Original Article

Risk factor assessment of rheumatoid arthritis in North Kerala

Binoy Paul , Rosh Pariyapurath

Abstract

Objective: Rheumatoid arthritis (RA) is a multifactorial disease; it leads to disabling and painful chronic inflammatory arthritis. Its onset may be delayed or even prevented by modifying the risk factors involved. Many genetic, epigenetic, and environmental factors are implicated in the pathogenesis of RA. The objectives of this case-control study were to assess various risk factors in our population and to compare the same with age- and sex-matched controls.

Methods: We studied 118 cases with RA diagnosed using the EULAR criteria. In total, 581 age- and sex-matched controls were selected. Each individual was administered a separate questionnaire regarding their risk factors (known risk factors were studied). The implicated dietary factors were incorporated in a food frequency questionnaire (FFQ) and administered to both cases and controls. Comparison was made between those who consume an item at a particular frequency, who consume less, and who consume nothing at all. Among those who consume, each group was re-compared. Statistical analysis was conducted using Statistical Package for Social Sciences (IBM Corp.; Armonk, NY, USA).

Results: There was significant relationship for family history, periodontitis, history of chikungunya, and sun exposure (p<0.05). Association with various food items was studied using the FFQ, but the relationship was inconsistent, probably due to consumption of modified diet by the persons with RA. Also, a majority of cases were females and nonsmokers for assessing an association with smoking habits.

Conclusion: In our population, previous infections (e.g., chikungunya and poor oral hygiene with periodontitis) were the prominently observed risk factors. Also, smoking was less common among women, and probably contributed less, as majority of cases were females. For dietary pattern association, a prospective cohort study may be needed.

Keywords: Rheumatoid arthritis, risc factors, periodontitis, chikungunya, environmental

Introduction

Rheumatoid arthritis (RA) is a disabling and painful chronic inflammatory arthritis that can lead to extreme functional disability if not adequately treated; it is also the second commonest disease after to osteoarthritis. It is a multisystem inflammatory disease primarily affecting synovial joints. There are several genetic, epigenetic, and environmental factors implicated in the pathogenesis of RA. These factors vary in different populations, and there are several studies from different populations relating these pathogenic factors, both negative and positive. This suggests that RA is a multifactorial disease, the onset of which may be delayed or even prevented by modifying the risk factors involved. Also, several risk factors, such as genetic factors, may not be modifiable. Many newer risk factors with variable effects are being proposed.

Autoantibodies and cytokines can develop many years prior to the diagnosis of RA. Thus, clinical RA develops in phases. There is an asymptomatic phase of genetic risk over which environmental exposures occur, followed by an immune activation phase, which can be asymptomatic. Autoantibodies and inflammatory markers are found in the serum. This phase may be followed by a phase of active disease, which starts as minor articular symptoms and later results in frank arthritis. Initially, arthritis in many cases is unclassifiable according to the 2010 ACR/European League against Rheumatism (EULAR) criteria. With time, the disease evolves and can then be classified as RA by established criteria (1). Evolution of disease from undifferentiated inflammatory polyarthritis to classical RA may take up to 5 years (2). Thus, a genetically susceptible individual when exposed to environmental risk factors, it triggers autoimmunity with autoantibody production, and further exposures can cause further immune dysregulation and ultimately symptomatic inflammatory arthritis. Many have a long preclinical phase during which autoantibodies develop, and this is the time where we can modify the risk factors and further delay progression. Many environmental and

Department of Medicine, KMCT Medical College, Kerala, India

Address for Correspondence:
Pariyapurath Rosh, Department of Medicine, KMCT Medical College, Kerala, India

E-mail: dr.rosh5834@gmail.com

dietary factors influence the disease onset. The environmental factors implicated include smoking habits, vitamin D levels, periodontitis, and previous infection such as chikungunya. Dietary factors include W3 fatty acids, salt intake, fruits and vegetables, coffee and tea, some with predisposition and others with protection. The objective of the present study was to assess different etiologic factors and their association with RA in our population in Calicut, Kerala, India.

Genetic factors

Having a first-degree relative with RA increases the RA risk by 3- to 9-folds compared with that of the general population. It may be due to the influence of shared genetic and/or environmental factors (3). More than 30 novel risk loci are identified by genome association studies in addition to well-established associations with the *HLA-DRB1* "shared epitope" (HLA-SE) alleles (4). Interactions between HLA-SE and potentially other risk alleles and environmental factors may contribute to RA pathogenesis (5-7). Models that incorporate genetic, serologic, and lifestyle/environmental factors can predict the risk of developing RA more precisely than any of these factors alone (6, 8).

