

Association of history of allergies and influenza-like infections with laryngeal cancer in a case–control study

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Abstract Prior studies suggest that history of allergy and infections early in life might be inversely associated with cancer. We explored the association between allergies, recent influenza infections and laryngeal cancer risk. We used data from a case–control study which included 229 cases of laryngeal cancer and 769 population controls matched for age and sex. History of a physician-diagnosed allergy, influenza-like infections in the past 5 years, smoking, alcohol consumption and occupational exposure to carcinogens were self-reported. Allergies were classified into two groups (Type I and Type IV), according to the underlying immunologic mechanism. Conditional logistic regression models were fitted using laryngeal cancer as the outcome, adjusting for smoking, alcohol consumption and occupational exposure and stratified for age and sex. Having any allergy was not associated significantly with laryngeal cancer. Although Type I and Type IV allergies were non-significantly associated with laryngeal cancer, Type IV allergies showed a strong inverse association after adjusting for smoking and alcohol (OR 0.50, 95 % CI 0.22–1.2). Participants who reported at least one influenza-like infec-

tion during the past 5 years were significantly less likely to have laryngeal cancer (OR 0.57, 95 % CI 0.39–0.81). After considering fever (≥ 38.5 °C) as a criterion for influenza infection, the association between influenza infection and laryngeal cancer was even stronger (OR 0.29, 95 % CI 0.13–0.63). We found no significant association between any allergy and laryngeal cancer, some indication of an inverse association between Type IV allergy and laryngeal cancer, whereas recent influenza infections were inversely associated with laryngeal cancer risk.

Keywords Laryngeal cancer · Influenza virus · Infection · Allergy

Introduction

The association between a history of allergies or other atopic conditions and cancer risk has been studied extensively [1–4]. Several recent reviews have concluded that the direction of the association depends on the types of

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atopy and cancer, with evidence suggesting inverse associations with any allergic reaction for several malignancies including those of the pancreas, colon and rectum, and brain, and positive associations with asthma, but not allergic reactions in general for lung cancer.

Two possible explanations have been proposed to account for the inverse association between allergies and several cancer types. The “immunosurveillance hypothesis” suggests that there are people with hyperactive immune systems that are very “aggressive” against allergens and also very effective in detecting and combating malignant cells, thus protecting individuals from cancer. Therefore, a history of allergies is a marker of an efficient immunosurveillance system [5]. The alternative explanation, known as the “prophylaxis hypothesis”, suggests that allergic symptoms directly protect tissues from environmental substances and microorganisms that might be carcinogenic and alert the individual to avoid contact with them in the future. As a result, the “prophylaxis hypothesis” predicts that the inverse association between allergy and cancer should be more evident in human tissues and organs that interface with the external environment, such as the larynx [6].

Larynx is one of the sites in which cancer incidence has been found to be lower among individuals with a history of allergy, compared to the general population [7–9]. A recent meta-analysis showed that having allergies is associated with a reduced risk of head and neck squamous cell carcinomas (HNSCC) [10]. However, several studies have not taken into account factors that might confound the relationship between allergies and laryngeal cancer, in particular smoking, alcohol and occupational exposures [11–13]. Allergy is less frequent among smokers [14] and consumption of alcohol has been found to increase levels of IgE [15].

Contrary to the history of allergies, data on the possible association between influenza infection and cancer are scarce. Childhood influenza infections [16] and history of recent common colds or gastroenteric influenza [17] have been associated with a reduced risk of cancer in adult life, but there is a paucity of data on a possible biological mechanism that would explain this association. It has been hypothesized that some infectious pathogens might be cross-reactive with proteins produced by cancer cells. Thus, prior infections might lead to immune surveillance against those proteins and increased immune response against cancer cells [18, 19]. If this is true, it could be expected that certain childhood infections may be protective against some types of cancer later in life, but also that an infection during the early stages of carcinogenesis might be able to delay the progression of the disease.

