# Autoimmune diseases and female-specific cancer risk: A systematic review and meta-analysis

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ABSTRACT

*Objectives:* Among the over 80 different autoimmune diseases, psoriasis (PsO), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) are common representatives. Previous studies indicated a potential link with cancer risk, but suffered often from low statistical power. Thus, we aimed to synthesize the evidence and quantify the association to different female-specific cancer sites.
*Methods:* The systematic review was performed according to PRISMA guidelines. A search string was developed for the databases PubMed, Web of Science, Cochrane Library and Embase. Results were screened independently by two investigators and the risk of bias was assessed using the ROBINS-E tool. Meta-analyses were performed using inverse variance weighted random-effects models. Statistical between-study heterogeneity was quantified by calculating Cochran's Q, $\tau^2$, and Higgins' $I^2$ statistics. Sources of heterogeneity were analyzed and adjusted for within an intensive bias assessment in the form of meta-regression, outlier, influential, and subgroup analyses. A range of methods were used to test and adjust for publication bias.
*Results:* Of 10,096 records that were originally identified by the search strategy, 45 were included in the meta-analyses. RA was inversely associated with both breast and uterine cancer occurrence, while PsO was associated with a higher breast cancer risk. Outlier-adjusted estimates confirmed these findings. Bias assessment revealed differences in geographic regions, particularly in RA patients, with higher estimates among Asian studies. An additional analysis revealed no association between psoriatic arthritis and breast cancer.
*Conclusions:* RA seems to reduce the risk of breast and uterine cancers, while PsO appears to increase breast cancer risk. Further large studies are required to investigate potential therapy-effects and detailed biological mechanisms.

## 1. Introduction

Autoimmune diseases (ADs) affect approximately 5–8 % of the world population and more than 80 different ADs including systemic as well as organ specific diseases have been described [1,2]. Incidence rates have increased considerably in the past decades, especially in Westernized societies [3]. Their common pathology are chronic inflammatory processes due to a malfunction, in which the immune system attacks the body's own healthy cells, tissues, and organs. Common representatives of ADs affecting the skin and joints are psoriasis (PsO, prevalence: 2–3 %), rheumatoid arthritis (RA, prevalence: 0.5–1 %), and ankylosing spondylitis (AS, prevalence: 0.3 %) [1]. ADs can greatly affect the patient's quality of life, are associated with different comorbidities and some of them have been linked to the risk of malignancy [4–8].

PsO was shown to have an 1.2 increased risk of overall cancer [9].

Patients with RA have a modest increased risk of 10 % in overall malignancy compared with the general population [10]. For AS, the overall risk of developing cancer was 14 % higher compared to controls [11]. Smitten et al. already pointed out that previous reported estimates of standardized incidence ratios close to one for overall cancer risk in patients with RA could indicate an increased risk for some cancer sites and a decreased risk for others [12]. Therefore, it is necessary to investigate site-specific cancer risk. PsO, RA, and AS have previously each been linked to different cancer sites, e.g. lymphoma, cancer of the skin, esophageal, liver, lung, bladder, head, neck, and pancreatic cancer [9, 10,13–16].

Women are generally more often affected by ADs. One explanation for this are the major endocrinological transitions (i.e. puberty, pregnancy, and menopause) that women undergo during their lifetime [17]. Endocrine transition states affect the immune system, which in turn may

be linked with the development of ADs [17]. In this context, the risk of developing female-specific cancer after diagnosis of certain ADs is of particular interest.

There is a need for a better understanding which ADs are associated with which cancer sites. Single observational studies on low prevalence diseases are often underpowered and results can vary from one to another study. Therefore, this study will summarize the epidemiological evidence to date for a specific selection of ADs and female-specific cancer sites. The aim of our systematic review and meta-analysis is to investigate whether the presence of PsO, RA, and AS affects the development of breast, ovarian, uterine, cervical, vulvar and vaginal cancers and to evaluate the heterogeneity patterns within a comprehensive bias analysis.

## 2. Methods

### 2.1. Scope of the review

The initial aim was the investigation of the link between inflammatory arthritis represented by RA, AS, and psoriatic arthritis (PsA) and female-specific cancers. Outcomes were not restricted to certain female-specific cancer sites. Scoping the literature revealed an insufficient number of studies on PsA that were suitable for the research question. As PsA is a sub-group of PsO that has overlapping biological pathways despite different clinical symptoms [18,19], we included PsO instead of PsA as the exposure. However, an additional analysis was conducted only for the association between PsA and breast cancer, which was not part of the primary analyses. Analyses with other outcomes were not possible due to the lack of appropriate studies. Related materials can be found in Supplementary Tables 2 and 4 and Supplementary Figs. 1, 4, and 10.

The study protocol was previously registered in the International prospective register of systematic reviews PROSPERO (Registration ID: CRD42023414571). The systematic review was conducted following the PRISMA statement guidelines [20].

### 2.2. Literature search

At first, a search strategy was developed and tailored to each database. We searched PubMed, Embase (via Ovid), Cochrane Library and Web of Science from inception until June 6, 2023. Google Scholar was used for additional hand searching. We used controlled vocabulary such as Medical Subject Headings (MeSH terms) and Boolean operators as well as free-text terms. Full search strings for each database are provided in Supplementary Table 1. We did not apply any 'Filter' options. All results were downloaded into the reference management software Endnote 20 and deduplicated according to the proposed method of Bramer et al. [21].

## 3. Study selection

Two investigators (S.F. and D.F.) independently screened the titles and abstracts and selected potentially relevant articles for full-text screening. We also hand searched reference lists of key studies and studies that cited these studies (i.e. backward and forward citation searching). During full-text review we evaluated whether the identified articles met the eligibility criteria for the review question and collected relevant information for assessing the methodological quality. Disagreements were resolved through discussion. The eligibility criteria were defined as the following: 1) quantitative study design 2) full text available in English language 3) study in female adults 4) autoimmune disease (RA, PsO, AS) prior to cancer diagnosis as exposure 5) female-specific cancer (breast, ovarian, endometrial, cervical, vaginal, or vulvar cancer) as outcome 6) risk estimate along with 95% confidence intervals (CI). We excluded conference abstracts, case reports and review articles and studies that had no control group without RA, PsO or

AS, respectively. If the same study appeared more than once, only the most recent article was considered.

### 3.1. Data extraction and evaluation of the study

Study data were extracted and checked independently by two investigators (S.F. and D.F.) using a standardized data extraction form. The following information was extracted (if available): authors, publication year, study design, country, number of women with PsO or RA or AS, number and origin of controls, incident cases of female-specific cancer, risk estimates including 95% confidence intervals (CI), use of synthetic or biologic disease modifying antirheumatic drugs (DMARDs), follow-up time, study duration and adjustment variables.

Methodological quality of the studies was evaluated using ROBINS-E tool (Risk Of Bias in Non-randomized Studies – of Exposures) for observational epidemiological studies [22]. The seven bias domains consist of: 1) bias due to confounding, 2) bias arising from measurement of the exposure, 3) bias in selection of participants into the study (or into the analysis) 4) bias due to post-exposure interventions, 5) bias due to missing data 6) bias arsing from measurement of the outcome, 7) bias in selection of the reported result. This assessment was also carried out twice and independently. Results were presented using the robvis visualization tool [23].

