Risk of Malignancy in Juvenile-Onset Arthritis (Brief Report)

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Abstract: *Objective*: An increased risk for certain types of malignancies has been reported in rheumatoid arthritis (RA) patients. Comparable risks may exist in juvenile-onset arthritis due to its pathophysiological similarities with adult rheumatoid arthritis. Our objective was to investigate the relationship between juvenile-onset arthritis and risk of malignancy.

Methods: A systematic review of the published literature was performed. Articles reporting data concerning the observed cancer rates in patients with juvenile-onset arthritis versus the general population rates were further assessed. The standardized incidence ratios (SIR) of observed to expected cases were retrieved from the studies and pooled in order to determine the overall risk of malignancy in patients with juvenile-onset arthritis.

Results: The pooled SIR for overall cancer was 1.4 (95% Confidence Interval, CI 1.2-1.7). However, study data were not homogenous: certain studies showed a significantly increased risk of malignancy overall in juvenile-onset arthritis, but others showed that there was no significant increase in cancer risk overall. The pooled SIR for hematological malignancies was 1.7 (95% CI 1.2-2.4) across all studies.

Conclusions: Existing data on malignancy risk in juvenile-onset arthritis are conflicting. Additional data are needed in order to definitively establish the presence or absence of an association between juvenile-onset arthritis and cancer risk.

Keywords: Juvenile idiopathic arthritis, standardized incidence ratio, cohort studies, malignancy, review.

INTRODUCTION

Juvenile-onset arthritis, or juvenile idiopathic arthritis (JIA), is an inflammatory arthropathy occurring in children under the age of 16. The disease seems to be more prevalent in Caucasian ethnic groups and less so in African-American and other non-Caucasian populations [1]. The overall incidence is approximately 11.7 out of 100 000 according to a study conducted on children in the United States [2]. The peak age of onset for JIA is between the ages of 1 to 3 [3]. In various studies, it has been suggested that there is an increased incidence of malignancies such as lymphoma in adult patients with rheumatoid arthritis (RA) compared to the general population [4]. As the pathology and disease progression of juvenile-onset arthritis and adult-onset RA bear resemblances, it is possible that having underlying juvenile-onset arthritis may also cause an increased risk of developing similar comorbidities such as cancer [5]. We performed a systematic review and pooled analysis of current existing cohort studies in order to examine the risk of malignancy in juvenile-onset arthritis compared to the general population.

METHODS

A review was performed of published peer review articles that documented cancer incidence data in juvenile-onset arthritis. This was done by searching for relevant studies according to the PRISMA statement [6], focusing particularly on observational cohort studies in biomedical electronic databases. A search strategy using Boolean logics and search terms for juvenile-onset arthritis ("Arthritis, Juvenile," "juvenile rheumatoid arthritis," "juvenile idiopathic arthritis," "juvenile chronic arthritis," and the various subtypes of JIA) and malignancy ("neoplasms," "malignancy," "cancer") was elaborated in order to identify relevant English and French language studies that were published from 2000-2016.

In addition to conducting a systematic search for primary articles, the bibliographies of review articles and primary studies were screened for additional pertinent articles. Each article of potential interest was reviewed in order to determine if they met inclusion criteria. Studies included in the final analysis were cohort studies that reported observed and expected cases of malignancies and had precise definitions for juvenile-onset arthritis, including JIA and cancer classification. The observational studies included were also assessed for quality using the STROBE checklist [7].

A primary pooled analysis was performed by extracting information on the total number of cases of cancer observed, as well as the total expected number of cases of cancer reported in the studies. The number of observed cases of malignancies was compared to the number of expected cases using standardized

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incidence ratios (SIRs), which is the ratio of the number of observed to expected cancer cases. The observed and expected events were pooled across all selected articles in order to obtain a pooled overall SIR. 95% confidence intervals for the pooled SIR were calculated based on the Bayar's approximation of the exact Poisson distribution [8]. SIRs were also pooled and calculated for hematological malignancies and for different categories of drug exposure (usage of disease-modifying antirheumatic drugs (DMARDs,) such as methotrexate (MTX), and biologic agents), where possible.

