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Atopy and prostate cancer in men: Is there a link between circulating levels of IgE and PSA?

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Abstract

Background: Atopy has been investigated as a potential risk factor for prostate cancer. IgE antibodies may be major players in protective responses against tumours, through engendering antigen presentation and enhancing adaptive immune responses targeted towards a specific allergen, but potentially also against tumour-associated antigens such as prostate-specific antigen (PSA). We therefore cross-sectionally investigated associations between circulating levels of PSA and IgE in the National Health and Nutrition Examination Survey 2005-2006.

Methods: We focused on all men aged 40+ years with measurements for PSA and IgE, and no previous diagnosis of prostate cancer (n=1,312). We estimated the association between total and specific IgE concentration and levels of PSA with logistic regression models, adjusted for age, ethnicity/race, education, smoking status, body mass index (BMI), physical activity status, and history of asthma.

Results: Both total IgE and the sum of specific IgE were inversely associated with the risk of having PSA levels ≥10 ng/ml, though most findings were not statistically significant. The odds ratios for the second and third tertile of total IgE as compared to the first were 0.21 (95%CI: 0.06-0.72) and 0.42 (0.08-2.31). The odds ratio for sum of abnormal specific IgE measurements was 0.77 (0.44-1.34).

Conclusion: Despite statistical insignificance, the observed trend warrants further research given the increasing evidence of the role of atopy and IgE antibodies in protective responses against tumours. A lifecourse approach of measuring IgE, specific subtypes, and other markers of the humoral immune system (i.e. IgG) could shed more light on its potential anti-cancer characteristics.

Key words: prostate cancer, IgE, PSA, atopy

Précis

This cross-sectional analysis did not find a strong association between levels of total and specific IgE and PSA. However, given increasing evidence on the role of atopy in anti-tumour activity, further research is needed.

List of abbreviations

BMI: Body mass index

CI: Confidence interval

HR: Hazard ratio

NCHS: National Center for Health Statistics

NHANES: National Health and Nutrition Examination Survey

OR: Odds ratio

PSA: Prostate-specific antigen

RR: Relative risk

sIgE: Allergen-specific IgE

tIgE: Total IgE

Introduction

Atopy, defined as the propensity to develop IgE antibodies against environmental allergens, has been investigated as a potential risk factor for prostate cancer – with studies reporting positive associations as well as null findings [1-3]. A meta-analysis in 2009 concluded that the positive association of atopy, assessed by allergen-specific IgE (sIgE) or skin prick testing, with prostate cancer (relative risk [RR]: 1.43, 95% confidence interval [CI]: 1.08-1.91) warrants further investigation [4]. Several studies have since investigated the link between allergies, asthma and prostate cancer. A Taiwanese cohort study of 12,372 men found that asthma increases the risk of prostate cancer (hazard ratio [HR]: 2.36, 95%CI: 1.22-4.57) [5]. A Canadian case-control study also observed a positive association with ever reporting asthma, but no link with history of allergies [6]. Another Canadian cohort study based on 16,934 men also found a 25% increased risk of prostate cancer for men reporting a history of asthma [7]. Interestingly, the Health Professionals Follow-up Study, including 798 lethal prostate cancer cases during 995,176 person-years, observed that ever having a diagnosis of asthma was inversely associated with risk of lethal or fatal prostate cancer [8]. Men with hay fever onset in the distant past were more likely to develop (fatal) prostate cancer. Currently, no explanation for the difference in the direction of the epidemiological associations for asthma and hay fever with prostate cancer has been proposed [8].

From a biological perspective, there is also a need to further investigate IgE as an objective measurement of atopy in contrast to self-reported allergy data, and its potential role in prostate carcinogenesis. Prostate-specific antigen (PSA), which is detected in the serum of prostate cancer patients, has been widely evaluated for diagnostic and prognostic purposes, but recently also as a target of immunotherapy [9]. IgE antibodies may confer immunological protection against tumours by triggering antigen presentation and enhancing adaptive immune responses targeted towards specific allergens and possibly against tumour antigens such as PSA and therefore against PSA-expressing tumour cells [10]. The generation and persistence of memory T cells specific for homologous epitopes between allergens and

tumour antigens could also mediate anti-PSA effects and consequently anti-tumour protective functions, a concept that has received some attention in the field of allergy. For instance, the frequency of CD4+ T cells recognising epitopes of Can f 5, a dog-specific allergen, is 10-fold higher in allergic individuals and these cells are more likely to display IL-5-highTh2-biased phenotypes [11]. If these cells cross-react with prostate cancer antigen peptides displayed on cancer cells, they could provide protective PSA-reactive immune surveillance.

