

Cancer risk in patients with allergic rhinitis, asthma and atopic dermatitis: a nationwide cohort study in Taiwan

Chian-Yaw Hwang^{1,2}, Yi-Ju Chen^{1,3}, Ming-Wei Lin⁴, Tzeng-Ji Chen⁵, Szu-Ying Chu^{1,2}, Chih-Chiang Chen^{1,2}, Ding-Dar Lee^{1,2}, Yun-Ting Chang^{1,2}, Wen-Jen Wang^{1,2} and Han-Nan Liu^{1,2,6}

¹ Department of Dermatology, Taipei Veterans General Hospital, Taipei, Taiwan

² Department of Dermatology, National Yang-Ming University, Taipei, Taiwan

³ Department of Dermatology, Taichung Veterans General Hospital, Taichung, Taiwan

⁴ Institute of Public Health, National Yang-Ming University, Taipei, Taiwan

⁵ Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

⁶ Department of Dermatology, National Defense Medical Center, Taipei, Taiwan

It has long been a debate that whether atopy is a risk factor or protective factor for cancer. However, no large-scale study of different cancers in patients with atopic diseases has been conducted among Asians. Here, we conducted a nationwide study to evaluate the cancer risk in patients with allergic rhinitis (AR), asthma and atopic dermatitis (AD). Drawing on Taiwan's National Health Insurance Research Database, 225,315 patients with AR, 107,601 patients with asthma and 34,263 patients with AD without prior cancers were identified in the period from 1996 to 2008. The standard incidence ratio (SIR) of each cancer was calculated. Although the overall cancer risks in patients with atopic symptoms were not increased, the risks were slightly elevated in female patients with AR or asthma (SIR: 1.13 and 1.08, AR and asthma, respectively) and slightly decreased in males patients with AR. Those aged 20–39 years-old possessed the highest risk. A higher risk of developing brain cancer was found in patients with atopic diseases, and patient with AR or asthma also had an elevated risk of developing cancer of kidney and urinary bladder. In contrast, the risk of nonmelanoma skin cancer was lower in patients with AR and asthma. Compared to patients with only one atopic disease, those with more than one atopic disease had lower cancer risks. Our data suggests that the association between atopy and cancer is site-specific.

Atopy affects a great number of patients nowadays, and the prevalence has been rising in recent decades.^{1–3} Atopy is regarded as an abnormal hyperreactive state of the immune system.^{4–6} Allergic rhinitis (AR) and asthma represent the respiratory tract symptoms of atopy. Atopic dermatitis (AD),

on the other hand, is the cutaneous manifestation of atopy, which presents as a chronic, relapsing and pruritic dermatitis.^{3,4,7,8} The close association between AR, asthma and AD is well documented.^{7–9}

As the immune system affects oncogenesis greatly,^{9–16} it raises interest to study how the dysregulated immune system in atopic diseases influences cancer development. One hypothesis is that the hyperactivated immune system could suppress cancer cells. Conversely, the chronic inflammation is also considered a predisposing factor for cancers.^{14,16} Many studies focused on the association between atopy and cancer have been carried out and yielded conflicting results.^{4–6,11–22} Inconsistencies among studies may be explained by the fact that many of the studies involve self-reported allergic conditions and symptoms, small sample sizes, and hospital-based recruitment.¹⁷ A recent study in United Kingdom has reported that patients with AD have an increased incidence of cancer overall as well as of specific cancer subtypes, including lymphoma, melanoma and nonmelanoma skin cancer (NMSC).¹⁸

With the increasing prevalence of atopy, the long-term health consequence of these patients is becoming more and more important. The epidemiologic data on association between atopic diseases and cancer provides useful information for primary prevention and etiology research. Although previous literature has discussed the risk of cancers in patients with atopic diseases, the study subjects were mostly

Key words: allergic rhinitis, asthma, atopic dermatitis, cancer risk, Taiwan

Abbreviation: AD: atopic dermatitis; AR: allergic rhinitis; CI: confidence interval; ICD-9-CM: International Classification of Disease, Revision 9, Clinical Modification; NMSC: nonmelanoma skin cancer; NHI: National Health Insurance; NHIRD: National Health Insurance Research Database; OR: odds ratio; SIR: standard incidence ratio

Grant sponsor: Taipei Veterans General Hospital; **Grant number:** V99C1-090, V100D-002-3; **Grant sponsor:** National Science Council, Executive Yuan, Taiwan; **Grant number:** NSC 97-2314-B-010-031

DOI: 10.1002/ijc.26105

History: Received 30 Nov 2010; Accepted 16 Mar 2011; Online 31 Mar 2011

Correspondence to: Yun-Ting Chang, MD, PhD, Department of Dermatology, Taipei Veterans General Hospital and National Yang Ming University, No. 201, Sec. 2, Shih-Pai Rd., Taipei 112, Taiwan, Tel: +886-2-2875-7340, Fax: +886-2-2875-7666, E-mail: ytchang@vghtpe.gov.tw

Table 1. Demographic data of the patients with allergic rhinitis, asthma, and atopic dermatitis enrolled in our study

