Risk of Overall and Site-specific Cancers in Behçet Disease: A Nationwide Population-based Study in Taiwan

Li-Hui Wang, Wei-Ming Wang, Sheng-Min Hsu, Sheng-Hsiang Lin, and Chi-Chang Shieh

ABSTRACT. ***Objective.*** The relationship between autoimmune disease and cancer is complex while large-scale epidemiological studies of cancer risk in Behçet disease (BD) have not been reported. Therefore, we conducted a nationwide population-based cohort study.

Methods. By using the National Health Insurance Research Database of 23 million people in Taiwan, we identified 1314 new patients with BD without previous cancer from 2000–2009 as a cohort. Standardized incidence ratios (SIR) of overall and site-specific cancers in patients with BD in comparison with the general population were calculated from 2000–2011.

Results. Among the 1314 patients with BD, 30 developed cancers (9 men and 21 women). In overall cancer risk analysis, patients with BD had a higher risk (SIR 1.5, 95% CI 1.03–2.11). Among them, female patients with BD (SIR 1.8, 95% CI 1.14–2.7), but not male patients with BD (SIR 1.08, 95% CI 0.53–1.98), have a higher risk of overall cancer. In site-specific cancer risk analysis, patients with BD had a higher risk of non-Hodgkin lymphoma (SIR 8.3, 95% CI 2.1–22.7), hematological malignancy (SIR 4.2, 95% CI 1.3–10.2), and female breast cancer (SIR 2.2, 95% CI 1.004–4.1). The cancer risk was highest within the first-year followup (SIR 2.7, 95% CI 1.3–5.1), with 75% of the hematological malignancies found within the first year.

Conclusion. This nationwide cohort study of cancer risk in patients with BD provides important information about the relationship between BD and malignancies. The results can be useful for cancer surveys in the future. (J Rheumatol First Release April 1 2015; doi:10.3899/jrheum.140770)

Key Indexing Terms:
BEHÇET DISEASE CANCER RISK HEMATOLOGICAL MALIGNANCY
LYMPHOMA BREAST CANCER

Behçet disease (BD) is an autoimmune-mediated systemic vasculitis. Common manifestations include recurrent oral ulcers, ocular inflammation, genital ulcers, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease, and arthritis[1].

Cancer is a major global health problem and a common cause of death worldwide. The relationship between autoimmune disease and cancer has been a puzzling clinical question for immunologists[2,3,4]. The immune system can protect against cancer[5,6], but chronic inflammation may itself promote cancer[7,8]. Therefore, autoimmune diseases may have an ambivalent role in suppressing and promoting cancers.

Large-scale epidemiological studies or population-based studies with regard to cancer risk in many autoimmune diseases have previously reported. These diseases include rheumatoid arthritis (RA)[9], systemic lupus erythematosus (SLE)[10], dermatomyositis[11], Sjögren syndrome[12], and systemic sclerosis[13], but not BD. Because BD is a rare disease, there have been only a few published studies on the relationship between BD and cancer. Some of them were hospital-based chart reviews[14,15,16,17], while others were case reports with reviews of related literature[18,19]. Among these studies, 2 found that hematological malignancy was the most common cancer in patients with BD[15,17]. These reports, however, lacked the analysis of overall and site-specific cancer risk in patients with BD.

To prove the long-suspected relationship between BD and cancers, we conducted a nationwide population-based cohort study to compare the overall and site-specific cancer risks

From the Institute of Clinical Medicine, College of Medicine, National Cheng Kung University; Division of Immunology, Department of Pediatrics, Kuo General Hospital; Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, and Department of Ophthalmology, National Cheng Kung University Hospital, Tainan, Taiwan.

L.H. Wang, MD, Immunologist, Division of Immunology, Department of Pediatrics, Kuo General Hospital; W.M. Wang, MS, Biostatistician, Clinical Research Center; S.M. Hsu, MD, PhD, Ophthalmologist, Department of Ophthalmology, National Cheng Kung University Hospital; S.H. Lin, PhD, Assistant Professor of Biostatistics, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University; C.C. Shieh, MD, PhD, Professor of Immunology, Rheumatology and Pediatrics, Institute of Clinical Medicine, National Cheng Kung University, and Division of Allergy, Immunology and Rheumatology, and Department of Pediatrics, National Cheng Kung University Hospital.