### 3.2. Data synthesis and statistical analysis

The measures reported in the studies consisted of standardized incidence ratios (SIR), incident rate ratios (IRR), odds ratios (OR), hazard ratios (HR), and relative risks (RR). As the incidence rates of the cancer sites investigated are low [24], all measures approximate the underlying RR and therefore were used for calculating pooled estimates in meta-analyses. This approximation was ensured for point estimates in form of ORs and HRs according to the formulas $RR = \frac{OR}{(1-p)+(p \cdot OR)}$ and $RR = \frac{1-e^{HR \cdot \ln (1-p)}}{p}$, respectively, where $p$ is the incidence rate of the respective outcome in the unexposed group [25,26].

Three estimates with 0 as the reported lower CI limits on the RR-scale were excluded to avoid infinite variances during the meta-analyses [27, 28]. One 99.9 % CI was transformed into a 95 % CI [29]. Estimates for uterine and endometrial cancer were combined. Estimates for vulva, vagina and female genital organs were combined if the studies defined female genital organs as vulva and vagina. If it was unclear which female genital organs were included, or if they included much more than only vulva and vagina, we did not consider the estimate.

We used inverse variance weighted (IVW) random-effects models to pool the estimates derived from the selected studies and used the Paule-Mandel method to estimate the between-study variance. This iterative approach was shown to outperform the often used DerSimonian and Laird as well as the restricted maximum likelihood estimators for binary outcomes [30]. Statistical between-study heterogeneity was quantified by calculating Cochran's Q, $\tau^2$, and Higgins' $I^2$ statistics. Bias assessment consisted of outlier and influence analyses including leave-one-out analysis and Baujat Diagnostics, to identify studies with a high leverage and notable distortion on the respective pooled estimates. Outlier-adjusted estimates were calculated using fixed-effects (plural) models (also known as mixed models) and compared to the estimates from principal analyses regarding consistency and robustness.

Heterogeneity structures were analyzed by subjecting the associations that included at least 10 studies to further analyses. Along with predefined theoretical rationale, multi-model inference was applied to explore potentially important predictors explaining differences in effect sizes. Then, multiple meta-regression models were performed and the robustness was validated using permutation tests. The geographic region (Europe, North America/Australia, Asia), risk of bias (moderate vs. high risk), study duration, and the number of incident cases (with the outcome-specific median as cut-off) were considered as predictors in the

meta-regression models. Subgroup analyses were carried out to illustrate specific differences.

Small study bias, which was considered as a proxy for potential publication bias, was assessed by visually evaluating funnel plots and performing both Egger's test and Begg's test for funnel plot asymmetry, if number of studies for an association was at least 10. Bias-corrected estimates were calculated using the trim and fill method and the PET-PEESE (precision-effect test – precision-effect estimate with standard error) model based on an $\alpha = 0.1$. As the requirement of no substantial between-study heterogeneity (defined as $I^2 < 60\%$) was violated in some of the meta-analyses, these methods were performed on both the unadjusted and the outlier-corrected estimates. Additionally, the three-parameter selection model (3PSM) with a cut-off of 0.06 was performed to assess the publication bias using the Likelihood Ratio test at a threshold of $\alpha = 0.1$ and calculate bias-adjusted estimates. Finally, a robust Bayesian meta-analysis was conducted to quantify the presence of heterogeneity, publication bias and the effect itself represented by the Bayes Factor and to calculate model-averaged estimates. All the evidence from the methods above was used to address the plausibility of publication bias and to evaluate the presence of an effect from different perspectives.

All analyses were conducted on the multiplicative RR-scale. Unless otherwise stated above, statistical tests were performed two-sided considering a significance threshold of 0.05. P-values in the principal meta-analyses were adjusted for multiple testing using the false discovery rate (FDR) correction. All analyses were done using the statistical software R (version 4.3.2) mainly with the packages *meta* (version 6.5–0), *metafor* (version 4.4–0), *dmetar* (version 0.1.1), *weightr* (version 2.02), *RoBMA* (version 3.1.0), and *ggplot2* (version 3.4.4).

## 4. Results

The search strategy identified 10,096 records (after deduplication) in the four databases PubMed, Embase, Cochrane Library and Web of Science. After title, abstract, and full-text screening, 45 studies were finally included in the meta-analysis. The PRISMA flow chart of the study selection process is presented in Fig. 1.

### 4.1. Characteristics of included studies

Most of the included studies investigated the female-specific cancer risk in patients with RA (n = 29). Accordingly, 14 studies investigated PsO and 10 AS. There were 22 studies from Europe, 13 from Asia, 7 from North America, 2 from Australia and one study from multiple regions. Most of the studies were cohort studies with an average follow-up time of 6.9 years (SD: 3.6, range: 2.1–19.2). The study characteristics of all included studies (where available) are presented in Supplementary Table 3. Risk of Bias assessment is presented in Supplementary Fig. 2. Nearly all of the studies had a risk of bias due to limited adjustment for confounding. Few studies had a high to very high risk for selection bias (Supplementary Fig. 3).

### 4.2. Primary analyses

Considering 45 studies that covered the *trans*-ethnic population, the IVW random-effects models revealed inverse associations between RA and both breast and uterine cancer with pooled RR = 0.86 (95 % CI: 0.81 to 0.92, $P_{FDR} = 2.77 \cdot 10^{-4}$) and RR = 0.71 (95 % CI: 0.60 to 0.84, $P_{FDR} = 5.19 \cdot 10^{-4}$), respectively (Fig. 2). Furthermore, PsO was positively related to breast cancer (RR = 1.09 (95 % CI: 1.03 to 1.15, $P_{FDR} = 0.020$)). Despite a consistent point estimate, there was no association between PsA and breast cancer (Supplementary Fig. 10). The point estimate for the association of PsO and ovarian cancer was slightly increased but failed to reach statistical significance after FDR adjustment. However, substantial heterogeneity was observed in all of these models with $I^2$ values ranging between 0.52 and 0.96 as well as the Cochran's Q test with $P$ values between $3.9 \cdot 10^{-156}$ and 0.02 (Fig. 2). There was no evidence of further associations between the ADs assessed and any of the female-specific cancer sites after adjustment for multiple testing.
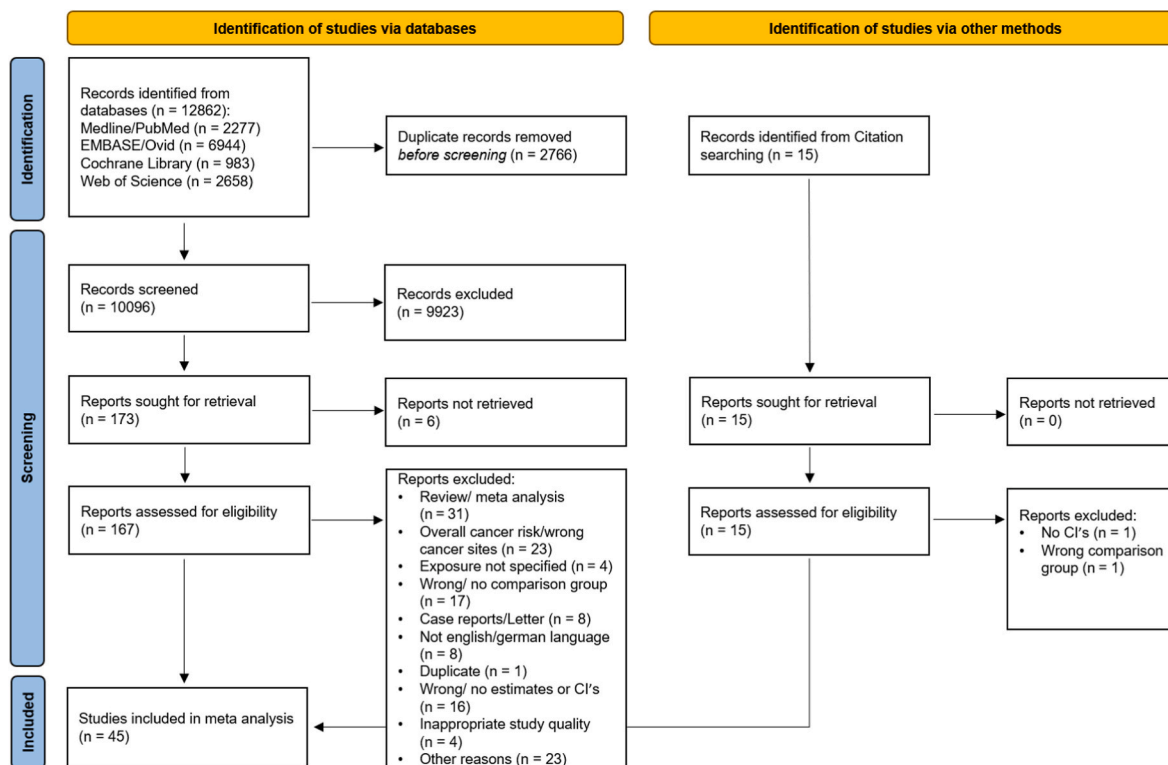


