NSAIDs and Colorectal Cancer Risk: Do Administrative Data Support a Chemopreventive Effect?

Elizabeth B. Lamont, MD, MS^{1,2}, Lauren E. Dias, MD^{1,3}, and Diane S. Lauderdale, PhD⁴

¹Massachusetts General Hospital Cancer Center, Boston, MA, USA; ²Departments of Medicine and Health Care Policy, Harvard Medical School, 180A Longwood Ave, Boston, MA 02115, USA; ³North Shore Medical Center, Peabody, MA, USA; ⁴Department of Health Studies, University of Chicago, Chicago, IL, USA.

BACKGROUND: Randomized trials show non-steroidal anti-inflammatory drugs (NSAIDs) reduce precancerous polyps. Observational studies of the NSAID aspirin (ASA) suggest that it reduces invasive colorectal cancer (CRC) incidence, but because ASA use may also be a marker for healthy behaviors, these studies may be subject to selection bias. We sought to estimate the effectiveness of NSAIDs in CRC prevention in the population of elderly Medicare beneficiaries, minimizing this selection bias.

METHODS: With National Ambulatory Medical Care Survey data, we find that patients with a diagnosis of osteoarthritis (OA) are 4.4 times more likely to concurrently have NSAID use documented than patients without such a diagnosis. We use this figure to estimate the expected NSAID-mediated reduction in CRC risk associated with a diagnosis of OA. Using Survival Epidemiology and End-Results (SEER)-Medicare data, we compare cases of elderly Medicare beneficiaries diagnosed with CRC in 1995 to persons without CRC to determine if their odds of antecedent OA differ.

RESULTS: We estimate the expected NSAID-mediated reduction in CRC associated with an OA diagnosis to be between 6 and 16% (i.e., RR, 0.84–0.94). In the SEER-Medicare data, we find that individuals with a diagnosis of OA in Medicare claims in the previous 3 years had 15% lower odds of being diagnosed with CRC than individuals whose claims did not reflect antecedent OA (OR 0.85, 95%CI 0.80–0.91).

CONCLUSIONS: This case-control study finds that elderly Medicare beneficiaries with histories of OA have 15% lower odds of developing CRC. These results are consistent with a preventive role for NSAIDs in CRC among the elderly.

KEY WORDS: colorectal cancer; prevention; aging.

DOI: 10.1007/s11606-007-0256-7

© 2007 Society of General Internal Medicine 2007;22:1166–1171

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common solid tumor and the second most common cause of cancer death.¹

The majority of CRCs are thought to arise as the result of a series of molecular changes that transform normal colonic epithelial cells to adenomatous polyps and, ultimately, to invasive cancers. A number of agents including NSAIDs, folic acid, calcium, and estrogens potentially inhibit polyp development and/or transformation into invasive cancer.² Of these, NSAIDs have been the most widely studied. These agents inhibit both cyclooxygenase-1 and cyclooxygenase-2 (COX-2), enzymes involved in prostaglandin synthesis. COX-2 overexpression is thought to play an important role in colon carcinogenesis, as it is not elevated in normal colonic epithelium, but has been found to be elevated in 40% of colonic adenomas and up to 90% of sporadic CRC.^{3,4}

Multiple randomized controlled trials (RCTs)^{5–11} show NSAIDs prevent polyps and numerous observational studies including case-control trials^{12–14}, and cohort studies^{15–17} suggest they also reduce the risk of subsequent invasive CRC by a similar magnitude. Estimates from both the polyp prevention trials and most observational studies of CRC risk suggest the effect size of NSAIDs on each of these end points to be between approximately 0.50 and 0.80. Whereas 2 RCTs and one recent cohort study have reported no association between NSAIDs and incident CRC^{18–20}, the lower doses employed and/or the shorter duration of use may explain the lack of effect. However, because regular use of the NSAID aspirin may be a marker of high-quality cardio-preventive care and other healthy behaviors, the lower risk of CRC among “NSAID users” in observational studies could be due to selection bias and unmeasured confounding related to the subset taking aspirin.

