Association between Cancer and Contact Allergy– a linkage Study

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Article focus

- Cancer and allergy have previously been shown to be associated. Mostly the associations found are inverse, which have found support in the immune surveillance theory, as an enhanced tumour immunosurveillance could be hypothesized in allergic individuals.
- These epidemiological studies have predominantly been done on type I allergy, while the present study finds comparative association between type IV allergy and cancer.

Key messages

- The present study adds knowledge about associations between contact allergy and cancer, which have not previously been investigated.
- Of interest, we find an association between bladder cancer and contact allergy. Though we don't have enough power to study specific allergen association, this is interesting as an association between bladder cancer and hair dye use have previously been found.

Strengths and limitations of this study

- The present study is unique in looking at cancer and its possible association to a type IV allergy, and can only be done due to large validated patient registers
- As this is not a prospective cohort study, it lacks the possibility to prove causation

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Competing interest's statement

The authors declare they have no competing interests

Contributor statements

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 made final approval of the version to be published

Abstract

Background:

Contact allergy is a prevalent. It is estimated that about 20% of the general population is allergic to one or more of the chemicals that constitutes the baseline patch test panel. While many studies have investigated associations between type I allergic disorders and cancer, only very few studies have investigated the association between cancer and contact allergy. We therefore aimed to investigate the possible association between a contact allergy and cancer by linking two clinical databases.

Methods:

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

Results:

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

Conclusion:

Contact allergy was significantly associated with three cancer groups. Two of these (breast and non-melanoma skin cancer) were inversely associated with contact allergy, and additionally brain cancer in women had a trend for an inverse association. This tend to support the immunosurveillance hypothesis (i.e. sufferers of allergy are less likely to get cancer due to a triggered immune system), while the positive association to bladder cancer possibly could be due to accumulations of chemical metabolites in the bladder. However, the background for these associations is uncertain and not

necessarily the result of causality. Nevertheless, our findings add to the limited knowledge that exists about contact allergy and the hazards of cancers.

Introduction

About 20% of Danish adults are contact allergic to at least one of frequent chemicals and metals in our 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 threshold [3]. Allergic contact dermatitis is a cutaneous delayed-type hypersensitivity reaction, mediated by hapten-specific T-cells, in which CD8+ type 1 T-cells are effector cells in normal contact hypersensitivity responses, while CD4+ T-cells are mainly endowed with down-regulatory functions [4]. A possible association between allergic hypersensitivity reactions, as observed in atopic diseases and the unrestrained cell growth in cancer has intrigued researchers for decades. Studies have reported both positive and inverse associations for allergic disorders, while some have not found any significant associations, reviewed in Sherman et al. [5]. Most current epidemiological studies indicate that atopic diseases may be associated with a reduced risk of cancer [6]. However, one important problem affecting many epidemiological studies on associations between atopy and cancer is the variability between studies in the definition of atopy. Additionally, some studies have included patients with allergic contact dermatitis which is problematic as the immune response is very different [6]. Few studies have investigated the relationship between contact allergy and cancer. Contact allergy to metal dental restorations was shown to be a potential risk factor for intra-oral squamous cell carcinoma [7], while glioma appear to be inversely associated with self-reported contact dermatitis [8]. Thus, it remains unclear whether two very 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 some prevalent autoimmune diseases such as diabetes and inflammatory bowel disease [9-11]. We set out to investigate 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, 16,922 (6,113 men and 10,809 women) patients with dermatitis were patch tested for contact allergy with the European baseline series 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 Ltd, Oy, Finland) on Scanpor tape® (Norgesplaster A/S, Alpharma, Vennesla, Norway) for occlusion. Occlusion time was 48 hours 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 patch test reading result for each of the days, but in the present study, a binary variable was constructed. Thus, a positive patch test reaction at any day of reading to any allergen in the European baseline series was considered positive.

Linkage study:

At birth, or on immigration, all Danish residents are given 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.

