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Asthma status is associated with decreased risk of aggressive urothelial bladder cancer

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Abstract

Previous studies suggested an association between atopic conditions and specific cancers. The results on the association with urothelial bladder cancer (UBC) are scarce and inconsistent. To evaluate the association between asthma and risk of UBC, we considered 936 cases and 1022 controls from the Spanish Bladder Cancer/EPICURO Study (86% males, mean age 65.4 years), a multicenter and hospital based case-control study conducted during 1998–2001. Participants were asked whether they had asthma and detailed information about occupational exposures, smoking habits, dietary factors, medical conditions, and history of medication was collected through face-to-face questionnaires performed by trained interviewers. Since asthma and UBC might share risk factors, association between patients' characteristics and asthma was studied in UBC controls. Association between UBC and asthma was assessed using logistic regression unadjusted and

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adjusted for potential confounders. The complex interrelationships, direct, and mediating effect of asthma on UBC, were appraised using counterfactual mediation models.

Asthma was associated with a reduced risk of UBC (odds ratio (OR)=0.54, 95% confidence interval (CI) 0.37, 0.79) after adjusting for a wide range of confounders. No mediating effect was identified. The reduced risk associated with asthma was restricted to patients with high-risk non-muscle invasive (OR=0.25, 95%CI 0.10, 0.62) and muscle invasive UBC (OR=0.32, 95%CI 0.15, 0.69).

Our results support that asthma is associated with a decreased risk of UBC, especially among aggressive tumors. Further work on the relationship between asthma and other atopic conditions and cancer risk should shed light on the relationship between immune response mechanisms and bladder carcinogenesis.

Keywords

Bladder cancer; Asthma; Atopic diseases; Risk; Case-control study; Counterfactual mediation models

INTRODUCTION

Urothelial bladder cancer (UBC) is one of the major cancer types in Europe. It ranks in the 6th and 14th position in men and woman, respectively, with an age-standardized incidence rate of 18 per 100,000 person-year for men and 3.4 for women [1]. Up to 85% of UBC do not invade the muscle (non-muscle-invasive bladder cancer, NMIBC). Low-grade NMIBC are characterized by high recurrence rate (30% to 85%) but an overall good prognosis. This is reflected in high costs that make NMIBC one of the most expensive diseases to manage[2]. Patients with tumors that invade the muscle (MIBC) have a worse prognosis: 50% of them die from their cancer with a five year relative survival rate for metastatic disease of only 5%[2].

Evidence exists on the role of chronic inflammation in bladder carcinogenesis [3]. An increased risk of squamous cell carcinoma of the bladder has been observed in patients with *Schistosoma haematobium* infestation or protracted catheter use, both responsible for chronic urothelial inflammation and/or concurrent infection [3,4]. Further, oxidants from tobacco smoke or from specific occupational exposures activate inflammatory cells which, in turn, generate high levels of reactive oxygen species (ROS) [5]. In addition, a protective effect of long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) has been reported [7] and an association with urinary tract infections (UTIs) has been suggested [8].

Asthma is a complex and heterogeneous condition characterized by chronic airway inflammation and airway hyper-reactivity and by symptoms of recurrent wheezing, coughing and shortness of breath [9]. Asthma is increasingly viewed not as a single disease but as an heterogeneous trait consisting of multiple phenotypes [9], among which the most frequent is T helper type 2 (Th2)-associated asthma, strongly related to atopy and allergy.

Research on the association between atopic diseases and malignancy is part of the emerging interdisciplinary field of AllergoOncology [10,11], which focuses on determining the interrelationships between cancer and IgE-mediated and Th2-biased cellular responses. The first papers in this field appeared in the sixties [12,13] and to date researchers have provided evidence of a negative association between atopic conditions and several malignancies such as pancreatic cancer, glioma, leukemia, and colorectal cancer, while positive associations have been observed between asthma and lung cancer (for a review see [14)]. Two main theories may explain the relationship between atopic conditions and cancer. According to the immune-surveillance hypothesis [15] , atopic status is characterized by hyper-stimulation of an immune response that has enhanced ability to eradicate malignant cells at an early stage of tumor development. An alternative hypothesis relates to the constant state of inflammation that characterizes atopic subjects, atopy playing a role in carcinogenesis via various inflammatory mediators [16]

So far, few studies about the association between asthma and bladder cancer have been published, reporting conflicting results. Both Vesterinen *et al.* [17] and Kim *et al.* [18] identified an increased risk of bladder cancer related to asthma, although in the first study the increased risk was observed only in males. On the contrary, one study showed an inverse association between history of atopy (seasonal hay fever or asthma) and malignancy of endodermal origin (lung, gut, bladder, prostate) [19] and an additional one found no correlation between both conditions [20].

