Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis

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INTRODUCTION — Rheumatoid arthritis (RA) is a common disorder that may have plagued ancient people, although it has been recognized with increased frequency since the 19th century [1]. In the mid-19th century, Garrod was the first to distinguish RA from gout and rheumatic fever. In one study of the period from 1955 to 2007, following four decades (1955 to 1994) of decline, the incidence of RA during the subsequent interval (1995 to 2007) appeared to increase [2].

The cause of RA is not known, but many possible etiologies have been identified. Important etiologic clues have been suggested by the identification of unique features of populations with a predilection for RA. As an example, the observation of geographic clustering of the disorder in ancient skeletons implies an important role for environmental factors, which are still poorly defined [1]. In addition to environmental factors, hormonal, genetic, infectious, and other variables also contribute to RA in some manner.

Multiple different factors probably interact in genetically susceptible hosts to initiate polyarticular synovitis. Once started, the process ultimately becomes self-perpetuating. (See "Pathogenesis of rheumatoid arthritis".)

The epidemiology, risk factors for, and possible causes of rheumatoid arthritis will be reviewed here. The pathogenesis of the synovitis in this disorder, including the roles of T cells, B cells, and cytokines, is discussed separately. (See "Pathogenesis of rheumatoid arthritis".)

EPIDEMIOLOGY — The annual incidence of rheumatoid arthritis (RA) has been reported to be around 40 per 100,000. The disease prevalence is about 1 percent in Caucasians but varies between 0.1 percent (in rural Africans) and 5 percent (in Pima, Blackfeet, and Chippewa Indians) [3,4]. Women are affected two to three times more often than men.

RA can occur in patients at any age. The peak onset is between the ages of 50 and 75, and, because of the consistently higher rates in females, the prevalence of RA in females over age 65 is up to 5 percent. In data from the Medical Expenditure Panel Survey, RA was shown to result in significant reductions in employment, productivity, and function with attendant negative economic impact, reflected in its effects upon the gross national product (GNP) [5]. The lifetime risk of RA in adults is 3.6 percent (1 in 28) for women and 1.7 percent (1 in 59) for men [6].

GENDER-SPECIFIC FACTORS — Gender-specific factors affect susceptibility to rheumatoid arthritis (RA) in ways that remain incompletely understood. Women are two to three times more likely to develop RA than men, perhaps due in part to the stimulatory effects of estrogen on the immune system. Estrogen inhibits T-suppressor cell function and enhances T-helper cell function [7]. In addition, estrogen receptors are present on synovial cells and memory T cells, and a receptor polymorphism has been associated with the disease [8].

Various reproductive factors may contribute to the cause of RA, as illustrated by the following observations:

- The risk of RA is increased by nulliparity.

- Pregnancy is often associated with remission of the disease in the last trimester, but postpartum disease flares are common. (See "Rheumatoid arthritis and pregnancy".)

- The risk of RA may be reduced by breastfeeding for one year or more [9].

Maternal-fetal human leukocyte antigen (HLA) associations may also interact to affect the manifestations of RA. In one study, women with RA were more likely to experience a remission during pregnancy if there were maternal-fetal disparities in HLA class II antigens [10]. Such mismatches may produce blocking antibodies to class II major histocompatibility complex (MHC) antigens that inhibit activation of T cell clones essential for ongoing synovitis.

Men with RA frequently have lower than normal testosterone levels. This was illustrated in a study of bioavailable testosterone in 104 male RA patients and 99 controls; hypogonadal levels of testosterone were present in a significantly greater proportion of patients (32 versus 7 percent, respectively) [11]. Lower levels of the androgenic hormone dehydroepiandrosterone (DHEA) and higher concentrations of estradiol have also been found in men with RA, an effect that is not related to glucocorticoid therapy [12]. It is uncertain whether such changes in hormone levels are simply the result of chronic inflammation or whether men with abnormal testosterone and estrogenic hormone levels are at an increased risk of developing RA.

Male sex also appears to affect disease phenotype [13]. Compared with female RA patients, male patients have significantly later disease onset, are more likely to be rheumatoid factor (RF)-positive, and have higher titers of anti-citrullinated peptide/protein antibodies (ACPA). Male patients are also more likely to have histories of smoking and to possess copies of the shared epitope. (See 'HLA and non-HLA susceptibility genes' below.)

