Systematic Review and Meta-Analysis

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Risk of malignancy in Behcet disease

A meta-analysis with systematic review

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Abstract

Background: Several studies have reported the association of Behcet disease (BD) with the risk of diverse kinds of cancers. However, its association is controversial. Therefore, we conducted a bioinformatics-analysis to explore any possible association.

Methods: We obtained relevant findings published before October 2018 through literature survey of the PubMed, EMBASE, and Web of Science databases. STATA 12.0 software was used for statistical analysis.

Results: After screening, the meta-analysis comprised 5 studies. We observed a significant positive association between BD and enhanced malignancy risk (pooled relative risk [RR], 1.19; 95% confidence interval [CI]: 1.09–1.30), especially for hematological cancer (pooled RR, 2.58; 95% CI: 1.61–3.55) and thyroid cancer (pooled RR, 1.25; 95% CI: 1.04–1.47). However, high heterogeneity was also observed in the results (I^2 = 81.3%). Subgroup analysis indicated that female BD patients from Korean population are at highest predisposition to overall malignancy. Besides, publication bias was not observed with our choice of surveys.

Conclusion: We conclude that patients suffering from BD have an overall increased risk for malignancy. Greater numbers of exhaustive temporal studies are essential for definitive inferences.

Abbreviations: BD = Behcet disease, OR = odds ratio, RR = relative risk.

Keywords: Behcet disease, malignancy development, meta-analysis, risk factors

1. Introduction

Behcet disease (BD) is a relapsing, multisystemic, and chronic vasculitis, which was first proposed by Behcet in 1937. It is an uncertain etiology marked with periodic oral ulcers and includes blood vessels, gastrointestinal tract, mucocutaneous layers, and central nervous system, which negatively affects the quality of life.[1] BD pathogenesis has not yet been fully explored. However, there are clear indications to the fact that pathophysiology of BD involves autoimmune dysfunction. Immunosuppression therapy and detection of autoantibodies in BD patients are indicative of the same.[2] Furthermore, it is reported that Asian countries especially China, Japan, and Korea have high prevalence of BD.[3]

Epidemiological surveys clearly validate the prevalence of a high risk of malignancy in a variety of rheumatic diseases including systemic lupus erythematosus, systemic sclerosis, dermatomyositis, etc.[4–6] However, the correlation between malignant diseases especially solid tumor and BD is fairly unknown. We do not have enough evidence to explain their correlation. Thus, the present study involves a systemic literature review and bioinformatics analysis to explore the relationship between BD and cancer risk.

2. Methods

Preferred Reporting Items for Systematic Review and Meta-analysis statement and the Meta-analysis Of Observational Studies in Epidemiology guidelines [7,8] were followed for conducting the above study.

2.1. Search strategy

Relevant literatures were reviewed in PubMed, EMBASE, and Web of Science on March 2019. We used the following keywords ("BD" OR "Behcet's syndrome" OR "Behcet disease" or "Behcet syndrome") and ("cancer" OR "neoplasm" OR "tumor" OR "malignancy"). No language or the date of publication restriction was applied in our literature search.

2.2. Inclusion criteria

Our meta-analysis included the following inclusion: study design of case or control cohort; the medical history of BD patients

Editor: Daryle Wane.

Consent for publication: The manuscript has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere.

Ethical statement: Ethics committee approval is not included as it is commonly accepted that case reports do not require such approval. Our work did not use patients' data that would allow identifying them, thus no ethical approval is required.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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How to cite this article: Wang X, Peng Y, Gao J, Han S, Li Y. Risk of malignancy in Behcet disease. Medicine 2019;98:44(e17735).

Received: 3 May 2019 / Received in final form: 11 September 2019 / Accepted: 27 September 2019

http://dx.doi.org/10.1097/MD.0000000000017735

including the cancer as the outcome readout; odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs); and duration of follow-up to note the possible malignant outcome. We did not include the studies which did not consider the effect size and duplicate publications and conference abstracts without publication.

2.3. Obtaining data and quality assessment

Necessary information from the selected articles was extracted by 2 authors independently.

The following information was extracted from each article: name of the first author; publication year; country; and results of the study and total period of study, gender distribution for occurrence, the number of BD patients having malignancy, different cancer types among the patients, OR/RR values and 95% CIs for different categories, and quality score.

