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Cancer risk and mortality in asthma patients: A Swedish national cohort study

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ABSTRACT

Background. Previous studies found an increased risk of cancer in hospitalized asthma patients, but it is not known whether patients from primary health care show a similar risk pattern. In addition, it is unclear whether the diagnosis of asthma can influence the prognosis of subsequent cancer.

Methods. Asthma patients were identified from Swedish inpatient, outpatient, and primary health care registers, and were linked to the Swedish Cancer Registry to identify subsequent diagnoses of cancer. Standardized incidence ratios (SIRs) were used to examine the risk of cancer in asthma patients compared with subjects without asthma. In addition, we used Cox proportional hazards regression to estimate hazard ratios (HRs) for mortality in patients with both asthma and cancer.

Results. A total of 10 649 cancers were diagnosed in patients with previous asthma, with a SIR of 1.19 (95% CI 1.17–1.21). A total of 15 cancer sites showed an increased incidence, whereas two cancer sites showed a decreased risk. Non-allergic asthma showed the highest risk of cancer (SIR = 1.25, 95% CI 1.18–1.32), followed by unspecified asthma (SIR = 1.22, 95% CI 1.19–1.25), status asthmaticus (SIR = 1.19, 95% CI 1.02–1.39), and allergic asthma (SIR = 1.14, 95% CI 1.06–1.22). The risk of cancer was similarly increased in asthma patients diagnosed in primary health care and those diagnosed in hospitals. Cancer patients with previous asthma had increased mortality, with a HR of 1.55 (95% CI 1.50–1.60). HRs ranged from 1.09 to 1.94 for different sites/types of cancer.

Conclusions. Patients with asthma, irrespective of whether they were treated in primary health care or hospitals, had an increased risk of cancer. In addition, cancer patients with previous asthma had a worse prognosis compared with those without asthma, suggesting that these patients may require a multidisciplinary approach to manage the comorbidity.

Asthma is a common chronic inflammatory disease of the airways, with an estimated number of 235–300 million individuals in 2011 [1–3]. Both genetic and environmental factors contribute to the development of asthma [1]. An upregulated Th2 immune response and a downregulated Th1 response are traditionally thought to drive the development of asthma [1,4,5]; however, recent evidence suggests that the innate immune system is also involved in the pathogenesis of asthma [6]. Dysregulation of immune function in asthma patients may be associated with an alternated incidence of cancer [7].

Our previous study reported an increased incidence of cancer in hospitalized asthma patients [8]. However, asthma patients treated in hospitals may represent severe cases, and the results may not apply directly to the overall population with asthma as most asthma patients can be diagnosed and treated in primary health care or hospital outpatient clinics. To address the shortcoming of this previous study, we revisited this research question and identified asthma patients from primary health care and hospital inpatient and outpatient clinics, and examined their risk of subsequent cancer. Asthma is a heterogeneous disease that includes predominantly allergic asthma, non-allergic asthma, and status asthmaticus. The different subtypes of asthma may show different patterns of cancer risk

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due to different pathophysiology. In the current study, we also examined the cancer risk after diagnosis of asthma by asthma subtype.

The impact of asthma on cancer prognosis has not been thoroughly studied. It is reasonable to assume that cancer patients with asthma will have higher mortality than cancer patients without asthma, but it is not known whether asthma affects cancer-specific mortality. We aimed to address this unanswered question in this study.