Using the unique identifier number, the contact allergy database from Gentofte Hospital, a tertiary referral centre, was linked 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 has been reviewed previously by Storm et al. 1997[14]. Cancer types were defined according to the Nordic Cancer Registry

(NORDCAN Database, http://www.ancr.nu/nordcan.asp). The cancer types "other leukemia" and acute "leukemia" in the NORDCAN database was however omitted from data analyses as we considered the grouping "leukemia" 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. In case there was no positive patch test reading, the age at first patch test procedure was used instead. 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 analyzed 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. Finally, we inserted interaction terms between gender and each cancer subtype (e.g. sex*colon cancer, sex*lung cancer, etc.) in the regression analysis to test whether we had to stratify the analyses by gender. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using logistic regression. All data analysis was done using SPSS version 15 (SPSS Inc., Chicago, IL, USA)

Results

Among 16,922 patients patch tested in the selected time period, 6,065 (35.8%) had a positive reaction to at least one allergen on at least one occurrence. The prevalence of contact allergy was however different between the sexes, as the prevalence was 26.1% in male patients and 41.4% in female patients. The study population has previously been detailed (Carlsen, BC et al. 2007) [15]. Briefly, the mean and median prevalence of contact allergy across test years were respectively, 37.1 % (SD 3.37) and 36.8 % (Range 28.3% - 43.9%). Thus, only small changes in the frequency of positive reactions were observed across test years.

After linkage with the Danish Cancer Registry, 3,200 (18.9%) dermatitis patients were identified with a benign tumour and/or a malignant cancer diagnosis, and 1,207 (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; CI95%= 1.02-1.20). Using logistic regression analyses with contact allergy as the dependent variable, we calculated odds ratios for different cancer groups and adjusted the analysis for sex and age. Breast and non-melanoma skin cancer in both genders were found to be inversely and significantly associated with contact allergy, while there was a trend for an inverse association between contact allergy and brain cancer in women. 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 gender. However, we only found a significant interaction term for brain/CNS cancer. Thus, when a subsequent adjusted regression analysis was performed in female dermatitis patients only, a trend towards an inverse association was found between brain/CNS cancer and contact allergy; (p = 0.080; OR = 0.36 (CI95%= 0.12-1.13). Table 2 shows the cancer types, adjusted for age and sex, which were associated with contact allergy. The cancer types were Breast cancer (OR= 0.80; 95%CI = 0.65-0.98), skin cancer (non-melanoma) (OR = 0.83; 95%CI = 0.70-0.97), brain/CNS cancer in women (OR=0.36; 95%CI = 0.12-1.13) and bladder cancer which were positively associated with contact allergy (OR = 1.44; 95%CI = 1.02-2.05).

Discussion

We found a significant and inverse association between contact allergy and, respectively, breast cancer and non-melanoma skin cancer and a significant and positive association between contact allergy and bladder. Additionally, brain/CNS cancer in women had a trend toward an inversely associated with contact allergy. The associations were identified by performing record linking of

two databases: one of contact allergy test outcomes and one of cancer diagnoses, i.e. the Danish Cancer Registry. Patients with contact allergy entered the allergy database following referral to a tertiary university dermatology clinic, generally because of chronic dermatitis and by referral from private dermatology clinics and general physicians. Patch testing classified the patients into groups with and without contact allergy (based on the outcome of patch testing). Apparently, those with positive patch test reactions had a decreased risk of having breast cancer and non-melanoma skin cancer, while they had an increased risk of having bladder cancer. Additionally, women with positive patch test reactions had reduced risk of brain*/CNS cancer (insignificant trend). These associations are interesting since hospitalization bias would generally lead to a positive association and not a negative association. Additionally, possible associations may have been diluted as both cases and controls were from the same database consisting of patch tested dermatitis patient. Population-based studies are often preferable to patient-based studies by virtue of unbiased estimation of prevalence and risk; however when evaluating risk factors for contact allergy they often have limited power [16].

We chose to use logistic regression analyses for several reasons. First, the time span from the development of contact allergy to the diagnosis was established is unknown and likewise for cancer. Second, our objective was not to establish causality but rather to test whether a skewed immune system towards delayed type hypersensitivity is positively or negatively associated with cancer. Third, we have with success applied this type of regression analysis in previous studies investigating diabetes and inflammatory bowel disease ([10;11]). Fourth, it has been suggested that the advantages of Cox regression are mainly found when analyzing high baseline risks which was not the case in this study [17]. .