Address correspondence to Dr. C.C. Shieh and Dr. S.H. Lin, Institute of Clinical Medicine, National Cheng-Kung University, 138 Sheng-Li Road, Tainan 70403, Taiwan. E-mail: cshieh@mail.ncku.edu.tw, shlin922@mail.ncku.edu.tw

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among patients with BD against the cancer risks of the general population by using insurance claims data in Taiwan.

MATERIALS AND METHODS

Study design. We conducted a population-based retrospective cohort study by retrieving patients with BD from the 23 million people of Taiwan's National Health Insurance Research Database (NHIRD)[20] after receiving approval from the Institutional Review Board of Kuo General Hospital (No. B-13-K009). The study process is shown in Figure 1.

Data source. Taiwan's NHI program is a mandatory single-payer health insurance system in which all citizens are required to participate. It began in 1995 and covers more than 99% of the entire population. For research purposes, the NHI database has been released to the researchers in an electronically encrypted form called the NHIRD since 1999. The NHIRD contains detailed healthcare data such as sex, age, diagnosis, and treatment. There are 31 categories of catastrophic illness as defined by Taiwan's NHI, including cancer and specific autoimmune diseases. Once a patient is definitely diagnosed as having a certain catastrophic illness, the attending physician will help the patient to apply for a catastrophic illness certificate (CIC) to be exempt from copayment after a formal review[21].

Cohort of patients with BD. We identified the people of Taiwan's NHIRD with a definite diagnosis of BD for the first time between January 1, 2000, and December 31, 2009. Patients with cancer before BD were excluded. The diagnostic accuracy of BD was confirmed by the International Classification of Diseases, 9th ed (ICD-9) code 136.1 and the registry for catastrophic illness. Because of the need for longterm treatment, all patients with BD can apply for a CIC in Taiwan once the diagnosis of BD is confirmed based on the criteria of the International Study Group for BD[22] without considering socioeconomic factors. The criteria for BD are recurrent oral ulceration plus any 2 of the following: (1) recurrent genital ulceration, (2) eye lesions, (3) skin lesions, or (4) positive pathergy test. Copies of the medical records were requested to prove that the clinical features met the criteria while applying for a BD CIC.

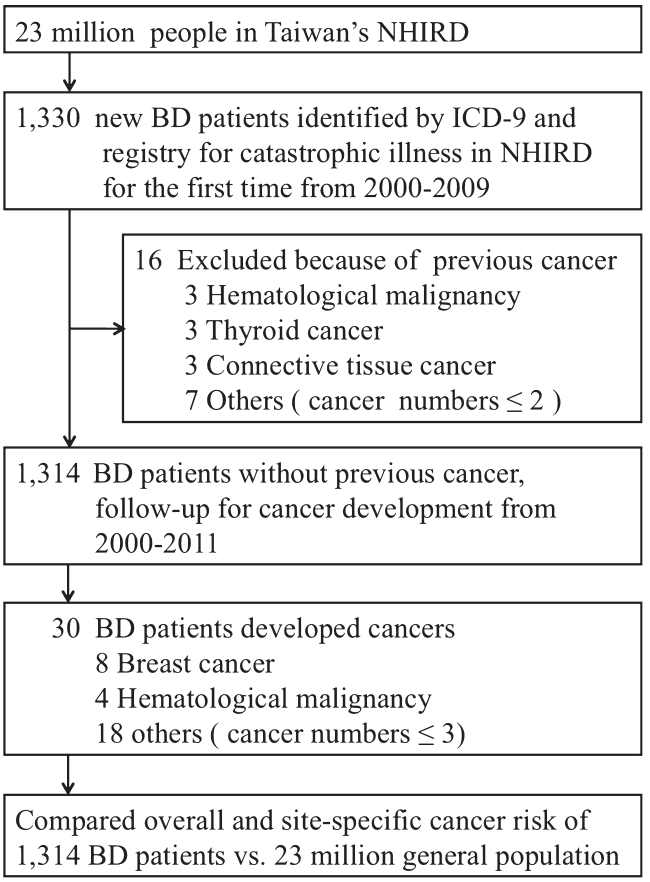

Figure 1. Flow chart of the study process. NHIRD: National Health Insurance Research Database; BD: Behçet disease; ICD-9: International Classification of Diseases, 9th ed.