Given the greater use of NSAIDs by patients with osteoarthritis (OA), we use existing data sources containing information about the associations between NSAIDs and OA and OA and CRC to provide a window into the effectiveness of NSAIDs in CRC prevention. Given that NSAID use among those with OA is more likely to be *therapeutic* (i.e., for pain management) rather than *preventative*, it is not likely to be a marker of receipt of preventive care. We similarly compare prior OA for female breast cancer cases and controls to explore whether an association between OA and these screening-detected cancers could be due to differential medical care.

MATERIALS AND METHODS

Data Sources

We used data from the 1993–1994 National Ambulatory Medical Survey (NAMCS)²¹ to determine rates of NSAID use among elderly OA patients. NAMCS is an annual national sample survey of visits to office-based physicians that is

Received January 23, 2007

Revised April 5, 2007

Accepted May 24, 2007

Published online June 19, 2007

designed to collect objective reliable information about the provision and use of ambulatory medical care services in the United States. It utilizes a multistage probability design with the physician-patient office visit as the sampling unit. Data include patient demographics, diagnoses, and current medications, both over-the-counter and prescription. The National Center for Health Statistics oversees NAMCS and conducts data quality audits routinely and estimates the medical and drug coding error rate to be 0–1%.²²

We used data from the Survival Epidemiology and End-Results (SEER)-Medicare program to study the association between OA and subsequent CRC diagnoses in elderly Medicare beneficiaries and the association between OA and subsequent breast cancer diagnoses among elderly female Medicare beneficiaries. The SEER-Medicare data are an NCI-sponsored linkage of the clinical data collected by the SEER registries with health services billing claims collected by Medicare for administrative purposes²³. The SEER program collects information regarding the diagnosis and treatment of patients with cancer from 11 geographically diverse tumor registries to monitor trends in incidence and survival²⁴. To facilitate comparisons between Medicare enrollees with cancer and those without, the NCI has created a data file that identifies a 5% random sample of Medicare beneficiaries residing in SEER areas and whether or not they have a cancer listed in SEER.

Medicare is a federally sponsored health insurance program administered by the Centers for Medicare and Medicaid Services (CMS) whose beneficiaries include more than 96% of all US citizens aged 65 and older²⁵. CMS maintains billing records of ambulatory, inpatient, home health, hospice, and other claims for all beneficiaries not enrolled in risk contract health maintenance organizations (HMOs). To determine the study population's inpatient and ambulatory medical services (regardless of whether they were in SEER or not), we used 3 types of Medicare files for the analyses: the Medicare Provider Analysis and Review (MEDPAR) file; the Outpatient Standard Analytic File (OUTPAT); and the National Claims History (NCH) file.

NSAID use by OA Diagnosis

We studied 18,379 patient-physician office visits within NAMCS data over 1993–1994 to determine the magnitude of the association between a diagnosis of OA and NSAID use among the elderly. Specifically, we restricted our analysis to those visits with patients aged 65 or older on the day of the visit. We evaluated the physician diagnostic fields for the presence of ICD-9-CM code 715 indicating "osteoarthritis and allied disorders" and each of the generic medication fields for the presence of 1 of 26 possible NSAIDs (Appendix).

CASE/CONTROL STUDY

Disease Ascertainment

We used the SEER file to identify male and female patients who had been diagnosed with pathologically confirmed stage I–IV adenocarcinoma of the colon or rectum and female patients who had been diagnosed with pathologically confirmed stage I–IV carcinoma of the breast in 1995 (i.e., 1/1/95 to 12/30/95). We included all patients who were at least 68 years of age on 1/1/95, continuously enrolled in both Medicare parts A and B, and not enrolled in an HMO in the 36 months preceding

disease status ascertainment. Date of disease ascertainment was the date of diagnosis for the cases operationalized as the first day of the month (i.e., January–December) and year (i.e., 1995) of diagnosis as reported in SEER. The final analytic sample of cases consisted of 4,599 individuals with CRC and 4,250 individuals with breast cancer.