GENETIC SUSCEPTIBILITY — Substantial data have emerged about the importance of genetic risk factors for rheumatoid arthritis (RA).

Twin, sibling, and family studies — Twin and sibling studies implicate genetic factors in the susceptibility for RA. Monozygotic twins have a higher concordance than dizygotic twins for developing RA. In two studies of twins, the concordance for monozygotic twins was 12 to 15 percent versus 3.5 percent for dizygotic twins [14,15]. In addition, the standardized incidence ratio for RA was 3 in offspring of affected parents, 4.6 in siblings, 9.3 in multiplex families, and 1.2 in spouses [16]. Furthermore, there was an increased frequency of ankylosing spondylitis (AS), scleroderma, Sjögren's syndrome, systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, pernicious anemia, sarcoid, psoriasis, granulomatosis with polyangiitis (Wegener's), asthma, and polymyalgia rheumatica (PMR) in relatives of patients with RA [16].

Other data have shown that sibship concordance rates are consistently higher when probands have severe disease, thereby suggesting that RA may develop when several genetic and environmental factors are present in the same individual. From these and similar data, it has been estimated that genetic factors contribute from 53 to 65 percent of the risk of developing RA [17]. However, other studies have suggested that genetic factors may contribute less to risk than environmental factors. Among over 65,000 women in the Nurses Health Study the presence of a first-degree relative with RA or systemic lupus erythematosus (SLE) was associated with a significantly increased risk for RA after adjustment for environmental factors (HR 3.59, 95% CI 2.94-4.37), and the risks associated with environmental factors, including smoking, overweight, body mass index, and premenopausal status remained significant after adjusting for familial RA or SLE [18]. The proportion of risk attributable to the environmental factors collectively was 41 percent, while the risk attributable to the family history (familial RA/SLE) was 21 percent.

HLA and non-HLA susceptibility genes — The contribution of human leukocyte antigen (HLA) and other genes to disease susceptibility, severity, and treatment response in RA is discussed in detail separately but will be briefly reviewed here. (See "HLA and other susceptibility genes in rheumatoid arthritis".)

Among the growing list of genetic risk factors for RA, significant overlap exists with genes identified as risk factors for other autoimmune diseases, including SLE, inflammatory bowel disease, multiple sclerosis, and

ankylosing spondylitis [19]. Newly recognized genetic markers associated with RA include an allele of the Fc-gamma receptor, a polymorphism marker in the beta2-adrenergic receptor, and a low-inducible allele of the cytochrome P450 subtype 1A2 [20]. Why a given genetic factor can be associated with a variable pattern of organ-system involvement in different disease states is not known. (See "Overview of autoimmunity".)

The firmest link between a genetic susceptibility factor and RA is the association of the disease with an epitope in the third hypervariable region of the HLA-DR beta-chains, known as the "shared epitope." Individuals with the sequence leu-glu-lys-arg-ala in residues 67, 70, 71, 72, and 74 have a much higher incidence and prevalence of RA than those who do not have this epitope [21]. This sequence is found in DR4 and DR14 and some DR1 beta-chains. The DR4 beta-chains with the strongest associations with RA are DR-beta*0401, DR-beta*0404, DR-beta*0101, and DR-beta*1402. Although this finding has been demonstrated in many cohorts, such as those of northern European heritage, Israeli Jews, Yakima Indians, and Koreans, it does not appear to apply to all populations. Among African-Americans, for example, other genetic risk factors, many still undefined, appear to contribute significantly to disease susceptibility and severity.

Other genetic polymorphisms — Microsatellites and single nucleotide polymorphisms are being studied extensively in RA. For example, polymorphisms of the tumor necrosis factor (TNF)-alpha promoter have been associated with RA, and others have been linked to better therapeutic responses to TNF inhibitors. Statistically significant associations between response to anti-TNF therapy and an RA risk allele at the PTPRC gene locus (also known as CD45) have been found [22,23].

