0889-857X/01 $15.00 + .00

# THE EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

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Epidemiology is the study of the distribution and determinants of disease in human populations.[21] This definition is based on two fundamental assumptions: first, that human disease does not occur at random and, second, that human disease has causal and preventive factors that can be identified through systematic investigation of different populations or subgroups of individuals within a population in different places or at different times. As a result, epidemiologic studies include simple descriptions of the manner in which disease appears in a population (i.e., levels of disease frequency as well as incidence and prevalence, mortality, trends over time, geographic distributions, and clinical characteristics) and descriptions of the role of putative risk factors for disease occurrence. Incidence studies include all new cases of a specified condition arising in a defined population over a specified time period, and prevalence studies include all patients with the condition who are present in a population at a particular point in time. As shown in Figure 1, prevalence cohorts exclude patients who died or left the population soon after their incidence date, and they include patients arising in different populations who moved into the cohort after their incidence date. Because of this, there is a greater potential for bias to be introduced in prevalence cohorts as compared to incidence cohorts. Thus, population-based incidence cohorts are superior to prevalence cohorts for descriptive epidemiologic studies.

Epidemiologic studies of risk factors fall into three major categories: prospective cohort studies, retrospective cohort studies, and case-control studies. The relation between these is illustrated in Figure 2. In a prospective cohort study, a study population is assembled, none of whom have experienced the outcome of interest, and is followed forward into the future. People in the cohort are classified according to those characteristics that might be related to outcome, that is, putative risk factors. These people are then observed over time to determine which of them experience the outcome. The analysis addresses the

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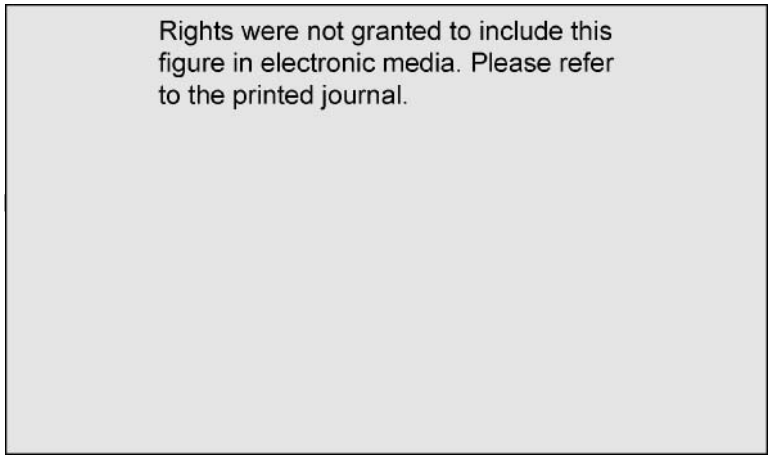


**Figure 1.** The difference in cases for incidence and prevalence studies (*Adapted from* Fletcher RH, Fletcher SW, Wagner EH (eds): Clinical Epidemiology–The Essentials, vol 2. Baltimore, Williams & Wilkins, 1988, p 87; with permission.)

question of whether people who were exposed to the risk factor were more likely to develop the outcome compared with those who were not exposed. In a retrospective cohort study, the cohort of individuals is identified from past records and followed forward up to the present. Data regarding historical exposure to the putative risk factor are collected retrospectively, typically by examination of medical records. As in a prospective cohort study, retrospective cohort

