

Smoking: a preventable cause of rheumatoid arthritis

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RHEUMATOID ARTHRITIS (RA) AFFECTS 1% OF THE POPULATION. GENETIC AND ENVIRONMENTAL factors have long been known to contribute to the development of RA. Exposure to cigarette smoke was first linked with RA more than twenty years ago.¹

Smoking is now recognised as the most established environmental risk factor for the development of RA.²

The presence of the human leukocyte antigen (HLA)-DRB1 genes including the shared epitope (SE) regions have the strongest genetic association with RA. Smoking is associated with anti-citrullinated protein/peptide antibody (ACPA)-positive cases of RA.³ ACPA-positivity correlates with disease severity.

A recent study has further underlined the importance of smoking in the development of RA. It found that smoking is responsible for 35% of ACPA-positive cases in a dose-dependent manner (55% in patients with two copies of SE alleles). Furthermore, risk of RA in ex-smokers diminished with time.⁴

The Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study from Sweden collated data on incident RA cases and controls matched for age, gender and residential area. Genetic, antibody and questionnaire information was collected from 1,205 cases and 872 controls recruited between May 1996 and December 2003. The questionnaire enquired about: current and previous smoking history, time points for starting and stopping smoking and number of cigarettes smoked per day. SE alleles were genotyped from cases and controls who contributed blood samples.

Sixty-one per cent of cases were ACPA-positive. Smokers with more than a 20 pack-year history had an odds ratio (OR) of 2.6 (95% CI: 2.0-3.3, $p < 0.0001$) for the development of RA compared with non-smokers. Smokers with less than a nine pack-year history had an OR of 1.2 (95% CI: 1.0-1.6, $p = 0.084$) indicating that risk of RA rose with increasing duration of exposure to cigarettes. Furthermore, the risk of developing ACPA-positive RA diminished with time after stopping smoking. The excess fraction (EF) of cases of RA attributable to smoking was 35% (95% CI: 25%-45%). This attribution was higher in men (42%) than women

(31%). Finally, presence of SE alleles increased the risk of ACPA-positive RA in smokers to 55% in homozygotes and 29% in heterozygotes compared with 11% in cases with no SE alleles.

This study suggests that risk of RA diminishes with time after stopping smoking especially in intermediate smokers (defined as those with a 10-19 pack-year history). A large cohort study of female nurses has previously demonstrated an increased relative risk of development of rheumatoid factor-positive RA in current and ex-smokers. It did not demonstrate any reduction in risk in women who had stopped smoking, however, the study did not differentiate between heavy and moderate smokers.⁵

The EIRA data reports the impact of smoking on the development of RA in a dose-dependent manner. It also relates the effects of smoking and amount smoked to the number of SE alleles present.

This study is not a recommendation for genetic testing of relatives of patients with RA. However, there is compelling evidence to recommend that those with a family history of RA should stop smoking. The study demonstrated that cessation of smoking, especially in patients with a light (0-9) to intermediate (10-19) pack-year history, reduced the risk of developing ACPA-positive RA.

The effect of smoking cessation in individuals already diagnosed with RA is unknown.

This study provides further evidence that cigarette smoking is associated with the development of RA. There is a need for public health campaigns to educate the public regarding this risk. Encouragement of smoking cessation is especially warranted in relatives of patients with RA.

‘There is compelling evidence to recommend that those with a family history of RA should stop smoking’

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