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Allergic Diseases and Head and Neck Cancer: A Systematic Review and Meta-analysis

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ABSTRACT

Allergic disorders such as asthma, atopic dermatitis, and allergic rhinitis affect a large portion of the global population. The relationship between allergies and cancer has been studied extensively, but results remain inconsistent for head and neck cancer. The aim of this meta-analysis is to evaluate whether there is a negative association between allergic disorders and head and neck cancer. A systematic search of five databases was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Cohort- and case-control studies examining allergies and head and neck cancer were included. Random-effect and fixed-effect models were used to calculate pooled relative risk, with heterogeneity assessed via the I2 and Cochrane's Q-test. Subgroup and sensitivity analyses were performed to explore variations by study design, allergy type, and cancer site. Twenty-five studies with 3.6 million participants were included. No significant overall association was found between allergic diseases and head and neck cancer (meta-RR: 0.89; 95% confidence intervals (CI): 0.76–1.05). Subgroup analyses revealed protective effects for asthma (meta-RR: 0.81; 95% CI: 0.70–0.95) and food allergies (meta-RR: 0.73; 95% CI: 0.54–0.99). Allergic rhinitis showed negative associations with oropharyngeal cancer (meta-RR: 0.76; 95% CI: 0.69–0.84) and hypopharyngeal cancer (meta-RR: 0.65; 95% CI: 0.55–0.78), but a positive association with nasopharyngeal cancer (meta-RR: 1.67; 95% CI: 1.15–2.43). These findings suggest complex relationships between allergies and head and neck cancer, with negative and positive associations varying by allergy type and cancer site. Further research is needed to clarify these associations.

Keywords: Allergies; Association; Head and neck cancer; Meta-analysis; Nasopharynx; Systematic review

INTRODUCTION

Allergic diseases affect approximately 10%–30% of the global population and place a significant burden on healthcare systems worldwide.[1,2] These conditions are mediated by T helper type 2 (T_H2) cells, which drive B cell differentiation into plasma cells that release immunoglobulin E (IgE).[3–5] The development of allergy involves a complex interplay among genetic predisposition, epigenetic modifications, environmental exposures, microbiota composition, and immune system regulation.[4]

Epidemiological evidence regarding the relationship between allergic diseases and cancer remains

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inconclusive, as both inverse and positive associations have been reported depending on cancer type and site.[6,7] Four main mechanistic hypotheses have been proposed. The immune surveillance hypothesis posits that elevated IgE levels and activated effector cells (e.g., monocytes, natural killer cells) may facilitate the recognition and elimination of transformed cells, reducing cancer risk.[8,9] Conversely, the chronic inflammation hypothesis suggests that persistent allergic inflammation may promote carcinogenesis through oxidative DNA damage and impaired apoptosis.[10,11] The prophylaxis hypothesis asserts that symptoms such as sneezing or coughing may expel carcinogens prior to malignant transformation.[12,13] Lastly, the inappropriate T_H2 skewing hypothesis argues that allergic individuals' T_H2 dominance may impair T_H1-mediated tumor immunity by directing IgE responses toward allergens instead of tumor antigens.[14]

Although inverse associations have been observed in cancers such as pancreatic cancer, childhood leukemias, and brain tumors,[7,15] positive associations (e.g., asthma with lung cancer) have also been reported.[16] In contrast, the relationship between allergic diseases and head and neck cancer (HNC) remains sparsely studied and inconclusive.[17–19] Well-established risk factors for HNC include male sex, tobacco and alcohol use, betel nut chewing, and infection with human papillomavirus (HPV) and Epstein Barr virus (EBV).[17,20,21] Additional regional exposures—such as opium use in Iran and betel nut chewing in East and Southeast Asia—further influence HNC incidence.[22,23] HPV is causally implicated in oropharyngeal carcinoma, increasingly prevalent in Western countries,[24] while EBV contributes to nasopharyngeal carcinoma in endemic regions, where genetic susceptibility and dietary exposures (e.g., nitrosamines) also play roles.[25]

To date, a meta-analysis published in 2013, which included 14 studies, reported an inverse association between allergic rhinitis and HNC risk, suggesting that allergic diseases may be confer a protective effect.[26] Given the limited and outdated data, it is timely to conduct an updated systematic review and meta-analysis. The objective of this study is to evaluate whether allergic disorders are inversely associated with HNC, thereby assessing their potential role as protective factors.