An increased risk of RA with single nucleotide polymorphism of the protein tyrosine phosphatase N22 (PTPN22) gene that encodes a phosphatase involved in intracellular T cell signaling has been confirmed in several different populations [24]. The same PTPN22 polymorphism may also increase the rate of progression of RA [25]. STAT4, which encodes a transcription factor that transmits signals induced by several key cytokines, has been reported to be a risk factor for both RA and systemic lupus erythematosus, suggesting a shared pathway for these to autoimmune disorders [26]. Additional nucleotide polymorphisms related to T-cell activation and the nuclear factor kappa-B (NFκB) pathway have also been linked to RA [27].

CIGARETTE SMOKING — Cigarette smoking is a strong risk factor for the development of rheumatoid arthritis (RA), particularly in individuals with the shared epitope [28]. The magnitude of the overall effect of smoking was evaluated in a retrospective report utilizing data on over 370,000 women from the Women's Health Cohort Study [29]. Women who smoked at least 25 cigarettes a day for more than 20 years had a relative risk of 1.4 for developing RA compared with those who had never smoked [29]. Multivariate analysis revealed that the duration of use, but not the number of cigarettes smoked per day, was significantly associated with increased risk. A similar association with smoking and RA was noted in monozygotic and dizygotic twins discordant for RA [30] and in a prospective population-based study of incident RA in women [31].

In addition to increasing disease susceptibility, cigarette smoking may also be a risk factor for greater disease severity. Compared with those who had never smoked, patients with a 25 or more pack-year smoking history are more likely to be seropositive, have nodules, or have radiographically apparent erosions [32,33].

A nationwide case-control study from Denmark evaluated the links between genes, environment, and inflammation in a study of 515 patients with RA and 533 sex- and age-matched population controls [34]. In this study, smoking among carriers of the shared epitope was estimated to account for 36 percent of all RA that was associated with anti-citrullinated peptide/protein antibodies (ACPA). The following findings were reported:

- Individuals who were homozygous for the shared epitope had an elevated risk of ACPA-positive RA but not ACPA-negative RA. The odds ratio (OR) for ACPA-positive RA was 17.8 (95% CI 11-29).
- Strong combined gene-environment effects were observed, with markedly increased risks of ACPA-positive RA among shared epitope homozygotes who were:

- Heavy smokers (OR 53, 95% CI 18-154)
- Heavy coffee drinkers (OR 53, 95% CI 16-183)
- Oral contraceptive users (OR 45, 95% CI 15-131)

- Obesity has been associated with development of ACPA-negative RA (OR 3.5, 95% CI 1.7-6.9) [35].

The authors of the Danish study concluded that a distinction should be made between RA that is associated with ACPA and that which is not, because these subtypes are likely to represent disease entities with distinct etiologies.

Smoking cessation may help prevent the development of RA. This was suggested in a population-based study in the United States in which women who had stopped smoking more than ten years before entering the study did not share an increased risk of developing RA with their peers who were actively smoking [36]. In a large Swedish study, smokeless tobacco (eg, moist snuff) did not increase the risk of chronic inflammatory diseases, suggesting that inhaled components of cigarette smoke other than nicotine may be more important than nicotine itself in etiology [37].

Smoking and the shared epitope — Individuals who are genetically predisposed to RA as a result of carriage of one or more alleles of the shared epitope appear to be at higher risk for developing RA if they also smoke cigarettes. (See 'HLA and non-HLA susceptibility genes' above.)

In a nationwide study in the United Kingdom of RA-discordant twins, 13 pairs of twins were also discordant for cigarette smoking. Among these twins, the smoker was the twin with RA in 12 of the 13 cases [30].

A genetic-environmental link was also noted in a retrospective study of 858 Swedish patients with recently diagnosed RA and 1048 controls [38]. There was a marked increase in risk associated with cigarette smoking. Compared with those who never smoked, the relative risk in current smokers with one or two shared epitopes was 2.3- and 5.6-fold higher, respectively. The relative risk was even higher (5.5 and 15.7) in patients who were rheumatoid factor (RF)-positive.

