Lowering the Risk of Prostate Cancer with NSAIDs: Moving Towards Chemoprevention

Roberts RO, Jacobson DJ, Girman CJ, et al. A population-based study of daily nonsteroidal anti-inflammatory drug use and prostate cancer. Mayo Clin Proc 2002;77:219–25.

Study Overview

<u>Objective</u>. To examine the association between daily use of nonsteroidal anti-inflammatory drugs (NSAIDs) and prostate cancer.

<u>Design</u>. Prospective cohort study.

<u>Setting and participants</u>. 1362 white men aged 50 to 79 years living in Olmsted County, MN, were randomly selected in January 1990 from among participants in a longitudinal study of lower urinary tract symptoms (the Olmstead County Study of Urinary Symptoms and Health Status). Men were excluded if at baseline they had a diagnosis of prostate cancer, prostate surgery, urethral stricture or surgery, bladder cancer or surgery, or other medical conditions known to affect normal urinary tract function other than benign prostatic hyperplasia.

<u>Methods</u>. Participants completed a self-administered questionnaire at baseline to assess medical history, urinary tract symptoms, and sociodemographics. Daily medications (prescription and nonprescription) and family history were elicited via a structured interview. This information was reassessed by questionnaire biennially. A retrospective review of medical records from 1992 through 1996 was conducted to determine a diagnosis of prostate cancer. Additionally, the Rochester Epidemiology Project surgical and diagnostic computer databases, as well as the Mayo Clinic tumor registry, were searched for diagnoses of prostate cancer.

<u>Main outcome measures</u>. Logistic regression was used to evaluate the association between NSAID use and prostate cancer. Family history, urologic history, and comorbidities were examined as potential confounders.

<u>Main results</u>. Men with a histologically proven diagnosis of prostate cancer during a median follow-up of 5 years were included in the analysis. 23/569 (4%) NSAID users and 68/793 (9%) nonusers (*P* = 0.001) developed prostate cancer during follow-up (6249 person-years). The relative odds of developing prostate cancer were 0.45 (95% confidence interval [CI], 0.28 to 0.73) among NSAID users compared with nonusers. In person-year analyses, the incidence of prostate cancer was 8.4 per 1000 person-years and 18.5 per 1000 person-years in NSAID users and nonusers, respectively. This association directly correlated with increasing age. For NSAID users aged 50 to 59 years, 60 to 69 years, and 70 to 79 years, the relative odds of prostate cancer were 0.88 (95% CI, 0.36 to 2.18), 0.4 (95% CI, 0.19 to 0.82), and 0.17 (95% CI, 0.06 to 0.45), respectively. Also, the proportion of men who used NSAIDs increased with age, with 54% of those aged 70 to 79 years on daily NSAIDs. Among all NSAID users, 77% were taking aspirin alone. There was no association between self-reported family history of prostate cancer and the development of prostate cancer.

At baseline, NSAID users had a statistically disproportionate share of benign prostatic hyperplasia (60% of users versus 44% of nonusers), prostatitis (11% versus 7%), diabetes (10% versus 4.4%), and history of myocardial infarction (MI) (36% versus 8%). In the year prior to enrollment, NSAID users had more physician visits (54% users versus 38% nonusers), prostate-specific antigen (PSA) determinations (median, 1 versus 0), and digital rectal exams (4% versus 3%). More nonusers withdrew and were lost to follow-up (5% versus 9%). In a model adjusting for age, urologic disease, comorbidities, and physician visits in the year prior to enrollment, the relative odds of the association between prostate cancer and NSAID use were 0.37 (95% CI, 0.22 to 0.62).

<u>Conclusion</u>. Daily use of NSAIDs may be associated with a lower incidence of prostate cancer in men 60 years or older.

Commentary

Prostate cancer is the most common cancer among men (excluding non-melanoma skin cancers), with an estimated incidence of 198,000 in 2001, and is second only to lung cancer in related mortality [1]. PSA testing has accounted for a large proportion of the increased incidence between the early 1980s and mid-1990s, though the impact of earlier treatment on survival is still debated [2]. Primary chemoprevention has been a focus of several recent and ongoing studies. Vitamin E and selenium have suggested benefit in several case-control

and cohort studies [3]. These agents, along with finasteride, a 5-α-reductase inhibitor, are each being studied in current large prospective primary chemoprevention trials that will take several years to mature.

Another focus of recent cancer chemoprevention trials has been on the use of NSAIDs. Several epidemiologic studies have shown a reduction in risk for adenomatous polyps and suggest benefit in invasive colorectal, esophageal, breast, ovarian, and prostate cancers. NSAID inhibition of cyclooxygenase-2 (COX-2), an enzyme associated with inflammation and the conversion of arachidonic acid to prostaglandins, may prevent oxidation of procarcinogens, increased cell growth, and decreased apoptosis. Preclinical data suggest that prostate cancer cells have increased levels of prostaglandin and COX-2.

Roberts et al conducted a well-designed prospective study demonstrating an inverse association between daily NSAID use and the development of prostate cancer. This association was more apparent with increasing age and was not affected by family history. As the authors point out, potential referral and recall biases were limited by the cohort's random selection and reporting of current medications. The study also is strengthened by its capture of prostate cancer prevalence through self-report, chart review, and registry searches.

However, it is important to consider some potential limitations of this study. Baseline characteristics were not evenly divided. Specifically, NSAID users tended to be older, diabetic, and have a prior history of MIs—perhaps not a group that would be as actively screened for prostate cancer as nonusers. Incidence directly correlates with screening. Perhaps not using NSAIDs is a marker of a man more likely to be screened. Unfortunately, the study does not have data on the rates of screening by digital rectal exams or PSA testing, although the rates of each in the year prior to enrollment would tend to mask any association. Moreover, there are no data on daily NSAID dose, duration, or onset of use, and regular (not daily) use was not assessed. Still, the findings taken together with other chemoprevention studies in cancer are provocative and deserving of further prospective evaluation looking at dose, duration, and screening rates.

Applications for Clinical Practice

At this time, there is not enough evidence to recommend daily NSAIDs in an effort to prevent prostate cancer, and further study is warranted. Other prospective controlled chemoprevention trials are currently in progress looking at vitamin E and selenium, but it may take several years before preliminary data are known.

–Review by David R. Spigel, MD

References

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