MATERIALS AND METHODS

Search Strategy

The methodology was designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses Guidelines (PRISMA).[27] A comprehensive literature search was conducted using the following databases: PubMed, Web of Science, Cochrane Library, Medline (Ovid), and Wiley Online library. A general Boolean search string, applicable across multiple databases was used. Advanced search options were used to target titles specifically, with the following search terms: "Cancer" OR "tumor" OR "malignancy" OR "malignancies" OR "carcinoma" AND "Allergy" OR "allergies" OR "allergic" OR "atopy" OR "atopic" OR "rhinitis" OR "eczema" OR "asthma" OR "hay fever" OR "hive" OR "hypersensitivity" OR "hypersensitivities". Search result pages were saved as files and imported into Zotero software (version 7.0.8; Corporation for Digital Scholarship, Vienna, VA, USA) where duplicates were manually removed. Titles and abstracts were screened, after which potentially eligible articles were sought for retrieval in full text. In addition to the database searches, published review articles were screened for additional studies. Retrieved articles subsequently underwent careful evaluation based on preselected eligibility criteria.

Study Selection

The research question was developed using the Population, Exposure, Outcome (PEO) framework. Studies were included in this meta-analysis if they met the following inclusion criteria: the population consisted of human adults from any country, the exposure was allergic disease, and the outcome was any type of HNC. Eligible study designs included cohort and case-control studies. The exclusion criteria were review articles, cross-sectional studies, commentary articles, non-English articles, studies involving pediatric populations, and animal studies. No restrictions were imposed on the time frame for the year of publication.

Data Extraction and Quality Assessment

Data items such as authors' names, publication year, country, study design, sample size, participant sex, allergy types, follow-up period, cancer sites, exposure confirmation, outcome confirmation and risk estimate (including relative risk (RR), odds ratio (OR), hazard ratio (HR), standardized incidence ratio (SIR) and standardized mortality ratio (SMR)) were collected from each included study. Study quality was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates

three key categories: selection, comparability, and exposure/outcome. Studies scoring≥7 out of 9 points were considered to be of high quality.

Primary and Secondary Outcomes

Both the primary and secondary outcomes related to the association between allergic disorders and HNC risk were evaluated. The primary outcome was the overall association between any allergic condition and HNC, assessed through pooled risk estimates such as RR, OR, HR, SIR, and SMR, with attention to the direction and strength of the association. Secondary outcomes included subgroup analyses by allergy subtype (e.g., asthma, eczema, hay fever), specific HNC sites (e.g., oral, pharyngeal, laryngeal), sex-based differences, and study design (cohort vs case-control). Additional analyses involved sensitivity testing by excluding studies of low quality or those lacking adjustment for smoking status. The assessment of heterogeneity using the I^2 statistic and Cochrane's Q-test (with prediction intervals when applicable). Furthermore, publication bias was evaluated through Egger's test and funnel plot inspection.

Statistical Analysis

Stata software (Version 18.0; StataCorp LLC, College Station, TX, USA) was used for statistical analysis. Meta-analysis was performed using the Metan command,[28] wherein risk estimates from individual studies were pooled together as meta-RR with 95% confidence intervals (CI) and weighted in an inverse-variance random-effects model. For studies that only reported risk estimates stratified by allergy type, cancer site or sex, a fixed-effect model was applied to calculate a summary-RR for each study. The Exact method[29] was used to calculate RR with 95% CI for two studies that only reported raw frequency numbers without adjusting for covariates. The I^2-statistic and Cochrane's Q-test were used to assess heterogeneity between studies. An I^2 value<25% indicates low heterogeneity, 25%–50% moderate heterogeneity, and>50% substantial heterogeneity.[30] A p value<0.05 derived from Cochrane's Q-test indicates statistically significant heterogeneity.

Egger's regression test and visual inspection of a funnel plot for asymmetry were used to assess potential publication bias or small-study effects.[31,32] Sensitivity analysis was carried out by excluding one study a time to see the effect on the overall pooled risk estimate and heterogeneity, by excluding studies with a NOS score<7, and by excluding studies that did not adjust for smoking. Subgroup analysis was performed based on study design, allergy type and cancer site. In the subgroup analysis, a fixed-effect model was used if I^2<25% and a random-effect model was used if I^2≥25%. To visualize the uncertainty in pooled risk estimates that come with substantial heterogeneity, 95% prediction intervals (PI) were calculated if the number of studies per analysis was≥5 and I^2≥25%. PIs illustrate the plausible range of risk estimates that might be observed in future studies, and they were calculated with the following formula:

$$LL_{\{pred\}} = M - t_{\{\alpha,k-2\}} \cdot \sqrt{\{T^2 + V_M\}}$$
$$UL_{\{pred\}} = M + t_{\{\alpha,k-2\}} \cdot \sqrt{\{T^2 + V_M\}}$$

where LL_{pred} and UL_{pred} is the lower and upper limit of the PI, M is the pooled risk estimate, V_M is the variance of the pooled risk estimate, T^2 is the heterogeneity variance, and $t_{\alpha,k-2}$ is the critical value from t-distribution, where k is the number of studies and α is the significance level.[33]

RESULTS

Literature Search and Study Characteristics

The details of the literature search and selection process are presented in Figure 1. A total of 4914 potential studies were found in the preliminary database search. After duplicate removal, screening and eligibility assessment, 22 articles[26,34–54] was included from the database search. Three additional articles[55–57] was found through citation-searching the reference lists of 3 review articles.[7,15,26]

In total, 25 studies (Table 1) with 3 678 530 participants were included in this review, of these 14 were cohort studies and 11 were case-control studies. Twenty out of 25 studies were given a NOS score of≥7 out of 9.

