

# Annals of the Rheumatic Diseases

## Leaders

### Smoke gets in your joints?

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Two of the commonest causes of death in patients with rheumatoid arthritis (RA) are ischaemic heart disease and respiratory infection, both of which should be exacerbated by cigarette smoking. I shall not insult the readership of *the Annals* by listing the many other reasons why patients with RA should not smoke. The paper by Saag *et al*, in this issue suggests yet another reason that we may not have thrust persuasively at our patients to date.<sup>1</sup> This is that smoking may aggravate their RA.

The aetiology of RA and pathogenesis of progression to severe RA seem to share much in common. For example being female predisposes to RA, and is associated with more severe articular disease.<sup>2</sup> Being seropositive for rheumatoid factor (RF) associates with RA, and the higher the titre the more severe the RA.<sup>3</sup> Possessing the shared epitope predisposes to RA, and the presence of these alleles leads to more severe disease, particularly when the person has inherited two copies.<sup>4</sup> What we see in RA is a threshold effect. Certain variables seem to push people over an arbitrary line of what we label as the disease. The more of these variables that they possess, the further over the threshold they are pushed, and express more severe RA.

Therefore it would not be setting a precedent, and would strengthen the case, if it was shown that cigarette smoking both predisposes to RA, and in a dose related effect, leads to more severe RA. How close are we to confirming these possibilities?

A number of individual studies and a review by Silman<sup>5</sup> have considered the evidence for and against cigarette smoking in predisposing to RA. Table 1 summarises the evidence. The epidemiology of RA is hardly ever without controversy. However, on balance most of the good evidence supports a weak association between both RA, RF production, and cigarette smoking. Therefore it seems reasonable to go on to ask whether smoking influences the course of the articular disease once it has started.

Saag *et al*<sup>1</sup> took case histories and performed examinations on 336 RA patients ascertained from a hospital database. Hand *x* rays were taken and scored by Larsen's method. Blood was taken for RF. Smoking histories were expressed in pack years. In summary seropositivity for RF, radiographic erosions, and rheumatoid nodules

were all associated with significantly higher levels of pack years. There was a dose dependent relation between pack years and both RF positivity and radiographic erosions. An increasing gradient of risk for erosions was seen from distant ex-smokers to recent ex-smokers to current smokers. As a slight dampener to these overall trends, an association between smoking and Larsen score was only seen at lower levels of damage.

The strengths of this important study are: (1) The study size was sufficiently large to provide robust estimates of effect. (2) Objective outcome measures were used with radiographic erosions, RF positivity, and nodules. (3) Appropriate adjustment for confounders was undertaken and confirmed an independent association of pack years of cigarette smoking with RF erosions and nodules, even after confounders had been taken into account.

The principal weaknesses of the study are: (1) It is cross sectional and relies on memory and therefore recall bias for smoking history is possible. However, it is unlikely that severe RA patients will be more inclined to falsely recall heavy cigarette consumption than milder disease sufferers. (2) The possibility that severe RA leads to increased cigarette smoking cannot be completely ruled out. (3) Other potential disease modifiers in smokers that could be different from non-smokers have not been studied. Diet and

Table 1 Evidence for and against the possibility that cigarette smoking predisposes to rheumatoid arthritis

For	Against
Three prospective cohort studies show increased risk. <sup>6-8</sup>	A retrospective case-control study showed a protective effect. <sup>12</sup>
A population based case control study shows increased risk. <sup>9</sup>	RA is more common in women than in men. Smoking is the opposite.
Monozygotic twin study shows increased risk for RA and smoking. <sup>10</sup>	Little geographical variation in RA though in the developed world smoking levels vary considerably. <sup>5,13</sup>
Smoking associates with rheumatoid factor production. <sup>5</sup>	RA may be declining, <sup>13</sup> whereas cigarette smoking is generally increasing.
Atmospheric pollution can contribute to RF positivity, and clean air legislation may have led to its decline. <sup>11</sup>	Smoking is generally more common in lower social classes, unlike RA. <sup>11</sup>
RA is a modern disease and cigarette smoking is a modern epidemic.	Smoking reduces the risk of other chronic inflammatory diseases such as ulcerative colitis. <sup>14</sup>

exercise could be important for example, although the authors found no sociodemographic differences.

So where does this get us? There is good evidence to suggest that cigarette smoking has a small but significant impact on pre-disposing to RA. We now have the first piece of evidence to suggest that in keeping with a threshold model, once the disease has started, continuing to smoke may be detrimental to disease outcome.

How might cigarettes predispose to RA and make it more severe? I like the line already alluded to by Silman.<sup>5</sup> RA seems to be a relatively modern disease. Pollution and cigarette smoking are modern epidemics. Population studies have shown that pollution can lead to RF positivity.<sup>5</sup> Cigarette smoking is a highly localised form of concentrated pollution. Could cigarettes lead to RF production, and then increase the chance of RA? Could ongoing auto-contamination cause further stimuli to immune and inflammatory pathways leading to worsening RA? Could the increase in clean air and decline in popularity of smoking be contributing to the decrease in RA over the past 30 years?<sup>11 13</sup> Could the rising rates of cigarette smoking in young women be associated with a cohort of higher disease incidence and greater disease severity in this subgroup? Currently, we can but speculate. Prospective studies are needed to confirm the possibility that cigarettes aggravate RA and we need testable hypotheses to answer why cigarettes may be important in the aetiology and pathogenesis of RA. In the meantime however, I will be telling my RA patients that in addition to themany medical and social reasons why they should stop cigarettes, smoking may aggravate their RA. In addition to

education, diet, exercise, and weight reduction, it may be one more aspect of self efficacy that leads to improved outcomes.

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