The increase in risk associated with smoking in individuals with the shared epitope may be affected primarily by citrullination of proteins in inflamed tissues. This was suggested in a study in which the association between smoking and RA was strongest (relative risk 21) among individuals with antibodies to citrullinated proteins as detected by the anti-cyclic citrullinated peptide (anti-CCP) assay for ACPA [39]. In contrast, there was no evidence of an interaction between smoking and the shared epitope in patients who were ACPA-negative, including a subset who were ACPA-negative but RF positive (see "Pathogenesis of rheumatoid arthritis", section on 'Citrullinated proteins and peptides'), nor was an association noted between cigarette smoking, ACPA status, or carriage of shared epitope in a study of 300 African American patients with RA [40].

Another study evaluated the genetic-environment-immune link in 515 Danish RA patients [41]. Of these, 309 had ACPA; of 456 tested, 262 had the shared epitope. The odds ratio (for RA) for those having both the shared epitope and having ACPA was 17.8. For the ACPA-positive, shared epitope-positive RA patients, the odds ratio for those who smoked was 52.6 to 57.4 (versus 17.4 in nonsmokers). For those who consumed alcohol the odds ratio, was 10.5 to 27 (for non-drinkers the odds-ratio was 50.1). The odds ratio for those who drank coffee was 27.4 to 53.3 (versus 13.0 for non-coffee drinkers). The odds ratio for women who used oral contraceptives was 44.6 (versus 32.3 for non-users). Furthermore, the odds ratio for ACPA-positive, shared epitope homozygous patients who were unmarried was 177 and was 243 for those without a job. The authors concluded that smoking among carriers of the shared epitope (either heterozygotes or homozygotes) accounted for 36 percent of all ACPA-positive RA patients.

As mentioned above, some have interpreted these data to indicate that the shared epitope is a marker for ACPA rather than an independent risk factor for RA per se. Peptidyl arginase deiminase (PADI) is the enzyme that modifies arginine residues to citrulline. One haplotype in the PADI 4 gene leads to increased

levels of the enzyme and susceptibility to RA in some Asian populations [42]. In a study from Korea of 341 RA patients, PADI 4 haplotypes were associated with "seropositive" (eg, ACPA-positive) RA of short disease duration, while the shared epitope was associated with longstanding, seropositive RA [43].

In addition to the shared epitope, there may be other genetic components that predispose to the development of more severe disease in smokers. Among a group of 96 mostly Caucasian women with RA, 30 were homozygous for a nonfunctional allele at the M1 locus for the enzyme glutathione S-transferase (GSTM1) [44]. Among these women, those who smoked had significantly more severe joint damage than those who had never smoked (Larsen score 113 versus 83, respectively) [44]. The relation between smoking and disease severity was not seen in the 66 women with at least one functional GSTM1 allele. Antibodies to the CEP-1 peptide from citrullinated alpha-enolase show an association with HLA-DRB1*0401, *0404, PTPN22, and smoking cigarettes [45].

POSSIBLE ROLE OF INFECTION — The above hormonal, genetic, and environmental risk factors, although important in determining susceptibility to rheumatoid arthritis (RA), are neither necessary nor sufficient to cause the disease. Thus, additional factors must be present to trigger disease onset. Infection has long been suspected to be an inciting factor in RA [45-50]. However, no specific bacterial infection has been proven to cause RA. Viral pathogens also remain an active area of investigation.

Several cellular mechanisms have been identified that could facilitate activation of inflammation by infectious agents. Two examples are toll-like receptors (TLRs) and the inflammasome complex:

- Toll-like receptors recognize preserved structures in bacteria and, when activated by inflammatory mediators such as cytokines or chemokines, can stimulate antigen-presenting cells, enhance adaptive immune responses, and trigger inflammatory mediator release. Many of these TLRs, especially 3 and 4, are expressed by rheumatoid synovial tissue [51,52]. In addition, bacterial peptidoglycans in RA synovial tissue have the potential to activate TLRs [53]. (See "Toll-like receptors: Roles in disease and therapy".)

- The inflammasome complex is critical to the recognition of infectious pathogens. One component of this complex is cryopyrin, a protein that is abundant in rheumatoid synovium [54]. (See "Cryopyrin-associated periodic syndromes and related disorders", section on 'Pathogenesis'.)