	Case number	Age (mean $\pm$ SD)	Follow-up time (years)	Cancer case number	Age of cancer diagnosis (mean $\pm$ SD)	Prevalence ¹ (%)
Allergic rhinitis						
Total	225,315	30.76 $\pm$ 20.88	5.27	3,191	61.24 $\pm$ 16.75	22.58
Male	111,490	29.78 $\pm$ 21.76	5.34	1,731	65.08 $\pm$ 16.11	21.74
Female	113,825	31.72 $\pm$ 19.92	5.19	1,460	56.69 $\pm$ 16.35	23.47
Asthma						
Total	107,601	35.17 $\pm$ 26.35	6.10	2,888	67.32 $\pm$ 14.51	10.78
Male	54,650	33.62 $\pm$ 27.23	6.17	1,685	69.41 $\pm$ 13.42	10.66
Female	52,951	36.77 $\pm$ 25.32	6.04	1,203	64.39 $\pm$ 15.45	10.92
Atopic dermatitis						
Total	34,263	23.94 $\pm$ 20.36	5.27	319	59.64 $\pm$ 18.98	3.43
Male	15,514	22.48 $\pm$ 21.42	5.45	181	63.57 $\pm$ 18.53	3.03
Female	18,749	25.15 $\pm$ 19.35	5.12	138	54.50 $\pm$ 18.34	3.87
Allergic rhinitis with atopic dermatitis						
Total	16,015	19.37 $\pm$ 18.37	4.36	77	59.05 $\pm$ 22.10	1.61
Male	7,816	17.03 $\pm$ 18.38	4.59	42	63.95 $\pm$ 21.04	1.52
Female	8,199	21.60 $\pm$ 18.09	4.15	35	53.18 $\pm$ 21.90	1.69
Allergic rhinitis with asthma						
Total	29,720	20.30 $\pm$ 25.07	6.15	456	68.62 $\pm$ 14.84	5.74
Male	27,567	29.63 $\pm$ 23.89	5.93	347	60.88 $\pm$ 16.18	5.80
Female	57,287	27.38 $\pm$ 24.61	6.04	803	65.28 $\pm$ 15.90	5.68
Asthma with atopic dermatitis						
Total	9,027	16.74 $\pm$ 20.18	5.04	50	61.34 $\pm$ 22.18	0.90
Male	4,817	14.92 $\pm$ 19.77	5.22	34	62.32 $\pm$ 21.57	0.94
Female	4,210	18.83 $\pm$ 20.45	4.84	16	59.26 $\pm$ 23.29	0.87
Allergic rhinitis with both asthma and atopic dermatitis						
Total	7,134	12.45 $\pm$ 16.57	6.07	23	54.91 $\pm$ 26.63	0.72
Male	3,906	10.85 $\pm$ 15.65	6.18	15	57.12 $\pm$ 25.39	0.76
Female	3,228	14.39 $\pm$ 17.43	5.95	8	50.78 $\pm$ 28.36	0.67

Abbreviations: SD: standard deviation.

¹Overall prevalence from 1996 to 2008.

drawn from Caucasian population.^{1,4-6,11-21} To the best of our knowledge, no large-scale study of different malignancies in patients with atopic diseases of Asian origin has been reported. In our study, we conducted a nationwide study to evaluate the cancer risk in Chinese patients with AR, asthma and AD.

Material and Methods

Data source

The Taiwan National Health Insurance Research Database (NHIRD) is a claims database maintained by the Department of Health and the National Health Research Institutes of Taiwan. The National Health Insurance (NHI) program was launched in Taiwan on March 1, 1995. It covered 96.16% of the total population in 2000,²³ and by the end of 2008, 22.9

million of Taiwan's 23.0 million people had been enrolled in the program. In 1999, under the NHIRD project, the NHI Bureau began to release to the public all claims data in electronic format. The NHIRD is one of the largest insurance databases in the world, and its data has been used in many epidemiologic studies.²⁴⁻²⁶

The database provides scrambled patient identification number, birth date, gender, diagnostic codes in the format of the International Classification of Disease, Revision 9, Clinical Modification (ICD-9-CM), medications and date of visit to medical institutes. In our study, a total of 1,000,000 persons (about 5% of Taiwan's population) were randomly selected from the Taiwan NHIRD. All the enrollees were followed up from 1996 to 2008.

NHI beneficiaries who suffer from certain major diseases can apply for a catastrophic illness certificate, which grants

Table 2. The standardized incidence ratio of cancer in patients with allergic rhinitis, stratified by gender

