THE RISK-BENEFIT PROFILE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) AS CHEMOPREVENTIVES

by

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(Under the Direction of Bradley C. Martin)

ABSTRACT

Numerous experimental, epidemiological and clinical trails have suggested non-steroidal anti-inflammatory drug(NSAID) usage potentially reduces the risk of developing cancers. Since NSAIDs are relatively inexpensive, NSAIDs may offer a possible strategy to reduce the burden of cancer. However, before NSAIDs canbe considered as chemopreventives, their potential benefit must be weighed against the risks of their adverse events.

We purposed to establish the risk-benefit profile of NSAIDs as chemopreventives against solid tumor cancers i.e.digestive, lung, breast, gynecologic, prostate and urinary tract cancers. We sought to determine any association between NSAID usage and incident cancers, as well as NSAID-related gastrointestinal(GI) and renal adverse events.

Two separate retrospective cohort studies were conducted using Georgia(GA) and North Carolina(NC) Medicaid claims. Medicaid recipients aged 50-100 who had at least 2 years continuous eligibility were analyzed. We excluded subjects, who had any diagnoses of cancer, GI, or renal diseases within their first year of eligibility. Cohorts members were followed until the earliest occurrence of:(1)outcomes of interest:cancers, GI events(i.e.GI ulcers and hemorrhage) and renal events(e.g.renal failure),(2)loss of eligibility,(3)death, or (4)end of study

(December 31,2001 for GA cohort; December 31,1998 for NC cohort). All outcome occurrences were determined by searching for claims with indicative ICD-9-CM codes. NSAID exposure was identified by searching the National Drug Code in the prescription files. For each NSAID prescription, the strength and prescribed quantifies were kept to further explore a dose-response relationship. Survival Analysis was used to calculate all relative risks.

The significant chemopreventive benefit of NSAIDs was established against colorectal, esophageal, lung, prostate, and endometrial cancer. Besides no correlation between incidence rate of pancreatic cancer and NSAID usage, any NSAID exposure was possibly associated with the risk reduction in breast, lung, gastric, liver, gynecologic and urinary tract cancers. There was no increased risk of GI or renal adverse effects with NSAID prescribing in this population. The dose-response relationship between NSAID use and incident cancer, as well as their adverse events was delineated. The higher the cumulative exposure, the lower the incident cancer and NSAID adverse event risks. Further research is needed since questions about optimal chemopreventive dose schedule of NSAIDs are unanswered.

INDEX WORDS: Risk-Benefit Profile, Non-Steroidal Anti-Inflammatory Drugs, NSAIDs, Aspirin, Cox-2 Inhibitors, Chemoprevention, Cancer

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To my parents, Kitichai and Lakana Koompalum, whose love and support are reassuring.

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CHAPTER 1

INTRODUCTION AND SPECIFIC AIMS

Background

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are among the most popular, relatively inexpensive, and widely used drugs because of their many therapeutic applications: anti-inflammatory, anti-pyretic, analgesic, and the cardiovascular benefits of aspirin. There is growing evidence that NSAIDs may reduce the incidence of some cancers, particularly for colorectal cancer (CRC). NSAIDs may offer a possible strategy to reduce the worldwide burden of cancer. Before a strategy of widely advocating the use of NSAIDs to prevent various cancers can be considered, we need a better understanding of the risk-benefit profile of NSAIDs. The potential benefit of NSAID usage on many types of cancers must be weighed against the risks of NSAID-induced adverse events, which primarily include gastrointestinal (GI) and renal impairments.

Protective effects of NSAIDs against CRC has been robustly demonstrated. It is estimated that NSAID users are 33% to 67% less likely to be diagnosed with CRC than nonusers {Friedman 1998, Rosenberg 1998, Smalley 1999, Giovannucci 1994, Garcia-Rodriguez 2001, Collet 1999, Giovannucci 1995, Gridley 1993, Kune 1998, Muscat 1994, Peleg 1994, Rosenberg 1991, Baron 2003, Sandler 2003}. A recent prospective study confirmed that both short-term and long-term regular use of aspirin is inversely associated with risk of colorectal adenoma, especially at higher doses {Chan 2004}. Additionally, a Cochrane review concluded that the risk of recurrent sporadic adenomatous polyps reduced by 23% after 1-3 years of aspirin usage