Quality of retained studies was assessed using the Newcastle-Ottawa scale.[9] Studies were qualified based on scores obtained. We designated a maximum score of 9 points for 8 items. If the study scored more than 6 points, it would be considered as high quality.

2.4. Statistical methods

The correlation of BD with the risk of malignancy was assessed using RR values and the corresponding 95% CI. We expected similar estimates in terms of RR from SIRs/HRs/ORs as the risk of cancer is generally low. Therefore, readouts of all studies were converted to RR for subsequent meta-analysis.[10] STATA 12.0 (StataCorp, College Satation, TX) was used to perform statistical analyses. Heterogeneity was accessed by the I^2 statistic. We defined the heterogeneity value of 25%, 50%, and 75% as low, medium, and high, respectively. P values less than .1 indicated significant presence of heterogeneity. Publication bias was evaluated through funnel plots and Begg tests, wherein asymmetrical funnel plot and P less than .05 indicated the presence of bias.[11,12] We explored heterogeneity through subgroup analysis. The same test done by systems based on gender, country, and specific cancers helped to unravel the factors affecting heterogeneity.

3. Results

3.1. Study selection and characteristics

Figure 1 represents the flow diagram elucidating the literature survey steps. We found 7201 records in the online databases and

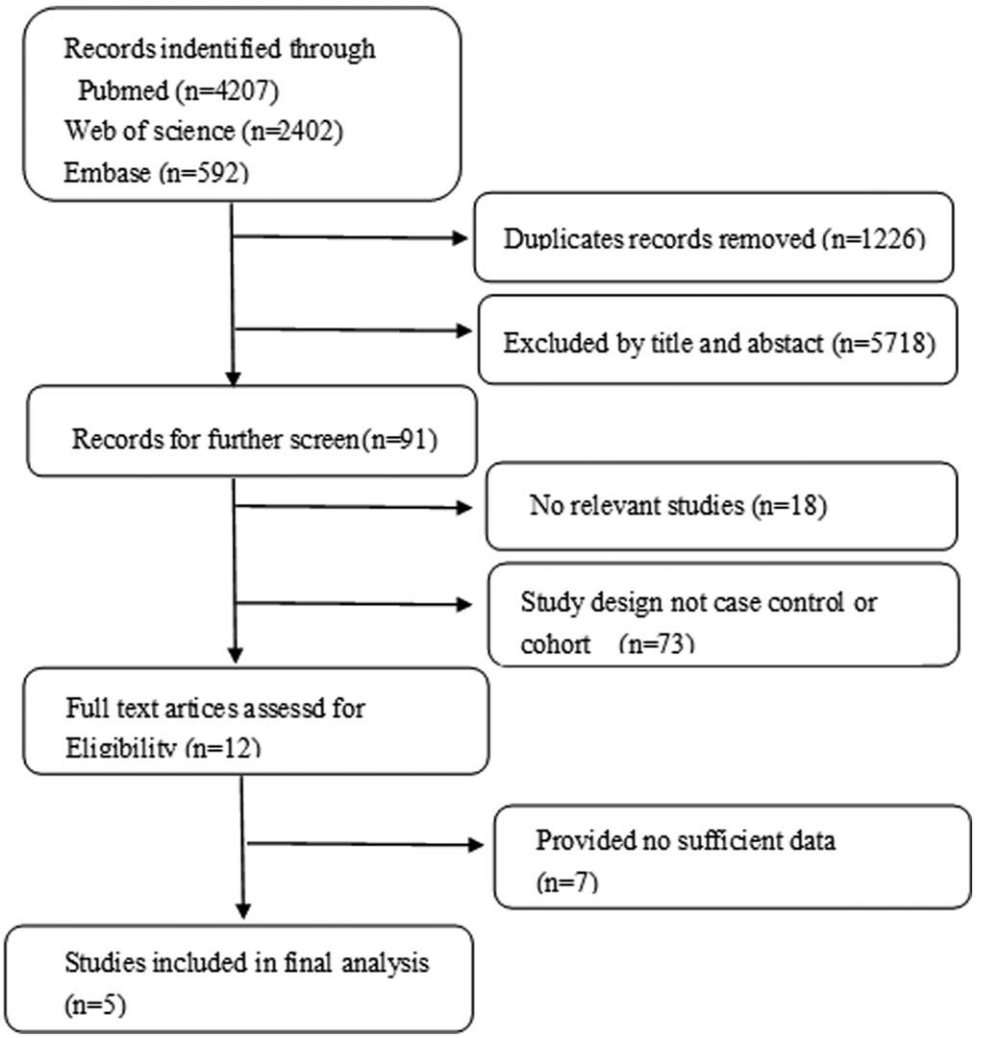

Figure 1. Flow chart of literature search in the meta-analysis.

Table 1

Characteristics of selected studies on Behcet disease and risk of malignance.

Study	Year	Country	Study period	Sex	BD patients with cancer	Estimate of relative risk	Quality
Han et al	2018	Korean	2011–2014	F/M	12	SIR	7
Na et al	2018	Korean	2007–2014	F/M	451	HR	8
Jung et al	2017	Korean	2013–2014	F/M	72	SIR	7
Yu et al	2016	China	1997–2010	F/M	37	SIR	6
Wang et al	2015	China	2000–2009	F/M	30	SIR	7

