 132024399	3'-UTR	A/C	0.21	OPA
CSF2RB	rs13055341	22:35667718	3' flanking	A/G	0.14	OPA
CSF2RB	rs131840	22:35663740	synonymous	G/A, P648P	0.18	OPA
CSF2RB	rs131842	22:35665719	3' flanking	A/G	0.19	OPA
CSF2RB	rs131843	22:35667355	3' flanking	G/A	0.29	OPA
CSF2RB	rs1534880	22:35659057	intronic	G/C	0.44	OPA
CSF2RB	rs16845	22:35656389	nonsynon	C/G, E249Q	0.06	OPA
CSF2RB	rs16846	22:35655779	synonymous	G/A, C234C	0.04	OPA
CSF2RB	rs16997517	22:35663882	nonsynon	G/A, P696S	0.03	OPA
CSF2RB	rs17811365	22:35652766	intronic	A	**0.00***	OPA
CSF2RB	rs2075941	22:35648461	intronic	G/A	0.47	OPA
CSF2RB	rs6000488	22:35651806	intronic	G/A	0.11	OPA
CSF2RB	rs6000495	22:35664899	3' flanking	G/A	0.18	OPA
CSF2RB	rs738149	22:35660195	intronic	G/A	0.27	OPA
CSF2RB	rs909486	22:35653934	intronic	G/A	0.45	OPA
IL4R	rs1805010	16:27263704	nonsynon	A/G, I75V	0.43	KBIO
IL4R	rs1805011	16:27281373	nonsynon	A/C, E400A	0.12	KBIO
IL4R	rs1805015	16:27281681	nonsynon	A/G, S503P	0.16	OPA
IL4R	rs1805016	16:27282428	nonsynon	A/C, S752A	0.05	KBIO
IL4R	rs2234895	16:27265428	synonymous	G/A, N167N	0.08	OPA
IL4R	rs2234897	16:27281113	synonymous	A/G, F313F	0.02	OPA
IL4R	rs2239347	16:27266522	intronic	A/C	0.45	OPA
IL4R	rs3024530	16:27258188	intronic	A/G	0.43	OPA
IL4R	rs3024544	16:27260858	intronic	G/A	0.13	OPA
IL4R	rs3024577	16:27265704	intronic	A/G	0.43	OPA
IL4R	rs3024578	16:27265852	intronic	G/A	0.07	OPA
IL4R	rs3024586	16:27267542	intronic	G/A	0.04	OPA
IL4R	rs3024590	16:27268129	intronic	G/A	0.51	OPA
IL4R	rs3024604	16:27270731	intronic	A/G	0.08	OPA

Gene	SNP	Chromosomal location	SNP context	Alleles (Maj/Min), amino acid	Control MAF	Genotyping platform
IL4R	rs3024610	16:27271659	intronic	G/A	0.53	OPA
IL4R	rs3024622	16:27272954	intronic	G/C	0.32	OPA
IL4R	rs3024629	16:27273531	intronic	G/A	0.06	OPA
IL4R	rs3024633	16:27274000	3'-UTR	A/G	0.08	OPA
IL4R	rs3024647	16:27275473	intronic	A/G	0.16	OPA
IL4R	rs3024656	16:27277110	intronic	G/A	0.32	OPA
IL4R	rs3024668	16:27279450	intronic	G/A	0.07	OPA
IL4R	rs3024678	16:27282197	nonsynon	G/A, P675S	0.02	BOTH
IL4R	rs8832	16:27283288	3'-UTR	G/A	0.42	OPA
IL13RA1	rs2247035	X:117756115	intronic	C/A	0.16	OPA
IL13RA1	rs2254672	X:117810809	3'-UTR	A/C	0.15	OPA
IL13RA1	rs2495630	X:117743282	5' flanking	G/A	0.16	OPA
IL13RA1	rs2495636	X:117809926	3'-UTR	A/G	0.16	OPA
IL13RA1	rs6603441	X:117745349	promoter	A/C	0.32	OPA
IL13RA2	rs535036	X:114143913	3' flanking	A/C	0.14	OPA
IL13RA2	rs5946039	X:114150878	intronic	T/A	0.16	OPA
IL13RA2	rs5988198	X:114157839	intronic	A/C	0.13	OPA

*rs2069616 was monomorphic, likely due to probe failure, HapMap MAF 0.48; rs17811365 was monomorphic, HapMap MAF 0.067.