The aims of this study were to evaluate the association between asthma and risk of UBC and to examine whether this association varies by UBC sub-phenotypes as well as by known and shared risk factors.

MATERIALS AND METHODS

Study population

The study population included participants from the Spanish Bladder Cancer (SBC)/ EPICURO Study. This is a hospital-based case-control study conducted during 1998–2001 in 18 hospitals from five areas in Spain as described elsewhere [21]. All newly diagnosed, histologically confirmed UBC patients between 20 and 80 years of age were included. Control subjects were selected from patients admitted to participating hospitals for primary diagnoses believed to be unrelated to the UBC risk factors. The main reasons for hospital admission were diseases of the digestive system (49%) such as hernia (37%), appendicitis (3%) or other intestinal diseases (9%), injuries (31%) such as fractures (24%), hydrocele (12%), circulatory disorders (4%), dermatological disorders (2%) and other diseases (2%). Controls were individually matched to the cases for age (within 5-years), gender, ethnic origin and region of residence. Ethical approval was obtained from the centers' institutional ethics committee, and written consent was obtained from each subject.

Data collection

Out of 1,457 eligible cases and 1,465 controls, 84% and 87% were interviewed, respectively. Patient information was collected by trained monitors using a questionnaire administered via

computer assisted personal interview (CAPI). This included patient demographic characteristics, occupational exposures, smoking habits, dietary factors, medical conditions, and history of medication use. All participants were asked whether they ever had asthma and/or chronic obstructive pulmonary disease (COPD). Since COPD is related to age and smoking-associated tumors [22], we considered separately subjects with asthma from those with COPD using a four-level variable: (1) Asthma only, (2) Asthma and COPD, (3) COPD only, and (4) Neither asthma nor COPD.

We considered all available environmental exposures and lifestyle factors which may act as potential confounders for the association between UBC and asthma [23]. Participants who had ever worked in high-risk occupations, such as workers in the printing, textile, transportation, electrical/gas/sanitary services and hotel/lodging industries, among others, were classified as at 'high-risk occupational exposure' [24]. Current smokers were defined as subjects that reported smoking regularly within a year of the reference date and former smokers as subjects that quit regular smoking >1 year before participation in the study. Regular smokers were classified into two groups according to the pack-years smoked (<40 or ≥40 pack-years). Never smokers were those subjects who never smoked more than 100 cigarettes in their life. Fruit and vegetable intake over the 5 years before diagnosis (cases) or before interview (controls) was estimated using a modified semi-quantitative frequency food questionnaire of 127 items, previously validated in Spain [25]. We ascertained whether participants had ever consumed coffee and the average amount consumed per day during adult life, both for decaffeinated and regular coffee [26]. Medical history regarding urinary tract infection and related treatment, urinary stones and diabetes was also collected. Participants reported lifetime use of any anti-inflammatory or analgesic drug [6] and consumption of commonly used drugs (i.e., aspirin, paracetamol, and metamizol) as well as a broader but homogeneous category of NSAIDs. 25-hydroxyvitamin D3 (plasma 25(OH)D3) levels, that are negatively associated with UBC risk [27] and asthma [28], were determined in patients from whom plasma was available (1130 cases and 1038 controls) [27].

Clinico-pathological data regarding tumor characteristics was collected from cases after resection and revised by a panel of expert pathologists. Tumors were subsequently classified in three sub-phenotypes according to tumor stage (T) and histologic grade (G) as low-risk NMIBC (Ta G1/Ta G2), and high-risk NMIBC (Ta G3/T1 G2/T1 G3) and MIBC (T≥ 2) [29].