Followup for cancer development. The included patients with BD were followed up for cancer development until December 31, 2011. The followup times were calculated from the application date of the BD CIC to a diagnosis of cancer, the end of records in the NHIRD (mostly due to death, disappearance, or emigration from Taiwan), or until December 31, 2011. The diagnostic accuracy of cancer was confirmed by a cancer ICD-9 code (140–208) and the registry for catastrophic illness in the NHIRD. *In situ* malignancy did not qualify for a CIC and therefore was not included in our study. To apply for a cancer CIC, pathological reports or imaging studies supporting the diagnosis of cancer were provided. Only patients fulfilling the criteria of a specific cancer diagnosis were issued a cancer CIC.

Statistical analysis. To examine whether patients with BD had a higher risk for developing cancer in comparison with the general population, we calculated the standardized incidence ratios (SIR; a ratio of observed to expected cancers)[23,24] of overall and site-specific cancers in patients with BD. The observed number was the newly diagnosed cancer cases in this BD cohort while the expected cancer number was calculated according to the average cancer incidence rate (2000–2011) of the general population standardized for sex and age, and then multiplied by the person-years of this BD cohort. Taiwan cancer incidence can be obtained from the Taiwan Cancer Registry[25] or the Catastrophic Illness Dataset of the NHIRD. In our study, we used the latter to calculate the cancer incidence in the general population as follows: we collected the 12-year (2000–2011) data of the general population and new cancer cases, and then used the average cancer incidence rate (average new cancer cases per year divided by average general population) as a standard. Further, we calculated the SIR by the followup time. Because hematological malignancy occurred mostly within the first-year followup in our BD cohort, we further compared whether the development time of cancer was different between hematological malignancy and other cancers in patients with BD. The 95% CI and the p values in our study were calculated by Mid-P exact test[26].

RESULTS

Prevalence of BD in Taiwan. There were 1526 patients with BD in 2009 in Taiwan identified by BD ICD-9 and the registry for catastrophic illness in Taiwan's NHIRD. The prevalence of BD in 2009 in Taiwan was 6.6 cases per 100,000 persons.

BD cohort. A total of 1330 patients with BD were newly diagnosed from 2000 to 2009 from the population of 23 million. After excluding 16 patients with previous cancer, a total of 1314 patients with BD were included in our cohort study. The 16 excluded patients with BD with previous cancers included 3 hematological malignancies, 3 thyroid cancers, 3 connective tissue cancers, and 7 other specific cancers (Figure 1).

Characteristics of patients with BD. In our 1314 BD cohort, 548 were men and 766 were women. The mean age of newly diagnosed BD was 37.4 ± 12.9 years old, with most (79.5%) aged 16–49 years. BD did occur in children, but it was uncommon. The proportion of juvenile-onset Behçet disease[27] (onset < 16 years old) was 4.3%. The mean duration

of the followup of these patients with BD from 2000–2011 was 7.0 ± 2.8 years (Table 1).

Overall cancer risk of patients with BD. Among these 1314 patients with BD without previous cancer, a total of 30 patients (2.3%), 9 men and 21 women, were identified as having cancer from 2000–2011. The SIR of overall cancer in patients with BD as compared with the general population in Taiwan's NHIRD after standardizing for sex, age, and time period was 1.50 (95% CI 1.03–2.11), 1.08 (95% CI 0.53–1.98) in male patients with BD, and 1.80 (95% CI 1.14–2.70) in female patients with BD. Generally, patients with BD had a higher risk of overall cancer. Among them, female patients with BD, but not male patients with BD, did have a higher risk of overall cancer (Table 2).

Site-specific cancer risk of patients with BD. We then analyzed whether there were changes in the risk of site-specific cancers. The most common cancers in our BD cohort were 8 cases of female breast cancer and 4 cases of hematological malignancies. The statistically significant results ($p < 0.05$) of SIR in the site-specific cancers included a higher risk of hematological malignancy (SIR 4.21, 95% CI 1.34–10.16, $p = 0.019$), especially non-Hodgkin lymphoma (NHL; SIR 8.33, 95% CI 2.12–22.68, $p = 0.006$), and female breast cancer (SIR 2.16, 95% CI 1.004–4.11, $p = 0.049$). The highest SIR was found in testicular cancer (SIR 16.67, 95% CI 0.83–82.2, $p = 0.06$), but it did not reach statistical significance because only 1 case was found. The cancer risk, however, did not increase significantly in the specific sites often involved in patients with BD, such as the oral cavity, eyes, external genital area (scrotum, penis, vulva, and vagina), skin, and gastrointestinal tract[1] (Table 3).

