Cervical And Vaginal/Vulvar Malignancies Risk In Women With Rheumatoid Arthritis (RA)

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Abstract: *Objective*: Given recent concerns about cervical dysplasia with RA medications, we performed a literature review and a pooled analysis to examine the relative risk of cervical and vaginal cancers in RA.

Methods: We conducted a literature search covering 2007- 2014. A pooled analysis was conducted: the total numbers of cancers expected and observed across all studies were respectively summed for different cancer types (cervical and vaginal/vulvar cancers). As some studies pooled vaginal and vulvar cancers together, we did not discern between the two for the purpose of this study. Using these pooled estimates, standardized incidence ratios (SIRs) were calculated, demonstrating the relative risk of the cancers in RA, versus the general population.

Results: Our search strategy retrieved 13 papers. Our pooled SIR estimates were 0.82, 95% confidence interval, CI, 0.73-0.92 for cervical cancer in RA and 1.04, 95% CI 0.80-1.34 for vaginal/vulvar cancer in RA.

Conclusion: Our simple pooled analysis was consistent with a relatively lower cervical cancer risk in RA versus the general population, while the data did not establish if the risk of vaginal/vulvar cancer was different from the general population. Cervical cancer screening in RA will continue to be important, particularly as evolving treatment strategies may affect future risk.

Keywords: Rheumatoid arthritis, cervical cancer, vaginal cancer, vulvar cancer.

INTRODUCTION

Rheumatoid arthritis [RA] affects up to 1% of the developed world [1]. Malignancy is a major co-morbidity associated with RA [2-4]. Moreover, women comprise the majority of RA patients, thus it is important to explore the occurrence of cervical and vaginal cancers in RA. Cervical cancer causes approximately a quarter of a million deaths worldwide every year in the general population [5] and cervical dysplasia is significantly increased in rheumatic disease populations like systemic lupus (SLE). Vaginal cancer is also increased in SLE, and like cervical cancer, is associated with human papillomavirus (HPV) infection [6]. We performed a literature review of peer-reviewed articles evaluating vaginal and cervical cancers in RA, and a pooled analysis to examine the relative risk of these cancers in RA, compared to the general population.

MATERIALS AND METHODS

Eligibility Criteria

For our study, we included original published peer-reviewed prospective or retrospective observational cohort or nested case-control studies, documenting cervical and vaginal cancer incidence in adult RA patients. The studies were only included if they provided standardized incidence ratios (SIR) or enough information to be able to calculate them, such as the observed and expected cancer incidence (based on general population cancer rates). We limited our analyses to English and French articles.

Information Sources and Search Strategy

We conducted a literature search using MEDLINE/PUBMED and EMBASE, covering January 1st, 2007 to July 24th, 2014. The search terms used included: (Rheumatoid Arthritis or Inflammatory Arthritis or primary chronic polyarthritis or chronic progressive polyarthritis or rheumatic arthritis or rheumatic polyarthritis or chronic articular rheumatism) and (Cervical Cancer or Cervical Neoplasm or Cervical Carcinoma(s), Cervical Tumor or Cervical Adenocarcinoma(s) or Cervical Carcinogenesis or Cervical Sarcoma(s) or Vagina(-al) Cancer or Vagina(-al) Tumor or Vagina(-al) Adenocarcinoma or Vagina(-al) Carcinoma or Malignancy(-ies) and Vulva(r) Cancer or Vulva(r) Neoplasm or Vulva(r) Carcinoma or Endometrial Sarcoma or Vulva(r) Tumor or Vulva(r) Malignancy) and (cohort analysis/ or longitudinal study/ or prospective study/ or follow up/ or cohort$.tw. or followup.mp. or case control study/ or hospital based case control study/ or population based case control study/ or cancer epidemiology/ or (cancer adj3 epidemiolog*).mp. or observational study/ or observational method/) [7].

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We also reviewed the bibliographies and references of the included studies and published reviews, to identify any additional papers of relevance. We excluded studies that only looked at a subset of RA patients, such as cohorts formed by exposure to specific treatments.

After the initial search, we screened the titles and abstracts to identify all potentially relevant studies. Then we then reviewed the remaining full texts to confirm which articles met our inclusion criteria.

We then abstracted the following data: author, study year, publication year, method of cancer ascertainment, location of study, average follow up years, average age groups sample size, study design, observed events, expected events, SIR, and confidence intervals. A primary simple pooled analysis was conducted: the total numbers of cancers expected and observed across all studies were respectively summed for each of the different cancer types (cervical and vaginal/vulvar cancers). As some studies pooled vaginal and vulvar cancers together, we did not discern between the two for this study. Using the total number of observed and pooled expected cancers across all studies, we then formed a pooled standardized incidence ratio (SIR) which is the ratio of the number of observed cancers divided by the number expected. We generated 95% confidence intervals for the SIRs, by treating the number of observed cancers as a Poisson-distributed variable, then finding its related interval from published tables [8].

