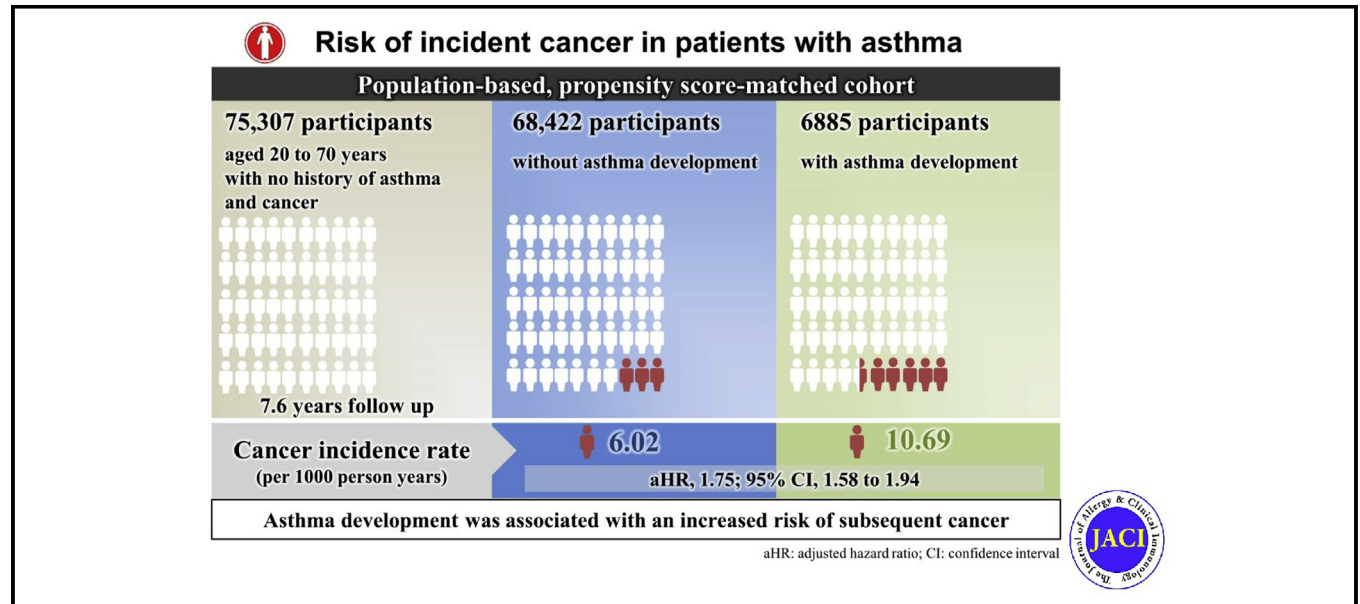


Incidence of cancer after asthma development: 2 independent population-based cohort studies

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GRAPHICAL ABSTRACT



Background: Evidence regarding the risk of cancer development after asthma diagnosis is controversial and inconclusive.

Objective: This study sought to determine whether asthma is associated with an increased risk for incident cancer.

Methods: Two independent, population-based, longitudinal cohorts were examined, and estimated hazard ratios were determined using Cox regression. One group consisted of an unmatched cohort of 475,197 participants and a propensity score-matched cohort of 75,307 participants from the National Health Insurance Service-National Sample Cohort (NHIS-NSC; claims-based data from 2003 to 2015). The other group consisted of 5,440 participants from the Ansan-Ansung cohort (interview-based data from 2001 to 2014).

Results: The NHIS-NSC matched cohort had 572,740 person-years of follow-up, 6,885 people with new asthma diagnoses, and

68,422 people without asthma diagnoses. Adults with asthma had a 75% greater risk of incident cancer overall. The excess risk for incident cancer was greatest during the first 2 years after asthma diagnosis, and this risk remained elevated throughout follow-up. Patients with nonatopic asthma had a greater risk of overall cancer than those with atopic asthma. A high cumulative dose of inhaled corticosteroids among asthma patients was associated with a 56% reduced risk of lung cancer, but had no effect on the risk of overall cancer. The results from the NHIS-NSC unmatched cohort and the Ansan-Ansung cohort were similar to the primary results from the NHIS-NSC matched cohort.

Conclusions: Asthma development was associated with an increased risk of subsequent cancer in 2 different Korean cohorts. Our findings provide an improved understanding of the pathogenesis of asthma and its relationship with carcinogenesis and suggest that clinicians should be aware of the higher risk of

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incident cancer among patients with asthma. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)**Key words:** *Asthma, cancer, chronic inflammation, carcinogenesis, tumor mutation burden*

Asthma is the most common chronic respiratory disease, affecting an estimated 358 million people worldwide in 2015.¹⁻³ Asthma is associated with several comorbidities whose prevalences have increased in recent years, including obesity, metabolic syndrome, diabetes mellitus type 2, mental disorders, and cardiovascular diseases, as well as with numerous previously recognized factors such as rhinitis, atopy, chronic obstructive pulmonary disease (COPD), and gastroesophageal reflux disease.⁴⁻⁶ However, previous studies have obtained mixed results on the association between asthma and cancer, with reports of positive associations,⁷⁻¹¹ no association,^{8,10,12-18} and negative associations.¹⁹⁻²³ For example, Liu et al⁷ showed that asthma increased the overall risk of cancer by 19%, but Kallen et al¹⁹ suggested that asthma decreased the overall risk of cancer. However, previous studies on this topic were limited by small sample sizes, inadequate adjustment for confounding factors that could affect cancer development, use of cross-sectional or case-control designs, or focus on specific cancer types.⁷⁻²³ Moreover, an inflammatory response may mediate the link between asthma and lung cancer,²⁴⁻²⁶ and use of an inhaled corticosteroid (ICS) could possibly reduce the risk of incident cancer in patients with asthma.²⁵

Therefore, we comprehensively investigated the association of the incidence of several types of cancer after new asthma diagnosis and the association of ICS use and cancer risk during a mean follow-up time of 8.5 years for the first cohort (nationwide full unmatched cohort), 7.6 years for the second cohort (nationwide propensity score–matched cohort), and 11.5 years for the third cohort. Each cohort was an independent population-based cohort of Korean adults who had no history of asthma or cancer at baseline.

METHODS

Two different and independent cohorts were examined: the National Health Insurance Service–National Sample Cohort (NHIS-NSC) and the Ansan-Ansung cohort. The NHIS-NSC is a large-scale, population-based cohort study consisting of a 2.2% representative sample of the Korean standard population.^{27,28} The study protocol was approved by the Institutional Review Board of the Armed Force Medical Command (AFMC-18-IRB-047). The Ansan-Ansung cohort study is a population-based prospective cohort study conducted by the Korea Center for Disease Control and Prevention.²⁹ The protocol for the present study was approved by the Institutional Review Board of the Korea Center for Disease Control and Prevention and Armed Force Medical Command (AFMC-19-IRB-001), and written informed consent was provided by all participants.

NHIS-NSC full unmatched cohort

Data were from individuals 20 to 70 years of age who received ≥1 general health examination between January 1, 2002, and December 31, 2015. For each participant, the cohort entry date (individual index date) was the date of the first general health screening examination and/or diagnosis of asthma. Among the initial 526,766 participants, subjects were excluded if the questionnaire was incomplete (n = 22,682); if blood test results were missing (n = 1,312); if there was a previous diagnosis of asthma based on a general health examination, previous assignment of the J45 or J46 code from the

Abbreviations used

aHR:	Adjusted hazard ratio
COPD:	Chronic obstructive pulmonary disease
HR:	Hazard ratio
ICD-10:	International Classification of Disease 10th revision
ICS:	Inhaled corticosteroid
NHIS-NSC:	National Health Insurance Service–National Sample Cohort

International Classification of Disease, 10th revision (ICD-10), and/or previous use of asthma-related medications (n = 31,212); or if there was a previous diagnosis of cancer based on a general health examination and/or previous assignment of the C ICD-10 code (n = 6,862). The final sample size was 475,240 participants.

Baseline information was obtained for each subject at the first general health examination. Age, sex, region of residence, and household income were obtained from insurance eligibility data. Body mass index and blood pressure were measured, and serum glucose and total cholesterol were obtained from fasting blood samples. Smoking habits, physical activity, and frequency of alcohol consumption were obtained by self-reported questionnaires. History of diabetes mellitus, stroke, hypertension, acute pyelonephritis, allergic rhinitis, and atopic dermatitis were defined by assignment of ≥2 claims using the appropriate ICD-10 code.

Asthma was defined using the ICD-10 code J45 (asthma) and/or code J46 (status asthmaticus), with ≥3 claims as an outpatient within 1 year and/or ≥1 claim as an inpatient and the use of asthma-related medications (ICS and systemic corticosteroids, long- and short-acting β_2 -agonists, and/or leukotriene antagonists).³⁰ COPD was defined using ICD-10 codes J43 to J44 (except J43.0), with ≥3 claims as an outpatient within 1 year and/or at least 1 claim as an inpatient and the use of COPD-related medications (ICS and systemic corticosteroids, long- and short-acting β_2 -agonists, short- or long-acting muscarinic antagonists, and/or leukotriene antagonists).³⁰ Cancer was defined using ICD-10 code C ≥3 times within 1 year as an outpatient or as an inpatient with a C code.²⁷ Due to the special insurance benefits provided to patients with cancer, this code is rigorously reviewed by NHIS to ensure accurate diagnoses.