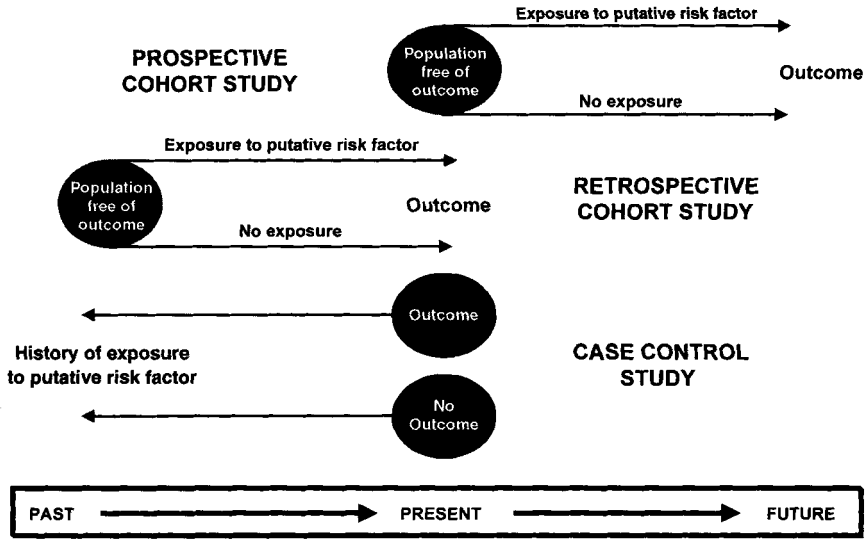


**Figure 2.** Epidemiologic studies of risk factors.

studies also compare the frequency of the outcome in exposed patients as compared to unexposed patients. In a case-control study, two cohorts are assembled, one that has the outcome of interest and another that is free of the outcome of interest. Data regarding exposure to the putative risk factor in the two groups are collected retrospectively so as to determine whether patients with the outcome of interest were more likely to have had a history of the exposure of interest compared with those who were free of the outcome of interest. Of these three study designs, prospective cohort studies have fewer potential biases than the other two; however, they are frequently not feasible because they typically require extended follow-up, often 5 to 10 years or more into the future. A detailed comparison of the potential biases involved in retrospective cohort studies and case-control studies is beyond the scope of this article but can be readily found in numerous epidemiologic publications.[21, 30, 61] In this article, we review data on the descriptive epidemiology (incidence, prevalence, and survival) and risk factors associated with rheumatoid arthritis (RA).

## DESCRIPTIVE EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

### Incidence

The most reliable estimates of incidence, prevalence, and mortality in RA are those derived from population-based studies. Several of these have been conducted in a variety of geographically and ethnically diverse populations. The Norfolk Arthritis Register is a prospective population-based database that was established to study new cases of inflammatory arthritis as they occurred in the community and to follow them prospectively to investigate the natural history of the condition. This data resource is the first primary care–based register of incidence cases of RA ever assembled.[71] One hundred four newly diagnosed cases of RA that fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA at the time of presentation between 1990 and 1991 were identified. The annual incidence per 100,000 population was 35.9 for women and 14.3 for men (Table 1). RA was rare in men under 45 years of age. The incidence of RA in men rose steeply with age. In women, the incidence rose up to the age of 45 years and plateaued until the age of 75 years, after which it declined.[71] In a subsequent report, these same investigators explored the estimation of the incidence of RA in 1990 by allowing each criterion to "carry forward" once it had been satisfied on a single occasion.[78] They showed that if up to 5 years elapsed between symptom onset and the time the criteria were applied cumulatively, the estimates rose by 75% and 93% for women and men, respectively, reaching 54/100,000 for women and 24.5/100,000 for men. These estimates more accurately reflect the true incidence of RA. These findings also emphasize the importance of long-term follow-up of patients with undifferentiated polyarthritis and of applying the ACR criteria cumulatively so as to accurately estimate the incidence of RA.

Numerous studies have been undertaken in Finland describing the epidemiology of RA. Estimates of the incidence and prevalence have been derived from several surveys based on computerized data registers covering the entire Finnish population. A recent review summarized the results of five national health interviews covering a 30-year period.[1] The incidence of clinically significant RA in these surveys was approximately 29 to 35.5 per 100,000 adult population over the study years (1975, 1980, 1985, and 1990) (see Table 1). The incidence of clinically significant RA in Finland was estimated at approximately 40/100,000

**Table 1.** INCIDENCE OF RHEUMATOID ARTHRITIS

| Author | County/Region | Years of Study | Age Range (years) | Sample Size | Annual Incidence Rate Per 100,000 Population |
|---|---|---|---|---|---|
| Uhlig et al, 1998[73] | Oslo, Norway | 1988–1993 | 20–79 | 550 | 25.7 O<br>36.7 F<br>13.8 M |
| Symmons et al, 1994[71] | Manchester, United Kingdom | 1990–1991 | 15–85+ | 104 | 35.9 F<br>14.3 M |
| Kaipiainen-Seppanen et al, 1996[38] | Finland | Four 1-year periods: 1975, 1980, 1985 and 1990 | 16–85+ | 1321 | 1975: 29.0<br>1980: 35.5<br>1985: 35.0<br>1990: 29.5 |
| Gabriel et al, 1999[23] | Olmsted County, Minnesota | 1955–1985 | 35–85+ | 425 | 75.3 0 (95% CI: 68.0–82.5)<br>98.1 F (95% CI: 87.1–109.1)<br>49.7 M (95% CI: 40.5–58.9) |
| Jacobsson et al, 1994[36] | Pima Indians, Arizona | 1965–1990 | 25–65+ | 78 | 1966–1973 1974–1982 1983–1990<br>8.9 0*6.2 0*3.8 0*<br>11.5 F*7.5 F*4.9 F*<br>5.9 M*4.6 M*2.7 M* |
| Drosos et al, 1997[18] | Northwest Greece (Ioannina) | 1987–1995 | 16–75+ | 428 | 24.0 0<br>36.0 F<br>12.0 M |
| Dugowson et al, 1991[19] | Seattle, Washington | 1987–1990 | 18–64 (women only) | 81 | 23.9 F |