In this article we use the term 'juvenile-onset arthritis' because some of the studies included only juvenile rheumatoid arthritis, and some of the studies included a broader group of juvenile idiopathic arthritis (JIA). Because of this, and because the studies did not always use JIA criteria that the clinical community currently employ, we felt it was most correct to simply use the term 'juvenile-onset arthritis" in our paper.

RESULTS

1465 citations were identified in the first screening of the databases. 13 articles were further reviewed after the first screen and 6 articles were included in the final analysis (see Figure **1** and Table **1**).

The resulting pooled SIR of the six identified cohort studies (see Table **2**) was 1.4 (95% CI 1.2-1.7) which indicates that overall malignancy risk seems to be increased in patients with underlying juvenile-onset arthritis. However, it is important to note that methodology varied between studies, and the results were not homogeneous.

More specifically, methodology varied between studies in how incident cancer cases were identified. The majority of studies identified were administrative data-based. Thus, physician billing and hospitalization claims data were the primary sources of data used in the identification of juvenile-onset arthritis cases, and billing and hospitalization claims were also used to identify cancer cases among those subjects with juvenile-onset arthritis. In three studies, cancer cases were identified using medical claims data [9-11]. However, in the three other studies, cancer cases were identified using their respective regional or national cancer registries [12-14]. Pooling and calculating the SIRs for these 2 different groups of data suggests that the use of different methods for cancer outcome identification may drive at least some of the heterogeneity of results. In the first group of studies using claims data to identify cases of malignancy, the pooled SIR of the three studies was 3.3 (95% CI 2.4-4.3) whereas in the second group using cancer registry

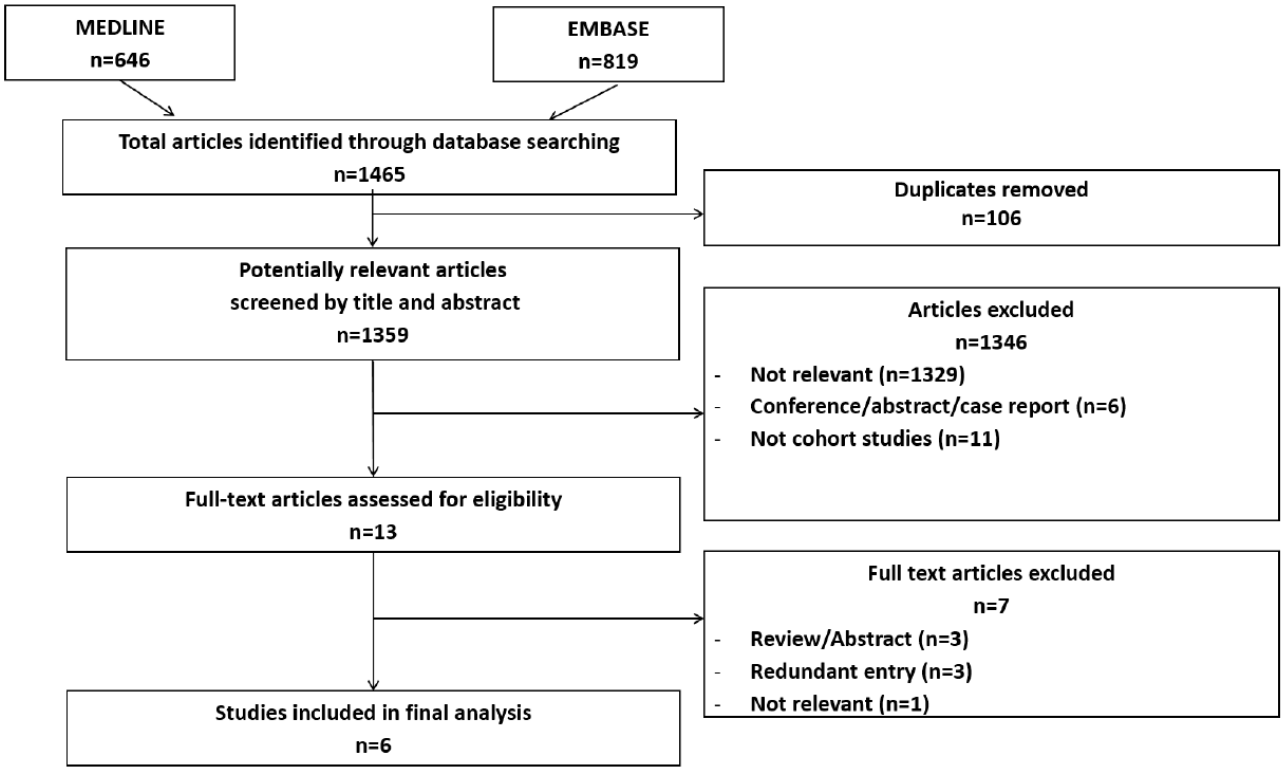

Figure 1: PRISMA flow diagram.