Environmental factors

Smoking

Smoking is the most studied and implicated preventable risk factor for RA, as proven by many twin, case-control, and cohort studies (9-25). This association was consistent for RF+ RA for male and female smokers, as observed in a meta-analysis (26). A dose-dependent effect of pack-years of smoking was suggested by some studies with a population-attributable risk of 18%-25% (22, 23). Risk for RA exponentially increases among smokers as it interacts with all alleles of the SE (26). There may be geographical variations in the association between smoking, ACPA, and RA, as some studies are against specificity for ACPA+ RA (27-29). Passive smoking and smokeless tobacco do not seem to increase the risk of RA (22, 30).

Periodontitis

Periodontitis is implicated as a risk factor for the development of many immune-related chronic inflammatory diseases. Oral bacteria, such as *Porphyromonas gingivalis,* are strong markers of disease status. Many studies have shown the association of RA with periodontitis. The role of citrullination and subsequent autoantibody responses as well as the role of mediators released as a result of bacterial colonization have been proposed in the pathogenesis of RA (31, 32). Influx of oxygen-consuming

inflammatory cells and the overproduction of reactive oxygen species leads to posttranslational modification (33, 34). There is also enzymatic posttranslational modification (cleavage of extracellular proteins by matrix metalloproteases, bacterial proteases, or citrullination by PAD enzymes (35-37). *P. gingivalis* expresses both arginine-specific proteases and PAD and may be linked to the inflammatory process in RA (33, 38).

There appears an increased prevalence of periodontitis and a higher rate of tooth loss in patients with RA in comparison with that in the general population, as suggested by several studies (39-45). RA may also be more prevalent among patients with periodontitis (42, 46). Higher antibody titers against *P. gingivalis* and positive correlation with ACPA have been reported in patients with RA (46, 47).

Vitamin D

Vitamin D deficiency is implicated in the pathogenesis of several autoimmune conditions. It's role as an immunoregulatory hormone also is documented. Many dietary intake-based prospective studies have failed to show any association between vitamin D and RA, except for the Iowa WHS (48-51). Dietary intake is not the sole determinant of vitamin D status, because it may also be affected by latitude and sunlight exposure. Even with serum vitamin D3 levels, some studies have failed to show any association (52).

Infections and RA

Many infections, particularly those with *articular* manifestations, such as Epstein Barr virus*,* Parvo virus B19, chikungunya virus, and some bacteria, have been implicated as risk factors for RA. Mechanisms by which this predisposition is different in different situations. For example, in case of Epstein Barr virus, it is probably gp110 molecular mimicry; in case of Parvo virus B19, it is alteration of function of FLS; and in certain bacterial infections, it is the cell wall mediated TLR 2 activation which is implicated.

Frequent outbreaks of chikungunya fever with polyarthralgia have been observed, which is also proposed as a risk factor for the future development of RA, as suggested by human as well as animal studies (53-55).

Meat

A diet high in protein is considered an etiology of RA (56). However, many studies are also in the favor of a low-protein diet leading to the improvement of RA symptoms (57-60). The prevalence of RA is higher in countries with greater consumption of red meat (61). Pattison

et al. (62) reported the first prospective investigation of red meat and risk for inflammatory polyarthritis and showed that higher intakes of both red meat and total protein increased the risk for IP, whereas meat iron showed no association. However, there are also some studies that have failed to show any association. For example, a large prospective cohort study conducted among subjects of the Nurses' Health Study failed to demonstrate any association (63).

High-salt diet

Studies in animal models and on human cells have shown an effect of sodium chloride (NaCl) on T_H17 cells in promoting inflammation, which may be the reason for its proposed association with RA. However, this association was seen in some studies that were conducted only among smokers with RA (64).

Fruits and vegetables

Consumption of fruits and vegetables has several health benefits, which may be largely related to their antioxidant properties. Vitamins C and E, lycopene, carotenoids, flavonoids, and possibly fructose-mediated urate production are probably important in this regard (65). There are also some studies that suggest that vitamin C and β-kryptoxanthin (a carotenoid) have protective roles, and some studies concerning dietary zinc supplements also exist (66-69). Some studies found no benefit of antioxidants, despite testing multiple parameters of antioxidant content (70, 71). Some observational studies examined whole foods, showing a protective role (72).

Omega-3 fatty acids and fish

Several of studies have shown that omega-3 fatty acids decrease the severity of RA or have a preventive role (73-82). Olive oil consumption is one among the best studied omega-3 fatty acids, and fish oil has proven benefits (83). The prospective Danish Diet, Cancer, and Health population-based cohort study of RA failed to confirm a protective effect of olive oil; however, the consumption of oily fish did, show a trend toward a protective effect (70).

Methods

The present study was a case-control study. Patients who were diagnosed with RA and who satisfied the diagnostic criteria when they visited our OPD were included, whereas age- and sex-matched individuals without RA, irrespective of other parameters and comorbidities, were used as controls.

Informed consent was obtained from all participants. The study was approved by the Institutional Ethics Committee of the KMCT Medical College.