To further understand the role of atopy in the development of prostate cancer, we therefore cross-sectionally investigated the associations between circulating levels of PSA and IgE in the National Health and Nutrition Examination Survey (NHANES) 2005-2006 [12].

Methods

Study population

Data was obtained from the NHANES 2005-2006, a national survey designed to assess the health and nutritional status of the civilian non-institutionalised US population [12]. In 1999, the survey became a continuous programme that has adaptable components on a variety of health and nutrition measurements to meet emerging needs. It examines a nationally representative sample of about 5,000 persons each year. These persons are located in counties across the country, 15 of which are visited each year. It was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board and all participants gave informed consent.

All participants who completed a household interview were also invited to undergo Health Examination Components. Total IgE (tIgE) was measured in 94.1% of those aged 20 years or older and 92.4% also had data available for 19 different sIgE. For the current study, we focused on all men aged 40 years or older who had measurements for both PSA and IgE and had no previous diagnosis of prostate cancer (n=1,312). The latter was defined based

on questionnaire information related to prostate biopsies, cancer diagnoses, and PSA follow-ups.

Allergen-specific IgE and total IgE measurement

The Pharmacia Diagnostics ImmunoCAP 1000 System was used to measure tIgE and sIgE. The latter was measured to a panel of 19 allergens [12]: *Alternaria alternate, Apergillus fumigatus,* Bermuda grass (*Cynodon dactylon*), birch (*Betula verrucose*), cat dander, cockroach (*Blatella germanica*), dog dander, dust mite (*Dermatophagoides farina*, *D. pteronyssinus*), egg white, milk, mouse urine proteins, oak (*Quercus alba*), peanut (*Arachis hypgaea*), ragweed (*Ambrosia elatior)*, rat urine proteins, Russian thistle (*Salsola kali)*, rye grass (*Lolium perenne)*, and shrimp (*Pandalus borealis*). We assessed sIgE by the sum of positive sIgE according to their detection limit. We further categorised the total sum of sIgE into 0, 1-2, and 3+. Since tIgE was not normally distributed we transferred it into $\log_{10}$ units [13].

PSA measurements

The Beckman Access Immunoassay System with the Hybritech Total PSA Assay (Beckman Coulter, Fullerton, CA) was used to measure serum levels of PSA (ng/mL) [12]. For the analyses, we dichotomised PSA based on the following values for abnormal levels: ≥10ng/mL [14-16].

Other covariates

Other covariates were obtained from the questionnaire and physical examination data [12]. In addition to age, we included race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, and other), education (<9th grade, secondary school, and higher education), smoking status (current, former, never), body mass index (BMI; kg/m^2), moderate or vigorous activity during the last 30 days (yes/no), and history of asthma (yes/no).

Statistical analyses

Descriptive statistics were obtained for the total study population and by levels of circulating PSA (≥10 ng/nL). We calculated age-standardised proportions and means (based on 20-year age groups of the 2000 US Census Standard Population).

We then estimated the association between tIgE and sIgE and levels of PSA with univariate and multivariate logistic regression models. The latter were adjusted for age, ethnicity/race, education, smoking status, BMI, physical activity status, and history of asthma. We evaluated continuous levels and tertiles of tIgE and dichotomised and categorised levels of the sum of sIgE. An additional stratification by race/ethnicity was conducted, as well as by history of asthma. To provide further insight into the potential effects of different types of sIgE, we also looked into the proportion of positivity by PSA levels.

All analyses were adjusted for the NHANES complex sampling design using Taylor series linearization methods through SAS statistical software (version 9.4, Cary, NC) survey procedures (surveyfreq, surveymeans, surveylogistic) according to the NHANES specifications.

Results

Out of 1,312 men 21 had levels of PSA≥10 ng/mL. They were slightly older than those with PSA <10 ng/mL and were more likely to be non-Hispanic white (91 vs 70%). Further differences in terms of education, smoking behaviour, and physical activity levels can be observed in Table 1. On average, their total IgE was higher, while their sum of sIgE was lower.

Table 2 illustrates the odds ratio (OR) for having PSA levels ≥10ng/mL based on levels of total and specific IgE. Both were inversely associated with the risk of having PSA levels ≥10 ng/ml, though most findings were not statistically significant. The ORs for the second and

third tertile of total IgE as compared to the first were: 0.21 (95%CI: 0.06-0.72) and 0.42 (0.08-2.31), respectively. The OR for sum of abnormal specific IgE measurements was 0.77 (95%CI: 0.44-1.34).