Table 1. Characteristics of 1314 patients with Behçet disease. Values are mean ± SD or n (%).

Characteristic	Value
Age at diagnosis, yrs	
Male	36.9 ± 12.9
Female	37.7 ± 12.9
All	37.4 ± 12.9
Age, male, yrs	
< 16	23 (4.2)
16–29	154 (28.1)
30–39	152 (27.7)
40–49	132 (24.1)
50–59	62 (11.3)
≥ 60	25 (4.6)
All	548 (100)
Age, female, yrs	
< 16	33 (4.3)
16–29	185 (24.2)
30–39	207 (27.0)
40–49	215 (28.1)
50–59	98 (12.8)
≥ 60	28 (3.7)
All	766 (100)
Duration of followup, yrs	
Male	7.1 ± 2.7
Female	6.9 ± 2.9
All	7.0 ± 2.8

Cancer risk according to followup time. In an average 7-year followup of these patients with BD, the cancer risk was highest within the first-year followup (SIR 2.70, 95% CI 1.26–5.13). With the increase in followup time, the SIR of cancer decreased gradually. Moreover, we listed the significantly increased site-specific cancers (hematological malignancy and breast cancer) according to the diagnosis time of followup years. Most hematological malignancies were diagnosed within the first year, but breast cancer did not have this tendency (Table 4). We further analyzed whether the development time of cancer was different between hematological malignancy and other cancers in patients with BD. Among the hematological malignancies, 3 of 4 (75%) were diagnosed within the first-year followup. In contrast, among nonhematological malignancies, only 5 of 26 (19.2%) were diagnosed within the first-year followup. Hematological and nonhematological malignancies in patients with BD therefore had different times of diagnosis after the initial diagnosis of BD ($p = 0.025$; Table 5).

DISCUSSION

The prevalence of BD in Taiwan was 6.6 cases per 100,000 persons in 2009, which was lower than the prevalence in Turkey, Japan, and China, but higher than the prevalence in Hong Kong, the United States, and the United Kingdom[28,29]. BD is rare and therefore it is difficult to study its involvement with cancer risk. Our first nationwide cohort study of BD by using the NHIRD in Taiwan is, to our knowledge, the first study about the overall and site-specific cancer risk of BD. Our results showing the correlation between BD and specific cancers provide important information in clarifying the relationship between this debilitating autoimmune disease and the risk of malignancy.

Based on the understanding of BD as an autoimmune disease, it is interesting, but not too surprising, to find that in our study, patients with BD were associated with a higher risk of hematological malignancy (SIR 4.2), especially of NHL (SIR 8.3). This result is consistent with 2 previous hospital-based studies reporting that hematological malignancy was the most common cancer in BD[15,17]. Although the pathogenesis and clinical presentation vary in different autoimmune diseases, higher risks of hematological malignancy and lymphoma in patients with certain autoimmune diseases had been reported previously, such as those with RA[9], SLE[10], and Sjögren syndrome[12]. Immune-mediated inflammation and treatment with immunosuppressive agents are the common features among these autoimmune diseases, including BD. The possible mechanisms of hematological malignancy development (especially lymphoma) in autoimmune diseases[30,31] include the following: (1) B cell and T

Table 2. Risk of overall cancer in patients with BD by sex and age. Cancer incidence in Taiwan was the average cancer incidence from 2000–2011.

Sex and Age	Observed, n	Cancer Incidence in Taiwan, Per 1000 Person-yrs	Person-yrs of BD Cohort	Expected	SIR (95% CI)
Male, yrs					
< 16	0	0.138	160.2	0.02	0
16–39	0	0.531	2277.6	1.21	0
40–59	5	3.765	1316.7	4.96	1.01 (0.37–2.23)
≥ 60	4	14.551	147.3	2.14	1.87 (0.59–4.51)
All	9	—	3901.8	8.33	1.08 (0.53–1.98)
Female, yrs					
< 16	0	0.116	212.1	0.02	0
16–39	4	0.714	2813.5	2.01	1.99 (0.63–4.80)
40–59	13	3.773	2107.7	7.95	1.64 (0.91–2.73)
≥ 60	4	9.147	185.6	1.70	2.35 (0.75–5.68)
All	21	—	5318.9	11.68	1.80 (1.14–2.70)
Total					
All	30	—	9220.7	20.01	1.50 (1.03–2.11)

Age of observed is the age at cancer diagnosis. Age of person-year is the age of BD cohort adjusted with followup time. Observed: newly diagnosed cancer cases of the BD cohort. Expected: cancer incidence (per 1000 person-yrs) × person-years of BD cohort ÷ 1000. SIR: observed ÷ expected. BD: Behçet disease; SIR: standardized incidence ratio.