We analyzed self-reported data on allergies and history of recent influenza infection and the risk of laryngeal cancer in a case–control study in Germany, adjusting for major lifestyle and occupational risk factors.

Methods

Study design and study population

This population-based case–control study was conducted in Germany with 229 histologically confirmed cases of laryngeal cancer (response proportion 89.2 %) between 1998 and 2000. The study region covered a population of about 2.7 million people in the German cities of Heidelberg, Mannheim, Ludwigshafen, Darmstadt, and Heilbronn that are situated in South-West Germany. Cases and controls were restricted to Germans aged up to 80 years who were registered as citizens in the study region. 769 population controls were selected randomly from the population registries of the study area and were frequency-matched 3:1 to cases for age and sex (response proportion 62.4 %). Ethical clearance was received by the ethical committee of the University of Heidelberg and written consent was obtained from the participants through collaborating physicians. The study design has been described in more detail elsewhere [11, 12].

All participants were interviewed and a detailed, comprehensive questionnaire was used to collect data on smoking, alcohol consumption, occupational exposure and history of allergies and influenza infections [11]. Current smoking status and history of tobacco use were assessed through a series of questions in which participants were asked to report their daily, weekly and monthly consumption of cigarettes during their lifetime, which could be divided in periods, so as to take into account the variation in average consumption over time. The use of cigars, cigarillos and pipes was also taken into account, assuming that one cigar was equivalent to four cigarettes, one cigarillo to two cigarettes and one gram of tobacco smoked with a pipe equivalent to one cigarette [11, 20]. Participants were asked to recall and report their daily, weekly or monthly alcohol consumption 10 years before interview. Average daily consumption (in grams of ethanol) was calculated as the sum of ethanol consumed through all common alcoholic beverages, assuming the following ethanol content: beer 5 %, wine, fruit wine or sparkling wine 10 %, aperitif and liquors 20 % and spirits 40 %. This average was considered as a proxy of lifetime alcohol consumption.

Education was grouped in three levels according to the years of school attended following the German educational system: 9 years or less (low, “Hauptschule”), 10 years (middle, “mittlere Reife”) and more than 10 years (high, “(Fach-)Hochschulreife”).

People with occupational exposure to various substances may be more likely to develop laryngeal cancer [13], but it is also possible that they might misinterpret skin reactions to these substances as allergies. To control for both these aspects, we used data from the detailed lifetime occupational history section of the questionnaire. Data were

collected on every occupation since people had started working, including working period, job title, industry and nature of work. Occupational exposure to jobs with a likely exposure to smoke, dust, gases and vapors was quantified using a carcinogenic agent index (CAI), which has been described in detail elsewhere [21] and has been recently used to adjust for occupation exposure in the context of laryngeal cancer [22]. Each job title included in this index was assigned a number from 1 to 10, according to the level of exposure (10 being the highest). A weighted index was used in the analysis as a continuous variable constructed from all jobs performed during lifetime.

All participants were asked whether they had ever been diagnosed with an allergy by a physician. Those who responded that they had an allergy were subsequently asked to name their allergies in an open question. Self-reported allergies were then classified into two groups, according to the underlying immunologic mechanism (Type I and Type IV hypersensitivity reaction) [23]. Allergies to feathers, foods, pollens, hair, dust, insect stings and bites, antibiotics and other drugs were included in the Type I group, whereas allergies to chemicals, detergents, insecticides, ointments and various skin allergies were included in the Type IV group. For comparative reasons, we also followed the approach by Stott-Miller et al. [24] who grouped individual allergies following two approaches as foods, pollen, drugs, inhalants or other, and also as airborne, antibiotics, foods, animals or other.