Cancer	Total		Male		Female	
	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)
Brain	41/26.87	1.53 (1.09–2.07)	23/15.20	1.51 (0.96–2.27)	18/11.72	1.54 (0.91–2.43)
Breast	384/319.08	1.20 (1.09–1.33)	5/1.49	3.36 (1.08–7.83)	379/313.09	1.21 (1.09–1.34)
Colon	254/249.11	1.02 (0.90–1.15)	139/149.16	0.93 (0.78–1.10)	115/100.64	1.14 (0.94–1.37)
Esophagus	48/70.34	0.68 (0.50–0.90)	43/65.41	0.66 (0.48–0.89)	5/5.78	0.86 (0.28–2.02)
Hematological malignancy	196/159.47	1.23 (1.06–1.41)	104/95.95	1.08 (0.89–1.31)	92/63.97	1.44 (1.16–1.76)
Hypopharynx	18/29.00	0.62 (0.37–0.98)	18/28.66	0.63 (0.37–0.99)	0/0.74	0
Kidney	87/32.98	2.64 (2.11–3.25)	52/22.00	2.36 (1.76–3.10)	35/11.13	3.14 (2.19–4.37)
Lung	399/380.19	1.05 (0.95–1.16)	255/264.37	0.96 (0.85–1.09)	144/117.90	1.22 (1.03–1.44)
Nasal cavity	17/6.21	2.74 (1.59–4.38)	13/4.56	2.85 (1.52–4.88)	4/1.69	2.36 (0.64–6.04)
Nasopharynx	81/61.84	1.31 (1.04–1.63)	52/44.70	1.16 (0.87–1.53)	29/17.53	1.65 (1.11–2.38)
Pleura	1/2.33	0.43 (0.01–2.39)	0/1.97	0	1/0.38	2.61 (0.03–14.53)
Rectum	141/172.09	0.82 (0.69–0.97)	85/112.00	0.76 (0.61–0.94)	56/60.82	0.92 (0.70–1.20)
Retroperitoneum	8/7.00	1.14 (0.49–2.25)	0/4.43	0	8/2.59	3.08 (1.33–6.08)
Skin, melanoma	7/7.84	0.89 (0.36–1.84)	4/4.52	0.88 (0.24–2.26)	3/3.33	0.90 (0.18–2.63)
Skin, NMSC	36/89.66	0.40 (0.28–0.56)	18/52.71	0.34 (0.20–0.54)	18/37.17	0.48 (0.29–0.77)
Small intestine	5/12.73	0.39 (0.13–0.92)	3/8.17	0.37 (0.07–1.07)	2/4.61	0.43 (0.05–1.57)
Thyroid gland	119/81.21	1.47 (1.21–1.75)	24/17.11	1.40 (0.90–2.09)	95/63.43	1.50 (1.21–1.83)
Tongue	41/57.46	0.71 (0.51–0.97)	32/50.06	0.64 (0.44–0.90)	9/8.00	1.12 (0.51–2.13)
Urinary bladder	105/85.21	1.23 (1.01–1.49)	77/64.04	1.20 (0.95–1.50)	28/21.77	1.29 (0.85–1.86)
Others ²	1,204/1161.34	1.04 (0.98–1.10)	784/780.84	1.00 (0.93–1.08)	420/386.11	1.09 (0.99–1.20)
All	3,191/3134.05	1.02 (0.98–1.05)	1,731/1851.74	0.93 (0.89–0.98)	1,460/1290.19	1.13 (1.07–1.19)

Abbreviations: CI: confidence interval; E: expected case number; NMSC: nonmelanoma skin cancer; O: observed case number; SIR: standardized incidence ratio.

¹Expected cancer cases were based on estimates of general population in Taiwan in 2007, after age and gender adjustment. ²Malignancies of biliary system, bone, uterine cervix, connective tissue, endocrine glands, eye, gum, larynx, lip, liver, mouth floor, nervous system other than brain, oropharynx, ovary, pancreas, prostate, salivary glands, stomach, testis, thymus, uterus, and ill-defined sites. Numbers in bold type denote statistically significant standardized incidence ratio.

Table 3. The standardized incidence ratio of cancer in patients with allergic rhinitis, asthma, and atopic dermatitis, stratified by gender and age

Age (years)	Total		Male		Female	
	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)
Allergic rhinitis						
0–19	81/62.60	1.29 (1.03–1.61)	42/37.09	1.13 (0.82–1.53)	39/25.56	1.53 (1.08–2.09)
20–39	387/246.69	1.57 (1.42–1.73)	122/94.71	1.29 (1.07–1.54)	265/152.22	1.74 (1.54–1.96)
≥40	2,723/2475.72	1.10 (1.06–1.14)	1,567/1490.73	1.05 (1.00–1.10)	1,156/986.89	1.17 (1.10–1.24)
All	3,191/3134.05	1.02 (0.98–1.05)	1,731/1851.74	0.93 (0.89–0.98)	1,460/1290.19	1.13 (1.07–1.19)
Asthma						
0–19	41/36.85	1.11 (0.80–1.51)	22/22.74	0.97 (0.61–1.46)	19/14.14	1.34 (0.81–2.10)
20–39	147/80.91	1.82 (1.53–2.14)	54/31.06	1.74 (1.31–2.27)	93/49.87	1.86 (1.51–2.28)
≥40	2,700/2401.87	1.12 (1.08–1.17)	1,609/1446.91	1.11 (1.06–1.17)	1,091/943.24	1.16 (1.09–1.23)
All	2,888/2870.96	1.01 (0.97–1.04)	1,685/1760.26	0.96 (0.91–1.00)	1,203/1116.67	1.08 (1.02–1.14)
Atopic dermatitis						
0–19	12/13.44	0.89 (0.46–1.56)	8/7.50	1.07 (0.46–2.10)	4/5.95	0.67 (0.18–1.72)
20–39	44/28.29	1.56 (1.13–2.09)	12/8.50	1.41 (0.73–2.47)	32/19.75	1.62 (1.11–2.29)
≥40	263/231.30	1.14 (1.00–1.28)	161/133.18	1.21 (1.03–1.41)	102/98.01	1.04 (0.85–1.26)
All	319/327.60	0.97 (0.87–1.09)	181/185.38	0.98 (0.84–1.13)	138/144.15	0.96 (0.80–1.13)

Abbreviations: CI: confidence interval; E: expected case number; O: observed case number; SIR: standardized incidence ratio.

¹Expected cancer cases were based on estimates of general population in Taiwan in 2007, after age and gender adjustment. Numbers in bold type denote statistically significant standardized incidence ratio.