SNP = Single Nucleotide Polymorphism, Maj = major allele, Min = minor allele, OPA = Illumina multiplex platform, Oligo Pool All, KBIO = Kbioscience platform, UTR = untranslated region, nonsynon = Nonsynonymous coding SNP.

Supplemental Table 2. Relationship between tag SNPs in CSF2, IL3, IL4, IL13 and related receptors, CSF2RB, IL4R, IL13RA1, and IL13RA2 with pollen allergies among controls, and with squamous cell cervical cancer, Seattle Metropolitan Area, 1986-1998

	Controls				Risk of allergies among controls		SCC Cases		SCC risk relative to all controls	
	No pollen allergy		Pollen allergy		Per allele				Per allele	
SNPs	n	(%)	n	(%)	OR*	(95% CI)	n	(%)	OR*	(95% CI)
CSF2										
rs25882										
AA	214	(64.1)	94	(54.3)	ref		166	(60.4)	ref	
AG	102	(30.5)	69	(39.9)	1.3	(0.9-1.7)	95	(34.5)	1.0	(0.7-1.2)
GG	18	(5.4)	10	(5.8)			14	(5.1)		
rs27438										
GG	211	(62.8)	91	(52.3)	ref		159	(56.6)	ref	
AG	106	(31.5)	71	(40.8)	1.3	(1.0-1.8)	105	(37.4)	1.0	(0.8-1.3)
AA	19	(5.7)	12	(6.9)			17	(6.0)		
CSF2RB										
rs13055341†										p>0.05
AA	236	(70.2)	130	(74.7)	ref		220	(78.3)	ref	
AG	93	(27.7)	42	(24.1)	0.8	(0.5-1.2)	58	(20.6)	0.7	(0.5-1.0)
GG	7	(2.1)	2	(1.2)			3	(1.1)		
rs131840										
GG	223	(67.0)	114	(66.3)	ref		193	(70.4)	ref	
AG	103	(30.9)	53	(30.8)	1.0	(0.7-1.5)	68	(24.8)	1.0	(0.7-1.3)
AA	7	(2.1)	5	(2.9)			13	(4.7)		
rs131842										
AA	240	(71.4)	113	(64.9)	ref		179	(63.7)	ref	
AG	80	(23.8)	52	(29.9)	1.2	(0.9-1.7)	90	(32.0)	1.1	(0.9-1.5)
GG	16	(4.8)	9	(5.2)			12	(4.3)		
rs131843										
GG	174	(51.8)	90	(51.7)	ref		147	(52.3)	ref	
AG	130	(38.7)	70	(40.2)	1.0	(0.7-1.3)	112	(39.9)	1.0	(0.8-1.2)
AA	32	(9.5)	14	(8.1)			22	(7.8)		
rs1534880										
GG	115	(34.2)	51	(29.3)	ref		88	(31.3)	ref	
CG	152	(45.2)	82	(47.1)	1.2	(0.9-1.5)	130	(46.3)	1.0	(0.8-1.2)
CC	69	(20.5)	41	(23.6)			63	(22.4)		
rs16845†										
CC	298	(89.0)	145	(83.3)	ref		255	(90.7)	ref	
CG	36	(10.7)	29	(16.7)	1.7	(1.0-2.8)	23	(8.2)	0.7	(0.4-1.1)
GG	1	(0.3)	0	(0.0)			3	(1.1)		
rs16846†										
GG	314	(93.5)	160	(91.9)	ref		262	(93.2)	ref	
AG	22	(6.5)	14	(8.1)	1.2	(0.6-2.5)	18	(6.4)	1.0	(0.6-1.8)
AA	0	(0.0)					1	(0.4)		
rs16997517†										
GG	322	(95.8)	159	(91.4)	ref		274	(97.5)	ref	
AG	14	(4.2)	15	(8.6)	**2.2**	**(1.0-4.7)**	5	(1.8)	**0.4**	**(0.2-0.9)**