Despite the expected role of infection in the etiology of RA, a population-based case-control study involving over 3000 patients with RA in Sweden failed to demonstrate an increased risk of RA with antecedent infections, including gastroenteritis, urinary tract infection, genital infection, prostatitis, sinusitis, tonsillitis, or pneumonia [55]. However, gastroenteritis, urinary tract infections, and genital infections before clinical onset of RA, but not other types of infections, were associated with a reduced risk of RA (OR 0.71, 95% CI 0.63-0.80; OR 0.78, 95% CI 0.68-0.90; and OR 0.80, 95% CI 0.64-1.00; respectively). The explanation for these findings is not known; one unproven hypothesis is that the "protective" infection may alter the host microbiome in some way that influences disease risk. (See 'Gut microbiome' below.)

Bacterial infection — Among the bacteria that have been suspected as inciting factors in RA are *Proteus mirabilis* [46], Mycoplasma species [47-49], and *Porphyromonas gingivalis* [45,50]. However, despite intensive study of these and other organisms, there is as yet no proof of bacterial infection as a contributor to RA.

Porphyromonas gingivalis — Periodontal disease has been associated with RA in a number of studies [56-61]; a relationship with disease severity has also been suggested [56,61]. The major etiologic agent associated with the pathogenesis of periodontitis is *Porphyromonas gingivalis*. *P. gingivalis* contains the enzyme peptidyl arginine deiminase (PADI), which allows the bacteria to generate citrullinated peptides in vivo, leading to the hypothesis that, in a genetically susceptible individual (carrying the shared epitope), the presence of such peptides may contribute to breaking tolerance to endogenous citrullinated antigens, potentially resulting in production of anti-citrullinated peptide/protein antibodies (ACPA) and contributing to the development of RA [45,50,57]. Additionally, *P. gingivalis* expresses other proteinases that may also play a role in this process [50].

A study of RA patients and their unaffected relatives, from among a genetically predisposed population, has documented that anti-*P. gingivalis* antibodies were associated with ACPA but not with rheumatoid factor (RF) [62]. Thus, in addition to cigarette smoking, another environmental factor, the infectious agent *P. gingivalis*, is associated with ACPA and RA in the presence of the shared epitope; this has been further supported by a study demonstrating a role for oral infection interacting with susceptibility genes and smoking in a subset of patients [63]. Additional studies are needed to clarify the relationships among these different factors.

Gut microbiome — Studies focused on the gut microbiome have been an additional area of interest, as this collection of organisms strongly influences the development of the innate and adaptive host immune systems [64]. A possible role for these bacteria in RA has been suggested by a study in which the expanded presence of intestinal *Prevotella copri*, together with a reduction in other bacteria, including Bacteroides species, was significantly more common in untreated patients with new-onset RA compared with healthy controls, or patients with chronic (treated) RA or psoriatic arthritis [65]. Additionally, the *Prevotella copri* present in the patients with new-onset RA appeared to differ genetically from those present in the healthy controls, and induced colonization of the intestine by these bacteria in a mouse model of gut inflammation was pro-inflammatory. The clinical importance of these findings in RA is uncertain.

Viral infection — Studies evaluating viruses as possible etiologic factors among patients with RA have been more profitable than similar studies for bacteria. Isolates of Rubella antigen and adenoviral nucleotide sequences, for example, have been obtained from synovial specimens. In addition, lymphocytes from several patients are readily activated by cytomegalovirus antigens [66].

Epstein-Barr virus (EBV) and retroviruses have been best studied. There are conflicting data on the role of human parvovirus B19 in RA [67,68].

Epstein Barr virus — A significant effort has been devoted to evaluating a possible association between EBV and RA. This work was prompted in part by the finding in 1975 and in later studies of an antibody in the sera of rheumatoid patients that reacted with an Epstein Barr nuclear antigen [69,70].