Use of an ICS during the follow-up period was recorded. The cumulative ICS dose was calculated as the total dose of prescribed ICS medication and converted to fluticasone-equivalent dosages for comparison of different types of ICSs.²⁶

Atopic asthma was defined as asthma with 1 more atopic disorder (allergic rhinitis or atopic dermatitis), and nonatopic asthma as asthma without any atopic disorder.³¹

NHIS-NSC propensity score–matched cohort

Propensity scores were derived from the predicted probability of subjects with asthma versus without asthma using a logistic regression model with adjustment for confounding by age, sex, frequency of alcohol consumption, region of residence, body mass index, systolic blood pressure, diastolic blood pressure, fasting blood glucose, serum total cholesterol, history of diabetes mellitus, stroke, hypertension, Charlson comorbidity index, household income, smoking, and physical activity. Propensity score–matching was used to reduce potential confounders and to balance the baseline covariates of the 2 groups.³² A “greedy nearest-neighbor” algorithm was used to match patients in the 2 groups in a 1:10 ratio.³³ Adequacy of matching was assessed by comparing propensity score densities (see Fig E1 in this article’s Online Repository at www.jacionline.org), distribution (see Fig E2 in this article’s Online Repository at www.jacionline.org), and standardized mean differences. This approach calculates the population mean difference of the 2 groups and is more meaningful than assessing *P* values from *t* tests.³⁴

To reduce immortal time bias, the cohort index date (individual index date) was set to the same date as asthma diagnosis in subjects and matched

TABLE I. Demographic and clinical characteristics of subjects in the NHIS-NSC (n = 475,197)

Characteristic	Full unmatched cohort (n = 475,197)			Propensity score-matched cohort (n = 75,307)		
	Individuals without incident asthma	Individuals with incident asthma	SMD*	Individuals without incident asthma	Individuals with incident asthma	SMD*
Total, n (%)	468,234 (98.5)	6,963 (1.5)		68,422 (90.9)	6,885 (9.1)	
Follow-up (y), mean ± SD	8.88 ± 3.92	7.49 ± 3.19		7.62 ± 3.62	7.46 ± 3.17	
Age (y), mean ± SD	47.56 ± 12.23	49.49 ± 11.91	0.006	49.28 ± 11.89	49.30 ± 11.81	0.002
Male, n (%)	241,104 (51.5)	4,015 (57.7)	0.124	39,580 (57.8)	3,972 (57.7)	0.003
Region of residence, n (%)			0.010			0.003
Rural	242,469 (51.8)	3,641 (52.3)		35,896 (52.5)	3,603 (52.3)	
Urban	225,765 (48.2)	3,322 (47.7)		32,526 (47.5)	3,282 (47.7)	
Body mass index (kg/m ²), n (%)			0.042			0.010
<25	331,823 (70.9)	4,810 (69.1)		47,095 (68.8)	4,754 (69.0)	
25-30	119,652 (25.6)	1,909 (27.4)		19,017 (27.8)	1,890 (27.5)	
≥30	16,759 (3.6)	244 (3.5)		2,310 (3.4)	241 (3.5)	
Systolic blood pressure (mm Hg), mean ± SD	120.97 ± 15.45	122.07 ± 15.63	0.070	121.98 ± 15.44	121.98 ± 15.56	<0.001
Diastolic blood pressure (mm Hg), mean ± SD	75.99 ± 10.72	76.67 ± 10.84	0.063	76.67 ± 10.75	76.68 ± 10.81	<0.001
Fasting blood glucose (mg/dL), mean ± SD	94.54 ± 26.02	95.29 ± 28.16	0.028	95.33 ± 28.37	95.21 ± 28.06	0.004
Serum total cholesterol (mg/dL), mean ± SD	190.92 ± 41.56	192.00 ± 48.64	0.024	191.68 ± 48.37	191.88 ± 48.70	0.004
History of diabetes mellitus, n (%)	22,598 (4.8)	758 (10.9)	0.228	7,047 (10.3)	757 (11.0)	0.023
History of stroke, n (%)	4,882 (1.0)	121 (1.7)	0.061	1,177 (1.7)	121 (1.8)	0.002
History of hypertension, n (%)	51,624 (11.0)	1,783 (25.6)	0.385	17,425 (25.5)	1,762 (25.6)	0.002
Charlson comorbidity index, n (%)			0.050			0.018
0	371,843 (79.4)	5,540 (79.6)		54,132 (79.1)	5,478 (79.6)	
1	86,853 (18.5)	1,276 (18.3)		12,729 (18.6)	1,260 (18.3)	
≥2	9,538 (2.1)	147 (2.1)		1,561 (2.3)	147 (2.1)	
Household income, n (%)			0.259			0.010
Low (0-39th percentiles)	105,069 (22.4)	2,084 (29.9)		20,103 (29.4)	2,053 (29.8)	
Middle (40th-79th percentiles)	195,082 (41.7)	3,160 (45.4)		31,228 (45.6)	3,129 (45.4)	
High (80th-100th percentiles)	168,083 (35.9)	1,719 (24.7)		17,091 (25.0)	1,703 (24.7)	
Smoking, n (%)			0.108			0.008
Never smoker	289,724 (61.9)	3,970 (57.0)		38,721 (56.6)	3,923 (57.0)	
Ex-smoker	41,384 (8.8)	613 (8.8)		6,151 (9.0)	608 (8.8)	
Current smoker	137,126 (29.3)	2,380 (34.2)		23,550 (34.4)	2,354 (34.2)	
Alcoholic drinks per week, n (%)			0.081			0.008
<1	283,689 (60.6)	3,985 (57.2)		38,963 (56.9)	3,934 (57.1)	
1-2	131,294 (28.0)	2,042 (29.3)		20,451 (29.9)	2,034 (29.5)	
3-4	38,837 (8.3)	661 (9.5)		6,416 (9.4)	651 (9.5)	
≥5	14,234 (3.0)	275 (3.9)		2,592 (3.8)	266 (3.9)	
Physical activity sessions per week, n (%)			0.033			0.006
0	209,923 (44.8)	3,181 (45.7)		31,008 (45.3)	3,137 (45.6)	
1-2	120,770 (25.8)	1,820 (26.1)		17,963 (26.3)	1,800 (26.1)	
3-4	61,507 (13.1)	896 (12.9)		8,914 (13.0)	891 (12.9)	
5-6	36,714 (7.8)	536 (7.7)		5,260 (7.7)	532 (7.7)	
7	39,320 (8.4)	530 (7.6)		5,277 (7.7)	525 (7.6)	

SMD, Standardized mean difference.

*SMD < 0.1 indicates no major imbalance. All SMD values were <0.02 in the propensity score-matched cohort.

comparators. Overall, there were 6,885 adults with new asthma diagnoses and 68,422 matched adults without asthma.

Ansan-Ansung cohort

See [supplementary text](#) in this article's Online Repository at www.jacionline.org.

Statistical analysis

In the NHIS-NSC cohort, follow-up started on the baseline examination or asthma diagnosis and ended on December 31, 2015, at death, or at development of cancer. Cases with cancer diagnoses within 31 days after asthma diagnosis (n = 43) were excluded from analysis to reduce the potential of surveillance bias.²⁷ The following factors were considered potential confounders: age (20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years); sex; cumulative ICS dose (none, low, and high); history of COPD; frequency of

alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week); region of residence (rural vs urban); body mass index (<25, 25-30, and ≥30 kg/m²); yearly mean systolic blood pressure (continuous), diastolic blood pressure (continuous), fasting blood glucose level (continuous), and serum total cholesterol level (continuous); history of diabetes mellitus, stroke, and hypertension; Charlson comorbidity index; household income (low, middle, and high); smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1-2, 3-4, 5-6, and 7 sessions per week) (Table I, and see Table E1 in this article's Online Repository at www.jacionline.org). The Charlson comorbidity index (using ICD-10 codes) was calculated as reported previously.²⁷ A directed acyclic graph was used to identify adequate potential mediators (see Fig E3 in this article's Online Repository at www.jacionline.org). This graph provides a visualization of the causal association between asthma ("exposure") and risk of cancer ("outcome").³⁵

Main and sensitivity analysis. For each cohort, the "exposure" was development of asthma (time-varying exposure) and the "end point" was development of cancer (see Fig E4 in this article's Online Repository at