The allergy database had a median age of 47 years, and the patients that also appeared in the cancer register had a median age of 60 years. Some of the analyzed patients may therefore develop cancer when they get older; however with a median age of 47 years, some of the malignant tumors may already have developed. It should be emphasized that contact allergy to prevalent allergens such as

nickel and cobalt is typically developed early in life, i.e. prior to development of most cancers. There are more females than males in the allergy database, and likewise there are also more females with a positive patch test reactions, which is in accordance with the literature [15].

The present study is unique in the sense that it is only possibly to perform record cross-linkage of registers due to the personal identifier given to all Danish citizens at birth or at immigration. Furthermore, the allergen database is composed of patients patch tested at a hospital in the capital region of Denmark, a region were there is limited industrial exposure due to pesticide manufacturing, synthetic rubber processing, petrochemical refinery etc. that might lead to cancer. Instead many of the patients with contact allergy are allergic to cosmetic ingredients and metals from jewellery which gives no immediate confounding due to working conditions know to cause cancer. A negative patch test response might be due to tolerance of the individual as most individuals are exposed to contact allergens, and a positive patch test response could therefore be implicative of an efficient immune system lending support to the immunosurveillance hypothesis. The positive association to bladder cancer might be due to accumulations of metabolites from contact allergens in the bladder, which is somewhat supported by a study showing an increased frequency of micronuclei in urothelial cells of hair dye users [18].

We cannot account for smoking in our study, although smoking may increase the risk of developing nickel contact allergy and some types of cancer [19;20]. However, we do not find any association to lung or oral cancers, which are positively associated with smoking [21]. We do however find a positive association with bladder cancer that could be somewhat caused by smoking, as smoking is a known risk factor for bladder cancer [22]. Smoking can additionally be a risk factor for non-melanoma skin cancer [23;24], a modest risk factor for brain cancer [25;26] and might be a risk factor for breast cancer [27], however as these cancer types were inversely associated with contact allergy , a bias caused by smoking would therefore rather have weakened the association. Most of contact allergy patients have been treated intermittently with topical steroids and only a minority with systemic immunosuppressants. The later treatment may be associated with non-melanoma skin

cancer as TNF-α-inhibitors and prednisone have been shown to increase the risk of non-melanoma skin cancer in rheumatoid arthritis patients [28]. Additionally, a study on squamous cell carcinoma found a positive association in patients hospitalized for chronic diseases including skin disease and among these allergic contact dermatitis [29]. In our study, we found an inverse association between contact allergy and non-melanoma skin cancer, and treatment bias could possibly have weakened this inverse association

Self-reported contact eczema have previously been found to be inversely correlated to glioma and meningioma [8]. The self-reported contact eczema even had the lowest OR of any of the allergic conditions for both glioma and meningioma, though the confidence interval for meningioma was wide and close to one. Glioma patients have been shown to suffer from impaired immunity [30], whether the suppression is evident before diagnosis of the tumour is not known. If the reduced risk associated with allergies was an effect of immunosuppression induced by the tumour, current allergic diseases would be expected to be associated with a decreased risk. It has been suggested that hair dyeing can increase the risk of glioma [31;32]; however we find an inverse association even though hair dyeing is a risk factor for development of e.g. p-phenylenediamine (PPD) contact allergy. Hair dyeing may additionally be a risk factor for the development of bladder cancer [18;33]. In our study we find a positive association between contact allergy and bladder cancer, which may be caused by PPD contact allergy. Hair dyeing does not appear to be related with breast cancer [34]. It would have been interesting if we could have analyzed possible association between specific allergens and the significant cancer types, in the current dataset. However, we do not have enough power to analyze these associations.

Different hypothesis have been suggested to explain the association between allergy and cancer. To explain positive associations the “antigenic stimulation” hypothesis has been suggested, in which it is speculated that the increased stimulation of cell growth in allergy and chronic inflammation increase the likelihood of mutation of dividing stem cells and malignant proliferation [5]. To explain inverse associations, the immunosurveillance hypothesis has been suggested in which the allergic

symptoms is the side effect of hyperimmunity and are therefore not the result of causation. Additionally, tumours may suppress the immune system systemically and in the microenvironment of the tumour [35], as seen for glioma patients that have a lower count of CD4+T cells overall and an increased fraction of CD4+FOXP3+T cells in the remaining fraction [36]

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, smoking e.g. and studies focusing on specific chemical exposures are required to further increase our understanding of the role of contact allergies in the development of cancer. However, if these relations are etiological, it has implications for understanding how contact allergy can affect cancer development and vice versa.