Methods

This retrospective cohort study was approved by the Ethics Committee at Lund University, Sweden. Data used in this study were retrieved from a range of nationwide databases, including the Swedish Hospital Discharge Register, the Swedish Outpatient Register, the Primary Health Care Registers in the counties of Stockholm and Skåne, the Swedish Cancer Registry, the Swedish National Population and Housing Census [9], the Cause of Death Register, and the Emigration Register. The Swedish Hospital Discharge Register contains hospital discharge records for all Swedish residents. Data were initially collected in 1964 by 26 regional health authorities, and the register includes complete nationwide data from 1987 onward. It is estimated that it contains information on 99% of all public hospitalizations. Each year, around 1.5 million records are added to the Hospital Discharge Register. A recent external review suggests that the overall accuracy of diagnoses in this register is about 85–95% [10]. The information for each hospitalization comprises dates of admission and discharge, hospital and clinic codes, and up to eight discharge diagnosis codes, the first of which defines the principal cause of hospitalization. The Swedish Outpatient Register was created in 2001 by the National Board of Health and Welfare with close to 100% coverage for public hospitals. The Primary Health Care Register in Stockholm covers 75 primary health care centers in Stockholm and the middle of Sweden for the period 1 January 2001 to 30 June 2007 and contains data on all medical diagnoses in these primary health care centers. The Primary Health Care Register in Skåne contains data on medical diagnoses from primary health care centers in Skåne, located in southern Sweden, for 1973–2010. The Swedish Cancer Registry was founded in 1958 and has close to 100% coverage at the present time. It is maintained by the National Board of Health and Welfare. In Sweden, it is compulsory for clinicians and pathologists/cytologists to report all newly diagnosed cancers to the Cancer Registry [11]. The Swedish National Population and Housing Census includes information on individual-level characteristics, such as year of birth, sex, and country of birth. The Cause of Death Register includes the date and cause of death for each individual who died between 1961 and 2010. The Emigration Register includes the dates of immigration and/or emigration. All linkages were performed using individual national identification numbers, which were replaced with serial numbers in order to preserve anonymity. A total of 35 cancer sites were covered. However, we present data for cancer sites for which least 40 patients with asthma were recorded.

All asthma patients who had visited primary health care or hospital inpatient and outpatient clinics were identified from the above medical registers. Asthma patients with diagnoses in more than one register were treated as unique individuals, and were followed from the last visit to a hospital or primary health care clinic. We used International Classification of Diseases (ICD) codes to identify patients with asthma between 1987 and 2010. The following ICD codes were used: ICD-9: 493 (1987–1996); and ICD-10: J45-J46 (1997–2010). We further used ICD-9 code 493A and ICD-10 code J450 to identify predominantly allergic asthma, ICD-9 code 493B and ICD-10 code J451 to identify non-allergic asthma, ICD-9 code 493X and ICD-10 code J459 to identify unspecified asthma, and ICD-10 code J46 to identify status asthmaticus. Asthma patients with ICD codes not listed above were not included in the analyses of subtype-specific risk, which means that the total for the four subtypes of asthma is lower than the total number of asthma patients. We excluded asthma patients with two or more different subtypes (22% of all asthma patients), which means that only asthma patients with one subtype were included in this study. All patients diagnosed with cancer before the diagnosis of asthma were excluded from the study. We further linked the included asthma patients to the Swedish Cancer Registry to identify all incident cases of cancer during the study period. Asthma patients identified in multiple registers were excluded when we calculated cancer risk for the different registers (Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1001497).

For patients with asthma, we calculated person-years at risk of cancer from the date of diagnosis of asthma to the date of the first primary cancer diagnosis, death, emigration, or the end of the study period (31 December 2010), whichever was earliest. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed (O) and expected (E) number of cancer cases using the indirect standardization method, which were used in many of our

previous studies [12,13]. The following formula was used:

$$SIR = \frac{\sum_{j=1}^{\mathcal{J}} o_j}{\sum_{j=1}^{\mathcal{J}} n_j \lambda_j^*} = \frac{O}{E^*},$$

$O = \sum o_j$ denotes the total number of observed cases in the study group; E^* (expected number of cases) is calculated by applying stratum-specific standard incidence rates (λ^*_j) obtained from the reference group (all individuals without asthma) to the stratum-specific person-years at risk (n_j) in the study group; O_j represents the observed number of cases that cohort subjects contribute to the jth stratum; and $\mathcal{J}$ represents the strata defined by the cross-classification of the following adjustment variables: age (5-year groups), sex, time period (5-year groups), socioeconomic status, and geographic region of residence. 95% confidence intervals (CIs) were calculated assuming a Poisson distribution.