{Asano and McLeod 2004}. Despite promising findings of NSAIDs' protective effect against CRC, there are not many studies examining the possible effects of NSAID use on the risk of other cancers. A meta-analysis of 9 studies revealed a statistically significant reduction in esophagus cancer in persons who had any NSAID use {Corley 2003}. A weaker 20% risk reduction between NSAID use and breast cancer was reported in a meta-analysis of 14 studies {Khuder 2001}, the Long Island population-based case-control study {Terry 2004} and the Iowa Women's Health Cohort study {Johnson 2002}. Evidence for chemoprevention of lung cancer is controversial. While some studies found no relationship between NSAID use and lung cancer {Paganini-Hill 1989}, others have found that NSAIDs can reduce the risk of lung cancer by 32-47%{Schreinemachers 1994, Muscat 2003, Moysich 2002, Thun 1993}, and a 68% risk reduction in smokers {Harris 2002}. The possible effect of NSAIDs on prostate cancer has not been widely studied. Some studies found no connection between NSAID use and prostate cancer {Leitzmann 2002} and some suggested increasing risk {Friis 2003, Langman 2000, Sorensen 2003}. Nonetheless, Nelson & Harris {Nelson 2000} observed a strong chemoprevention role of NSAIDs with 65% prostate cancer risk reduction. Limitations of the previous studies, particularly for the case control studies, include potential recall bias when NSAID use was self-ascertained. Furthermore, since there are inconsistencies in establishing the dose or duration, measurement of known confounders and types of confounders adjusted for in these analyses, definitive conclusion of association is impossible to make.

One of the remaining questions is the effect of dose, duration, and recency of NSAID use on any chemopreventive effect. Evidence of dose-response relationship between NSAID doses and duration and cancer risk are still inconclusive. Some evidence suggests that the benefit of NSAIDs would subside after it is discontinued {Rosenberg 1998, Garcia-Rodriguez 2001,

Smalley 1999, Giovannucci 1994}. In other words, pharmacologically, any chemopreventive effect may be reversible due to the reversible inhibition of COX enzymes of most NSAIDS or reproduction of COX enzymes in target tissue when aspirin is used. For example, the CRC risk was similar in non-NSAID users and NSAID users, who discontinued NSAID use for 60 days {Garcia-Rodriguez 2001} to 1 year {Friedman 1998}.

The well-documented adverse effects of NSAIDs, which include gastrointestinal (GI) complications (i.e. GI bleeding, perforation, and ulcer) and renal complications (i.e. acute renal failure), limit of the potential use of NSAIDs as chemopreventives. The risk of NSAID related GI complications is 3-5 times more likely in NSAID users {Ofman 2002}. However, several studies have shown evidence that the risk for NSAID associated GI events is highest at the initiation of a regimen and then the risk tapers over time {Gabriel 1991, Garcia Rodriguez 1998, Smalley 1995}. Several observational studies have similarly reported decreasing risks of GI complications when NSAIDs were taken over longer durations {Garcia Rodriguez 1998, Smalley 1995}. For instance, among current users, the constant risk of GI complications during the first year of NSAID use and was roughly 7 times more likely than non-users {Garcia Rodriguez 1998}. The risk of GI complications, however, was cut nearly half for NSAID exposure >1 year. (RR, 3.5; 95%CI, 2.0-6.0) {Garcia Rodriguez 1998}. Gastric mucosal adaptation has been reported in both animal and human studies and may account for the decreasing risk of NSAID exposure over time {Fitzpatrick 1999, Lipscomb 1996}. Unlike NSAIDs, selective COX-2 inhibitors are associated with fewer GI ulcer complications than NSAIDs {Buttgereit 2001}.

Another major complication of NSAIDs involves deterioration in renal function, i.e. acute renal failure, chronic renal failure, and end-stage renal disease, especially in persons with pre-existing impaired renal function {Henry 1992}. Griffin and colleagues reported that persons

who currently use NSAIDs were almost 1.6 times more likely to be hospitalized for acute renal failure than ones who never used NSAIDs {Griffin 2000}. Although the highest risk was within first 30 days of use, the risk was similar in those who discontinued NSAID use for at least 30 days {Griffin 2000}. Regular use of NSAID also increased the risk of chronic renal failure 2.5 fold {Fored 2001}. Similarly, the risk of ESRD rose with higher cumulative doses of NSAIDs {Perneger 1994}. In contrast, the surprising results of the Physician's Heath Cohort study showed no association between self-reported cumulative NSAID uses over 14 year and risk of renal dysfunction in men {Rexrode 2001}.