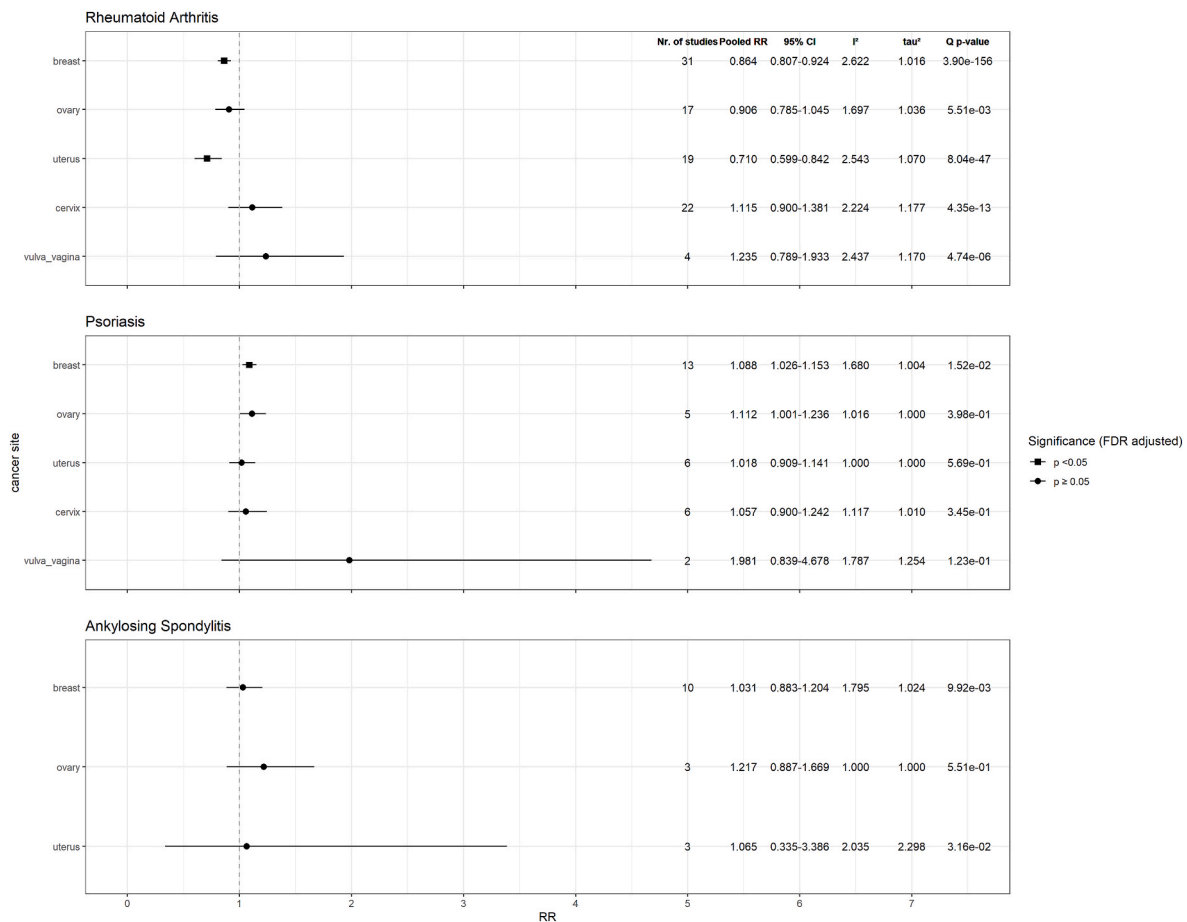**Fig. 1.** PRISMA flowchart of the study selection process.

**Fig. 2.** Pooled estimates in form of relative risk and 95% confidence intervals from inverse-variance weighted random effects meta-analyses for the effect of autoimmune diseases on female-specific cancer sites. Notable associations after FDR-adjustment of p-values are presented by squared point estimates. The heterogeneity statistics are shown on the right.

### 4.3. Outliers and influential studies

Regarding the extensive heterogeneity ($I^2 = 0.96$), the outlier analysis identified two outliers (Chen et al., 2011 [31], Parikh-Patel et al., 2009 [32]) in the RA-breast cancer association (Supplementary Fig. 5). According to the Baujat Diagnostics and the leave-one-out analysis, both studies had the highest contributions to overall heterogeneity, but with different degrees of influence on the pooled estimate. Removal of these studies substantially lowered the heterogeneity ($I^2 = 0.11$, $\tau^2 = 7 \cdot 10^{-4}$, $P_Q = 0.3$) and led even to a stronger estimate (RR = 0.86; 95 % CI: 0.83 to 0.89) (Supplementary Fig. 5). The 95% prediction interval changed from [0.66 to 1.13] to [0.81 to 0.92].

The study of Chen et al. was also responsible for more than a half of heterogeneity in the RA-uterine cancer association and had a strong influence on the initial pooled estimate. After removal, the outlier-corrected estimate decreased to RR = 0.66 (95% CI: 0.57 to 0.75) with reduced heterogeneity ($I^2 = 0.41$, $\tau^2 = 0.03$, $P_Q = 0.04$). The 95% prediction interval changed notably to [0.45 to 0.97] (Supplementary Fig. 5).

For the PsO-breast cancer relation the outlier analysis and the influence analysis came to slightly different results. After removing the study of Stern et al. the outlier-corrected estimate was RR = 1.08 (95% CI: 1.04 to 1.12), the 95% prediction interval was 1.00–1.17, and heterogeneity was reduced to $I^2 = 0.41$, $\tau^2 = 7 \cdot 10^{-4}$, $P_Q = 0.07$ (Supplementary Fig. 6). However, according to the Baujat diagnostics and the leave-one-out analysis Schairer et al. was the most influential study with the highest contribution to between-study heterogeneity, so that removal of this study reduced the $I^2$ to 0.2. Nonetheless, removal of each

of the studies yielded in consistent estimates, which supported the result from the primary analysis.

