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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Asthma, Asthma Medications, and Prostate Cancer Risk

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Abstract

Background: The aim of this study was to assess whether a history of asthma or the use of asthma medications is associated with prostate cancer risk.

Methods: Of 16,934 men participating in the Melbourne Collaborative Cohort Study, 1,179 were diagnosed with prostate cancer during an average follow-up of 13.4 years to the end of December 2007. Information on asthma history was obtained at baseline interview. Participants were asked to bring their current medications to the study center. The names of the drugs were entered into a form and coded. Asthma medications were categorized into four groups and corresponding hazard ratios (HR) were estimated from Cox regression models adjusted for country of birth.

Results: Asthma was associated with a small increase in prostate cancer risk [HR 1.25; 95% confidence interval (95% CI), 1.05-1.49]. The HRs for use of medications were 1.39 (95% CI, 1.03-1.88) for inhaled glucocorticoids, 1.71 (95% CI, 1.08-2.69) for systemic glucocorticoids, 1.36 (95% CI, 1.05-1.76) for bronchodilators, and 0.78 (95% CI, 0.45-1.35) for antihistamines. The HRs for asthma and asthma medication use changed only slightly after mutual adjustment.

Conclusions: A history of asthma and the use of asthma medications, particularly systemic glucocorticoids, are associated with an increased risk of prostate cancer, although it is difficult to disentangle the effects of asthma medications from those of asthma per se.

Impact: These findings, if confirmed in independent studies, might lead to the identification of new risk factors for prostate cancer. *Cancer Epidemiol Biomarkers Prev; 19(9); 2318–24. ©2010 AACR.*

Introduction

Asthma is a chronic inflammatory disease of the lungs causing increased airways reactivity to various stimuli. Allergy and asthma are indicators of altered immune system dynamics and an excessive inflammatory response (1). A number of studies have investigated asthma and allergies, including hay fever, eczema, and allergies to medications, as risk factors for cancer, often as part of comprehensive investigations on other risk factors (2). Generally, allergies seem to be associated with a decreased risk of pancreatic cancer (2, 3) and non-Hodgkin lymphoma (4), whereas the observed association between a history of asthma and increased risk of lung cancer might be due to confounding by smoking (2).

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Inflammation is considered an important pathway for prostate carcinogenesis (5), and it is possible that men with a hyperactive immune system that produces excessive inflammatory responses are at increased risk of prostate cancer.

A recent meta-analysis of the few studies that have investigated the association between atopy and prostate cancer risk (assessed by allergen-specific IgE or skin prick testing) reported evidence of a modest association (6). The same meta-analysis reported that the estimated pooled odds ratio (OR) for asthma was consistent with no association with prostate cancer risk, but there was evidence of heterogeneity across studies (6).

In this prospective cohort study, we assessed the relationship between history of asthma and prostate cancer risk, overall and separately for nonaggressive and aggressive prostate cancers. We also examined associations between medications used to treat or prevent asthma and prostate cancer risk.

Materials and Methods

Subjects

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,514 people (17,045 men), ages 27 to 81 years at baseline (99.3% age 40-69). Recruitment occurred from 1990 to 1994 in the Melbourne

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metropolitan area. Subjects were recruited via the Electoral Rolls (registration to vote is compulsory for adults in Australia) advertisements and community announcements in local media (e.g., television, radio, newspapers). The Human Research Ethics Committee of the Cancer Council Victoria approved the study protocol. Subjects gave written consent to participate and for the investigators to obtain access to their medical records.

Men were excluded from the analysis if they had a confirmed diagnosis of prostate cancer or cancer of unknown primary site prior to baseline ($n = 106$) or had missing data on asthma ($n = 5$), leaving 16,934 men available for analysis.

Assessment of asthma and potential confounders

At baseline, a structured interview schedule was used to obtain information on potential risk factors, including age, country of birth, education, smoking habits, and previous medical conditions. Participants were first asked whether a doctor had ever told them that they had asthma or wheezy breathing. Those who responded affirmatively were asked the age at diagnosis and whether the condition required medication. Subjects completed a dietary questionnaire that was also used to calculate nutrients and energy intake (7). Body mass index was calculated from measured height and weight, whereas fat and fat-free mass were derived from measured resistance and reactance (8).

