Use of Nonsteroidal Anti-inflammatory Drugs and Incidence of Colorectal Cancer

A Population-Based Study

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Background: Previous observational studies have provided limited information on the effect of specific nonsteroidal anti-inflammatory drugs (NSAIDs) and different patterns of use (duration and dose) on the incidence of colorectal cancer.

Objective: To determine how patterns of use (duration, dose, and specific drug) of NSAIDs affect incidence of colorectal cancer.

Design: Population-based retrospective cohort study.


Subjects: Enrollees (n = 104,217) aged 65 years or older with at least 5 years of enrollment.

Main Outcome Measures: Incident histologically confirmed colorectal cancer.

Results: Users of nonaspirin NSAIDs for at least 48 months of the previous 5 years had a relative risk (RR) of 0.49 (95% confidence interval [CI], 0.24-1.00) for colon cancer when compared with those with no use of NSAIDs. Among those with more than 12 months of cumulative use, those using NSAIDs in the past year (recent users) had an RR of 0.61 (95% CI, 0.48-0.77), whereas those with no recent use had an RR of 0.76 (95% CI, 0.50-1.15). No specific NSAID offered a unique protective effect and low doses of NSAIDs appeared to be at least as effective as higher doses. Protection was most pronounced for right-sided lesions. The RR among recent users with more than 12 months of cumulative use was 0.81 (95% CI, 0.49-1.32) for rectal cancer, 0.77 (95% CI, 0.55-1.08) for left-sided colon cancer, and 0.48 (95% CI, 0.34-0.68) for right-sided colon cancer.

Conclusions: In this elderly population, long-term use of nonaspirin NSAIDs nearly halved the risk of colon cancer. This study was consistent with previous studies that suggest that duration of use but not daily dose of NSAIDs is an important factor for chemoprevention. Our data also suggest that the protective effect is shared by most NSAIDs, and not confined to a small number of these drugs.

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Colorectal cancer is diagnosed in more than 130,000 individuals and results in 50,000 deaths each year, making it the second leading cause of cancer death in the United States.1 Despite the demonstrated efficacy of early detection programs in preventing mortality from colorectal cancer,2 most Americans do not receive appropriate colorectal cancer screening.3 Thus, the possibility of primary prevention of colorectal cancer by dietary, nutritional, or pharmaceutical interventions has great appeal.

There are several lines of evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) have a protective effect against colon cancer. Multiple observational studies4-14 using a variety of methodologies and populations have demonstrated a strong protective effect of NSAIDs (primarily aspirin) on incidence and/or mortality from colorectal cancer. In randomized clinical trials,15 the use of sulindac decreased the size and number of recurrent rectal polyps in patients with familial adenomatous polyposis syndrome—an inherited condition that results in colorectal cancer. In animal models of carcinogen-induced colorectal cancer the use of several NSAIDs reduce the number and size of tumors.16 The prime site of action of NSAIDs, cyclooxygenase (COX), is present in 2 forms: a constitutive form (COX-I) with homeostatic functions and an inducible form (COX-II) that appears to be important in inflammation and carcinogenesis.17 In humans, up-regulation of COX-II gene expression has been demonstrated in colon adenoma and colorectal carcinoma.18
SUBJECTS AND METHODS

DATA SOURCES

The sources of data for this study were administrative files from the Tennessee Medicaid program. Medicaid is a federally funded and state administered program, which provides medical coverage to disadvantaged populations. Tennessee Medicaid files used in this study included enrollment files, hospitalization claim files, and pharmacy claim files.

COHORT

Members of the cohort were identified from the Medicaid enrollment file that includes information on eligibility, enrollment status, and patient demographics. The cohort included enrollees of the Tennessee Medicaid program who were aged 65 years or older and had 5 years or more of continuous enrollment. The enrollment criterion was required to assure that 5 years of medication history was available. Individuals entered the cohort on the last of the following dates: attainment of 5 years of continuous Medicaid eligibility, attainment of age 65 years, or the study start date (January 1, 1985). Individuals left the cohort on the first of the following events: the diagnosis of an incident colorectal cancer, death, loss of eligibility, or the end of the study (December 31, 1992).