RESULTS

Our search strategy retrieved 1,698 research papers. After removing duplicates, 1,474 remained. We excluded 1,227 upon review of the titles and abstracts, which did not meet our inclusion criteria. Thus, we were left with 247 research papers of interest.

Of these, ten papers did not study RA subjects. Seven papers were excluded because they did not examine malignancy, but rather cancer mortality. Fifteen papers only examined specific RA subpopulations and so their subjects did not represent the generalized RA population. Thirty papers were excluded because they either studied cancer prevalence (not incidence) or did not provide expected cancer incidence or enough information to estimate this. Fifty-two papers were excluded because they were not original observational studies, and seventy-two papers did not look at malignancy at all. Forty-six papers were also excluded because they did not examine the cancers of interest, but looked only at other cancers associated with RA such as lung, kidney, liver neoplasms etc.

In the end, from the years 1993 to 2014, there were fifteen cohort studies that looked at the incidence of at least one of the cancers of interest [9-23]. Askling *et al.,* 2005 [10], Hemminiki *et al.,* 2008 [14] and Hemminiki *et al.,* 2012 [15] used data from the Swedish National Inpatient Register and the Swedish Cancer Register. To avoid data overlap, we included only Hemminiki *et al.,* 2012 [15] who used data between 1964 and 2008 and seemed to be the most inclusive of all three papers. Both Huang *et al.,* 2014 [16] and Chen *et al.,* 2011 [11] also used the same source and overlapping period to collect their data, more specifically the National Health Insurance Research Database. As a consequence, we only included Huang *et al.,* 2014 [16], for cervical cancers, who examined patients for a similar (but longer) period from 1996 to 2008. However, for vaginal cancers, we included Chen *et al*. because Huang *et al*. did not examine vaginal cancers and so there was no overlap.

Thus thirteen research papers were included in our final cervical cancer analysis and three in our vaginal/vulvar cancer analysis. These studied a total of 188,597 women with RA in the context of cervical cancer, which were observed for a total of 1,588,982 person-years and 94,581 women with RA in the context of vaginal/vulvar cancer for 471,611 person-years. Overall, 308 cervical cancers and 63 vaginal cancers were observed (see Tables **1** and **2**). The pooled SIRs were 0.82 (95% CI: 0.73-0.92) for cervical cancer and 1.04 (95% CI: 0.80-1.34) for vaginal/vulvar cancer.

DISCUSSION

Cervical and vaginal cancers are two important gynecological malignancies and it is essential to track the various patterns associated with these cancers to implement surveillance and prevention strategies. Statistical research in cervical cancer is complex because cervical, vulvar and vaginal cancers are related to HPV infection [14, 15, 24, 25]. In other autoimmune rheumatic diseases such as systemic lupus (SLE), there is a concern that HPV clearance is impaired or delayed, resulting in a persistent carriage of HPV, and risk of cervical dysplasia/neoplasia and vaginal/vulvar cancers [26, 27]. An increased risk of cervical dysplasia is well documented in SLE, along with an increased risk of vaginal/vulvar cancers

Table 1: Studies Assessing Observed and Expected Cervical Cancers in Women with Rheumatoid Arthritis