Statistical analysis

Univariate and bivariate analyses.—Variables were summarized as means, medians and standard deviations when continuous, and as percentages when categorical. During the curation of the data some cases were excluded from the analysis, thus breaking the matching structure; therefore, we applied unmatched tests and unconditional logistic regression models. The relationship between patient characteristics and asthma phenotypes and UBC was evaluated by chi2 test (nominal variables), chi2 test for trend (ordinal variables), and Kruskal-Wallis test (continuous variables). Associations between asthma and subject characteristics were studied only among controls.

Items that were statistically significantly associated with both asthma and UBC were included in the multiple models, together with age, gender and region to account for the

matched sampling. In particular, all multiple regression models were adjusted for tobacco smoking, a known risk factor for UBC, also associated with asthma prevalence and severity [30].

The association of asthma with UBC sub-phenotypes was assessed by estimating relative risk ratios (RRR) using multinomial regression models. Analyses were further stratified by smoking status.

Differences were considered statistically significant at $P<0.05$. All statistical analyses were performed using R version 3.2 [31], unless other otherwise indicated.

Imputation of missing values.—Missing values for all the variables considered for the analysis (Supporting information Table 1E) were imputed by using the *missForest* algorithm (R package *missForest* [32]), which is an iterative imputation method based on a random forest. All patients' information of interest for the analysis, including the outcome variable, was entered into the multiple imputation algorithm. After imputation of missing values the proportion of falsely classified entries for categorical variables was 0.11. The results reported are presented with substitutions made for missing values. Results obtained with the un-imputed data were used in a sensitivity analysis (Supporting information Table 4E).

Counterfactual mediation model.—We further explored the possibility that the association of asthma with UBC might be mediated by environmental risk factors. It is possible, for example, that UBC risk in smokers might be mitigated by the fact that subjects with asthma tend to smoke less [33]. By applying a counterfactual approach for mediation analysis, illustrated by the Directed Acyclic Graph in Figure 1E (Supporting information), the total effect (TE) of asthma on UBC (c) can be decomposed into a natural direct effect (NDE) of asthma on UBC (c') and a natural indirect effect (NIE) of asthma accounted by the effect of the putative mediators, such as smoking habits (a*b). In particular we applied the counterfactual approach proposed by Valeri and VanderWeele [34], that was extended to exposure-mediator interaction for binary mediators and outcomes: for this reason all categorical variables considered were dichotomized. Mediation models were fitted with the *paramed* module in STATA [35] and the standard errors were generated using Monte Carlo bootstrapping with 1000 replications.

RESULTS

Study population

In total, 1,958 subjects (936 cases and 1022 controls) with complete data on asthma were considered for analysis. 86% of the subjects were males and 82% were older than 55 years (Table 1).

Simple and multiple associations

Characteristics of controls stratified by asthma status is reported in Supporting information Table 2E. Prevalence of asthma among controls was 9.10%. Descriptive characteristics of controls by asthma status is reported in Supporting Information Table 2E. A positive association with asthma was observed with increased BMI, fruit and coffee consumption and

in subjects who were treated with phenazopyridine for UTI and regularly treated with metamizol (dipyrone) and other pyrazolone derivatives(Supporting information Table 3E). All these associations were confirmed after adjustment for age, gender and region.

Prevalence of asthma among cases was 5.45% and risk of UBC was lower for patients with asthma (adjusted for matching variables: OR=0.56, 95%CI 0.39–0.80) (Table 2). This negative association was confirmed when the model was further adjusted for covariates associated both with asthma and UBC, i.e. BMI, fruit consumption, coffee consumption, treatment for UTI, and smoking (OR=0.54, 95%CI 0.37–0.79, Table 2).

When the four-level variable that combines asthma and COPD was considered as predictor in a logistic regression model adjusted on matching variables, a significant negative association with UBC was observed for the 'asthma only' category (OR=0.48, 95%CI 0.28–0.83, P=0.008). The association with the 'asthma and COPD' category was borderline significant (OR=0.64, 95%CI 0.40–1.02, P=0.06), while no association was observed with COPD (OR=1.15, 95%CI 0.83–1.59, P=0.40). Similar results were obtained after adjustment for a wide range of confounders (Table 2). No association with decaffeinated coffee consumption was observed.

In sensitivity analyses, we compared estimates for the association between asthma and UBC using non-imputed data: the negative association between asthma and UBC was confirmed after adjustment for matching variables (OR=0.56, 95%CI 0.39–0.80, P=0.001). When the four-level variable was considered, the results were similar to those obtained using imputed data (Supporting information Table 4E).