EXPOSURE TO PRESCRIPTION NONASPIRIN NSAIDs

The Medicaid pharmacy claim file was used to quantify the use of prescription nonaspirin NSAIDs. This file includes the date that a specific drug was dispensed and the dose, quantity, and prescribed days' supply of the drug. Because most aspirin and salicylate use was nonprescription and thus not identified in pharmacy claims, these drugs were not included in the study.

Despite the compelling evidence that the use of NSAIDs lowers the risk of colorectal cancer, many questions remain. In a secondary analysis of the Physicians' Health Study, to our knowledge, the only randomized controlled clinical trial of aspirin and colon cancer, randomization to aspirin was not associated with a lower rate of colorectal cancer. Ongoing trials are testing the efficacy of aspirin in prevention of recurrent adenomatous polyps as secondary end points for demonstrating the efficacy of colorectal cancer chemoprevention. Aspirin was the sole or predominant NSAID evaluated in most of the epidemiological studies to date. Those studies that examined the effect of nonaspirin NSAIDs have had limited power to further define the influence of specific NSAID or patterns of use (dose and duration) on the incidence of colon cancer. Several studies have suggested that duration of NSAID use is important in lowering the risk of colon cancer. In fact, the relatively short duration (5 years) of the Physicians' Health Study has been one explanation for the lack of protection of aspirin in that clinical trial.

Adverse effects of presently available nonaspirin NSAIDs preclude clinical trials of these drugs for primary prevention of colorectal carcinoma in the general population. Observational studies of NSAID dose, duration of use, and of specific drugs are needed for planning future trials and to aid in the development of less toxic chemopreventive agents. More information is also needed to determine if the protective effect of NSAIDs varies with the anatomical tumor site, particularly whether this effect is similar for tumors of the colon and rectum. We used the database of the Tennessee Medicaid program that provides longitudinal information on prescription drug use to conduct a retrospective cohort study of the effects of prescription nonaspirin NSAIDs on the incidence of colorectal cancer among elderly individuals from 1985 to 1992.

RESULTS

The cohort consisted of 104,217 individuals who contributed 447,065 person-years of observation. The cohort reflected the demographics of the Medicaid population with a high proportion of women (76%), those older than 85 years (20%), and nonwhites (35%).
Among those who were classified by the medical records as currently using nonaspirin NSAIDs, the pharmacy files identified 7% as having no nonaspirin NSAID in the previous 5 years and 81% as having had at least 1 nonaspirin NSAID in the previous year.

IDENTIFICATION OF COLORECTAL CANCER

We sought to identify all subjects in the study population with incident histologically confirmed colorectal cancer. Subjects were identified by using the Medicaid hospitalization claim file to identify the first hospital claim during the study period of a cohort member with any discharge diagnosis of colon (International Classification of Diseases, Ninth Revision, Clinical Modification™ 153.0-153.9) or rectal (154.0-154.9) cancer. The medical records of 1277 subjects with candidate hospitalizations were reviewed by trained nurses who used a structured abstract to record confirmatory demographic information, clinical signs and symptoms (presence/absence of rectal bleeding, pain, and anemia), diagnostic information, location of the cancer(s), and pathologic information. Each abstract form was reviewed by one of us (W.S.) for completeness before double entry into a SAS dataset (SAS Institute Inc, Cary, NC). Determination of the stage of the tumor was made by one of us (W.S.) based on information obtained from the pathology reports and medical record. Classification of tumors as early- or late-stage tumors was performed by using criteria from the American Joint Committee on Cancer.28 All cases had biopsy-proven adenocarcinoma of the colon or rectum. Classification as a stage I, II, or III were based on pathologic findings at surgery. Stage IV cases were classified on the basis of either pathologic findings at surgery or on clinical evidence of metastasis.