Specific Aims

The goal of this study was to establish the risk-benefit profile of NSAIDs as chemopreventive agents against an array of cancers. We first sought to address this objective by conducting an exploratory study to identify any associations between NSAID usage and incident cancer in an array of solid tumors. For cancers for which NSAIDs had been previously studied (colorectal, lung, prostrate, and breast cancer), we aimed to confirm the potential chemopreventive benefit of NSAIDs and explore any dose-response relationship between NSAID use and incident cancer, as well as their common adverse events. In addition, we intended to delineate NSAID dose and duration effects on cancer incidence. We believe that information gathered from this may be used to motivate future controlled trials with these drugs as potential cancer prevention agents or influence future physicians' decisions regarding the use of NSAID in persons at risk for developing various cancers.

A Georgia Medicaid administrative claims databases were exploited to identify a cohort of persons 50-100 years of age with no history of cancer, and to retrieve NSAID utilization during period of study (1990–2001). To address the shortcomings of the exploratory analyses, our result was validated in an independent cohort built from North Carolina Medicaid recipients (1990–1998). Because our study was among the first to incorporate 2 independent data sources for similar populations (one to explore associations and the other to confirm associations), it was possible to gauge the validity and usefulness of these types of analyses using Medicaid claims data.

The Specific Aims of the research were to:

1) Determine whether the incidence of colorectal, lung, breast and prostate, among persons taking NSAIDs or COX-2-inhibitors are different than those not exposed to either NSAIDs or COX-2-inhibitors.
   A) Determine whether there is a dose-response relationship between NSAID exposure and colorectal, lung, breast and prostate cancer incidence
   B) Discover optimal dose and duration of NSAIDs as cancer chemopreventive agents
2) Determine whether the incidence of adverse events, namely GI and renal complications, among persons taking NSAIDs or COX-2-inhibitors are different than those not taking NSAIDs or COX-2-inhibitors.
   A) Determine whether there is a dose-response relationship between NSAID exposure and incidence of GI and renal complications
3) Explore whether use of NSAIDs and COX-2-inhibitors is associated with the incidence of cancer of the following sites: stomach, esophagus, liver, pancreases; bladder; kidneys; ovaries, cervix, and endometrium.

After this study successfully meets mentioned specific aims, these findings can then be used to inform researchers wishing to use similar claims data to identify other drugs or medical technologies that may influence various cancer incidences and or cancer mortality. Medicaid claims data are increasingly being used as a source for pharmacoepidemiologic studies because of the potential for long term follow up combined with well-established linkages between enrollment, medical and pharmacy encounter claims. By establishing and confirming associations between NSAID use and various cancers in this study, these findings can be used as evidence of the validity of these types of studies to seek out other drugs that may protect or increase the risk of various cancers.

Because this study was integrating both risks and benefits of NSAIDs and COX-2 inhibitors as primary and secondary prevention of various types of cancer, this study may motivate future clinical trials and influence physician prescribing behavior. Also, this study can also be used to provide estimates that can be inputted into cost-effective and decision-making indices to determine the value of NSAIDs as chemopreventive agents.

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CHAPTER 2

BACKGROUND AND SIGNIFICANCE

Cancer

Nearly 1.4 million Americans will be newly diagnosed of cancer and over half a million Americans will die of it in 2004. The cancer death rate is second only to that of cardiovascular disease {American Cancer Society 2004}. Cancer also poses an economic burden to the health care system, which stems from expensive medical costs, lost of productivity due to illness and lost of productivity due to premature death with an estimated total cost of $US 189.5 billion {American Cancer Society 2004}.

Cancer incidence increases with age for each race-gender group (Figure 2.1). For both males and females, cancer risks increase substantially after age 50, however the increase in incidence is much more pronounced for males. The most common cancer sites, accounting for more than 50% of new cases and deaths, include colorectal, prostate, breast and lung/bronchus cancer {American Cancer Society 2003}.

Cyclooxygenase and Carcinogenesis

Cancer is a result of a conglomeration of genetic mutations {American Cancer Society 2003}. Both intrinsic factors, such as inherited mutations, hormone and immune conditions, and extrinsic factors, including smoking, nutrition, and physical inactivity {American Cancer Society 2003}, alter a cell's DNA in 3 ways {Lynch 2002}: gain-of-function, i.e. activation of growth

promoting; loss-of-function, i.e. growth inactivation of tumor suppressor genes and apoptosis; and epigenetic alterations, i.e. aberrant gene expression and silencing.

