Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2011 January ; 20(1): 199–207. doi: 10.1158/1055-9965.EPI-10-0779.

Risk of cervical cancer associated with allergies and polymorphisms in genes in the chromosome 5 cytokine cluster

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Abstract

Background—Human papillomavirus is the acknowledged cause of cervical cancer. We hypothesized that allergies, characterized by hyperimmune reaction to common allergens andwhich 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, 1258 controls) conducted in Washington State. Logistic regression models yielded odds ratios (OR) and 95% confidence intervals (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.

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Keywords

Cervical cancer; HPV; allergy; cytokines

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).(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 one study reported a null finding between childhood allergies and cervical cancer in young women in a British cohort.(11) There are two 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 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 biologic basis for the most common causes of allergic symptoms (i.e., pollen) is rooted in an abnormal inflammatory response to normally harmless exogenous substances. Allergen-specific T-helper type 2 (Th2) cells produce IL4, 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 have 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 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 1258 controls available for the current analysis. Blood was drawn from willing participants (88.6% of cases, and 88.3% of controls) and peripheral leukocytes 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 (SNP) Selection

SNPs 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 (tagSNPs) were selected to maximize coverage of common variation in the genes including 4000 base pairs 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 re-sequencing 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 minor allele frequency of at least 0.02. All SNPs genotyped and their characteristics are listed in Supplemental Table 1. Ligand IL3 interacts with co-receptors 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 below), and thus did not pursue genotyping of tagSNPs in the *IL5* receptor alpha 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.

Lab Methods

DNA was extracted from buffy coats using a manual phenol/chloroform method. The Illumina GoldenGate platform was used to type 1536 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 one 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 – 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 – 0.994, averaging 0.989. Two SNPs 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 0.0–0.7% 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 (0.05/1288, the number of SNPs passing the OPA overall, including those not in this study); however, no SNPs in this analysis had a 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%). Polymerase chain reaction (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 10th study sample. HPV-DNA negative results were tested for PCR amplification of a 536-base pair (bp) or 268-bp fragment of the human beta-globin gene to determine whether any DNA was present, and 6.3% of the tumor blocks were beta-globin negative. Tissue for genotyping of HPV DNA was not collected from controls.

Statistical Analyses

All analyses were performed using the Stata statistical package (Stata Corp, College Station, TX). We used unconditional logistic regression models to compute odds ratios (OR) and 95% confidence intervals (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 versus 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 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 to 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 to 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 significance threshold of 0.05.(29) Using the Holm correction, results were ordered from lowest p-value to highest and then corrected by the number of tests, therefore the significance threshold is specific to each SNP.

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 to 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 one 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 one 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 microinvasive (stage 1a) SCC (RRR 0.7, 95% CI 0.5–0.9, LRT p compared to stage 2+ = 0.01) or stage 1b SCC (RRR 0.6, 95% CI 0.4–0.9, LRT p compared to stage 2+ = 0.04) associated with pollen allergies. This difference 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), 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 socioeconomic status 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 (χ^2 p=0.9), smoking (χ^2 p=0.6), household income (χ^2 p=0.3), or recency of Pap screening (χ^2 p=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% versus 33%, respectively, χ^2 p=0.06). There was a non-significant 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 non-significant difference in the risk estimates for SCC was due to a lower proportion of pollen allergies reported by those controls with less educational attainment (28.1%, compared to 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 to 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 odds ratios 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% versus 65.9%), to have had Pap screening in the three years prior to reference (89.2% versus 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 three years prior to diagnosis (57.7% versus 51.1%).

Among Caucasian controls, there was strong linkage disequilibrium between several SNPs in our data (see Supplemental Figure 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 below. The full genotype association results for the SNPs typed for the candidate genes in this study are presented in Supplemental 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, two 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* nonsynonomous 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 (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 hyper-immune 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.

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 non-differential based on case-control status, so, the bias would likely be toward the null. Additionally, 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, since allergy reporting was unrelated to most of the co-factors 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 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 (2005), Turner (2006), and Merrill (2007) 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.11 Montgomery, et al. (2002) reported no association between hay fever in childhood and cervical cancer using two 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 3–9, 1958 and March 5–11, 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. (2006), 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 variation 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 two theoretical biologic 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 then lower stage cancer because a longer time to tumor development increases the chances for tumors to be detectedat 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 non-specific 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 biologic mechanisms mediating this relationship may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: National Institutes of Health, National Cancer Institute grants: P01CA042792, R01CA112512.