Medical records were not reviewed for 176 potential cases for reasons including lost or incomplete records, or closed hospitals. The medical record was available for review and abstracted for 1101 subjects (86%) of whom, 293 were excluded for the following reasons: a clinical diagnosis of colorectal cancer but no histological confirmation in the medical record (n = 81); other diagnoses including anal carcinoma, in situ adenocarcinoma, or colorectal adenoma and/or polyp (n = 121); or a history of colon cancer only (n = 91). Thus, 808 subjects with histologically confirmed incident colon (n = 662) or rectal (n = 146) cancer were identified.

ANALYSIS

Tabulation of demographic and clinical characteristics was performed using SAS statistical software (Version 6.12).29 Univariate rates of cancer hospitalization were calculated by dividing the number of cases by the person-time in each stratum.

The initial analysis was performed for tumors of the colon only. Subsequent analysis, by anatomical site, included rectal tumors. The NSAID-associated gastrointestinal symptoms could increase utilization of lower gastrointestinal tract diagnostic testing and thus prevent some cases of colon cancer if precancerous polyps were removed during such an investigation. To evaluate whether such a bias occurred, the cohort was also classified by exposure to any of these tests in the previous 5-year period. Exposure to lower gastrointestinal tract tests was determined by claims for colonoscopy, sigmoidoscopy, and barium enema.

Poisson regression models were used to estimate multivariate rates and relative risks (RRs). Initially, the models included terms for demographics (year of diagnosis, sex, age, race, and rural vs urban county of residence) and indicators of health care utilization such as prior noncancer hospitalizations and the utilization of other (non-NSAID) types of medication.40 Variables that did not significantly change the estimate of risk were eliminated from the model in a stepwise fashion. The final model included terms for age, sex, race, calendar year, and NSAID-exposure category. All P values were 2-sided.

There were 662 subjects with colon cancer and 146 subjects with rectal cancer identified. Fifty-four percent of cancers were located distal to the transverse colon, and 53% were stage I or II. The use of NSAIDs at diagnosis did not affect cancer presentation: anemia (current NSAID users, 69%; nonusers, 73%; P = .48), rectal bleeding (users, 54%; nonusers, 45%; P = .21), abdominal pain (users, 56%; nonusers, 56%; P = .96), or tumor at stage I or II (users, 56%; nonusers, 52%; P = .64). The use of aspirin was noted in the medical record in 11% of cases; however, this did not vary significantly with the use of nonaspirin NSAID as ascertained from the pharmacy files.

For tumors of the colon, increased cumulative use of NSAIDs was associated with decreased rates of cancer (Table 1). The adjusted RR associated with 48 months of cumulative exposure was 0.49 (95% confidence interval [CI], 0.24-1.00) compared with no use of prescribed NSAIDs in the last 5 years. In contrast, cumulative use of an NSAID for less than 3 months did not alter the rate of colon cancer (RR, 0.97; 95% CI, 0.80-1.18). Similar protective effects were seen in all demographic subgroups.

The protective effect of NSAIDs against colon cancer was most pronounced for recent users, ie, those who used them during the previous 12 months (Table 2). Recent users with more than 12 months of cumulative use had an RR of colon cancer of 0.61 (95% CI, 0.48-0.77). Although the risk estimates suggested some protection for those with recent but short duration of use (RR, 0.84; 95% CI, 0.67-1.06) and those with longer duration of use, but no use in the past year (RR, 0.76; 95% CI, 0.50-1.15), neither of these estimates were significantly different than the other.

It is possible that most long-term users had more than 5 years of total use. Therefore, we examined those who appeared to have begun using NSAIDs more recently. New users were defined as those with no prescribed NSAID during the first year of the previous 5 years of observation and who had at least 12 months of use in the subsequent 48 months. These new users had a risk of colon cancer that was 53% of those who had used no NSAIDs in the last 5 years (RR, 0.53; 95% CI, 0.33-0.87).