Paul and Pariyapurath. Risk factor assessment of rheumatoid arthritis in North Kerala

Eur J Rheumatol 2018; 5(3): 184-90

A total of 118 cases and 581 controls were included. Of the 118 cases, 28% were older than 60 y, 57% were aged between 40 and 59 y, and 15% were younger than 40 y. Also, 87% were females and the remaining 13% were males. Almost 29% of the cases had a disease duration of more than 10 y, 33% between 5 and 10 y, and 38% less than 5 y. All patients were under standard treatment for RA with drugs, such as methotrexate, steroids, leflunomide, hydroxychloroquine, and NSAIDs; other comorbidities, such as diabetes, were less common among the cases than the controls. Each individual was administered a separate questionnaire regarding their risk factors (known risk factors were studied). The implicated dietary factors were incorporated in a food frequency questionnaire (FFQ) and were administered to both cases and controls. Comparison was made between those who consume an item at a particular frequency, those who consume less, and those who consume nothing at all. Among those who consume, each group was re-compared. Statistical analysis was conducted using SPSS.

Results

Genetic factors

In the present study, among the 118 cases, 15 (13%) had first-degree relatives with RA, two (0.02%) had second-degree relatives, and only 1 (0.01%) had a third-degree relative with RA. Among the controls, 15 (0.03%) had first-degree relatives, none had second-degree relatives, and two had third-degree relatives (Table 1). The p value was significant, showing a strong positive association, with an OR of 7.64.

Smoking

In our study group, majority of the cases were women and all were nonsmokers. Hence, the association could not be established.

Periodontitis

We compared the incidence of periodontitis among those with RA and an age- and sex-matched general population. The presence of periodontitis was assessed by personal interview and dental examination using probing pocket depth and clinical attachment loss. The extent of periodontitis was not graded. A total of 118 patients with RA and 581 age- and sex-matched controls were observed. Among these cases, 46 had periodontitis (39%); however, among the 581 controls, only 61 (11.73%), with p<0.05 and an OR of 5.84, showed a strong positive association between RA and periodontitis (Table 2).

Sun exposure

We assessed the average sun exposure for at least 1 hour per day in the open sun and the usage of covered clothes in the sun. We compared these results with those of controls (Tables 3 and 4).

Sun exposure and RA were negatively associated, which was statistically significant with (p<0.05). The comparison was based on sun exposure as well as the usage of covered clothes on a routine basis (OR=1.13). This association may be related to vitamin D, compounded by other factors like exercise.

History of chikungunya

We compared the clinical history of chikungunya in patients with RA and in controls. History of chikungunya was assessed by IgM positivity and typical symptoms during the epidemic of chikungunya as per hospital records. There was a significant association between the history of chikungunya and RA. Among all cases, there were 32.2% individuals with a history of chikungunya, whereas among controls, there were only 4.48% with a positive history, the p value being significant (Table 5) and OR of 8.73.

Meat consumption

We administered separate questionnaires for cases and controls regarding meat consumption, as frequency of servings taken. In our study, we could not find any positive association between meat consumption and RA. Actually, there was a negative correlation (Fig. 1), with an OR<1. The probable reason was that many of our patients with RA were long-term RA patients and were advised to take less amount of meat and a majority of patients were even following this. Thus, this negative association could not be taken as a real one, although the p value was significant.

Salt intake

The assessment of salt intake was difficult in our form of dietary practice, and we assessed it using the questionnaire related to excess salt intake in the form of specific food items: salted fish and meat, papads (a food item with high salt content), and pickles, according to number of servings per day/week/month. The comparison did not show any predisposition with salt intake; however, RA was less common in this group with a significant p value (Figs. 2-4). OR also showed a negative correlation. This may not be the real scenario as many of the patients with RA were under strict diet restrictions and low salt intake. To assess this association, a prospective cohort study is probably needed.

Vegetables and fruits

By personal interview, the average intake of fruits and vegetables was separately assessed.

Table 1. Family history

	Cases	Controls	p
Nil	100	564	
First degree	15	15	
Second degree	2	0	0.000
Third degree	1	2	

Table 2. Periodontitis

		p
Cases	39%	0.000
controls	11.73%	

Table 3. Sun exposure

	Cases	Controls	p
No	20	93	
Occasionally	86	264	0.000
Rarely	12	224	

Table 4. Wearing covered clothes

	Cases	Controls	p
No	78	347	
Usually	26	117	
occasionally	14	103	0.000
Rarely	0	14	

Table 5. h/o Chikungunya

	Present	Absent	p
Cases	32.2%	67.8%	
controls	04.48%	95.52%	0.000

Table 6. Vegetable intake

Daily	102/118	482/581	0.353
Weekly thrice	5/118	93/581	0.000
Weekly twice	6/118	3/581	0.455
Weekly once	2/118	3/581	
Occasionally	1/118		

Consumption among cases and controls was grouped as number of servings per day/week/month. Each group was then compared with the rest of the population and also with the exposed group (Figure 5).