Carcinogenesis is hypothesized to be a multi-step process starting with a genetic mutation progenitor {Lynch 2002}. The more the progenitor or its daughter cells replicate, the greater the probability of additional genetic alteration is. This is called a clonal expansion. A clonal expansion results in pre-malignant lesions and ultimately progress to malignant tumors. Traits of malignant transformation include uncontrolled cell growth, evasion of apoptosis, inductions of angiogenesis, severe genomic instability, local invasiveness and distant metastases {Lynch 2002}.

Although various pathways of carcinogenesis have been researched, prostaglandin biosynthesis and carcinogenesis is the most widely studied {Marks 1999}. Cyclooxygenase (COX) enzymes play a crucial role in prostaglandin biosynthesis by converting arachidonic acid (AA) to prostaglandins (PG) and thromboxanes (TX) {Morrow 2001}. There are two isoforms of the COX enzymes, COX-1 and COX-2, which are characterized by their physiological function and distribution in the body {Chan 2002, Janne 2000}. COX-1 is expressed continuously in most normal cells and tissues. It functions as a physiological regulator, i.e. gastrointestinal (GI) mucosa maintenance and platelet aggregation {Chan 2002}. In spite of its incessant expression in some kidney and brain areas, COX-2 is inducible during tissue damage, inflammatory responses, and carcinogenesis {Chan 2002}; it is induced by cytokines, growth factors, mitogens, and inflammatory processes {Chan 2002, Janne 2000, Roberts 2001}. Oncogenes and tumor promoters can also induce COX2 expression, which consequently induces tumor formation and progression {Subbaramaiah 2003}.

Elevation of COX expression, both isoforms, commonly occurs in cancerous tissues {Marks 1999}, as shown in Table 2.1. Although most premalignant and malignant tissue demonstrated overproduction of COX-2 enzymes {Subbaramaiah 2003}, COX-1 enzyme overexpression has also been found in ovary carcinomas {Dore 1998, Gupta 2003}.

The link between COX enzyme, especially COX-2, and carcinogenesis is observed in genetic studies. For example, development of mammary tumors was detected with high frequency in female mice with enhanced human COX-2 gene in mammary gland {Liu 2001}. Consistent with this study, mice with COX-2 overexpression in skin developed epidermal hyperplasia and dysplasia, typical signs of premalignant lesion {Neufang 2001}. Furthermore, induction of apoptosis of cancer cells and inhibition of tumor formation has been demonstrated in animals genetically depleted of the COX-2 gene and those administrated COX-2 inhibitors {Subbaramaiah 2003, Xu 2002}. For instance, mice with depleted COX-2 gene attenuated growth of intestinal tumors {Oshima 1996}. Elevations of COX-1, not COX-2, protein and mRNA were detected in ovarian cancer tissue samples. COX1 deficiency, as well as administrated COX-1 inhibitors, also protects against the formation of intestinal and skin tumors {Chulada 2000, Kitamura 2002}. Therefore, based on extensive evidence from genetic and pharmacological studies, it is possible that the decrease of prostaglandin levels results in a reduction of the rate of tumor creation, growth, and metastases {Subbaramaiah 2003}. Hence substances, which interfere with prostaglandin biosynthesis, may reduce the incidence of cancer.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

A principal mechanism of action of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), including aspirin (ASA) and non-aspirin NSAIDs (NANSAIDs), and selective COX-2 inhibitors is inhibition of COX enzymes by competing with arachidonic acid at the active site of cyclooxygenase {Roberts 2001}.

There are several potential mechanisms by which NSAIDs contribute to apoptosis, programmed cell death {Dannenberg 2001, Chan 2002}. Due to inhibition of COX enzymes, an increase of arachidonic acid triggers an upsurge of sphingomyelinase, which converts sphingomyelin to ceramide, a potent inducer of apoptosis {Chan 2002, Greenwald 2002}. NSAIDs also promote a failure in nuclear factor kappa B (NF-κB) activation by blocking the release of IκB from NF-κB, which possibly leads to apoptosis; NF-κB promotes cell survival and enhances proliferation {Chan 2002, Janne 2000}. Binding with the peroxisome-proliferator-activated receptor delta (PPARδ), NSAIDs interfere with the binding of the PPARδ to DNA {He 1999, Janne 2000}. As a result an affected cell is left unable to transcribe the genes necessary for its survival {He 1999}.