Additional support for a relationship includes the following findings:

- EBV is a polyclonal activator of B lymphocytes, including those that express rheumatoid factor.
- Patients with RA have an increased humoral and cellular immune response to EBV, *Brucella ovis*, and *Lactobacillus lactis* antigens that contain the QKRAA sequence, which is the same sequence found in the shared epitope [71].
- There are conflicting data whether B cells in the synovium of patients with RA are or are not more likely to harbor EBV RNA, particularly among those with human leukocyte antigen (HLA)-DR4 [72,73].
- Patients with RA may have an increased EBV viral load. This was suggested in a report in which 84 patients with RA were compared with 69 healthy controls and 22 patients with other rheumatic diseases [74]. The EBV DNA load was increased nearly 10-fold in patients with RA, remained stable over time, and was not influenced by treatment with disease-modifying antirheumatic drugs (DMARDs).
- Polymorphous lymphoproliferative disorder, containing large lymphoid cells together with small lymphocytes, plasma cells, macrophages, and/or eosinophils, develops in some patients with autoimmune diseases and is often EBV-associated [75].

Retroviruses — There is growing enthusiasm for the role of retroviruses as both a cause and amplifier of RA, since these viruses provide all of the required mechanisms to generate a chronic inflammatory and proliferative synovitis. A retrovirus can activate synovial monocytes and lining cells to induce cytokines and metalloproteases, which then bypass lymphocytes as a major causative component of the inflammatory response. By activating both T cells and synovial cells and perhaps by contributing superantigen from its own proteins, a retrovirus could promote the development of RA.

Human T-lymphotropic virus type I (HTLV-I), the etiologic agent of adult T cell leukemia-lymphoma, has often been associated with an inflammatory arthropathy in Japan [76]. In addition, women with RA in Japan have a fivefold higher seroprevalence of HTLV-I than controls [77]. However, none of the data suggests that this virus is causative. It is more likely that HTLV-I is another mild predisposing factor. Contrary to some earlier reports, investigators using a real-time polymerase chain reaction assay were unable to detect human retrovirus-5 proviral DNA in synovial tissue and blood from rheumatoid patients [78].

SUPERANTIGENS AND HEAT SHOCK PROTEINS — Superantigens can activate multiple clones of T cells (1 in 10 cells) through a largely major histocompatibility complex (MHC)-independent process. By comparison, a specific antigen presented in context of the human leukocyte antigen (HLA) class II cell surface antigens can activate only 1 in 10,000 T cells.

Examples of superantigens are the staphylococcal endotoxins and heat shock proteins (HSPs). HSPs are intracellular proteins induced by environmental insults, including heat, infectious agents, and oxidative injury, and are remarkably conserved across species.

The first possible link between HSPs, infection, and rheumatoid arthritis (RA) was the finding that the component of *Mycobacterium tuberculosis* used with Freund's adjuvant to produce "adjuvant arthritis" in rats was a 65 kD HSP [79].

There are two indirect findings supporting an association between HSPs and RA:

- The 65 kD protein activates lymphocytes from patients with RA [80].
- Antibodies against a human HSP were produced by B lymphocytes from rheumatoid synovial tissue that was transformed by Epstein-Barr virus (EBV) [81].

The most logical hypothesis implicating HSPs as causative in RA is that these proteins share antigenic determinants with other host proteins, thereby resulting in the development of cross-reacting antibodies that could induce an autoimmune response (ie, molecular mimicry). As an example, two proteins that possess the shared epitope (QKRAA) on DRß1*0401 are EBV gp110 and *Escherichia coli* dnaJ. The latter molecule is a heat shock protein and strongly antigenic. Specific antibodies against dnaJ cross-react with DRß1*0401 (Dw4)-positive cells, but not with cells that express other alleles [82]. (See "HLA and other susceptibility genes in rheumatoid arthritis".)

By cross-reactivity, some individuals with HLA-DR4 in whom T cells are skewed towards the epitope QKRAA because of positive selection may develop a systemic autoimmune response by producing high affinity antibodies against QKRAA; these autoantibodies could in turn lead to a self-perpetuating synovitis. Other patients who express HLA-DR4 might not have a peripheral T cell population skewed toward QKRAA and would, therefore, not mount an immune response sufficient to generate a synovitis [83].

In contrast, heat shock proteins have also been demonstrated to have disease suppressive activities. HSPs, added to cultures of human peripheral blood mononuclear cells, significantly inhibited secretion of interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha by these cells [84].