Abbreviations

HPV	Human Papillomavirus
SNP	single nucleotide polymorphism
SCC	squamous cell carcinoma
IL13	interleukin 13
IL13RA1	interleukin 13 receptor alpha, subunit 1
IL13RA2	interleukin 13 receptor alpha, subunit 2
IL4R	interleukin 4, receptor
MAF	minor allele frequency

Reference List

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55:74–108. [PubMed: 15761078]
2. Bosch FX, de Sanjose S. Human papillomavirus in cervical cancer. Curr Oncol Rep. 2002; 4:175–183. [PubMed: 11822990]
3. Halpert R, Fruchter RG, Sedlis A, Butt K, Boyce JG, Sillman FH. Human papillomavirus and lower genital neoplasia in renal transplant patients. Obstet Gynecol. 1986; 68:251–258. [PubMed: 3016625]
4. Penn I. Incidence and treatment of neoplasia after transplantation. J Heart Lung Transplant. 1993; 12:S328–S336. [PubMed: 8312352]
5. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst. 2000; 92:1500–1510. [PubMed: 10995805]
6. Clifford GM, Polesel J, Dal Maso L, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005; 97:425–432. [PubMed: 15770006]
7. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008; 123:187–194. [PubMed: 18435450]
8. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy. 2005; 60:1098–1111. [PubMed: 16076292]
9. Turner MC, Chen Y, Krewski D, Ghadirian P. An overview of the association between allergy and cancer. Int J Cancer. 2006; 118:3124–3132. [PubMed: 16395696]
10. Merrill RM, Isakson RT, Beck RE. The association between allergies and cancer: what is currently known? Ann.Allergy Asthma Immunol. 2007; 99:102–116. [PubMed: 17718097]
11. Montgomery SM, Ehlin AG, Sparen P, Bjorksten B, Ekblom A. Childhood indicators of susceptibility to subsequent cervical cancer. Br J Cancer. 2002; 87:989–993. [PubMed: 12434290]
12. Profet M. The function of allergy: immunological defense against toxins. Q Rev Biol. 1991; 66:23–62. [PubMed: 2052671]
13. Burnet M. Cancer: a biological approach. III. Viruses associated with neoplastic conditions. IV. Practical applications. Br Med J. 1957; 1:841–847. [PubMed: 13413231]
14. Mackay WD. The incidence of allergic disorders and cancer. Br J Cancer. 1966; 20:434–437. [PubMed: 5922249]
15. Eriksson NE, Holmen A, Hogstedt B, Mikoczy Z, Hagmar L. A prospective study of cancer incidence in a cohort examined for allergy. Allergy. 1995; 50:718–722. [PubMed: 8546265]
16. Markiewicz MA, Gajewski TF. The immune system as anti-tumor sentinel: molecular requirements for an anti-tumor immune response. Crit Rev Oncog. 1999; 10:247–260. [PubMed: 10468184]

