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Association between cancer and contact allergy: a linkage study

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ABSTRACT

Background: Contact allergy is a prevalent disorder. It is estimated that about 20% of the general population are allergic to one or more of the chemicals that constitute the European baseline patch test panel. While many studies have investigated associations between type I allergic disorders and cancer, few have looked into the association between cancer and contact allergy, a type IV allergy. By linking two clinical databases, the authors investigate the possible association between contact allergy and cancer.

Methods: Record linkage of two different registers was performed: (1) a tertiary hospital register of dermatitis patients patch tested for contact allergy and (2) a nationwide cancer register (the Danish Cancer Register). After linking the two registers, only cancer subtypes with 40 or more patients registered were included in the analysis. The final associations were evaluated by logistic regression analysis.

Results: An inverse association between contact allergy and non-melanoma skin- and breast cancer, respectively, was identified in both sexes, and an inverse trend for brain cancer was found in women with contact allergy. Additionally, a positive association between contact allergy and bladder cancer was found.

Conclusion: The inverse associations support the immunosurveillance hypothesis (ie, individuals with an allergy are less likely to get cancer due to a triggered immune system), while the positive association with bladder cancer could be due to accumulations of chemical metabolites in the bladder. The authors' findings add to the limited knowledge about contact allergy and the risk of cancer.

ARTICLE SUMMARY

Article focus

- Cancer and allergy have previously been shown to be associated. The associations are mostly inverse, adding weight to the theory that enhanced tumour immunosurveillance is present in allergic individuals.
- The epidemiological studies showing these findings were predominantly on type I allergy; the present study investigated the association between type IV allergy and cancer.

Key messages

- An association seemingly exists between contact allergy and cancer. In light of previous findings of an association between bladder cancer and hair-dye use, the association between bladder cancer and contact allergy we found is interesting.

Strengths and limitations of this study

- This is a novel study investigating cancer and its possible association with a type IV allergy. The analysis was possible due to large, validated patient registers.
- As this is not a prospective cohort study, it lacks the ability to prove causation.

PRESS RELEASE

INTRODUCTION

About 20% of Danish adults are contact-allergic to chemicals and metals common in the environment.[1 2] Contact allergy is caused by skin contact with low-molecular-weight non-protein chemicals, referred to as haptens, and can progress to allergic contact dermatitis if re-exposure exceeds the individual's threshold.[3] Allergic contact dermatitis is a cutaneous delayed-type hypersensitivity reaction mediated by hapten-specific T cells.[4] A possible association between type 1 allergic hypersensitivity reactions, as observed in atopic diseases, and the unrestrained cell growth in cancer has long intrigued researchers. Some studies have reported both positive and inverse associations for allergic disorders; others have not found any significant associations, as reviewed in Sherman *et al*.[5] Most recent epidemiological studies point towards atopic diseases being associated with a reduced risk of cancer.[6] However, a major problem affecting many epidemiological studies on associations between atopy and cancer is the different way in which the studies define atopy. Additionally, some studies have included patients with allergic contact dermatitis, which is problematic, as the immune response differs greatly.[6] To date, few studies have investigated the relationship between contact allergy and cancer. Contact allergy to metal dental restorations was found to be a potential risk factor for intraoral

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squamous cell carcinoma,[7] and glioma appeared inversely associated with self-reported contact dermatitis.[8] Thus, it remains unclear whether two prevalent disorders, cancer and contact allergy, are truly associated, and if so, in what direction. We have previously shown that contact allergy is inversely associated with autoimmune diseases such as type 1 diabetes and inflammatory bowel disease.[9–11] This is a descriptive exploratory investigation of the possible association between contact allergy and cancer by using cross-linkage between our contact allergy database and the national cancer database (the Danish Cancer Registry).

MATERIALS AND METHODS

Study population and allergy testing

From November 1984 to December 2008, patch tests for contact allergy using the European baseline series were performed on 16 922 (6113 men and 10 809 women) patients with dermatitis at the Department of Dermatology, Gentofte Hospital, Denmark. The outcome of patch testing, sex and date of birth were recorded in the allergy database. The European baseline series contains the most prevalent contact allergens in the environment for the European continent. Patch testing was performed on the upper back using Trolab allergens (Hermal, Reinbek, Germany) and Finn Chambers (8 mm Epitest, Oy, Finland) on Scanpor tape (Norgesplaster A/S, Alpharma, Vennesla, Norway) for occlusion. Occlusion time was 48 h, and the patches were read on Day 2, on Day 3 or 4, and on Day 5 or 7 according to international criteria from the International Contact Dermatitis Research Group (ICDRG).[12 13] A positive allergic reaction was defined as at least homogeneous erythema and infiltration in the test area. The database contains information on the patch-test reading result for each day, but in the present study, a binary variable was constructed. Thus, a positive patch-test reaction on any reading day to any allergen in the European baseline series was considered positive. The study population has been detailed previously.[14]

Linkage study

At birth, or on immigration, all those with residency in Denmark receive a unique and personal identifier number, a CPR number, which can be used for identification in databases. This enables linkage of individual data between databases.