Table 3. Risk of site-specific cancer in patients with Behçet disease.

Cancer Sites	Observed, n	Expected	SIR (95% CI)	p
Lip, oral, pharynx	3	2.22	1.35 (0.34–3.68)	0.567
Gastrointestinal tract	3	3.39	0.88 (0.22–2.41)	0.902
Liver	3	2.13	1.41 (0.36–3.83)	0.526
Lung	3	1.54	1.95 (0.50–5.30)	0.272
Skin	0	0.22	0	—
Female breast	8	3.70	2.16 (1.004–4.11)	0.049*
Female genital organ				
Uterus	1	0.48	2.08 (0.10–10.27)	0.465
Ovary	1	0.50	2.00 (0.10–9.86)	0.483
Vagina, labia majora, labia minora, clitoris, vulva	0	0.04	0	—
Male genital organ				
Prostate	1	0.33	3.03 (0.15–14.95)	0.325
Testis	1	0.06	16.67 (0.83–82.2)	0.060
Penis, epididymis, scrotum	0	0.01	0	
Bladder	1	0.41	2.44 (0.12–12.03)	0.401
Eye	0	0.01	0	—
Brain	1	0.27	3.70 (0.19–18.27)	0.267
Hematological malignancy	4	0.95	4.21 (1.34–10.16)	0.019*
NHL	3	0.36	8.33 (2.12–22.68)	0.006*
Leukemia	1	0.25	4.00 (0.20–19.73)	0.248

* $p < 0.05$. Observed: newly diagnosed cancer cases of the BD cohort. Expected: cancer incidence (per 1000 person-yrs) × person-years of BD cohort ÷ 1000. SIR: standardized incidence ratio; NHL: non-Hodgkin lymphoma.

cell activation have crucial roles in the pathogenesis of both autoimmunity and lymphoma, (2) immunosuppressive drugs may increase hematological malignancy risk, and (3) some autoimmune diseases and hematological malignancy have similar genetic susceptibility or environmental trigger factors (e.g., Epstein-Barr virus infection). In contrast, although oral cavity, eyes, external genital area, skin, and gastrointestinal tract are the specific sites often involved in patients with BD[1], the cancer risk did not increase significantly in these sites. Therefore, we could not directly prove the hypothesis that prolonged local inflammation may promote cancers.

Our findings of increased risk of female breast cancer in patients with BD have not been reported before. Based on the fact that BD occurs mostly at reproductive ages, it is reasonable to suppose that sex hormones may contribute to the pathogenesis of breast cancer. Past studies did not reveal significant changes in estrogen serum levels[32], but did highlight higher prolactin serum levels in patients with BD[33].

Table 4. Risk of cancer in patients with Behçet disease according to years of followup with significantly increased specific cancers enlisted.

Yrs of Followup	Observed, n	Expected	SIR	95% CI
< 1	Total: 8 3H: 2NHL, 1L 2B	2.96	2.70	1.26–5.13
1–3	Total: 9 3B	11.13	0.81	0.39–1.48
4–6	Total: 9 3B 1H: 1NHL	15.19	0.59	0.29–1.09
≥ 7	Total: 4	9.57	0.42	0.13–1.01

Observed: newly diagnosed cancer cases of the BD cohort. Expected: cancer incidence (per 1000 person-yrs) × person-years of BD cohort ÷ 1000. H: hematological malignancy; NHL: non-Hodgkin lymphoma; L: leukemia; B: breast cancer.

Table 5. Comparison between hematological and nonhematological malignancies in patients with Behçet disease according to the followup year.

Yrs of Followup	Hematological, n	Nonhematological, n
< 1	3	5
≥ 1	1	21

P = 0.025 by Mid-P exact test.