The association between UBC and asthma varied according to smoking status (p for interaction<0.001): the significant negative association with asthma, after adjustment for matching variables, was noted only in never (OR=0.30, 95%CI 0.11–0.80, P=0.02) and former smokers (OR=0.54, 95%CI 0.21–0.91, P=0.002) but not in current smokers (OR=0.68, 95%CI 0.35–1.34, P=0.27). Similar estimates were obtained when using the fully adjusted model (OR=0.32, 95%CI 0.12–0.87, P=0.02, OR=0.55, 95%CI 0.32–0.93, P=0.02 and OR=0.61, 95%CI 0.30–1.23, P=0.17 in never, former and current smokers, respectively). Analogous findings were observed when asthma without COPD was considered (OR=0.28, 95%CI 0.08–1.01, P=0.05 in never smokers, OR=0.45, 95%CI 0.20–1.02, P=0.06 in former smokers and OR=0.87, 95%CI 0.30–2.48, P=0.79 in current smokers) (data not shown in Tables).

When cases were grouped according to cancer sub-phenotypes, the reduced risk associated with asthma was restricted to patients with high-grade NMIBC (OR=0.37, 95%CI: 0.15–0.93) and MIBC (OR=0.35, 95%CI: 0.17–0.73) (Table 3).

Counterfactual mediation model.

BMI, fruit intake, treatment for UTI, and coffee intake, together with smoking met the criteria for a variable to be considered a mediator[36] as they were associated with both UBC and asthma and were included in this analysis. Results of mediation analyses confirmed the negative association between asthma and UBC (Supporting information Table 5E) and

suggested that no other risk factors for UBC act as mediators in the association between asthma and UBC. All the estimates accounted for possible interactions between asthma and the exposures and were adjusted by a wide range of confounders.

DISCUSSION

Using data from a large case-control study on UBC, we observed a negative association with asthma, especially in patients with aggressive UBC. This association remained consistent after controlling for smoking habits or other covariates that are commonly associated with both asthma and UBC and it was absent among subjects reporting COPD. Our results are in line with previous findings reporting a lower frequency of allergy in patients with endodermal malignancies (lung, gut, bladder and prostate) when compared to their matched controls [19]. To the best of our knowledge this is the first study that explores in detail the role of common potential risk factors in the association between atopic diseases and UBC, by considering a wide range of exposures and applying different statistical approached.

The biological basis for the suggested protective effect of atopic diseases on UBC is not known but could be due to antitumor effects of type I immunoglobulin E (IgE)-mediated immune activity. Asthma is a complex disease that consists of several phenotypes [37]: more than half of patients with asthma also report atopy [38]. In atopic asthma, exposure to environmental allergens induces the development of T-helper 2 (Th2) cells, whose activity is associated with increased IgE levels in blood and increased numbers of inflammatory cells including neutrophils, followed by eosinophils, monocytes, and lymphocytes. Many IgE effector cells, such as eosinophils, basophils, and mast cells, may infiltrate solid tumors with the potential to play an important role in antitumor activity [39]. Tumor-associated tissue eosinophilia has been associated with good prognosis in bladder [40] in addition to laryngeal carcinoma and lung adenocarcinoma[41]. Moreover, reports applying immunotherapeutic approaches and recent *in vitro* and *in vivo* studies suggest that eosinophils are tumoricidal in bladder cancer [42]. Increased levels of both IgE and eosinophils have been observed in other disorders such as helminthic infections, for which the deadliest complication is bladder cancer [43]. Zacharia *et al.* hypothesized that, in helminth-endemic areas, individuals that exhibit strong atopic responses will be less often affected by bladder cancer than individuals that respond less strongly or not at all [43].

The mechanisms involved in the association of non-atopic asthma to UBC may be similar to those of atopic asthma, as suggested by El-Zein M *et al.* [20] who observed a similar decreased effect on UBC both for allergic and non-allergic asthma. Th2-associated inflammation and IgE production are also features of non-atopic or intrinsic asthma, although the etiology of what drives this process remains unknown [44].

The negative association between UBC and asthma was more prominent among patients with aggressive UBC, including high-risk NMIBC and MIBC. There is extensive genetic evidence in the literature supporting the notion that the high-risk NMIBC is a precursor to the MIBC [2,45] suggesting that distinct genetic and microenvironmental features of the aggressive tumors underlie the association with immune responses.

