# Evidence for Smoking–Severe RA Link Bolstered

BY JENNIE SMITH

FROM THE ANNALS OF RHEUMATIC DISEASES

Smoking is implicated in over a third of cases of the most severe and common form of rheumatoid arthritis, researchers in Sweden have found, and in one in five cases of RA overall.

Results from a population-based study strengthened the growing body of evidence that links smoking with development of anti-cyclic citrullinated peptide (anti-CCP) antibody–positive rheumatoid arthritis. In a dose-response manner, the link became stronger with heavier smoking, regardless of allele status.

The investigators, led by Henrik Källberg, Ph.D., of the Karolinska Institute in Stockholm, determined the excess fraction of RA cases attributable to smoking to be 20%, regardless of the presence of known genetic risk factors, which comprise single or dual copies of the HLA-DRB1 shared epitope. Smoking was estimated to be responsible for 35% of anti-CCP–positive cases (31% for women and 42% for men), and for each copy of the HLA-DRB1 shared epitope (SE) that was found, smoking was dose-dependently associated with an increased risk of anti-CCP–positive RA. In people with two copies of the HLA-DRB1 SE, 55% of anti-CCP–positive RA was attributable to smoking.

They also found an increased risk of developing RA (OR, 1.9; 95% confidence interval, 1.1-3.5) among heavy smokers without any genetic risk factors. "That was one really interesting finding," Dr. Källberg said in an interview. "As a heavy smoker, you are almost two times more likely to develop RA" even without the HLA-DRB1 SE alleles.

For their research, Dr. Källberg and colleagues collected blood samples and questionnaire information from 1,205 people who were diagnosed with RA according to the American College of Rheumatology's 1987 criteria, as well as 872 healthy controls matched for age, sex, and geographic location. The cases were part of the Swedish EIRA (Epidemiological Investigation of Rheumatoid Arthritis) cohort study.

The questionnaires solicited information on past and current smoking, thereby allowing investigators to classify each subject by smoking history (current and former smokers of 0-9, 10-19, and 20 pack-years, with 1 pack-year defined as equaling 20 cigarettes per day for 1 year). The investigators tested blood samples for anti-CCP antibody status and the presence of genotyped SE alleles.

The investigators calculated the odds ratios of developing RA associated with different smoking levels and SE alleles, together with 95% confidence intervals, by using logistic regression models. The interaction between smoking and the presence of SE alleles was evaluated as a departure from additive effects, and was estimated by calculating the attributable proportion due to interaction.

For former light and moderate smokers, the risk of developing RA declined and approached never-smoker levels the longer the person had not smoked since quitting. Former heavy smokers, however, continued to see elevated risk, even decades after quitting.

The dose-dependent association with smoking was "not a total surprise. We knew from earlier studies that there was some sort of relationship with the amount," Dr. Källberg said. "We just didn't expect it to be so clear cut."

The fact that ex–heavy smokers continued to see elevated risk does not mean that smokers shouldn't quit, Dr. Källberg said. "To some degree, the damage may be done, but we actually find that you gain something by quitting smoking. Quitting smoking can affect how well you respond to treatment."

Although smoking's presence in RA is smaller than in lung cancer, it is "similar to that seen for ischemic heart disease," the investigators wrote in their analysis. Furthermore, cardiovascular disease is associated with RA and is the major cause of premature death in people with RA (Ann. Rheum. Dis. 2010 [doi:10.1136/ard.2009.120899]).

Dr. Källberg and colleagues' study was funded by grants from the Swedish government; the insurance company AFA; the European Union; the Flight Attendant Medical Research Institute; National Institutes of Health; and the COMBINE (Controlling Chronic Inflammatory Diseases With Combined Efforts) project. Neither Dr. Källberg nor any of his colleagues declared conflicts of interest. ■

# Elderly With Arthritis: Opioids Riskier Than Other Analgesics

BY MARY ANN MOON

FROM ARCHIVES OF INTERNAL MEDICINE

Opioids were associated with more risks than were other analgesics in elderly patients taking the drugs for arthritis pain.

Although NSAIDs are known to pose certain risks, the results of the study "support the safety of [NSAIDs] compared with other analgesics," said Dr. Daniel H. Solomon and his associates at Brigham and Women's Hospital, Boston.