F = female; M = male; O = overall.
*Cases per 1000 person years at risk.

adult population.[1] Trends in RA incidence between 1975 and 1990 were also examined.[39] Among the 1321 incident cases identified during the 4-year study period, the authors noted a rise in the median age at onset (increasing from 50.2 to 57.8 years) and a simultaneous decline in the age-specific incidence rates in the younger individuals. The same authors studied the incidence of rheumatoid factor (RF)–positive RA and RF-negative polyarthritis.[38] In that study, the investigators demonstrated a decline of approximately 40% in the number of RF-negative RA cases in 1990 compared with the earlier years. This declining trend was statistically significant ($P = 0.008$). In fact, the decline in incidence of approximately 15% compared with previous study years was noted to affect (nearly exclusively) RF-negative disease.

We recently assembled an inception cohort of Rochester, Minnesota residents who were 35 years of age or older and had RA, as defined by the 1987 ACR criteria for RA,[4] first diagnosed between January 1, 1955 and January 1, 1985, with follow-up until January 1, 1995.[23] The overall age- and sex-adjusted annual incidence of RA among these residents aged 35 years and older (1955–1985) was 75.3 per 100,000 population(95% confidence interval [CI]: 68.0–82.5). The incidence was approximately double in women compared with that in men and increased steadily with age until the age of 85 years, after which the incidence decreased. Secular trends in the incidence of RA over the entire study period were demonstrated (Fig. 3). Incidence cases of RA were identified among a population-based cohort of Pima Indians in Arizona over the period 1965 through 1990. Among 2894 subjects, 78 incidence cases of RA were identified. The total age- and sex-adjusted incidence per 1000 population was 8.9 (95% CI: 5.9–11.9) in 1966 through 1973, 6.2 (95% CI: 3.8–8.6) in 1974 through 1982, and 3.8 (95% CI: 1.7–5.9) in 1983 through 1990. The age-adjusted incidence declined by 55% in men ($P$ trend = 0.225) and by 57% in women ($P$ trend = 0.017) after controlling for contraceptive use, estrogen use, and pregnancy experience.

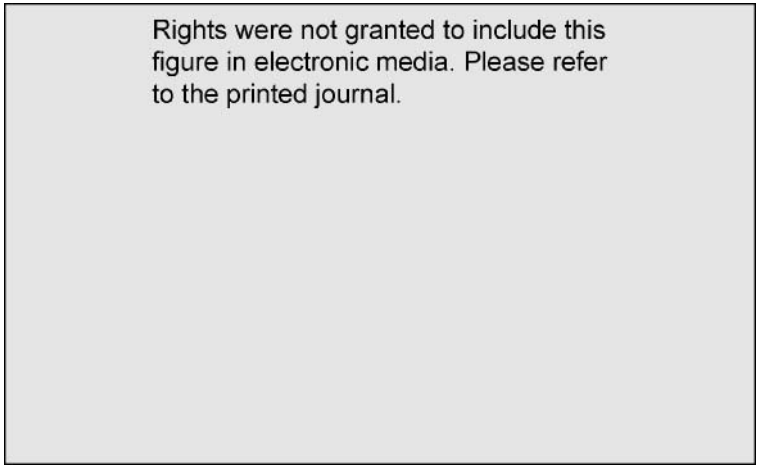


**Figure 3.** Annual incidence of rheumatoid arthritis in Rochester, Minnesota: Rate per 100,000 population by gender, 1955–1984. Each rate was calculated as a 3-year centered moving average. Square = *tot*; circle = *female*; triangle = *male*. (From Gabriel SE, Crowson CS, O'Fallow WM: The epidemiology of rheumatoid arthritis in Rochester, MN, 1955–1985. Arthritis Rheum 42:415–420, 1999; with permission.)

