Environmental influences on risk for rheumatoid arthritis

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Summary

Recent studies have increased our understanding of environmental exposures that modify risk for RA such as smoking and alcohol intake. Other factors such as birthweight, breastfeeding, socioeconomic status and region of birth have also been demonstrated to contribute to risk. ACPA status is associated with specific environmental factors and is therefore important to incorporate into present and future studies.

Keywords

environmental risk factors; epidemiology; gene–environment interaction; rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory joint disease worldwide [1]. Over the past 15 years, our understanding of RA pathogenesis has advanced with the identification of environmental and genetic risk factors for the disease. This review will focus on new environmental factors that modify risk for RA published in the past 2 years and will highlight studies that confirm, modify or refute risk factors that have been previously reported. These studies have demonstrated that diet, smoking, location of residence, socioeconomic status and birthweight can modify risk for RA. In addition, we will also review important updates on our understanding of gene–environment interactions in RA.
**Subsets of RA**

An important concept that has emerged in understanding risk factors for RA is the role of anti-citrullinated protein/peptide antibodies (ACPA), also known as antibodies to cyclic citrullinated peptides (anti-CCPs). ACPA is a more specific marker for RA than rheumatoid factor and is hypothesized to be involved with the pathogenesis of the disease [2,3]. Risk factors such as smoking have been found to have specific associations with ACPA-positive RA rather than ACPA-negative RA particularly in individuals who carry the shared epitope [4–6]. ACPA-positive status is also associated with recently identified genetic risk factors such as TRAF1-C5 [7]. The specific association of ACPA-positive RA with certain environmental and genetic risk factors that are not seen for ACPA-negative RA suggests distinct causes for these two subsets. It can be anticipated that the influence of environmental factors other than smoking may also differ between these two major subsets and possibly also within these subsets.

This information emphasizes that we are in the beginning of an era in which it will become possible to disentangle the complex interactions between different environmental and genetic risk factors and to understand what different pathologically associated immune reactions may be triggered in the context of various combinations of genes and environmental factors. We must carefully separate different subsets of RA in studies and descriptions of how environmental factors interact with genes in providing the basis for onset of and disease course for different forms of RA.

Having provided this general comment on the complexity as well as promise for studies on environmental factors and RA, the rest of this review will be devoted to the description of recent discoveries concerning the role of environment in this disease. Notably, almost all such studies have been conducted for RA without subdivision into subsets, and most studies on environment have not taken genetics into account.

**Smoking**

Smoking is the strongest known environmental risk factor for RA. This association was first described over a decade ago but has been further characterized recently with the use of ACPA tests [8,9]. A recent study found that tobacco smoking was specifically associated with an increased risk of ACPA-positive and not ACPA-negative RA [4]. As the majority of RA patients who are ACPA positive are also rheumatoid factor positive, these findings concur with previous studies which show an overall risk of RA for smokers, specifically for rheumatoid factor-positive RA [5,10].

The risk of RA increases with amount and duration of cigarette use [5]. Findings from a large prospective cohort study, the Nurses’ Health Study (NHS), showed a linear relationship between smoking and risk of RA whereby increasing doses of cigarettes (pack-years of smoking) was associated with an increased risk of RA [11]. The heaviest smokers with more than 40 pack-years had approximately two-fold increase of risk for RA than those who had never smoked. Furthermore, an individual remains at increased risk even after cessation for 20 years or more.

The risk of RA from smoking is further modified by the number of shared epitope copies suggesting gene–environment interaction. The shared epitope, a specific sequence of amino acids on the HLA-DRB1 allele, is the strongest known genetic risk factor for RA [12]. A report from the Swedish population-based case–control study Epidemiologic Investigation of Rheumatoid Arthritis (EIRA), in which RA cases are recruited within 1 year of onset, found that smokers who do not carry the shared epitope have a 1.5-fold elevated risk of developing ACPA-positive RA over nonsmokers who also do not carry the shared epitope. The risk of developing ACPA and RA for an individual who smokes and carries two copies of the shared
epitope is 21-fold higher than nonsmokers who do not carry the shared epitope; this greatly elevated risk is attributed to the gene–environment interaction between smoking and the shared epitope [6]. The authors also demonstrated that smoking increases the proportion of citrulline-positive cells in the lungs (conducted through bronchoalveolar lavage). Citrullinated cells were not present in nonsmokers. Through these findings, the authors hypothesized that smoking induces citrullination and that carriers of the shared epitope may be genetically predisposed to developing antibodies against citrulline.