History of influenza-like infections was assessed with the question “during the past 5 years (before your current disease), how often, on average per year, have you had a flu or a cold with symptoms like runny nose, sore throat, cough, hoarseness, pressure on the forehead or the paranasal sinuses for at least 3 days?” with possible responses “never”, “less than once a year”, “once a year”, “twice a year”, “three times a year” and “more than three times a year”. If they reported being sick at least once during the past 5 years, they were also asked whether these infections were usually accompanied with fever at least 38.5 °C, less than 38.5 °C or not at all. Respondents were then classified into two groups for the main analysis: those who had no influenza infection during the past 5 years and those who had at least one infection. A secondary analysis, in which respondents were classified into five groups based on the frequency of infections, was also conducted. Finally, we conducted a third analysis in which only people who had influenza-like symptoms and fever of at least 38.5° were considered as infected with the influenza virus.

Statistical analysis

For smoking, the cumulative number of cigarettes smoked was calculated and the number of pack-years (py) for each

person was used in the analysis. One pack-year corresponds to 20 cigarettes/day for 1 year, being equivalent to nearly 7,300 cigarettes. Pack-years were included in multivariate analyses as a log-transformed continuous variable ($\log(\text{py} + 1)$), which showed statistically the best model fit using the fractional polynomial technique. Average daily alcohol consumption was divided by 25, so as to improve interpretability of the results (odds ratios (OR) refer to an intake increase of 25 g of ethanol/day) and was included as an untransformed continuous variable, considering that it showed the best fit, using the same method [25].

We fitted three conditional logistic regression models to explore the association between having a history of any allergy and having a history of Type I or Type IV allergy and laryngeal cancer. All models were conditioned on the matching variables age and sex. The first model (univariate) included only the exposure variable. The second model adjusted for smoking and alcohol and the third model additionally adjusted for occupational exposure (CAI). Two logistic regression models were fitted to assess the association between influenza-like infection (three different definitions) and laryngeal cancer, one univariate and a second, adjusted for smoking and alcohol consumption.

Results

The majority of cases and controls were male (90.8 and 91.3 %, respectively) with a nearly identical age distribution due to the matching. Additional characteristics showing different patterns for smoking behavior, alcohol consumption and education were reported previously [11, 22]. 16.2 % of cases and 21.5 % of the controls reported having had at least one allergy. Type I allergies were much more common than Type IV allergies (13.1 versus 4.0 % in cases and 18.1 versus 6.5 % in controls), while 2 cases (0.9 %) and 24 controls (3.1 %) reported having a history of both Type I and Type IV allergies. 37.1 % of cases and 22.9 % of controls reported no influenza infections in the past 5 years, 21.2 % of cases and 25.8 % of controls reported fewer than one infection per year, 26.9 % of cases and 37.5 % of controls reported one infection per year and 14.5 % of cases and 13.9 % of controls two or more infections per year (Table 1).

Having any allergy was marginally non-significantly inversely associated with laryngeal cancer. Adjusting for smoking and alcohol consumption though, this association was attenuated. After the final adjustment for occupational exposure, history of any allergy and laryngeal cancer showed a weak but non-significant association (OR 0.87, 95 % CI 0.55–1.4) (Table 2).

Table 1 Characteristics of laryngeal cancer cases and controls, South-West Germany, 1998–2000