Nevertheless, our findings add to the limit knowledge that exists about contact allergy and the hazards of cancers.

Acknowledgments

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Tables

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

CANCER GROUPS (NORDCAN)	SEX						TOTAL
	Men			Women			
	Contact allergy	No contact allergy	Total	Contact allergy	No contact allergy	Total	
Pancreas	4	11	15	13	17	30	45
Brain/CNS	7	15	22	30	11	41	63
Cervix uteri	n/a	n/a	n/a	34	30	64	64
Leukemia	7	27	34	24	13	37	71
Lip, oral cavity and pharynx	15	30	45	16	12	28	73
Corpus uteri	n/a	n/a	n/a	48	38	86	86
Rectum and anus	14	41	55	29	17	46	101
Melanoma of skin	11	32	43	40	21	61	104
Prostate	36	86	122	n/a	n/a	n/a	122
Colon	9	43	52	43	29	72	124
Bladder etc.	33	63	96	21	22	43	139
Lung	26	83	109	41	42	83	192
Colorectal	23	83	106	71	46	117	223
Breast	0	0	0	248	151	399	399
Skin, non-melanoma	72	203	275	284	166	450	725
All sites but non-melanoma skin cancer	209	531	740	663	452	1,115	1,855
Total(allergy database)	**1,594**	**4,519**	**6,113**	**4,471**	**6,338**	**10,809**	**16,922**

Table 2 The final analysis outcome including the interaction variable Brain/CNS*Sex, all adjusted for age and sex

Cancer groups (NORDCAN)	ICD7	ICD10	p-value	OR	CI 95%
Bladder etc.	181	C65-68+ D09.0 + D41.4	0.040	1.44	1.02 - 2.05
Breast	170	C50	0.035	0.80	0.65 - 0.98
Skin, non-melanoma	191	C44+C46.0	0.021	0.83	0.70 - 0.97
Brain/CNS	193	C70-72+D32-33+D42-43	0.513	1.35	0.55 – 3.33
Brain/CNS *Sex	-	-	0.080	0.36	0.12 - 1.13

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.

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Association between Cancer and Contact Allergy: a linkage Study

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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 the 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 possibility to prove causation.

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Competing interests statement

The authors declare they have no competing interests.

Contributor statements

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

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Abstract

Background:

Contact allergy is a prevalent disorder. It is estimated that about 20% of the general population is 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, we 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 supports the immunosurveillance hypothesis (i.e. individuals with 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. Our findings add to the limited knowledge about contact allergy and the risk of cancer.

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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, 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 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 intra-oral 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).

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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 (6,113 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 Ltd, Oy, Finland) on Scanpor tape® (Norgesplaster A/S, Alpharma, Vennesla, Norway) for occlusion. Occlusion time was 48 hours 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 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 (Carlsen, BC et al. 2007) [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,

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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 (e.g. sex*colon cancer, sex*lung cancer, etc.) in the regression analysis to test whether we should stratify the analyses by sex. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using logistic regression. All data analysis was done using SPSS version 18 (SPSS Inc., Chicago, IL, USA)

Results

Among 16,922 patients patch tested in the selected period, 6,065 (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, 3,200 (18.9%) dermatitis patients were identified with a benign tumour and/or a malignant cancer diagnosis, and 1,207 (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-

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Deleted: The study population has previously been detailed (Carlsen, BC et al. 2007) [15]. Briefly, the mean and median prevalence of contact allergy across test years were respectively, 37.1 % (SD 3.37) and 36.8 % (Range 28.3% - 43.9%). Thus, only small changes in the frequency of positive reactions were observed across test years.
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value = 0.014, CI95%= 1.02–1.20). 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 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 (CI95%= 0.12–1.13). 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 were 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

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We chose to use logistic regression analyses for several reasons. First, the time span from the development o ... [1]

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], 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 hospitalized 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 confidence interval for meningioma was wide and close to one. Glioma patients have been shown to have impaired immunity [27], whether the suppression is evident before diagnosis of the tumour is unknown. 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 e.g. p-phenylenediamine (PPD) contact allergy. 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 PPD 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 due to lack of power this was not possible.