We used SEER-Medicare's 5% random sample of Medicare patients to identify appropriate control patients (i.e., those without histories of CRC or breast cancer). As we did for cases, we required that controls were at least 68 years of age on 1/1/95, had continuous enrollment in Medicare parts A and B, and were not enrolled in an HMO in the 36 months preceding disease status ascertainment (1/1/92–1/1/95). To ensure that the control group did not include patients with the cancers of interest (i.e., breast and CRC), we restricted our controls to those without either SEER or Medicare diagnoses for CRC or breast cancer in inpatient or ambulatory Medicare files in the 3 years before their inclusion in the analysis. Date of disease ascertainment was January 1, 1995 for all controls. The final analytic sample of controls consisted of 100,270 male and female individuals for comparison to CRC cases and 59,418 female individuals for comparison to breast cancer cases.

Exposure Ascertainment

For each case and control, we used the inpatient and ambulatory files to identify a diagnosis of osteoarthritis (ICD-9-CM 715) in the 36 months preceding disease status ascertainment. Prior work using these codes estimates that the positive predictive value of ICD-9 code 715 for osteoarthritis in the NCH file is 0.83.²⁶ Additionally, files were used to identify the procedure "total knee replacement" (CPT codes 27447, 27487, or 27486 and ICD-9 procedure codes 8154 or 8155) occurring in the 36 months preceding disease status ascertainment in the manner similar to Mahomed et al.²⁷ The procedure total knee replacement (TKR) was evaluated because it has a high correlation with OA.²⁸ For cases, this represented 3 years or 36 months before CRC or breast cancer diagnosis, and for controls, this represented an equivalent calendar period (i.e., 36 months before January 1, 1995).

Other Explanatory Variables

The Medicare denominator file provided information regarding age, sex, and race for cases and controls.

Evaluation of Differential Preventive Care for OA Patients

In addition to our comparison of OA among breast cancer cases and controls, we directly evaluated for the possibility and importance of differential endoscopic removal of polyps among the OA patients compared to non-OA patients. We estimated the proportion of those in our sample with large bowel endoscopy in the 3 years before disease ascertainment according to OA history and then evaluated the robustness of our key models to the addition of antecedent large bowel endoscopy. We operationalized large bowel endoscopy as the presence of CPT codes 44388–44394, 45330–45339, 45378–45385; HCPCS codes G0104, G0105, G0120; and ICD-9 procedure codes 4522–4525, 4542, 4543 in Medicare files.

Statistical Analyses

With NAMCS data, we determined the proportion of patient-physician visits of elderly patients where both NSAIDs and OA were noted. We applied sampling weights provided by the NCHS to adjust survey estimates to the population level. We tested the equivalence of proportion of NSAID use by OA history with a chi-squared test.

With SEER-Medicare data, we calculated the odds of a CRC diagnosis according to whether or not individuals had claims for OA in the 3 years preceding disease status ascertainment. We calculated the odds of a breast cancer diagnosis according to whether or not females had claims for OA in the 3 years preceding disease status ascertainment. We also calculated the odds of a CRC diagnosis according to whether or not individuals had claims for TKR in the 3 years preceding disease status ascertainment. All estimates were adjusted for age, sex, and race. All analyses were performed in STATA 8.0 SE (College Station, Texas).

RESULTS

OA and NSAID Use

Among the 18,379 patient-physician office visits studied, OA was recorded in an estimated 5% of all visits in both years, and an NSAID was recorded in 10% of all visits in both years. In 1993, 39% (95%CI, 32–48%) of visits with a recorded OA diagnosis also had an NSAID drug listed as an active medication. Among the remaining 1993 physician-patient visits (i.e., those where a diagnosis of OA was not recorded for the patient), only 9% (95%CI, 8–10%) had an NSAID drug listed as an active medication. The chi-squared test for the comparison of proportion of NSAID use according to OA status had $p < 0.001$. Results are similar for 1994. Thus, the expected difference in prevalence of NSAID use between visits with OA and visits without OA during these 2 years was 29%.