Table 4. The standardized incidence ratio of cancer in patients with asthma, stratified by gender

Cancer	Total		Male		Female	
	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)
Brain	38/19.44	1.95 (1.38–2.68)	21/11.34	1.85 (1.15–2.83)	17/8.14	2.09 (1.22–3.35)
Breast	214/218.60	0.98 (0.85–1.12)	0/1.50	0	214/214.80	1.00 (0.87–1.14)
Colon	255/255.74	1.00 (0.88–1.13)	127/152.99	0.83 (0.69–0.99)	128/103.21	1.24 (1.03–1.47)
Esophagus	46/60.30	0.76 (0.56–1.02)	42/54.39	0.77 (0.56–1.04)	4/6.39	0.63 (0.17–1.60)
Hematological malignancy	140/134.04	1.04 (0.88–1.23)	75/82.97	0.90 (0.71–1.13)	65/51.36	1.27 (0.98–1.61)
Hypopharynx	19/22.80	0.83 (0.50–1.30)	17/22.42	0.76 (0.44–1.21)	2/0.60	3.33 (0.37–12.03)
Kidney	79/29.73	2.66 (2.10–3.31)	39/19.86	1.96 (1.40–2.68)	40/9.97	4.01 (2.87–5.46)
Lung	575/403.89	1.42 (1.31–1.54)	392/282.82	1.39 (1.25–1.53)	183/122.64	1.49 (1.28–1.72)
Nasal cavity	3/5.38	0.56 (0.11–1.63)	2/4.04	0.50 (0.06–1.79)	1/1.37	0.73 (0.01–4.05)
Nasopharynx	35/39.74	0.88 (0.61–1.22)	26/28.52	0.91 (0.60–1.34)	9/11.39	0.79 (0.36–1.50)
Pleura	5/2.29	2.19 (0.70–5.11)	2/1.95	1.02 (0.12–3.70)	3/0.35	8.56 (1.72–25.00)
Rectum	150/173.80	0.86 (0.73–1.01)	91/111.73	0.81 (0.66–1.00)	59/62.53	0.94 (0.72–1.22)
Retroperitoneum	9/5.48	1.64 (0.75–3.12)	3/3.58	0.84 (0.17–2.45)	6/1.92	3.12 (1.14–6.79)
Skin, melanoma	10/7.57	1.32 (0.63–2.43)	5/4.42	1.13 (0.36–2.64)	5/3.16	1.58 (0.51–3.70)
Skin, NMSC	37/94.98	0.39 (0.27–0.54)	20/54.09	0.37 (0.23–0.57)	17/41.00	0.41 (0.24–0.66)
Small intestine	7/12.23	0.57 (0.23–1.18)	5/7.92	0.63 (0.20–1.47)	2/4.34	0.46 (0.05–1.66)
Thyroid gland	55/47.61	1.16 (0.87–1.50)	10/10.76	0.93 (0.44–1.71)	45/36.56	1.23 (0.90–1.65)
Tongue	32/38.68	0.83 (0.57–1.17)	24/32.64	0.74 (0.47–1.09)	8/6.31	1.27 (0.55–2.50)
Urinary bladder	111/90.13	1.23 (1.01–1.48)	79/67.10	1.18 (0.93–1.47)	32/23.46	1.36 (0.93–1.93)
Others ²	1,071/1085.68	0.99 (0.93–1.05)	707/741.15	0.95 (0.88–1.03)	364/348.35	1.04 (0.94–1.16)
All	2,888/2870.96	1.01 (0.97–1.04)	1,685/1760.26	0.96 (0.91–1.00)	1,203/1116.67	1.08 (1.02–1.14)

Abbreviations: CI: confidence interval; E: expected case number; NMSC: nonmelanoma skin cancer; O: observed case number; SIR: standardized incidence ratio.

¹Expected cancer cases were based on estimates of general population in Taiwan in 2007, after age and gender adjustment. ²Malignancies of biliary system, bone, uterine cervix, connective tissue, endocrine glands, eye, gum, larynx, lip, liver, mouth floor, nervous system other than brain, oropharynx, ovary, pancreas, prostate, salivary glands, stomach, testis, thymus, uterus, and ill-defined sites. Numbers in bold type denote statistically significant standardized incidence ratio.

exemption from copayment. All the cancers included in our study were listed in the catastrophic illness category. To be issued, a catastrophic illness certificate for a cancer, histological or cytological evidence of such disease is required. The claims of beneficiaries with a catastrophic illness certificate were gathered and distributed as a package.

As the data set used in our study consisted of de-identified secondary data released to the public for research purposes, our study was exempt from the requirement of institutional review board approval.

Patient selection

In the present study, to be designated as having a certain disease, the patient had to have a corresponding ICD-9-CM code in the diagnosis field, and the diagnosis had to be made by a specialist on the disease. The ICD-9-CM codes used for AR in our study were 477.0, 477.1, 477.2, 477.8 and 477.9; the related specialists were internists, allergists, pediatricians, family physicians and otolaryngologists. The ICD-9-CM code used for asthma in our study was 493; the related specialists were internists, pediatricians, chest medicine internists and family

physicians. The ICD-9-CM codes used for AD in our study were 691 and 691.8; the related specialists were dermatologists, pediatricians and allergists. Those who had already been diagnosed with cancers before enrollment were excluded.

All enrolled study subjects were followed until the diagnosis of first cancer, death, loss to follow-up in the database or the end of 2008. For those having more than one atopic disease, the enrollment began on the day when the second or third diagnosis was made. Subjects followed-up less than one month were excluded.

Cancer risk analysis

Cases of malignancies were identified in the same catastrophic illness database using the ICD-9-CM code of 140 to 208.91. Metastatic cancers (ICD-9-CM 196–199) and malignant neoplasm of ill-defined sites (ICD-9-CM 195) were excluded because the goal of our study was to evaluate the risk of primary cancers.