The association was inconsistent through the group. There appears to be a protective role for vegetables, because the consumption increases with a significant p value; however, this association was not consistent for green leafy vegetables (Table 6).

Eur J Rheumatol 2018; 5(3): 184-90

Paul and Pariyapurath. Risk factor assessment of rheumatoid arthritis in North Kerala
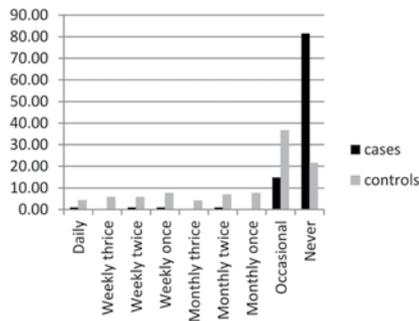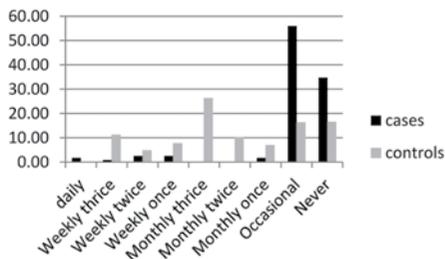

Figure 1. Data on meat consumption (plotted as percentage)
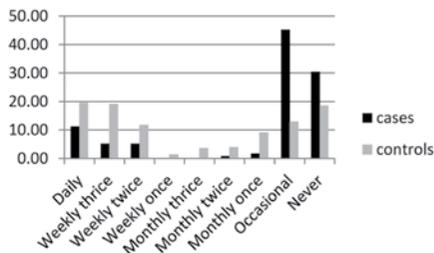
Figure 2. Data on pickles and salted food items (plotted as percentage)
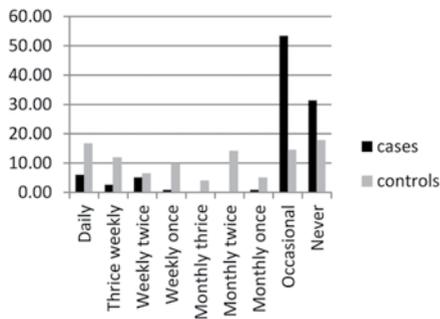
Figure 3. Data on use of papads (plotted as percentage)

Figure 4. Data on salted dry fish (plotted as percentage)

There also appears a trend toward protective roles for fruit; however, the association was not statistically significant (Table 7).

Fish consumption
We studied fish consumption among the patients with RA and age-matched controls as

Table 7. Fruit intake

	Cases %	Controls %	p (comparison with less/non exposed)	p (comparison among exposed)
D3	0	1	0.318	0.020
D2	0	4		0.011
D1	22	22		0.992
W3	25	28	0.278	0.270
W2	25	12	0.001	0.001
W1	6	4	0.176	0.581
M3	0	4	0.027	0.009
M2	3	5	0.362	0.135
M1	2	1	0.397	0.426
O	13	10	0.042	0.277
N	4	9	0.049	0.037

D3: thrice daily; D2: twice daily; D1: once daily; W3: thrice weekly; W2: twice weekly; W1: once weekly; M3: thrice monthly; M2: twice monthly; M1: once monthly; O: occasional; N: never (all in terms of at least one serving)

Table 8. Fish consumption

	Cases %	Controls %	p (comparison with less/non exposed)	p (comparison among exposed)
D3	0	1	0.318	0.020
D2	0	4		0.011
D1	22	22		0.992
W3	25	28	0.278	0.270
W2	25	12	0.001	0.001
W1	6	4	0.176	0.581
M3	0	4	0.027	0.009
M2	3	5	0.362	0.135
M1	2	1	0.397	0.426
O	13	10	0.042	0.277
N	4	9	0.049	0.037

D3: thrice daily; D2: twice daily; D1: once daily; W3: thrice weekly; W2: twice weekly; W1: once weekly; M3: thrice monthly; M2: twice monthly; M1 once monthly; O: occasional; N: never (all in terms of at least one serving)

the number of servings per day/month/week. Regarding fish, there was a stronger association throughout the group, with a more significant p value (Table 8). Comparison was made on the basis of daily consumption as well as whether consuming or not. Either way, a positive relationship was observed (OR=1.4 and 1.43, respectively).

Oily food and fried items
Consumption of oily food and fried bakery items was also studied in the same manner. Majority of the population used vegetable oil for cooking, which also included coconut oil (Tables 9 and 10). In fact, there was a negative association with OR<1. This may be due to

modified long-term dietary habits followed by patients on the physician's advice.

In conclusion, omega-3/PUFAs have an inconsistent association as obtained from daily oil usage; however, fish intake, particularly on a daily basis, has shown a protective effect against RA. Other parameters investigated were tea, coffee, alcohol, pan chewing, egg, milk, etc. These variables did not show any association with RA.

