Background/Aims

- First-degree relatives (FDRs) are at four-fold increased risk for rheumatoid arthritis (RA)
- RA risk factors include demographics, genetics, autoantibodies, and environmental factors
- Determining risk factors for inflammatory joint signs (IJS) in this high risk population may elucidate the transition from genetic susceptibility to inflammatory arthritis in pre-clinical RA
- Hypothesis: RA risk factors are associated with increased risk of IJS among FDRs without RA

Aims

1) To investigate whether known genetic, environmental, and serologic factors are associated with development of IJS
2) To evaluate whether these factors further interact to increase IJS risk in this high-risk population of FDRs

Methods

- Non-Hispanic white sera FDRs with covariates and complete joint examinations had genotyped samples pass quality control (n=966)
- 5 shared epitope alleles (DRB1*01, *0401, *0404, *0405, and *0406) genotyped using sequence-specific primers
- 45 non-HLA SNPs associated with RA among those with European ancestry genotyped on a custom Sequenom platform
- GRS50: genetic risk score from 50 RA risk alleles
- Weighted by natural logarithm of reported OR for RA risk in previous large genome-wide association studies
- Environmental factors: Cigarette smoking (cumulative pack-years and status), body mass index, education, and sex/parity
- Serologic factors: CCP2 and RF
- Logistic regression estimated ORs and 95% CIs for the associations of RA risk factors with US, adjusted for age/confounders
- Cross-sectional analysis at baseline (n=966)
- Interaction analysis for factors associated with US at baseline
- Prospective analysis in FDRs without baseline US (n=282)

Results

Table. Age-adjusted odds ratios for IJS at sites typical1 for RA in SERA

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>OR (95% CI) at baseline (n=966)</th>
<th>OR (95% CI) at 2-year follow-up (n=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Per year</td>
<td>1.03 (1.02-1.04)</td>
<td>1.08 (1.02-1.08)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td>1.59 (1.09-2.32)</td>
<td>2.66 (1.01-7.03)</td>
</tr>
<tr>
<td>Body mass index category</td>
<td>Normal/underweight</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td></td>
<td>Overweight/obese</td>
<td>0.93 (0.68-1.28)</td>
<td>1.49 (0.61-3.64)</td>
</tr>
<tr>
<td>Education</td>
<td>High school graduate</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td></td>
<td>Some college or greater</td>
<td>0.76 (0.53-1.10)</td>
<td>1.37 (0.42-4.46)</td>
</tr>
<tr>
<td>Sex/Parity</td>
<td>Female/parous</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td></td>
<td>Female/nulliparous</td>
<td>1.21 (0.76-1.95)</td>
<td>2.52 (0.76-8.35)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.77 (0.54-1.11)</td>
<td>0.91 (0.34-2.44)</td>
</tr>
<tr>
<td>RA GRS50</td>
<td>Low (&lt;Median)</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td></td>
<td>High (&gt;Median)</td>
<td>0.99 (0.73-1.35)</td>
<td>1.25 (0.52-2.83)</td>
</tr>
<tr>
<td>RA-related antibodies</td>
<td>CCP2 &lt;5 units or positive RF</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td></td>
<td>CCP2 &gt;5 units and negative RF</td>
<td>1.20 (0.66-2.19)</td>
<td>1.62 (0.55-4.80)</td>
</tr>
</tbody>
</table>

Figure. Combined effect of age and cigarette smoking on IJS at sites typical1 for RA at baseline in SERA (n=966)

Legend: 1 Inflammatory joint signs (IJS): any tender or swollen joints at MCP,PIP, wrist, elbow, or MTP joints; 1st MCP or MTP joints and findings deemed to be due to trauma or degenerative disease by examiner not included; N=222 US outcomes at baseline, N=27 IJS outcomes at the two-year follow-up.

Results Summary

- Smoking >10 pack-years was significantly associated with IJS at baseline (OR 1.59) and at 2-year follow-up (OR 2.66), compared to less intense smoking (p<0.05, Table)
- Increasing age was significantly associated with increased risk of IJS at baseline and at 2-year follow-up (p<0.05, Table)
- FDRs with age <50 and smoking >10 pack-years had the highest OR for developing US (Table)
- Younger age interacted with smoking for US (p=0.02, Figure)
- Weighted genetic risk score, composed of 50 RA risk alleles, was not associated with US risk among FDRs without RA (Table)
- RA-related autoantibodies (CCP2 and RF) were not significantly associated with US in this sample (Table)

Strengths/Limitations

- Strengths
  - Large sample size from multiple US sites of unaffected FDRs without RA symptoms at high risk of developing RA
  - Prior studies evaluating progression to RA among those with arthralgias were at a later phase in pre-clinical RA progression
  - Detailed, prospective data available on demographics, environmental factors, RA genetic factors, RA-related autoantibodies, and joint counts by physical examination
- Limitations
  - Analyses of serologic factors and US risk were limited due to few subjects with positive autoantibodies (1.5% with CCP2 >5 units)
  - Underpowered for genetic association analysis
  - 2-year prospective analyses had limited sample size

Conclusions

- Smoking and age were associated with both prevalent and incident US among this high-risk cohort of FDRs without RA
- We found a strong interaction of smoking pack-years and younger age for IJS, with highest risk in younger FDRs with >10 pack-years
- Smoking may induce inflammatory arthritis even in the absence of detectable serum autoantibodies
- Our findings add to the literature that smoking is an important, and potentially modifiable, risk factor during pre-clinical transitional phases of RA pathogenesis
- Further prospective investigations of the factors affecting the transitions between pre-clinical RA phases are warranted