To examine the prognosis in asthma patients with cancer, Cox's proportional hazards regression models were used to estimate hazard ratios (HRs) for cause-specific mortality. HRs indicate the relative risk of dying in the defined group (asthma patients) compared to the reference group (subjects not diagnosed with asthma). HRs were adjusted for age at cancer diagnosis, sex, time period, socioeconomic status, and region of residence. In this study, death as a result of a specific cancer (recorded as the underlying cause of death) was the primary end point; deaths due to other causes were censored. The proportional hazards assumption was tested using Schoenfeld residuals [14]. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

In Table I, we present the basic characteristics of asthma patients identified from primary health care, inpatient and outpatient clinics during the study period (1987–2010). A total of 439 455 patients were diagnosed with asthma. The median age at diagnosis of asthma was 49 for inpatients, 13 for outpatients, and 31 for primary health care patients. Asthma patients from hospital inpatient clinics had the longest follow-up time, with a median of 11 years.

The basic characteristics of patients with different asthma subtypes are shown in Table II. Asthma unspecified was the most common type, with 172 728 patients. Median age at diagnosis was highest for status asthmaticus and lowest for non-allergic asthma (56 vs. 6 years). Patients with allergic asthma had the longest follow-up time, with a median of six years.

In Table III we present the risk of cancer in asthma patients identified from all the medical sources. In total, we found 10 649 patients diagnosed with cancer, with an SIR of 1.19 (95% CI 1.17–1.21). A total of 15 cancer sites showed an increased SIR, including leukemia and cancers of the esophagus, stomach, colorectum, liver, pancreas, lung, prostate, testis, kidney, bladder, skin (squamous cell carcinoma), nervous system, and thyroid gland. The risk of melanoma and endometrial cancer was significantly decreased. Unspecified asthma was the largest group, and accounted for 60% of the observed cases. Non-allergic asthma showed the highest risk of cancer (SIR = 1.25, 95% CI 1.18–1.32), followed by unspecified asthma (SIR = 1.22, 95% CI 1.19–1.25), status asthmaticus (SIR = 1.19, 95% CI 1.02–1.39), and allergic asthma (SIR = 1.14, 95% CI 1.06–1.22).

Table I. Basic characteristics of patients with asthma by source of diagnosis.

Characteristics	Hospital Discharge Register only N (%)	Outpatient Register only N (%)	Primary Health Care Registers only N (%)	More than one register N (%)	All N (%)
Number of cases	80 956	18 2771	84 763	90 965	439 455
Gender					
Male	40 378 (49.9)	97 612 (53.4)	36 832 (43.5)	47 998 (52.8)	222 820 (50.7)
Female	40 578 (50.1)	85 159 (46.6)	47 931 (56.6)	42 967 (47.2)	216 635 (49.3)
Age at asthma diagnosis, years					
Median	49	13	31	15	17
Interquartile range	2–74	4–35	13–56	5–42	4–52
Follow-up time, years					
Median	11	3	5	3	4
Interquartile range	3–17	0–6	3–8	0–5	1–7
Time period					
1987–1996	56 618 (69.9)	0	10 370 (12.2)	1783 (2.0)	68 771 (15.7)
1997–2010	24 338 (30.1)	182 771 (100.0)	74 393 (87.8)	89 182 (98.0)	370 684 (84.3)
Geographical region					
Large cities	34 644 (42.8)	83 748 (45.8)	76 309 (90.0)	66 769 (73.4)	261 470 (59.5)
Southern Sweden	28 114 (34.7)	58 892 (32.2)	3057 (3.6)	14 435 (15.9)	104 498 (23.8)
Northern Sweden	18 198 (22.5)	40 131 (22.0)	5397 (6.4)	9761 (10.7)	73 487 (16.7)

Table II. Basic characteristics of patients with asthma by subtype.