Initial Meta-analysis

The first meta-analysis (Figure 2) showed a statistically insignificant negative association (for all studies combined meta-RR: 0.89; 95% CI: 0.76–1.05). For cohort studies (n=14), a statistically insignificant positive association was observed (meta-RR: 1.06; 95% CI: 0.87-1.30). In contrast, among case-control studies (n=11), a statistically significant negative association was found (meta-RR: 0.72; 95% CI: 0.55-0.95). The I^2-statistic was 93% overall, 81.6% for cohort studies, and 96.3% for case-control studies. Cochrane's Q-test

indicated significant heterogeneity, with $p<0.001$ for all studies combined as well as for cohort- and case-control studies analyzed separately. These tests showed significant heterogeneity. 95% prediction intervals for all studies, cohort studies and case-control studies were (0.43–1.86), (0.53-2.14) and (0.26-1.99), respectively.

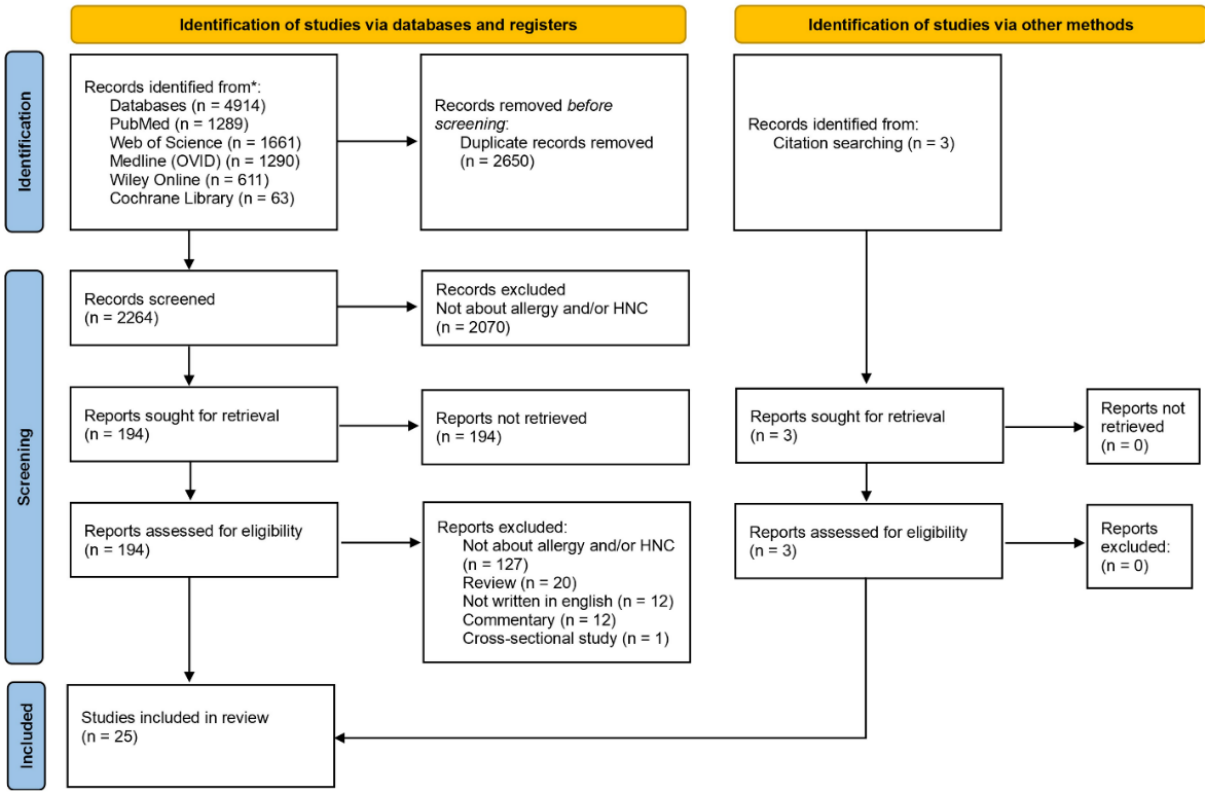

Figure 1. Literature search and study selection process. Flow diagram illustrating the step-by-step process of literature search, study selection, and inclusion/exclusion criteria in a systematic review or meta-analysis. N: number of studies; HNC: head and neck cancer.

Table 1. A detailed description of the included studies' characteristics.