### 4.4. Publication bias

Results of Egger's and Begg's tests and funnel plots indicated small-study bias in the primary, but not in the outlier-adjusted models for associations between RA and both breast cancer and uterine cancer (Supplementary Table 5). There was no evidence of funnel plot asymmetry for the association between PsO and breast cancer, which was supported by the 3PSM model (Supplementary Table 6). In contrast, the PET-PEESE approach indicated publication bias even in the outlier-adjusted models (Supplementary Table 7). The robust Bayesian meta-analysis found evidence for publication bias in the unadjusted RA-breast cancer association (BF = 2.9) but only weak evidence in RA-uterine (BF = 0.6) or PsO-breast (BF = 0.7) associations (Supplementary Table 8). Despite the somewhat weaker evidence of the Bayesian approach in the unadjusted models, all estimates adjusted for publication bias were similar to the initial results (Fig. 3).

In summary, there was evidence of small-study bias possibly due to publication bias especially in the RA-breast cancer and RA-uterine cancer models. However, after bias-adjustment, all analyses came to comparable results, supporting the findings from the primary analyses.

### 4.5. Subgroup analyses

Basically, multiple meta-regression and/or permutation test indicated differences between estimates regarding geographic regions
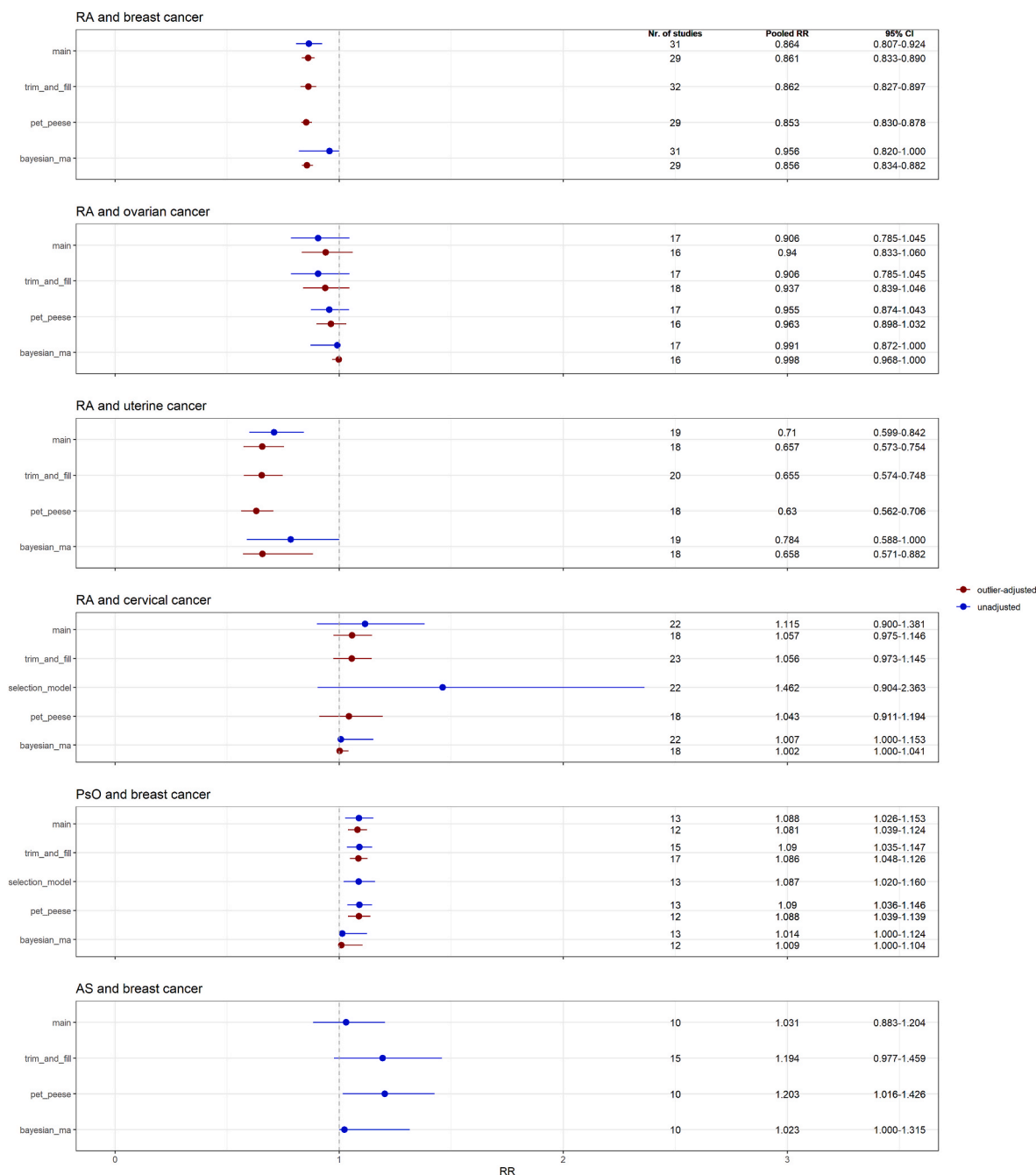
**Fig. 3.** Results of different methods assessing publication bias for the effects of autoimmune diseases on female-specific cancer sites when at least 10 studies per association were available. Pooled estimates are presented as relative risks (RRs) and 95% confidence intervals. Analyses were done for both the unadjusted and outlier-adjusted cases.

(Supplementary Table 9). Subgroup analysis for the RA-breast cancer associations revealed different estimates for different geographic regions ($P_Q = 0.021$) (Fig. 4). In particular, an inverse association was found only in Europeans (RR = 0.85; 95% CI: 0.80 to 0.91) with low heterogeneity of $I^2 = 0.27$. This estimate was consistent with the estimate in North Americans rather than Asians. Stronger differences were found for studies investigating the association between RA and uterine cancer ($P_Q = 2.7 \cdot 10^{-10}$). Estimates in individuals of European or North American ancestry showed consistently negative associations with low between-study heterogeneity and differed from those of Asian studies (moderate heterogeneity) in magnitude as well as direction. No notable geographic-specific differences were found in studies assessing the association between PsO and breast cancer ($P_Q = 0.29$), with the strongest

estimate and lowest heterogeneity in European women (Fig. 4). Generally, among RA patients, point estimates in Asians were considerably higher and partly inconsistent compared to estimates in North Americans. The lowest heterogeneity was found in European studies except the association with ovarian cancer ($I^2 = 0.36$).