We used the unique identifier number to link the contact allergy database from Gentofte Hospital, a tertiary referral centre, with the Danish Cancer Registry, which contains codes of cancer diagnosis from the International Classification of Diseases, 7th or 10th revision (ICD7 and ICD10). The Danish Cancer Registry is a population-based registry containing nationwide data on cancer cases since 1943. The history of the Danish Cancer Registry was reviewed by Storm *et al* in 1997.[15] Cancer types were defined according to the Nordic Cancer Registries (NORDCAN Database, http://www.ancr.nu/nordcan.asp). The cancer types 'other leukaemia' and acute 'leukaemia' in the NORDCAN database were omitted from data analyses, as we considered the grouping 'leukaemia' to cover immunological aspects of this cancer type and be representative. Table 1 shows cancer types used from the NORDCAN database. Only cancer types for which we found 40 or more patients after the linkage were included in the logistic regression analyses. Age was calculated as the age at first positive patch-test outcome. When there was no positive patch-test reading, the age at first patch-test procedure was used. Based on the number of patients in different age groups, patients were stratified into five groups: 0–29 years, 30–41 years, 42–52 years, 53–65 years and 65< years.

The combined data file was analysed using logistic regression analysis with the patch-test outcome (contact allergy: 'yes' vs 'no') as the dependent variable and different cancer types as the independent variables, and controlled for sex and age. Lastly, we inserted interaction terms between sex and each cancer subtype (eg, sex×colon cancer, sex×lung cancer, etc) in the regression analysis to test whether we should stratify the analyses by sex. ORs with 95% CIs were estimated using logistic regression. All data analyses were carried out using SPSS version 18.

RESULTS

Among 16 922 patients patch-tested in the selected period, 6065 (35.8%) had a positive reaction to at least one allergen on at least one occasion. The prevalence of contact allergy, however, differed between the sexes, as the prevalence was 26.1% in male patients and 41.4% in female patients.

After linkage with the Danish Cancer Registry, 3200 (18.9%) dermatitis patients were identified with a benign tumour and/or a malignant cancer diagnosis, and 1207 (37.7%) of these also had a positive patch test reaction. The distribution within different cancer groups (with ≥40 cases) is shown in table 1. Crude data analysis revealed a positive and significant association between being contact allergic and being registered in the cancer registry (Mantel–Haenszel common OR=1.1; p value=0.014, 95% CI 1.02 to 1.20). Using logistic regression analyses with contact allergy as the dependent variable, we calculated ORs for different cancer groups and adjusted the analysis for sex and age. Breast cancer and non-melanoma skin cancer in both sexes were found to be inversely and significantly associated with contact allergy; for women, there was a trend for an inverse association between contact allergy and brain cancer. Bladder cancer was found to be positively and significantly associated with contact allergy. The sex-specific association for brain cancer was identified by investigating different interaction terms between cancer subtypes and sex. However, we found a significant interaction term only for brain/CNS cancer. Thus, when a subsequent adjusted regression analysis was performed