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The allergy database had a median age of 47 years, and the patients that also appeared in the cancer register had a median age of 60 years. Some of the analyzed patients may therefore develop cancer when they get older; however with a median age of 47 years, some of the malignant tumors may already have developed. It should be emphasized that contact allergy to prevalent allergens such as nickel and cobalt is typically developed early in life, i.e. prior to development of most cancers. There are more females than males in the allergy database, and likewise there are also more females with a positive patch test reactions, which is in accordance with the literature

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The present study is unique in the sense that it is only possibly to perform record cross-linkage of registers due to the personal identifier given to all Danish citizens at birth or at immigration. Furthermore, the allergen database is composed of patients patch tested at a hospital in the capital region of Denmark, a region were there is limited indu ... [2]

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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.

Acknowledgments

Financial support from Aage Bang's Foundation and the Capital Region's Research Foundation is gratefully acknowledged.

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Different hypothesis have been suggested to explain the association between allergy and cancer. To explain positive associations the "antigenic stimulation" hypothesis has been suggested, in which it is speculated that the increased stimulation of cell growth in allergy and chronic inflammation increase the likelihood of mutation of dividing stem cells and malignant proliferation [5]. To explain inverse associations, the immunosurveillance hypothesis has been suggested in which the allergic symptoms is the side effect of hyperimmunity and are therefore not the result of causation. Additionally, tumours may suppress the immune system systemically and in the microenvironment of the tumour [35], as seen for glioma patients that have a lower count of CD4+T cells overall and an increased fraction of CD4+FOXI ... [10]

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Tables

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

CANCER GROUPS (NORDCAN)	SEX						TOTAL
	Men			Women			
	No contact allergy	Contact allergy	Total	No contact allergy	Contact allergy	Total	
Pancreas	11 24.4%	4 8.9%	15 33.3%	13 28.9%	17 37.8%	30 66.7%	45 100%
Brain/CNS	15 23.8%	7 11.1%	22 34.9%	30 47.6%	11 17.5%	41 65.1%	63 100%
Cervix uteri	n/a	n/a	n/a	34 53.1%	30 46.9%	64 100%	64 100%
Leukaemia	27 38.0%	7 9.9%	34 47.9%	24 33.8%	13 18.3%	37 52.1%	71 100%
Lip, oral cavity and pharynx	30 41.1%	15 20.5%	45 61.6%	16 21.9%	12 16.4%	28 38.4%	73 100%
Corpus uteri	n/a	n/a	n/a	48 55.8%	38 44.2%	86 100%	86 100%
Rectum and anus	41 40.6%	14 13.9	55 54.5%	29 28.7%	17 16.8%	46 45.5%	101 100%
Melanoma of skin	32 30.8%	11 10.6%	43 41.3%	40 38.5%	21 20.2%	61 58.7%	104 100%
Prostate	86 70.5%	36 29.5%	122 100%	n/a	n/a	n/a	122 100%
Colon	43 34.7%	9 7.3%	52 41.9%	43 34.7%	29 23.4%	72 58.1%	124 100%
Bladder etc.	63 45.3%	33 23.7%	96 69.1%	21 15.1%	22 15.8%	43 30.9%	139 100%
Lung	83 43.2%	26 13.5%	109 56.8%	41 21.4%	42 21.9%	83 43.2%	192 100%
Colorectal	83 37.2%	23 10.3%	106 47.5%	71 31.8%	46 20.6%	117 52.5%	223 100%
Breast	0	0	0	248 62.2%	151 37.8%	399 100%	399 100%
Skin, non-melanoma	203 28.0%	72 9.9%	275 37.9%	284 39.2%	166 22.9%	450 62.1%	725 100%
All sites but non-melanoma skin cancer	531 28.6%	209 11.3%	740 39.9%	663 35.7%	452 24.4%	1,115 60.1%	1,855 100%
Total(allergy database)	**4,519 26.7%**	**1,594 9.4%**	**6,113 36.1%**	**4,471 26.4%**	**6,338 37.5%**	**10,809 63.9%**	**16,922 100%**

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Table

Logistic analysis for the individual cancer group adjusted for age and sex. The last six rows are the final analysis outcome with the interaction variable and the significant cancer groups.