Study ID	Country	Risk estimate	Design	Sample size	Sex	Follow up,years	Allergy types	Cancer sites	Exposure confirmation	Outcome confirmation	Covariates	NOS (0-9)
Polednak et al, 1975	United States	-	Cohort	12 098	Male	-	Asthma	Oral, Pharynx	Self-report	Death certificates	-	5
Robinette et al, 1978	United States	RR	Cohort	19 100	Male	29	Asthma	Oral, pharynx, larynx	Register	Register	-	6
Vena et al, 1985	United States	OR	Case-control	17 744	Mixed	-	AR, asthma, urticaria	Oral, pharynx, larynx	Self-report	Hospital records, ICD-7	Age, smoking	6
Källen et al, 1993	Sweden	SMR	Cohort	64 346	Mixed	18	Asthma	HNC	Register database, ICD 8	Register database, ICD-7	Age, sex	7
Vesterinen et al, 1993	Finland	SIR	Cohort	77 952	Mixed	17	Asthma	Larynx	Register database	Register database, ICD-7	Age, sex, calendar period	7
Petronaiu et al, 1995	Brazil	-	Case-control	800	Mixed	-	AD, AR, asthma, skin rash	HNC	Self-report	Histologically confirmed	-	4
Bosetti et al, 2004	Italy	OR	Case-control	8314	Mixed	-	Allergy	Oral, pharynx, Larynx	Self-report	Histologically confirmed	Age, sex, tobacco, alcohol, BMI, family history, education level	7
Eriksson et al, 2005	Sweden	SIR	Cohort	13 811	Mixed	20 (9.5 median)	Atopy	Pharynx, Larynx	Skin prick test	Register database, ICD-7	Age, sex, calendar year	7
Hagströmer et al, 2005	Sweden	SIR	Cohort	15 666	Mixed	31(14.5 mean)	Asthma	Oral	Register database, ICD 7 -10	Register database, ICD-7	Age, sex, calendar period	7

Table 1. Continued...

Study ID	Country	Risk estimate	Design	Sample size	Sex	Follow up,years	Allergy types	Cancer sites	Exposure confirmation	Outcome confirmation	Covariates	NOS (0-9)
Ji et al, 2009	Sweden	SIR	Cohort	140 425	Mixed	40 (9.6 mean)	Asthma	HNC	Register database, ICD 7, 8 & 10	Register database, ICD-7	Age, sex, socioeconomic status, residential area	7
Engklide et al, 2011	Denmark	OR	Cohort	16 922	Mixed	24	Contact allergy	Oral, pharynx	Patch test	Register database, ICD-7,10	Age, sex	6
Hwang et al, 2012	Taiwan	SIR	Cohort	367 179	Mixed	12 (5.5 mean)	AR, AD, asthma	Oral, nasal, hypopharynx, oropharynx	Register database	Register database, ICD-9 CM	Age, sex	8
Michaud et al, 2012	United States	OR	Case-control	2207	Mixed	-	Allergy, asthma	Oral, oropharynx, larynx	Self-report	Histologically confirmed	Age, sex, tobacco, HPV, alcohol, ethnicity	8
Stott-Miller et al, 2012	United States	OR	Case-control	1013	Mixed	-	Airborne allergies, food allergies, drug allergies, antibiotic allergies	Oral, oropharynx	Self-report	Register database, ICD-O	Age, sex, ethnicity, tobacco, HPV, alcohol, education	7
Hsiao et al, 2013	Taiwan	OR	Case-control	488	Mixed	-	AR, asthma, food allergy, drug allergy, skin allergy	HNC	Self-report	Histologically confirmed	Age, sex, tobacco, betel nuts, education	8

Table 1. Continued...

Study ID	Country	Risk estimate	Design	Sample size	Sex	Follow up,years	Allergy types	Cancer sites	Exposure confirmation	Outcome confirmation	Covariates	NOS (0-9)
Chung et al, 2014	Taiwan	OR	Cohort	7196	Mixed	-	AR	Nasopharynx	Register database, ICD-9 CM	Register database, ICD-9 CM	Age, sex, tobacco, alcohol, income level	9
Lin et al, 2014	Taiwan	HR	Cohort	202 596	Mixed	10 (7.5 mean)	AR	Nasopharynx	Register database, ICD-9 CM	Register database, ICD-9 CM	Age, sex, hypertension, diabetes, asthma, AD	8
Skaaby et al, 2014	Denmark	HR	Cohort	14 849	Mixed	36.7 (11.8 mean)	Atopy against inhalant allergens	HNC	IgE test	Register database, ICD-7	Age, sex, tobacco, alcohol, BMI, education	9
Hemminki et al, 2014	Sweden	SIR	Cohort	138 732	Mixed	46 (8 mean)	AR	HNC	Register database, ICD-7-10	Register database, ICD-7	Age, sex, education, region	7
Liu et al, 2015	Sweden	SIR	Cohort	439 455	Mixed	23 (11 mean)	Asthma	HNC	Register database, ICD-9-10	Register database, ICD-9-10	Age, Sex, socioeconomic status, region, time period	8
Filippidis et al, 2015	Germany	OR	Case-control	859	Mixed	-	Allergy	Larynx	Self-report	Histologically confirmed	Age, sex, smoking, alcohol, occupational exposure	7

Table 1. Continued...