Characteristics	Predominantly allergic asthma N (%)	Non-allergic asthma N (%)	Unspecified asthma N (%)	Status asthmaticus N (%)
Number of cases	48 731	48 372	169 138	2809
Gender				
Male	25 945 (53.2)	25 864 (53.5)	85 559 (50.6)	1076 (38.3)
Female	22 786 (46.8)	22 508 (46.5)	83 579 (49.4)	1733 (61.7)
Age at asthma diagnosis, years				
Median	18	6	19	55
Interquartile range	10–36	2–38	3–62	34–72
Follow-up time, years				
Median	5	4	5	4
Interquartile range	2–9	2–7	2–9	2–7
Time period				
1987–1996	7305 (15.0)	4585 (9.5)	49 460 (29.2)	0
1997–2010	41 426 (85.0)	43 787 (90.5)	119 678 (70.8)	2809
Geographical region				
Large cities	26 961 (55.3)	24 233 (50.1)	92 439 (54.7)	1632 (58.1)
Southern Sweden	11 537 (23.7)	12 363 (25.6)	49 571 (29.3)	655 (23.3)
Northern Sweden	10 233 (21.0)	11 776 (24.3)	27 128 (16.0)	522 (18.6)

The risk of subsequent cancer in patients with asthma diagnoses in the Hospital Discharge Register, Primary Health Care Register, and Outpatient Register is presented in Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1001497. A total of 5245 patients had cancer diagnoses in the Hospital Discharge Register, giving a SIR of 1.23 (95% CI 1.20–1.27). Only non-allergic asthma and unspecified asthma showed an increased risk of cancer; the cancer risk for allergic asthma and status asthmaticus was not significant because of limited numbers of cases (data not shown). For specific sites/types of cancer, a total of 11 cancer sites showed an increased SIR, whereas the risk of melanoma was significantly decreased.

A total of 4497 patients were diagnosed with cancer in primary health care and hospital outpatient clinics, giving an SIR of 1.13 (95% CI 1.09–1.16). Allergic asthma, non-allergic asthma, and unspecified asthma showed an increased risk of cancer; the cancer risk for status asthmaticus was not significant because of the limited number of cases (data for allergic asthma and status asthmaticus not shown). For specific sites/types of cancer, risks of non-Hodgkin lymphoma and cancers of the esophagus, stomach, colon, lung, prostate, thyroid gland, and skin (squamous cell carcinoma) were found to be significantly increased, whereas melanoma and cancers of the endometrium, ovary, and connective tissue showed a decreased incidence.

In Table IV, we present the HRs for patients diagnosed with both asthma and cancer compared to patients with cancer only. Only cancer sites/types with more than 10 deaths are listed. For all types of asthma, the HR was 1.55 (95% CI 1.50–1.60). Mortality was highest for status asthmaticus (HR = 2.41, 95% CI 1.89–3.07). For specific sites/types of cancer, 16 cancer sites showed increased mortality, and the mortality patterns were consistent among different types of asthma, although some of them were not significant because of limited numbers of cases.

Discussion

In this retrospective cohort study, we identified all asthma patients who had visited primary health care, inpatient and outpatient clinics, and examined their subsequent risk of cancer. The main finding in this study is that the risk of cancer was significantly increased in asthma patients irrespective of whether they were treated in hospitals or primary health care. In addition, we found that asthma could affect the prognosis of subsequent cancer, with increased cancer mortality.

This study was consistent with our previous study, which showed an increased risk of cancer in asthma patients who were treated in the hospitals [8]. A 36% excess incidence of cancer was observed in previous studies, which was somewhat higher than we found here (SIR = 1.19). One possible reason for this discrepancy is that the study period in the current study (1987–2010) is somewhat shorter than that in the previous report (1965–2004). In addition, our previous study [8] found that asthma patients who visited hospitals before the 1970s had a higher risk of subsequent cancer compared to asthma patients diagnosed during later periods. This suggests that different diagnostic criteria and treatment strategies for asthma may affect the risk of cancer, which

Table III. SIRs for different cancers after diagnosis of asthma (inpatients, outpatients, and primary health care after 1987).