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

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Cancer groups (NORDCAN) ... [11]

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We chose to use logistic regression analyses for several reasons. First, the time span from the development of contact allergy to the diagnosis was established is unknown and likewise for cancer. Second, our objective was not to establish causality but rather to test whether a skewed immune system towards delayed type hypersensitivity is positively or negatively associated with cancer. Third, we have with success applied this type of regression analysis in previous studies investigating diabetes and inflammatory bowel disease (

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The present study is unique in the sense that it is only possibly to perform record cross-linkage of registers due to the personal identifier given to all Danish citizens at birth or at immigration. Furthermore, the allergen database is composed of patients patch tested at a hospital in the capital region of Denmark, a region were there is limited industrial exposure due to pesticide manufacturing, synthetic rubber processing, petrochemical refinery etc. that might lead to cancer. Instead many of the patients with contact allergy are allergic to cosmetic ingredients and metals from jewellery which gives no immediate confounding due to working conditions know to cause cancer. A negative patch test response might be due to tolerance of the individual as most individuals are exposed to contact allergens, and a positive patch test response could therefore be implicative of an efficient immune system lending support to the immunosurveillance hypothesis. The positive association to bladder cancer might be due to accumulations of metabolites from

contact allergens in the bladder, which is somewhat supported by a study showing an increased frequency of micronuclei in urothelial cells of hair dye users

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We cannot account for smoking in our study, although smoking may increase the risk of developing nickel contact allergy and some types of cancer

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. However, we do not find any association to lung or oral cancers, which are positively associated with smoking

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. We do however find a positive association with bladder cancer that could be somewhat caused by smoking, as smoking is a known risk factor for bladder cancer

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. Smoking can additionally be a risk factor for non-melanoma skin cancer

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, however as these cancer types were inversely associated with contact allergy , a bias caused by smoking would therefore rather have weakened the association. Most of contact allergy patients have been treated intermittently with topical steroids and only a minority with systemic immunosuppressants. The later treatment may be associated with non-melanoma skin cancer as TNF-α-inhibitors and prednisone have been shown to increase the risk of non-melanoma skin cancer in rheumatoid arthritis patients

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. Additionally, a study on squamous cell carcinoma found a positive association in patients hospitalized for chronic diseases including skin disease and among these allergic contact dermatitis

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. In our study, we found an inverse association between contact allergy and non-melanoma skin cancer, and treatment bias could possibly have weakened this inverse association

Self-reported contact eczema have previously been found to be inversely correlated to glioma and meningioma

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; however we find an inverse association even though hair dyeing is a risk factor for development of e.g. p-phenylenediamine (PPD) contact allergy. Hair dyeing may additionally be a risk factor for the development of bladder cancer [18;33]. In our study we find a positive association between contact allergy and bladder cancer, which may be caused by PPD contact allergy. Hair dyeing does not appear to be related with breast cancer [34]. It would have been interesting if we could have analyzed possible association between specific allergens and the significant cancer types, in the current dataset. However, we do not have enough power to analyze these associations.

Different hypothesis have been suggested to explain the association between allergy and cancer. To explain positive associations the "antigenic stimulation" hypothesis has been suggested, in which it is speculated that the increased stimulation of cell growth in allergy and chronic inflammation increase the likelihood of mutation of dividing stem cells and malignant proliferation [5]. To explain inverse associations, the immunosurveillance hypothesis has been suggested in which the allergic symptoms is the side effect of hyperimmunity and are therefore not the result of causation. Additionally, tumours may suppress the immune system systemically and in the microenvironment of

the tumour [35], as seen for glioma patients that have a lower count of CD4+T cells overall and an increased fraction of CD4+FOXP3+T cells in the remaining fraction [36]

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The final analysis outcome including the interaction variable Brain/CNS*Sex, all adjusted for age and sex

Cancer groups (NORDCAN)	ICD7	ICD10	p-value	OR	CI 95%
Bladder etc.	181	C65-68+ D09.0 + D41.4	0.040	1.44	1.02 - 2.05
Breast	170	C50	0.035	0.80	0.65 - 0.98
Skin, non-melanoma	191	C44+C46.0	0.021	0.83	0.70 - 0.97
Brain/CNS	193	C70-72+D32-33+D42-43	0.513	1.35	0.55 – 3.33
Brain/CNS *Sex	-	-	0.080	0.36	0.12 - 1.13

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.