Cohort follow-up and ascertainment of prostate cancer cases

Cases were men notified to the State Cancer Registries in Australia with a first diagnosis of adenocarcinoma of the prostate during follow-up from baseline interview to December 31, 2007. Gleason score or tumor grade was ascertained and used to categorize prostate cancer grade into low (Gleason score 2-4) moderate (Gleason score 5-7), and high (Gleason score 8-10). Classification of cases as aggressive and nonaggressive was made on the basis that only cases with a distant-stage or poorly differentiated tumor have excess mortality compared with the general population (9). Prostate cancer was therefore defined as "aggressive" if the Gleason score was >7 or if it was classified as poorly differentiated. Cases with stage T_4 or N+ (positive lymph nodes) or M+ (distant metastases) were classified as aggressive irrespective of the Gleason score or grade of tumor differentiation. Prostate cancer cause-specific deaths were also classified as aggressive. Deaths were identified from Victorian death records and from the National Death Index for those who died outside Victoria. Residential addresses were determined by record linkage to Electoral Rolls, from electronic phone books, and from responses to mailed questionnaires and newsletters. By the end of follow-up on December 31, 2007, 54 men (0.3%) were known to have left Australia and were considered lost to follow-up.

Medication audit at baseline

At baseline, participants were asked to bring all the current medications they were taking to the study center where the interviewer recorded the name of each medication on a form specifically designed for this purpose. One of the authors (MA), a specialist physician in respiratory medicine, coded medications that may be used to treat or prevent asthma into four groups: antihistamines, bronchodilators, inhaled glucocorticoids, and systemic glucocorticoids that include mainly tablets and injections. Some men reported using glucocorticoids in the form of creams, ointments, and drops possibly prescribed for various skin disorders like dermatitis and psoriasis and for inflammation of the eye. These medications were coded in a separate group labeled "topical glucocorticoids." There were 2,969 (18%) men who did not complete the medication audit, and were, therefore, excluded from analyses of baseline medication use.

Statistical analysis

Follow-up began at baseline and continued until diagnosis of prostate cancer or cancer of unknown primary site, death, date left Australia, or end of December 2007, whichever came first. Cox regression with age as the time axis was used to derive adjusted hazard ratios for men in each category of exposure. Men with asthma were categorized in two groups according to age at diagnosis using the median in the full cohort as cutoff value.

All final analyses included country of birth as a covariate with four categories (i.e., Australia, UK, Greece, and Italy). Further adjustment for other potential confounders including education, body mass index, fat and fat-free mass, smoking, alcohol consumption, and total energy intake did not materially change the estimated rate ratios.

Cox regression models based on competing risks were fitted using a data duplication method to test the heterogeneity in the rate ratios between aggressive and nonaggressive cancer (10). These analyses were done stratifying the Cox models for type of outcome (aggressive or nonaggressive prostate cancer), thus allowing the hazard function associated with the two types of failure to be different.

The association of prostate cancer risk with group of medication that can be used to treat asthma was estimated from the data obtained at the drug audit using a Cox regression model with and without adjusting for reported history of asthma. The data from the men who completed the drug audit were also used to investigate whether the association with asthma changed after adjustment for the use of different groups of medications.

A sensitivity analysis to investigate the effect of prevalent cancers (i.e., prostate cancer present but not diagnosed at baseline) on the association between asthma and asthma medications and prostate cancer risk was done by excluding the first two years of follow-up.

Statistical analyses were done using Stata 10.1 (Stata Corporation). The likelihood ratio test was used to test hypotheses whenever possible. The Wald test was used

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to test differences in the hazard ratios by age at diagnosis and use of medications to control asthma.

Results

From the 16,934 men eligible for the study, we identified 1,179 prostate cancers, including 329 aggressive tumors (28%) during an average of 13.4 years of follow-up per subject (227,280 total person-years observed). A total of 113 (10%) prostate cancer cases were diagnosed during the first two years of follow-up. Table 1 shows the distribution of age, country of birth, and asthma by disease status and tumor aggressiveness. At baseline 11% of men reported a history of asthma diagnosed by a doctor and this prevalence ranged from 12% for men born in Australia to 7% for men born in Italy or Greece. The median age at diagnosis of asthma was 32 years, with one quarter diagnosed during childhood (before their 10th birthday) and one quarter in late adulthood (50 years of age or above). Two thirds (67%) of asthmatic men

Table 1. Baseline characteristics of the 16,936 men participating in the Melbourne Collaborative Cohort Study by outcome status