	Controls				Risk of allergies among controls		SCC Cases		SCC risk relative to all controls	
	No pollen allergy		Pollen allergy		Per allele				Per allele	
SNPs	n	(%)	n	(%)	OR*	(95% CI)	n	(%)	OR*	(95% CI)
AA	0	(0.0)	0	(0.0)			2	(0.7)		
rs2075941										
GG	90	(27.3)	52	(30.4)	ref		73	(26.3)	ref	
AG	170	(51.5)	88	(51.5)	0.9	(0.7-1.1)	135	(48.6)	1.1	(0.9-1.4)
AA	70	(21.2)	31	(18.1)			70	(25.2)		
rs6000488†										
GG	263	(78.3)	134	(77.0)	ref		237	(84.3)	ref	
AG	69	(20.5)	36	(20.7)	1.2	(0.6-2.5)	38	(13.5)	**0.7**	**(0.5-1.0)**
AA	4	(1.2)	4	(2.3)			6	(2.1)		
rs6000495†										
GG	220	(65.5)	123	(70.7)	ref		198	(70.5)	ref	
AG	104	(30.9)	47	(27.0)	0.8	(0.5-1.2)	76	(27.0)	0.9	(0.6-1.2)
AA	12	(3.6)	4	(2.3)			7	(2.5)		
rs738149										
GG	178	(53.1)	101	(58.4)	ref		152	(54.1)	ref	
AG	142	(42.4)	62	(35.8)	0.9	(0.6-1.2)	102	(36.3)	1.2	(0.9-1.5)
AA	15	(4.5)	10	(5.8)			27	(9.6)		
rs909486										
GG	97	(28.9)	51	(29.3)	ref		86	(30.6)	ref	
AG	165	(49.1)	84	(48.3)	1.0	(0.8-1.3)	134	(47.7)	1.0	(0.8-1.2)
AA	74	(22.0)	39	(22.4)			61	(21.7)		
IL3										
rs181781†										
GG	274	(81.5)	130	(74.7)	ref		229	(81.5)	ref	
AG	59	(17.6)	41	(23.6)	1.5	(0.9-2.3)	51	(18.1)	0.8	(0.6-1.2)
AA	3	(0.9)	3	(1.7)			1	(0.4)		
rs2069803										
AA	121	(36.1)	77	(44.3)	ref		113	(40.2)	ref	
AG	165	(49.3)	75	(43.1)	0.8	(0.6-1.1)	131	(46.6)	1.0	(0.8-1.2)
GG	49	(14.6)	22	(12.6)			37	(13.2)		
rs31481										
GG	229	(68.2)	110	(63.2)	ref		187	(66.5)	ref	
AG	98	(29.2)	56	(32.2)	1.2	(0.9-1.7)	85	(30.2)	1.0	(.7-1.3)
AA	9	(2.7)	8	(4.6)			9	(3.2)		
rs40401										
GG	202	(60.1)	86	(49.4)	ref		154	(54.8)	ref	
AG	119	(35.4)	77	(44.3)	1.4	(1.0-1.9)	108	(38.4)	1.1	(0.8-1.4)
AA	15	(4.5)	11	(6.3)			19	(6.8)		
IL4										
rs2070874										
GG	237	(70.7)	113	(64.9)	ref		179	(63.7)	ref	
AG	89	(26.6)	53	(30.5)	1.2	(0.9-1.8)	80	(28.5)	1.3	(1.0-1.7)
AA	9	(2.7)	8	(4.6)			22	(7.8)		