Discussion
There is a positive association with a family history of RA among close relatives as seen in other studies. Regarding the environmental factors studied, there is a definite correlation

Paul and Pariyapurath. Risk factor assessment of rheumatoid arthritis in North Kerala

Eur J Rheumatol 2018; 5(3): 184-90

Table 9. Consumption of bakery items

	Cases %	Controls %	p (comparison with less/non exposed)	p (comparison among exposed)
D3		0.5	0.277	0.536
D2		0.9		0.353
D1	4.3	5.7		0.361
W3	0.9	24.6	0.000	0.000
W2	3.4	8.6	0.000	0.032
W1	6.9	4.6	0.937	0.035
M3		3.6	0.003	0.012
M2	1.7	2.8	0.136	0.400
M1	0.9	9.5	0.000	0.001
O	62.9	11	0.000	0.000
N	19	28	0.039	0.032

D3: thrice daily; D2: twice daily; D1: once daily; W3: thrice weekly; W2: twice weekly; W1: once weekly; M3: thrice monthly; M2: twice monthly; M1 once monthly; O: occasional; N: never (all in terms of at least one serving)

Table 10. Oily food/fried item intake

	Cases %	Controls %	p (comparison with less/non exposed)	p (comparison among exposed)
D3		0.2	0.000	0.000
D2		11.2		0.000
D1	17.9	36.8		0.000
W3	5.1	22.5	0.000	0.211
W2	5.1	9.3	0.000	0.193
W1	3.4	1.9	0.164	0.713
M3		0.3	0.321	0.077
M2		2.6	0.000	0.080
M1	2.6	0.7	0.553	0.000
O	47.9	5	0.000	0.008
N	17.9	9.5	0.007	0.000

D3: thrice daily; D2: twice daily; D1: once daily; W3: thrice weekly; W2: twice weekly; W1: once weekly; M3: thrice monthly; M2: twice monthly; M1 once monthly; O: occasional; N: never (all in terms of at least one serving)
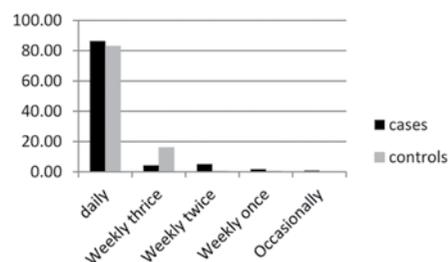
Figure 5. Data on use of vegetables (plotted as percentage)

with the history of chikungunya. Another association was obtained with sun exposure, which is negative. Vitamin D levels were not assessed.

Periodontitis was another factor found to be significantly associated with RA.

Regarding the food items studied, the consumption of vegetables and fruits seems to have a protective role; however, the significance is inconsistent. Another factor with a protective effect was fish intake.

This study was not supported by any financial aid. The authors report no conflicts of interest.

Study limitations
Genetic and environmental factors were easily comparable between the groups; however, many of the patients were long-term RA pa-

tients and it was difficult to obtain their dietary habits prior to disease development. Rather, many of them were advised by the treating clinician regarding the dietary modifications and the need to maintain an ideal body weight. Thus, many reported modified sorts of dietary habits. This was probably the reason for the lack of association with many dietary elements. For obtaining such details, a prospective cohort study is needed.

References

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-81. [CrossRef]
2. Symmons DP, Silman AJ. The Norfolk Arthritis Register (NOAR) Clin Exp Rheumatol 2003; 21: S94-9.
3. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum 2009; 60: 661-8. [CrossRef]
4. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat Genet 2010; 42: 508-14. [CrossRef]
5. Costenbader KH, Chang SC, De Vivo I, Plenge R, Karlson EW. Genetic polymorphisms in PTPN22, PADI-4, and CTLA-4 and risk for rheumatoid arthritis in two longitudinal cohort studies: evidence of gene-environment interactions with heavy cigarette smoking. Arthritis Res Ther 2008; 10: R52. [CrossRef]
6. Karlson EW, Chibnik LB, Kraft P, Cui J, Keenan BT, Ding B, et al. Cumulative association of 22 genetic variants with seropositive rheumatoid arthritis risk. Ann Rheum Dis 2010; 69: 1077-85. [CrossRef]
7. Mahdi H, Fisher BA, Kallberg H, Plant D, Malmström V, Rönnelid J, et al. Specific interaction

between genotype, smoking and autoimmunity to citrullinated alpha-enolase in the etiology of rheumatoid arthritis. Nat Genet 2009; 41: 1319-24. [CrossRef]

8. Karlson EW, Chang SC, Cui J, Chibnik LB, Fraser PA, De Vivo I, et al. Gene-environment interaction between HLA-DRB1 shared epitope and heavy cigarette smoking in predicting incident rheumatoid arthritis. Ann Rheum Dis 2010; 69: 54-60. [CrossRef]

9. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum 1996; 39: 732-5. [CrossRef]