In addition to apoptosis, other possible chemopreventive mechanisms of NSAIDs include inhibition of angiogenesis and activation of PPAR gamma (PPARγ). Since oxygen and nutrient supplies are crucial to cell survival, tumor cells stimulate angiogenesis, the expansion of new capillaries, to ensure their growth {Dannenberg 2001, Iniguez 2003}. Substantial studies suggest that COX-2 inhibitors have an ability to block the production of angiogenic factors and inhibit the migration of vascular endothelial cells {Iniguez 2003}. Even though COX-1 demonstrates a role in angiogenesis, particularly in intestinal polyposis {Chulada 2000} and ovarian carcinoma {Gupta 2003}, Masferer and colleagues observed that selective COX-1 inhibitors were unable to

suppress vasculature formation {Masferrer 2000}. Potential chemoprevention of PPARγ activation has been demonstrated in various cancer models, i.e. mammary gland, prostate, colon {Kopelovich 2002}. When PPARγ is activated, tumor cells stop growth and proliferation, as well as cell differentiation {Kopelovich 2002}. NSAIDs can bind and activate PPARγ {Lehmann 1997}, and thus modulate cell growth, proliferation and differentiation.

NSAID epidemiology

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) have long been used to relieve mild to moderate pain, fever and reduce inflammation. The National Health and Nutrition Examination Survey (NHANES) III estimates that proportion of the U.S. population aged 17 and over reporting monthly use of over-the-counter aspirin and ibuprofen are 37.6% and 24.2%, respectively, whereas 6.4% of them use prescription NSAIDs {Paulose-Ram 2003}.

Age and gender play an important role in prevalence of NSAID utilization. Based on NHANES data from 1994-1998, prevalence of OTC analgesic utilization was significantly greater in females than males across all ages {Paulose-Ram 2003}. For both genders, younger adults (17-44 years) were more likely to use ibuprofen, whereas older counterparts were more likely to use aspirin. While aspirin was used more in men (40%) than women (36%), ibuprofen was used more in women (29%) than men (19%). Although prescription NSAID use increased with age for both genders, females (8%) were more likely to use prescription NSAIDs (males; 5%).

NSAIDs and Chemoprevention of Cancer

Colorectal cancer

Colorectal cancer is the third most common cancer. Estimated new cases and deaths of colorectal cancer in year 2003 are 147,500 and 57,100 Americans, respectively {American Cancer Society 2003}. There are several factors thought to be contributing to the development of CRC {American Cancer Society 2002}. In addition to advanced age, CRC risk factors include family history of colorectal cancer or polyps and a history of inflammatory bowel disease. A person's lifestyle and health behaviors, such as smoking, alcohol consumption, obesity, dietary intakes and physical inactivity, are importantly associated with colorectal cancer risk as summarized in Table 2.2.

The potentially protective effect of NSAIDs against CRC has been robustly demonstrated in epidemiological studies in different populations and NSAID exposure measurement {Friedman 1998, Rosenberg 1998, Smalley 1999, Giovannucci 1994, Garcia-Rodriguez 2001, Collet 1999, Giovannucci 1995, Gridley 1993, Kune 1998, Muscat 1994, Paganini-Hill 1991, Paganini-Hill 1995, Peleg 1994, Rosenberg 1991}, as well as in two recent randomized, controlled trials (RCTs) {Baron 2003, Sandler 2003}. It is estimated that NSAID users are 33% to 67% less likely to be diagnosed with CRC {Friedman 1998, Rosenberg 1998, Smalley 1999, Giovannucci 1994, Garcia-Rodriguez 2001, Collet 1999, Giovannucci 1995, Gridley 1993, Kune 1998, Muscat 1994, Peleg 1994, Rosenberg 1991, Friis 2003, Sorensen 2003}.