Table 1: Study Characteristics

Author	Country	Data Used	Cohort Size	Average follow up (patient-years)	Female (percent)	JIA and cancer cohort identification method
Beukelman *et al.* 2012 [9]	United States	National U.S. Medicaid data	7812	1.61	64	JIA: ICD-9 claims codes and pharmacy claims meeting JIA classification criteria Cancer: ICD-9 claims codes for malignant neoplasm, procedure codes and pharmacy claims
Kok *et al.* 2014 [10]	Taiwan	Taiwan National Health Insurance Research Database	2892	6.40	44	JIA: ICD-9-CM claims codes meeting JIA classification criteria Cancer: ICD-9-CM claim codes for malignant neoplasm
Nordstrom *et al.* 2012 [11]	United States	PharMetrics Patient-Centric Database.	3605	1.65	71.5	JIA: ICD-9 claims codes meeting JIA classification criteria Cancer: ICD-9 claims codes for malignant neoplasm
Simard *et al.* 2010 [12]	Sweden	Swedish Patient Register	9027	14.5	55.6	JIA: ICD claims codes meeting JIA classification criteria Cancer: Swedish Cancer Register data
Thomas *et al.* 2000 [13]	UK	Hospital inpatient records	896	7.35	61	JIA: ICD claims codes for juvenile chronic arthritis Cancer: Scottish Cancer Registry data
Zahedi *et al.* 2016 [14]	Canada and US	Clinical JIA registries at 6 Canadian and American hospitals	5294	6.8	68	JIA: clinical data from hospital electronic medical records Cancer: regional cancer registries

Table 2: Cancer Rates and Risk in Patients with JIA

Author	Cancer events observed	Cancer events expected	SIR	95% Confidence interval	DMARD exposure
Beukelman *et al.* [9]	10	3	3.30	1.6 - 6.1	Stratified between no exposure, MTX exposure, and biologics exposure
Kok *et al.* [10]	33	10.4	3.21	2.2 - 4.5	Stratified between MTX exposure and biologics exposure
Nordstrom *et al.* [11]	4	0.99	4.03	2.56 - 5.99	Biologics naïve, MTX exposure
Simard *et al.* [12]	60	54.5	1.10	0.9 - 1.5	Not reported
Thomas *et al.* [13]	4	4.24	0.94	0.3 - 2.4	Not reported
Zahedi *et al.* [14]	9	10.9	0.82	0.38 - 1.5	50-60% of cohort exposed, specific data not reported

Table 3: Standardized Incidence Ratios (SIRs) for Malignancy Stratified According to Methotrexate (MTX) and Biologic Drug Exposures

Author	Overall SIR (95%CI)	SIR, No MTX (95%CI)	SIR, MTX (95%CI)	SIR, Biologic drugs (95%CI)
Beukelman *et al.* [9]	3.30 (1.6-6.1)	4.60 (1.7-10)	3.30 (0.7-9.5)	1.60 (0.03-8.3)
Kok *et al.* [10]	3.20 (2.2-4.5)	3.21 (2.01-5.05)	2.64 (0.65-7.53)	4.61 (0.23-23.61)
Nordstrom *et al.* [11]	4.03 (2.56-5.99)	-	-	-
Simard *et al*. [12]	1.10 (0.9-1.5)	1.00 (0.7-1.4)	-	-
Thomas *et al.* [13]	0.94 (0.3-2.4)	-	-	-
Zahedi *et al.* [14]	0.82 (0.38-1.5)	-	-	-

data, the pooled SIR of the three studies was 1.05 (95% CI 0.82-1.32).