Regarding the risk of bias classification, estimates from studies with high risk were in general more extreme with wider CIs and partly inconsistent compared to studies with moderate risk that were in line with the main results. However, except for the estimates of the RA-cervix association, differences in estimates could not be detected by the multiple meta-regression or the Cochran's Q test in subgroup analyses. No substantial differences were found considering the study duration and the number of incident cancer cases diagnosed during the study periods
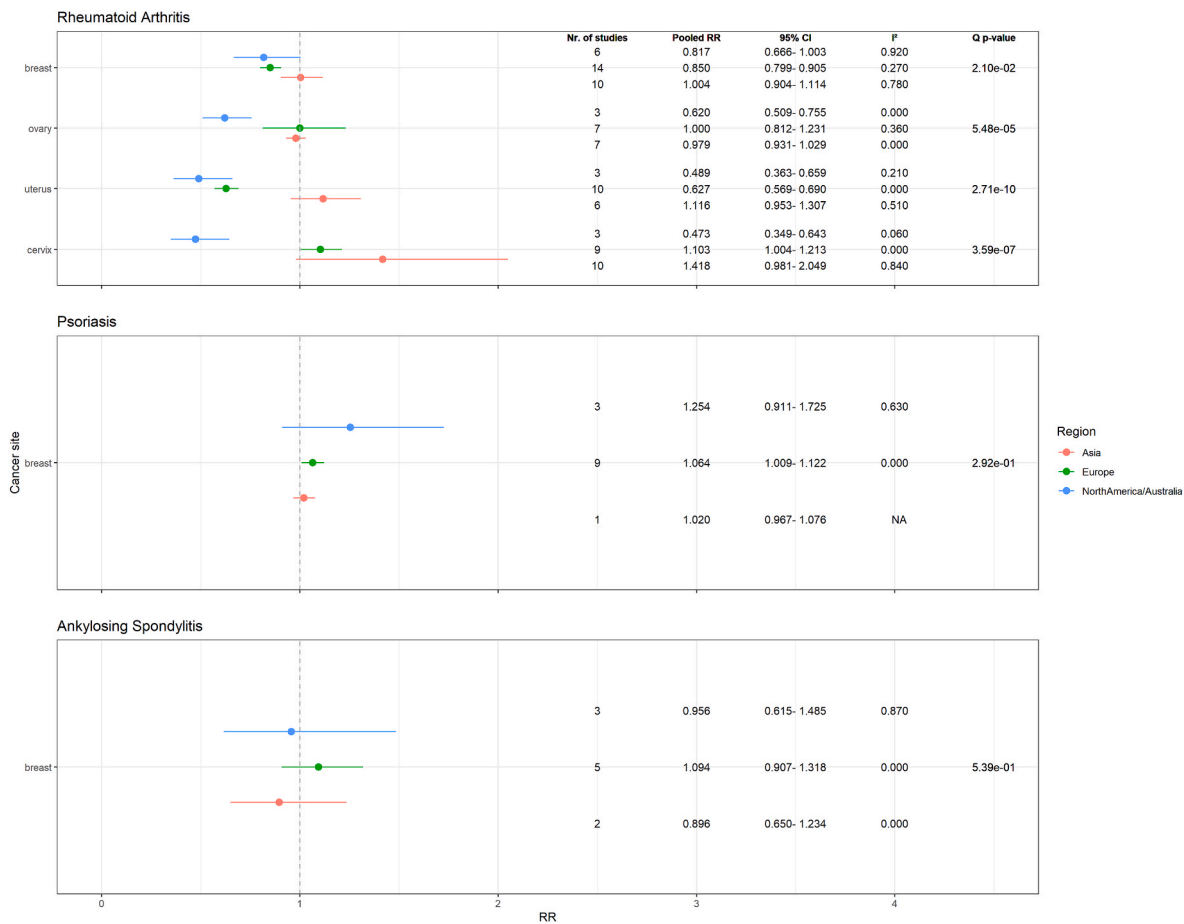
**Rheumatoid Arthritis**

| Cancer site | Nr. of studies | Pooled RR | 95% CI | I² | Q p-value |
|---|---|---|---|---|---|
| breast | 6 | 0.817 | 0.666- 1.003 | 0.920 | |
| | 14 | 0.850 | 0.799- 0.905 | 0.270 | 2.10e-02 |
| | 10 | 1.004 | 0.904- 1.114 | 0.780 | |
| ovary | 3 | 0.620 | 0.509- 0.755 | 0.000 | |
| | 7 | 1.000 | 0.812- 1.231 | 0.360 | 5.48e-05 |
| | 7 | 0.979 | 0.931- 1.029 | 0.000 | |
| uterus | 3 | 0.489 | 0.363- 0.659 | 0.210 | |
| | 10 | 0.627 | 0.569- 0.690 | 0.000 | 2.71e-10 |
| | 6 | 1.116 | 0.953- 1.307 | 0.510 | |
| cervix | 3 | 0.473 | 0.349- 0.643 | 0.060 | |
| | 9 | 1.103 | 1.004- 1.213 | 0.000 | 3.59e-07 |
| | 10 | 1.418 | 0.981- 2.049 | 0.840 | |

**Psoriasis**

| Cancer site | Nr. of studies | Pooled RR | 95% CI | I² | Q p-value |
|---|---|---|---|---|---|
| breast | 3 | 1.254 | 0.911- 1.725 | 0.630 | |
| | 9 | 1.064 | 1.009- 1.122 | 0.000 | 2.92e-01 |
| | 1 | 1.020 | 0.967- 1.076 | NA | |

Region
- Asia
- Europe
- NorthAmerica/Australia

**Ankylosing Spondylitis**

| Cancer site | Nr. of studies | Pooled RR | 95% CI | I² | Q p-value |
|---|---|---|---|---|---|
| breast | 3 | 0.956 | 0.615- 1.485 | 0.870 | |
| | 5 | 1.094 | 0.907- 1.318 | 0.000 | 5.39e-01 |
| | 2 | 0.896 | 0.650- 1.234 | 0.000 | |

**Fig. 4.** Subgroup analyses by geographic region of included studies showing the association between autoimmune diseases and female-specific cancer sites. Pooled estimates are given in form of relative risk and 95% confidence intervals from inverse-variance weighted random effects meta-analyses. The heterogeneity statistics are shown on the right.

(Supplementary Table 9, Supplementary Fig. 9).

## 5. Discussion

This study investigated the *trans*-ethnic associations between selected autoimmune diseases (RA, PsO, and AS) and female-specific cancer sites (breast, ovary, uterine, cervix, and vulva or vagina cancers). Considering 45 studies in the meta-analyses, it was found that RA decreases the risk for both breast and uterine cancer and identified PsO as a risk factor for breast cancer occurrence. We also found geographic-specific differences. No further associations were observed between the remaining combinations of ADs and female-specific cancers.

### 5.1. Associations with RA

Two previous meta-analyses revealed consistent but non-significant estimates for the association between RA and breast cancer risk (Simon et al.: SIR = 0.86, 95 % CI: (0.73, 1.01); Tian et al.: SIR = 0.86, 95 % CI: (0.72, 1.02)), while another meta-analysis of Smitten et al. fully supported our finding (SIR = 0.84, 95 % CI: (0.79, 0.90)) [10,12,33]. Furthermore, we found a decreased risk for uterine cancer in patients with RA which to our knowledge has not been investigated in other meta-analyses yet. However, a recently published Mendelian randomization (MR) study did not find an association between RA and uterine cancer in both European and East Asian populations [34]. The present study did not show an association between RA and ovarian or cervical cancers, what is in line with previous studies [10,34]. Results for vulva or vagina cancer sites cannot be compared due to the lack of studies not

included in this meta-analysis.