We then determined the expected NSAID-mediated CRC reduction associated with a diagnosis of OA by applying our estimate of 29% differential use of NSAIDs by OA patients to the reported range of risk reductions from RCTs of polyps. The lower bound of our estimate was 6% (RR 0.94) or 29% of the smallest risk reduction reported (i.e., 0.81)²⁹, and the upper bound was 16% (RR 0.84) or 29% of the largest risk reduction reported (i.e., 0.44).³⁰ Thus, we estimate a diagnosis of OA in the elderly would be associated with a 6–16% decrease in CRC (i.e., RR 0.84–0.94).

Case-Control Study

Of the 104,869 elderly Medicare beneficiaries who were included in the CRC analyses, 4,599 (4.4%) had a diagnosis of CRC and 100,270 (95.6%) were controls. Of the 63,668 elderly female Medicare beneficiaries who were included in the breast cancer analyses, 4,250 (6.7%) had a diagnosis of breast cancer and 59,418 (93.3%) were controls. The characteristics of the cases and controls are displayed in Table 1. Overall, 30.6% (95%CI 30.3–30.9%) of the Medicare beneficiaries studied had at least 1 claim of OA in the 36 months preceding disease ascertainment.

History of OA and CRC

During the 36-month ascertainment period, 1,254 of 4,599 CRC patients (prevalence of 273/1,000) compared with 30,640

Table 1. Characteristics of Colorectal and Breast Cancer Cases and Respective Controls

Variable	CRC Cases n=4,599	CRC Controls n=100,270	P	BC Cases n=4,250	BC Controls n=59,418	P
Age (mean)	78.9	77.2	<0.01	77.9	77.8	0.58
Female (%)	58	59	<0.01	100	100	NA
Race (prop)			<0.01			0.01
White	0.87	0.90		0.90	0.91	
Black	0.07	0.05		0.06	0.05	
Other	0.05	0.04		0.04	0.03	
Unknown	<0.01	<0.01		<0.01	<0.01	
No. of pts w/: Prior OA	1,254 273/ 1,000	30,640 306/ 1,000	<0.01	1,477 348/ 1,000	20,687 348/ 1,000	0.93
Prior TKR	38 8/ 1,000	1,381 14/ 1,000	<0.01	68 16/ 1,000	879 15/ 1,000	0.53

OA Osteoarthritis, TKR total knee replacement, BC breast cancer, CRC colorectal cancer, prop proportion

of 100,270 control patients (prevalence of 306/1,000) had ICD-9-CM codes indicating an antecedent OA (Fisher's exact $p < 0.001$). The unadjusted odds ratio (OR) of an antecedent OA diagnosis among those with newly diagnosed CRC compared to the control group was 0.85 (95%CI, 0.80–0.91), and when adjusted for demographics, the OR was 0.82 (95%CI, 0.77–0.88; Table 2). We evaluated for and found no interaction between sex and OA (results not shown).

History of TKR and CRC

During the 36-month ascertainment period, 38 of 4,599 CRC patients (prevalence of 83/1,000) compared with 1,381 of 100,270 control patients (prevalence of 138/1,000) had ICD-9-CM codes indicating an antecedent TKR (Fisher's exact $p = 0.001$). The unadjusted OR of an antecedent TKR procedure among those with newly diagnosed CRC compared to the control group was 0.60 (95%CI, 0.43–0.82), and when adjusted for demographics, the OR was 0.61 (95%CI, 0.44–0.85; Table 2).

History of OA and Breast Cancer

During the 36-month ascertainment period, 1,477 of 4,250 breast cancer patients (prevalence of 348/1,000) compared with 20,687 of 59,418 female control patients (prevalence of 348/1,000) had ICD-9-CM codes indicating an antecedent OA (Fisher's exact $p = 0.947$). The unadjusted OR of an antecedent OA diagnosis among those with newly diagnosed breast cancer compared to the female control group was 1.00 (95%CI, 0.93–1.06), and when adjusted for demographics, the OR was 0.99 (95%CI, 0.92–1.05; Table 2).