Stratified analyses according to age at diagnosis and gender were conducted. The standardized incidence ratios (SIRs) of the cancers were calculated.

Table 5. The standardized incidence ratio of cancer risk in patients with atopic dermatitis, stratified by gender

Cancer	Total		Male		Female	
	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)	O/E ¹	SIR (95% CI)
Brain	9/3.57	2.52 (1.15–4.79)	5/1.76	2.83 (0.91–6.61)	4/1.81	2.21 (0.60–5.67)
Breast	42/36.11	1.16 (0.84–1.57)	0/0.15	0	42/34.96	1.20 (0.87–1.62)
Colon	26/25.24	1.03 (0.67–1.51)	19/14.70	1.29 (0.78–2.02)	7/10.71	0.65 (0.26–1.35)
Esophagus	4/6.81	0.59 (0.16–1.50)	4/6.38	0.63 (0.17–1.60)	0/0.62	0
Hematological malignancy	21/19.56	1.07 (0.66–1.64)	11/11.19	0.98 (0.49–1.76)	10/8.50	1.18 (0.56–2.16)
Hypopharynx	3/2.77	1.08 (0.22–3.16)	3/2.78	1.08 (0.22–3.15)	0/0.08	0
Kidney	8/3.49	2.30 (0.99–4.52)	5/2.26	2.21 (0.71–5.16)	3/1.26	2.38 (0.48–6.94)
Lung	29/37.96	0.76 (0.51–1.10)	22/26.07	0.84 (0.53–1.28)	7/12.39	0.56 (0.23–1.16)
Nasal cavity	0/0.64	0	0/0.46	0	0/0.19	0
Nasopharynx	7/6.34	1.10 (0.44–2.27)	6/4.40	1.36 (0.50–2.97)	1/2.03	0.49 (0.01–2.74)
Pleura	1/0.22	4.46 (0.06–24.79)	1/0.19	5.27 (0.07–29.34)	0/0.04	0
Rectum	15/17.22	0.87 (0.49–1.44)	7/10.93	0.64 (0.26–1.32)	8/6.46	1.24 (0.53–2.44)
Retroperitoneum	1/0.98	1.02 (0.01–5.65)	1/0.64	1.56 (0.02–8.69)	0/0.35	0
Skin, melanoma	2/0.85	2.35 (0.26–8.47)	1/0.49	2.04 (0.03–11.37)	1/0.37	2.71 (0.04–15.11)
Skin, NMSC	7/9.36	0.75 (0.30–1.54)	5/5.29	0.94 (0.30–2.21)	2/4.12	0.49 (0.05–1.75)
Small intestine	0/1.28	0	0/0.80	0	0/0.50	0
Thyroid gland	10/9.86	1.01 (0.49–1.87)	1/1.71	0.58 (0.01–3.25)	9/7.97	1.13 (0.52–2.14)
Tongue	3/5.65	0.53 (0.11–1.55)	3/4.87	0.62 (0.12–1.80)	0/0.91	0
Urinary bladder	13/8.50	1.53 (0.81–2.62)	10/6.36	1.57 (0.75–2.89)	3/2.28	1.31 (0.26–3.84)
Others ²	128/113.75	1.13 (0.94–1.34)	77/62.58	1.23 (0.97–1.54)	51/50.87	1.00 (0.75–1.32)
All	319/327.60	0.97 (0.87–1.09)	181/185.38	0.98 (0.84–1.13)	138/144.15	0.96 (0.80–1.13)

Abbreviations: CI: confidence interval; E: expected case number; NMSC: nonmelanoma skin cancer; O: observed case number; SIR: standardized incidence ratio.

¹Expected cancer cases were based on estimates of general population in Taiwan in 2007, after age and gender adjustment. ²Malignancies of biliary system, bone, uterine cervix, connective tissue, endocrine glands, eye, gum, larynx, lip, liver, mouth floor, nervous system other than brain, oropharynx, ovary, pancreas, prostate, salivary glands, stomach, testis, thymus, uterus, and ill-defined sites. Numbers in bold type denote statistically significant standardized incidence ratio.

Statistical analysis

We examined the associations between atopic diseases (AR, asthma and AD) and cancer with SIR. SIR was calculated as the number of observed cancer cases arising among the atopic diseases cohort divided by the expected case number of cancer according to national age-specific, gender-specific and period-specific cancer rates. The 95% confidence interval (CI) of SIR was calculated using Byar's approximation. The expected cancer rates were obtained from the yearly reports of cancer rates from the Taiwan Cancer Registry.

Microsoft Office Excel 2003 (Microsoft, Redmond, Washington, DC.) was used to perform the statistical analysis.

Results

After excluding persons with dubitable basic data, such as conflicting gender or uncertain birthday, we short listed 512,722 male and 485,007 female subjects from the dataset. These subjects included 225,315 cases with AR, 107,601 cases with asthma, and 34,263 cases with AD who met our inclusion criteria from the ambulatory claims dataset. The detailed

demographic data and the prevalences of the atopic diseases are shown in Table 1.

Cancer risk in patients with AR

The SIRs of cancers in patients with AR are listed in Table 2. The overall cancer risk in patients with AR was not significantly different from that in the general population (SIR: 1.02, 95% CI: 0.98–1.05). When stratified by gender, the cancer risk was decreased in male patients (SIR: 0.93, 95% CI: 0.89–0.98) but increased in female patients (SIR: 1.13, 95% CI: 1.07–1.19). We also stratified the cases by age and found that the cancer risk was highest in those aged 20–39 years (SIR: 1.57, 95% CI: 1.42–1.73; Table 3).