In a few studies, patients were also stratified based on their exposure to disease-modifying agents, DMARDs. Table **3** reports the SIRs for malignancy risk based on DMARD exposure.

Hematological malignancies were also observed in these cohort studies. The pooled SIR for hematological malignancies was 1.7 (95% CI 1.2-2.4) across all studies.

DISCUSSION

The pooled overall SIR of 1.4 (95% CI 1.2-1.7) does indicate an overall increase in cancer risk in the studies identified. However, results were heterogeneous and stratifying for different cancer outcome identification methodologies showed that studies using physician billing and hospitalization claims data reported a significant increase in overall cancer risk (3.3, 95% CI 2.4-4.3) while studies using cancer registry data did not clearly show an increase in overall cancer risk (1.05, 95% CI 0.82-1.32).

Studies do suggest that using administrative data to identify cancer outcomes is inferior to cancer registry data. One study [15] comparing claims data to cancer registry data for breast cancer ascertainment showed that the claims data had a low positive predictive value of 43%, indicating many false positive cases. This could explain why the individual SIRs of cancer risk in JIA differ.

The differences in how subjects with juvenile-onset arthritis were identified may also explain the heterogeneity in results. According to a study by Stringer *et al*. [16] over a third of juvenile-onset arthritis cases identified in health care claims databases were false positives.

The effects of DMARDs and immunomodulatory therapy (methotrexate and biologics) on cancer risk in juvenile-onset arthritis are unclear, as several studies have not stratified their results based on treatment modality. One study has suggested the risk of malignancy in children using TNFα inhibitors is increased [17]. A similar relationship may exist with methotrexate and cancer risk in juvenile-onset arthritis [18]. However, a true causal relationship is uncertain due to the possibility of increased disease activity associated with higher underlying malignancy risk acting as a confounder in these cohorts.

In terms of the cohorts included in our analysis, the Beukelman and Kok studies stratified their populations based on unexposed patients, patients taking biologics and patients taking both MTX and biologics. They both showed lower risk of cancer in juvenile-onset arthritis patients treated with MTX, compared to unexposed patients (see Table **3**). However, due to wide confidence intervals and the heterogeneity of the data, the significance of these results is unclear. Similarly, in the Simard study, patients with JIA identified before 1987 appeared to not be at increased risk of cancer, whereas patients with JIA identified in 1987 and thereafter had higher rates of cancers overall (SIR 2.3, 95% CI 1.2-4.4). The authors note that 1987 was approximately the year MTX was introduced as a DMARD, and suggest this drug as the cause of the higher SIR in later years. However, that is not compatible with the results of Beukelman and Kok above. Moreover, patients that use stronger therapeutic agents frequently have higher disease inflammatory activity, which may also be a risk determinant for malignancy in juvenile-onset arthritis. Disease severity

in RA in particular correlates with increased lymphoma incidence [19] and a similar association may exist in JIA. It is also important to note that the literature on anti-TNFα inhibitors shows a dose dependent increase in risk of malignancy for RA patients treated with these agents [20]. Thus, both increased medication usage and increased disease activity are elements to consider when looking at the risk of malignancy in patients with juvenile-onset arthritis.

Across these studies, there is evidence that the risk of hematological malignancies specifically may be higher in juvenile-onset arthritis, versus the general pediatric population. The pooled SIRs across all studies was 1.7 (95% CI 1.2-2.4) for hematological malignancies. This is reminiscent of the increase seen for hematologic malignancies, specifically lymphoma, in adults with RA [4].

CONCLUSION

In conclusion, it is unclear if patients with juvenile-onset arthritis have an elevated risk of malignancy overall, although several studies suggest that juvenile-onset arthritis patients may have an elevated risk of hematological malignancies. Some of the heterogeneous results are likely due to differences in methodology between studies. Future studies of juvenile-onset arthritis and cancer risk are warranted, but adequate methodology is needed in order to ascertain the true cancer risks in juvenile-onset arthritis.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest

There are no conflicts of interest.

Ethical Approval

This article is a review of published studies and does not include any studies with human participants or animals performed by any of the authors.

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CONTRIBUTOR'S STATEMENT

WC and SB designed the study, drafted the manuscript, and approved the final manuscript as submitted.

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