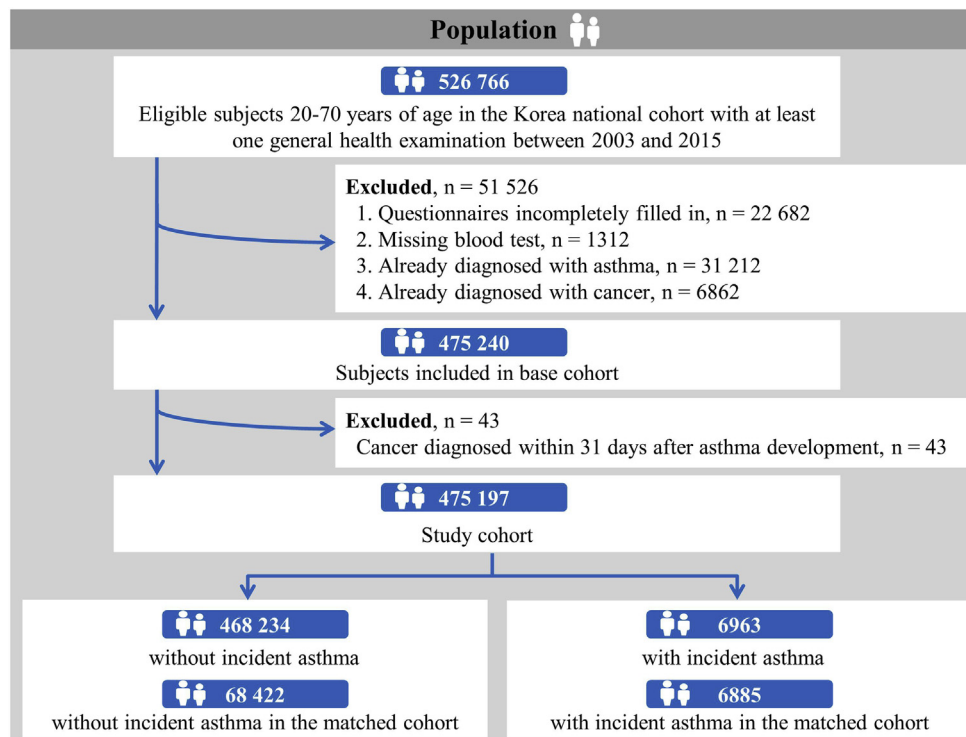


FIG 1. Disposition of subjects in the Korean NHIS-NSC.

www.jacionline.org). Data were analyzed by using Cox proportional hazards regression models and calculation of hazard ratios (HRs) and adjusted HRs (aHRs) with 95% CIs. The proportional hazards assumption was determined using Schoenfeld residuals and log(-log) survival plots. In NHIS-NCS cohort, a proportional hazard model was also used for the subdistribution of a competing event (death)³⁶ with similar results. In addition, several sensitivity analyses were conducted to reduce bias, in which there was stratification according to the time of asthma diagnosis, age, smoking status, exclusion of thyroid and stomach cancers,²⁷ and alternative cohort specifications for the NHIS-NSC (ie, alternative asthma definitions in which asthma was defined using ICD-10 codes J45 to J46 with ≥ 2 claims by a patient within 1 year and use of asthma-related medications or was restricted to subjects who had history of COPD³⁷) (see Table E2 in this article's Online Repository at www.jacionline.org). Furthermore, sensitivity analysis of the risk of incident acute pyelonephritis (null hypothesis) was performed. Statistical analyses were performed using SPSS (version 25.0; IBM Corp, Armonk, NY), R software (version 3.1.1; R Foundation, Vienna, Austria), and SAS (version 9.4; SAS Institute Inc, Cary, NC). Directed acyclic graphics were presented using Dagitty (version 2.3; <http://www.dagitty.net/>). Two-sided $P < .05$ was considered statistically significant.

RESULTS

We identified 468,234 adults without asthma and 6,963 adults with newly diagnosed asthma in the NHIS-NSC full unmatched cohort, and then matched 68,422 adults without asthma and 6,885 with newly diagnosed asthma to establish the NHIS-NSC propensity score-matched cohort (Fig 1). Table I shows the baseline characteristics of the NHIS-NSC full unmatched and matched cohorts. All standardized mean difference values were <0.02 in the matched cohort, indicating these 2 groups had no major imbalances of baseline characteristics.

NHIS-NSC matched cohort

During the follow-up period (duration, 7.60 ± 3.74 years), there were 3687 incident cancers, 549 in subjects who had newly diagnosed asthma (cancer incidence rate, 10.69 per 1000 person-years), and 3138 in those who did not develop asthma (cancer incidence rate, 6.02 per 1000 person-years) (Fig 2, Table II). Subjects with newly diagnosed asthma had a 75% greater risk of overall cancer after full adjustment for confounding (fully aHR, 1.75; 95% CI, 1.58-1.94) (Table II), and this relationship persisted after competing risk analysis for mortality (aHR, 1.62; 95% CI, 1.47-1.80). Analysis of the effect of atopic status indicated that subjects who with nonatopic asthma had a greater risk of overall cancer (aHR, 3.35; 95% CI, 2.88-3.89) compared with those who had atopic asthma (aHR, 1.36; 95% CI, 1.20-1.53).

To reduce the probability of detection bias or reverse causation, we also determined the effect of the time of asthma diagnosis on the HRs for overall cancer. The results indicated the association of incident cancer with time of asthma diagnosis remained statistically significant for asthma diagnosis times within 3 years (fully aHR, 1.64; 95% CI, 1.44-1.87), 3 to 5 years (aHR, 1.81; 95% CI, 1.50-2.20), and >5 years (aHR, 2.01; 95% CI, 1.66-2.45) (Table II).

Additional analysis indicated the excess risk for cancer following asthma diagnosis was greater during the 2 to 3 years after asthma diagnosis (fully adjusted HR, 2.27; 95% CI, 1.66 to 3.10), and this risk persisted throughout follow-up (Fig 3, and see Table E3 in this article's Online Repository at www.jacionline.org). The fully aHRs for all cancers were 1.35 (95% CI, 1.01-1.80) in years 0 to 1, 1.54 (96% CI, 1.11-2.14) in years 1 to 2, and 2.15 (95% CI, 1.77-2.62) in years 7 to 10.

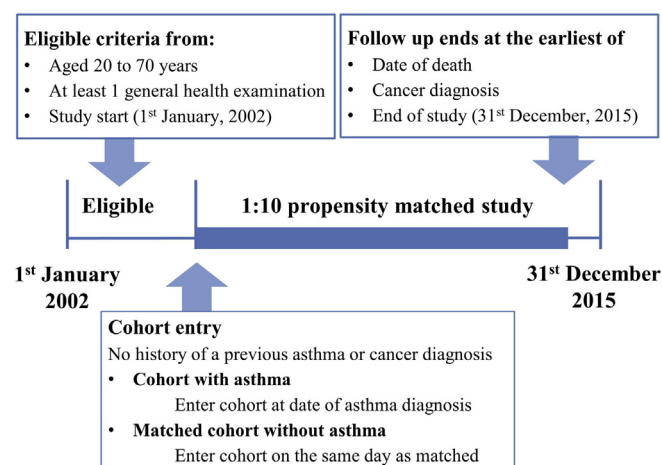


FIG 2. NHIS-NSC study population and propensity score-matched cohort.

Fig 4 shows the risk for different types of incident cancers following asthma diagnosis. Asthma was associated with a significantly increased risk for cancer of the bladder (fully aHR, 5.43; 95% CI, 3.24-9.09), lung (aHR, 2.78; 95% CI, 2.08-3.71), blood (aHR, 2.06; 95% CI, 1.04-4.06), oral cavity and esophagus (aHR, 2.02; 95% CI, 1.09-3.72), sex-specific (aHR, 1.94; 95% CI, 1.59-2.37), pancreas (aHR, 1.93; 95% CI, 1.16-3.20), stomach (aHR, 1.46; 95% CI, 1.01-2.10), liver (aHR, 1.44; 95% CI, 1.04-1.99), and colorectum (aHR, 1.37; 95% CI, 1.01-1.85).

We also compared the aHRs for incident cancer for adults of different ages and with different smoking statuses (Fig 5). This multivariable Cox regression indicated that asthma development remained significantly associated with incident cancer risk in all groups following stratification by age and smoking status (age <50 years: fully aHR, 1.67; 95% CI, 1.43-1.95; age ≥50 years: aHR, 1.84; 95% CI, 1.59-2.12; never smokers: aHR, 1.68; 95% CI, 1.47-1.93; ex-smokers: aHR, 1.48; 95% CI, 1.01-2.18; current smokers: aHR, 1.94; 95% CI, 1.62-2.33).

We also conducted a subgroup analysis of the relationship of incident cancer and cumulative ICS dose among asthma patients (Table III). This multivariable Cox regression indicated that a high cumulative dose of ICSs was significantly associated with a decreased risk of lung cancer (fully aHR, 0.44; 95% CI, 0.29-0.67), but had no effect on the risk of overall cancer (aHR, 0.84; 95% CI, 0.70-1.02).

First, sensitivity analysis indicated that incident cancer remained associated with asthma following use of stratification according to the time of asthma diagnosis (Table II), competing risk analysis (competing events: all-cause mortality and incident cancer; aHR, 1.62; 95% CI, 1.47-1.80), and exclusion of thyroid and stomach cancers, whose incidences are especially high incidences in Korea (see Table E4 in this article's Online Repository at www.jacionline.org). Second, a sensitivity analysis of the null hypothesis indicated that incident rate of acute pyelonephritis was not associated with asthma diagnosis (null hypothesis) (see Table E5 in this article's Online Repository at www.jacionline.org). Third, use of the same sensitivity tests in the NHIS-NSC full unmatched cohort also indicated that incident cancer remained associated with asthma diagnosis (see Tables E6 and E7 in this article's Online Repository at www.jacionline.org). Fourth, analyses using 4 different types of cohort specifications also showed a significantly increased risk of

incident cancer after asthma diagnosis (see Table E8 in this article's Online Repository at www.jacionline.org). These results are consistent with our primary results. Finally, the results from analysis of an external independent cohort (Ansan-Ansung cohort) were also consistent with our primary results (see Tables E9 and E10 in this article's Online Repository at www.jacionline.org).