	Controls				Risk of allergies among controls		SCC Cases		SCC risk relative to all controls	
	No pollen allergy		Pollen allergy		Per allele				Per allele	
SNPs	n	(%)	n	(%)	OR*	(95% CI)	n	(%)	OR*	(95% CI)
rs2227282										
CC	190	(54.3)	84	(46.1)	ref		142	(49.3)	ref	
CG	134	(38.3)	82	(45.1)	1.2	(0.9-1.6)	101	(35.1)	1.2	(0.9-1.5)
GG	84	(7.4)	16	(8.8)			45	(15.6)		
rs2243248†										
AA	278	(82.7)	151	(86.8)	ref		240	(85.4)	ref	
AC	55	(16.4)	23	(13.2)	0.7	(0.4-1.2)	40	(14.2)	0.9	(0.6-1.3)
CC	3	(0.9)	0	(0.0)			1	(0.4)		
rs2243263†										
CC	265	(78.9)	140	(80.5)	ref		228	(81.1)	ref	
CG	68	(20.2)	33	(19.0)	0.9	(0.6-1.4)	48	(17.1)	1.0	(0.7-1.4)
GG	3	(0.9)	1	(0.6)			5	(1.8)		
IL4R										
rs1805010										
AA	117	(34.4)	54	(29.8)	ref		82	(30.3)	ref	
AG	160	(47.1)	96	(53.0)	1.1	(0.8-1.4)	129	(47.6)	1.1	(0.9-1.4)
GG	63	(18.5)	31	(17.1)			60	(22.1)		
rs1805011										
AA	264	(78.8)	134	(74.4)	ref		214	(78.4)	ref	
AC	66	(19.7)	40	(22.2)	1.3	(0.8-1.8)	52	(19.0)	0.9	(0.7-1.3)
CC	5	(1.5)	6	(3.3)			7	(2.6)		
rs1805015										
AA	242	(71.8)	116	(66.7)	ref		199	(70.8)	ref	
AG	87	(25.8)	52	(29.9)	1.2	(0.9-1.7)	75	(26.7)	1.0	(0.7-1.3)
GG	8	(2.4)	6	(3.4)			7	(2.5)		
rs1805016†										
AA	312	(92.3)	156	(86.7)	ref		240	(89.6)	ref	
AC	26	(7.7)	24	(13.3)	**1.8**	**(1.0-3.3)**	26	(9.7)	1.0	(0.6-1.6)
CC	0	(0.0)	0	(0.0)			2	(0.7)		
rs2234895†										
GG	289	(85.8)	140	(80.5)	ref		243	(86.5)	ref	
AG	44	(13.1)	34	(19.5)	1.5	(0.9-2.5)	34	(12.1)	0.9	(0.6-1.3)
AA	4	(1.2)	0	(0.0)			4	(1.4)		
rs2234897†										
AA	326	(96.7)	167	(96.0)	ref		267	(95.0)	ref	
AG	11	(3.3)	7	(4.0)	1.3	(0.5-3.4)	14	(5.0)	1.5	(0.7-3.1)
GG	0	(0.0)	0	(0.0)			0	(0.0)		
rs2239347										
AA	112	(33.3)	50	(28.7)	ref		84	(29.9)	ref	
AC	168	(50.0)	92	(52.9)	1.1	(0.9-1.5)	137	(48.8)	1.1	(0.9-1.4)
CC	58	(16.7)	32	(18.4)			60	(21.4)		
rs3024530										
AA	115	(34.2)	54	(31.0)	ref		84	(29.9)	ref	
AG	159	(47.3)	89	(51.1)	1.0	(0.8-1.4)	136	(48.4)	1.1	(0.9-1.4)
GG	62	(18.5)	31	(17.8)			61	(21.7)		