Characteristic	Cases <i>n</i> (%)	Controls <i>n</i> (%)
Gender		
Female	21 (9.2)	67 (8.7)
Male	208 (90.8)	702 (91.3)
Age (years)		
≤50	23 (10.0)	78 (10.1)
51–60	74 (32.3)	251 (32.6)
61–70	84 (36.7)	252 (32.8)
71–80	48 (21.0)	188 (24.4)
Smoking (pack-years)		
0	9 (3.9)	203 (26.4)
>0–20	30 (13.1)	301 (39.1)
>20–40	79 (34.5)	146 (19.0)
>40	111 (48.5)	119 (15.5)
Alcohol consumption (g ethanol/day)		
≤25	64 (28.0)	354 (46.0)
>25–75	89 (38.9)	297 (38.6)
>75	76 (33.2)	118 (15.3)
Education (years of schooling)		
≤9	199 (86.9)	479 (62.3)
10	18 (7.9)	120 (15.6)
>10	12 (5.2)	170 (22.1)
Carcinogenic Agents Index (CAI)		
1–2.9	8 (3.5)	96 (12.5)
3–5.9	31 (13.5)	228 (29.6)
6–8.9	99 (43.2)	293 (38.1)
9–10	91 (39.7)	152 (19.8)
History of allergy (classification I)		
Type I only	28 (12.2)	115 (15.0)
Type IV only	7 (3.1)	26 (3.4)
Type I and Type IV	2 (0.9)	24 (3.1)
No allergy	192 (83.8)	604 (78.5)
History of allergy (classification II)		
Foods	5 (2.2)	16 (2.1)
Pollen, plants, grass and trees	10 (4.4)	78 (10.1)
Medications, drugs, immunization	11 (4.8)	34 (4.4)
Inhalants, moulds, dust, animals, tobacco	6 (2.6)	45 (5.9)
Other	14 (6.1)	41 (5.3)
History of allergy (classification III)		
Airborne (pollen, dust, mould)	15 (7.0)	98 (12.7)
Antibiotics	10 (4.4)	18 (2.3)
Foods	5 (2.2)	16 (2.1)
Animals	1 (0.4)	16 (2.1)
Other	14 (6.1)	59 (7.7)
History of influenza infection (past 5 years)		
No	85 (37.1)	176 (22.9)
Yes	144 (62.9)	593 (77.1)
Total	229	769

In the conditional logistic regression model that considered only allergy variables and did not adjust for any other factors, Type I (OR 0.71, 95 % CI 0.46–1.1) and Type IV allergies (OR 0.60, 95 % CI 0.29–1.3) were not significantly associated with laryngeal cancer. Adjusting for smoking behavior and alcohol consumption only or in combination with occupational exposure did not yield significant results (Table 2). Nevertheless, the effect size for Type IV allergy was not attenuated after adjusting for all the confounding factors (OR 0.51, 95 % CI 0.22–1.2), whereas the effect size for Type I allergy was null following adjustment. Similar models, in which allergies were grouped by substance [24] produced non-significant associations between each type of allergy and laryngeal cancer (data not shown), while restricting results to male participants yielded similar results.

Regarding influenza-like infections, participants who reported at least one infection during the past 5 years were significantly less likely to have laryngeal cancer (OR 0.50, 95 % CI 0.36–0.69). After adjusting for smoking and alcohol consumption, the inverse association was less pronounced, but still statistically significant (OR 0.57, 95 % CI 0.39–0.81) (Table 3). When we considered fever of at least 38.5° as an additional, essential criterion for characterizing an individual as infected by influenza, the association between influenza infection and laryngeal cancer remained significant and adjusting for confounding factors increased the strength of the association (OR 0.29, 95 % CI 0.13–0.62). When respondents were grouped according to the frequency of influenza-like infections, there was an inverse association between infections and laryngeal cancer for those who experienced an infection less than once or once a year (Table 3). Separate analyses for males only did not change the results.

Discussion

Data from the present case–control study showed that having a self-reported history of any allergy was marginally non-significantly inversely associated with laryngeal cancer, but indications of such an association disappeared after adjusting for common risk factors for laryngeal cancer, such as smoking and alcohol. Laryngeal cancer was not significantly associated with any specific type of allergy. Moreover, having had at least one influenza-like infection in the past 5 years was inversely associated with laryngeal cancer, even after adjusting for smoking, alcohol, education and occupational exposure to carcinogens.

The lack of association between history of any allergy and laryngeal cancer in our study is in contrast with several previous studies that observed inverse relationships [7–9].