In all patients with AR, eight cancers [brain cancer (SIR: 1.53), breast cancer (SIR: 1.20), hematological malignancy (SIR: 1.23), kidney cancer (SIR: 2.64), cancer of nasal cavities (SIR: 2.74), nasopharyngeal cancer (SIR: 1.31), thyroid cancer (SIR: 1.47) and bladder cancer (SIR: 1.23)] were found to have elevated risk. Among these, the risk of cancer of nasal cavities (SIR: 2.85) was significantly increased in male patients only,

Table 6. The standardized incidence ratio of cancer in patients with more than one atopic disease, stratified by gender

	O/E ¹	SIR (95% CI)
Allergic rhinitis with asthma		
Total	803/1022.05	0.79 (0.73–0.84)
Male	456/624.55	0.73 (0.66–0.80)
Female	347/400.59	0.87 (0.78–0.96)
Allergic rhinitis with atopic dermatitis		
Total	77/90.14	0.85 (0.67–1.07)
Male	42/51.13	0.82 (0.59–1.11)
Female	35/39.47	0.89 (0.62–1.23)
Asthma with atopic dermatitis		
Total	50/68.08	0.73 (0.55–0.97)
Male	34/42.24	0.80 (0.56–1.12)
Female	16/26.18	0.61 (0.35–0.99)
Allergic rhinitis with both asthma and atopic dermatitis		
Total	23/39.02	0.59 (0.37–0.88)
Male	15/23.08	0.65 (0.36–1.07)
Female	8/15.98	0.50 (0.22–0.99)

Abbreviations: CI: confidence interval; E: expected case number; O: observed case number; SIR: standardized incidence ratio.

¹Expected cancer cases were based on estimates of general population in Taiwan in 2007, after age and gender adjustment. Numbers in bold type denote statistically significant standardized incidence ratio.

whereas the risk of hematological malignancies (SIR: 1.44), nasopharyngeal cancer (SIR: 1.65) and thyroid cancer (SIR: 1.50) were significantly increased in female patients only. We also noted that the risks of brain cancer and bladder cancer were not significantly increased when stratified by gender. The risk of retroperitoneal cancer (SIR: 3.08) and lung cancer (SIR: 1.22) was elevated in females but not in the whole group.

The risks of esophageal cancer (SIR: 0.68), hypopharyngeal cancer (SIR: 0.62), rectal cancer (SIR: 0.82), NMSC (SIR: 0.40), small intestine cancer (SIR: 0.39) and tongue cancer (SIR: 0.71) were decreased in the overall patient population, but only the risk of NMSC was significantly decreased in both the genders.

Cancer risk in patients with asthma

The SIRs of cancers in patients with asthma are listed in Table 4. The overall cancer risk in patients with asthma was not significantly different from that in the general population. However, the overall cancer risk in female patients with asthma was higher than that in the general population (SIR: 1.08, 95% CI: 1.02–1.14). The risk of cancers in all patients was highest among those aged 20–39 years old (SIR: 1.82; Table 3).

In all patients with asthma, four cancers [brain cancer (SIR: 1.95), kidney cancer (SIR: 2.66), lung cancer (SIR: 1.42) and bladder cancer (SIR: 1.23)] were found to have elevated risk. The increased risk of bladder cancer did not reach statistical significance when stratified by gender.

The risk of NMSC (SIR: 0.39, 95% CI: 0.27–0.54) was decreased in patients with asthma. This was applied to both the genders.

Cancer risk in patients with AD

The SIRs of cancers in patients with AD are listed in Table 5. The overall cancer risk in patients with AD was not significantly different from that in the general population (SIR: 0.97, 95% CI: 0.87–1.09). When stratified by age, the risk was highest among those aged 20–39 years old (SIR: 1.56, 95% CI: 1.13–2.09; Table 3).

In all patients with AD, only brain cancer (SIR: 2.52, 95% CI: 1.15–4.79) was found to have increased risk, but the difference was not statistically significant when stratified by gender.

Cancer risk in patients with two or more atopic diseases

Compared to patients with only one atopic disease, those with more than one atopic disease had lower cancer risks. In AR patients with asthma and/or AD, the SIRs of cancers were lower than those with AR alone (SIR: 0.79 in patients with both AR and asthma; SIR: 0.59 in patients with AD, AR and asthma; Table 6). In patients with both asthma and AD, the SIR of cancers was lower than that in patients with asthma or AD alone (SIR: 0.73).

Discussion

Whether atopy is a risk factor or protective factor for cancer has long been debated.^{4–6,11–22} Many previous reports have shown varying results, which are thought to result from different study designs or definitions of atopy.^{4,5} Most of the studies were based on questionnaires or clinical diagnosis,⁵ and these could cause methodological bias.²¹ With the help of the nationwide claims database used in our study, we were able to acquire a large sample size while minimizing recall and selection bias.

A great effort has been made to assess the cancer risk in patients with AR, however, most of the studies yielded conflicting results.^{6,13,14,16,17,22} Koh *et al.* reported an increased risk of lung cancer in Singapore Chinese, and the risk was more significant in women.²² In our study, female patients with AR also had an increased lung cancer risk (SIR: 1.22), and this was not found in male patients with AR. In contrast, the risk of lung cancer was decreased in a study focused on Caucasians.⁶ This might indicate that genetic/epigenetic differences between these two ethnic groups may influence the pathogenesis of lung cancer.