DISCUSSION

We investigated the risk of incident cancer after asthma development in a large, population-based nationwide cohort (NHIS-NSC; n = 475,197) and in a population-based ongoing prospective cohort (Ansan-Ansung cohort; n = 5,440). Asthma development was associated with an increased risk of subsequent cancer incidence in both cohorts, and this risk was independent of age and smoking status. Moreover, the risk for cancer development was greatest during 2 to 3 years after asthma diagnosis, and an increased risk persisted for up to 10 years following asthma diagnosis. Moreover, asthma development was associated with a significantly increased risk of cancers of the bladder, lung, blood, oral cavity and esophagus, sex-specific, pancreas, stomach, liver, and colorectum.

A recent meta-analysis of 18 studies with 16,375,202 individuals reported that prior asthma was associated with increased risk of lung cancer,³⁸ which is consistent with our results. This is most likely because asthma and lung cancer are both associated with pathogenic airway inflammation.³⁸ However, evidence supporting a relationship of the risk of overall cancer, including lung cancer, after asthma development is controversial, in that previous studies have reported a positive association,^{7,8} no association,^{12,13} and a negative association.¹⁹ However, these previous studies had inadequate control of confounding factors,^{7,13,19} did not use rigorous definitions for asthma (ICD code claims^{7,13} vs ICD code claims with use of asthma medication), or did not consider all types of cancer.¹² Thus, previous studies reported that asthma had different associations (positive, none, or negative) with site-specific cancer risks as follows: colorectum (positive⁸ and none^{14,15}), pancreatic (positive⁸ and negative²⁰), breast (none^{8,10,16}), leukemia (positive,^{8,9} none,¹⁷ and negative^{21,22}), head and neck (none¹⁸ and negative²³), and prostate (positive^{8,10,11}). The previous studies that reported negative associations were limited by small sample sizes²³ and/or use of a case-control design.²⁰⁻²³ Our results indicated positive associations between asthma and cancers of the bladder, lung, blood, oral cavity and esophagus, sex-specific, pancreas, stomach, liver, and colorectum, but no association with cancers of the gallbladder, esophagus, brain and central nervous system, thyroid, and kidney.

The tumor mutation burden is defined as the frequency of mutations in tumor cells and varies among cancer types.³⁹ Cancers of the lung, bladder, stomach, colorectum, and pancreas have high mutational burdens, whereas cancers of the kidney, brain, and thyroid have low mutational burdens. We found that asthma development was significantly associated with cancers that have high mutational burdens (those of the lung, bladder, stomach, colorectum, and pancreas).

A possible reason for the above finding is that the same or similar inflammatory networks affect asthma and cancers with high mutational burdens.⁴⁰⁻⁴² Asthma is a chronic inflammatory disorder characterized by recurrent wheezing, chronic cough,

TABLE II. HRs for the risk of incident cancer following asthma diagnosis of subjects in the NHIS-NSC after propensity score-matching (n = 75,307)

Parameter (asthma)	n (%)	Cancer events	Person-years	Cancer incidence rate*	HR (95% CI)					
					Minimally adjusted†	P value	Additionally adjusted for potential mediators‡	P value	Fully adjusted§	P value
None	68,422 (90.9)	3,138	521,377.6	6.02	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Incident asthma	6,885 (9.1)	549	51,362.0	10.69	2.04 (1.86-2.23)	<.001	1.69 (1.53-1.89)	<.001	1.75 (1.58-1.94)	<.001
Atopic status										
None	68,422 (90.9)	3,138	521,377.6	6.02	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Atopic asthma	5,565 (7.4)	354	42,121.4	8.40	1.60 (1.44-1.79)	<.001	1.31 (1.16-1.48)	<.001	1.36 (1.20-1.53)	<.001
Nonatopic asthma	1,320 (1.8)	195	9,240.6	21.10	4.01 (3.47-5.64)	<.001	3.36 (2.88-3.90)	<.001	3.35 (2.88-3.89)	<.001
Time after asthma diagnosis (y)										
None	68,422 (90.9)	3,138	521,377.6	6.02	1.00 (reference)		1.00 (reference)		1.00 (reference)	
<3	4,408 (5.9)	321	28,179.7	11.39	2.30 (2.05-2.58)	<.001	1.82 (1.60-2.07)	<.001	1.64 (1.44-1.87)	<.001
≥3 to <5	1,280 (1.7)	115	11,847.6	9.71	1.77 (1.47-2.13)	<.001	1.57 (1.30-1.90)	<.001	1.81 (1.50-2.20)	<.001
≥5	1,197 (1.6)	113	11,334.7	9.97	1.75 (1.45-2.12)	<.001	1.57 (1.29-1.90)	<.001	2.01 (1.66-2.45)	<.001

Numbers in boldface correspond to significant differences ($P < .05$).

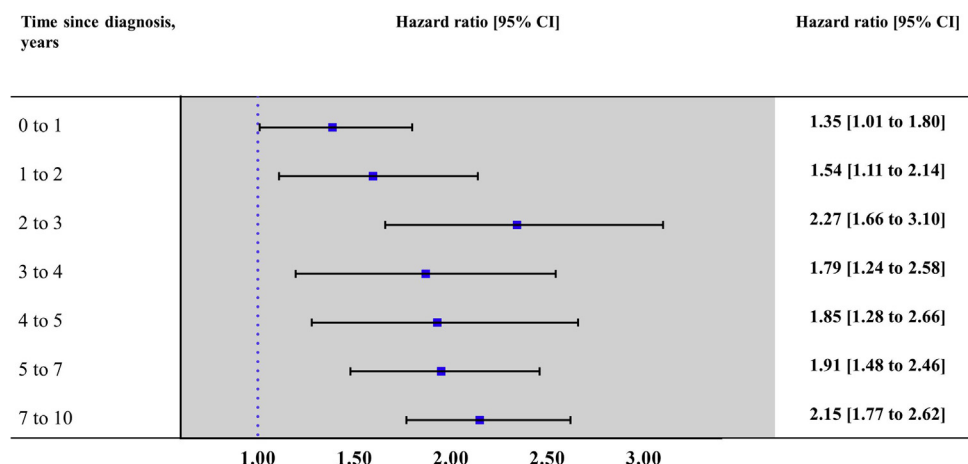
*Cancer incidence rate is expressed as per 1,000 person-years.

†Minimally adjusted: adjustment for age (20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years) and sex.

‡Additionally adjusted: adjusted for age, sex, cumulative ICS dose (none, low, and high dose), and history of COPD.

§Fully adjusted: adjustment for age, sex, cumulative ICS dose, history of COPD, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs urban), body mass index (<25, 25-30, and ≥30 kg/m²), yearly mean systolic blood pressure (continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1-2, 3-4, 5-6, and 7 sessions per week).

||Atopic asthma: asthma and at least 1 atopic disorder (allergic rhinitis or atopic dermatitis); nonatopic asthma: asthma without any atopic disorder.

**FIG 3.** Adjusted HRs for the risk of incident overall cancer at different times after asthma diagnosis in the propensity score-matched cohort (NHIS-NSC data).

dyspnea, and chest tightness.^{38,40} Positive associations have also been reported between chronic inflammation and increased risks of cancer, metastatic spread, and tumor progression.^{40,41} Chronic inflammation induces the activation of transcription factors (ie, nuclear factor- κ B, signal transducer and activator of transcription 3, and hypoxia-inducible factor 1) that lead to the formation of proinflammatory factors and the accumulation of tumorigenic factors in different anatomical microenvironments.^{40,41} In particular, activation of these transcription factors leads to upregulation of numerous molecules that support the malignant phenotype:^{40,41} proinflammatory cytokines (IL-1, IL-6, IL-23, TNF, TGF- β , epidermal growth factor, and receptor activator of nuclear factor- κ B ligand); inflammatory enzymes (prostaglandin-endoperoxidase H synthase 2 and lysyl oxidase); growth factors

(IL-6 and GM-CSF); proangiogenic factors (IL-8 and vascular endothelial growth factor); anti-apoptotic factors (B-cell lymphoma-extra large and cellular FLICE-inhibitory protein); invasion promoting factors (matrix metalloproteinases 2, 7, and 9, and urokinase-type plasminogen activator); prostaglandins; inducible nitric oxide synthase; and chemokines (C-C motif ligands 2 and 20 and IL-8). Upregulation of this cancer-related inflammatory network promotes inflammation-driven tumorigenesis.⁴⁰⁻⁴² In addition, according to the T_H2 immune skewing hypothesis, high serum IgE levels might lead to an inappropriate redirection of the T_H2 response, leading to decreased tumor eradication from T_H1.⁴³ The lack of T_H1-driven microenvironments, mediated by IFN- γ , IL-2, IL-3, GM-CSF, and TNF- α , leads to an inadequate cytotoxic effect by cytotoxic T lymphocytes and