The proportion of allergen-specific IgE by PSA levels is shown in Table 3. There was sIgE in both high and low PSA cohorts, with no clear patterns due to the rather small sample size.

Additional stratification by ethnicity or history of asthma did not alter the above findings (results not shown).

Discussion

This cross-sectional analysis suggests a consistent inverse association between levels of total and specific IgE and levels of PSA, though none of the findings were statistically significant.

Our findings do not support a strong association between IgE and PSA, and it is possible that potential links between allergic responses and the risk of developing PSA-producing prostate cancer may be more complex than any simple cause and effect relationship. It is possible that the disparities in reported associations [1-3] are manifestations of underlying immunological processes that may provide protection from the growth of prostate cancers in certain groups of individuals, but not in others. It can be envisaged then that stratifying particular individual groups based on allergic sensitization to specific allergens and autoantibodies to specific epitopes of these allergens may help delineate any such associations. This may also be the case for the relationship between IgE levels or allergies and PSA, and may consequently help us to identify any links between specific allergies in these patient groups and the risk of PSA-positive prostate cancer.

For instance, allergies to dog dander, also manifested by elevated IgE serum levels, have been associated with asthma prevalence and severity and allergic respiratory symptoms, including bronchial inflammation [17]. IgEs in patient sera are reported to recognise dog allergens such as the lipocalin family members (Can f 1, f 2, and f 4), the dog serum albumin Can f 3, which bears particular homology to human serum albumin [18-20], and the major dog allergen prostatic kallikrein, or Can f 5. Can f 5 has been identified in dog dander and urine and this protein is recognised by serum IgE antibodies from 70% of patients with dog allergies [21]. This allergen appears to share large structural similarities with human PSA, and anti-Can f 5 IgE antibodies in the blood of patients with dog allergies also appear to recognise human PSA [22]. This would support the notion that subsets of allergic individuals may also develop protective immune responses directed not only to allergens but also to tumour antigens. Such co-incidental cross-reactivities may in part explain some reported associations between allergies and lower levels of PSA. Consequently, an allergic response to particular allergenic molecules could provide a protective advantage that might explain a lower incidence of prostate cancer in only the subsets of individuals who develop antibodies to allergens that happen to cross-react with epitopes to tumour antigens. We found sIgE in both high and low PSA cohorts, with a proportion of IgE showing reactivity to dog allergens in both groups (Table 3). However, this dataset did not contain sufficient variation in data on dog dander, nor did it include detailed information on specific subtypes of dog allergens. These limitations, together with the low number of subjects with high PSA serum levels and lack of followup information on incidence of prostate cancer, do not permit interrogation of co-incidental antibody cross-reactivities to PSA and specific allergens or whether these might have any protective relevance.

Future studies could benefit from longitudinal measurements of IgE, as some allergies may arise at a young age and could elicit strong immunological responses manifested by asthmatic symptoms, high IgE titres to allergens, as well as heightened cellular responses including eosinophil activation [23]. Therefore, it is tempting to speculate that development of

a strong allergic response to an allergen with high homology to a tumour antigen may provide long-term resistance to the growth of some cancers expressing this target antigen, specifically for this subset of allergic individuals. Recent findings of an inverse association between a diagnosis of asthma, rather than overall allergies or hay fever, and the risk of lethal prostate cancer [8], may lend merit to this possibility.

Furthermore, future studies may contribute additional information on other markers of the humoral response. More specifically, the isotype of the antibodies raised to these allergens may not be confined to the IgE class and, therefore, different components of the humoral response should be delineated. Different antibody isotypes such as IgG1, known to provide immune activatory signals, IgG4 and IgA, which may be associated with long-term exposure to specific antigens or allergens [24-28], could also play key roles in immune surveillance. Activation of immune effector cells by a tumour antigen-specific IgE has recently been identified to trigger a cytokine signature known to occur in IgE-mediated clearance of parasitic infections [29]. It is then possible that the immunological context that could provide protection against tumour antigens may not be derived from atopy, but perhaps also from other conditions such as anti-parasitic responses, in which IgE, its effector cells, and Th2-biased immune responses could play key roles. Therefore, a wider study of immunological surveillance against antigens, including those associated with cancer, could provide novel perspectives on what constitutes protection from carcinogenesis.