### 5.2. Associations with PsO

Despite similar point estimates, two meta-analyses showed no association between PsO and breast cancer due to wider CIs [9,13]. However, the lack of associations with the remaining gynecological cancers sites (except the vulva and vagina cancers) was supported by the meta-analysis of Trafford et al. [9]. It has previously been reported that PsA, which is a subgroup disease of PsO that about 1 out of 4 patients with PsO develop during lifetime [35], was associated with an increased risk for breast cancer [36]. Despite a point estimate of 1.45, our additional meta-analysis for PsA did not confirm an association between PsA and breast cancer. However, there was a large between-study heterogeneity that could not be further assessed due to the low number of included studies. An explanatory approach of Vaengebjerg et al. for the association of PsO and cancer was that life style factors such as smoking and alcohol consumption had an association with PsO and they may also partially contribute to elevated risk estimates for cancer [13]. Obesity is another factor that due to its effect on immune cell function and chronic inflammation has been shown to play a role in both, development of PsO and breast cancer [37–41].

### 5.3. Associations with AS

We found no associations between AS and female-specific cancers. These results are in accordance with a meta-analysis of Deng et al. who investigated the relationships with breast cancer and cancer of the

female genital system [10]. One observational study found no associations with cervical cancer and vulvar and vaginal cancer sites [42]. Another study supported the lack of association with cervical cancer [28]. Since the latter study was excluded due to a lower CI limit of 0 on the RR-scale (and thus an infinite standard error), no meta-analysis was performed in our study for this outcome. However, study situation on AS and risk of other female-specific cancers is scarce. Historically, AS has been considered more common in men than in women. More recent studies, including a literature review from 2018, found that the ratio has decreased significantly, but women with AS are still under-recognized in clinical research, which contributes to the paucity of existing studies in this context. Furthermore, there are findings that women with AS suffer from diagnostic delay, higher disease activity, lower quality of life, and lower response rates to treatments [43]. These aspects highlight that further research is needed for women with AS including the investigation of female-specific cancer risk.

### 5.4. Geographic-stratified analyses

Our subgroup analyses revealed that female-specific cancer risk, especially in RA patients, differs depending on the geographic region. Similar to the present analyses, other studies also found region-specific differences in cancer risk with higher point estimates for Asia [11,33]. In general, there are known differences in the epidemiology of breast cancer between Asian and Western populations. The overall incidence rates are lower in Asian population, but there are also differences in age peak and mortality rates [44]. Differences in estimates regarding RA and breast cancer were also found in two recent MR studies [34,45]. However, the two studies contradict each other in the direction of the effect estimates for Europeans. Basically, our results agree with those of Yuan et al. with regard to the direction of point estimates. In particular, the MR-estimate for the Finish cohort (FinnGen database) is in line with our result for Europeans, which were mainly based on the Scandinavian population (Sweden, Denmark, Finland).

Different cancer susceptibilities in the geographic regions may result from lifestyle and environmental factors as well as genetic predisposition. Inconsistency in risk estimates may also be caused by different treatment guidelines regarding general indication and dosage in the respective countries [46]. Furthermore, there are also differences in the type, frequency and coverage of screening programs, e.g. in cervical cancer screening in high-, middle- and low-income countries or inhomogeneous breast cancer screening programs among Asian countries, which can also affect cancer incidence rates [47,48].

### 5.5. Potential biological mechanisms

Apart from the individual genetic predisposition, several biological mechanisms explaining the association between ADs and cancer risk, such as elevated levels of circulating inflammatory markers [49] or epigenetic modifications [50], have been discussed but many factors remain unclear. Considering the finding of decreased risk for some female-specific cancer sites, female hormonal factors may play a role in this context. Estrogen is associated with immunomodulating processes and takes on anti-inflammatory as well as pro-inflammatory roles [51, 52]. Decreased estrogen levels have been associated with all three diseases, RA, PsO and AS. A study from 1990 found lower estrogen levels in patients with active AS than in patients with inactive AS or controls [53]. Similarly, high estrogen levels and increased estrogen to progesterone-ratios have been associated with improvement of psoriatic symptoms [52,54]. Peak incidence of RA in women occurs at the time of menopause which is characterized by decreased production of sex hormones such as estrogen. On the other hand, RA disease activity is reduced in 75 % of pregnant women when estrogen levels are high [55]. Therefore, decreased hormone levels may be associated with the reduced risk for estrogen-related cancers. However, other studies reported no differences in estradiol levels in RA patients compared to controls, but in other female sex hormones such as luteinizing hormone and follicle-stimulating hormone [56]. Overall, the influence of hormones and hormonal imbalances in the association of ADs and hormone-related cancers is still a topic under research that may reveal further connections and treatment options in the future [57].

### 5.6. Potential treatment effects

For most of the ADs, it is not yet clear whether an increased risk for overall malignancy may be due to an underlying dysregulation of the immune system or the therapies used to treat the diseases. There is no known cure for ADs so far, but enormous advances in the symptomatic treatment and disease modifying management have been made in the last decades. The synthetic or biologic DMARDs are used for suppressing autoimmune activity (e.g. TNF-alpha-inhibitors). However, the DMARDs are used for a broad range of ADs and are not acting disease-specific, which is why they can cause adverse side effects like infections and malignancy [1,58,59]. Therefore, it would be necessary to control for the effect of DMARDs on the association between ADs and cancer. In our systematic review, only few studies distinguished between patients receiving a specific treatment (e.g. TNF alpha inhibitors) and biologic-naïve patients. Since the other studies either did not provide any information or were not stratified, it was not possible to determine specific treatment effects on women's cancer risk. Recently, a study summarizing the evidence of DMARDs and risk of overall malignancy reported that synthetic or biologic DMARDs such as Methotrexate or TNF inhibitors has not been shown to increase the cancer risk [60]. A Swedish population-based study confirmed this specifically for RA patients treated with TNF inhibitors, anti-CD20 or anti-IL-6 receptor, but they found a potential association of abatacept and overall malignancy risk [61]. Patients with AS treated with TNF inhibitors did also not show an increased risk for overall cancer compared to biologic naïve patients or the general population [62]. However, there is not sufficient evidence for the role of long-term use of JAK inhibitors and development of cancer yet [60].

### 5.7. Strengths and limitations

A strength of this systematic review and meta-analysis is that the most of included studies had a sufficiently long follow-up time and used register-based data, which minimizes selection bias. The rigorous bias assessment and a series of additional analyses focusing on minimizing heterogeneity and exploring its sources in terms of outliers and subgroups ensured the robustness of estimates.

However, there are several limitations. Between study heterogeneity arose from various sources that could not be directly controlled for. Dependent on the respective study, the sources were (1) variation in the follow-up time, (2) inhomogeneous diseases severity and diseases duration at time of inclusion, (3) insufficient confounder-adjustment leading to a large risk of bias, (4) differences in the time windows between study beginning and consideration of an incident cancer case, and (5) the lack of information on the therapies used or stratification by therapy, so that therapy-based effects could not be investigated. Nonetheless, we accounted as far as possible for heterogeneity using random-effects models and applied further statistical approaches to investigate causes of heterogeneity. In this way we were able to considerably reduce the heterogeneity within our bias assessment and confirm the results from initial analyses.

## 6. Conclusions

Especially in Western populations, RA may reduce the risk of breast and uterine cancers, while PsO appears to increase the risk of breast cancer. Differences in geographic regions were particularly detected in RA patients. However, the evidence is not yet sufficient for vulvar and vaginal cancer and also for AS in general. More large studies are needed

to investigate these diseases, potential therapy-effects and detailed biological mechanisms.