The gene–environment interaction between smoking and the shared epitope and risk of ACPA-positive RA was also observed in several other European cohorts [9,13,14]. A study of the presence or absence of ACPA or rheumatoid factor among RA cases only found no interaction between the shared epitope and smoking in predicting antibody positivity among three large North American cohorts [9,15].

With regards to rheumatoid factor-positive RA, a similar gene–environment interaction between smoking and the shared epitope has been observed for rheumatoid factor-positive RA in most studies with the exception of a female cohort of older onset RA [13,16,17]. The risk of developing RA from gene–environment interactions increases with the intensity of smoking. In the NHS, the highest risk of seropositive RA was in heavy smokers who carry two copies of the shared epitope with evidence for multiplicative interaction [18].

**Alcohol**

Alcohol consumption may decrease risk for RA. In a Danish study comparing those who consume alcohol and those who did not, individuals who consumed alcohol had an overall lower risk of developing ACPA-positive RA [4]. A dose-dependent effect was demonstrated in a subsequent study of two cohorts, EIRA and the Danish Case–Control Study of Rheumatoid Arthritis (CACORA). Alcohol consumption was based on patient questionnaires regarding alcohol consumption in the previous week, previous habitual consumption prior to RA onset (EIRA) and consumption 10 years before inclusion in the study (CACORA). Those with the highest consumption (≥5 drinks or 80 gm ethanol per week) had a decreased risk of RA on the order of 40–50% compared with those with low-to-no consumption (<0.5 g ethanol (ETOH) per week) [19•]. Furthermore, carriers of the shared epitope were found to have a more pronounced risk reduction with evidence for alcohol-shared epitope interaction. This reduction was found to be statistically significant in both the EIRA and CACORA cohorts in which nondrinkers were compared with those who had five or more drinks/week.

**Vitamin D**

Vitamin D is a hormone essential for bone and mineral homeostasis and is also involved in the regulation of cells in the innate and adaptive immune system through the vitamin D receptor (VDR) as a suppressor of pro-inflammatory responses [20]. Although vitamin D has been implicated in a decreased risk of autoimmune diseases such as type 1 diabetes and multiple sclerosis, its role in decreasing the risk of RA remains equivocal [21–23]. An inverse association between vitamin D intake and RA was found in the prospective cohort study, the Iowa Women’s Health Study [24]. In this study, vitamin D intake was assessed using the food frequency questionnaire and calculated by multiplying the frequency of consumption of each unit of food by the vitamin D content. Individuals in the highest tertile were taking more than 468 IU of vitamin D daily at baseline. This trend was not seen in the most recent study on vitamin D and risk of RA in the NHS in which increasing levels of vitamin D intake based on diet assessments at baseline and from multiple follow-up questionnaires prior to diagnosis were not found to be associated with decreased risk of RA even in the highest quintile taking more than 489 IU vitamin D per day [25•]. A study of vitamin D levels measured in serum collected prior to diagnosis in 79 preclinical RA patients compared with 139 controls found no difference
in vitamin D levels at any time point: 1 year, 2 years or at least 5 years prior to diagnosis [26].

**Protein and red meat**

Previous investigations have found that a period of fasting followed by a regimented vegetarian diet can decrease disease activity [27,28]. This led to investigations into whether protein and red meat intake play a role in increasing risk for developing RA. Indeed, increased red meat and protein intake was observed in an earlier study to be associated with an increased risk of inflammatory arthropathy [29]. However, a subsequent study in the NHS, utilizing RA as the outcome, showed no association between amount of protein, red meat, poultry, and fish consumption and modification of RA risk [30•].

**Oral contraceptives**

Because the majority of individuals who develop RA are women, estrogens have long been thought to influence the risk of developing disease. Past studies have demonstrated that oral contraceptives (OCP) may have a protective effect in the development of RA; however, this fact remains under debate [31–33,34•]. A recent study compared the prevalence of rheumatoid factor, which is often present before the development of RA in individuals on OCPs with the hypothesis that OCPs would be protective, and therefore individuals on OCPs would have a lower prevalence of rheumatoid factor than those who are not [35]. This study was conducted on mothers of children with type 1 diabetes in the Diabetes Autoimmunity in the Young (DAISY) study based in Colorado, United States. A lower prevalence of rheumatoid factor positivity in women on OCPs was observed compared with those who were not. This result suggests a protective effect of OCPs with regards to the development of rheumatoid factor, but not necessarily for RA.