This study has several strengths including its generalizibility following the use of nationally representative data. Therefore, it was also possible in our analysis to perform a stratified analysis by race/ethnicity. We were able to adjust for many potential confounding factors, but lacked information on prostate cancer diagnosis such that an increase in PSA measurements does not necessarily reflect carcinogenesis. Another limitation of this study is that it relies on one single measurement so that it may be prone to measurement error and within-person variation – with only 21 men having high levels of PSA. Repeated

measurements in a larger sample size may strengthen the accuracy of the direction of the association studied, so that it would be of interest to validate our findings in other population-based settings. As this dataset did not contain information on prostate cancer diagnosis, the results of the current study should only be used to generate more hypotheses on the role of IgE in prostate carcinogenesis.

Conclusion

Even though our study did not find a strong inverse association between IgE and PSA, the trend of the indication warrants further research, given the increasing evidence on the role of atopy and IgE antibodies in protective responses against tumours. A lifecourse approach of measuring IgE, specific subtypes, and other markers of the humoral immune system (i.e. IgG), could shed more light on its potential anti-cancer characteristics.

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

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Tables

Table 1: Age-standardised weighted characteristics in men with PSA and IgE measurements in NHANES 2005-2006.

	All	PSA <10	PSA ≥10
Population (N, unweighted)	1312	1291	21
Age (years; mean, SEM)	57.3, 0.3	57.3, 0.3	63.9, 0.6
Race/ethnicity (%)			
Non-Hispanic white	78.99	79.02	91.14
Non-Hispanic black	9.19	9.11	7.07
Mexican-American	5.58	5.58	1.79
Other	6.24	6.29	0.00
Education (%)			
< 9th grade	8.59	8.41	30.84
Secondary school	35.75	35.90	10.07
Higher education	55.65	55.68	59.09
BMI (kg/m^2; mean, SEM)	29.1, 0.2	29.1, 0.2	23.3, 1.5
Cigarette smoking (%)			
Never	39.02	38.83	54.57
Former	37.57	37.64	42.91
Current	23.41	23.53	2.52
History of asthma (%)	11.46	11.48	4.27
Moderate or vigorous activity (%)	63.53	63.46	45.74
PSA (ng/ml; mean, SEM)	1.6, 0.1	1.4, 0.1	20.4, 2.3
Total IgE (kU/L; mean, SEM)	171.5, 14.2	172.6, 14.3	201.34,
Allergen-specific IgE: ≥ 1 positive (%)	42.27	43.53	37.22

Table 2: Unadjusted and adjusted odds ratios for the association between IgE and PSA≥10 ng/ml.

	Unadjusted OR (95%CI)	**Adjusted OR^ (95%CI)**
Total IgE (per log_{10} changes)	0.66 (0.28-1.58)	0.70 (0.28-1.73)
Total IgE (tertiles)		
<31.2 kU/L	1.00 (Ref)	1.00 (Ref)
31.2-113 kU/L	0.27 (0.09-0.80)	0.21 (0.06-0.72)
≥113 kU/L	0.45 (0.11-1.96)	0.42 (0.08-2.31)
Allergen-specific IgE: ≥ 1 positive (%)	0.26 (0.07-0.92)	0.30 (0.08-1.18)

^ Adjusted for age, ethnicity/race, education, smoking status, BMI, history of asthma, and physical activity status

Table 3: Proportion of allergen-specific IgE by PSA status.

	PSA <10 ng/ml	**PSA ≥10 ng/ml**
Dust mite (*Dermatophagoides farina*)	5.17	6.09
D. pteronyssinus	16.16	6.09
Cat dander	12.01	4.14
Dog dander	10.09	4.14
Cockroach (*Blatella germanica*)	11.72	7.66
Alternaria alternate	7.39	0.00
Peanut (*Arachis hypgaea*)	7.57	0.00
Egg white	3.26	3.50
Milk	4.74	4.14
Ragweed (*Ambrosia elatior*)	14.06	0.00
Rye grass (*Lolium perenne*)	17.75	5.56
Bermuda grass (*Cynodon dactylon*)	13.45	0.88
Oak (*Quercus alba*)	9.58	0.00
Birch (*Betula verrucose*)	9.45	0.00
Shrimp (*Pandalus borealis*)	7.20	6.09
Aspergillus fumigatus	5.87	4.14
Russian thistle (*Salsola kali*)	9.78	0.00
Mouse urine proteins	0.26	0.00
Rat urine proteins	1.82	0.00