Study	Cancer Ascertainment Method	Comparator	Country	Female N	Mean Person-Years Follow Up	Female Person-Years	Observed	Expected	Standardized Incidence Ratio	95% Confidence Intervals
Huang *et al.* 2014	ICD-9-CM codes from the National Health Insurance Research Databases and Registry of Catastrophic Illness Database	general Taiwanese population	Taiwan	23680	7.4	175232	60	74.0	0.81	0.63-1.04
Hemminki *et al.* 2012	ICD-9 codes from the Swedish Hospital Discharge Register and the Nation-Wide Swedish Cancer Registry	patients not hospitalized for any autoimmune diseases	Sweden	38881	18.8	731954	105	93.8	1.12	0.92-1.36
Yamada *et al.* 2011	IORRA cohort patient self-reports	general Japanese population	Japan	6189	3.4	21211	4	2.9	1.36	0.37-3.49
Parikh-Patel *et al.* 2009	ICD-9 codes from California OSHPD patient hospital discharge data set and California Cancer Registry data set	general California population	USA	65236	4.8	313133	47	110.0	0.43	0.31-0.57
Abasolo *et al.* 2008	EMECAR RA cohort; Cancer was ascertained from the medical records and verified with the patient during the study visit.	GLOBOCAN database general population of Spain	Spain	568	2.7	1538	1	0.2	4.10*	0.10-22.70
Wolfe and Michaud 2007	US National Data Bank for Rheumatic Diseases longitudinal study of RA outcomes semiannual questionnaires	Population cancer rates from the US Surveillance, Epidemiology, and End-Results database	USA	10818	4.5	48582	4	5.0	0.80	0.40-1.90
Thomas *et al.* 2000	ICD-9; ICD-10 codes hospital in-patient records and the Scottish Cancer Registry	national cancer incidence rates of the Scotland general population	Scotland	19543	5.7	113333	26	29.2	0.89	0.58-1.31
Cibere *et al.* 1997	University of Saskatchewan Rheumatic Disease Unit semi-annual mailing of the Stanford Health Assessment Questionnaire and patient follow-up and Provincial Cancer Registry	province of Saskatchewan population	Canada	577.5	17.4	10049	1	2.0	0.49	0.06-2.76
Mellemkjaer *et al.* 1996	ICD-8 codes of Danish Hospital Discharge Register and Danish Cancer Registry	Danish population	Denmark	14647	7.0	102529	40	36.9	1.10	0.80-1.50
Morimoto *et al.* 1995	RA patients living in Osaka prefecture and treated at the Center for Adult Diseases were matched against the files of the Osaka Cancer Registry	Osaka general population	Japan	524	6.1	3196	3	1.4	2.15	0.43-6.27
Gridley *et al.* 1993	ICD-7 and ICD-8 codes in Swedish Hospital Inpatient Register and National Swedish Cancer Registry	Uppsala Health Care Region cancer incidence rates	Sweden	7933.0	8.6	68224	17	18.9	0.90	0.50-1.40
TOTAL				188597	7.86	1588982	308	374.37	0.82	0.73-0.92

Table 2: Studies Assessing Observed and Expected Vaginal/Vulvar Cancers in Women with Rheumatoid Arthritis

Study	Cancer Ascertainment method	Comparator	Country	Female N	Mean Person-Years Follow Up	Female Person-Years	Observed	Expected	Standardized Incidence Ratio	95% Confidence Intervals
Chen *et al*. 2011	ICD-9 codes from the Registry of Catastrophic Illness Database	general Taiwanese population	Taiwan	18527	5.9	109309	5	2.96	1.69	1.54-1.84
Parikh-Patel *et al*. 2009	ICD-9 codes from California OSHPD patient hospital discharge data set and California Cancer Registry data set	general California population	USA	65236	4.8	313133	56	56.6	0.99	0.75-1.29
Wolfe and Michaud 2007	US National Data Bank for Rheumatic Diseases longitudinal study of RA outcomes semiannual questionnaires	Population cancer rates from the US Surveillance, Epidemiology, and End-Results	USA	10818	4.55	49169	2	0.74	2.7	0.80-8.60
TOTAL				94581	5.08	471611	63	60.3	1.04	0.80-1.34

