

Rheumatoid Arthritis and Lung Cancer: You Probably Heard It Before



Smoking is probably one of the worst public health issues that each one of us can influence ourselves. It is nearly 60 years since the 2 epidemiologists Sir Richard Doll and Bradford Hill described a strong association between smoking and increased risk of lung cancer¹. Smoking has also since been associated with cardiovascular diseases and rheumatoid arthritis (RA)²⁻⁵, among other diseases.

Smoking is so far the most established environmental risk factor for developing RA, especially RA characterized by presence of antibodies to citrullinated proteins (anti-cyclic citrullinated peptide, anti-CCP)^{4,5}. Smoking is therefore a very important confounder to consider when studying a possible association between RA and lung cancer. In this issue of *The Journal*, Khurana, *et al* report an increased risk for lung cancer among US veterans with RA⁶. This finding extends the information about this connection, which has been described in other studies on RA and cancer⁷⁻¹¹. It is not clear, however, whether the increased risk of developing cancer is due to coexisting risk factors such as smoking, to RA disease itself, to RA treatment, or simply to earlier detection of cancer because of intense medical surveillance. In addition to the above, potential strong associations between certain phenotypes of RA (e.g., presence of certain antibodies) and a specific cancer may be diluted. This dilution appears if RA in total (all RA phenotypes associated and not associated with cancer are mixed) is used without stratifying for different RA phenotypes in the analytical process. One conceptual example of this diversity of causes is illustrated by the strong association between smoking and anti-CCP-positive RA, and the lack of association between smoking and anti-CCP-negative RA. If one were about to investigate a potential association between smoking and RA without considering a certain phenotype (in this case the presence of an antibody), the strong association between anti-CCP-positive RA and smoking would be diluted by the lack of association between anti-CCP-negative RA and

smoking. If one then adds the possibility of genetic risk factors being involved in the disease development, the pattern of disease mechanisms gets even more complicated. Interaction between susceptibility genes and smoking regarding risk to develop anti-CCP-positive RA has been observed in several studies recently³⁻⁵, pinpointing that RA is indeed a complex disease caused by multiple interacting and noninteracting factors. So far, there is little evidence for common susceptibility genes regarding RA and lung cancer. In a recent whole-genome study on lung cancer the most significant odds ratio was found for alleles in the region that codes for a nicotinic acetylcholine receptor subunit on chromosome 15¹². Based on results from a recent whole-genome association study on RA, there was little evidence for alleles on chromosome 15 being involved in RA¹³. The lack of studies showing overlapping susceptibility genes might indicate that it is primarily environmental factors such as smoking or RA itself that are of importance in the development of lung cancer among patients with RA.

In the report by Khurana, *et al*, the authors made an effort to rule out the possibility of smoking as a confounder, and they found some evidence for an association between RA and lung cancer in nonsmokers, although it was not significant when adjusted for age, race, and asbestos exposure. Unfortunately, no data were available on duration and intensity of smoking in the Veterans Affairs database that could have been used to investigate the role of smoking further.

There is little evidence for traditional RA treatment as a potential cancer initiator¹⁴, whether concerning solid cancers or lymphomas. In lymphomas, where the association with RA has been most obvious, it was recently demonstrated that disease activity in RA, rather than treatment with traditional disease modifying antirheumatic drugs, was primarily associated with lymphoma development¹¹.

Regarding newer treatments, it seems too early to draw

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any conclusions regarding a possible association between tumor necrosis factor- α (TNF- α) blockade and increased risks of lung cancer in RA patients¹⁴. However, in a large observational study, increased risks associated with TNF- α blockade were observed for skin cancer but not for lung cancer⁷.

One conclusion we can draw so far is that more research is needed, including different kinds of studies and settings, in order to resolve the complex puzzle of environmental and genetic risk factors for complex diseases such as RA and lung cancer. In this context, the article from Khurana, *et al* is a valuable contribution, but more needs to be done. We need to find distinct phenotypes for RA and lung cancer; to consider both genetic and environmental factors; to consider different biases, study designs, and analytical methods; and to consider animal studies for a more complete understanding of whether RA can initiate cancer in some contexts. But even before these questions have been answered, everyone can do something to prevent both RA and lung cancer. You probably heard it before: Help patients and the public to quit or never begin smoking.

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