6944 were removed from our analysis based on title, duplicates, and abstract review. Furthermore, 91 longlisted articles were further screened based on their full text. We finally involved 5 studies in our meta-analysis.[13–17] We selected only population-based case–control studies. As for the Newcastle-Ottawa scale, 4 out of 5 studies were of high quality as they scored more than 6 points. Table 1 summarizes the details of characteristics and scores of the studies.

3.2. Overall analysis

Overall meta-analysis was performed on all studies that reported one or more cancer events associated with BD (pooled RR, 1.19; 95% CI: 1.09–1.30, Fig. 2). However, the studies exhibited significant heterogeneity ($I^2 = 81.3\%$; $P = .000$).

3.3. Subgroup analysis

We explored factors affecting heterogeneity through subgroup analysis based on gender, country, and types of malignancy (Table 2). We found an increased risk for hematological cancer (pooled RR, 2.58; 95% CI: 1.61–3.55), especially the leukemia and non-Hodgkin lymphoma, and thyroid cancer (pooled RR, 1.25; 95% CI: 1.04–1.47) but not for other organ cancers. Interestingly female BD patients from Korean population showed higher risk for developing malignancy (pooled RR, 1.73; 95% CI: 1.36–2.10; pooled RR, 1.18; 95% CI: 1.07–1.29, respectively). However, female patients and those from Korean population also reflected heterogeneity ($I^2 = 50.7\%$; 83.5%, respectively).

3.4. Publication bias and sensitivity analysis

We addressed publication bias through Funnel plot and Begg test. We did not observe any obvious asymmetry in funnel plot (supplementary Fig. 1, http://links.lww.com/MD/D316). The P value of Begg test was $>.05$, clearly showing no publication bias in our meta-analysis. Pooled RR values did not alter drastically upon sequential omission of individual studies. Thus, the sensitivity analysis showed our meta-analysis method to be reliable.