10. Hazes JM, Dijkmans BA, Vandenbroucke JP, de Vries RR, Cats A. Lifestyle and the risk of rheumatoid arthritis: cigarette smoking and alcohol consumption. Ann Rheum Dis 1990; 49: 980-2. [CrossRef]

11. Hutchinson D, Shepstone L, Moots R, Lear JT, Lynch MP. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. Ann Rheum Dis 2001; 60: 223-7. [CrossRef]

12. Krishnan E. Smoking, gender and rheumatoid arthritis-epidemiological clues to etiology. Results from the behavioral risk factor surveillance system. Joint Bone Spine 2003; 70: 496-502. [CrossRef]

13. Krishnan E, Sokka T, Hannonen P. Smoking-gender interaction and risk for rheumatoid arthritis. Arthritis Res Ther 2003; 5: R158-62. [CrossRef]

14. Olsson AR, Skogh T, Wingren G. Comorbidity and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis. Ann Rheum Dis 2001; 60: 934-9. [CrossRef]

15. Olsson AR, Skogh T, Wingren G. Aetiological factors of importance for the development of rheumatoid arthritis. Scand J Rheumatol 2004; 33: 300-6. [CrossRef]

16. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum 2004; 50: 3085-92. [CrossRef]

17. Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population-based case-control study, using incident cases. Ann Rheum Dis 2003; 62: 835-41. [CrossRef]

18. Symmons DP, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DG, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum 1997; 40: 1955-61. [CrossRef]

19. Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. J Rheumatol 1999; 26: 47-54.

20. Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology 1994; 5: 525-32.

21. Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. Contraception 1987; 35: 457-64. [CrossRef]

22. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med 2006; 119: 503-9. [CrossRef]

23. Criswell LA, Merlino LA, Cerhan JR, Mikuls TR, Mudano AS, Burma M, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. Am J Med 2002; 112: 465-71. [CrossRef]

24. Heliövaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. J Rheumatol 1993; 20: 1830-5.

25. Karlson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. Arthritis Rheum 1999; 42: 910-7. [CrossRef]

26. Klareskog L, Stolt P, Lundberg K, Bengtsson C, Grunewald J, Rönnelid J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006; 54: 38-46. [CrossRef]

27. Lee HS, Irigoyen P, Kern M, Lee A, Batliwalla F, Lee A, et al. Interaction between smoking, the shared epitope, and anti-cyclic citrullinated peptide: a mixed picture in three large North American rheumatoid arthritis cohorts. Arthritis Rheum 2007; 56: 1745-53. [CrossRef]

28. Bang SY, Lee KH, Cho SK, Lee HS, Lee KW, Bae SC. Smoking increases rheumatoid arthritis susceptibility in individuals carrying the HLA-DRB1 shared epitope, regardless of rheumatoid factor or anti-cyclic citrullinated peptide antibody status. Arthritis Rheum 2010; 62: 369-77.

29. Mikuls TR, Sayles H, Yu F, Levan T, Gould KA, Thiele GM et al. Associations of cigarette smoking with rheumatoid arthritis in African Americans. Arthritis Rheum 2010; 62: 3560-8. [CrossRef]

30. Carlens C, Hergens MP, Grunewald J, Ekbom A, Höglund CO, Askling J, et al. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. Am J Respir Crit Care Med 2010; 181: 1217-22. [CrossRef]

31. Agnihotri R, Gaur S. Rheumatoid arthritis in the elderly and its relationship with periodontitis: areview. Geriatr Gerontol Int 2014; 14: 8-22. [CrossRef]

32. Bingham CO 3rd, Moni M. Periodontal disease andrheumatoid arthritis: the evidence accumulates for complex pathobiologic interactions. Curr Opin Rheumatol 2013; 25: 345-53 [CrossRef]

33. Hendler A, Mulli TK, Hughes FJ, Perrett D, Bombardieri M, Houri-Haddad Y, et al. Involvement of autoimmunity in the pathogenesis of aggressive periodontitis. J Dent Res 2010; 89: 1389-94. [CrossRef]

34. Waddington RJ, Moseley R, Embery G. Reactive oxygen species: a potential role in the pathogenesis of periodontal diseases. Oral Dis 2000; 6:138-51. [CrossRef]

35. Murphy G, Nagase H. Reappraising metalloproteinasesin rheumatoid arthritis and osteoarthritis: destruction or repair? Nat Clin Pract Rheumatol 2008; 4: 128-35. [CrossRef]

36. Moelants EA, Loozen G, Mortier A, Martens E, Opdenakker G, Mizgalska D, et al. Citrullination and proteolytic processing of chemokines by Porphyromonas gingivalis. Infect Immun 2014; 82: 2511-19. [CrossRef]

37. van Venrooij WJ, Vossenaar ER, ZendmanAJ. Anti-CCP antibodies: the new rheumatoid factor in the serology of rheumatoid arthritis. Autoimmun Rev 2004; 1: S17-9.