Because the protective efficacy of NSAIDs was limited primarily to recent users with at least 12 months of...
cumulative use, the analysis of specific NSAID use and dose included only events and person-time meeting these criteria (Table 3). With the exception of piroxicam (RR, 2.65; 95% CI, 1.09-6.42), each of the individual drugs had a protective effect. Ibuprofen (RR, 0.63; 95% CI, 0.31-1.27), the most commonly prescribed NSAID, appeared to be as protective as other drugs. Nine percent of NSAID use was classified as “high-dose,” 80% as “moderate-dose,” and 11% as “low-dose” use. Higher average doses were not associated with increased protection. High-dose use was associated with an adjusted RR of 0.77 (95% CI, 0.41-1.44) compared with RR estimates of 0.59 (95% CI, 0.45-0.78) and 0.53 (95% CI, 0.26-1.08) for moderate- and low-dose users. Exclusion of 20 mg of piroxicam yielded an RR estimate for high-dose users of 0.52 (95% CI, 0.23-1.18). Analysis by dose did not affect the findings for individual drugs.

The protective effect of NSAIDs was observed for colon cancers at both early and late stages. The adjusted RR associated with the recent use of NSAIDs of more than 12 months’ duration was 0.58 (95% CI, 0.42-0.82) for stages I and II cancers and 0.66 (95% CI, 0.45-0.96) for stages III and IV tumors.

Among recent users with more than 12 months of cumulative use, the RR of colon or rectal cancer was 0.64 (95% CI, 0.51-0.79). Individuals with this pattern of use had a 19% lower rate of rectal cancer, which was not significantly different from the rate among nonusers (RR, 0.81; 95% CI, 0.49-1.32). This pattern of use was associated with a 39% lower rate of colon cancer (RR, 0.61; 95% CI, 0.48-0.77), a marked lowering of risk that is both clinically and statistically significant. Although the pattern of risk with increasing duration of use was similar for all sites, this effect was most pronounced for the cancers of the right colon (those proximal to the splenic flexure) where the adjusted RR for recent users with more than 12 months of exposure was 0.48 (95% CI, 0.34-0.68) (Table 4).

We assessed the potential confounding effect of NSAID-associated diagnostic testing by conducting an analysis of cohort members with no lower gastrointestinal tract tests in the previous 5 years. Among this population, the adjusted RR of colon cancer among recent users with more than 12 months of cumulative use was 0.63 (95% CI, 0.49-0.81).

**COMMENT**

In the study cohort of individuals aged 65 years or older, continuous and long-term use of nonaspirin NSAIDs reduced the risk of colon cancer by as much as 50%. This study confirms previous observations that the use of non-aspirin NSAIDs is protective<sup>1,14</sup>, shows that a substantial protective effect is present with 4 years of use, but that this effect may become attenuated after use ceases; demonstrates that high doses are not required for protection; demonstrates that the effect on incidence is not caused by an increased rate of diagnostic testing and secondary prevention of cancer by polypectomy; and suggests that most commonly prescribed NSAIDs decrease the risk for colon cancer.

The protective effect of NSAIDs appears to be dependent on continuous, long-term use. Our analyses suggest that some level of continuous use is necessary to main-
tainty a substantial degree of protection, and that the duration of use needed for protection is between 1 and 4 years. In previous observational studies, use of aspirin 16 days per month, or use of nonaspirin NSAIDs on more than 25% of days in the previous 4 years were associated with increased protection when compared with less intense NSAID exposures. Our finding that the protective effect diminished among those with no use in the past 12 months is consistent with the findings of a previous study in which aspirin was the predominant NSAID.

The protective efficacy of nonaspirin NSAIDs against rectal cancer in this study was smaller than that observed for colon cancer and is not statistically significant. In addition, among colon cancers, the effect of NSAIDs was more pronounced for right-sided cancers. This finding is consistent with some, but not all, studies that have examined the effect of NSAIDs by the site of the cancer. Because our study had limited power for individual sites, the differences we observed between sites may be attributable to chance. However, in our data there was a consistent trend of greater protection against right-sided cancers at all levels of NSAID exposure, suggesting that this was not a chance finding. There are biological differences between right- and left-sided colon cancers; however, it is unclear how NSAIDs interact with these factors.

Ibuprofen, the most commonly prescribed of the nonaspirin NSAIDs in our population, appears to be at least as effective as other specific drugs. The point estimates of RR for all the specific NSAIDs, with the exception of piroxicam, were less than 1.0. However, the power to quantify the effect of individual drugs was limited.