Cancer site/type	Predominantly allergic asthma			Non-allergic asthma			Unspecified asthma			Status asthmaticus			Total		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	8	0.66	0.28–1.32	13	0.77	0.41–1.31	117	1.19	0.99–1.43	3	1.56	0.29–4.60	187	1.11	0.96–1.28
Esophagus	5	1.18	0.37–2.78	7	0.92	0.37–1.91	81	**1.81**	1.44–2.25	0			125	**1.69**	1.40–2.01
Stomach	14	1.36	0.74–2.28	30	1.36	0.92–1.94	191	**1.40**	1.20–1.61	0			291	**1.37**	1.22–1.54
Small intestine	0			3	0.75	0.14–2.23	31	1.35	0.92–1.92	0			48	1.22	0.90–1.62
Colon	33	0.88	0.61–1.24	101	**1.42**	1.16–1.73	558	**1.29**	1.19–1.40	9	1.08	0.49–2.06	923	**1.30**	1.22–1.39
Rectum	27	1.33	0.87–1.93	46	1.24	0.91–1.65	232	1.05	0.92–1.19	6	1.43	0.51–3.13	409	**1.13**	1.02–1.24
Liver	10	0.99	0.47–1.82	33	**1.57**	1.08–2.21	163	**1.30**	1.10–1.51	2	0.95	0.09–3.50	258	**1.29**	1.14–1.46
Pancreas	10	0.96	0.46–1.77	25	1.23	0.80–1.82	163	**1.37**	1.17–1.60	5	2.39	0.75–5.63	260	**1.35**	1.19–1.52
Lung	50	1.31	0.98–1.73	123	**1.86**	1.55–2.22	794	**2.11**	1.96–2.26	20	**2.56**	1.56–3.96	1266	**1.97**	1.87–2.09
Breast	118	1.09	0.91–1.31	121	0.91	0.75–1.09	723	1.00	0.93–1.08	16	0.97	0.55–1.58	1342	1.01	0.95–1.06
Cervix	12	1.01	0.52–1.77	12	1.36	0.70–2.38	56	1.12	0.85–1.46	2	1.73	0.16–6.37	105	1.07	0.88–1.30
Endometrium	18	1.08	0.64–1.71	19	0.65	0.39–1.01	130	**0.78**	0.65–0.93	4	1.11	0.29–2.87	212	**0.74**	0.65–0.85
Ovary	10	0.74	0.35–1.37	15	0.82	0.46–1.36	98	0.97	0.78–1.18	2	0.97	0.09–3.57	159	0.89	0.76–1.04
Prostate	96	1.09	0.89–1.34	188	**1.19**	1.02–1.37	1036	**1.14**	1.07–1.21	18	1.00	0.59–1.59	1698	**1.13**	1.08–1.19
Testis	22	**1.70**	1.06–2.58	3	1.05	0.20–3.11	22	1.07	0.67–1.63	0			68	**1.36**	1.06–1.72
Kidney	11	0.89	0.44–1.59	34	**1.60**	1.11–2.24	161	**1.37**	1.17–1.60	2	0.96	0.09–3.54	262	**1.35**	1.19–1.52
Urinary bladder	21	0.95	0.59–1.45	51	1.20	0.90–1.58	323	**1.27**	1.13–1.42	10	2.07	0.99–3.82	521	**1.26**	1.15–1.37
Melanoma	27	0.74	0.48–1.07	27	0.81	0.53–1.18	151	**0.81**	0.69–0.95	0			276	**0.78**	0.70–0.88
Skin, squamous cell	30	1.32	0.89–1.89	48	0.98	0.72–1.30	357	1.11	0.99–1.23	8	1.24	0.53–2.45	617	**1.18**	1.09–1.28
Nervous system	36	1.20	0.84–1.67	41	**1.43**	1.03–1.94	186	**1.30**	1.12–1.50	1	0.41	0.00–2.35	332	**1.24**	1.11–1.38
Thyroid gland	14	1.71	0.93–2.88	5	0.85	0.27–2.00	44	1.32	0.96–1.77	0			90	**1.37**	1.10–1.69
Endocrine glands	10	0.89	0.42–1.64	19	1.45	0.87–2.27	76	1.04	0.82–1.30	1	0.74	0.00–4.24	147	1.15	0.97–1.35
Connective tissue	1	0.18	0.00–1.01	4	0.64	0.17–1.64	32	0.93	0.63–1.31	2	3.40	0.32–12.49	53	0.87	0.65–1.14
Non-Hodgkin lymphoma	33	**1.54**	1.06–2.17	43	**1.39**	1.01–1.88	175	0.98	0.84–1.14	4	1.19	0.31–3.06	316	1.04	0.93–1.16
Hodgkin's disease	8	1.05	0.45–2.08	7	2.04	0.81–4.23	21	0.99	0.61–1.51	0			47	1.09	0.80–1.45
Myeloma	10	1.56	0.75–2.89	16	1.34	0.76–2.18	64	0.90	0.69–1.15	2	1.52	0.14–5.57	133	1.14	0.96–1.36
Leukemia	21	0.94	0.58–1.44	45	**1.38**	1.01–1.85	199	**1.16**	1.01–1.34	5	1.70	0.54–4.01	348	**1.17**	1.05–1.30
All cancers	674	**1.09**	1.01–1.18	1102	**1.21**	1.14–1.28	6282	**1.20**	1.17–1.23	123	1.18	0.98–1.41	10649	**1.19**	1.17–1.21