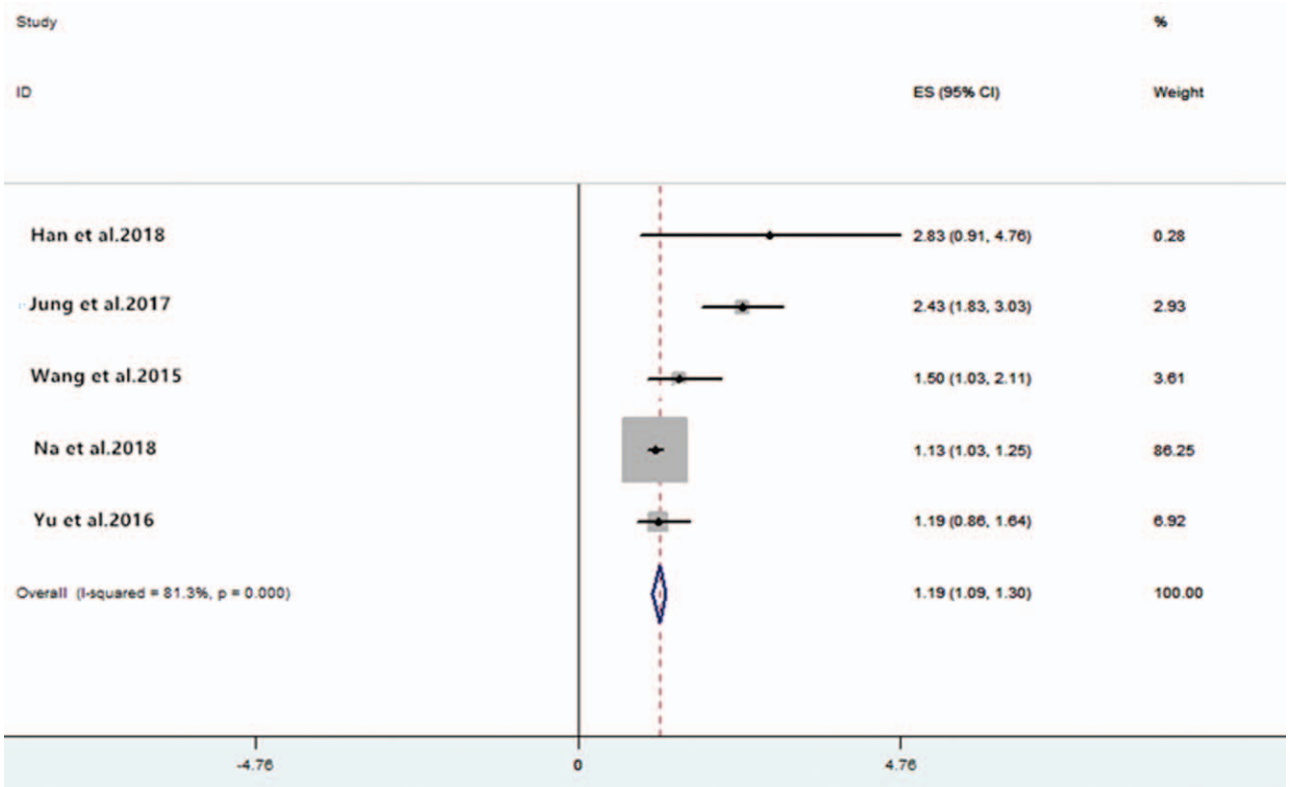

Figure 2. Forest plots depicting malignancy risk and Behcet disease.

Table 2

Pooled relative risks of various malignance and subgroup analysis.

Characteristic	Number of studies	Pooled RR (95% CI)	Heterogeneity	
			I^2, %	*P* value
Overall cancer	5	1.19 (1.09, 1.30)	81.3	.000
Total patients				
Female	5	1.73 (1.36, 2.10)	50.7	.108
Male	5	1.30 (0.88, 1.72)	74.7	.008
Country				
Korean	3	1.18 (1.07, 1.29)	83.5	.000
China	2	1.30 (0.98, 1.61)	0	.362
Malignancies				
Lung cancer	5	1.08 (0.71, 1.45)	0	.661
Cancer of digestive system	5	0.87 (0.72, 1.01)	1.8	.435
Cancer of urinary organs	5	1.73 (0.98, 2.48)	0	.955
Brain and CNS	4	1.80 (0.76, 2.83)	0	.796
Thyroid	3	1.25 (1.04, 1.47)	0	.998
Bone and articular cartilage	2	4.24 (−9.09 17.57)	0	.512
Breast cancer	4	0.93 (0.70, 1.16)	3	.378
Cancer of male genital system	4	1.85 (0.98, 2.66)	0	.776
Cancer of female genital system	5	0.84 (0.51, 1.18)	0	.774
Hematological cancer	5	2.58 (1.61, 3.55)	20.1	.271
Leukemia	4	5.24 (2.22, 8.25)	0	.856
Non-Hodgkin lymphoma	3	6.98 (1.17, 12.79)	0	.811
Other cancers	3	1.37 (−0.08, 2.83)	33.3	.200

CI = confidence interval, RR = relative risk.

