EDITORIAL

Rheumatoid Arthritis, Aspirin, and Gastrointestinal Cancer

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Epidemiologic studies of rheumatoid arthritis (RA) continue to provide intriguing clues about cancer cause and prevention. Reported in this issue of the Journal are data obtained by Gridley et al. (1) suggesting that the incidence of colorectal cancer, and perhaps other gastrointestinal malignancies, is 30%-40% lower than expected in RA patients. These findings provide further support for the hypothesis, advanced from other sources (2-6), that regular use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may protect against colorectal cancer occurrence. It is well known that these agents inhibit the action of cyclooxygenase, an enzyme in the arachidonic acid metabolic cascade. This enzyme is essential for production of prostaglandins, which, in turn, appear to promote tumor growth in animal models (7). While the exact biochemical and cellular mechanisms by which such promotion occurs are not clear, they may well involve the growth and progression of large-bowel polyps to full-blown cancer.

The study by Gridley et al. (1) also reaffirms the well-established observation that hematologic malignancies (apparently mostly non-Hodgkin’s lymphoma) occur with increased frequency in persons with RA (8-10). Presumably, this propensity reflects heightened, chronic, immunologic activity in RA that in some manner favors the emergence of malignant lymphoid clones. An alternate mechanism in some cases may be the effect of immunosuppressive and cytotoxic drugs in the treatment of severe RA (11).

The investigation undertaken by Gridley et al. (1) is a collaborative effort between epidemiologists in Sweden and the United States, linking data from the National Swedish Cancer Registry with population-based clinical records of RA (11683 cases) diagnosed during a 19-year period in a 5-county Swedish area with a population of over a million persons. The study has full population coverage and is able to rely on accurate clinical diagnoses for RA as well as cancer. In addition, the study size is sufficient to allow precise examination of site-specific cancer frequencies. Only one other study has been larger: an analysis in Finland (from 1959 through 1968) (10) also suggested decreased gastrointestinal cancer mortality.

Such observations are of special interest because they are consistent with three other sets of data, all of which, on balance, suggest the ability of aspirin and other NSAIDs to reduce risk of colorectal cancer occurrence. First, numerous experiments have shown that various NSAIDs inhibit the growth of chemically induced colon cancers in rodents. Effects seem dose-related and appear at various intervals after induction of tumor (7). Second, clinical experience, especially using the NSAID sulindac, indicates regression of colorectal adenomatous polyps after treatment in patients with familial polyposis syndromes (2,3). In one instance, this effect was inducible in a small, double-blinded, controlled crossover study (3).

The third line of evidence comes from human epidemiologic studies of colon cancer itself. Four such studies have been reported, three of which suggest that regular aspirin use is accompanied by about a 40%-50% reduction in large-bowel cancer occurrence. Two of these three were case-control studies (4,5) based on series of incident colorectal cancers (715 and 1326 cases, respectively). The third study (6) evaluated data from 1388 patients with colon cancer who died during a 6-year prospective mortality follow-up in a cohort of over 660000 men and women. Although none of these three studies could measure actual doses of aspirin use, clear dose-response patterns were seen in the third study when frequency of regular use was considered. In contrast, the fourth study (12), which was smaller in size, performed follow-up of 13987 elderly (average age, 73 years old) retired persons over 7 years and found a slight increase in risk of colon cancer among persons reporting regular aspirin use at the study’s start.

In the context of these diverse data, observations in patients with RA are of particular value. Assuming that virtually all such patients use NSAIDs regularly, such studies provide an independent perspective on the effects of these agents and, in the process, suggest indirectly that the findings in other populations are unlikely to be due to biases in study design, in patient selection, or in determination of outcome. Like all observational epidemiologic studies, however, these other studies cannot fully discount such biases. It remains possible, therefore, that the findings may reflect either early detection of colon cancer because of aspirin-induced bleeding (and hence lower death frequencies in mortality studies) or misclassification of aspirin users who may stop aspirin use when symptoms of bowel cancer first appear. Before clinical and public health strategies can be considered for preventing colorectal cancer through regular NSAID use, these uncertainties need to be addressed through

*See "Notes" section following "References."
appropriate randomized clinical trials. Such trials will need to explore not only the validity of the effect of NSAIDs but also its relationship to dose.

Although colorectal cancers are a common form of human cancer, an adequate clinical trial to test the preventive effect of aspirin or other NSAIDs would still require a very large test population as well as a prolonged trial duration, especially if a range of dose levels were to be tested. The difficulty of such a trial would be made even greater by the need for its design to accommodate the current widespread use of aspirin in preventing cardiac disease and stroke. An alternative and more practical trial might be to test the effectiveness of aspirin or other NSAIDs in preventing or slowing the recurrence or progression of colorectal polyps (13). In such studies, a much smaller patient population and a shorter duration of follow-up might be required. Assuming that an effect on polyp recurrence or progression could be taken as a surrogate for colorectal cancer prevention, such a trial would be a logical next step and one upon which definitive public health strategies might be based. In the meantime, further epidemiologic, clinical, and experimental studies may surface, like the studies of rheumatoid arthritis reported here, to assist in our understanding of how NSAIDs may relate to human cancer occurrence.

References


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