Study ID	Country	Risk estimate	Design	Sample size	Sex	Follow up,years	Allergy types	Cancer sites	Exposure confirmation	Outcome confirmation	Covariates	NOS (0-9)
Liao et al, 2016	Taiwan	OR	Case-control	1444	Mixed	-	AR, asthma, skin allergy, drug allergy, food allergy	Oral, oropharynx, hypopharynx, larynx	Self-report, IgE test	Histologically confirmed	Age, sex, smoking, alcohol, betel nut, education	8
D´arcy et al, 2019	United States	OR	Case-control	1 754 575	Mixed	-	AR, AD, Asthma	Oral, nasal, nasopharynx, hypopharynx, oropharynx, larynx, salivary glands	Register database, ICD-7	Register database, ICD-O-3	Age, sex, COPD, socioeconomic status	9
Guo et al, 2023	United States	HR	Cohort	360 084	Mixed	13.3 mean	Asthma	Oral, Pharynx	Register database, ICD-9-10	Register database, ICD-9-10	Age, sex, ethnicity, tobacco, COPD, diabetes, hypertension	8
Fekrazad et al, 2024	Iran	OR	Case-control	675	Mixed	-	AR, AD, asthma, food allergy, drug allergy	Oral, pharynx, larynx	Self-report	Register database, ICD-O-3	Age, sex,tobacco, alcohol, opium oral health status, socioeconomic status	8