AUTOANTIBODIES — Since the discovery of rheumatoid factor (RF) in 1940, much research has linked this autoantibody to the pathophysiology of severe rheumatoid arthritis (RA). Although it is clear that the presence of RF alone does not cause RA, there is no doubt that patients with significant RF titers have a greater likelihood of extraarticular disease than do seronegative patients. Classic experiments by Hollander and colleagues showed RF injected into the joint of a patient with RA led to a marked inflammatory response, in contrast to the injection of IgG [85].

RF and anti-citrullinated peptide/protein antibodies (ACPA) may be present in the blood prior to the appearance of arthritis [86-91]. The following observations illustrate the range of findings:

- In a cohort study of healthy individuals from Finland, 9 of 129 subjects with positive RF subsequently developed seropositive RA over a 10 year investigation period, compared with only 12 of 7000 subjects with negative tests (7 versus 0.2 percent) [86].

- In a report of 83 patients with RA who had stored blood samples available as a result of blood donation or prenatal testing, the prevalence of ACPA was significantly higher in patients preceding diagnosis than in controls (34 versus 5 percent) [87]. There was also a significant increase in the prevalence of RFs of all isotypes (17, 19, and 33 percent for RF of IgG, IgM, and IgA isotype, respectively).

- In a case-control study of 79 patients with RA who had stored serum available from blood donations prior to the development of RA (1 to 51 samples per patient, dating up to 15 years prior onset of RA), 49 percent had detectable ACPA and/or anti-IgM RF on at least one occasion and 41 percent had ACPA detectable when symptoms first developed [88].

- In a nested case-control study of 69 patients diagnosed with RA for whom stored pre-diagnosis blood samples were available, marked elevations in several cytokines, cytokine receptors, and chemokines were present before disease onset compared with controls [91]. Notably, levels were particularly increased in individuals also positive for anti-cyclic citrullinated peptide (anti-CCP) and RF, and, after disease onset, immune system activation was more generalized.

Although these autoantibodies may represent clinically silent disease, the development of such autoantibodies can also be viewed as a risk factor for the later development of disease. The sensitivity of a positive ACPA **and** a positive RF in the 1.5 years prior to diagnosis has ranged from 18 to 30 percent and the specificity from 99 to 100 percent.

The combination of ACPA with the genetic markers, the shared epitope, and PTPN22 greatly increases the risk for the development of RA [92].

OCCUPATIONAL EXPOSURES — Occupational exposure to dust and fibers may increase the risk of developing rheumatoid arthritis (RA).

- **Silica** – Silica exposure increased the risk for the development of RA in Swedish men, independent of cigarette smoking [93]. These results are consistent with the conclusions of an earlier meta-analysis of 10 studies that concluded there was a significant association between occupational exposure and RA (relative risk 3.43, 95% CI 2.25-5.22) [41].

- **"World Trade Center dust"** – Increased risk of systemic autoimmune disease, including RA, was evident in a study of firefighters and other emergency responders with exposure to the aerosolized dust at the site of the 2001 terrorist attacks upon the World Trade Center (WTC) in New York City [94]; this dust was composed of pulverized cement, glass fibers, silica, asbestos, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and polychlorinated furans and dioxins. Prolonged work at the site over the subsequent 10.5 months was associated with elevated risk of systemic immune-inflammatory diseases, most commonly RA, and also spondyloarthritis, inflammatory myositis, systemic lupus erythematosus (SLE), systemic sclerosis, antiphospholipid syndrome, Sjögren's syndrome, and granulomatosis with polyangiitis. The risk of new autoimmune disease, during 12 years of follow-up, increased 13 percent for every month of exposure to the "WTC dust" compared with controls (conditional odds ratio 1.13, 95% CI 1.02-1.26), independent of acute exposure on the day of the attack. The diversity of inflammatory disease phenotypes reported is surprising and lacks a mechanistic molecular explanation.

- **Other occupational exposures** – Other occupations associated with an increased risk of developing RA include electrical work, wood work, and those that involve asbestos exposure [95].