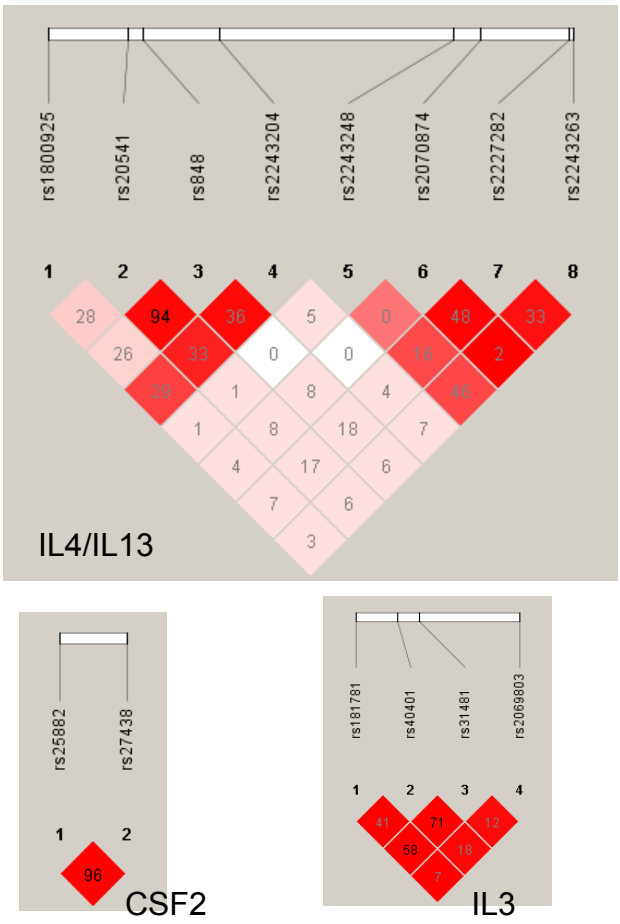
	Controls				Risk of allergies among controls		SCC Cases		SCC risk relative to all controls	
	No pollen allergy		Pollen allergy		Per allele				Per allele	
SNPs	n	(%)	n	(%)	OR*	(95% CI)	n	(%)	OR*	(95% CI)
rs3024544†										
GG	261	(77.4)	126	(72.8)	ref		222	(79.0)	ref	
AG	67	(19.9)	44	(25.4)	1.3	(0.9-2.0)	56	(19.9)	0.8	(0.6-1.2)
AA	9	(2.7)	3	(1.7)			3	(1.1)		
rs3024577										
AA	100	(30.2)	53	(31.0)	ref		75	(27.4)	ref	
AG	175	(52.9)	93	(54.4)	0.9	(0.7-1.2)	136	(49.6)	1.2	(1.0-1.5)
GG	56	(16.9)	25	(14.6)			63	(23.0)		
rs3024578†										
GG	295	(86.5)	143	(80.3)	ref		247	(90.5)	ref	
AG	37	(10.9)	31	(17.4)	1.6	(1.0-2.7)	30	(11.0)	0.8	(0.6-1.3)
AA	4	(1.2)	0	(0.0)			2	(0.7)		
rs3024586†										
GG	309	(91.7)	161	(92.5)	ref		254	(90.4)	ref	
AG	26	(7.7)	12	(6.9)	0.9	(0.5-1.8)	27	(9.6)	1.4	(0.8-2.3)
AA	2	(0.6)	1	(0.6)			0	(0.0)		
rs3024590										
GG	75	(22.3)	43	(24.7)	ref		84	(30.2)	ref	
AG	175	(52.1)	90	(51.7)	0.9	(0.7-1.2)	124	(44.6)	0.9	(0.7-1.1)
AA	86	(25.6)	41	(23.6)			70	(25.2)		
rs3024604†										
AA	289	(84.8)	140	(78.7)	ref		242	(88.6)	ref	
AG	44	(12.9)	34	(19.1)	1.5	(0.9-2.5)	35	(12.8)	0.9	(0.6-1.3)
GG	4	(1.2)	0	(0.0)			4	(1.5)		
rs3024610										
GG	63	(18.8)	45	(26.0)	ref		80	(28.5)	ref	
AG	178	(53.0)	88	(50.9)	0.8	(0.6-1.0)	130	(46.3)	0.9	(0.7-1.1)
AA	95	(28.3)	40	(23.1)			71	(25.3)		
rs3024622										
GG	156	(46.3)	75	(43.1)	ref		125	(44.5)	ref	
CG	155	(46.0)	81	(46.6)	1.1	(0.9-1.5)	115	(40.9)	1.2	(0.9-1.4)
CC	26	(7.7)	18	(10.3)			41	(14.6)		
rs3024629†										
GG	297	(88.1)	152	(87.4)	ref		242	(86.1)	ref	
AG	40	(11.9)	21	(12.1)	1.0	(0.6-1.8)	38	(13.5)	1.1	(0.7-1.7)
AA	0	(0.0)	1	(0.6)			1	(0.4)		
rs3024633†										
AA	293	(85.9)	142	(79.8)	ref		241	(88.3)	ref	
AG	39	(11.4)	31	(17.4)	1.6	(0.9-2.6)	37	(13.6)	0.9	(0.6-1.4)
GG	5	(1.5)	1	(0.6)			2	(0.7)		
rs3024647†										
AA	250	(74.2)	114	(65.5)	ref		201	(71.5)	ref	
AG	77	(22.8)	56	(32.2)	**1.5**	**(1.0-2.3)**	70	(24.9)	1.0	(0.7-1.3)
GG	10	(3.0)	4	(2.3)			10	(3.6)		