	Prostate cancer cases*		Noncases
	Nonaggressive (*n* = 840)	Aggressive (*n* = 329)	(*n*=15,755)
	No. (%)	No. (%)	No. (%)
Age at baseline (years)			
<50	107 (13)	22 (7)	5,049 (32)
50-59	290 (35)	99 (30)	4,890 (31)
≥60	443 (52)	208 (63)	5,816 (37)
Country of birth			
Australia/New Zealand	608 (72)	238 (72)	10,223 (65)
United Kingdom	74 (9)	22 (7)	1,298 (8)
Italy	90 (11)	49 (15)	2,257 (14)
Greece	68 (8)	20 (6)	1,977 (13)
Asthma			
No	734 (87)	295 (90)	14,116 (90)
Yes	106 (13)	34 (10)	1,639 (10)
Medications, no†	30 (29)	8 (24)	536 (33)
Medications, yes	73 (71)	25 (76)	1,075 (67)
Age at diagnosis ≤32 y‡	42 (41)	15 (45)	811 (51)
Age at diagnosis >32 y	60 (59)	18 (55)	779 (49)
Medications (from drug audit)§			
Inhaled glucocorticoids			
No	682 (96)	271 (94)	12,581 (97)
Yes	27 (4)	18 (6)	377 (3)
Systemic glucocorticoids			
No	696 (98)	283 (98)	12,829 (99)
Yes	13 (2)	6 (2)	129 (1)
Antihistamines			
No	698 (98)	287 (99)	12,756 (98)
Yes	11 (2)	2 (1)	202 (2)
Bronchodilators			
No	668 (94)	270 (93)	12,390 (96)
Yes	41 (6)	19 (7)	568 (4)

*A tumor was classified as aggressive if Gleason score was >7 or stage was advanced (T_4 or N+ or M+). Deaths attributed to prostate cancer were also classified as aggressive. We were not able to define aggressiveness for six cases because Gleason score and tumor stage were not available.

†In subjects reporting history of asthma; information was missing for 32 men.

‡In subjects reporting a history of asthma; information was missing for 54 men. This variable was categorized using the median value of age at diagnosis of asthma in the full cohort (32 years) as cutoff value.

§A total of 2,969 subjects did not complete the medication audit. Systemic glucocorticoids include mainly glucocorticoids administered as tablets or injections.

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Table 2. Hazard ratios (95% confidence intervals) for the association between history of asthma reported at baseline and incidence of prostate cancer

	All tumors*		Tumor aggressiveness†		
	HR (95% CI)	P‡	Nonaggressive HR (95% CI)	Aggressive HR (95% CI)	P§
Asthma					
No	Reference		Reference	Reference	
Yes	1.25 (1.05-1.49)	0.02	1.33 (1.08-1.63)	1.08 (0.76-1.54)	0.32
Yes and no medications‖	1.12 (0.81-1.54)		1.23 (0.85-1.77)	0.86 (0.42-1.73)	
Yes and medications‖	1.29 (1.05-1.58)	0.06	1.35 (1.06-1.72)	1.16 (0.77-1.75)	0.56
Age at diagnosis ≤32 y	1.17 (0.90-1.54)		1.20 (0.88-1.64)	1.15 (0.68-1.94)	
Age at diagnosis >32 y	1.29 (1.03-1.63)	0.06	1.42 (1.09-1.85)	1.03 (0.64-1.66)	0.52
Medications (drug audit)¶					
Inhaled glucocorticoids	1.39 (1.03-1.88)	0.04	1.19 (0.81-1.75)	1.95 (1.21-3.14)	0.12
Systemic glucocorticoids	1.71 (1.08-2.69)	0.03	1.68 (0.97-2.92)	1.83 (0.81-4.13)	0.87
Antihistamines	0.78 (0.45-1.35)	0.4	0.95 (0.52-1.73)	0.41 (0.10-1.65)	0.28
Bronchodilators	1.36 (1.05-1.76)	0.03	1.30 (0.95-1.79)	1.47 (0.92-2.34)	0.68

NOTE: Hazard ratios are estimated from Cox regression with age as time metric. Estimates are adjusted for country of birth.
*The analysis of asthma was based on 16,934 men including 1,179 prostate cancer cases. The analysis of medications from the drug audit was based on 13,965 men including 1,007 prostate cancer cases (2,797 men did not participate in the drug audit).
†Estimates from the Cox regression including tumor aggressiveness as stratum. The analysis of asthma was based on 16,924 men, including 840 nonaggressive and 329 aggressive prostate cancers. Ten cases were excluded because we were not able to define aggressiveness. The analysis of medications from the drug audit was based on 13,956 men, including 709 nonaggressive and 289 aggressive prostate cancers.
‡Likelihood ratio test comparing a full model with a model excluding the given variable(s).
§Test of heterogeneity in the hazard ratios between aggressive and nonaggressive tumors.
‖Subjects who reported clinician-diagnosed asthma were asked whether they used medications to treat their asthma.
¶Medications that may be used to treat or prevent asthma reported at the baseline medication audit. HRs associated with taking versus not taking specified medications.

reported using medications to control the disease and this proportion was higher for men diagnosed at an older age (>32 years, 77%) than for men diagnosed at an earlier age (≤32 years, 59%; $P < 0.001$).

