

# Smoking, lung function, and rheumatoid factors

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## Abstract

**Positive rheumatoid factor (RF) reactions commonly precede the onset of clinically manifest rheumatoid arthritis (RA). Thus if items associated with RF reactions were traced at the community level this might provide clues to the cause of RA. The relations between smoking and lung functions and the occurrence of RA and RFs in a population sample representative of the adult Finnish population were studied. Rheumatoid factor testing was performed for 7124 subjects (89% of the sample) by the sensitised sheep cell agglutination test. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1</sub>) were measured with spirometry. 'False positive' RF reactions occurred twice as often in current smokers and ex-smokers than in those who had never smoked. The prevalence of high titres was fourfold greater among current smokers than among those who had never smoked. These associations were statistically significant and independent of age, FVC, and FEV<sub>1</sub> in both sexes. The women with airflow limitation (FEV<sub>1</sub>/FVC <70%) had a significantly increased occurrence of RFs which was independent of their smoking history, but no such relationship was found in men. The results suggest an impact of smoking on RF production; a follow up study may show whether the raised RF titres in smokers will be reflected as an increased incidence of RA.**

Rheumatoid arthritis (RA) is a multisystemic disease, in which several forms of lung affection may occur. Rheumatoid arthritis is occasionally complicated by pleurisy, pulmonary nodules, interstitial pulmonary fibrosis, and obliterative bronchiolitis.<sup>1 2</sup> The patients with rheumatoid lung disorder are often strongly positive for rheumatoid factors (RFs).<sup>3-6</sup> In addition to the distinct lung disorders mentioned above, low grade disease of the respiratory tract, and even considerable impairment of respiratory function, may occur in RA in spite of radiologically normal lungs.<sup>7-10</sup> The pathophysiological basis of the lesions is still controversial.<sup>11-15</sup> Smoking is likely to increase the severity of rheumatoid pulmonary changes, but similar changes occur also in patients who have never smoked.<sup>2 5 12 14</sup>

Rheumatoid lung disorder, characterised by RF positivity, can antedate joint disease; some patients never develop joint symptoms.<sup>1 3 15 16</sup> On the other hand, the onset of clinically manifest RA is often preceded by positive RF reactions,<sup>17-20</sup> implying that factors associated

with 'false positive' RF reactions might be risk factors for RA. Accordingly, changes in RF titre due to these factors might be reflected in the incidence of RA. We studied the relations between smoking, lung function, and the occurrence of serum RFs in a large population sample representing the adult Finnish population.

## Subjects and methods

The Mini-Finland Health Survey was designed to study the epidemiology of major public health problems, especially musculoskeletal, cardiovascular, respiratory, and mental disorders. The study sample was a two stage cluster sample selected to be representative of the Finnish population aged 30 years or over. It consisted of 8000 people from 40 areas. The examinations were carried out in 1978-80 in the mobile clinic of the Social Insurance Institution in two main phases: a screening phase and a re-examination phase. A total of 7217 subjects participated in the screening phase. Information was gathered through questionnaires and an interview by a nurse. Examinations performed on all included posteroanterior and lateral chest radiography, spirometry, and joint function testing. A blood sample was taken for serological studies. The re-examination, including a clinical examination, for the subjects with symptoms or findings suggestive of any of the diseases under study was carried out by seven specially trained doctors.

## SMOKING HISTORY

The data of smoking history were obtained at a standard interview. Three categories were used: those who had never smoked, ex-smokers, and current smokers (those smoking every day, or almost every day, at least one cigarette, cigar, or pipe—the great majority were cigarette smokers).

## LUNG FUNCTION

Lung function was studied with spirometry (Vitalograph spirometer, Vitalograph digital meter). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1</sub>) were measured; the quotient FEV<sub>1</sub>/FVC (%) was used as a measure of expiratory flow. Results of two technically faultless measurements were recorded and corrected to BTPS (body temperature and pressure, saturated with water vapour) values. The highest reading was taken as the final result. Specially trained laboratory nurses made the measurements using the same apparatus throughout the whole study.