	Controls				Risk of allergies among controls		SCC Cases		SCC risk relative to all controls	
	No pollen allergy		Pollen allergy		Per allele				Per allele	
SNPs	n	(%)	n	(%)	OR*	(95% CI)	n	(%)	OR*	(95% CI)
rs3024656										
GG	148	(43.9)	83	(47.7)	ref		155	(55.2)	ref	
AG	154	(45.7)	76	(43.7)	0.9	(0.7-1.2)	105	(37.4)	**0.8**	**(0.6-1.0)**
AA	35	(10.4)	15	(8.6)			21	(7.5)		
rs3024668†									0.661	
GG	295	(86.5)	148	(83.1)	ref		241	(88.3)	ref	
AG	41	(12.0)	24	(13.5)	1.2	(0.7-2.0)	34	(12.5)	1.1	(0.7-1.6)
AA	1	(0.3)	2	(1.1)			6	(2.2)		
rs3024678†										
GG	327	(95.1)	175	(96.2)	ref		269	(96.1)	ref	
AG	17	(4.9)	7	(3.8)	0.8	(0.3-2.0)	11	(3.9)	0.9	(0.4-1.9)
AA	0	(0.0)	0	(0.0)			0	(0.0)		
rs8832										
GG	109	(32.4)	54	(31.2)	ref		79	(28.1)	ref	
AG	175	(52.1)	85	(49.1)	1.1	(0.8-1.4)	139	(49.5)	1.2	(1.0-1.5)
AA	52	(15.5)	34	(19.7)			63	(22.4)		
IL13										
rs1800925										
GG	236	(70.0)	97	(55.7)	ref		177	(63.2)		
AG	92	(27.3)	65	(37.4)	**1.7**	**(1.3-2.4)**	89	(31.8)	1.1	(0.8-1.4)
AA	9	(2.7)	12	(6.9)		**p=0.0007**	14	(5.0)		
rs20541					0.052					
GG	225	(66.8)	100	(57.5)	ref		178	(63.3)		
AG	99	(29.4)	65	(37.4)	1.4	(1.0-1.9)	85	(30.2)	1.0	(0.8-1.3)
AA	13	(3.9)	9	(5.2)			18	(6.4)		
rs2243204†										
GG	280	(83.3)	138	(79.3)	ref		233	(82.9)		
AG	52	(15.5)	32	(18.4)	1.2	(0.8-2.0)	44	(15.7)	0.9	(0.6-1.3)
AA	4	(1.2)	4	(2.3)			4	(1.4)		
rs848										
CC	220	(65.3)	97	(55.7)	ref		176	(62.6)		
AC	103	(30.6)	67	(38.5)	1.3	(1.0-1.8)	85	(30.2)	1.0	(0.8-1.3)
AA	14	(4.2)	10	(5.7)			20	(7.1)		
IL13RA1										
rs2247035										
CC	241	(70.7)	129	(72.5)	ref		202	(74.0)	ref	
AC	88	(25.8)	39	(21.9)	0.9	(0.6-1.3)	68	(24.9)	1.0	(0.8-1.3)
AA	8	(2.3)	6	(3.4)			11	(4.0)		
rs2254672										
AA	241	(71.5)	127	(73.0)	ref		200	(71.2)	ref	
AC	87	(25.8)	41	(23.6)	0.9	(0.7-1.3)	70	(24.9)	1.0	(0.8-1.4)
CC	9	(2.7)	6	(3.4)			11	(3.9)		
rs2495630										