Table 2 Association of history of (a) any allergy and (b) Type I and Type IV allergies with laryngeal cancer, South-West Germany, 1998–2000

	Controls <i>n</i> (%)	Cases <i>n</i> (%)	Model 1		Model 2		Model 3	
			OR ₁	95 % CI ₁	OR ₂	95 % CI ₂	OR ₃	95 % CI ₃
Any allergy								
No (reference)	604 (78.5)	192 (83.8)	1.00		1.00		1.00	
Yes	165 (21.5)	37 (16.2)	0.68	0.46–1.0	0.82	0.53–1.3	0.87	0.55–1.4
Type I allergy ^a								
No (reference)	630 (81.9)	199 (86.9)	1.00		1.00		1.00	
Yes	139 (18.1)	30 (13.1)	0.71	0.46–1.1	0.93	0.57–1.5	0.99	0.60–1.6
Type IV allergy ^a								
No (reference)	719 (93.5)	220 (96.1)	1.00		1.00		1.00	
Yes	50 (6.5)	9 (3.9)	0.60	0.29–1.3	0.52	0.23–1.2	0.51	0.22–1.2

Model 1: Logistic regression model for having any allergy, stratified for age and sex; Model 2: Logistic regression model for having any allergy, adjusted for smoking and alcohol consumption, stratified for age and sex; Model 3: Logistic regression model for having any allergy, adjusted for smoking, alcohol consumption and occupational exposure to carcinogens, stratified for age and sex

^a Type 1 and Type 4 allergies are simultaneously estimated in these models

Table 3 Alternative definitions for the association of history of influenza-like infection with laryngeal cancer, South-West Germany, 1998–2000

	Controls <i>n</i> (%)	Cases <i>n</i> (%)	Model 1 ^a		Model 2 ^a	
			OR ₁	95 % CI ₁	OR ₂	95 % CI ₂
At least one influenza-like infection in the past 5 years						
No (reference)	176 (22.9)	85 (37.1)	1.00		1.00	
Yes	593 (77.1)	144 (62.9)	0.50	0.36–0.69	0.57	0.39–0.81
Influenza-like infections in the past 5 years						
No (reference)	176 (22.9)	85 (37.4)	1.00		1.00	
Less than once/year	198 (25.7)	48 (21.1)	0.51	0.34–0.77	0.59	0.37–0.93
Once/year	288 (37.5)	60 (26.4)	0.43	0.29–0.63	0.48	0.31–0.73
Twice/year	77 (10.0)	20 (8.8)	0.52	0.29–0.92	0.64	0.34–1.2
More than twice/year	30 (3.9)	14 (6.2)	1.00	0.50–2.0	0.99	0.45–2.2
Influenza-like infections with fever ≥38.5 in the past 5 years						
No (reference)	696 (90.5)	217 (95.6)	1.00		1.00	
Yes	73 (9.5)	10 (4.4)	0.45	0.23–0.88	0.29	0.13–0.62

Model 1: Logistic regression model including only the variable for recent influenza infection, stratified for age and sex; Model 2: Logistic regression model for recent influenza infection, adjusted for smoking and alcohol consumption, stratified for age and sex

^a Adjusting variables smoking behavior and alcohol consumption not shown

Inverse association has also been reported between allergy and HNSCC, but a recent meta-analysis showed an effect only for case–control and not cohort studies [10]. One possible explanation for this discrepancy could be the fact that some studies might not have adequately controlled for laryngeal cancer risk factors. Most studies adjust for smoking and alcohol, but these data are not always available, especially in cohort studies, which therefore might be more susceptible to confounding [10]. Apart from smoking and alcohol, we could also adjust for occupational exposure to carcinogens, thus reducing the unmeasured confounding. Nevertheless, it has to be noted that our data showed no significant association between allergy and cancer even

before adjusting using a recently introduced occupational exposure index [22]. Adjusting for educational level yielded results almost identical to the ones presented for all analyses.

