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Higher incidence of rheumatoid arthritis in patients with symptomatic osteoarthritis or osteoarthritis-related surgery: a nationwide, population-based, case–control study in Taiwan

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ABSTRACT

Objectives: To investigate the risk of incident rheumatoid arthritis in patients with symptomatic osteoarthritis or osteoarthritis-related surgery using a nationwide health claims database.

Design: A nationwide, population-based, case–control study.

Setting: Taiwan's National Health Insurance Research Database.

Participants: A total of 1147 patients (aged 20–100 years) with rheumatoid arthritis and 5735 controls who were frequency-matched for sex, 10-year age interval and year of catastrophic illness certificate application date (index year) were identified.

Main outcome measure: All participants were retrospectively traced, up to 14 years prior to their index year, for diagnosis of osteoarthritis or osteoarthritis-related surgery. Multivariate logistic regression analyses were conducted to quantify the association between rheumatoid arthritis and osteoarthritis.

Results: The risks of rheumatoid arthritis were significantly higher in patients with symptomatic osteoarthritis (adjusted OR=5.24, p<0.001) and osteoarthritis-related surgery (adjusted OR=2.27, p<0.001).

Conclusions: This large nationwide, population-based, case–control study showed a higher risk of rheumatoid arthritis in Taiwanese patients with symptomatic osteoarthritis. Our findings were consistent with the hypothesis that osteoarthritis might be a triggering factor of rheumatoid arthritis in environment-sensitised and genetically susceptible individuals.

Strengths and limitations of this study

- The major strength of this study is the use of a nationwide, population-based claim database, which could minimise recall and selection bias.
- The major limitation of the study was the lack of information on radiographic reports, serological data and lifestyle habits of the patients.
- Another limitation of the study was the possibility of misclassification because the diagnosis of osteoarthritis or osteoarthritis-related surgery was based solely on International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis and its prevalence increases markedly with age, reaching its highest level in people over 65 years of age.[1] In Taiwan, the average age-adjusted annual incidence and prevalence of RA were 15.8 and 80.3/100 000, respectively.[2] The pathogenesis of RA is complex, involving environmental as well as genetic factors.[3] There is a long-induction period for the development of RA, which can broadly be divided into three stages. First, environmental factors, such as smoking, trigger the formation of anticitrullinated protein antibodies (ACPAs) in genetically susceptible individuals. A second hit, such as a virus infection or trauma, elicits an inflammatory response that causes protein citrullination in the joints. These citrullinated proteins then become recognisable by ACPAs. Third, the pre-existing ACPAs react with the citrullinated proteins in the joints, leading to a vicious cycle that results in a chronic inflammation of the joints.[4]

We speculated that osteoarthritis (OA) might be a possible second hit factor. OA is one of the most common musculoskeletal diseases in Taiwan, with a self-reported prevalence of 20–24% in men and 34–35% in women, among those aged 65–84 years.[5] The incidence of symptomatic OA is elevated in

middle-aged individuals and the development of OA also requires a long time. OA was originally thought to be a degenerative disease due to 'wear and tear', but the current understanding of the disease is that inflammatory process can also be a key element in the development and progression of OA.[6] Inflammatory cytokines, such as tumour necrosis factor α, interleukin (IL)-1 and IL-6, which are known to play a crucial role in the pathogenesis of RA,[7] are also involved in the pathophysiological events of OA.[8] Most importantly, the critical point of the second hit, protein citrullination, is an inflammation-dependent reaction, rather than a specific event that can only be found in patients with RA.[9] Although the amount of citrullinated proteins is very high in the synovial tissue among patients with RA,[10] there is evidence suggesting that citrullinated proteins can also be detected immunohistologically in the synovial tissue among some patients with OA.[11] Therefore, we speculated that OA might play a role in the pathogenesis of RA. The aim of this case–control study was to explore the risk of incident RA in patients with symptomatic OA or OA-related surgery, using a nationwide health claims database in Taiwan.

MATERIALS AND METHODS

Study design and data source

This study used a nationwide, population-based, case–control study design based on the data available from the National Health Insurance Research Database (NHIRD) in Taiwan.[12]

The study protocol was reviewed and approved by the institutional review board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan (number B10004021). Since patient information was anonymised and de-identified prior to analysis, the need for written informed patient consent was waived by the institutional review board.

Identification of cases and controls

Using the 1997 to 2010 catastrophic illness data file, a part of the NHIRD, cases were defined as new and successful applicants for the certificate of catastrophic illness with RA (International Classification of Diseases, ninth revision, clinical modification, ICD-9-CM code 714.0). In Taiwan, patients with RA can apply for catastrophic illness certificates from the National Health Insurance Administration (NHIA) to become exempt from copayments for healthcare costs related to RA. The certificate is issued to patients only after their medical records, laboratory data and imaging results have been reviewed by at least two rheumatologists. The index date was defined as the date of first application of catastrophic illness certificate in the cases.