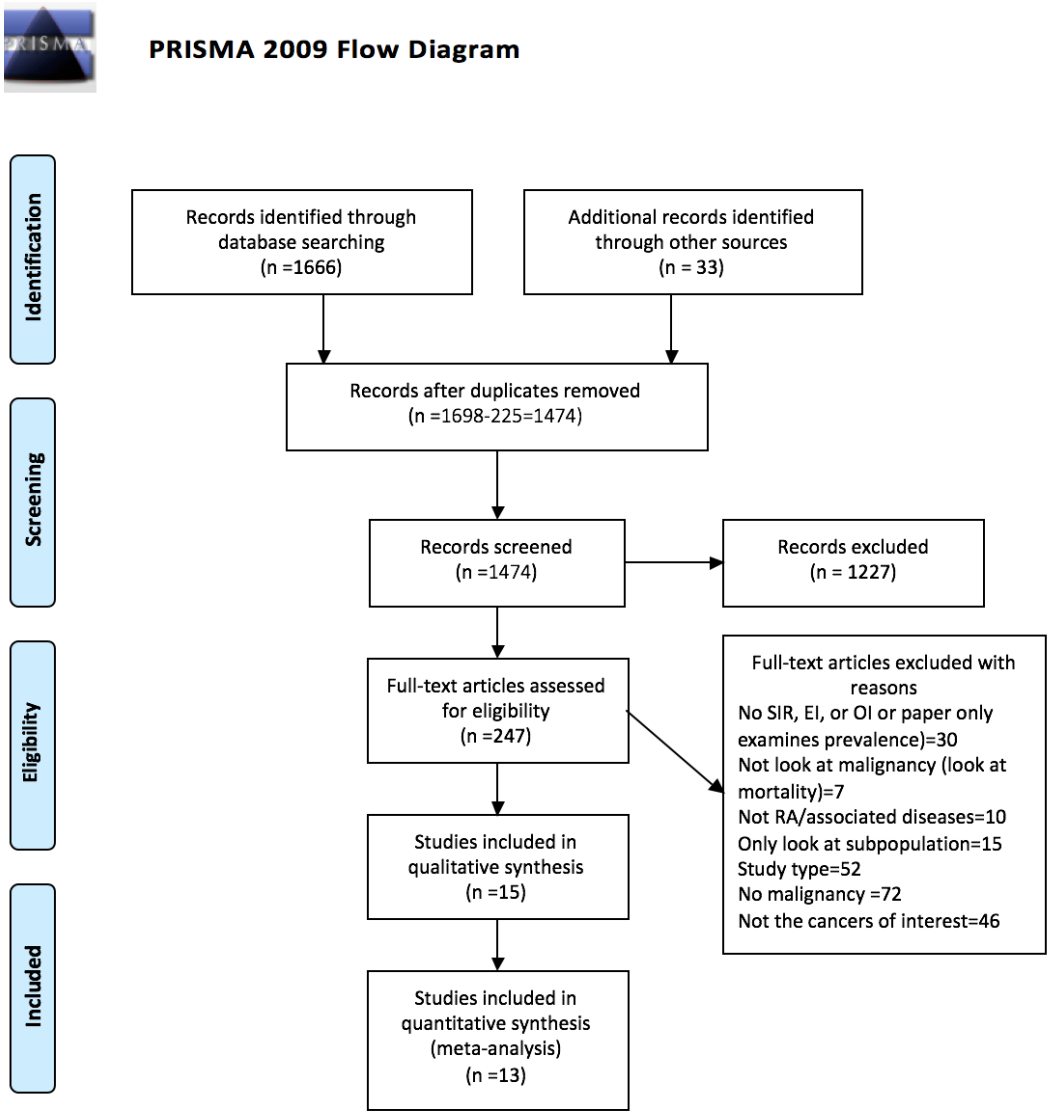
[28, 29]. However, there is very little data to indicate whether cervical cancer itself is increased in SLE compared to the general population; in part, the difficulty is likely because this is a fairly rare cancer in absolute terms

In RA, at least one study has found that women with RA, in general, are at elevated risk of cervical dysplasia and that this risk appeared to be augmented with the use of tumor necrosis factor (TNF) inhibitors [30]. Earlier studies found an increased risk of HPV infection in RA patients treated with disease-modifying agents (DMARDs) [12, 31] and with prednisone [31].

In any pooled analysis, the results are only as good as the data within the primary reports. A potential limitation is that several studies relied at least in part on patient self-reports, although attempts were often made to confirm those cancers, using medical records. Consequently, some cases could have been missed, or alternatively over-reported. However, excluding from our analysis, the studies that employed self-report to identify cancers did not appreciably alter the total SIR or its confidence intervals. Chen *et al*. also disclosed that in their paper RA itself could have been misclassified due to the use of an administrative database. This is a limitation present with most of the studies we examined but does not necessarily explain why the SIR estimate for cervical cancer was *below* the null value.

As is shown in Table **1**, although for most studies the SIR for cervical cancer in RA were close or below 1.0, in some cases the point estimate was well above 1, but in all cases the confidence intervals were relatively wide and included the possibility of a decreased cervical cancer risk in RA compared to the age-matched general population rates. As noted above, in some cases the means of cancer ascertainment varied between studies, while the general population comparator appeared to be reasonably homogeneous. In some cases, the demographics were clearly different (for example some studies arose from purely Asian populations, such as Taiwan or Japan, while others arose from largely Caucasian populations, such as Sweden) but this did not translate to clear differences in the SIR point estimates.

One might expect patients with RA to be more closely followed than the general population, so pre-malignant lesions may be detected and dealt with very promptly. Was that the case, this would presumably lead to a lower than expected cervical cancer risk in RA. However, so far, RA patients have been shown to have similar cancer screening to the general population



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and so the issue of surveillance bias may be less likely [32]. Still, in general, it is felt that any women who are immunosuppressed may be at increased risk for cervical dysplasia, thus women with RA should continue to undergo cancer screening as per regional guidelines. Our recent review of the issue in SLE found that in this population, most authors recommend adherence to general population screening measures, particularly cervical screening [33].

In summary, we were unable to establish if the rate of vaginal/vulvar cancers in RA was any different from the general population. The suggestion of lower incidence of cervical cancers versus the general population is unexplained. Cervical cancer screening in RA should still be adhered to, particularly as evolving treatment strategies may affect future risk.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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