OTHER RISK MODIFIERS

- **Alcohol** – Alcohol intake may reduce the risk of developing rheumatoid arthritis (RA) [28,96,97]. A systematic review and meta-analysis of eight prospectively performed studies involving 195,029 participants, including 1878 with RA, found that low to moderate alcohol consumption, but not high consumption, was inversely associated with the development in RA (RR 0.86, 95% CI 0.78-0.94) [97]. As an example, in a prospective study of a population-based cohort of over 34,000 women in Sweden, the moderate use of alcohol (drinking at least four glasses of alcohol weekly) resulted in a greater than one-third reduction in the risk of developing RA, compared with never drinking alcohol (relative risk 0.63, 95% CI 0.42-0.96).

- **Obesity** – Obesity may also play a role in development of RA [35,98,99]. In one study, involving an inception cohort of 813 patients diagnosed with RA between 1980 and 2007, a history of obesity was associated with a statistically significant increased risk of developing RA (OR 1.24, 95% CI 1.01-1.53) [98]; half of the increase in the incidence of RA observed in women in the study population since the 1980's could be attributed to increased rates of obesity. In addition, observations from two very large prospective cohorts (the Nurses Health Studies) also found trends suggesting an increased risk of RA among overweight and obese women; the increases in risk were statistically significant among overweight and obese patients with RA diagnosed at age 55 or younger (HR 1.45, 95% CI 1.03-2.03, and 1.65, 95% CI 1.34-2.05, respectively [99].

- **Other** – Various additional factors have been studied for their potential impact on risk of developing RA. Increased birthweight is associated with increased risk for RA, while duration of breastfeeding and socioeconomic status are inversely associated with RA risk [28]. Posttraumatic stress disorder may also increase the risk of RA, consistent with other evidence of the association between stress and physical disorders, particularly autoimmune disease [100]. Atopic dermatitis has also been associated with an increased the risk of RA [101]. High consumption of red meat does not increase the risk for developing RA, and the evidence for roles of vitamin D and oral contraceptives remains equivocal [28].

SUMMARY

- The annual incidence of rheumatoid arthritis (RA) is approximately 40 per 100,000, and the prevalence is about 1 percent in Caucasians but differs in other populations. Women are affected two to three times more often than men. RA can occur in patients at any age, and the peak onset is between the ages of 50 and 75. The lifetime risk of RA in adults is 3.6 percent (1 in 28) for women and 1.7 percent (1 in 59) for men. (See 'Epidemiology' above.)

- Gender-specific factors affect susceptibility to RA in ways that remain incompletely understood. (See 'Gender-specific factors' above.)

- Substantial data have emerged about the importance of genetic risk factors for RA from studies of twins and siblings, human leukocyte antigen (HLA) and non-HLA susceptibility genes, and other polymorphisms. The firmest link between a genetic susceptibility factor and RA is the association of the disease with an epitope in the third hypervariable region of the HLA-DR beta-chains, known as the "shared epitope." (See 'Genetic susceptibility' above.)

- Cigarette smoking is a strong risk factor for the development of RA, particularly in individuals with the shared epitope. (See 'Cigarette smoking' above.)

- A role for viral or bacterial infection as an inciting trigger for RA has been hypothesized, but no single agent has been proven responsible. Some studies implicate a role for toll-like receptors, the inflammasome, and responses to superantigens in linking infection and the autoimmune arthritis process. (See 'Possible role of infection' above and 'Superantigens and heat shock proteins' above.)

- Patients with significant rheumatoid factor (RF) titers have a greater likelihood of extraarticular disease than do seronegative patients, although RF alone does not cause RA. RF and anti-citrullinated peptide/protein antibodies (ACPA) may be present in the blood prior to the appearance of arthritis, and

the combination of ACPA with the genetic markers, the shared epitope, and PTPN22 greatly increases the risk for the development of RA. (See 'Autoantibodies' above.)

- Various occupational and other exposures as well as environmental and other factors have been associated with modifying the risk for the development of RA. Obesity is associated with increased risk of RA, while mild to moderate alcohol use may reduce risk. (See 'Occupational exposures' above and 'Other risk modifiers' above.)

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