Drosos et al[18] investigated the records of patients at rheumatology clinics of universities and general hospitals and private clinics in Ioannina, Greece. Cases were identified according to the 1987 ACR criteria for RA, and population data were based on the 1991 National Census. A total of 428 cases of RA were identified during the study period, with annual incidence fluctuating between 12 and 36 per 100,000 population. A review of the incidence rates from the seven major population-based epidemiologic studies (see Table 1) reveals substantial variation in incidence rates across the different studies and across periods of time within the studies. Although some of this variation is accounted for by the differing age ranges of the various study populations (e.g., the high incidence rate in the study by Gabriel et al[23] is partially a result of the older age of the study population), these data emphasize the dynamic nature of the epidemiology of RA.

## Prevalence

As noted previously, there have been a relatively small number of studies reporting the incidence of RA, and these studies have yielded highly variable results (see Table 1). There are many more studies in the literature that provide estimates of the number of people with current disease (prevalence) in a defined population (Table 2). Although these studies suffer from a number of methodologic limitations,[45] the remarkable finding across these studies is the uniformity of prevalence figures in developed populations, which is generally between 0.5% and 1% of the adult population.[1, 7, 11, 18, 23, 36, 42, 47, 58, 70] Our own data demonstrated an overall prevalence of RA on January 1, 1985 of 1.07% (95% CI: 0.94–1.20). The prevalence among women was approximately double that in men. Women had a prevalence of RA of 1.37% compared with 0.74% in men.[23]

## Survival

The first mortality study of RA was published by Cobb et al.[12] In that study, 583 RA patients admitted to the Massachusetts General Hospital were followed for a mean of 9.6 years. The mortality rates among the RA patients were similar to those among controls without RA (24.4 deaths per 1000 patients per year compared with an expected number of 18.9). There have been numerous subsequent studies examining mortality in RA. These studies have consistently demonstrated an increased mortality in patients with RA when compared with expected rates in the general population (Table 3). Two studies have specifically

**Table 2.** PREVALENCE OF RHEUMATOID ARTHRITIS

| Author | County/Region | Prevalence (%) |
|---|---|---|
| Kvien et al, 1997[42] | Oslo, Norway | 0.437 |
| Stojanovic et al, 1998[70] | Belgrade, Yugoslavia | 0.69 |
| Cimmino 1998[11] | Genova, Italy | 0.33 |
| Boyer et al, 1998[7] | Anchorage, Alaska | 0.62–1.78 |
| Jacobsson et al, 1994[36] | Pima Indians, Arizona | 0.15–1.0 |
| Aho et al, 1998[1] | Finland | 0.8 |
| Drosos et al, 1997[18] | Northwest Greece | 0.21–0.48 |
| Gabriel et al, 1999[23] | Olmsted County, Minnesota | 1.07 |

**Table 3.** RESULTS OF RHEUMATOID ARTHRITIS MORTALITY STUDIES

| Author, and Publication Year | Number of Cases | Standardized Mortality Ratio |
|---|---|---|
| Monson and Hall 1976[48]* | 570 | 1.86 |
| Myllykangas-Luosujarwvi et al, 1995[50] | 1186 | 1.37 |
| Isomaki et al, 1975[35] | 122 | 1.77 |
| Wolfe et al, 1994[79] | 922 | 2.26 |
| Pincus et al, 1984[56] | 75 | 1.31 |
| Allebeck et al, 1981[3]* | 84 | 1.32 |
| Allebeck et al, 1982[2] | 473 | 2.48 |
| Prior et al, 1984[57] | 199 | 2.98 |
| Jacobsson et al, 1993[37]* | 79 | 1.28 |
| Cobb et al, 1953[12] | 137 | 1.29 |
| van Dam et al, 1961[74] | 231 | 1.32 |
| Duthie et al, 1964[20] | 75 | 1.66 |
| Reilly et al, 1990[59] | 63 | 1.62 |
| Lewis et al, 1980[43] | 46 | 1.40 |
| Mutru et al, 1985[49] | 352 | 1.64 |
| Gabriel et al, 1999[24] | 425 | 1.38 |

*Population-based studies.