4. Discussion

Our study is a novel work in the field of systematic review and meta-analysis highlighting the connection of BD with malignancy. We concluded association of BD with overall increased cancer susceptibility (pooled RR, 1.19; 95% CI: 1.09–1.30). We also found high degree of heterogeneity. Thereafter, the source of heterogeneity was assessed via subgroup analysis, which found that most of the heterogeneity was attributable to gender and country factors; especially male and Korean (Table 2).

During subgroup analysis of specific cancer types, we observed that BD reflects an increased risk of association with hematological cancer (pooled RR, 2.58; 95% CI: 1.61–3.55) and thyroid cancer (pooled RR, 1.25; 95% CI: 1.04–1.47) through subgroup analysis of different cancer types. Our findings were consistent with previous studies.[18,19] Besides, Turesson et al and Baecklund et al reported that broad categories of autoimmune disorders, including rheumatoid arthritis, Sjogren syndrome, are associated with an advanced risk for hematologic cancer.[4,20] As for the mechanism, some researchers considered that chronic activation, B or T cell stimulation, and different inflammatory cytokines including interleukin (IL)-6, IL-8, TNF are involved in BD just like the pathogenic mechanisms of hematologic cancers. Moreover,HLA-B27, as the major MHC class I, is also associated with BD.[13,20,21] Furthermore, thyroid cancer in solid tumors was the first time shown to have correlation to BD. In the past, BD was observed to be connected to incidence of solid tumors of breast, uterus, thyroid, and stomach in some case and case series, but it was difficult to determine whether BD had a greater risk of solid cancers.[18] Our meta-analysis indicated it to be sufficient to monitor patients with BD for the development of hematological and thyroid cancer. However, our results do need to be further examined because of a low number of studies.

It was interesting to note that females reflected an increased risk of association with cancer (pooled RR, 1.73; 95% CI: 1.36–2.10) during the subgroup analysis. As we all know, inflammatory could accelerate epigenetic alterations and could cause inflammation-related carcinogenesis, which chronic inflammation is thought to be a causal factor in cancer briefly.[2,6,20] However, it is well appreciated BD runs a less severe disease course among the females. To the contrary, males have a distinctly more severe course, particularly associated with pulmonary vascular disease.[22,23] This counter-intuitive finding of more cancer among the females deserves attention. Some scholars suppose that sex hormones may contribute to the pathogenesis of cancer because of the relationship between breast cancer and BD.[13] However, our analysis did not reflect the increased risk of association with breast cancer, and past studies did not prove significant changes in estrogen serum levels included the higher prolactin serum levels.[24] Therefore, the result needs to be further investigation in the future.

The strength of our studies is as follows: Firstly, it is a novel meta-analysis with a large cohort to evaluate the association between BD and malignancy, wherein all of the included studies are population-based work. Moreover, subgroup and sensitivity analyses helped to determine the possible influential causes to affect the results and thereby increased the strength of our findings. Thirdly, the study involved exhaustive literature review to explore the connection between BD and the risk of malignancy. Finally, most of the studies included in our work were of high quality. These characteristics make our research findings more convincing.

Like other studies, our work was also not devoid of limitations. There are several limitations that must be considered. First, though our work focused on the risk for malignancy in patients with BD. The included studies involved different design and demographic characteristics, which can introduce bias in the readouts. Second, the malignancies reported in the studies were not characterized in detail, thereby limiting definitive conclusions through subgroup analyses. Third, all of the included studies were performed in Asian population and hence extrapolating the

conclusions to worldwide population would be erroneous. Fourth, the meta-analysis could be questioned of publication bias as we included only 5 studies though the *P* value of Begg test was >.05. At last, there was bias in use of literature search portals which omitted out Google scholar (GS) due to institutional limitation in access.

5. Conclusion

Our study concludes higher risk of BD patients to be afflicted with malignancy. The finding should be validated in bigger cohorts for firm conclusions. Moreover, we wish our analysis will identify future direction for research in BD.

Author contributions

Conceptualization: Xin Wang, Yu Peng, Jun Gao, Yongning Li.
Data curation: Xin Wang.
Formal analysis: Yu Peng.
Investigation: Xin Wang, Yongning Li.
Methodology: Yu Peng, Shiyuan Han.
Visualization: Jun Gao.
Writing – original draft: Xin Wang.
Writing – review & editing: Xin Wang, Yongning Li.

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