Bold type indicates that the 95% CI does not include 1.00.
CI, confidence interval; O, observed cases; SIR, standardized incidence ratio.
Person–years for predominantly allergic asthma, non–allergic asthma, unspecified asthma, status asthmaticus, and total asthma were 376 347, 282 958, 1 313 656, 14 864, and 2 595 841, respectively.

may partly explain the difference between the two studies together with the decreased prevalence of smoking. For specific sites/types of cancer, the risk pattern was basically the same compared to the previous study. For instance, the highest risk was for lung cancer (SIR = 1.97), followed by esophageal cancer (SIR = 1.69), which is in accordance with the results in the previous study. Smoking is a risk factor for both lung cancer and asthma. The observed positive association between asthma and lung cancer can at least in part be explained by residual confounding due to smoking and/or early symptoms/inverse causality [15]. Gastro-esophageal reflux caused by β-adrenergic medication may partly explain the increased risk of esophageal cancer [16]. Moreover, immunosuppressive treatment, such as systemic glucocorticoid treatment in patients with asthma, is associated with cellular and humoral immunosuppression, which may result in an increased risk of cancer development.

We have previously reported that the risk of cancer was highest during the first year of follow-up after the diagnosis of asthma [8], suggesting that lead time bias could explain part to the increase for some site-/type-specific cancers. In addition, reverse causality may be possible as patients with lung cancer may present with asthma-like symptoms and may initially be diagnosed with asthma. However, the increased mortality due to lung cancer in patients with asthma (Table IV) suggests that reverse mortality may play a minor role, because lung cancer patients had a similar prognosis irrespective of the presenting symptoms.

Table IV. HRs for different cancers diagnosed after asthma (inpatients, outpatients, and primary health care after 1987).