History of TKR and Breast Cancer

During the 36-month ascertainment period, 68 of 4,250 breast cancer patients (prevalence of 16/1,000) compared with 879 of

Table 2. Crude and Adjusted Associations Between Antecedent Osteoarthritis Diagnoses or Procedures in Medicare Data and Subsequent Invasive Breast or Colorectal Cancer Diagnoses in SEER Data (N=104,869)

	Colorectal cancer		Breast Cancer	
	Odds Ratios (95%CI)		Odds Ratios (95%CI)	
	Crude	Adjusted*	Crude	Adjusted*
OA	0.85 (0.80–0.91)	0.82 (0.77–0.88)	1.00 (0.93–1.06)	0.99 (0.92–1.05)
TKR	0.60 (0.43–0.82)	0.61 (0.44–0.85)	1.08 (0.84–1.39)	1.06 (0.82–1.36)

OA Osteoarthritis, TKR total knee replacement

*Adjusted for age, sex (for colorectal patients) and race

59,418 female control patients (prevalence of 15/1,000) had ICD-9-CM codes indicating an antecedent TKR (Fisher's exact $p=0.512$). The unadjusted OR of an antecedent TKR procedure among those with newly diagnosed breast cancer compared to the female control group was 1.08 (95%CI, 0.84–1.39), and when adjusted for demographics, the OR was 1.06 (95%CI, 0.82–1.36; Table 2).

History of Large Bowel Endoscopy and OA

Among the 31,899 patients with antecedent OA diagnoses in Medicare files, 20.2% had any claim consistent with large bowel endoscopy in the 3 years preceding disease status determination compared to only 13.9% among 72,999 patients without antecedent OA diagnoses (chi-squared test $p<0.001$).

While we found that antecedent large bowel endoscopy was itself associated with a 26% reduction in odds of CRC diagnosis (OR 0.74; 95%CI, 0.67–0.81), we also found that its addition to the model only modestly changed the magnitude of the association between antecedent OA and CRC (OR 0.84; 95%CI, 0.78–0.90; see Table 3). Thus, whereas those with histories of OA are more likely to undergo large bowel endoscopy, the association between OA and CRC that we describe does not appear to be mediated by endoscopic polyp removal.

DISCUSSION

We find that elderly Medicare beneficiaries with OA have 15% lower odds of being diagnosed with CRC than those beneficiaries without this diagnosis (OR 0.85; 95%CI, 0.80–0.91). We also find that the magnitude of the odds reduction is similar to what would be expected from the estimated excess use of NSAIDs by those with OA (expected risk reduction 0.84–0.94). The TKR analyses support the association, and the breast cancer and large bowel endoscopy analyses suggest little confounding by differential health care or preventive health behaviors. Taken together, results suggest that NSAID chemoprevention may explain the reduced odds of developing CRC among elderly Medicare beneficiaries with OA.

Our findings have large public health implications, as they support the hypothesis that some portion of the secular decreases in the incidence of CRC over the last 20 years are attributable to secular increases in NSAID use (Lamont and Dias, under review). Since the NSAID ibuprofen was approved by the Federal Drug Administration (FDA) for over-the-counter marketing in 1984, the incidence of CRC has fallen approximately 13%, from 57/100,000 persons in 1985 to 49/100,000

persons in 2002. Given our estimates of 10% NSAID use reported among all elderly patient–physician visits, it is conceivable that as much as 46% of the decrease in CRC incidence (i.e., 6 percentage point absolute reduction) may be related to NSAID use. Further, our results suggest that there is likely a very large, previously occult and apparently accidental force of cancer prevention within the population of elderly Americans that has more to do with symptomatic treatment of a common comorbidity associated with aging than with physicians' purposeful targeted anticancer intervention. However, given well-described risks associated with NSAIDs (e.g., bleeding, kidney damage), we agree with the United States Preventative Services Task Force that NSAIDs should not be used by average risk individuals with the intent of preventing CRC.³¹ Whereas routine use of NSAIDs for CRC prevention is currently limited only to a small group of individuals with high risk of CRC (e.g., those with familial CRC syndromes), this research does support the importance of further pharmacologic research directed at developing less toxic preventive agents whose risk and benefit profile would support broader use by lower risk individuals.