examined trends in mortality over time. Both concluded that the excess mortality associated with RA has remained unchanged over the past two to three decades.[14, 24] The standardized mortality ratios in these studies varied from 1.28 to 2.98 (see Table 3). These findings suggest that the introduction of new treatments has had little impact to date on RA mortality in the community. The effect of these new agents on RA mortality may not be apparent for another 5 to 10 years, however. A number of investigators have examined the underlying causes for the excess mortality.[14, 22, 57, 76] These reports suggest increased risk from gastrointestinal, respiratory, cardiovascular, infectious, and hematologic diseases among RA patients compared with controls. RA not only takes its toll on functional status and quality of life but also significantly reduces life expectancy.

## RISK FACTORS ASSOCIATED WITH RHEUMATOID ARTHRITIS

A number of risk factors have been suggested as important contributors to the development or progression of RA. Of these, the best studied have been genetics, infectious agents, oral contraceptive medications, smoking, and formal education.

### Genetics

The familial nature of RA has long been recognized,[15, 33] suggesting that genetic risk factors are important in the etiology of this disease. Genetic studies of RA have focused primarily on the role of the major histocompatibility locus in RA. Several investigators have demonstrated important associations between specific human leukocyte antigen (HLA) alleles (i.e., HLA-DR4 and HLA-DR1) and susceptibility to RA.[25, 51, 69] There is controversy, however, regarding the mode

of inheritance (i.e., recessive vs dominant)[16, 27, 80] and the characteristics of the association (i.e., are there specific disease susceptibility loci, or do they simply affect disease severity?).[16, 77] Irrespective of the mode of inheritance and the role of HLA-associated susceptibility gene(s), the relation between HLA-DR alleles and RA is insufficient to explain the familial nature of the disease.[28, 60] The observations of high RA incidence rates, more severe clinical disease, and familial aggregation among certain North American Indian populations,[15, 17, 32, 36, 44, 52, 65] combined with the unusually low incidence of RA in other populations,[18] all lend support to the hypothesis of a genetic predisposition to RA. A study of the genetic epidemiology of RA identified variables associated with risk for RA in first-degree relatives of probands.[44] These analyses identified gender and age at onset in the proband as important risk factors, with relatives of male probands having the greatest cumulative risk of RA. Complex segregation analyses indicated that a small proportion of all cases of RA may be attributed to a highly penetrant recessive gene. In this model, the largest proportion of genetic cases of RA would be expected to occur in men affected before the age of 40 years. Significant heterogeneity in the inheritance of RA and in the distribution of risk for RA among first-degree relatives was demonstrated. A recent study examined familial aggregation of RA in the Netherlands and analyzed the effect of proband characteristics on the concordance rates for RA.[6] Cross-sectional hospital-based surveys were used to identify familial RA (i.e., affected sib-pair families). The estimated prevalence for familial RA was 9.8%, and familial aggregation of RA was estimated to occur preferentially in large siblings.[6] Probands with familial RA were more often RF-positive and had a longer follow-up period. Male gender and history of joint replacements were associated with higher concordance for RA.

## Infectious Agents

One feature of RA disease occurrence that might point to an environmental component is evidence of secular trends or disease clusters in time or space. Data from our own population-based incidence studies demonstrate secular trends in the incidence of RA.[23] Using the population-based data resources of the Norfolk Arthritis Register based in the East Anglia region of the United Kingdom, Silman and colleagues[62] conducted time trend and spatial clustering analyses on 687 incident cases of inflammatory joint disease identified between January 1, 1990 and December 31, 1994. These results demonstrated no evidence of a consistent seasonal variation in the onset of disease, that is, there was no suggestion of any localized "epidemic" in time. Modest evidence for spatial clustering was demonstrated, with nonrandom distribution observed in one geographic area. There was also no evidence of time or seasonal clustering of these incident cases. These investigators did demonstrate some evidence of time-independent spatial clustering within the northwestern part of the study area, however. Unfortunately, the small sample size precluded any definitive conclusions. Further investigation into local factors that might explain this finding is underway.[62]

The possibility of a host environment interaction has been discussed in detail in a number of recent review articles.[34, 63, 64, 66] Human parvovirus infection has been linked to the occurrence of inflammatory polyarthritis, but its role in the development of RA is less clear. Data from the Norfolk Arthritis Register, which has the benefit of ascertaining cases close in time to disease onset, showed that only 2.7% of patients with polyarthritis had evidence of recent human

parvovirus B19 infection, suggesting that such infection does not explain more than a small proportion of RA cases.[26]

### Estrogens

The possibility that oral contraceptives offer a protective effect against the development of RA has been proposed by numerous investigators. Brennan and colleagues[8] recently reviewed the 17 studies investigating this association and noted that 11 showed a protective effect and 6 did not. These investigators also provided their own results based on 115 incident cases of inflammatory polyarthritis, showing that current oral contraceptive use does protect against the development of RA, with an adjusted odds ratio (OR) of 0.22 (95% CI: 0.06–0.85).