Neither of the classifications we used for allergies yielded significant associations with laryngeal cancer for any specific group of allergies. We did find indications of a strong inverse association between Type IV allergy and laryngeal cancer (adjusted OR 0.51), but it did not reach statistical significance, possibly because the number of cases and controls who reported having a Type IV allergy was quite small. Participants were asked to report only allergies diagnosed by a physician. Therefore, some

misclassification might have occurred, as some people might have had undiagnosed allergies as well. There is no standard approach to classify and group allergies and there is great variation between studies [26]. We used the Type I and Type IV allergy classification approach as these two categories reflect different physiological responses and, therefore, might reflect different roles in carcinogenesis, even though people who had a Type I allergy were more likely to report a Type IV allergy as well, compared to non-allergic individuals. A previous study has found an inverse association between a history of Type IV allergy and certain types of cancer, such as non-melanoma skin and breast cancer, but no association with oral cancer [27]; whereas another study concluded that Type I allergy seems not to be related to cancer risk [28].

Our study showed a clear association between report of at least one influenza-like infection in the past 5 years and laryngeal cancer. There are few studies that have explored similar associations. In most cases, inverse associations between childhood infections and adult cancer risk have been found [16, 29]. We collected data regarding influenza-like infections during the past 5 years (or the 5 years prior to diagnosis). Thus, we were only able to associate relatively recent influenza infections to cancer risk. In past studies, recent common colds or gastroenteric influenza have been associated with a reduced risk of cancer [17]. Infections with symptoms similar to influenza were self-reported. Thus, it is quite likely that some infections not caused by influenza virus—common colds, for example—might have been reported. When we analyzed our data incorporating fever above 38.5° in the influenza-like symptoms, which would be expected to reduce misclassification, the association became stronger and remained statistically significant.

It has been suggested that infections “prepare” the immune system to have a more efficient response against cancer cells, either through immunity specific to cellular proteins which are involved in both infections and carcinogenesis or through cross-reactive pathogen-specific immunity [19]. This hypothesis has been proposed to explain the role of childhood infections, but our results might support a similar hypothesis for recent infections in adults as well, given that frequent infections were inversely associated with laryngeal cancer. Nevertheless, this was only true for up to two infections per year; more frequent infections (more than twice per year) were not associated with laryngeal cancer, indicating that the relationship might be quite complex. The frequency of recent infections may be an indicator of past infections, but considering that cancer has a long period of progression, the association might imply that the immune response triggered by influenza infections can be important even after carcinogenesis has started. Unmeasured

confounding may also be a possible explanation of this relationship.

All data on the history of allergies and influenza infections were self-reported. No objective data, such as might be obtained from blood samples or medical records, to verify the participants’ responses could be obtained. Moreover, despite the detailed description of symptoms that are characteristic of influenza infection, it is hard to distinguish influenza infections from common colds or other diseases. Therefore, a proportion of the respondents might have given inaccurate answers, which would lead to misclassification. Nevertheless, it is reasonable to assume that any misclassification must have been non-differential, which would bias the results towards the null. In that case, the real association between influenza and laryngeal cancer would be stronger than what our results showed, but there might also be an association between allergy and laryngeal cancer that we could not detect. Having an allergy diagnosed by a doctor is something that people should be able to easily recall though, since it is a diagnosis that they must usually take into account in their daily lives. Additionally, some people may confuse reactions to occupational exposures with allergies and falsely report them as allergies. The inclusion of the occupational index (CAI) in the multivariate models allowed us to partially control for such misconceptions, taking occupational exposures into account.

On the other hand, we were able to collect detailed data on smoking, alcohol consumption, occupational exposure to known carcinogens and education. Thus, we could control for several confounding factors, whereas most previous studies have controlled for only some of the potentially confounding variables.

Conclusion

Our analysis showed no association between any allergy and laryngeal cancer and some indication of an inverse association between Type IV allergy and laryngeal cancer in this case-control study. Recent influenza infections were inversely associated with laryngeal cancer risk, even after adjusting for major risk factors. Whether such an association represents causation or some unmeasured confounding remains unclear. A prospective cohort study, with objective records of influenza infections might be able to clarify the nature of the association between influenza infections and laryngeal cancer.

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Conflict of interest The authors declare that they have no conflict of interest.

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