In our model, we hypothesized that the role of asthma status on UBC was mediated by environmental risk factors. The mediation models suggested that asthma directly affects risk of UBC, at least for the available exposures in the study. However, other factors may play a role in the causal pathway, such as the use of corticosteroids or genetic factors. Hence, further studies are needed to better understand the mechanism underlying the association between asthma status and UBC.

Our study has some limitations. Recall bias for asthma might have affected our estimates. Nevertheless the prevalence of asthma among controls in our study was comparable to the rates reported in the literature [46]. Moreover the lack of association with COPD indicates that the protective effect of asthma was not only due to recall bias. Confounding was dealt with by controlling for several risk factors known to be associated with UBC and that showed to be associated also with asthma. Even though asthma was not associated with smoking status among controls, we accounted for smoking habits in all our multiple models, because of the know association between smoking and respiratory diseases [30]. A possible misclassification of COPD as asthma was excluded after a sensitivity analysis that showed an inverse association between 'only asthma' and UBC and no association with COPD. We also accounted for occupations that are thought to be at high risk for UBC, since asthma patients might avoid jobs (e.g. in printer industries) characterized by contact with some carcinogens, such amines or polycyclic aromatic hydrocarbons, which are often also irritants. Although occupational asthma attributable to amines is infrequent [47], we cannot exclude that the negative association with UBC is independent from such exposures.

One of the main strengths of our study relates to the populations under study. The study is based on a large sample size that enabled a precise estimate of the association between asthma and UBC. Furthermore, cases were histologically confirmed and reflect the real spectrum of UBC patients. For both cases and controls detailed individual data on demographics, lifestyle, and environmental exposures were available enabling us to properly control for the main potential confounders. A further strength regards to the use of the counterfactual mediation model, which confirmed the negative association between asthma and UBC.

Our results support that asthma is associated with a decreased risk of UBC. These findings corroborate results from previous studies linking atopic status and cancer. Future studies should consider other atopic conditions to provide further evidences to the role of the immune response mechanisms in bladder carcinogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

MIBC	Muscle invasive bladder cancer
NMIBC	Non-muscle invasive bladder cancer
COPD	Chronic obstructive pulmonary disease
NDE	Natural direct effect
NIE	Natural indirect effect
NSAIDs	Non-steroidal anti-inflammatory drugs
SBC	Spanish Bladder Cancer
TE	Total effect
UBC	Urothelial bladder cancer
UTI	Urinary tract infection

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86. [PubMed: 25220842]
2. Knowles MA, Hurst CD. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. Nat Rev Cancer 2015;15:25–41. [PubMed: 25533674]
3. Michaud DS. Chronic inflammation and bladder cancer. Urol Oncol Semin Orig Investig 2007;25:260–8.
4. Relationship between Schistosomiasis and Bladder Cancer.
5. Qiu M, Chen L, Tan G, Ke L, Zhang S, Chen H, Liu J. A reactive oxygen species activation mechanism contributes to JS-K-induced apoptosis in human bladder cancer cells. Sci Rep 2015;5:15104. [PubMed: 26458509]
6. Fortuny J, Kogevinas M, Garcia-Closas M, Real FX, Tardón A, Garcia-Closas R, Serra C, Carrato A, Lloreta J, Rothman N, Villanueva C, Dosemeci M, Malats N, Silverman D. Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain. Cancer Epidemiol Biomarkers Prev 2006;15:1696–702. [PubMed: 16985032]
7. Fortuny J, Kogevinas M, Fortuny J, Kogevinas M, Real FX. Use of Analgesics and Nonsteroidal Anti-inflammatory Drugs , Genetic Predisposition , and Bladder Cancer Risk in Spain Use of Analgesics and Nonsteroidal Anti-inflammatory Drugs , Genetic Predisposition , and Bladder Cancer Risk in Spain. 2006;1696–702.
8. Vermeulen SH, Hanum N, Grotenhuis a J, Castaño-Vinyals G, van der Heijden a G, Aben KK, Mysorekar IU, Kiemeney L a. Recurrent urinary tract infection and risk of bladder cancer in the Nijmegen bladder cancer study. Br J Cancer 2014;112:594–600. [PubMed: 25429525]
9. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 2012;18:716–25. [PubMed: 22561835]

10. Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, Capron M, Penichet ML, Rodríguez J a., Siccardi a. G, Vangelista L, Riemer a. B, Gould H. AllergoOncology: the role of IgE-mediated allergy in cancer. Allergy 2008;63:1255–66. [PubMed: 18671772]
11. Jensen-Jarolim E, Pawelec G. The nascent field of AllergoOncology. Cancer Immunol Immunother 2012;61:1355–7. [PubMed: 22911119]
12. Johnson KJ. The relation of cancer to allergy. J Lancet 1966;86:5–11. [PubMed: 5900921]
13. Fisherman EW. Does the allergic diathesis influence malignancy? J Allergy 1960;31:74–8. [PubMed: 13823262]
14. Cui Y, Hill AW. Atopy and Specific Cancer Sites: a Review of Epidemiological Studies. Clin Rev Allergy Immunol 2016;51:338–52. [PubMed: 27277132]
15. Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, Capron M, Penichet ML, Rodríguez J a., Siccardi a. G, Vangelista L, Riemer a. B, Gould H. AllergoOncology: The role of IgE-mediated allergy in cancer. Allergy Eur J Allergy Clin Immunol 2008;63:1255–66.
16. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 2005;60:1098–111. [PubMed: 16076292]
17. Vesterinen E, Pukkala E, Timonen T, Aromaa A. Cancer Incidence among 78 000 Asthmatic Patients. Int J Epidemiol 1993;22:976–82. [PubMed: 8144310]
18. Kim WJ, Lee HL, Lee SC, Kim YT, Kim H. Polymorphisms of N-acetyltransferase 2, glutathione S-transferase mu and theta genes as risk factors of bladder cancer in relation to asthma and tuberculosis. J Urol 2000;164:209–13. [PubMed: 10840461]
19. Cockcroft DW, Klein GJ, Donevan RE, Copland GM. Is there a negative correlation between malignancy and respsiratory atopy? Ann Allergy 1979;43:345–7. [PubMed: 517816]
20. El-Zein M, Parent M-E, Kâ K, Siemiatycki J, St-Pierre Y, Rousseau M-C. History of asthma or eczema and cancer risk among men: a population-based case-control study in Montreal, Quebec, Canada. Ann Allergy Asthma Immunol 2010;104:378–84. [PubMed: 20486327]
21. Samanic C, Kogevinas M, Dosemeci M, Malats N, Real FX, Garcia-Closas M, Serra C, Carrato A, García-Closas R, Sala M, Lloreta J, Tardón A, Rothman N, Silverman DT. Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. Cancer Epidemiol Biomarkers Prev 2006;15:1348–54. [PubMed: 16835335]
22. van de Schans SAM, Janssen-Heijnen MLG, Biesma B, Smeenk FWJM, van de Poll-Franse LV, Seynaeve C, Coebergh JWW. COPD in cancer patients: Higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. Eur J Cancer 2007;43:2194–202. [PubMed: 17884463]
23. Malats N, Real FX. Epidemiology of Bladder Cancer. Hematol Oncol Clin North Am 2015;29:177–89. [PubMed: 25836927]
24. Samanic CM, Kogevinas M, Silverman DT, Tardón A, Serra C, Malats N, Real FX, Carrato A, García-Closas R, Sala M, Lloreta J, Rothman N, Dosemeci M. Occupation and bladder cancer in a hospital-based case-control study in Spain. Occup Environ Med 2008;65:347–53. [PubMed: 17951336]
25. García-Closas R, García-Closas M, Kogevinas M, Malats N, Silverman D, Serra C, Tardón A, Carrato A, Castaño-Vinyals G, Dosemeci M, Moore L, Rothman N, Sinha R. Food, nutrient and heterocyclic amine intake and the risk of bladder cancer. Eur J Cancer 2007;43:1731–40. [PubMed: 17596928]
26. Villanueva CM, Silverman DT, Murta-Nascimento C, Malats N, Garcia-Closas M, Castro F, Tardon A, Garcia-Closas R, Serra C, Carrato A, Rothman N, Real FX, Dosemeci M, Kogevinas M. Coffee consumption, genetic susceptibility and bladder cancer risk. Cancer Causes Control 2009;20:121–7. [PubMed: 18798002]
27. Amaral AFS, Méndez-Pertuz M, Muñoz A, Silverman DT, Allory Y, Kogevinas M, Lloreta J, Rothman N, Carrato A, Rivas Del Fresno M, Real FX, Malats N. Plasma 25-Hydroxyvitamin D3 and bladder cancer risk according to tumor stage and FGFR3 status: A mechanism-based epidemiological study. J Natl Cancer Inst 2012;104:1897–904. [PubMed: 23108201]
28. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 2007;120:1031–5. [PubMed: 17919705]