Lower-dose long-term use of NSAIDs appears to be at least as effective as higher-dose use. The point estimate for use of high-dose nonaspirin NSAIDs was influenced by the fact that virtually all person-time receiving piroxicam was defined as high dose. Exclusion of 20 mg of piroxicam from the high-dose groups yielded RR estimates virtually identical to that for low-dose users. In this population, consistent, long-term use was a more important determinant than dose in preventing colon cancer.

Piroxicam, which has been used in many animal models of cancer chemoprevention, is associated with increased risk in our data. Because there is nothing in the literature to suggest that piroxicam increases risk for colon cancer, this was an unexpected outcome. Case presentations among those who used piroxicam exclusively did not differ significantly from those not receiving NSAIDs in terms of clinical bleeding, pain, or presence of anemia. We would interpret this isolated finding with caution because it is based on small numbers and there was no adjustment for multiple comparisons in the analysis by specific NSAIDs. In addition, piroxicam has been shown to be protective in several animal models of cancer.

The use of aspirin was not studied because most aspirin use in this cohort was likely to be nonprescription use that would not be detected by pharmacy claims. Use of over-the-counter NSAIDs (ibuprofen, naproxen, and ketoprofen) would also be missed by pharmacy claims. In addition, use of pharmacy claims provides only limited information on compliance with the prescribed regimen. Thus, it is likely that there is some misclassification of NSAID exposure because of noncompliance, use outside of the prescribed days’ supply, or use of nonprescription products. Among those study patients with colorectal cancer, we found no association between use of aspirin as recorded in the medical record and prescription NSAID use, suggesting that such misclassification is nondifferential and thus any bias introduced is toward the null hypothesis.

Information on some risk factors of cancer such as weight, diet, and family history of cancer was not available and thus these factors could not be controlled for in the analysis. In other studies, inclusion of terms for body mass index, fat intake, or history of family cancer had only a minor impact on the risk estimates of the effect of NSAIDs on colon cancer.

The use of NSAIDs is associated with adverse effects such as dyspepsia, peptic ulcer disease, and renal failure. Previous studies of similar cohorts of elderly Tennessee Medicaid enrollees demonstrated an excess rate of hospitalization of 1.3 per 100 person-years for peptic ulcer disease and an excess expenditure of more than $100 per person per year for gastrointestinal tract-related disorders among regular users of NSAIDs. Thus, usual doses of these nonaspirin NSAIDs have an adverse effect profile that makes them unsuitable candidates for colon cancer prophylaxis in the patient with average risk. Low-dose aspirin (ie, 325 mg every other day) has a much lower adverse effect profile. Such doses were not associated with protection from colon cancer in the Physicians’ Health Study, although observational data suggest that this level of exposure may be sufficient. The potential efficacy of low-dose aspirin is being tested in randomized controlled trials that use adenomatous polyp

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<th>Time Since Last Use of NSAIDs, y</th>
<th>Cumulative Use of NSAIDs in Past 5 y, mo</th>
<th>Rectum, No.</th>
<th>RR (95% CI)</th>
<th>Left, No.</th>
<th>RR (95% CI)</th>
<th>Right, No.</th>
<th>RR (95% CI)</th>
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<td>0.81 (0.49-1.32)</td>
<td>47</td>
<td>0.77 (0.55-1.08)</td>
<td>39</td>
<td>0.48 (0.34-0.68)</td>
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* Tennessee Medicaid 1985-1992 enrollees 65 years or older. Relative risk (RR) and 95% confidence interval (CI) estimated by Poisson regression model including terms for sex, age, race, and calendar year. Right indicates locations proximal to the splenic flexure. Ellipses indicate not applicable.
incidence as a secondary end point for colon cancer. Newer agents, such as the selective COX-II inhibitors, which are potentially less toxic than traditional non-aspirin NSAIDs, must be demonstrated to be safer alternatives before considering them for trials of cancer prophylaxis. Until the efficacy of safer chemopreventive alternatives to traditional NSAIDs has been demonstrated, patients should be advised that adherence to the well-established guidelines for early detection will decrease mortality from colorectal cancer by 20% to 40%.2

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REFERENCES