Previous studies almost invariably indicated a higher lung cancer risk in patients with asthma,^{6,13,14,17} and this was in agreement with our findings. Chronic inflammation was postulated as one of the possible reasons. This could also explain the elevated risk of nasal cavity cancers in patients with AR. The risk of prostate cancer was found to be increased in some studies,^{6,13,14} but we did not have such result.

The comorbid cancer profile of AR and asthma showed certain overlap in our study. Owing to the similar pathophysiology of these two diseases, it was not surprising. Even

though AR and asthma are atopy presenting in respiratory tract,⁹ the risks of skin cancer were also decreased (SIR of NMSC: 0.40 and 0.39 in patients with AR and asthma, respectively). This supported that atopy is not a disease of a single organ, but more of a systemic response. Individuals with allergy, including AR and/or asthma, are usually at lower risk of glioma but not of other types of brain cancer.¹⁷ Contrariwise, the risk of brain cancer in patients with AR and asthma were both elevated in our study population. Because histological information was not mandatorily recorded in the database, only one of them was clearly recorded as having glioma. In our study, patients with AR and asthma also shared a raised risk of kidney and bladder cancer. Previous study has shown an increased risk of bladder cancer in patients with asthma.¹⁹ However, increased risk of kidney cancer in patients with atopic diseases has not been reported before.^{4-6,13,14,16-21} One of the most frequently used medications in managing these atopic diseases is glucocorticoid.²⁷⁻²⁸ Although several cancers including bladder cancer were associated with systemic glucocorticoid exposure, kidney cancer was not among them.²⁸⁻³⁰ Further study is needed to elucidate the association between atopy and renal malignancies. Other malignancies associated with AR or asthma include leukemia, non-Hodgkin's lymphoma, breast cancer, colorectal cancer, prostate cancer and melanoma.^{13,14,17} But many of the results are inconsistent between different studies.

Although previous studies have shown an inverse association between eczema and brain tumors,⁴ the overall risk of brain cancer was increased in our study. Among these nine patients with brain tumors, one had malignant meningioma, one had anaplastic astrocytoma, two had cerebellar brain cancer and five were recorded as having brain cancer without mentioning specific histological types. A recent study in United Kingdom using the Health Improvement Network database has reported that patients with AD have an increased incidence of NMSC.¹⁸ On the other hand, Ming et al. demonstrated an inverse association of developing NMSC in patients with AD.³¹ In our study, the risk of NMSC was decreased (SIR: 0.75), but it did not reach statistical significance. Many other cancers have also been reported with either increased or decreased risk in patients with AD, these included hematologic malignancy,^{5,14,18,21} melanoma,¹⁸ pancreatic cancer,^{5,11} ovarian cancer,¹⁴ esophageal cancer^{11,14} and prostate cancer.⁶ However, we did not find such association in Taiwanese patients with AD.

Atopy is regarded as a hyperreactive state of the immune system. The activated immune system increases the surveillance of malignant cells, leading to a protective effect against cancer development.^{5,14} Eosinophil and IgE, which play an important role in atopy, also exhibit cytotoxicity toward cancer cells and tumor suppressing ability.³²⁻³³ On the other hand, chronic inflammation also causes the affected organs to be more prone to cancer.^{5,14} If we look into these three atopic diseases (AR, asthma and AD) individually, the cancer risks were not lower than those in the general population. In patients with more than one atopic diseases, the protective effect became more prominent. Similar finding was found in several previous studies.^{15,34} The results suggest that more atopic comorbid diseases might elicit stronger immune surveillance ability and lead to better protection against cancer.

There are some limitations of our study. First, laboratory data, disease severity and environmental exposure were not documented in the database, so we were unable to analyze and control for factors such as serum IgE concentration, result of skin pricking test, smoking and alcohol consumption. The lacking of histological information also made cancer subtyping impossible. Second, the case numbers of some cancers were small, and some of the SIRs were of borderline significance. The interpretation of these SIRs should be made with caution. Third, the follow-up time was not very long in our study. Some cancers may require longer latency to develop.^{11,35} Also, given that there are diverse definitions of atopic disease, misclassification may exist.

In conclusion, we find the association between atopy and cancer to be rather complex. Although the overall cancer risks were not increased in patients with atopic diseases, they were slightly elevated in female patients with AR and asthma. The patients with atopic diseases aged 20-39 years old possess the highest risk of cancer compared to other age groups. The association between atopy and cancer is site-specific. Patients with more than one atopic disease tend to possess lower cancer risks.

Acknowledgements

Our study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes (Registered number: 98074). The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

References

- Carrozzi L, Viegi G. Allergy and cancer: a biological and epidemiological rebus. *Allergy* 2005;60:1095-97.
- Gergen PJ, Turkeltaub PC, Sempos CT. Is allergen skin test reactivity a predictor of mortality? Findings from a national cohort. *Clin Exp Allergy* 2000;30:1717-23.
- Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003;361:151-60.
- Wang H, Diepgen TL. Atopic dermatitis and cancer risk. *Br J Dermatol* 2006;154:205-10.
- Lindelof B, Granath F, Tengvall-Linder M, Ekblom A. Allergy and cancer. *Allergy* 2005;60:1116-20.
- Wang H, Rothenbacher D, Low M, Stegmaier C, Brenner H, Diepgen TL. Atopic diseases, immunoglobulin E and risk of cancer of the prostate, breast, lung and colorectum. *Int J Cancer* 2006;119:695-701.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483-94.
- Bieber T. Atopic dermatitis. *Ann Dermatol* 2010;22:125-37.
- Cookson W. The immunogenetics of asthma and eczema: a new focus on the