Table 1 Sex-specific distribution of cancer types and contact allergy

Cancer groups (NORDCAN)	Sex						
	Men			Women			
	No contact allergy	Contact allergy	Total	No contact allergy	Contact allergy	Total	Total
Pancreas	11	4	15	13	17	30	45
	24.4%	8.9%	33.3%	28.9%	37.8%	66.7%	100%
Brain/CNS	15	7	22	30	11	41	63
	23.8%	11.1%	34.9%	47.6%	17.5%	65.1%	100%
Cervix uteri	NA	NA	NA	34	30	64	64
				53.1%	46.9%	100%	100%
Leukaemia	27	7	34	24	13	37	71
	38.0%	9.9%	47.9%	33.8%	18.3%	52.1%	100%
Lip, oral cavity and pharynx	30	15	45	16	12	28	73
	41.1%	20.5%	61.6%	21.9%	16.4%	38.4%	100%
Corpus uteri	NA	NA	NA	48	38	86	86
				55.8%	44.2%	100%	100%
Rectum and anus	41	14	55	29	17	46	101
	40.6%	13.9	54.5%	28.7%	16.8%	45.5%	100%
Melanoma of skin	32	11	43	40	21	61	104
	30.8%	10.6%	41.3%	38.5%	20.2%	58.7%	100%
Prostate	86	36	122	NA	NA	NA	122
	70.5%	29.5%	100%				100%
Colon	43	9	52	43	29	72	124
	34.7%	7.3%	41.9%	34.7%	23.4%	58.1%	100%
Bladder, etc	63	33	96	21	22	43	139
	45.3%	23.7%	69.1%	15.1%	15.8%	30.9%	100%
Lung	83	26	109	41	42	83	192
	43.2%	13.5%	56.8%	21.4%	21.9%	43.2%	100%
Colorectal	83	23	106	71	46	117	223
	37.2%	10.3%	47.5%	31.8%	20.6%	52.5%	100%
Breast	0	0	0	248	151	399	399
				62.2%	37.8%	100%	100%
Skin, non-melanoma	203	72	275	284	166	450	725
	28.0%	9.9%	37.9%	39.2%	22.9%	62.1%	100%
All sites but non-melanoma skin cancer	531	209	740	663	452	1115	1855
	28.6%	11.3%	39.9%	35.7%	24.4%	60.1%	100%
Total (allergy database)	4519	1594	6113	4471	6338	10 809	16 922
	26.7%	9.4%	36.1%	26.4%	37.5%	63.9%	100%

The cancer types are sorted ascendingly according to the total number of patients with the respective cancer type. Only cancer types with ≥40 patients were included in the logistic regression analyses. CNS, central nervous system.

only in female dermatitis patients, a trend towards an inverse association was found between brain/CNS cancer and contact allergy (p=0.080; OR=0.36 (95% CI=0.12 to 1.13)). Table 2 shows the ORs for each cancer type, adjusted for age and sex, and the final analysis outcome, which included bladder, breast, brain/CNS and skin cancer (non-melanoma), as well as the brain/cancer×sex interaction.

DISCUSSION

We found a significant and inverse association between contact allergy and breast cancer and non-melanoma skin cancer, respectively, as well as a significant and positive association between contact allergy and bladder cancer. Additionally, brain/CNS cancer in women was inversely associated with contact allergy, albeit the p value was above 0.050 (p value=0.08).

The allergen database used in the study comprises patients patch-tested at Gentofte hospital, and as such the patch tests have been scored uniformly over the years. The hospital lies in the capital region of Denmark, a region where there is limited industrial exposure from pesticide manufacturing, synthetic rubber processing, petrochemical refinery, etc, which gives no immediate confounding due to working conditions known to cause cancer.

We did not account for smoking in our study, although smoking may increase the risk of developing nickel contact allergy and some types of cancer.[16 17] However, we found no association with lung or oral cancers, which are positively associated with smoking,[18] but we did find a positive association with bladder cancer, which could have been partially caused by smoking, as smoking is a known risk factor for bladder cancer.[19] Smoking can also be a risk factor for non-melanoma skin cancer,[20 21]

Table 2 Logistic analysis for the individual cancer group adjusted for age and sex

Cancer groups (NORDCAN)	p Value	OR (95% CI)
Pancreas	0.184	1.50 (0.83 to 2.72)
Brain/CNS	0.159	0.66 (0.38 to 1.16)
Cervix uteri	0.503	1.18 (0.73 to 1.94)
Leukaemia	0.233	0.73 (0.43 to 1.23)
Lip, oral cavity and pharynx	0.496	1.18 (0.73 to 1.92)
Corpus uteri	0.797	1.06 (0.69 to 1.62)
Rectum and anus	0.470	0.85 (0.55 to 1.31)
Melanoma of skin	0.262	0.79 (0.51 to 1.20)
Prostate	0.455	1.16 (0.78 to 1.73)
Colon	0.215	0.78 (0.53 to 1.15)
Bladder, etc	0.039	1.44 (1.02 to 2.05)
Lung	0.720	1.06 (0.78 to 1.43)
Colorectal	0.187	0.82 (0.61 to 1.10)
Breast	0.031	0.80 (0.65 to 0.98)
Skin, non-melanoma	0.020	0.82 (0.70 to 0.97)
All sites but non-melanoma skin cancer	0.415	0.96 (0.86 to 1.06)
Final logistic analysis		
Bladder, etc	0.040	1.44 (1.02 to 2.05)
Breast	0.035	0.80 (0.65 to 0.98)
Skin, non-melanoma	0.021	0.83 (0.70 to 0.97)
Brain/CNS	0.513	1.35 (0.55 to 3.33)
Brain/CNS×sex	0.080	0.36 (0.12 to 1.13)

The last six rows are the final analysis outcome with the interaction variable and the significant cancer groups. CNS, central nervous system.

a modest risk factor for brain cancer,[22 23] and is speculated to be a risk factor for breast cancer.[24] However, as these cancer types were inversely associated with contact allergy, a bias caused by smoking would have weakened the association.