Because an increased prolactin level has been shown to be significantly associated with increased breast cancer[34], prolactin level is likely to play a role in the increased risk of female breast cancer in patients with BD. In our overall cancer risk study, female patients with BD had a higher risk than male patients. Because there were 8 female patients with breast cancer, the increase in breast cancer numbers among female patients with BD was the key factor in the higher overall cancer risk among women.

In our study, the cancer risk was highest within the first-year followup, and with the increase of the followup time, the cancer risk decreased gradually. The result was similar to previous studies with regard to SLE[10], RA[9], and Sjögren syndrome[12]. A possible explanation in previous studies was that these autoimmune patients had more chances to visit the doctor and receive examinations[9,12], which might result in an earlier detection of cancer compared with the general population because of surveillance bias. However, surveillance bias cannot fully explain why up to 75% of hematological malignancies were found within the first year, but other cancers did not have this tendency to appear early in the followup course (Tables 4 and 5). Most hematological malignancies found within the first year might be another key factor contributing to a higher cancer risk within the first year. The earlier appearance of hematological malignancies than nonhematological malignancies may be explained by these possibilities: (1) BD and hematological malignancy have some similar pathogenesis[30,31], leading to the early occurrence of hematological malignancy in patients with BD; and (2) the development of hematological malignancy was quicker than other cancers (e.g., breast cancer) after the trigger factors. Screening for hematological malignancies early after the diagnosis of BD is a reasonable recommendation based on our results.

Even though our nationwide database of the NHIRD was relatively large, the cohort of 1314 patients with BD and 30 cases of cancer was not large enough to analyze each site-specific cancer correctly. For example, testicular cancer had the highest specific cancer risk (SIR 16.7, 95% CI 0.8–82.2, p = 0.06), but it did not reach statistical significance because only a single case was identified (Table 3). If we had a larger number of patients with BD with cancer, we might be able to test whether testicular cancer risk really increases in patients with BD. Our case number of BD, however, may be underestimated because we included only patients with CIC for BD. The patients with CIC can be exempt from copayment for medical treatment, but the application of CIC requires additional review based on the criteria of the International Study Group for BD without considering the economic need. Although it is possible that some patients with BD opted not to apply for a CIC and therefore were not included in our study, our strategy of including only the patients with BD with CIC ensured that all the patients with BD fulfilled the diagnostic criteria of the disease. Patients with BD who later develop cancer, meanwhile, are not likely to opt out of CIC application because of the heavy financial burden of cancer treatment. Therefore, we believe that the investigative strategy of using CIC in the NHIRD study is a valid approach for identifying the patients with a confirmed autoimmune disease who developed cancer in their disease course, as in previous reports[9,10,12]. Another limitation of our investigative approach using the NHIRD based on analysis of the claims data is that we cannot further dissect the pathogenic mechanisms with measurement of biomarkers. Further clinical and laboratory studies are needed to clarify the relationship between BD and cancer.

Our study provides useful information for cancer surveys. First, female patients with BD had a higher risk of overall cancer. Second, BD was associated with higher cancer risks of NHL, hematological malignancy, and breast cancer. Third, cancer risk, especially for hematological malignancies, was higher within the first year after the BD diagnosis. The mechanism underlying the changes in specific cancer risk merit further investigation in the future.

REFERENCES

1. Reynolds N. Vasculitis in Behcet's syndrome: evidence-based review. Curr Opin Rheumatol 2008;20:347-52.
2. Hagemann T, Balkwill F, Lawrence T. Inflammation and cancer: a double-edged sword. Cancer Cell 2007;12:300-1.
3. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011;331:1565-70.

4. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883-99.
5. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715-27.
6. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol 2011; 29:235-71.
7. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539-45.
8. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res 2006;4:221-33.
9. Chen YJ, Chang YT, Wang CB, Wu CY. The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan. Arthritis Rheum 2011;63:352-8.
10. Liang JA, Sun LM, Yeh JJ, Lin WY, Chang SN, Sung HC, et al. Malignancies associated with systemic lupus erythematosus in Taiwan: a nationwide population-based cohort study. Rheumatol Int 2012;32:773-8.
11. Kuo CF, See LC, Yu KH, Chou IJ, Chang HC, Chiou MJ, et al. Incidence, cancer risk and mortality of dermatomyositis and polymyositis in Taiwan: a nationwide population study. Br J Dermatol 2011;165:1273-9.
12. Weng MY, Huang YT, Liu MF, Lu TH. Incidence of cancer in a nationwide population cohort of 7852 patients with primary Sjogren's syndrome in Taiwan. Ann Rheum Dis 2012;71:524-7.
13. Chatterjee S, Dombi GW, Severson RK, Mayes MD. Risk of malignancy in scleroderma: a population-based cohort study. Arthritis Rheum 2005;52:2415-24.
14. Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine 2003;82:60-76.
15. Ahn JK, Oh JM, Lee J, Koh EM, Cha HS. Behcet's disease associated with malignancy in Korea: a single center experience. Rheumatol Int 2010;30:831-5.
16. Na SY, Shin J, Lee ES. Morbidity of solid cancer in Behçet's disease: analysis of 11 cases in a series of 506 patients. Yonsei Med J 2013;54:895-901.
17. Lin Y, Li G, Zheng W, Tian X, Zhang F. Behcet's disease associated with malignancy: a report of 41 Chinese cases. Int J Rheum Dis 2014;17:459-65.
18. Cengiz M, Altundag MK, Zorlu AF, Gullu IH, Ozyar E, Atahan IL. Malignancy in Behcet's disease: a report of 13 cases and a review of the literature. Clin Rheumatol 2001;20:239-44.
19. Kaklamani VG, Tzonou A, Kaklamanis PG. Behçet's disease associated with malignancies. Report of two cases and review of the literature. Clin Exp Rheumatol 2005;23 Suppl 38:S35-41.
20. Yeh HY, Wu JC, Haschler I, Chen TJ, Wetter T. Taiwan's National Health Insurance Research Database: administrative health care database as study object in bibliometrics. Scientometrics 2011;86:365-80.
21. National Health Insurance Administration. Catastrophic illness patients. [Internet. February 25, 2015.] Available from: www.nhi.gov.tw/English/webdata/webdata.aspx?menu=11&menu_id=596&WD_ID=596&webdata_id=3180
22. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078-80.
23. Columbia University Mailman School of Public Health. Cohort study: standardized incidence ratio (SIR). [Internet. Accessed February 25, 2015.] Available from: epiville.ccnmtl.columbia.edu/99interactive/sir.html
24. Merrill RM, Timmreck TC. Design strategies and statistical methods in descriptive epidemiology. Introduction to epidemiology. Sudbury: Jones & Bartlett Publishers; 2006:90-1.
25. Taiwan Cancer Registry. Department of Health. [Internet. Accessed February 25, 2015.] Available from: tcr.cph.ntu.edu.tw/main.php?Page=N1
26. Greenland S, Rothman KJ. Fundamentals of epidemiology data analysis. In: Rothman KJ, Greenland S, Lash TL, eds. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008:213-37.
27. Kitaichi N, Miyazaki A, Stanford MR, Iwata D, Chams H, Ohno S. Low prevalence of juvenile-onset Behcet's disease with uveitis in East/South Asian people. Br J Ophthalmol 2009;93:1428-30.
28. Yurdakul S, Yazici H. Behcet's syndrome. Best Pract Res Clin Rheumatol 2008;22:793-809.
29. Calamia KT, Wilson FC, Icen M, Crowson CS, Gabriel SE, Kremers HM. Epidemiology and clinical characteristics of Behçet's disease in the US: a population-based study. Arthritis Rheum 2009; 61:600-4.
30. Baecklund E, Smedby KE, Sutton LA, Askling J, Rosenquist R. Lymphoma development in patients with autoimmune and inflammatory disorders—what are the driving forces? Semin Cancer Biol 2014;24:61-70.
31. Martin DN, Mikhail IS, Landgren O. Autoimmunity and hematologic malignancies: associations and mechanisms. Leuk Lymphoma 2009;50:541-50.
32. Cil AP, Karabulut AA, Koçak M. Assessment of ovarian stromal artery Doppler characteristics and serum hormone levels in patients with Behçet disease. Diagn Interv Radiol 2010;16:288-92.
33. Proença H, Ferreira C, Miranda M, Castanheira-Dinis A, Monteiro-Grillo M. Serum prolactin levels and Behcet disease. Eur J Ophthalmol 2007;17:404-7.
34. Tworoger SS, Eliassen AH, Zhang X, Qian J, Sluss PM, Rosner BA, et al. A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. Cancer Res 2013;73:4810-9.