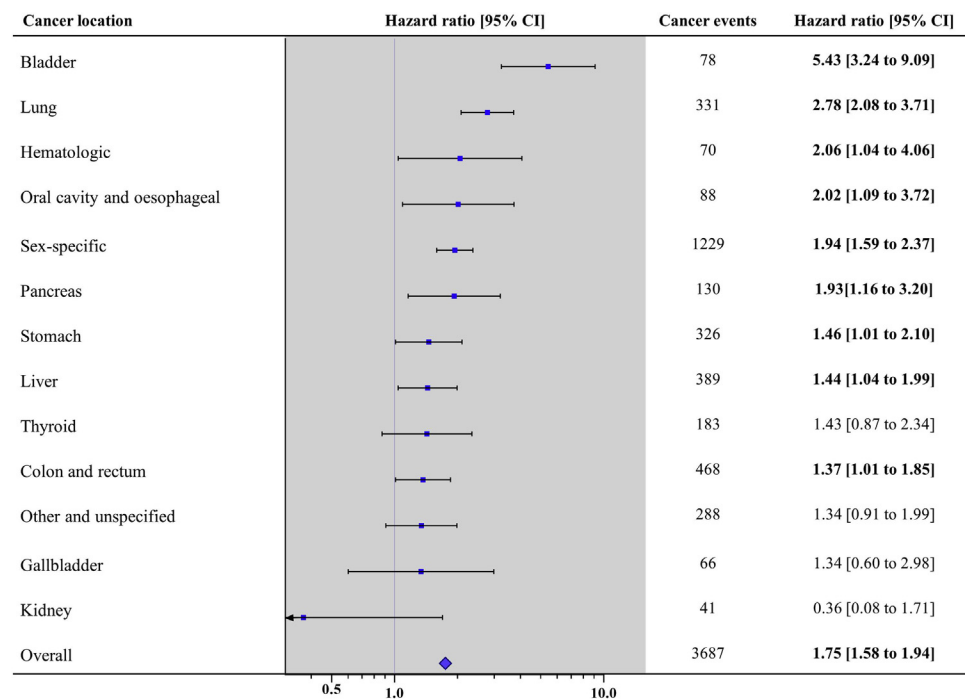


FIG 4. Adjusted HRs for the risk of incident cancer at different locations after asthma diagnosis in the propensity score-matched cohort (NHIS-NSC data).

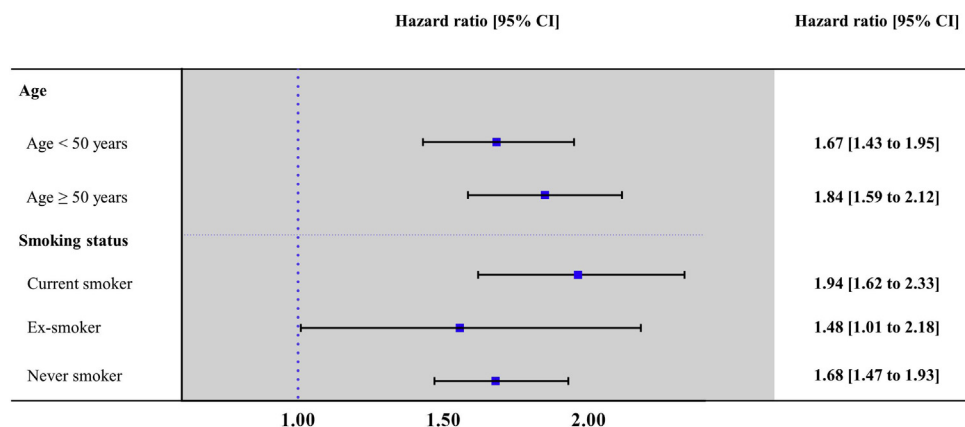


FIG 5. Adjusted HRs for the risk of incident cancer after asthma diagnosis, with stratification by subject age and smoking status, in the propensity score-matched cohort (NHIS-NSC data).

M1 macrophages, which potentially downregulates processes that promote tumor eradication.⁴³

Our findings suggested that patients with nonatopic asthma had a greater risk of overall cancer than those with atopic asthma. An allergic response mediated by IgE against carcinogenic molecules and tumor antigens can protect against malignancy transformation and subsequent oncogenesis.⁴³ Thus, past studies showed that allergic rhinitis and/or atopic dermatitis were associated with a decreased risk of cancer.⁴⁴⁻⁴⁶ However, asthma has a complex and heterogeneous pathogenesis and is characterized by a combination of allergic and nonallergic inflammation.⁴⁷ In fact, previous studies showed that several allergic diseases (asthma, atopic dermatitis, and allergic rhinitis) were

associated with a decreased risk of overall cancer.^{13,14,46} In addition, a recent study also hypothesized that nasal polyp, depending on the presence of asthma as a marker for moderate to severe eosinophilic type 2 reaction, would decrease head and neck cancer risk, but found that all types of nasal polyps increase risk of head and neck cancer, which is consistent with our results.⁴⁸

Interestingly, previous studies reported that ICS use reduced the risk of lung cancer by 21% in the general population,²⁴ by 56% in patients with asthma,²⁵ and by 30% in patients with COPD.²⁶ We also found that ICS use reduced the risk of lung cancer by 56% in patients with asthma. These results may be explained by the ICS-mediated reduction of local inflammation.²⁴⁻²⁶ Although allergic reactions⁴³ and asthma-related medications,

TABLE III. Subgroup analysis of asthma patients using the Cox proportional hazards model to determine the relationship of cumulative ICS doses with subsequent overall cancer and subsequent lung cancer in the NHIS-NSC

Covariate	Full unmatched cohort (asthma n = 6963)		Propensity score-matched cohort (asthma n = 6885)	
	All cancer	Lung cancer	All cancer	Lung cancer
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Cumulative dose of ICSs				
None	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Low	0.89 (0.65-1.22)	0.52 (0.24-1.10)	0.87 (0.63-1.19)	0.54 (0.25-1.14)
High	0.83 (0.69-1.01)	0.43 (0.28-0.64)	0.84 (0.70-1.02)	0.44 (0.29-0.67)

Risk factors were adjusted for age, sex, history of COPD, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs urban), body mass index (<25, 25-30, and ≥ 30 kg/m²), yearly mean systolic blood pressure (continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1-2, 3-4, 5-6, and 7 sessions per week).

Numbers in boldface correspond to significant differences ($P < .05$).

such as ICSs,²⁴⁻²⁶ might protect against lung cancer, asthma is a complex and heterogeneous disorder that has a mixture of features of allergic and inflammatory responses.⁴⁷ Therefore our research provides real-world evidence for a link between asthma and risk of overall cancer.

The present study had several limitations. First, our diagnoses of asthma and cancer in the NHIS-NSC data were based on insurance claims. Use of these claims data may have led to an overestimation of the incidence of asthma. To account for this, we also established a more strict asthma definition (ICD code claims^{7,13} vs ICD code claims with use of asthma-related medication), an adjustment not performed in previous studies. The claims-based definition of asthma in the NHIS-NSC led to an incidence of 1.47%, and the interview-based (physician-diagnosed) definition in the Ansan-Ansung cohort led to an incidence of 0.94%. Thus, these 2 cohorts, which used different asthma definitions, had similar incidences of asthma. With respect to cancer in Korea, the NHIS carefully reviews all diagnoses because of the potential implications for special insurance benefits. Therefore, we consider our cancer diagnoses to be reliable.²⁷

A second limitation is that we did not have information on cancer stage and severity, asthma phenotype and severity, or disease management for either cohort. In addition, the ages of participants at recruitment were 20 to 70 years (NHIS-NSC) and 40 to 69 years (Ansan-Ansung cohort). Therefore, our findings are not applicable to younger or older populations.

A third limitation is that we could not perform a meaningful analysis of the different types of cancer or time-specific risk of cancer after newly diagnosed asthma for the Ansan-Ansung cohort due to the small sample size. The reported differences in HRs for cancer risk in each cohort may be due to differences in the definitions used for asthma, recruitment ages, and the small sample size of Ansan-Ansung cohort.

Despite these limitations, to our knowledge, this is the first study to investigate the association of the risk of cancer after asthma development in a general population of adults using 2 different cohorts. We also compared the 2 different data sets that reported links between cancer and asthma, one using claims-based data and the other using interview-based data. Furthermore, to reduce survival bias, we performed several sensitivity analyses and propensity score-matching in claims-based data. The strengths of our study were the large sample sizes of the cohorts (475,197 and 5,440 subjects) and their

long follow-up times (means of 8.5 and 11.5 years). Thus, our use of 2 independent cohorts increases the generalizability and reliability of our results and provides strong evidence that development of asthma is associated an increased risk of subsequent cancer.

Conclusions

Asthma development was associated with an increased risk of subsequent cancer in 2 independent cohorts in Korea, and this relationship remained after adjustment for age and smoking status. Our analysis of different types of cancer indicated that asthma increased the risk of cancers of the bladder, lung, blood, oral cavity and esophagus, sex-specific, pancreas, stomach, liver, and colorectum. The risk of cancer development was greatest at 2 to 3 years after asthma diagnosis, and this increased risk persisted for at least 10 years. Patients with nonatopic asthma had a greater risk of overall cancer than those with atopic asthma. A high cumulative dose of ICSs among patients with asthma was associated with a decreased risk of lung cancer, but had no effect on the risk of overall cancer. Our results thus provide an improved understanding of the relationship between the pathogenesis of asthma and the pathogenesis of cancer and suggest that clinicians should be aware of the greater risk of incident cancer in patients with asthma.