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#### RHEUMATOID FACTOR TESTS

The sensitised sheep cell agglutination (Waller-Rose) test was performed for 7124/8000 (89%) people, who form the population of this study. The occurrence of RFs in this series has been described elsewhere.<sup>21</sup> The serum samples were kept frozen at  $-20^{\circ}\text{C}$  until 1986, when the sera of those positive in the Waller-Rose test and those with clinical arthritis were retested for RFs by the latex slide test and enzyme linked immunosorbent assay (ELISA). Data on RF isotypes have been published,<sup>21</sup> and were available for this study.

#### PERIPHERAL ARTHRITIS

Peripheral arthritis was verified on the basis of medical history, symptoms, and clinical examination.<sup>22</sup> For the purpose of this study RA was defined as a peripheral arthritis not fulfilling the criteria for other forms of specific arthritis, such as psoriatic arthropathy or ankylosing spondylitis with peripheral joint disease. At the clinical examination all patients defined as having RA had evidence of active inflammation or deformities in at least two limb joints (138 cases). Of these cases, those positive in the sensitised sheep cell agglutination test, latex slide test, or both, are referred to as seropositive RA cases (59 cases).<sup>22</sup> Other subjects positive in the sensitised sheep cell agglutination test had no arthritis and are referred to as 'false positive' cases (149 cases).

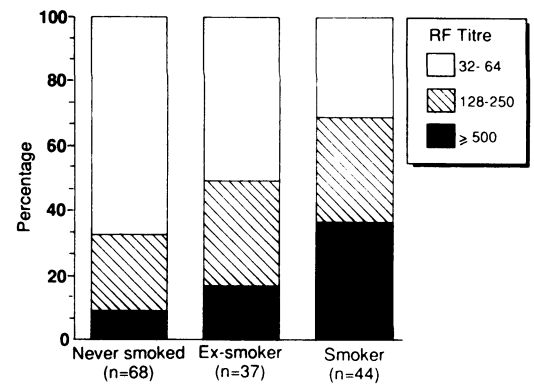
#### STATISTICAL METHODS

The association between smoking history and expiratory flow and the occurrence of RFs was estimated with a logistic regression model.<sup>23</sup> Age (years) was used as a continuous variable, whereas the other confounding and explanatory variables were classified. Relative risks (estimated as odds ratios) and their 95% confidence intervals were based on the model. The  $\chi^2$  test for trend<sup>24</sup> was used to test the gradient of RF titre according to smoking.

#### Results

'False positive' RFs were found to occur about twice as often in current and former smokers as in those who had never smoked. This association was independent of age and expiratory flow in both men and women (table 1).

In the cases with 'false positive' RFs the



Distribution of rheumatoid factor titre (sensitised sheep cell agglutination test) by smoking history in 'false positive' cases. Tests for trends (proportion of each titre by category of smoking): titre 32-64:  $\chi^2$  13.79,  $p < 0.001$ ; titre 128-250:  $\chi^2$  1.04, non-significant; titre  $\geq 500$ :  $\chi^2$  12.76,  $p < 0.001$ .

distribution of RF titres differed significantly between the smoking categories (figure). As compared with those who had never smoked, the prevalence of high titres ( $\geq 500$ ) was 1.8-fold among ex-smokers and 4.1-fold among current smokers. The trends of low and high titres were statistically significant ( $p < 0.001$ ), whereas the proportions of intermediate titres were distributed evenly between the smoking categories.

The women with FEV<sub>1</sub>/FVC less than 70% had a more than twofold greater occurrence of 'false positive' RFs than those with normal values (FEV<sub>1</sub>/FVC  $\geq 80\%$ ) (table 2). The difference in RF positivity (titre  $\geq 32$ ) between these groups was statistically significant even when adjusted for age and smoking history. The odds ratio, however, did not increase with increasing RF titre. No such relation was found in men. Forced vital capacity was not associated with the presence of RFs in either RA or 'false positive' cases.