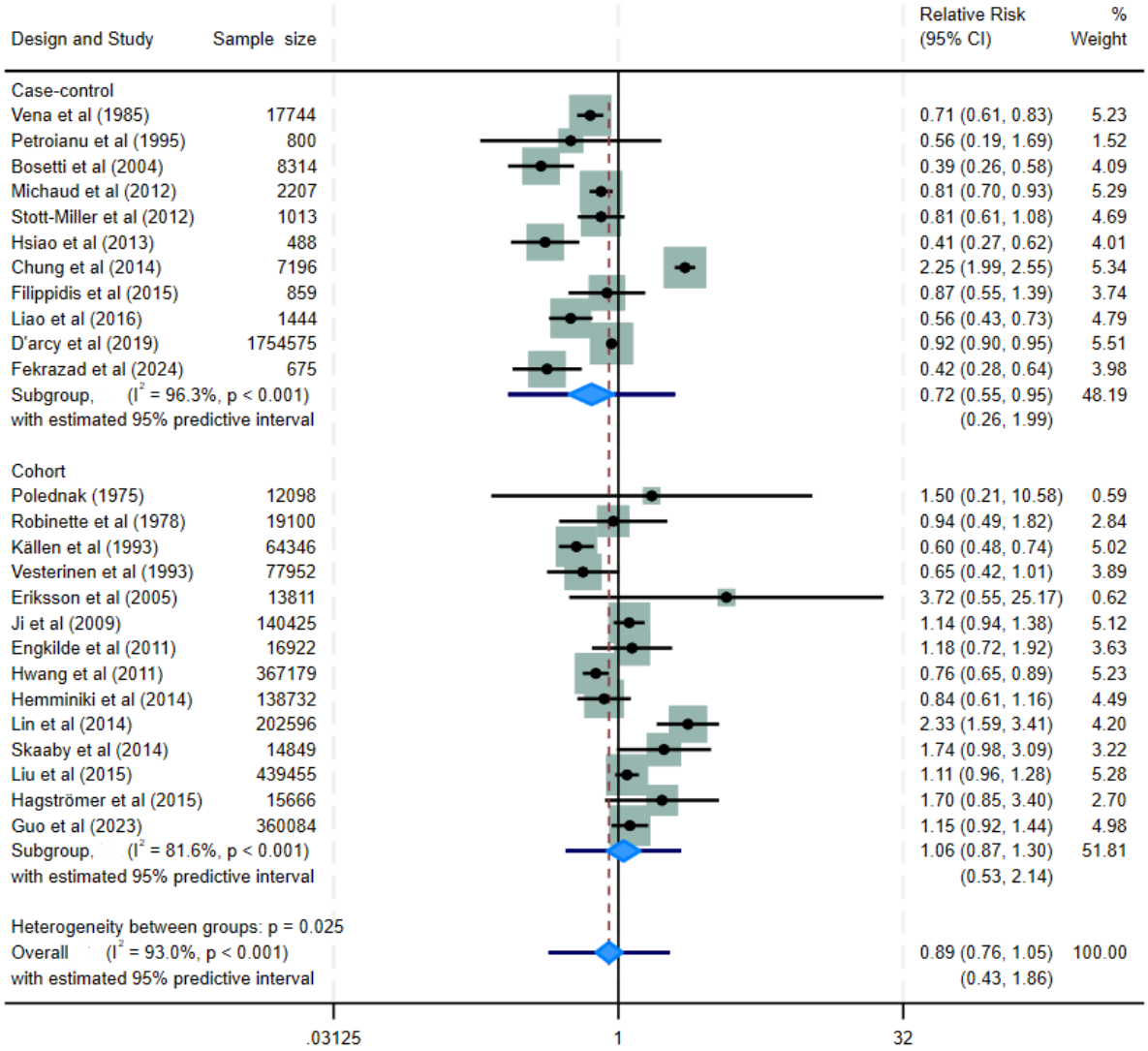

Figure 2. Forest plot of meta-analysis. Black dots represent the risk estimates from each study, with attached lines indicating their 95% confidence intervals. A 95% confidence interval that does not include 1 indicates statistical significance at the *p*<0.05 level. The sizes of the green squares reflect the weight of each study in the meta-analysis. The blue diamond represents pooled relative risk, with the accompanying blue lines showing prediction intervals.

Sensitivity Analysis

In the sensitivity analysis, when excluding studies with a NOS-score <7, the combined estimate (meta-RR: 0.90; 95% CI: 0.75–1.08) was almost unaffected, with I^2=94.2% and Q-test of p<0.001. When studies that did not adjust for smoking were excluded, the risk estimate was lower but remained statistically insignificant (meta-RR: 0.80; 95% CI: 0.62–1.03) with I^2= 96% and a Q-test with p<0.001. In the one-by-one exclusion sensitivity analysis, excluding most studies resulted in meta-RRs ranging from 0.87 to 0.92, with 95% CIs spanning from 0.72 to 0.79 (lower) and 1.03 to 1.11 (upper), and I^2 consistently exceeding 93%. When the study by Chung et al was excluded, the meta-RR dropped to 0.84 (95% CI: 0.74–0.95), indicating a statistically significant negative association, with I^2 reduced to 84.1%. Similarly, excluding the study by Lin et al resulted in a meta-RR of 0.86 (95% CI 0.73–1.00), which was borderline significant, with I^2 remaining high at 92.9%.

Publication Bias

In the funnel plot (Figure 3), a slight asymmetry is visible, with a few more studies on the left than on the right. The Egger's regression test (p=0.904) indicates no evidence of publication bias. A few outlier studies with large (right) and small (left) risk estimates are slightly distant from the funnel. At the lower end of the plot where the standard errors are larger, the dots spread more widely, and the funnel plot is somewhat skewed to the right, may suggest the presence of a minor small-study effect.

Subgroup Analysis

The in-depth subgroup analysis (Table 2) revealed variations in associations based on exposure type and cancer site, with notable differences in heterogeneity. Regarding exposure types and HNC overall, significant negative associations were observed for asthma (meta-RR: 0.81; 95% CI: 0.70–0.95; I^2=79.9%) and food allergy (meta-RR: 0.73; 95% CI: 0.54–0.99; I^2=31.9%). The low heterogeneity observed for food allergy indicates more consistent findings across studies. In contrast, skin allergy showed no significant association with HNC (meta-RR: 0.90; 95% CI: 0.63–1.29; I^2=85.7%) showed no significant association, while also having high heterogeneity. When the analysis was stratified by cancer site, asthma was significantly negatively associated with oral cavity cancer (meta-RR: 0.73; 95% CI: 0.54–0.97, I^2=65.5%) and laryngeal cancer (meta-RR: 0.75; 95% CI: 0.58–0.97, I^2=31.5%). The low heterogeneity observed for laryngeal cancer suggests a more reliable risk estimate. AR demonstrated a significant negative association with hypopharyngeal cancer (meta-RR: 0.65; 95% CI: 0.55–0.78; I^2 = 0%) and oropharyngeal cancer (meta-RR: 0.76; 95% CI: 0.69–0.84; I^2=0%), both with low heterogeneity. Nasopharyngeal cancer (meta-RR: 1.67; 95% CI: 1.15–2.43; I^2=92.2%), however, showed a significant positive association, where heterogeneity remained high. PIs, when calculated, generally remained wide, reflecting variability across studies.