38. McGraw WT, Potempa J, Farley D, Travis J. Purification, characterization, and sequence analysisof a potential virulence factor from Porphyromonasgingivalis, peptidylargininedeiminase. Infect Immun 1999; 67: 3248-56.

39. de Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. J Rheumatol 2008; 35: 70-6.

40. Dissick A, Redman RS, Jones M, Rangan BV, Reimold A, Griffiths GR, et al. Association of periodontitis with rheumatoid arthritis: a pilot study. J Periodontol 2010, 81: 223-30. [CrossRef]

41. Rosamma J, Sreeraj R, Sameera GN, Binoy JP. Association between chronic periodontitis and rheumatoid arthritis: a hospital based case-control study. Rheumatol Int 2013; 33: 103-9. [CrossRef]

42. Tolo K, Jorkjend L. Serum antibodies and loss of periodontal bone in patients with rheumatoid arthritis. J Clin Periodontol 1990; 17: 288-91. [CrossRef]

43. Mercado FB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. J Periodontol 2001; 72: 779-87. [CrossRef]

44. Mercado F, Marshall RI, Klestov AC, Bartold PM. Is there a relationship between rheumatoid arthritis and periodontal disease? J Clin Periodontol 2000; 27: 267-72. [CrossRef]

45. Nesse W, Abbas F, van der Ploeg I, Spijkervet FK, Dijkstra PU, Vissink A. Periodontal inflamed surface area: quantifying inflammatory burden. J Clin Periodontol 2008; 35: 668-73. [CrossRef]

46. McGraw WT, Potempa J, Farley D, Travis J. Purification, characterization, and sequence analysis of a potential virulence factor from porphyromonasgingivalis, peptidylarginine deiminase. Infect Immun 1999; 67: 3248-56.

47. Rosenstein ED, Greenwald RA, Kushner LJ, Weissmann G. Hypothesis: the humoral immune response to oral bacteria provides a stimulus for the development of rheumatoid arthritis. Inflammation 2004; 28: 311-18. [CrossRef]

48. Kostoglou-Athanassiou I, Athanassiou P, Lyraki A, Raftakis I, Antoniadis C. Vitamin D and rheumatoid arthritis. Ther Adv Endocrinol Metab 2012; 3: 181-7. [CrossRef]

49. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-81. [CrossRef]

50. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. Arthritis Rheum 2004; 50: 72-7. [CrossRef]

51. Costenbader KH, Feskanich D, Holmes M, Karlson EW, Benito-Garcia E. Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. Ann Rheum Dis 2008; 67: 530-5. [CrossRef]

52. Nielen MM, van Schaardenburg SD, Lems WF, van de Stadt RJ, de Koning MH, Reesink HW, et al. Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. Arthritis Rheum 2006; 54: 3719-20. [CrossRef]

53. Bouquillard E, Combe B. Rheumatoid arthritis after Chikungunya fever: a prospective follow-up study of 21 cases Ann Rheumatic Dis 2009; 68: 1505-6. [CrossRef]

54. Nakaya HI, Gardner J, Poo YS, Major L, Pulendran B, Suhrbier A. Gene profiling of Chikungunya virus arthritis in a mouse model reveals significant overlap with rheumatoid arthritis. Arthritis Rheum 2012; 64: 3553-63. [CrossRef]

55. Binoy J P, Geetha P, Shanu P M, Emil JT. Clinical Profile and Long Term Sequaele of Chikungunya fever. Indian J Rheumatol 2011; 1: 12-9.

56. Buchanan WW, Laurent RM. Rheumatoid arthritis: an example of ecological succession? Can Bull Med Hist 1990; 7: 77-91. [CrossRef]

57. Sköldstam L. Fasting and vegan diet in rheumatoid arthritis. Scand J Rheumatol 1986; 15: 219-221 [CrossRef]

58. Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, Laerum E, Eek M, Mowinkel P, et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. Lancet. 1991; 338: 899-902. [CrossRef]

59. Kjeldsen-Kragh J, Haugen M, Forre O, Laache H, Malt UF. Vegetarian diet for patients with rheumatoid arthritis: can the clinical effects be explained by the psychological characteristics of the patients? Br J Rheumatol 1994; 33: 569-75. [CrossRef]

60. Nenonen MT, Helve TA, Rauma AL, Hanninen OO. Uncooked, lactobacilli-rich, vegan food and rheumatoid arthritis. Br J Rheumatol 1998; 37: 274-81. [CrossRef]

61. Grant WB. The role of meat in the expression of rheumatoid arthritis. Br J Nutr 2000; 84: 589-95. [CrossRef]

62. Pattison DJ, Symmons DP, Lunt M, Welch A, Luben R, Bingham SA, et al. Dietary risk factors for the development of inflammatory polyarthritis: evidence for a role of high level of red meat consumption. Arthritis Rheum 2004; 50: 3804-12. [CrossRef]