Although most patients with contact allergy have been treated intermittently with topical steroids, only a minority have been treated with systemic immunosuppressants. The latter treatment might be associated with non-melanoma skin cancer, as TNF-α-inhibitors and prednisolone have been shown to increase the risk of non-melanoma skin cancer in rheumatoid-arthritis patients.[25] Additionally, a study on squamous-cell carcinoma found a positive association in patients hospitalised for chronic diseases, including skin disease and among these allergic contact dermatitis.[26] In our study, we found an inverse association between contact allergy and non-melanoma skin cancer, and treatment biases could therefore have weakened this inverse association.

Self-reported contact eczema has been found to be inversely correlated to glioma and meningioma.[8] The self-reported contact eczema had the lowest OR of any of the allergic conditions for both glioma and meningioma, although the CI for meningioma was wide and close to 1. Glioma patients have been shown to have impaired immunity,[27] and it is unknown whether the suppression is evident before diagnosis of the tumour. It has been suggested that hair dyeing can increase the risk of glioma[28 29]; however, we found an inverse association, even though hair dyeing is a risk factor for development of p-phenylenediamine contact allergy, for example. Hair dyeing may also be a risk factor for developing bladder cancer.[30 31] In our study, we found a positive association between contact allergy and bladder cancer, which may be caused by p-phenylenediamine contact allergy. Hair dyeing does not appear to be related to breast cancer.[32]

It would have been interesting if we had analysed possible associations between specific allergens and cancer types in the current dataset, but owing to a lack of power, this was not possible.

Various hypotheses have been put forward to explain the associations between allergy and cancer. The 'antigenic stimulation' hypothesis has been suggested to explain positive associations. In this hypothesis, it is speculated that the increased stimulation of cell growth in allergy and chronic inflammation increases the likelihood of mutation of dividing stem cells and malignant proliferation.[5] To explain inverse associations, the immunosurveillance hypothesis has been suggested, where the allergic symptoms are the side effect of hyperimmunity. Additionally, tumours may suppress the immune system systemically and in the microenvironment of the tumour,[33] as seen in glioma patients, who have a lower count of CD4+T cells overall and an increased fraction of CD4+FOXP3+T cells in the remaining fraction.[34]

In conclusion, contact allergy was found to be associated with four different cancer subtypes. Most of the associations were inverse, which might support the immunosurveillance hypothesis. The reason for these relations is uncertain and not necessarily the result of causality. More

refined analyses, adjusting for social class and smoking, for instance, and studies focusing on specific chemical exposures are required to further our understanding of the role of contact allergies in the development of cancer. However, if these relations are aetiological, there are implications for understanding how contact allergy can affect cancer development and vice versa.

Our findings add to the limited knowledge of the association between contact allergy and cancer.

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Competing interests None.

Contributors KE, TM and JDU designed the study. KE and JPT analysed and interpreted the data. KE and JPT drafted the manuscript, and all authors revised it critically. All authors gave their final approval of the version to be published.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract Yes "a linkage Study" in the title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Yes
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Yes, explain that type 1 allergy associations have previously been reported and that
Objectives	3	State specific objectives, including any prespecified hypotheses YES
Methods		
Study design	4	Present key elements of study design early in the paper YES
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES
Bias	9	Describe any efforts to address potential sources of bias YES
Study size	10	Explain how the study size was arrived at YES
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why YES
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding YES
		(*b*) Describe any methods used to examine subgroups and interactions YES
		(*c*) Explain how missing data were addressed N/A
		(*d*) If applicable, explain how loss to follow-up was addressed N/A
		(*e*) Describe any sensitivity analyses N/A

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES were applicable
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram Not used
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Not possible
		(b) Indicate number of participants with missing data for each variable of interest Register data
		(c) Summarise follow-up time (eg, average and total amount) N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time YES
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES
		(*b*) Report category boundaries when continuous variables were categorized No continuous variable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES
Discussion		
Key results	18	Summarise key results with reference to study objectives YES
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES
Generalisability	21	Discuss the generalisability (external validity) of the study results YES
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based No specific funding for the present paper, but 2 general grants, mentioned in the Acknowledgments section

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.