The distributions of IgA, IgG, and IgM RFs were analysed for their associations with smoking and lung functions (data not shown). Although the current smokers with 'false positive' RF reactions had more frequently raised levels of IgG RFs than those who had never smoked, this difference was not seen when the subjects were stratified according to the sensitised sheep cell agglutination titre. No notable differences in the proportions of RF isotypes were found between the categories of FVC or FEV<sub>1</sub>/FVC.

Table 1 Relative risk of rheumatoid factor (RF, sensitised sheep cell agglutination test) positivity by smoking history. Odds ratio and 95% confidence interval (CI) adjusted for age and FEV<sub>1</sub>/FVC\*

| Smoking history | Total number | 'False positives' |            |            |                |            |            | Seropositive RA |            |            |
|-----------------|--------------|-------------------|------------|------------|----------------|------------|------------|-----------------|------------|------------|
|                 |              | RF $\geq 32$ †    |            |            | RF $\geq 64$ † |            |            | n               | Odds ratio | 95% CI     |
|                 |              | n                 | Odds ratio | 95% CI     | n              | Odds ratio | 95% CI     |                 |            |            |
| <b>Women</b>    |              |                   |            |            |                |            |            |                 |            |            |
| Non-smoker      | 2997         | 55                | 1.0        |            | 32             | 1.0        |            | 34              | 1.0        |            |
| Ex-smoker       | 364          | 10                | 1.7        | 0.8 to 3.4 | 8              | 2.3        | 1.0 to 5.2 | 5               | 1.7        | 0.7 to 4.6 |
| Smoker          | 495          | 12                | 1.4        | 0.7 to 2.8 | 11             | 2.3        | 1.1 to 4.8 | 4               | 1.1        | 0.4 to 3.2 |
| <b>Men</b>      |              |                   |            |            |                |            |            |                 |            |            |
| Non-smoker      | 967          | 13                | 1.0        |            | 10             | 1.0        |            | 4               | 1.0        |            |
| Ex-smoker       | 1114         | 27                | 1.6        | 0.8 to 3.2 | 21             | 1.7        | 0.8 to 3.6 | 8               | 1.5        | 0.5 to 5.1 |
| Smoker          | 1187         | 32                | 2.1        | 1.1 to 4.1 | 28             | 2.5        | 1.2 to 5.2 | 4               | 0.9        | 0.2 to 3.9 |

\*FEV<sub>1</sub>=forced expiratory volume in one second; FVC=forced vital capacity.  
†Cases positive for RF with two different cut off limits (titre  $\geq 32$  and  $\geq 64$ ).

Table 2 Relative risk of rheumatoid factor (RF, sensitised sheep cell agglutination test) positivity by expiratory flow (FEV<sub>1</sub>/FVC).<sup>\*</sup> Odds ratio and 95% confidence interval (CI) adjusted for age and smoking history

| FEV <sub>1</sub> /FVC (%) | Total number | 'False positives' |            |            |         |            |            | Seropositive RA |            |            |
|---------------------------|--------------|-------------------|------------|------------|---------|------------|------------|-----------------|------------|------------|
|                           |              | RF ≥32†           |            |            | RF ≥64† |            |            |                 |            |            |
|                           |              | n                 | Odds ratio | 95% CI     | n       | Odds ratio | 95% CI     | n               | Odds ratio | 95% CI     |
| <b>Women</b>              |              |                   |            |            |         |            |            |                 |            |            |
| ≥80.0                     | 2254         | 42                | 1.0        |            | 29      | 1.0        |            | 19              | 1.0        |            |
| 70.0-79.9                 | 1415         | 24                | 0.8        | 0.5 to 1.4 | 16      | 0.8        | 0.4 to 1.5 | 20              | 1.1        | 0.5 to 2.2 |
| <70.0                     | 187          | 11                | 2.7        | 1.3 to 5.7 | 6       | 2.0        | 0.8 to 5.3 | 4               | 1.3        | 0.4 to 4.2 |
| <b>Men</b>                |              |                   |            |            |         |            |            |                 |            |            |
| ≥80.0                     | 1714         | 30                | 1.0        |            | 26      | 1.0        |            | 8               | 1.0        |            |
| 70.0-79.9                 | 1214         | 32                | 1.1        | 0.6 to 1.9 | 25      | 1.0        | 0.5 to 1.8 | 5               | 0.5        | 0.2 to 1.8 |
| <70.0                     | 340          | 10                | 1.0        | 0.4 to 2.2 | 8       | 0.8        | 0.3 to 2.0 | 3               | 0.8        | 0.2 to 3.8 |