Our findings are consistent with prior studies reporting variation in CRC risk by sex and race. Relative to men, women had 16% lower odds of being diagnosed with CRC, which is similar to results from the national endoscopy database and likely relate to protective effects of endogenous and exogenous [e.g., hormone replacement therapy (HRT)] estrogens.³² Our finding of 46% higher odds of developing CRC for blacks relative to whites is consistent with multiple previous reports.^{33–35}

A comparative advantage of this study over more traditional observational studies on this topic is that it minimizes confounding related to preventive medical care. For example, among cohorts of otherwise healthy individuals, aspirin use for persons aged 50 and older may be a marker of high-quality preventive care, and thus, negative associations between this NSAID and subsequent CRC may be confounded by a variety of factors including low-fat diet, exercise, and cancer screening. Because we focus on patients who are taking NSAIDs for

Table 3. Multivariable Regression Results for Odds CRC Diagnosis With and Without History of Endoscopy

Variable	OR	95%CI	OR	95%CI
History of OA	0.82	0.77–0.88	0.84	0.78–0.90
History of Large Bowel Endoscopy	–	–	0.74	0.67–0.81
Age				
68–69	1.00	Referent	1.00	Referent
70–79	2.34	2.04–2.68	2.33	2.02–2.66
80–89	3.40	2.95–3.91	3.37	2.89–3.82
90–99	3.40	2.84–4.08	3.32	2.70–3.89
100–110	2.77	1.28–5.98	2.67	1.20–5.59
Sex				
Male	1.00	Referent	1.00	Referent
Female	0.84	0.79–0.89	0.83	0.79–0.89
Race				
White	1.00	Referent	1.00	Referent
Black	1.46	1.30–1.65	1.46	1.29–1.64
Other	1.45	1.27–1.65	1.43	1.26–1.63
Unknown	0.68	0.41–1.13	0.68	0.41–1.12

OA Osteoarthritis

*The table displays results of two multivariable logistic regression models (all covariates are shown) that estimate the odds of colorectal cancer diagnosis among elderly Medicare beneficiaries.

management of pain from OA and not prevention, there is less worry that our exposure is conflated with preventive care. While we have taken a different approach that minimizes this problem, there are limitations to this approach (see below) that are not present in more traditional cohort studies. Yet, that we find a consistent magnitude of effect to those studies adds further evidence that this is likely a causal association.

There are limitations to the study related to the data sources. With respect to the NAMCS data, the sampling frame includes the entire US (not just SEER regions), information pertains to ambulatory visits by individuals who seek medical care, and the unit of analysis is distinct patient–physician encounters, not necessarily distinct patients, which could lead us to underestimate the size of the confidence by failing to account for the clustering of encounters within individual patients. Further, type, dose and duration of NSAID use are not available in this data source. Limitations to Medicare data include shortcomings in race coding, inconsistent information on HMO enrollees, and lack of certain relevant clinical variables (e.g., smoking history, family history, fat intake, obesity, physical activity, HRT).^{36–39} Given that prior research has shown that HRT use is more common among women with OA than women without OA, our results, showing a lack of a sex/OA interaction, is reassuring on this matter.⁴⁰ Similarly, given that prior research has shown that individuals with OA are more likely to smoke, to have high body mass indexes, and be inactive, we would expect these unmeasured confounders to spuriously attenuate the CRC–OA association (i.e., favor the null hypothesis of no association).^{41–43} Finally, the 3-year look-back that we impose is not long enough to fully track CRC screening.

In summary, analysis of observational data sources show that elderly Medicare beneficiaries with histories of OA are less likely to be diagnosed with invasive CRC relative to those without histories of OA. Furthermore, the magnitude of the CRC odds reduction associated with a diagnosis of OA is consistent with what would be expected from the observed greater use of NSAIDs among elderly individuals with OA. This research suggests that NSAIDs may be effective in the prevention of CRC in the population of elderly Medicare beneficiaries.