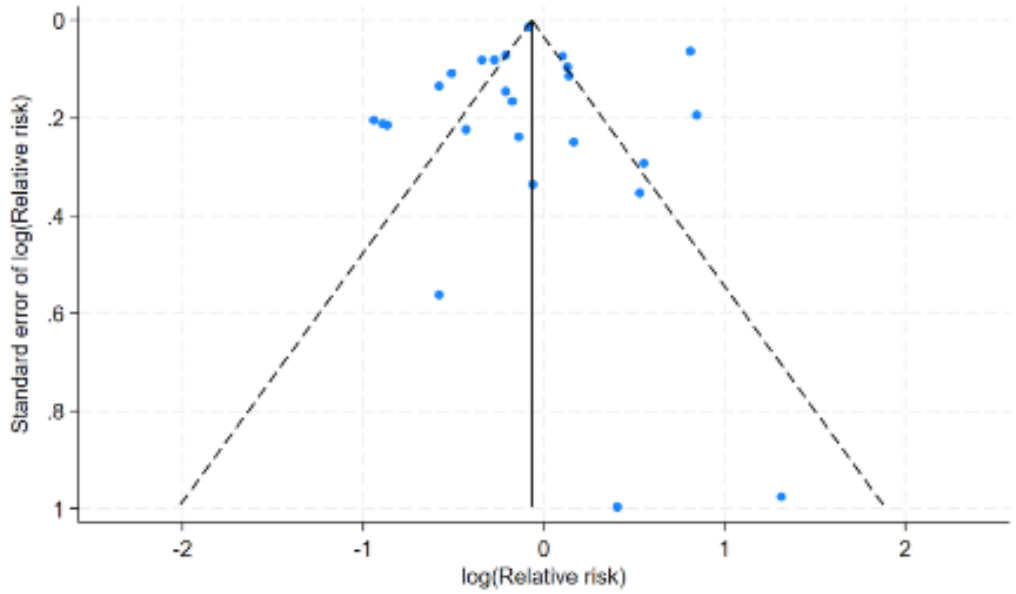

Figure 3. Funnel plot with 95% pseudo confidence intervals. The funnel plot shows slight asymmetry with a few outliers, but Egger's test (p=0.904) indicates no evidence of publication bias. Each dot represents a study and the line in the middle is the log-transformed meta-relative risk. The standard error tends to be higher in studies with smaller sample sizes.

Table 2. Subgroup analysis by design, exposure, and cancer site.

HNC	n	Meta-RR (95% CI)	95% PI	I^2 (%)
All studies combined	25	0.89 (0.76–1.05)	0.43–1.86	93.0
By design				
Cohort	14	1.06 (0.87–1.30)	0.53–2.14	81.6
Case-control	11	0.72 (0.55–0.96)	0.26–1.99	96.3
N ≥ 5-7	20	0.90 (0.75–1.08)	0.41–1.99	94.2
Adjusts for smoking	12	0.80 (0.62–1.03)	0.30–2.12	96.0
By exposure				
AR	8	0.88 (0.39–1.11)	0.21–3.64	97.7
Asthma	13	0.81 (0.70–0.95)	0.49–1.36	79.9
Skin allergy[a]	7	0.90 (0.63–1.29)	0.31–2.60	85.7
Food allergy	5	0.73 (0.54–0.99)	0.37–1.47	31.9
Drug allergy	4	0.65 (0.39–1.09)		62.7
By cancer site				
Oral cavity				
AR	4	0.59 (0.36–0.94)		88.9
Asthma	5	1.73 (0.54–0.97)	0.29–1.84	65.5
Skin allergy[a]	4	1.11 (0.92–1.35)		0.00
Nasal cavity				
AR	2	1.61 (0.61–4.28)		92.2
Asthma	2	1.02 (0.78–1.33)		0.0
Skin allergy[a]	1			
Nasopharynx				
AR	4	1.67 (1.15–2.43)		92.2
Asthma	2	0.91 (0.70–1.17)		0.0
Skin allergy[a]	1			
Oropharynx				
AR	2	0.76 (0.69–0.84)		0.0
Asthma	3	0.82 (0.55–1.21)		60.9
Skin allergy[a]	2	0.76 (0.25–2.36)		82.0
Hypopharynx				
AR	3	0.65 (0.55–0.78)		0.0
Asthma	3	0.75 (0.55–1.00)		0.0
Skin allergy[a]	3	1.10 (0.58–2.09)		46.0
Larynx				
AR	3	0.61 (0.31–1.21)		64.1
Asthma	5	0.75 (0.58–0.97)	0.38–1.47	31.5
Skin allergy	3	1.19 (0.95–1.49)		0.0

Includes AD, urticaria, and contact dermatitis.

AD: atopic dermatitis; AR: allergic rhinitis; CI: confidence interval; HNC: head and neck cancer; n: number of studies; NOS: Newcastle-Ottawa scale; PI: prediction interval; RR: relative risk.

DISCUSSION

Our meta-analysis showed that the nature of the association between allergies and HNC varies depending on the anatomical site of cancer development. The meta-RR of all studies combined did not show a statistically significant association. Excluding low quality studies in our sensitivity analysis did not affect the overall result, which can be explained by the fact that studies with low precision receive lower weights in the meta-analysis automatically. Interestingly, exclusion of studies that did not adjust for smoking as a confounder resulted in a lower meta-RR which was still not statistically significant. The one-by-one exclusion analysis revealed, however, that the studies by Chung et al[34] and Lin et al[46] which exclusively studied allergic rhinitis (AR) and the risk of nasopharyngeal carcinoma (NPC), skewed the overall result towards a positive association, thereby making the overall result insignificant. As was shown in our subsequent subgroup analysis, NPC stands out as being positively associated with AR, while oral, hypopharynx and oropharynx cancer are negatively associated with AR, suggesting a protective effect. Furthermore, food allergies and asthma were found to have a significant negative association with HNC overall.