## Funding

## CRediT authorship contribution statement

**Simone Fischer:** Formal analysis, Writing – original draft. **Christa Meisinger:** Conceptualization, Writing – review & editing. **Dennis Freuer:** Formal analysis, Funding acquisition, Methodology, Project administration, Writing – original draft.

## Declaration of competing interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2024.103187.

## References

[1] L. Fugger, L.T. Jensen, J. Rossjohn, Challenges, progress, and prospects of developing therapies to treat autoimmune diseases, Cell 181 (1) (2020) 63–80.

[2] National Academies of Sciences, Engineering, and medicine, in: Enhancing NIH Research on Autoimmune Disease, 2022. Washington (DC).

[3] A. Lerner, P. Jeremias, T. Matthias, The world incidence and prevalence of autoimmune diseases is increasing, IJCD 3 (4) (2016) 151–155.

[4] F. Matcham, I.C. Scott, L. Rayner, M. Hotopf, G.H. Kingsley, S. Norton, et al., The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis, Semin. Arthritis Rheum. 44 (2) (2014) 123–130.

[5] J. Greenfield, M. Hudson, E. Vinet, P.R. Fortin, V. Bykerk, C.A. Pineau, et al., A comparison of health-related quality of life (HRQoL) across four systemic autoimmune rheumatic diseases (SARDs), PLoS One 12 (12) (2017) e0189840.

[6] J. Amaya-Amaya, L. Montoya-Sánchez, A. Rojas-Villarraga, Cardiovascular involvement in autoimmune diseases, BioMed Res. Int. 2014 (2014) 367359.

[7] A. Matusiewicz, J. Stróżyńska-Byrska, M. Olesińska, Polyautoimmunity in rheumatological conditions, International journal of rheumatic diseases 22 (3) (2019) 386–391.

[8] L.C. Cappelli, A.A. Shah, The relationships between cancer and autoimmune rheumatic diseases. Best practice & research, Clin. Rheumatol. 34 (1) (2020) 101472.

[9] A.M. Trafford, R. Parisi, E. Kontopantelis, C.E.M. Griffiths, D.M. Ashcroft, Association of psoriasis with the risk of developing or dying of cancer: a systematic review and meta-analysis, JAMA Dermatol 155 (12) (2019) 1390–1403.

[10] T.A. Simon, A. Thompson, K.K. Gandhi, M.C. Hochberg, S. Suissa, Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis, Arthritis Res. Ther. 17 (1) (2015) 212.

[11] C. Deng, W. Li, Y. Fei, Y. Li, F. Zhang, Risk of malignancy in ankylosing spondylitis: a systematic review and meta-analysis, Sci. Rep. 6 (1) (2016) 32063.

[12] A.L. Smitten, T.A. Simon, M.C. Hochberg, S. Suissa, A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis, Arthritis Res. Ther. 10 (2) (2008) R45.

[13] S. Vaengebjerg, L. Skov, A. Egeberg, N.D. Loft, Prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis, JAMA dermatology 156 (4) (2020) 421–429.

[14] C. Pouplard, E. Brenaut, C. Horreau, T. Barnetche, L. Misery, M.-A. Richard, et al., Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies, Journal of the European Academy of Dermatology and Venereology JEADV 27 (Suppl 3) (2013) 36–46.

[15] L.-M. Sun, C.-H. Muo, J.-A. Liang, S.-N. Chang, F.-C. Sung, C.-H. Kao, Increased risk of cancer for patients with ankylosing spondylitis: a nationwide population-based retrospective cohort study, Scand. J. Rheumatol. 43 (4) (2014) 301–306.

[16] M. Bittar, S. Merjanah, R. Alkilany, M. Magrey, Malignancy in ankylosing spondylitis: a cross-sectional analysis of a large population database, BMC rheumatology 6 (1) (2022).

[17] M.K. Desai, R.D. Brinton, Autoimmune disease in women: endocrine transition and risk across the lifespan, Front. Endocrinol. 10 (2019) 265.

[18] V. Caputo, C. Strafella, A. Termine, A. Dattola, S. Mazzilli, C. Lanna, et al., Overview of the molecular determinants contributing to the expression of Psoriasis and Psoriatic Arthritis phenotypes, J. Cell Mol. Med. 24 (23) (2020) 13554–13563.

[19] D.H. Ciocon, A.B. Kimball, Psoriasis and psoriatic arthritis: separate or one and the same? Br. J. Dermatol. 157 (5) (2007) 850–860.

[20] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Int. J. Surg. 88 (2021) 105906.

[21] W.M. Bramer, D. Giustini, GB de Jonge, L. Holland, T. Bekhuis, De-duplication of database search results for systematic reviews in EndNote, Journal of the Medical Library Association JMLA 104 (3) (2016) 240–243.

[22] J. Higgins, R. Morgan, A. Rooney, K. Taylor, K. Thayer, R. Silva, C. Lemeris, A. Akl, W. Arroyave, T. Bateson, N. Berkman, P. Demers, F. Forastiere, B. Glenn, A. Hróbjartsson, E. Kirrane, J. LaKind, T. Luben, R. Lunn, A. McAleenan, L. McGuinness, J. Meerpohl, S. Mehta, R. Nachman, J. Obbagy, A. O'Connor, E. Radke, J. Savović, M. Schubauer-Berigan, P. Schwingl, H. Schunemann, B. Shea, K. Steenland, T. Stewart, K. Straif, K. Tilling, V. Verbeek, R. Vermeulen, M. Viswanathan, S. Zahm, J. Sterne, (ROBINS-E Development Group), Risk of bias in non-randomized studies - of exposure (ROBINS-E): launch version, 20 June 2023. Available from: https://www.riskofbias.info/welcome/robins-e-tool.

[23] L.A. McGuinness, J.P.T. Higgins, Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments, Res. Synth. Methods 12 (1) (2021) 55–61.

[24] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today. [December 1, 2023]; Available from: https://gco.iarc.fr/today..

[25] R.L. Grant, Converting an odds ratio to a range of plausible relative risks for better communication of research findings, Br. Med. J. 348 (2014) f7450.

[26] E. Shor, D. Roelfs, Z.M. Vang, The "Hispanic mortality paradox" revisited: meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality, Soc. Sci. Med. 186 (2017) 20–33.

[27] J. Askling, C.M. Fored, L. Brandt, E. Baecklund, L. Bertilsson, N. Feltelius, et al., Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists, Ann. Rheum. Dis. 64 (10) (2005) 1421–1426.

[28] P.-A. Dugue, M. Rebolj, J. Hallas, P. Garred, E. Lynge, Risk of cervical cancer in women with autoimmune diseases, in relation with their use of immunosuppressants and screening: population-based cohort study, Int. J. Cancer 136 (6) (2015) E711–E719.

[29] C. Schairer, R.M. Pfeiffer, S.M. Gadalla, Autoimmune diseases and breast cancer risk by tumor hormone-receptor status among elderly women, Int. J. Cancer 142 (6) (2018) 1202–1208.

[30] A.A. Veroniki, D. Jackson, W. Viechtbauer, R. Bender, J. Bowden, G. Knapp, et al., Methods to estimate the between-study variance and its uncertainty in meta-analysis, Res. Synth. Methods 7 (1) (2016) 55–79.

[31] Y.-J. Chen, Y.-T. Chang, C.-B. Wang, C.-Y. Wu, The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan, Arthritis Rheum. 63 (2) (2011) 352–358.