- epithelium. *Nat Rev Immunol* 2004;4: 978–88.
10. Pardoll D. Does the immune system see tumors as foreign or self? *Annu Rev Immunol* 2003;21:807–39.
 11. Hagstromer L, Ye W, Nyren O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. *Arch Dermatol* 2005;141: 1123–7.
 12. Bosetti C, Talamini R, Franceschi S, Negri E, Giacosa A, La Vecchia C. Allergy and the risk of selected digestive and laryngeal neoplasms. *Eur J Cancer Prev* 2004;13: 173–6.
 13. Talbot-Smith A, Fritschi L, Divitini ML, Mallon DF, Knuiman MW. Allergy, atopy, and cancer: a prospective study of the 1981 Busselton cohort. *Am J Epidemiol* 2003; 157:606–12.
 14. Turner MC, Chen Y, Krewski D, Ghadirian P. An overview of the association between allergy and cancer. *Int J Cancer* 2006;118:3124–32.
 15. Vajdic CM, Falster MO, de Sanjose S, Martinez-Maza O, Becker N, Bracci PM, Melbye M, Smedby KE, Engels EA, Turner J, Vineis P, Costantini AS, et al. Atopic disease and risk of non-Hodgkin lymphoma: an InterLymph pooled analysis. *Cancer Res* 2009;69:6482–9.
 16. Vojtechova P, Martin RM. The association of atopic diseases with breast, prostate, and colorectal cancers: a meta-analysis. *Cancer Causes Control* 2009;20:1091–105.
 17. Merrill RM, Isakson RT, Beck RE. The association between allergies and cancer: what is currently known? *Ann Allergy Asthma Immunol* 2007;99:102–16.
 18. Arana A, Wentworth CE, Fernandez-Vidaurre C, Schlienger RG, Conde E, Arellano FM. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. *Br J Dermatol* 2010;163:1036–43.
 19. Vesterinen E, Pukkala E, Timonen T, Aromaa A. Cancer incidence among 78,000 asthmatic patients. *Int J Epidemiol* 1993;22: 976–82.
 20. Eriksson NE, Holmen A, Hogstedt B, Mikoczy Z, Hagmar L. A prospective study of cancer incidence in a cohort examined for allergy. *Allergy* 1995;50:718–22.
 21. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. *J Natl Cancer Inst* 2007;99: 1544–50.
 22. Koh WP, Yuan JM, Wang R, Seow A, Lee HP, Yu MC. Chronic rhinosinusitis and risk of lung cancer in the Singapore Chinese Health Study. *Int J Cancer* 2008; 123:1398–402.
 23. Bureau of National Health Insurance. Available at: <http://www.nhi.gov.tw/english/index.aspx>. Accessed April 28, 2011.
 24. Chen YJ, Chang YT, Wang CB, Wu CY. The risk of cancer in rheumatoid arthritis patients: a nationwide cohort study in Taiwan. *Arthritis Rheum*, in press.
 25. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC, Lee DD, Chang YT, Wang WJ, Liu HN. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007. *Acta Derm Venereol* 2010;90:589–94.
 26. Kung YY, Chen YC, Hwang SJ, Chen TJ, Chen FP. The prescriptions frequencies and patterns of Chinese herbal medicine for allergic rhinitis in Taiwan. *Allergy* 2006; 61:1316–8.
 27. Meltzer EO, Szwarcberg J, Pill MW. Allergic rhinitis, asthma, and rhinosinusitis: diseases of the integrated airway. *J Manag Care Pharm* 2004;10:310–7.
 28. Severi G, Baglietto L, Muller DC, English DR, Jenkins MA, Abramson MJ, Douglass JA, Hopper JL, Giles GG. Asthma, asthma medications, and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2010;19: 2318–24.
 29. Dietrich K, Schned A, Fortuny J, Heaney J, Marsit C, Kelsey KT, Karagas MR. Glucocorticoid therapy and risk of bladder cancer. *Br J Cancer* 2009;101:1316–20.
 30. Patel AS, Karagas MR, Perry AE, Spencer SK, Nelson HH. Gene-drug interaction at the glucocorticoid receptor increases risk of squamous cell skin cancer. *J Invest Dermatol* 2007;127:1868–70.
 31. Ming ME, Levy R, Hoffstad O, Filip J, Abrams BB, Fernández C, Margolis DJ. The lack of a relationship between atopic dermatitis and nonmelanoma skin cancers. *J Am Acad Dermatol* 2004;50:357–62.
 32. Munitz A, Levi-Schaffer F. Eosinophils: 'new' roles for 'old' cells. *Allergy* 2004;59: 268–75.
 33. Van Hemelrijck M, Garmo H, Binda E, Hayday A, Karagiannis SN, Hammar N, Walldius G, Lambe M, Jungner I, Holmberg L. Immunoglobulin E and cancer: a meta-analysis and a large Swedish cohort study. *Cancer Causes Control* 2010; 21:1657–67.
 34. Turner MC, Chen Y, Krewski D, Ghadirian P, Thun MJ, Calle EE. Cancer mortality among US men and women with asthma and hay fever. *Am J Epidemiol* 2005;162:212–21.
 35. Eriksson NE, Mikoczy Z, Hagmar L. Cancer incidence in 13811 patients skin tested for allergy. *J Investig Allergol Clin Immunol* 2005;15:161–6.