Acknowledgments: This study used the linked SEER-Medicare Database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Information Services and the Office of Strategic Planning, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The authors thank participants of the Dana-Farber/Harvard Cancer Center Cancer Outcomes Program seminar for comments and suggestions regarding the analyses and Drs. Nicholas Christakis, David Cutler, Jack Iwashyna, Steve Joffe, Mary Beth Landrum, and Alan Zaslavsky for methodologic advice and comments on the manuscript. The authors also thank Susan Schappert of the National Center for Health Statistics and Dr. Jeff Linder for statistical advice regarding the NAMCS data files. This research was supported by a grant from the National Cancer Institute (EBL, grant K07 CA93892).

Conflict of Interest: None disclosed.

Corresponding Author: Elizabeth B. Lamont, MD, MS; Departments of Medicine and Health Care Policy, Harvard Medical School, 180A Longwood Ave, Boston, MA 02115, USA (e-mail: lamont@hcp.med.harvard.edu).

APPENDIX

Table 4. NAMCS Generic Drug Names and Codes Defined as NSAIDs

NAMCS Generic Drug Name	NAMCS Generic Drug Code
Aspirin	50410
Celecoxib	70002, 70169
Choline Salicylate	51200, 70596
Diclofenac	57082, 80004
Diffunisal	51763, 94113
Etodolac	52186
Fenoprofen	52220
Flurbiprofen Sodium	52353
Ibuprofen	52730
Indomethacin	52770
Ketoprofen	52978
Ketorolac Tromethamine	92502
Meclofenamate	53277, 53278
Meloxicam	70121
Nabumetone	56525, 94179
Naproxen	53880, 70222, 94125
NSAID	94072
Oxaprozin	57086
Phenylbutazone	54450
Piroxicam	54528
Rofecoxib	70026
Salsalate	55165
Sulindac	55615
Tolmetin	55885
Valdecoxib	70425
Zomepirac	56275

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin.* 2005;55(1):10–30.
2. Janne P, Mayer R. Chemoprevention of colorectal cancer. *N Engl J Med.* 2000;342:1960–8.
3. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology.* 1994;107:1183–8.
4. Fujita T, Matsui M, Takaku K, et al. Size- and invasion-dependent increase in cyclooxygenase 2 levels in human colorectal carcinomas. *Cancer Res.* 1998;58:4823–6.
5. Labayle D, Fischer D, Vielh P, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology.* 1991;101(3):635–9 (Sep).
6. Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg.* 1993;80(12):1618–9 (Dec).
7. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med.* 1993;328(18):1313–6.
8. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med.* 2000;342(26):1946–52.
9. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med.* 2003;348:883–90.
10. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med.* 2003;348:891–9.
11. Chan AT, Giovannucci EL, Schernhammer ES, et al. A prospective study of aspirin use and the risk for colorectal adenoma. *Ann Intern Med.* 2004;140:157–66.
12. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *J Natl Cancer Inst.* 1991;83:355–8.