[32] A. Parikh-Patel, R.H. White, M. Allen, R. Cress, Risk of cancer among rheumatoid arthritis patients in California, Cancer Causes Control 20 (6) (2009) 1001–1010.

[33] G. Tian, J.-N. Liang, Z.-Y. Wang, D. Zhou, Breast cancer risk in rheumatoid arthritis: an update meta-analysis, BioMed Res. Int. 2014 (2014) 453012.

[34] S. Yuan, J. Chen, X. Ruan, M. Vithayathil, S. Kar, X. Li, et al., Rheumatoid arthritis and risk of site-specific cancers: mendelian randomization study in European and East Asian populations, Arthritis Res. Ther. 24 (1) (2022) 270.

[35] F. Alinaghi, M. Calov, L.E. Kristensen, D.D. Gladman, L.C. Coates, D. Jullien, et al., Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies, J. Am. Acad. Dermatol. 80 (1) (2019) 251–265.e19.

[36] K.M. Wilton, C.S. Crowson, E.L. Matteson, Malignancy incidence in patients with psoriatic arthritis: a comparison cohort-based incidence study, Clin. Rheumatol. 35 (10) (2016) 2603–2607.

[37] T. Scully, A. Ettela, D. LeRoith, E.J. Gallagher, Obesity, type 2 diabetes, and cancer risk, Front. Oncol. 10 (2020) 615375.

[38] C.M. Friedenreich, C. Ryder-Burbidge, J. McNeil, Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms, Mol. Oncol. 15 (3) (2021) 790–800.

[39] K.A. Brown, Metabolic pathways in obesity-related breast cancer, Nat. Rev. Endocrinol. 17 (6) (2021) 350–363.

[40] Xu Cheng, Jie Ji, Ting Su, Hong-Wei Wang, Zhong-Lan Su, The association of psoriasis and obesity: focusing on IL-17a-related immunological mechanisms, International Journal of Dermatology and Venereology 4 (2) (2021) 116–121.

[41] A. Budu-Aggrey, B. Brumpton, J. Tyrrell, S. Watkins, E.H. Modalsli, C. Celis-Morales, et al., Evidence of a causal relationship between body mass index and psoriasis: a mendelian randomization study, PLoS Med. 16 (1) (2019) e1002739.

[42] K. Hemminki, X. Liu, J. Ji, A. Forsti, J. Sundquist, K. Sundquist, Effect of autoimmune diseases on risk and survival in female cancers, Gynecol. Oncol. 127 (1) (2012) 180–185.

[43] T. Rusman, R.F. van Vollenhoven, I.E. van der Horst-Bruinsma, Gender differences in axial spondyloarthritis: women are not so lucky, Curr. Rheumatol. Rep. 20 (6) (2018) 35.

[44] S.P.L. Leong, Z.-Z. Shen, T.-J. Liu, G. Agarwal, T. Tajima, N.-S. Paik, et al., Is breast cancer the same disease in Asian and Western countries? World J. Surg. 34 (10) (2010) 2308–2324.

[45] Y.-C. Xu, J.-X. Wang, Y.-R. Chu, H. Qian, H.-Y. Wang, F. Wang, Diseases of the musculoskeletal system and connective tissue and risk of breast cancer: mendelian

randomization study in European and East Asian populations, Front. Oncol. 13 (2023) 1170119.

[46] T. Koike, K. Inui, How can the treatment of rheumatoid arthritis be improved in Japan? Int. J. Clin. Rheumatol. 10 (4) (2015) 235–244.

[47] L. Bruni, B. Serrano, E. Roura, L. Alemany, M. Cowan, R. Herrero, et al., Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. The Lancet, Global health 10 (8) (2022) e1115–e1127.

[48] J.C. Sitt, C.Y. Lui, L.H. Sinn, J.C. Fong, Understanding breast cancer screening– past, present, and future, Hong Kong medical journal = Xianggang yi xue za zhi 24 (2) (2018) 166–174.

[49] N. Michels, C. van Aart, J. Morisse, A. Mullee, I. Huybrechts, Chronic inflammation towards cancer incidence: a systematic review and meta-analysis of epidemiological studies, Crit. Rev. Oncol.-Hematol. 157 (2021) 103177.

[50] L. Hui, Z. Ziyue, L. Chao, Y. Bin, L. Aoyu, W. Haijing, Epigenetic regulations in autoimmunity and cancer: from basic science to translational medicine, Eur. J. Immunol. 53 (4) (2023) e2048980.

[51] R.H. Straub, The complex role of estrogens in inflammation, Endocr. Rev. 28 (5) (2007) 521–574.

[52] R. Gratton, C. Del Vecchio, L. Zupin, S. Crovella, Unraveling the role of sex hormones on keratinocyte functions in human inflammatory skin diseases, Int. J. Mol. Sci. 23 (6) (2022).

[53] F.J. Jimenez-Balderas, R. Tapia-Serrano, J.I. Madero-Cervera, S. Murrieta, G. Mintz, Ovarian function studies in active ankylosing spondylitis in women. Clinical response to estrogen therapy, J. Rheumatol. 17 (4) (1990) 497–502.

[54] C. Guillet, C. Seeli, M. Nina, L.V. Maul, J.-T. Maul, The impact of gender and sex in psoriasis: what to be aware of when treating women with psoriasis, International journal of women's dermatology 8 (2) (2022) e010.

[55] U. Islander, C. Jochems, M.K. Lagerquist, H. Forsblad-d'Elia, H. Carlsten, Estrogens in rheumatoid arthritis; the immune system and bone, Mol. Cell. Endocrinol. 335 (1) (2011) 14–29.

[56] R. Cevik, S. Em, A. Gur, K. Nas, A.J. Sarac, L. Colpan, Sex and thyroid hormone status in women with rheumatoid arthritis: are there any effects of menopausal state and disease activity on these hormones? Int. J. Clin. Pract. 58 (4) (2004) 327–332.

[57] A. Losada-García, S.A. Cortés-Ramírez, M. Cruz-Burgos, M. Morales-Pacheco, C. D. Cruz-Hernández, V. Gonzalez-Covarrubias, et al., Hormone-related cancer and autoimmune diseases: a complex interplay to be discovered, Front. Genet. 12 (2021) 673180.

[58] S. Shams, J.M. Martinez, J.R.D. Dawson, J. Flores, M. Gabriel, G. Garcia, et al., The therapeutic landscape of rheumatoid arthritis: current state and future directions, Front. Pharmacol. 12 (2021) 680043.

[59] S. Steeland, C. Libert, R.E. Vandenbroucke, A new venue of TNF targeting, Int. J. Mol. Sci. 19 (5) (2018).

[60] K. Krüger, DMARD(„disease-modifying antirheumatic drug")-Therapie bei früherer und aktiver Tumorerkrankung, Zeitschrift fur Rheumatologie 82 (3) (2023) 206–211.

[61] V. Huss, H. Bower, H. Wadström, T. Frisell, J. Askling, Short- and longer-term cancer risks with biologic and targeted synthetic disease-modifying antirheumatic drugs as used against rheumatoid arthritis in clinical practice, Rheumatology 61 (5) (2022) 1810–1818.

[62] K. Hellgren, L. Dreyer, E.V. Arkema, B. Glintborg, L. Jacobsson, L.-E. Kristensen, et al., Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers, Ann. Rheum. Dis. 76 (2016) 105–111.