Clinical implications: Our findings provide that clinicians should be aware of the higher risk of incident cancer among patients with asthma.

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Supplementary material

Method

Ansan-Ansung cohort

This is a population-based, ongoing, prospective cohort study conducted by the KCDC.¹ Each cohort in Ansan (an urban community) and Ansung (a rural community) recruited Korean men and women aged 40 to 69 years using two-stage cluster sampling. Each subject received a baseline examination (2001 to 2002) and biennial follow-up examinations that consisted of a questionnaire-based interview, a blood test, and a physical examination.

All data were from individuals who received 12 years of follow-up examinations (final examination: 2013 to 2014). Among 5906 participants, subjects were excluded if the questionnaire was incomplete ($n = 13$), if there was a previous diagnosis of asthma ($n = 220$), or if cancer was present based on the baseline examination ($n = 237$). The final sample size was 5440 participants.

Baseline data were obtained for all subjects at the first examination. The following information was obtained by self-reported questionnaires and the personal medical interview: age, sex, region of residence (Ansan [urban] or Ansung [rural]), household income, smoking habits, alcohol consumption, history of asthma, all-cause cancer, diabetes mellitus, stroke, COPD, and hypertension. The incidence of asthma was defined by affirmative answers to the following question:² "Have you ever been diagnosed with asthma by a doctor?". The incidence of all-cause cancer was defined by affirmative answers to the following question: "Have you ever been diagnosed with all-cause cancer by a doctor?". Body mass

index and blood pressure were measured by physicians. Serum glucose and total cholesterol level were obtained from fasting blood samples.

Statistical Analysis

Ansan-Ansung cohort

In the Ansan-Ansung cohort, follow-up for all participants started at the baseline examination (2001 to 2002) and ended at the 12-year follow-up examination (2013 to 2014), death, or development of cancer. The following factors were considered potential confounders: age (20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years), sex, alcohol consumption (continuous), region of residence (Ansung vs. Ansan), body mass index (<25, 25–30, ≥ 30 kg/m², and unknown), systolic blood pressure (continuous), diastolic blood pressure (continuous), fasting blood glucose (continuous), serum total cholesterol (continuous), history of diabetes mellitus, stroke, hypertension, and COPD, household income (low, middle, and high), and smoking history (never smoker, ex-smoker, and current smoker).

For each cohort, the “exposure” was development of asthma (time-varying exposure) and the “end point” was development of cancer. Data were analyzed by using Cox proportional hazards regression models and calculation of HRs and aHRs with 95% CIs. The proportional hazards assumption was determined using Schoenfeld residuals and log(-log) survival plots.

Results

NHIS-NSC full unmatched cohort

Our analysis of the NHIS-NSC full unmatched cohort indicated that 6963 (1.5%) asthma events occurred during 8.47 years of follow-up (SD, 3.91) of 475,197 Korean adults (Table I). Relative to those without asthma, subjects who developed asthma were more likely to be male, have a low household income, be current smokers, have a high cumulative dose of ICS, and have more comorbidities (diabetes and hypertension) (all SMDs > 0.1).

During the follow-up period, there were 20,674 incident cancer events in the NHIS-NSC, 556 in subjects who developed asthma, and 20,118 in those who did not develop asthma. Subjects who developed asthma had a 95% greater risk of overall cancer after full adjustment for confounding (fully adjusted HR, 1.95; 95% CI, 1.78 to 2.14), and this relationship persisted after competing risk analysis for mortality (aHR, 1.88; 95% CI, 1.73 to 2.05) (Table EV). By atopic status, subjects who developed non-atopic asthma had a greater risk of overall cancer (aHR, 3.58; 95% CI, 3.10 to 4.13), compared with those who developed atopic asthma (aHR, 1.55; 95% CI, 1.39 to 1.73).

Table EVI shows the risk for different types of incident cancers following asthma development. Asthma development was associated with a significantly increased risk of cancer of the bladder (fully adjusted HR, 5.46; 95% CI, 3.45 to 8.63), lung (aHR, 2.09; 95% CI, 1.65 to 2.65), blood (aHR, 1.84; 95% CI, 1.02 to 3.30), oral cavity and oesophageal (aHR, 1.73; 95% CI, 1.04 to 2.88), sex-specific (aHR, 3.58; 95% CI, 3.00 to 4.28), pancreas (aHR, 1.80; 95% CI, 1.11 to 2.90), stomach (aHR, 1.57; 95% CI, 1.15 to 2.14), liver (aHR, 1.47; 95% CI, 1.10 to 1.96), and colorectum (aHR, 1.39; 95% CI, 1.06 to 1.82).

We also conducted a subgroup analysis of the relationship of incident cancer and cumulative ICS dose among asthma patients (Table III). This multivariable Cox regression indicated that a high cumulative dose of ICSs was significantly associated with a decreased risk of lung cancer (fully adjusted HR, 0.43; 95% CI, 0.28 to 0.64), but had no effect on the

risk of overall cancer (aHR, 0.83; 95% CI, 0.69 to 1.01).

To reduce the probability of detection bias or reverse causation, we also determined the HRs for overall cancer according to the time after asthma diagnosis (Table EV). The results indicated the association of incident cancer with time of asthma diagnosis remained statistically significant for asthma diagnosis times within 3 years (fully adjusted HR 1.47; 95% CI, 1.31 to 1.66), 3 to 5 years (aHR, 2.72; 95% CI, 2.26 to 3.28), and more than 5 years (aHR, 4.76; 95% CI, 3.95 to 5.74). Moreover, a sensitivity analysis indicated that incident cancer remained associated with asthma development after exclusion of thyroid and stomach cancers, cancers that have high incidences in Korea. Finally, a sensitivity analysis of null hypothesis indicated that incident acute pyelonephritis did not associate with asthma development (null hypothesis; Table EIV)

Ansan-Ansung cohort

Our analysis of the Ansan-Ansung cohort indicated 51 (0.9%) asthma events occurred during 62,670 person-years of follow-up (mean follow-up, 11.52 years; standard deviation, 1.80) of 5,440 Korean adults (Table EVIII). During the follow-up period, there were 543 incident cancer events, 7 in subjects who developed asthma (cancer incidence rate, 24.65 per 1000 person years), and 536 in those who did not develop (cancer incidence rate, 8.59 per 1000 person years) (Table EIX). Thus, individuals who developed asthma had a 3.4-fold greater risk of overall cancer (fully adjusted HR, 3.40; 95% CI, 1.61 to 7.22).

Supplement references

1. Kim Y, Han B-G, Ko GESg. Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. *International journal of epidemiology* 2017; 46:e20-e.

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E Figure Legends

Figure EI. Density of propensity scores before and after matching.

Figure EII. Distributions of propensity scores before and after matching. Before matching, the mean (standard deviation) propensity scores of the non-asthma and asthma groups were 0.014 (0.007) and 0.018 (0.010), respectively. After matching, these scores were 0.018 (0.010) and 0.018 (0.010), respectively.

Figure EIII. Directed acyclic graph showing the implicitly assumed causal association between asthma (“exposure”) and risk of cancer (“outcome”) in the NHIS-NSC before and after matching. Confounders, potential mediators, and exposure-outcome associations are indicated.

Figure EIV. Disposition of study populations in the **(A)** NHIS-NSC full unmatched cohort, **(B)** NHIS-NSC matched cohort, and **(C)** Ansan-Ansung cohort.

Table E1. Demographic and clinical characteristics of individuals not used for propensity score-matching in the NHIS-NSC.

Characteristic	Full unmatched cohort (n = 475 197)		Propensity score-matched cohort (n = 75 307)	
	Individuals without	Individuals with	Individuals without	Individuals with
	incident asthma	incident asthma	incident asthma	incident asthma
Total, n (%)	468 234 (98.5)	6963 (1.5)	68 422 (90.9)	6885 (9.1)
Yearly updated mean of systolic blood pressure, mmHg, yearly updated mean (SD)	122.13 (13.01)	125.09 (13.65)	124.20 (13.54)	125.09 (13.68)
Yearly updated mean of diastolic blood pressure, mmHg, yearly updated mean (SD)	76.14 (8.37)	77.08 (8.36)	77.09 (8.43)	77.06 (8.37)
Yearly updated mean of fasting blood glucose, mg/dL, yearly updated mean (SD)	97.26 (21.75)	99.83 (22.86)	99.63 (24.70)	99.76 (22.76)
Yearly updated mean of serum total cholesterol, mg/dL, yearly updated mean (SD)	193.58 (33.13)	197.10 (34.35)	194.44 (34.12)	197.08 (34.37)

History of COPD, n (%)	2191 (0.5)	540 (7.8)	467 (0.7)	538 (7.8)
History of allergic rhinitis, n (%)	241 277 (51.5)	5607 (80.5)	37 078 (54.2)	5550 (80.6)
History of atopic dermatitis, n (%)	2191 (0.5)	540 (7.8)	1462 (2.1)	257 (3.7)
Cumulative dose of ICSs, n (%)				
None	455 265 (97.2)	4607 (66.2)	66140 (96.7)	4558 (66.2)
Low (below median)	7509 (1.6)	620 (8.9)	1275 (1.9)	613 (8.9)
High (above median)	5460 (1.2)	1736 (24.9)	1007 (1.5)	1714 (24.9)

Abbreviations here: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; NHIS-NSC, National Health Insurance

Service-National Sample Cohort; SD, standard deviation.