Overall, asthma was associated with an increased risk of prostate cancer ($P = 0.02$; Table 2). The increase in risk of prostate cancer for men with a history of asthma compared with men without such a history was small but significant [hazard ratio (HR), 1.25; 95% confidence interval (95% CI), 1.05-1.49). The HR for men who used medications to control asthma (1.29; 95% CI, 1.05-1.58) was not significantly different from the HR for men who did not use medications to control asthma (1.12; 95% CI, 0.81-1.54; Wald test for the difference, $P = 0.46$). Similarly, the HR for men who reported a history of asthma diagnosed at an older age (1.29; 95% CI, 1.03-1.63) was not significantly different from the HR for men who reported a history of asthma diagnosed at an early age (1.17; 95% CI, 0.90-1.54; Wald test for the difference, $P = 0.58$). The HR associated with asthma for nonaggressive prostate cancer (1.33; 95% CI, 1.08-1.63) was not significantly different from the HR for aggressive prostate cancer (1.08; 95% CI, 0.76-1.54; P for heterogeneity = 0.32).

The proportions of participants using inhaled glucocorticoids, systemic glucocorticoids, antihistamines, or bronchodilators at baseline were 3%, 1%, 2%, and 5%, respectively. The corresponding HRs for the use of these medications were 1.39 (95% CI, 1.03-1.88), 1.71 (95% CI, 1.08-2.69), 0.78 (95% CI, 0.45-1.35), and 1.36 (95% CI, 1.05-1.76), respectively (Table 2). We did not observe any association between the use of topical glucocorticoids and prostate cancer risk (HR, 0.95; 95% CI, 0.49-1.83).

When the analysis was limited to men who completed the medication audit the HR for asthma was 1.18 (0.98-1.43; Table 3). This estimate was only slightly reduced by adjusting for use of medications. The HRs for use of medications after adjusting for asthma were 1.30 (95% CI, 0.92-1.84) for inhaled glucocorticoids, 1.64 (95% CI, 1.04-2.59) for systemic glucocorticoids, 1.29 (95% CI, 0.95-1.76) for bronchodilators, 0.76 (95% CI, 0.44-1.31) for antihistamines, and 0.90 (95% CI, 0.47-1.74) for topical glucocorticoids. There was no statistical evidence of interaction between

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Table 3. Hazard ratios (95% confidence intervals) from Cox regression models including asthma and the classes of medications

	HR* (95% CI)	P†
Model 1		
Asthma		
No	Reference	
Yes	1.18 (0.98-1.43)	0.09
Model 2		
Asthma		
No	Reference	
Yes	1.09 (0.88-1.36)	0.43
Inhaled glucocorticoids		
No	Reference	
Yes	1.30 (0.92-1.84)	0.14
Model 3		
Asthma		
No	Reference	
Yes	1.16 (0.95-1.40)	0.14
Systemic glucocorticoids		
No	Reference	
Yes	1.64 (1.04-2.59)	0.03
Model 4		
Asthma		
No	Reference	
Yes	1.07 (0.86-1.35)	0.54
Bronchodilators		
No	Reference	
Yes	1.29 (0.95-1.76)	0.11
Model 5		
Asthma		
No	Reference	
Yes	1.19 (0.98-1.44)	0.08
Antihistamines		
No	Reference	
Yes	0.76 (0.44-1.31)	0.32

NOTE: Medication information was derived from a medication audit done at baseline. These analyses were based on 13,965 men that completed the medication audit.

*Estimates were obtained using Cox regression models with age as time metric adjusted for country of birth, each model including variables for both asthma and the given drug class.

†Wald test.

use of these medications and reported history of asthma (all tests for interaction, $P > 0.05$). The exclusion of the first two years of follow-up (men possibly with undetected prostate cancer at baseline) did not materially change the results, and no statistically significant difference in the HRs was observed by duration of follow-up (results not shown).

Discussion

We found that a reported history of asthma and the use of some medications to treat or prevent asthma, particularly systemic glucocorticoids, was associated with an increased prostate cancer risk.