13. **Sansbury LB, Millikan RC, Schroeder JC, Moorman PG, North KE, Sandler RS.** Use of nonsteroidal antiinflammatory drugs and risk of colon cancer in a population-based, case-control study of African Americans and Whites. *Am J Epidemiol.* 2005;162(6):548-58.
14. **Thun MJ, Namboodiri MM, Heath CW Jr.** Aspirin use and reduced risk of fatal common cancer. *N Engl J Med.* 1991;325:1593-6.
15. **Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC.** Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann Intern Med.* 1994;121(4):241-6.
16. **Giovannucci E, Egan KM, Hunter DJ, et al.** Aspirin and the risk of colorectal cancer in women. *N Engl J Med.* 1995;333(10):609-14.
17. **Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS.** Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA.* 2005;294(8):914-23.
18. **Sturmer T, Glynn RJ, Lee I-M, Manson JE, Buring JE, Hennekens CH.** Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. *Ann Intern Med.* 1998;128:713-20.
19. **Cook NR, Lee IM, Gaziano JM, et al.** Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA.* 2005;294(1):47-55.
20. **Sturmer T, Buring JE, Lee IM, Kurth T, Gaziano JM, Glynn RJ.** Colorectal cancer after start of non-steroidal anti-inflammatory drug use. *Am J Med.* 2006;119(6):494-502.
21. **National Center for Health Statistics.** NAMCS description. Available at: <http://www.cdc.gov/nchs/about/major/ahcd/namcsdes.htm>. Accessed January 22, 2007.
22. **National Center for Health Statistics.** NAMCS data collection and processing. <http://www.cdc.gov/nchs/about/major/ahcd/impnam.htm>. Accessed April 4, 2007.
23. **National Cancer Institute.** SEER-Medicare linked database. Available at: <http://healthservices.cancer.gov/seermedicare/>. Accessed January 22, 2007.
24. **National Cancer Institute.** SEER: surveillance epidemiology and end results. Available at: <http://seer.cancer.gov/>. Accessed January 22, 2007.
25. **Hatten J.** Medicare's common denominator: the covered population. *Health Care Financ Rev.* 1980;53-64.
26. **Katz JN, Barrett J, Liang MH, et al.** Sensitivity and positive predictive value of Medicare part B physician claims for rheumatologic diagnoses and procedures. *Arthritis Rheum.* 1997;40(9):1594-600.
27. **Mahomed NN, Barrett J, Katz JN, Baron JA, Wright J, Losina E.** Epidemiology of total knee replacement in the United States Medicare population. *J Bone Jt Surg.* 2005;87A(6):1222-8.
28. **Quam JP, Michet CJ, Wilson MG, et al.** Total knee arthroplasty: a population-based study. *Mayo Clin Proc.* 1991;66(6):589-95.
29. **Baron JA, Cole BF, Sandler RS, et al.** A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med.* 2003;348:891-899.
30. **Giardiello FM, Hamilton SR, Krush AJ, et al.** Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med.* 1993;328(18):1313-6.
31. **U.S. Preventive Services Task Force.** Aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer. <http://www.ahrq.gov/clinic/uspstf/uspstfasc.htm>. Accessed April 4, 2007.
32. **McCashland TM, Brand R, Lyden E, de Garmo P.** Gender differences in colorectal polyps and tumors. *Am J Gastroenterol.* 2001;96:882-6.
33. **Troisi RJ, Freedman AN, Devesa SS.** Incidence of colorectal carcinoma in the U.S. *Cancer.* 1999;85:1670-6.
34. **Anderson WF, Umar A, Brawley OW.** Colorectal carcinoma in black and white race. *Cancer Metastasis Rev.* 2003;22:67-82.
35. **Parker SL, Davis KJ, Wingo PA, Ries LA, Heath CW Jr.** Cancer statistics by race and ethnicity. *CA Cancer J Clin.* 1998;48:31-48.
36. **Lauderdale DS, Goldberg J.** The expanded racial and ethnic codes in the Medicare data files: their completeness of coverage and accuracy. *Am J Public Health.* 1996;86(5):712-6.
37. **Fisher ES, Baron JA, Malenka DJ, Barrett J, Bubolz TA.** Overcoming potential pitfalls in the use of Medicare data for epidemiologic research. *Am J Public Health.* 1990;80:1487-90.
38. **Mitchell JB, Bubolz T, Paul JE, et al.** Using Medicare claims for outcomes research. *Med Care.* 1994;32:JS38-51.
39. **Lauderdale D, Furner SE, Miles TP, Goldberg J.** Epidemiological uses of Medicare data. *Epidemiol Rev.* 1993;15(2):319-27.
40. **Cooley HM, Stankovich J, Jones G.** The association between hormonal and reproductive factors and hand osteoarthritis. *Maturitas.* 2003;45(4):257-65.
41. **Amin S, Niu J, Guermazi A, et al.** Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. *Ann Rheum Dis.* 2007;66(1):18-22.
42. **Ding C, Cicuttini F, Scott F, et al.** Natural history of knee cartilage defects and factors affecting change. *Arch Intern Med.* 2006;166(6):651-8.
43. **Hirata S, Ono R, Yamada M, et al.** Ambulatory physical activity, disease severity, and employment status in adult women with osteoarthritis of the hip. *J Rheumatol.* 2006;33(5):939-45.