Controls were selected from a random sample of the ambulatory care data file of the 2000 Longitudinal Health Insurance Database (LHID2000) with the inclusion period of 1 January 1997 to 31 December 2011. The LHID2000 contains the claim data and registration files of both, ambulatory and inpatient care expenditures, for one million individuals randomly sampled from the 2000 Registry for Beneficiaries of the NHIRD.

Individuals identified as cases were excluded from the selection. Five controls per case were selected based on frequency matching for sex, 10-year age interval and index year. The index year was defined as the same year of the index date of the matched case. The index date for each of the control participants was assigned by using the date of a randomly selected ambulatory visit for a given index year.

Identification of osteoarthritis

The cases and controls were both linked to the LHID2000, which retrospectively traced their ambulatory medical visits occurring between 1 January 1997 and 31 December 2011. OA was defined by ICD-9-CM code 715.xx or A-code A431. To increase the accuracy of ascertainment, only patients who had at least three instances of ambulatory claims of OA that occurred within a period of 90 days were included. In addition, patients with OA diagnosed after the index date were excluded.

Furthermore, the risk of RA between patients with severe cases of OA that required surgical treatment was also evaluated to avoid the potential differential misclassification caused by detection bias as a result of increased medical surveillance in patients at their early stages of RA (prior to a definitive diagnosis of RA). The inpatient data set of the 1997–2011 NHIRD was used to identify inpatients who required OA-related surgery based on the primary inpatient diagnosis code of ICD-9-CM 715.xx. Patients with OA-related surgery after the index date were excluded from the analyses. In addition, patients diagnosed with diabetes (ICD-9-CM code 250) before the index date were identified and adjusted in the statistical models.

Statistical analysis

Sex and age groups between cases and controls were compared with χ^2 test or Mann-Whitney U-test, as appropriate. Multivariate unconditional logistic regression analyses were used to assess the risk of RA in patients with symptomatic OAs or OA-related surgery. A two-tailed p value of <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics software package, V.22.0 (IBM Corp, Armonk, New York, USA).

RESULTS

We identified 1147 patients newly diagnosed with RA and having a certificate of catastrophic illness as cases, and 5735 non-RA controls frequency-matched for sex, 10-year age interval and index year. The overall median age for the cases and controls was 53 years, and the female to male ratio was 3.3:1. As cases and controls were sampled using frequency matching, there were no

Table 1 Characteristics of patients with rheumatoid arthritis and frequency-matched controls (N=6882)

Variable	n (%) Cases 1147 (16.7)	Controls 5735 (83.3)	p Value
Sex			>0.999
Male	266 (23.2)	1330 (23.2)	
Female	881 (76.8)	4405 (76.8)	
Age (years)			>0.999
20–29	68 (5.9)	340 (5.9)	
30–39	112 (9.8)	560 (9.8)	
40–49	257 (22.4)	1285 (22.4)	
50–59	326 (28.4)	1630 (28.4)	
60–69	204 (17.8)	1020 (17.8)	
70–79	139 (12.1)	695 (12.1)	
80–89	38 (3.3)	190 (3.3)	
90–99	3 (0.3)	15 (0.3)	
Median (minimum–maximum)	54 (20–93)	53 (20–97)	0.532
Osteoarthritis	497 (43.3)	979 (17.1)	<0.001
Osteoarthritis-related surgery	47 (4.1)	86 (1.5)	<0.001
Diabetes mellitus	153 (13.3)	373 (6.5)	<0.001

Per cent are column percentages except in the header row where they are row percentages.

significant differences in their age and sex distribution (table 1). The proportion of symptomatic OA was significantly higher in cases (43.3%) than in controls (17.1%) (p<0.001). For OA-related surgery, its proportion was also significantly higher in cases (4.1%) compared with controls (1.5%) (p<0.001). In addition, a higher proportion of cases (13.3%) had diabetes mellitus compared with controls (6.5%) (p<0.001).

Table 2 shows the risks of RA in patients with symptomatic OA or OA-related surgery. The risk of RA was significantly higher among patients with symptomatic OA (adjusted OR=5.24, p<0.001) or OA-related surgery (adjusted OR=2.27, p<0.001) compared with controls. Similar patterns were observed in male and female patients, except that the significance level among males for OA-related surgery was marginal (p=0.061). With stratified analyses by three age categories, associations of largest magnitude were observed in the youngest age group (20–50 years old) in both symptomatic OA (adjusted OR=10.36, p<0.001) and OA-related surgery (adjusted OR=6.20, p=0.007) (table 3). The risks of RA were significantly higher in patients with OA or OA-related surgery in all three age groups.