**Birthweight**

High birthweight (>4 kg) was found to be associated with as high as a three-fold increased risk of RA in a case-control study conducted in Sweden [36]. A recent population-based study using the NHS found a similar association in which babies weighing greater than 4.54 kg (9.9 lb) at birth compared with babies who were 3.2–3.85 kg (7.0–8.5 lbs) had a two-fold risk of developing RA [37•]. No significant difference in risk was seen when stratified by rheumatoid factor status. Although the biologic mechanism behind this association is unknown, it is hypothesized that this may be due to hypothalamic–pituitary axis (HPA) dysfunction which is associated with both RA and individuals with high birthweight [38,39].

**Breast feeding**

Amelioration of RA has been observed during pregnancy with exacerbation in the postpartum period. Therefore, investigators sought to assess whether risk of disease is modified by breastfeeding. A recent study found that long-term breastfeeding of greater than or equal to 13 months was associated with a significant reduction of the risk of RA [34•]. These findings corroborate with a previous study which found that breastfeeding more than 12 months was inversely related to the development of RA with a lower risk with longer duration of breast feeding [40].

**Socioeconomic status**

There is an inverse association between socioeconomic status measured by education and occupational class and risk of RA [41]. A recent Danish case–control study found that this risk was highly associated with rheumatoid factor positive RA and not rheumatoid factor-negative
RA [42]. There was a two-fold lower risk of RA when comparing individuals with the longest education compared with those with the lowest level of education. These results agree with a previous population-based case–control study in Sweden (EIRA) in which the risk of RA in patients without university degrees was 40% higher compared with those with university degrees. For patients whose occupation required manual labor, the risk was 20% more than nonmanual workers. When stratified by rheumatoid factor status, this association was also stronger for rheumatoid factor and RA [41].

**Geography**

Location of birth and current residence in the United States is associated with differential risk of RA. In a study conducted within the NHS, the United States was divided into five regions: West, Mid-West, Mid-Atlantic, Northeast and Southeast. In women who lived in the same region at birth into adulthood, the risk was highest among those living in the mid-West and Northeast. Those living in the Northeast had as high as 45% elevated risk compared with those in the West if comparing the population at different time points of birth: ages 15 and 30 years [43•].

Individuals in lower latitudes may also have an earlier onset of RA compared with higher latitudes. In a study comparing the age of onset of patients in Mexico compared with Canada, on average, Mexican patients were 12 years younger than Canadians; however, neither the analysis was adjusted for autoantibody status nor were genetic differences taken into account [44].

**Conclusion**

Studies of the impact of environmental factors on risk of developing RA, as well other multifactorial diseases, are associated with several methodological and practical problems. As evidenced in this review, the literature on environmental risk factors is relatively scarce with frequent lack of reproducibility of findings particularly with dietary factors. The two major acceptable methods, population-based case–control studies and cohort studies, have provided the majority of our current knowledge on environmental factors in RA. Oftentimes as in the case of smoking, breast feeding and socioeconomic status, both case–control and cohort studies have arrived at the same results. Case–control studies in RA are generally better powered and can provide quantification of the magnitude of effect of the environmental exposures and gene–environment interactions. The drawback is the risk of bias in recruitment of cases and recall bias in responses from cases with RA compared with controls. Thus, the best case–control studies are those that are carried out in newly diagnosed patients (to minimize recall bias) and in which both cases and controls are recruited from the same defined study population (e.g. EIRA). Cohort studies are usually less subject to both these biases but often have a low power in uncommon diseases such as RA, particularly when there is a long follow-up period. In these cases, the associations between environmental exposures (which may change over time) and RA often are underestimated, unless environmental conditions have been repeatedly measured (e.g. NHS). Optimally, results from the two approaches should be combined.

Advances in our understanding of environmental risk factors can lead to avenues of research exploring how these factors may play a role in the pathogenesis of the disease. On review of the literature, it has become increasingly clear that the ACPA-positive RA phenotype is associated with specific environmental risk factors and that genetics, particularly the HLA-shared epitope, has demonstrated an increasingly important role through gene–environment interactions. It is crucial that these factors be taken into account in future studies on environmental risk in RA.
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

34. Pikwer M, Bergstrom U, Nilsson JA, et al. Breast-feeding, but not oral contraceptives, is associated with a reduced risk of rheumatoid arthritis. Ann Rheum Dis. 2008 (in press). This nested case–control study from the Malmö Diet and Cancer Study based in Sweden observed an association that longer duration of breast feeding was associated with a reduced risk of RA; no modification of risk was found with OCP use.

37. Mandl LA, Costenbader KH, Simard J, Karlson EW. Is birthweight associated with risk of rheumatoid arthritis? Data from a large prospective cohort study. Ann Rheum Dis. 2008 [Epub ahead of print]. This study conducted within the NHS demonstrated that higher birthweight of more than 4.54 kg was associated with up to a two-fold increased risk of RA in adulthood.


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