Table E2. Sensitivity analyses, external validation, and justification.

Sensitivity analysis (1 to 10)	Cohort	Justification
External validation (11)		
1. Risk of incident cancer at different times after asthma diagnosis (< 3, ≥3 to <5, and ≥5 years)	NHIS-NSC matched cohort	Cohort entry time can affect cancer risk. We repeated the main analysis by analysis of the time of cancer after asthma diagnosis.
2. Competing risk (competing events: all-cause mortality and incident cancer) following asthma diagnosis	NHIS-NSC matched cohort	A competing risk is all-cause mortality that hinders the observation of an incident cancer event or modifies the probability of a cancer event.
3. Risk of incident cancer following asthma diagnosis, excluding thyroid and stomach cancers	NHIS-NSC matched cohort	We repeated the analysis after exclusion of thyroid cancers and stomach cancers, which have high incidences in Korea.
4. Testing null hypotheses of the risk of incident acute pyelonephritis following asthma diagnosis	NHIS-NSC matched cohort	We considered the additional analysis using a null outcome tracer (incident acute pyelonephritis) to confirm our main results of causality.

5. Risk of incident cancer at different times after asthma diagnosis (< 3, ≥3 to < 5, and ≥ 5 years)	NHIS-NSC full unmatched cohort	Cohort entry time can affect cancer risk. We repeated the main analysis by of time of cancer after asthma diagnosis
6. Competing risk (competing events: all-cause mortality and incident cancer) following asthma diagnosis	NHIS-NSC full unmatched cohort	A competing risk is all-cause mortality that hinders the observation of an incident cancer event or modifies the probability of a cancer event.
7. Risk of incident cancer following asthma diagnosis, excluding thyroid and stomach cancers	NHIS-NSC full unmatched cohort	We repeated the analysis after exclusion of thyroid cancers and stomach cancers, which have high incidences in Korea
8. Testing null hypotheses of the risk of incident acute pyelonephritis following asthma diagnosis	NHIS-NSC full unmatched cohort	We considered the additional analysis using a null outcome tracer (incident acute pyelonephritis) to confirm our main results of causality.
9. Redefined cohort using alternative asthma definition [*]	NHIS-NSC full unmatched cohort	To investigate the sensitivity of the results to an alternative definition of asthma
10. After restricting to subjects with a history of COPD	NHIS-NSC full unmatched cohort	To exclude the effect of COPD on the risk of cancer

11. External independent cohort	Ansan-Ansung cohort	Our use of two independent cohorts (one using claims-based data and the other using interview-based data) increases the generalizability and reliability of our main results.
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Abbreviations here: COPD, chronic obstructive pulmonary disease; NHIS-NSC, National Health Insurance Service-National Sample Cohort.

* Asthma was defined using the criteria of the International Classification of Disease, 10th revision code J45-46 (at least 2 claims within 1 year and use of asthma-related medication).

Table E3. Ratio of adjusted hazard ratios* for the risk of incident overall cancer at different times after asthma diagnosis in the propensity score-matched cohort (NHIS-NSC data).

Time since diagnosis, years	Ratio	Ratio of aHR* [95% CI]
1 to 2	“1 to 2”-to-“0 to 1”	1.14 [0.74 to 1.77]
2 to 3	“2 to 3”-to-“0 to 1”	1.67 [1.09 to 2.56]
3 to 4	“3 to 4”-to-“0 to 1”	1.33 [0.83 to 2.11]
4 to 5	“4 to 5”-to-“0 to 1”	1.37 [0.86 to 2.18]
5 to 7	“5 to 7”-to-“0 to 1”	1.41 [0.96 to 2.08]
7 to 10	“7 to 10”-to-“0 to 1”	1.59 [1.12 to 2.26]

Abbreviations here: aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; NHIS-NSC, National Health Insurance Service-National Sample Cohort.

* Risk factors were adjusted for age, sex, cumulative ICS dose, history of COPD, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs. urban), body mass index (<25, 25–30, and ≥ 30 kg/m²), yearly mean systolic blood pressure

(continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1–2, 3–4, 5–6, and 7 sessions per week).

Number in bold correspond to significant differences ($P < 0.05$).

Table E4. Sensitivity analysis of the risk of incident cancer following asthma diagnosis, excluding thyroid and stomach cancers in the NHIS-NSC propensity score-matched cohort.

Cancer	All cancer		Excluding thyroid cancer		Excluding gastric cancer		Excluding thyroid and gastric cancer	
	aHR*	<i>P</i> value	aHR*	<i>P</i> value	aHR*	<i>P</i> value	aHR*	<i>P</i> value
None	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Incident Cancer	1.75 [1.58 to 1.94]	<0.001	1.77 [1.59 to 1.97]	<0.001	1.79 [1.61 to 2.00]	<0.001	1.82 [1.63 to 2.04]	<0.001

Abbreviations here: aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; NHIS-NSC, National Health Insurance Service-National Sample Cohort.

* Risk factors were adjusted for age, sex, cumulative ICS dose, history of COPD, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs. urban), body mass index (<25, 25–30, and ≥ 30 kg/m²), yearly mean systolic blood pressure (continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1–2, 3–4, 5–6, and 7 sessions per week).

Number in bold correspond to significant differences ($P < 0.05$).

Table E5. Sensitivity analysis of the risk of incident acute pyelonephritis following asthma diagnosis (null hypothesis) in the NHIS-NSC data.

Cohort	Outcome	Total	Events (%)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Full unmatched cohort	None	468 234	13612 (2.9)	1.00 (reference)	1.00 (reference)
	Incident acute pyelonephritis	6963	187 (2.7)	0.91 [0.78 to 1.05]	0.90 [0.78 to 1.04]
Matched cohort	None	68422	2263 (3.3)	1.00 (reference)	1.00 (reference)
	Incident acute pyelonephritis	6885	173 (2.5)	1.02 [0.87 to 1.19]	1.02 [0.88 to 1.20]

Abbreviations here: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICS, inhaled corticosteroid;

NHIS-NSC, National Health Insurance Service-National Sample Cohort.

* Risk factors were adjusted for age and sex.

Number in bold correspond to significant differences ($P < 0.05$).

Table E6. Main analysis and sensitivity analysis of the risk of incident cancer following asthma diagnosis of subjects in the entire NHIS-NSC unmatched cohort (n = 475 197).

				HR (95% CI)	
	Total	Event	Events (%)	Minimally adjusted*	Fully adjusted [§]
Main analysis					
None	468 234	Cancer	20 118 (4.3)	1.00 (Reference)	1.00 (Reference)
Incident asthma	6963	Cancer	556 (8.0)	2.44 [2.24 to 2.65]	1.95 [1.78 to 2.14]
Sub-analysis (atopic status [†])					
None	468 234	Cancer	20 118 (4.3)	1.00 (Reference)	1.00 (Reference)
Atopic asthma	5622	Cancer	358 (6.4)	1.93 [1.74 to 2.15]	1.55 [1.39 to 1.73]
Non-atopic asthma	1341	Cancer	198 (14.8)	4.64 [4.01 to 5.31]	3.58 [3.10 to 4.13]
Sensitivity analysis (time after asthma diagnosis)					

None	468 234	Cancer	20 118 (4.3)	1.00 (Reference)	1.00 (Reference)
< 3	4457	Cancer	325 (7.3)	2.21 [1.98 to 2.46]	1.47 [1.31 to 1.66]
≥3 to < 5	1289	Cancer	116 (9.0)	2.44 [2.03 to 2.93]	2.72 [2.26 to 3.28]
≥ 5	1217	Cancer	115 (9.4)	3.47 [2.89 to 4.17]	4.76 [3.95 to 5.74]
Competing risk analysis					
None	468 234	All-cause mortality and cancer	23,634 (5.0)	1.00 (Reference)	1.00 (Reference)
Incident asthma	6963	All-cause mortality and cancer	620 (8.9)	2.27 [2.01 to 2.46]	1.88 [1.73 to 2.05]
Sensitivity analysis (excluding thyroid cancer)					
None	466 814	Cancer	18698 (4.0)	1.00 (Reference)	1.00 (Reference)
Incident asthma	6942	Cancer	535 (7.7)	2.56 [2.35 to 2.79]	2.01 [1.83 to 2.20]
Sensitivity analysis (excluding gastric cancer)					

None	466 180	Cancer	18 064 (3.9)	1.00 (Reference)	1.00 (Reference)
Incident asthma	6917	Cancer	510 (7.4)	2.54 [2.32 to 2.77]	2.01 [1.82 to 2.21]
Sensitivity analysis (excluding thyroid and gastric cancer)					
None	464 760	Cancer	16 644 (3.6)	1.00 (Reference)	1.00 (Reference)
Incident asthma	6896	Cancer	489 (7.1)	2.69 [2.46 to 2.94]	2.07 [1.88 to 2.29]

Abbreviations here: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICS, inhaled corticosteroid; NHIS-NSC, National Health Insurance Service-National Sample Cohort.

* Minimally adjusted: adjustment for age (20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years) and sex.

§ Fully adjusted: adjustment for age, sex, cumulative ICS dose, history of COPD, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs. urban), body mass index (<25, 25–30, and ≥ 30 kg/m²), yearly mean systolic blood pressure (continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1–2, 3–4, 5–6, and 7 sessions per week).