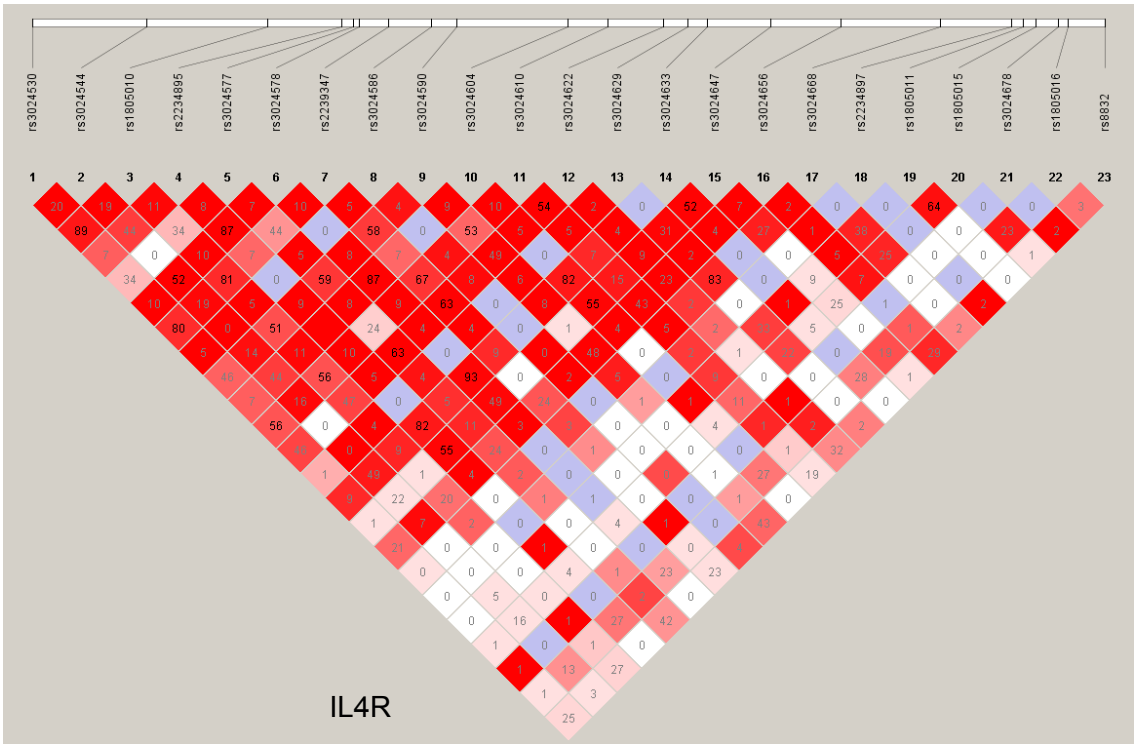
	Controls				Risk of allergies among controls		SCC Cases		SCC risk relative to all controls	
	No pollen allergy		Pollen allergy		Per allele				Per allele	
SNPs	n	(%)	n	(%)	OR*	(95% CI)	n	(%)	OR*	(95% CI)
GG	237	(69.5)	126	(70.8)	ref		197	(72.2)	ref	
AG	90	(26.4)	41	(23.0)	0.9	(0.7-1.3)	73	(26.7)	1.0	(0.8-1.3)
AA	10	(2.9)	7	(3.9)			11	(4.0)		
rs2495636										
AA	241	(70.7)	125	(70.2)	ref		200	(250.0)	ref	
AG	87	(25.5)	43	(24.2)	1.0	(0.7-1.4)	70	(87.5)	1.0	(0.8-1.3)
GG	9	(2.6)	6	(3.4)			11	(13.8)		
rs6603441										
AA	160	(47.6)	77	(44.3)	ref		124	(45.4)	ref	
AC	146	(43.5)	74	(42.5)	1.2	(0.9-1.5)	117	(42.9)	1.0	(0.8-1.3)
CC	30	(8.9)	23	(13.2)			32	(11.7)		
IL13RA2										
rs535036										
AA	253	(75.1)	132	(75.9)	ref		199	(71.1)	ref	
AC	72	(21.4)	39	(22.4)	0.9	(0.6-1.5)	70	(25.0)	1.2	(0.9-1.6)
CC	12	(3.6)	**3**	(1.7)			11	(3.9)		
rs5946039										
TT	238	(70.6)	122	(70.1)	ref		202	(71.9)	ref	
AT	92	(27.3)	46	(26.4)	1.1	(0.8-1.6)	72	(25.6)	0.9	(0.7-1.3)
AA	7	(2.1)	6	(3.4)			7	(2.5)		
rs5988198										
AA	257	(75.4)	135	(75.8)	ref		201	(251.3)	ref	
AC	68	(19.9)	36	(20.2)	0.9	(0.6-1.5)	71	(88.8)	1.2	(0.9-1.6)
CC	12	(3.5)	**3**	(1.7)			9	(11.3)		