29. Guey LT, García-Closas M, Murta-Nascimento C, Lloreta J, Palencia L, Kogevinas M, Rothman N, Vellalta G, Calle ML, Marenne G, Tardón A, Carrato A, García-Closas R, Serra C, Silverman DT, Chanock S, Real FX, Malats N. Genetic susceptibility to distinct bladder cancer subphenotypes. Eur Urol 2010;57:283–92. [PubMed: 19692168]
30. Polosa R, Thomson NC. Smoking and asthma: Dangerous liaisons. Eur Respir J 2013;41:716–25. [PubMed: 22903959]
31. R Development Core Team R, R Core Team. R: A Language and Environment for Statistical Computing. R Found. Stat. Comput1:409.
32. Stekhoven DJ, Bühlmann P. Missforest-Non-parametric missing value imputation for mixed-type data. Bioinformatics 2012;28:112–8. [PubMed: 22039212]
33. Cerveri I, Cazzoletti L, Corsico AG, Marcon A, Niniano R, Grosso A, Ronzoni V, Accordini S, Janson C, Pin I, Siroux V, De Marco R. The impact of cigarette smoking on asthma: A population-based international cohort study. Int Arch Allergy Immunol 2012;158:175–83. [PubMed: 22286571]
34. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods 2013;18:137–50. [PubMed: 23379553]
35. StataCorp 2013 Stata Statistical Software Release 13. College Station, TX: StataCorp LP.,
36. Baron RM, Kenny D a. Baron & Kenny, 1986. J. Pers. Soc. Psychol1986;51:1173–82. [PubMed: 3806354]
37. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, Lemanske RF, Wardlaw AJ, Wenzel SE, Greenberger PA. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol 2011;127:355–60. [PubMed: 21281866]
38. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? Thorax 1999;54:268–72. [PubMed: 10325905]
39. Gatault S, Legrand F, Delbeke M, Loiseau S, Capron M. Involvement of eosinophils in the anti-tumor response. Cancer Immunol Immunother 2012;61:1527–34. [PubMed: 22706380]
40. Costello R, O'Callaghan T, Sébahoun G. Eosinophils and antitumour response. Rev Med Interne 2005;26:479–84. [PubMed: 15908052]
41. Josephs DH, Spicer JF, Karagiannis P, Gould HJ, Karagiannis SN. IgE immunotherapy. A novel concept with promise for the treatment of cancer. MAbs 2014;6:54–72. [PubMed: 24423620]
42. Huland E, Huland H. Tumor-associated eosinophilia in interleukin-2-treated patients: evidence of toxic eosinophil degranulation on bladder cancer cells. J Cancer Res Clin Oncol 1992;118:463–7. [PubMed: 1618895]
43. Zacharia B, Sherman P. Atopy, helminths, and cancer. Med Hypotheses 2003;60:1–5. [PubMed: 12450762]
44. Murdoch JR, Lloyd CM. Chronic inflammation and asthma. Mutat Res - Fundam Mol Mech Mutagen 2010;690:24–39.
45. López-Knowles E, Hernández S, Kogevinas M, Lloreta J, Amorós A, Tardón A, Carrato A, Kishore S, Serra C, Malats N, Real FX, EPICURO Study Investigators. The p53 pathway and outcome among patients with T1G3 bladder tumors. Clin Cancer Res 2006;12:6029–36. [PubMed: 17062677]
46. Urrutia I, Aguirre U, Sunyer J, Plana E, Muniozguren N, Martínez-Moratalla J, Payo F, Maldonado JA, Anto JM, Estudio de Salud Respiratoria de la Comunidad Europea. [Changes in the prevalence of asthma in the Spanish cohort of the European Community Respiratory Health Survey (ECRHS-II)]. Arch Bronconeumol 2007;43:425–30. [PubMed: 17692242]
47. Fernández-Nieto M, Quirce S, Sastre J. Occupational asthma in industry. Allergol Immunopathol (Madr) 2006;34:212–23. [PubMed: 17064651]
48. Barnes NC. The properties of inhaled corticosteroids: Similarities and differences. Prim. Care Respir. J2007;16:149–54. [PubMed: 17530144]