Cancer site/type	Predominantly allergic asthma			Non-allergic asthma			Unspecified asthma			Status asthmaticus			Total		
	D	HR	95% CI	D	HR	95% CI	D	HR	95% CI	D	HR	95% CI	D	HR	95% CI
Upper aerodigestive tract	1	1.02	0.14 – 7.25	0			36	**2.08**	1.50 – 2.88	0			43	**1.66**	1.23 – 2.24
Esophagus	4	1.37	0.51 – 3.64	5	1.70	0.71 – 4.08	57	1.26	0.97 – 1.64				81	1.19	0.96 – 1.48
Stomach	9	**3.23**	1.68 – 6.22	23	**2.62**	1.74 – 3.95	114	**1.62**	1.35 – 1.95				178	**1.88**	1.62 – 2.18
Colon	9	1.15	0.60 – 2.21	41	**1.55**	1.14 – 2.10	203	**1.28**	1.12 – 1.47	4	2.16	0.79 – 5.64	318	**1.32**	1.18 – 1.47
Rectum	5	0.78	0.32 – 1.88	11	1.27	0.70 – 2.29	49	1.00	0.75 – 1.32	1	0.94	0.13 – 6.65	84	0.99	0.80 – 1.23
Liver	6	1.48	0.67 – 3.30	20	1.12	0.72 – 1.74	105	**1.24**	1.02 – 1.50	1	0.74	0.10 – 5.26	166	**1.28**	1.10 – 1.50
Pancreas	8	1.42	0.71 – 2.84	21	1.16	0.75 – 1.78	142	**1.51**	1.28 – 1.78	3	0.79	0.26 – 2.46	221	**1.45**	1.27 – 1.65
Lung	32	0.93	0.66 – 1.32	89	1.15	0.93 – 1.41	555	1.09	1.00 – 1.18	15	**3.42**	2.06 – 5.68	870	**1.09**	1.02 – 1.17
Breast	7	0.85	0.40 – 1.78	16	1.33	0.81 – 2.17	109	**1.62**	1.34 – 1.96	6	**9.56**	4.30 – 21.24	169	**1.64**	1.41 – 1.91
Cervix	1	1.00	0.14 – 7.13	3	3.02	0.98 – 9.38	11	0.83	0.46 – 1.50	0			23	1.33	0.88 – 2.01
Endometrium	1	1.86	0.26 – 13.24	0			17	**1.72**	1.07 – 2.78	0			22	**1.63**	1.07 – 2.48
Ovary	3	1.47	0.48 – 4.57	7	1.14	0.54 – 2.38	51	**1.51**	1.14 – 1.98	1	4.83	0.68 – 34.31	75	**1.47**	1.17 – 1.85
Prostate	8	0.87	0.43 – 1.73	30	0.78	0.54 – 1.11	187	1.06	0.92 – 1.23	1	0.78	0.11 – 5.52	266	1.01	0.90 – 1.14
Kidney	4	1.96	0.73 – 5.22	8	1.30	0.65 – 2.60	62	**1.51**	1.18 – 1.94	1	4.54	0.64 – 31.97	91	**1.58**	1.29 – 1.94
Urinary bladder	3	1.21	0.39 – 3.74	17	**1.67**	1.04 – 2.69	82	**1.31**	1.06 – 1.63	2	1.16	0.29 – 4.62	125	**1.35**	1.13 – 1.61
Melanoma	3	2.16	0.70 – 6.69	2	0.84	0.21 – 3.36	16	1.18	0.72 – 1.93				27	1.32	0.91 – 1.93
Nervous system	7	0.80	0.36 – 1.79	8	0.92	0.46 – 1.83	57	**1.50**	1.16 – 1.95	0			85	**1.29**	1.04 – 1.60
Thyroid gland	0			1	4.09	0.57 – 29.08	5	0.82	0.34 – 1.97				14	1.66	0.98 – 2.82
Connective tissue	0			1	1.40	0.20 – 9.98	11	**2.87**	1.58 – 5.19	0			13	**1.94**	1.12 – 3.36
Non-Hodgkin lymphoma	5	0.72	0.30 – 1.72	14	1.11	0.66 – 1.87	63	**1.43**	1.11 – 1.83	4	**4.48**	1.69 – 11.88	106	**1.43**	1.18 – 1.74
Myeloma	3	0.58	0.19 – 1.79	7	1.30	0.62 – 2.72	32	**1.94**	1.37 – 2.74	0			61	**1.51**	1.18 – 1.95
Leukemia	4	0.77	0.29 – 2.06	11	1.10	0.61 – 1.98	55	1.21	0.93 – 1.58	4	**8.39**	3.16 – 22.29	100	**1.39**	1.14 – 1.70
All cancers	148	**1.22**	1.04 – 1.43	391	**1.47**	1.33 – 1.63	2335	**1.54**	1.48 – 1.60	46	**2.39**	1.79 – 3.19	3607	**1.55**	1.50 – 1.60