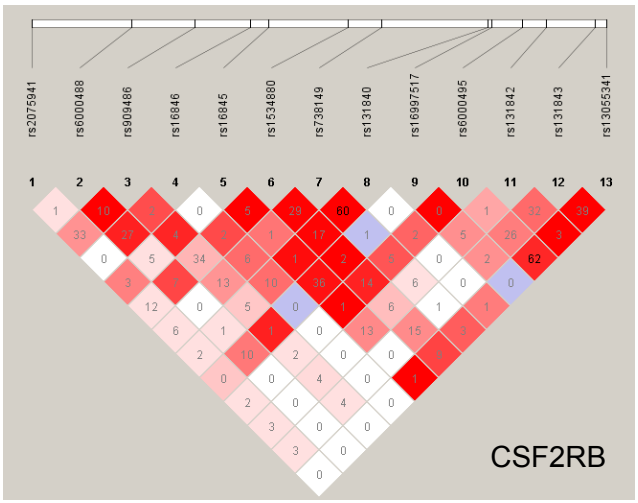
* Models are log-additive modeling of the genotypes, adjusted for race (white, non-white) and age (linear).

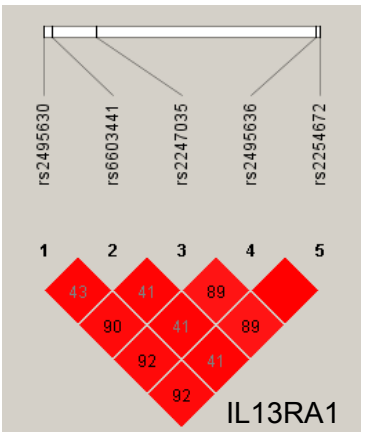
† Dominant modeling used due to one or more cells with < 5 participants.

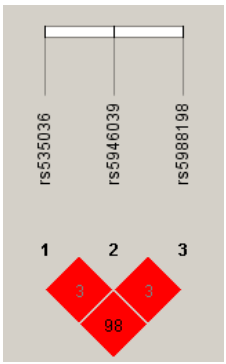


Supplemental Figure 1.


rs3024530
rs3024544
rs1805010
rs2234895
rs3024577
rs3024578
rs2239347
rs3024586
rs3024590
rs3024604
rs3024610
rs3024622
rs3024629
rs3024633
rs3024647
rs3024656
rs3024668
rs2234997
rs1805011
rs1805015
rs3024678
rs1805016
rs8832
IL4R


rs2075941
rs6000488
rs909486
rs16846
rs16845
rs1534880
rs738149
rs131840
rs16997517
rs6000495
rs131842
rs131843
rs13055341
CSF2RB


rs2495630
rs6603441
rs2247035
rs2495636
rs2254672
IL13RA1


rs535036
rs5946039
rs5988198
IL13RA2

Supplemental Figure 1 continued

Figure 1. Linkage Disequilibrium plots for ligand genes: CSF2, IL3, IL4-IL13, CSF2RB, IL4R, IL13RA1, IL13RA2. Numbers in squares are r-squared valued. SNPs are positioned as they are across the chromosome. Shading indicates linkage based on D'.