Findings of potential protective effects can possibly be explained both by the immune surveillance hypothesis and the prophylaxis hypothesis. Symptoms of asthma and AR, like coughing or sneezing, may help to expel potential carcinogens from affected tissues. However, this does not fully explain the observed protective effect from food allergies, which suggests a more systemic mechanism such as T_H2- and IgE mediated activity to be involved. Regarding AR and NPC however, it is reasonable to assume that chronic inflammation may drive the process of increased cancer risk, since the malignant tissue lies near the site of inflammatory response. This would align well with previous findings that various forms of chronic sinonasal inflammatory disorders increases the risk of NPC.[58–60] However, since the pathogenesis of NPC in endemic areas is associated with EBV in 95% of cases,[61] the increased risk would also be consistent with the T_H2 skewing hypothesis, because it has been demonstrated that $CD4^+$ T-cells specific to EBV-antigens are primarily of the T_H1 class rather than T_H2.[62] This suggests that AR potentially compromise the host's defense against EBV-mediated malignant cell transformation.

During the quality assessment of the included studies, several potential sources of bias were identified. Case-control studies, which produced a statistically significant negative association (meta-RR: 0.72; 95% CI: 0.55–0.95) in our meta-analysis, mostly relied on self-reported history of allergic disease among subjects. This reliance introduces a risk of recall bias,[63] potentially leading to overreporting of allergic disorders and, consequently, an exaggerated negative association. On the other hand, the case-control study by D'arcy et al which stood out with a remarkably large sample size (n=1 754 575) and reported a significant negative association with high precision (RR: 0.92; 95% CI: 0.90–0.95), relied exclusively on information obtained from register databases. Cohort studies, on the other hand, reported a non-significant positive association (meta-RR: 1.06; 95% CI: 0.87–1.30). These studies also used register databases to confirm allergic disorders among subjects, reducing the risk of recall bias. However, reliance on such data often resulted in the inability to adjust for potential confounding variables like HPV-infection or lifestyle factors such as tobacco and alcohol consumption. This could potentially skew the overall risk estimate upwards.

Moreover, we excluded 12 articles written in languages other than English, which may have introduced language bias in our meta-analysis.

Our funnel plot showed a slight asymmetry; however, Egger's regression test did not show any evidence of publication bias. Both these methods are less reliable in the presence of substantial heterogeneity between studies, as they assume that the included studies estimate the same underlying effect size.[64] Therefore, it is likely that the asymmetry observed in our funnel plot is a result of the heterogeneity itself, rather than due to publication bias.

A limitation of this meta-analysis was that substantial heterogeneity persisted even through in-depth subgroup analysis, which made many of the risk estimates generally unreliable. For this reason, our results must be interpreted with great caution. To visualize the effect of high heterogeneity, we calculated PIs. However, for subgroups with fewer than 10 studies and smaller sample sizes, the estimation of study variance becomes less stable. For this reason, PIs must also be viewed as less reliable in subgroups with fewer studies.

Given the discrepancies in our results and high heterogeneity, future systematic review should have

focus on a single type of allergic exposure or restrict the analysis to specific anatomical sites of cancer. Any residual heterogeneity should be thoroughly explored by advanced meta-regression. Additionally, we recommend that new original studies use database-derived data to confirm exposure and adjust for important confounders. Studies examining HNC more broadly should report risk estimates separately for each studied anatomical site, so that results of future meta-analyses may achieve more statistical power. Apart from observational studies, new insights could potentially be gained by studying the causal relationship with Mendelian randomization, which is a method that utilizes genetic variants as proxies for risk factors to determine causality while minimizing reverse causality and confounding.[65] Another approach could involve investigating the potential for IgE-molecules similar to the ongoing studies utilizing IgE-based therapies for pancreatic cancer and ovarian cancer.[66,67]

CONCLUSIONS

This meta-analysis found no significant association between all combined allergic diseases and HNC. However, subgroup analyses, revealed a significant negative association between asthma and HNC, both overall and within specific subtypes. AR also demonstrated significant negative associations in several subgroups, while exhibiting a significant positive association with NPC. These findings suggest a complex relationship between allergic conditions and cancer. Due to substantial heterogeneity, the results need to be interpreted with caution. Future studies should focus on specific allergic exposures in relation to distinct cancer types.

STATEMENT OF ETHICS

Not applicable.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

All data extracted and analyzed in this systematic review were obtained from previously published studies, which are cited in the reference list. All available data were included.

AI ASSISTANCE DISCLOSURE

The authors declare that no generative artificial intelligence (AI) was used in the conduct of the research, data extraction, or manuscript preparation. All text and analyses were performed by the authors.

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