DISCUSSION

This nationwide, population-based study showed that patients with symptomatic OA or those who had received an OA-related surgery exhibited a higher risk of developing RA. OA-related surgery in addition to OA was used in this study to minimise the chance of detection bias as a result of increased medical surveillance in patients prior to their definitive diagnosis of RA. Our previous study showed that the number of ambulatory medical visits increased several years prior to a definitive diagnosis of RA.[13] The increase in medical attention among these patients may, therefore, potentially lead to a detection bias. To this end, we included only patients with OA with persistent symptoms, defined as those who had made at least three instances of ambulatory claims of OA within a period of 90 days. Nevertheless, the early joint symptoms in patients prior to a definitive diagnosis of RA can be mild and self-limited, and can potentially be misclassified as OA. Therefore, we also evaluated the risk of RA among patients with OA severe enough to require surgical intervention. Since the need for OA-related surgery depends on the severity of OA and is based on careful clinical evaluations, it should not be affected by detection bias as a result of increased medical surveillance. Furthermore, the identification of OA-related surgery is highly reliable because approval must first be obtained from the Taiwan NHIA prior to any total knee replacement or total hip replacement procedure is performed. Applications are reviewed by experienced orthopaedists, based on strict case payment guidelines.[14] Regarding the types of OA-related surgery among the 47 patients who were subsequently diagnosed with RA, total knee replacement (66%, 31/47) was the most frequent procedure performed followed by other OA-related surgery such as arthroscopy of the knee joint

Table 2 Risks of rheumatoid arthritis in patients with osteoarthritis or osteoarthritis-related surgery, stratified by sex (N=6882)

Variable	All n=6882, 100% Adjusted OR* (95% CI)	p Value	Male n=1596, 23.2% Adjusted OR† (95% CI)	p Value	Female n=5286, 76.8% Adjusted OR† (95% CI)	p Value
Osteoarthritis						
No	1.00		1.00		1.00	
Yes	5.24 (4.42 to 6.22)	<0.001	6.74 (4.68 to 9.72)	<0.001	4.89 (1.03 to 5.93)	<0.001
Osteoarthritis-related surgery						
No	1.00		1.00		1.00	
Yes	2.27 (1.55 to 3.32)	<0.001	2.32 (0.96 to 5.61)	0.061	2.28 (1.50 to 3.47)	<0.001

*Adjusted for sex, age and diabetes mellitus.
†Adjusted for age and diabetes mellitus.

Table 3 Risks of rheumatoid arthritis in patients with osteoarthritis or osteoarthritis-related surgery, stratified by three age categories (N=6882)

	Age category (years)					
	20–50 n=2870, 41.7%		51–60 n=1837, 26.7%		≥61 n=2175, 31.6%	
Variable	Adjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Osteoarthritis						
No	1.00		1.00		1.00	
Yes	10.36 (7.36 to 14.59)	<0.001	4.34 (3.22 to 5.85)	<0.001	4.15 (3.16 to 5.46)	<0.001
Osteoarthritis-related surgery						
No	1.00		1.00		1.00	
Yes	6.20 (1.65 to 23.24)	0.007	3.77 (1.17 to 12.12)	0.026	2.08 (1.36 to 3.20)	0.001

The ORs were adjusted for age, sex and diabetes mellitus.

(15%, 7/47), total hip replacement (11%, 5/47) and miscellaneous (8%, 4/47).

Although findings from this study are consistent with the hypothesis that patients with OA might have an elevated risk of developing RA, it is premature to conclude that OA is a 'second hit' in the pathogenesis of RA. The increased expression of proinflammatory cytokines in synovial tissues observed in patients with RA and also in those with OA, suggests a link between the two disorders. Nevertheless, anti-inflammatory cytokines such as IL-4, IL-10 and IL-13, have also been suggested to be involve in the pathogenesis of OA.[6] Since OA and RA are leading causes of disability in elderly people, and can impose substantial burden and impact on individuals and the society,[15 16] further investigation is warranted to clarify the inter-relationship among OA, genetic factors such as HLA-DRB1-shared epitope alleles, the quantity and type of citrullinated proteins in joints and the risk of RA development.

Two limitations of this study deserve mentioning. First, since our data source is based on a claim database, radiographic reports, serological data (including inflammatory markers such as rheumatoid factor and ACPAs), or lifestyle habits such as smoking, are unavailable. Although smoking is an important risk factor for RA, the prevalence of smoking in Taiwan was under 5% for women and only 1.8% among women 55 years or older.[17] Thus, the higher risk of RA in female patients with symptomatic OA and OA-related surgery observed in this study should not be confounded by smoking. Second, the identification of OA and OA-related surgery was dependent on ICD-9-CM codes, and errors due to miscoding cannot be completely ruled out. Nonetheless, the Taiwan NHIA routinely performs expert reviews on random samples of medical claims to ensure their accuracy.

In conclusion, this large nationwide, population-based, case–control study showed that patients with OA and OA-related surgery exhibited a higher risk of developing RA. Our findings provided support to the hypothesis that OA can potentially act as a triggering factor of RA in environment-sensitised and genetically susceptible individuals.

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Contributors All the authors revised and approved the contents of the submitted article. M-CL and K-CL conceptualised the idea of the manuscript. MK conducted statistical analysis of data. M-CL, K-CL, MK and N-SL made substantial contributions to interpretation of data. M-CL and MK wrote the manuscript. All the authors carried out a critical revision of the manuscript for important intellectual content.

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