There have been a smaller number of studies, including three case-control and two cohort studies, on the association between postmenopausal estrogen use and RA, again yielding conflicting results. One case-control study by Carette et al[10] found no effect, although another by Vandenbroucke et al[75] found a sevenfold reduction in risk among current users. These studies have been criticized for inconsistent inclusion criteria for RA cases, potential recall bias, incomplete evaluation of postmenopausal use of estrogen, and responder bias. The first cohort study by Hernandez-Avila et al[31] included too few women using estrogen replacement therapy (ERT) to provide a reliable estimate of its effect. A later cohort study by Spector et al[68] found a relative risk (RR) of 1.62 (95% CI: 0.56–4.74), which reduced toward unity (RR = 1.08; 95% CI: 0.3–6.75) after adjustment for potential confounders. A number of limitations exist within this study, including that of protopathic bias (i.e., that self-selection occurs for estrogen therapy at the time of menopause for those with undiagnosed joint symptoms). Other biases may exist in the ERT cohort in this study, because they were selected from a menopause clinic. This study also had extremely low power (20%) to be able to detect a large (50%) reduction in risk, because too few individuals in the study were ever on ERT.

Although the bulk of the evidence points to a protective role for estrogens in the etiology of RA, additional research is needed to resolve this controversy.

## Smoking

A study assessing the relation between smoking and the development of RA identified a significant association for the development of RA among male smokers compared with male nonsmokers (OR = 2.38; 95% CI: 1.45–3.92). Although the risk in women was also elevated, it was not statistically significant (OR = 1.14; 95% CI: 0.80–1.62). The effect in men was stronger for seropositive RA, where the OR was 4.77 (95% CI: 2.09–10.9).[72] More recently, Karlson and colleagues[41] studied the association of cigarette smoking with risk of RA among 377,481 female health professionals in the Women's Health Cohort Study. After adjusting for potential confounders, duration (but not intensity) of smoking was associated with a significantly increased risk of RA ($P < 0.01$). These findings add to the growing body of evidence suggesting that smoking is an independent risk factor in the development of RA.[29, 40, 67]

### Formal Education

The risk of self-reported arthritis as well as several other chronic diseases has been found to be inversely related to the level of formal education.[55] Low levels of formal education have also been associated with increased mortality[53] as well as poor clinical status[9, 53, 54] in patients with RA. Notably, in a recent case-control study, the risk of RA was unrelated to years of education,[46] and no relation was found between the onset of RA and indicators of socioeconomic deprivation using employment categories as indicators for social class.[5] Although most of the evidence points to a low level of formal education as a risk factor for RA, this finding has not been consistently demonstrated in all studies. Moreover, the mechanism for this possible excess risk is unknown.

## SUMMARY

Studies of the descriptive epidemiology of RA indicate a population prevalence of 0.5% to 1% and a highly variable annual incidence (12–1200 per 100,000 population) depending on gender, race/ethnicity, and calendar year. Secular trends in RA incidence over time have been shown in several studies, supporting the hypothesis of a host-environment interaction. People with RA have a significantly increased risk of death compared with age- and sex-matched controls without RA from the same community. The determinants of this excess mortality remain unclear; however, reports suggest increased risk from gastrointestinal, respiratory, cardiovascular, infectious, and hematologic diseases among RA patients compared with controls. Despite extensive epidemiologic research, the etiology of RA is unknown. Several risk factors have been suggested as important in the development or progression of RA. These include genetics, infectious agents, oral contraceptives, smoking, and formal education. Epidemiologic research is an essential contributor to our understanding of RA.

### Acknowledgments

The author thanks Deborah Fogarty for her assistance in the preparation of this manuscript and Michele Doran, MD, for her contribution to the section on estrogens as a risk factor associated with RA.

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