The strengths of this study are its prospective design, large number of cases, low loss to follow-up (only 0.3% of men left Australia during the follow-up period), and virtually complete ascertainment of cases (cases having been ascertained through the State Cancer Registries in Australia). The information on asthma and use of medications was collected at baseline so it was unlikely that bias due to differential recall occurred. Moreover, questions on self-reported physician-diagnosed asthma, like the ones we used, have been found to be highly specific and more reliable than symptom-based questions or questionnaires asking respondents if they have ever had asthma (11, 12).

One limitation of this study was the lack of information on the type of asthma and its natural history. We did not collect information on coexisting allergies like allergic eczema and rhinitis, allergy to house dust mite, or allergy to medications. We were, therefore, unable to distinguish between allergic asthma and nonallergic, or intrinsic, asthma (13, 14), a distinction that might have helped in interpreting our results.

Studies that have investigated possible associations between asthma or allergies and prostate cancer risk are few. Two American cohort studies, one of members of the Seventh-day Adventist church in California (15) and the other of participants in the National Health and Nutrition Survey (NHANES I; ref. 16), examined the risk of different types of cancer associated with self-reported asthma and found no association with prostate cancer, as did a Finnish study that compared cancer incidence in a cohort of asthmatic men with the incidence in the general population (17). A more recent study of 1,552 men in Busselton, Western Australia (18), including 86 prostate cancer cases, reported an association between allergy to house dust mite, determined using skin-prick testing, and increased risk of prostate cancer (HR, 2.90; 95% CI, 1.26-6.68). This study also reported suggestive evidence that men who reported a history of asthma had a higher risk of prostate cancer (HR, 1.89; 95% CI, 1.00-3.60). With the exception of the Finnish study that was based on 256 prostate cancer cases, the estimates from all these studies were based on a small number of cases. A much larger study of almost half a million participants in the Cancer Prevention Study II study reported the risk of dying of prostate cancer for men with asthma and/or hay fever was similar to the risk for other men (relative risk, 0.94, 95% CI, 0.86-1.02; ref. 19).

Despite our study having limited statistical power to detect modest to moderate differences in the hazard ratios by prostate cancer aggressiveness, our results did not provide evidence that the observed associations were limited to nonaggressive prostate cancer. This suggests

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that these associations are unlikely to be an artifact due to confounding with prostate-specific antigen testing. A possible explanation for the association between asthma and prostate cancer risk is that chronic or excessive immune stimulation leads to malignant transformations. Although a local inflammatory process in the respiratory system is unlikely to affect the behavior of the cells in the prostate per se, it might be an indicator of a general propensity of the immune system to overreact to antigens. An alternative explanation is that asthma does not increase prostate cancer risk per se but through the use of medications. Indeed it is difficult to disentangle the effects due to asthma itself from those due to medications for asthma as the two factors are strongly correlated.

We found suggestive evidence that asthmatic men who reported taking medications for their asthma have slightly higher risk of prostate cancer than those asthmatic men who reported not taking medications specifically for asthma. If this difference exists, it suggests that more severe asthma and inflammation could be more strongly associated than mild asthma with the risk of prostate cancer. Further research is needed to investigate this possibility.

Of all medications potentially used for asthma, systemic glucocorticoids showed the strongest association with prostate cancer risk. This association remained statistically significant and virtually unaltered after adjusting for asthma. A limitation of our study is that we did not collect information on the reasons for medication use and when the taking of such medication started. We found no association between use of topical glucocorticoids and prostate cancer risk. We did not collect information on dose, but we found no association with topical glucocorticoids, a small association with inhaled glucocorticoids, and a moderate association with systemic glucocorticoids. It is premature to propose that the use of systemic glucocorticoids is responsible for the observed associations, but it is possible that these medications, which suppress the immune system, increase the risk of prostate cancer. There is ample literature showing increased risk of various types of cancer for strongly immunosuppressed transplant patients, but the risk of prostate cancer specifically was not increased in these patients (20). Only few studies investigated whether more commonly used immunosuppressive medications such as glucocorticoids are associated with increased risk of cancer. A recent population-based study of bladder cancer reported an increased risk associated with the use of glucocorticoids for one month or longer (21). A Danish study that linked the North Jutland Prescription Database to the Danish Cancer Registry reported that the number of prescriptions of glucocorticoids was associated with an increased risk of squamous cell carcinoma and basal cell carcinoma of the skin, and non-Hodgkin lymphoma (22). None of these studies were prospective cohorts and, to our knowledge, no prior studies have examined the risk of prostate cancer in relation to glucocorticoid use.

The observed associations need to be confirmed by independent prospective studies. Further studies are needed to clarify the possible mechanisms underlying these associations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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