17. Castaing M, Youngson J, Zaridze D, et al. Is the risk of lung cancer reduced among eczema patients? Am J Epidemiol. 2005; 162:542–547. [PubMed: 16093291]
18. Akdis M. Healthy immune response to allergens: T regulatory cells and more. Curr Opin Immunol. 2006; 18:738–744. [PubMed: 17023149]
19. Kanehisa M, Goto S, Furumichi M, Tanabe M, Hirakawa M. KEGG for representation and analysis of molecular networks involving diseases and drugs. Nucleic Acids Res. 2010; 38:D355–D360. [PubMed: 19880382]
20. Gilles S, Mariani V, Bryce M, et al. Pollen allergens do not come alone: pollen associated lipid mediators PALMS shift the human immune systems towards a TH2-dominated response. Allergy Asthma Clin Immunol. 2009; 5:3. [PubMed: 19946407]
21. Loose D, Van de Wiele C. The immune system and cancer. Cancer Biother Radiopharm. 2009; 24:369–376. [PubMed: 19538060]
22. Cormier SA, Taranova AG, Bedient C, et al. Pivotal Advance: eosinophil infiltration of solid tumors is an early and persistent inflammatory host response. J Leukoc Biol. 2006; 79:1131–1139. [PubMed: 16617160]
23. Mattes J, Hulett M, Xie W, et al. Immunotherapy of cytotoxic T cell-resistant tumors by T helper 2 cells: an eotaxin and STAT6-dependent process. J Exp Med. 2003; 197:387–393. [PubMed: 12566422]
24. Munitz A, Levi-Schaffer F. Eosinophils: 'new' roles for 'old' cells. Allergy. 2004; 59:268–275. [PubMed: 14982507]
25. Daling JR, Madeleine MM, McKnight B, et al. The relationship of human papillomavirus-related cervical tumors to cigarette smoking, oral contraceptive use, and prior herpes simplex virus type 2 infection. Cancer Epidemiol Biomarkers Prev. 1996; 5:541–548. [PubMed: 8827359]
26. Hankey BF, Ries LA, Edwards BK. The surveillance, epidemiology, and end results program: a national resource. Cancer Epidemiol Biomarkers Prev. 1999; 8:1117–1121. [PubMed: 10613347]
27. Kbiosciences KASPar genotyping method [Internet]. Available from: http://www.kbioscience.co.uk/lab%20services/SNP%20Genotyping/genotyping_chemistry.html.
28. Daling JR, Madeleine MM, Schwartz SM, et al. A population-based study of squamous cell vaginal cancer: HPV and cofactors. Gynecol Oncol. 2002; 84:263–270. [PubMed: 11812085]
29. Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scandinavian Journal of Statistics. 1979; 6:65–70.
30. Beghe B, Hall IP, Parker SG, et al. Polymorphisms in IL13 pathway genes in asthma and chronic obstructive pulmonary disease. Allergy. 2010; 65:474–481. [PubMed: 19796199]
31. Black S, Teixeira AS, Loh AX, et al. Contribution of functional variation in the IL13 gene to allergy, hay fever and asthma in the NSHD longitudinal 1946 birth cohort. Allergy. 2009; 64:1172–1178. [PubMed: 19254294]
32. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol. 2005; 116:377–383. [PubMed: 16083793]
33. Ivansson EL, Rasmussen F, Gyllensten UB, Magnusson PK. Reduced incidence of cervical cancer in mothers of sons with allergic rhinoconjunctivitis, asthma or eczema. Int J Cancer. 2006; 119:1994–1998. [PubMed: 16721814]
34. Sherman PW, Holland E, Sherman JS. Allergies: their role in cancer prevention. Q Rev Biol. 2008; 83:339–362. [PubMed: 19143335]
35. Magone MT, Whitcup SM, Fukushima A, Chan CC, Silver PB, Rizzo LV. The role of IL-12 in the induction of late-phase cellular infiltration in a murine model of allergic conjunctivitis. J Allergy Clin Immunol. 2000; 105:299–308. [PubMed: 10669851]
36. Cohen S. Cytokine profile data. Immunol Today. 2000; 21:199–200. [PubMed: 10740244]

Table 1

Characteristics of Cervical Squamous Cell Carcinoma Case and Controls, Seattle Metropolitan Area, 1986–1998

	Controls (N=1258)		Cases (N=561)	
Characteristic	**n**	**(%)**	**N**	**(%)**
Reference age (years)				
18–40	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)
$15–30,000	360	(29.0)	161	(29.0)
$30–45,000	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 (years)				
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				

	Controls (N=1258)		Cases (N=561)	
Characteristic	**n**	**(%)**	**N**	**(%)**
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)

Table 2

Association of cervical squamous cell cancer with self-reported history of allergies, Seattle Metropolitan Area, 1986–1998

	Controls (n=1258)		SCC Cases (N=561)			
Allergy History	**n**	**(%)**	**n**	**(%)**	**OR***	**(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†	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)

*Adjusted for age at reference date, smoking (never, former, current), number of lifetime sex partners.

†Includes allergies to cats, dogs, horses, cows, rabbits, bee stings, and responses of “other” or “all animals.”

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***	**(95% CI)**	**n**	**(%)**	**OR***	**(95% CI)**
CSF2RB										
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)**
AA	0	(0.0)	0	(0.0)		p=0.039§	2	(0.7)		p=0.035§
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)		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§**	14	(5.0)		
IL4R										
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)		p=0.045	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)

	Controls						SCC Cases			
	No pollen allergy		Pollen allergy		Risk of allergy among controls		SCC		SCC risk relative to all controls	
SNPs	N	(%)	n	(%)	OR*	(95% CI)	n	(%)	OR*	(95% CI)
GG	10	(3.0)	4	(2.3)		p=0.041§	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§

*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.

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

‡Genotyped on Kbioscience platform.

§Result significant after Holm correction.