[‡] Atopic asthma: asthma and at least 1 atopic disorder (allergic rhinitis or atopic dermatitis); non-atopic asthma: asthma without any atopic disorder.

Number in bold correspond to significant differences ($P < 0.05$).

Table E7. Adjusted hazard ratios for the risk of incident cancer at different locations after asthma diagnosis in the NHIS-NSC.

Cancer location	Full unmatched cohort (n = 475 197)		Propensity score-matched cohort (n = 75 307)	
	Cancer events	aHR [95% CI] [*]	Cancer events	aHR [95% CI] [*]
Bladder	352	5.46 [3.45 to 8.63]	78	5.43 [3.24 to 9.09]
Lung	1696	2.09 [1.65 to 2.65]	331	2.78 [2.08 to 3.71]
Hematologic	425	1.84 [1.02 to 3.30]	70	2.06 [1.04 to 4.06]
Oral cavity and esophageal	612	1.73 [1.04 to 2.88]	88	2.02 [1.09 to 3.72]
Sex-specific [§]	5730	3.58 [3.00 to 4.28]	1229	1.94 [1.59 to 2.37]
Pancreas	686	1.80 [1.11 to 2.90]	130	1.93[1.16 to 3.20]
Stomach	2100	1.57 [1.15 to 2.14]	326	1.46 [1.01 to 2.10]
Liver	2482	1.47 [1.10 to 1.96]	389	1.44 [1.04 to 1.99]
Thyroid	1441	1.23 [0.79 to 1.92]	183	1.43 [0.87 to 2.34]

Colon and rectum	2766	1.39 [1.06 to 1.82]	468	1.37 [1.01 to 1.85]
Other and unspecified	1762	1.38 [0.98 to 1.94]	288	1.34 [0.91 to 1.99]
Gallbladder	355	1.58 [0.77 to 3.22]	66	1.34 [0.60 to 2.98]
Kidney	267	0.52 [0.13 to 2.16]	41	0.36 [0.08 to 1.71]

Abbreviations here: aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; NHIS-NSC, National Health Insurance Service-National Sample Cohort.

* Risk factors were adjusted for age, sex, cumulative ICS dose, history of COPD, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs. urban), body mass index (<25, 25–30, and ≥ 30 kg/m²), yearly mean systolic blood pressure (continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1–2, 3–4, 5–6, and 7 sessions per week).

§ Sex-specific cancers are defined as breast, ovary, and prostate cancers.

Number in bold correspond to significant differences ($P < 0.05$).

Table E8. Hazard ratios for the risk of incident cancer after asthma diagnosis using alternative cohort specifications.

Cohort specification	Asthma definition	aHR [95% CI]
NHIS-NSC matched cohort (primary analysis)	Based on claims data (asthma n = 6885)*	1.75 [1.58 to 1.94]
NHIS-NSC full unmatched cohort	Based on claims data (asthma n = 6963)*	1.95 [1.78 to 2.14]
NHIS-NSC cohort A	Alternative asthma definition (asthma n = 10 154) [§]	2.25 [2.00 to 2.53]
NHIS-NSC cohort B (COPD excluded)	Based on claims data (asthma n = 6423) [‡]	1.80 [1.64 to 1.98]^{**}
Ansan-Ansung cohort	Based on personal interview	3.40 [1.61 to 7.22]^{§§}

Abbreviations here: aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; NHIS-NSC, National Health Insurance Service-National Sample Cohort.

* Asthma was defined using the criteria of the International Classification of Disease, 10th revision code J45 (asthma) and/or code J46 (status asthmaticus), with at least 3 claims by an outpatient within 1 year and/or at least 1 inpatient hospitalization claim and the use of asthma-related medications, including inhaled and systemic corticosteroids, long and short-acting β 2-agonists, and/or leukotriene antagonists

[§] Asthma was defined using the criteria of the International Classification of Disease, 10th revision code J45-46, with at least 2 claims by a patient within 1 year and the use of asthma-related medications (asthma n = 10 154).

[‡] Cohort B was restricted to subjects with a history of COPD (asthma n = 6423).

^{||} Risk factors were adjusted for age, sex, cumulative ICS dose, history of COPD, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs. urban), body mass index (<25, 25–30, and ≥ 30 kg/m²), yearly mean systolic blood pressure (continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1–2, 3–4, 5–6, and 7 sessions per week).

^{***} Risk factors were adjusted for age, sex, cumulative ICS dose, frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week), region of residence (rural vs. urban), body mass index (<25, 25–30, and ≥ 30 kg/m²), yearly mean systolic blood pressure (continuous), yearly mean diastolic blood pressure (continuous), yearly mean fasting blood glucose (continuous), yearly mean serum total cholesterol (continuous), history of diabetes mellitus, stroke, and hypertension, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1–2, 3–4, 5–6, and 7 sessions per week).

^{§§} Risk factors were adjusted for age, sex, alcohol consumption (continuous), region of residence (rural vs. urban), body mass index (<25, 25–30, ≥ 30 kg/m², and unknown), systolic blood pressure (continuous), diastolic blood pressure (continuous), fasting blood glucose (continuous), serum total cholesterol (continuous), history of diabetes mellitus, stroke, COPD, and hypertension, household income (low, middle, and high), and smoking (never smoker, ex-smoker, and current smoker).

Number in bold correspond to significant differences ($P < 0.05$).

Table E9. Demographic and clinical characteristics of subjects in the Ansan-Ansung cohort (n = 5440).

Characteristic	Entire cohort	Incident asthma	
		No	Yes
Total, n (%)	5440 (100)	5389 (99.1)	51 (0.9)
Age, years (SD)	51.06 (8.31)	51.05 (8.30)	52.12 (8.53)
Sex, male (%)	2593 (47.7)	2563 (47.6)	30 (58.8)
Region of residence, n (%)			
Rural (Ansung)	2599 (47.8)	2572 (47.7)	27 (52.9)
Urban (Ansan)	2841 (52.2)	2817 (52.3)	24 (47.1)
Body mass index, kg/m ² , n (%)			
< 25	2422 (44.5)	2404 (44.6)	18 (35.3)
25–30	1705 (31.3)	1688 (31.3)	17 (33.3)

≥ 30	206 (3.8)	204 (3.8)	2 (3.9)
Unknown	1107 (20.3)	1093 (20.3)	14 (27.5)
Systolic blood pressure, mmHg, mean (SD)	119.69 (18.26)	119.67 (18.27)	121.41 (17.57)
Diastolic blood pressure, mmHg, mean (SD)	79.57 (11.92)	79.56 (11.93)	80.04 (11.10)
Fasting blood glucose, mg/dL, mean (SD)	91.76 (21.01)	91.80 (21.09)	87.08 (7.31)
Serum total cholesterol, mg/dL, mean (SD)	198.27 (35.44)	198.31 (35.48)	193.25 (30.85)
History of diabetes mellitus, n (%)	216 (4.0)	216 (4.1)	0 (0.0)
History of stroke, n (%)	47 (0.9)	47 (0.9)	0 (0.0)
History of COPD, n (%)	26 (0.5)	26 (0.5)	0 (0.0)
History of hypertension, n (%)	745 (13.7)	733 (13.5)	12 (23.5)
Household income, n (%)			

Low	2577 (47.4)	2551 (47.3)	26 (51.0)
Middle	2396 (44.0)	2376 (44.1)	20 (39.2)
High	467 (8.6)	462 (8.6)	5 (9.8)
Smoking, n (%)			
Never smoker	3304 (60.7)	3274 (60.8)	30 (58.8)
Ex-smoker	863 (15.9)	854 (15.8)	9 (17.6)
Current smoker	1273 (23.4)	1261 (23.4)	12 (23.5)
Alcohol consumption, g/day, mean (SD)	8.99 (20.18)	9.00 (20.18)	7.86 (19.85)

Abbreviations here: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table E10. Hazard ratios for the risk of incident cancer following asthma diagnosis of subjects in the Ansan-Ansung cohort (n = 5440).

Parameter	N (%)	Cancer events	Person- years	Cancer incidence rate [*]	HR (95% CI)					
					Crude	<i>P</i> value	Model 1	<i>P</i> value	Model 2	<i>P</i> value
Ansan-Ansung cohort										
None	5389 (99.1)	536	62 386.0	8.59	1.00 (reference)		1.00 (reference) [§]		1.00 (reference) [‡]	
Incident asthma	51 (0.9)	7	284.0	24.65	3.42 [1.62 to 7.22]		3.63 [1.42 to 2.02]		3.40 [1.61 to 7.22]	<0.001

Abbreviations here: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICS, inhaled corticosteroid.

^{*} Cancer incidence rate is expressed as per 1000 person-years.

[§] Risk factors were adjusted for age (20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years) and sex.

[‡] Risk factors were adjusted for age, sex, alcohol consumption (continuous), region of residence (rural vs. urban), body mass index (<25, 25–30, ≥30 kg/m², and unknown), systolic blood pressure (continuous), diastolic blood pressure (continuous), fasting blood glucose (continuous), serum total cholesterol (continuous), history of diabetes mellitus, stroke, COPD, and hypertension, household income (low,

middle, and high), and smoking (never smoker, ex-smoker, and current smoker).

Number in bold correspond to significant differences ($P < 0.05$).