Novelty and Impact

This study corroborates the notion that asthma is associated with a reduced risk of cancer by reporting sound results and characterizing the association between asthma and bladder cancer risk. Impact of these results could be on primary prevention interventions as well as in increasing the efficacy of bladder cancer treatment by modifying the immunological status of the patients. The inverse association is restricted to the aggressive forms of bladder cancer, those that benefit of immunotherapy.

Table 1.

Characteristics of subjects included in the study, by UBC status, Spain, 1998–2001

Characteristics		Cases (N=936)	%	Controls (N=1022)	%	*P*
Gender	Males	807	86.22	874	85.52	0.66
	Females	129	13.78	148	14.48	
Age, years	15–54	160	17.09	183	17.91	0.09
	55–64	197	21.05	253	24.76	
	65–69	208	22.22	239	23.39	
	70–74	201	21.47	196	19.18	
	≥75	170	18.16	151	14.77	
Region	Barcelona	154	16.45	187	18.30	0.84
	Vallès	115	12.29	121	11.84	
	Elche	73	7.80	73	7.14	
	Tenerife	171	18.27	180	17.61	
	Asturias	423	45.19	461	45.11	
Smoking status *	Never smoker	166	17.74	374	36.59	<0.0001
	Former smoker	369	39.42	395	38.65	
	Light smoker	163	17.41	122	11.94	
	Heavy smoker	238	25.43	131	12.82	

* Light smoker: regular smoker of <40 pack years; heavy smoker: regular smoker of ≥40 pack years.

Table 2.

Association between UBC and asthma status, Spain, 1998–2001

Total	N	Cases, N (%)	Controls N (%)	OR*	95% CI*	P*	OR$	95% CI$	P$
Asthma									
No	1814	885 (94.6%)	929 (90.9%)	1			1		
Yes	144	51 (5. 5%)	93 (9.1%)	0.56	0.39, 0.80	**0.001**	0.54	0.37, 0.79	**0.001**
Asthma and /or COPD									
None	1647	797 (85.1%)	850 (83.2%)	1			**1**		
Only asthma	64	20 (2.14%)	44 (4.31%)	0.48	0.28, 0.83	**0.008**	0.50	0.28, 0.88	**0.02**
Only COPD	167	88 (9.40%)	79 (7.73%)	1.19	0.86, 1.63	0.40	1.07	0.76,1.50	0.69
Asthma & COPD	80	31 (3.31%)	49 (4.79%)	0.67	0.43,1.07	0.06	0.59	0.36,0.96	**0.03**

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; RRR, relative risk ratio; UBC, urothelial bladder cancer.

*Estimates adjusted by age, gender and region.

$Estimates adjusted by age, gender, region, smoking status, BMI, fruit consumption (in tertitles), coffee consumption (daily cups of coffee), use of medication/ phenazopyridine to treat UTI

Table 3.

Association between sub-phenotypes of UBC and asthma status, Spain, 1998–2001

UBC subtype	N cases	RRR*	95% CI*	*P**	RRR$	95% CI$	*P*$
Low-risk NMIBC	522	0.78	0.53, 1.16	0.22	0.77	0.51, 1.16	0.21
High-risk NMIBC	176	0.28	0.11, 0.69	**0.006**	0.25	0.10, 0.62	**0.003**
MIBC	238	0.32	0.15, 0.67	**0.003**	0.32	0.15, 0.69	**0.003**

Abbreviations: CI, confidence interval; NMI, non-muscle invasive; MI, muscle invasive; RRR, relative risk ratio; UBC, urothelial bladder cancer

Estimates are obtained with multinomial regression models, * adjusted by age, gender and region and $by age, gender, region, smoking status, BMI, fruit consumption (in tertiles), coffee consumption (daily cups of coffee), use of medication/ phenazopyridine to treat UTI