Bold type indicates that the 95% CI does not include 1.00.
CI, confidence interval; D, deaths; HR, hazard ratio.

As the number of asthma patients was higher in this study than in the previous one, we could examine cancer risk by type of asthma. It is unfortunate that most patients were diagnosed with unspecified asthma, which accounted for 60% of the observed cases. However, the risk of cancer was also increased for other types of asthma, although some cancer sites did not show a significant increase because of the limited number of cases. It should be noted that the cancer risk for some types of asthma was very high, such as the risk of lung cancer in patients with unspecified asthma (SIR = 2.18).

Another interesting finding in this study is that cancer patients with a previous diagnosis of asthma had a worse prognosis compared to cancer patients without asthma. In total we found that 16 cancer sites showed increased mortality, and the risk of death ranged from 1.09 to 1.94. A few underlying mechanisms could explain the observed findings. The first is that cancer patients with previous asthma may be more vulnerable, both physically and psychologically, compared to cancer patients without asthma. They may receive less aggressive therapy, or the treatment process may be interrupted due to serious complications, leading to increased mortality and decreased life expectancy. We unfortunately lack information about treatment in our database. The second is that asthma patients have a high risk of developing other comorbid conditions, including rhinitis, nasal polyposis, gastro-esophageal reflux disease, vocal cord dysfunction, bronchiectasis, and some autoimmune diseases [17–19]. It is known that increased comorbidity may be a disadvantage for cancer survival [20,21]. TNF is a major therapeutic target in a range of chronic inflammatory disorders, including asthma [22,23]. Genetic polymorphism of TNF receptor-associated factor 1 (TRAF1) is involved in the onset and/or perpetuation of the inflammatory process [22,23], and is also involved in the regulation of anti-apoptotic pathways [24,25], which may be related to the increased mortality in cancer patients with asthma compared to those without asthma. Thus, it is important to utilize multidisciplinary treatment options in patients with both cancer and asthma to improve survival. A similar approach has been introduced in patients with diabetes and cancer to improve their prognosis [26].

An important strength of this study is that we used both national wide (Hospital Inpatient Register and Outpatient Registers) and regional medical

records (Primary Health care Register in Stockholm and Skåne). This allowed us to identify a large majority of all patients in Sweden diagnosed with asthma during the study period, and the number of patients included in this study is large enough to guarantee reliable risk estimates. In addition, all the data were retrieved from Swedish registers with high quality. The retrospective study design and the completeness of the follow-up of patients offer additional strength of the current study.

One limitation of this study is the lack of information on medication and treatment and other individual related factors, such as smoking. It is known that smoking is a risk factor for asthma and it may affect the incidence of subsequent cancer and be related to cancer prognosis [27]. In addition, some of the findings may be due to chance because of multiple comparisons. Such bias could be avoided by adjusting the CIs to the number of comparisons, but there is no agreement on how the adjustment should be made. However, only two negative associations were found in this study, suggesting that most of the positive associations could be true findings.

In summary, patients with asthma, irrespective of whether they are treated in primary health care or hospitals, had an increased risk of cancer. We found that a total of 15 cancer sites showed an increased incidence. In addition, cancer patients with previous hospitalization for asthma had a worse prognosis compared with patients without asthma, suggesting that cancer patients with asthma may require a multidisciplinary approach to manage the comorbidity.

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Supplementary material available online

Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1001497.