63. Benito-Garcia E, Feskanich D, Hu BF, Mandl AL, Karlson WE. Protein, iron, and meat consumption and risk for rheumatoid arthritis: a prospective cohort study. Arthritis Res Ther 2007; 9: R16. [CrossRef]

64. Sundström B, Johansson I, Rantapää-Dahlqvist S. Interaction between dietary sodium and smoking increases the risk for rheumatoid arthritis: results from a nested case- control study. Rheumatology 2015; 54: 487-93. [CrossRef]

65. Lotito SB, Frei B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? Free Radic Biol Med 2006; 41: 1727-46. [CrossRef]

66. Pattison DJ, Harrison RA, Symmons DP. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. J Rheumatol 2004; 31: 1310-9.

67. Pattison DJ, Silman AJ, Goodson NJ, Lunt M, Bunn D, Luben R, et al. Vitamin C and the risk of developing inflammatory polyarthritis: prospective nested case-control study. Ann Rheum Dis 2004; 63: 843-7. [CrossRef]

68. Pattison DJ, Symmons DP, Lunt M, Welch A, Bingham SA, Day E, et al. Dietary beta-cryptoxanthin and inflammatory polyarthritis: results from a population-based prospective study. Am J Clin Nutr 2005; 82: 451-5. [CrossRef]

69. Cerhan JR, Saag KG, Merlino LA, Mikuls TR, Criswell LA. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. Am J Epidemiol 2003; 157: 345-54. [CrossRef]

70. Pedersen M, Stripp C, Klarlund M, Olsen SF, Tjonneland AM, Frisch M. Diet and risk of rheumatoid arthritis in a prospective cohort. J Rheumatol 2005; 32: 1249-52.

71. Costenbader KH, Kang JH, Karlson EW. Antioxidant intake and risks of rheumatoid arthritis and systemic lupus erythematosus in women. Am J Epidemiol 2010; 172: 205-16. [CrossRef]

72. Linos A, Kaklamani VG, Kaklamani E, Koumantaki Y, Giziaki E, Papazoglou S, et al. Dietary factors in relation to rheumatoid arthritis: a role for olive oil and cooked vegetables? Am J Clin Nutr 1999; 70: 1077-82. [CrossRef]

73. Volker D, Fitzgerald P, Major G, Garg M. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. J Rheumatol 2000; 27: 2343-6.

74. Remans PH, Sont JK, Wagenaar LW, Wouters-Wesseling W, Zuijderduin WM, Jongma A, et al. Nutrient supplementation with polyunsaturated fatty acids and micronutrients in rheumatoid arthritis: clinical and biochemical effects. Eur J Clin Nutr 2004; 58: 839-45. [CrossRef]

75. Geusens P, Wouters C, Nijs J, Jiang Y, Dequeker J. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis. A 12-month, double-blind, controlled study. Arthritis Rheum 1994; 37: 824-9. [CrossRef]

76. Nielsen GL, Faarvang KL, Thomsen BS, Jensen LT, Hansen TM, Lervang HH, et al. The effects of dietary supplementation with n-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomized, double blind trial. Eur J Clin Invest 1992; 22: 687-91. [CrossRef]

77. van der Tempel H, Tulleken JE, Limburg PC, Muskiet FA, van Rijswijk MH. Effects of fish oil supplementation in rheumatoid arthritis. Ann Rheum Dis 1990; 49: 76-80. [CrossRef]

78. Kremer JM, Jubiz W, Michalek A, Rynes Rl, Bartholomew LE, Bigaouette J, et al. Fish-oil fatty acid supplementation in active rheumatoid arthritis. A double-blinded, controlled, crossover study. Ann Intern Med 1987; 106: 497-503. [CrossRef]

79. Kremer JM, Bigauoette J, Michalek AV, Lininger L, Huyck C, Timchalk MA, et al. Effects of manipulation of dietary fatty acids on clinical manifestations of rheumatoid arthritis. Lancet 1985; 1: 184-7. [CrossRef]

80. Cleland LG, James MJ. Rheumatoid arthritis and the balance of dietary N-6 and N-3 essential fatty acids. Br J Rheumatol 1997; 36: 513-4. [CrossRef]

81. Recht L, Helin P, Rasmussen JO, Jacobsen J, Lithman T, Schersten B. Hand handicap and rheumatoid arthritis in a fish-eating society (the Faroe Islands). J Intern Med 1990; 227: 49-55. [CrossRef]

82. Horrobin DF. Low prevalences of coronary heart disease (CHD), psoriasis, asthma and rheumatoid arthritis in Eskimos: are they caused by high dietary intake of eicosapentaenoic acid (EPA), a genetic variation of essential fatty acid (EFA) metabolism or a combination of both? Med Hypotheses 1987; 22: 421-8. [CrossRef]

83. Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M, Nelson JL. Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. Epidemiology 1996; 7: 256-63. [CrossRef]