<sup>\*</sup>FEV<sub>1</sub>=forced expiratory volume in one second; FVC=forced vital capacity.

†Cases positive for RF with two different cut off limits (titre ≥32 and ≥64).

## Discussion

After appropriate stimulation peripheral blood lymphocytes of most healthy subjects can be induced to produce RFs.<sup>25</sup> Infections and immunisations have been shown to cause transient RF production<sup>26, 27</sup> that depends on continued immunological stimulation. For example, in subacute bacterial endocarditis antibiotic treatment led to a rapid decrease in RF titre.<sup>26</sup> Very little is known about the causes of persistently positive RF reactions. In patients with RA RFs are produced in large amounts and often during their whole lifetime. The role of RFs in the pathogenesis of RA is unknown, yet it is commonly believed that immune complexes containing RFs constitute a self-perpetuating system amplifying the synovial inflammatory process.<sup>28</sup> This interpretation, however, does not explain the common occurrence of RFs before clinical RA, as in this phase there is no humoral evidence of inflammation.<sup>29</sup>

Only a small minority of the subjects with 'false positive' RF reactions will develop RA,<sup>17</sup> but the risk increases with increasing RF titre.<sup>20</sup> An association exists between RA and certain histocompatibility markers, particularly HLA-DR4,<sup>30, 31</sup> but the occurrence of RFs in subjects without RA is not associated with these markers.<sup>32-34</sup> It is not known whether the genesis of RFs is different in the subjects who will develop RA and in those remaining healthy.

In epidemiological studies carried out in England by Lawrence and associates<sup>35</sup> seropositive subjects without RA more often had radiological evidence of pulmonary fibrosis in the upper zones of the lungs and thickening of the basal pleura than seronegative subjects. 'False positive' RF reactions occurred more often in urban than rural areas, but no association was found with smoking. On the other hand, Mathews *et al.*, from Australia, provided tentative evidence for a somewhat increased prevalence of 'false positive' RF reactions among smokers.<sup>36</sup> In our series, which is considerably larger, RFs were not associated with either radiological findings or urban surroundings (data not shown), but we found a significant association between smoking and the occurrence of 'false positive' RF reactions. The proportion of smokers increased with increasing RF titre, suggesting a causal relation. High titre antinuclear antibodies in smokers have been reported previously by Mathews *et al.*<sup>36</sup>

The emphasis of our study was on subjects with 'false positive' RF reactions. The number of patients with RA was too small for any detailed analysis. As FEV<sub>1</sub>/FVC mainly shows obstruction of the middle sized airways, functional debility of the small airways might have gone undetected.

Interestingly, the non-arthritic women with markedly decreased FEV<sub>1</sub>/FVC had a significantly increased occurrence of RFs independently of their smoking history. This supports an earlier finding of a connection between severe dyspnoea and occurrence of RFs among women participating in an Australian health survey.<sup>36</sup> Whether this RF production is a mark of underlying rheumatoid lung affection is not known.

The association of smoking and 'false positive' RF reactions, particularly in the highest titre group, was sufficiently strong for it to have biological significance. The recent reports of an increased incidence of RA among smokers<sup>37, 38</sup> are of considerable interest, as RFs often precede clinical RA. One can postulate a chain of events from an exogenous trigger (such as smoking) to the development of RA in genetically susceptible subjects through increased RF production. A follow up of this survey may enable us to find out whether raised RF titres of smokers predict the development of RA.

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