Few studies have examined the relative risks of the three major analgesic groups: NSAIDs, opioids, and coxibs (selective cyclooxygenase-2 inhibitors). "Postmarketing surveillance data from usual care cohorts provide an opportunity to examine comparative safety across a wid- range of events and can complement safety data from randomized controlled trials. However, imbalance in baseline population characteristics confounds many postmarketing surveillance studies," Dr. Solomon and his colleagues noted (Arch. Intern. Med. 2010;170:1968-78).

"Propensity score–matched analyses may provide better balance of confounders and facilitate relatively straightforward comparative safety analyses," they added.

To compare safety, the researchers performed a propensity-matched cohort analysis using information from a Medicare database of pharmaceutical coverage for low-income elderly residents of Pennsylvania and New Jersey in 1999-2005. The study population included 12,840 adults with rheumatoid arthritis or osteoarthritis who began using one of the three types of analgesics during the study period and were followed for at least 1 year.

Overall, adverse safety event rates were high for all three groups, with the rate of adverse events leading to hospitalization being greater than 100 per 1,000 person-years for all three types of analgesics. Opioid users had the highest rates of serious adverse events. In particular, the rate of hip, pelvis, wrist, or humerus fractures was 101 per 1,000 person-years in the opioid group, compared with 19 per 1,000 person-years in the coxib group and 26 per 1,000 person-years in the NSAID group.

Even though a link between opioids and fractures has been reported previously, "the strength of the association we observed is larger than in previous reports," Dr. Solomon and his associates said.

Compared with NSAIDs, opioids (hazard ratio, 1.77) and coxibs (HR, 1.28) were associated with elevated risk for cardiovascular events such as MI, stroke, heart failure, revascularization, and cardiac death. That "unexpected" finding regarding such severe events warrants further study, the investigators noted.

Compared with NSAIDs, risk for upper GI bleeding, lower GI bleeding, or bowel obstruction was similarly high for opioid users (HR, 1.07) but was lower for coxib users (HR, 0.60).

In general, opioid users experienced the most adverse events over time, while NSAID users experienced the fewest.

In addition, "opioid users experienced moderate risk early in treatment," the investigators noted, while the other groups did not.

Opioid users had significantly higher all-cause mortality (75 deaths per 1,000 person-years) than did either NSAID users (48 deaths per 1,000 person-years) or coxib users (47 deaths per 1,000 person-years). ■

**VITALS**

**Major Finding:** Opioid users had higher rates of overall adverse events, severe adverse events, cardiovascular events, fractures, and all-cause mortality than did NSAID users or coxib users.

**Data Source:** A propensity score–matched cohort analysis involving 12,840 elderly patients taking opioids, NSAIDs, or coxibs for rheumatoid arthritis or osteoarthritis pain.

**Disclosures:** The study was supported by the Agency for Healthcare Research and Quality. Dr. Solomon reported being an unpaid member of a celecoxib trial executive committee sponsored by Pfizer and an unpaid member of the data safety monitoring board for an analgesic trial sponsored by Pfizer.

**VIEW ON THE NEWS**

## Oversight in the Statistical Methods

The propensity matching was meticulous in this study, leading to well-balanced baseline characteristics among the three treatment groups.

This reassures readers that the observational study design is as robust as possible, and that treatment effects alone account for the observed differences among opioid, NSAID, and coxib users.

However, there is a single unmeasured confounder that calls into question the validity of some of the study findings: the use of over-the-counter NSAIDs, said Dr. William C. Becker and Dr. Patrick G. O'Connor.

It is likely that "a significant proportion" of patients in the opioid group were also taking NSAIDs, because "physicians routinely recommend antiinflammatory medication in addition to opioids to achieve therapeutic synergy in the treatment of arthritis," they noted.

"It seems implausible that a group of 'opioid-only' elderly patients" who were actually taking supplemental NSAIDs would have a higher risk of adverse cardiovascular events, GI bleeding, and acute kidney injury than would a group taking NSAIDs alone, because these are all known effects of NSAID therapy.

Despite this limitation, "the data on falls and fracture from this . . . study are nonetheless compelling and carry important clinical implications," Dr. Becker and Dr. O'Connor said.

DR. BECKER *and* DR. O'CONNOR *are in general internal medicine at Yale University, New Haven, Conn. They reported no financial disclosures.*

*These comments were taken from their invited commentary accompanying Dr. Solomon's report (Arch. Intern. Med. 2010;170:1986-8).*