Two randomized, controlled trials examining the protective effect of aspirin against colorectal adenomas were recently published in New England Journal of Medicine. Baron and colleagues examined the protective effect of aspirin against colorectal adenomas by randomly

assigning patients with recent history of adenoma to one of 3 treatment arms: aspirin 325mg/day, aspirin 81mg/day and placebo {Baron 2003}. Of 1121 randomized patients, 97% underwent a follow-up colonoscopy examination; average duration of follow-up was 33 months. Colorectal adenoma were found in 47 % of the patients in the placebo group, 38% of those given 81mg/day, and 45% of those given 325mg/day. After adjusting for covariates, the relative risk, compared with placebo, were 0.83 (95%CI, 0.70-0.98) and 0.95 (95%CI, 0.80-1.12) in the 81mg and 325mg group, respectively. They concluded that aspirin reduced the risk of recurrent adenomas among patients with a recent history of adenoma. The study also found that GI bleeding rates trended higher in both aspirin groups than in the placebo group, but the differences were not significant. The effect of aspirin on recurrent of colorectal adenomas in patients with previous colorectal cancer, was investigate by randomly assigning patients with previous colorectal cancer to either aspirin 325mg/day or placebo group {Sandler 2003}. Of 635 randomized patients, 81% had at least one colonoscopic examination and median duration of follow up was 31 months. Colorectal adenomas were found in 17% of the aspirin group, which was significantly lower than 27% found in the placebo group. After adjustment for covariates, patients given 325mg/day aspirin were less likely to have a new adenoma than those given placebo. (RR, 0.65; 95%CI, 0.46-0.91). They also found that aspirin delayed the development of adenomas. Similar rates of adverse effects were seen in both groups.

In the US Physicians Health Study, 22,071 male physicians with no history of cancer were randomly assigned to 325mg of aspirin every other day or to placebo. After a mean duration of follow-up of 5 years, the relative risk of colorectal cancer in aspirin group was 1.1 (95%CI: 0.8-1.5) {Sturmer 1998}. No associations between aspirin use and CRC incidence were found. Since the aspirin dose used in this study (975mg/week) were similar to ones used in Baron and Sandler et al (567-2275mg/week), this may suggest continuous duration of use may have been insufficient for the expected effect to be observed.

Breast cancer

Breast cancer is the most common cancer among American women {Jemal 2003}. Risk factors of developing breast cancer are summarized in Table 2.3. In addition to family history, reproductive events are recognized to affect the risk of breast cancer. Early age at menarche, late menopause, older age at first birth, and nulliparous increase risk of breast cancer. Moreover, dietary consumption of fat and alcohol is reported to be weakly positively correlated with breast cancer risk {Hunter 1996, Hamajima 2002}.

Despite promising findings of NSAIDs' protective effect against CRC, a weaker association between NSAID use and breast cancer has been reported. Khuder and colleagues conducted a meta-analysis of 14 studies to examine the chemopreventive property of NSAIDs against breast cancer {Khuder 2001}. The meta-analysis included 7 studies that showed no effect and 7 studies that did. As a result, it concluded that the risk of breast cancer is reduced by nearly 20% (OR, 0.82; 95% CI, 0.75-0.89). Aspirin use was associated with a 20-30% risk reduction on breast cancer; the estimated odd ratios were 0.79 (95% CI, 0.59-1.06) for cohort,

and 0.70 (95% CI, 0.61-0.81) for case-control studies. A connection between non-aspirin NSAID use and risk of breast cancer was not reported in the meta-analysis. There were insufficient data to estimate effect of either duration or frequency of NSAID use on the risk of breast cancer. Nonetheless, Harris and colleagues suggested that risk of breast cancer reduced significantly when women took any NSAIDs at least 3 times per week for at least 1 year {Harris 1996, Harris 1999}. The protective effect of NSAID use appears to wane after discontinued use for more than 1 year {Cotterchio 2001}.

Consistent with the meta-analysis, the Iowa Women's Health Cohort study (RR, 0.80; 95% CI, 0.67-0.95) and the Long Island population-based case-control study (RR, 0.80; 95% CI, 0.66-0.97), not included in the meta analysis, confirmed the protective property of NSAIDs against breast cancer {Johnson 2002, Terry 2004}. It also presented evidence of an inverse relationship between frequency of aspirin use and risk of breast cancer (p trend <0.001) {Johnson 2002}.

Lung Cancer

Lung cancer is the second most common cancer diagnosed in the United States and the leading cause of death in both men and women, accounting for 13% of all cancers and 28% of all cancer deaths {American Cancer Society 2003}. The incidence of lung cancer in a given population largely reflects its prevailing smoking habit; 87% of all lung cancer deaths are attributable to smoking {Centers for Disease Control and Prevention 1993}. Although cigarette smoking is thought to be the primary risk factor for lung cancer, there are several other risk factors contributing to lung cancer summarized in Table 2.4. Persons exposed to other cancer-

causing substances (carcinogens) have a greater chance of developing lung cancer if they smoke. In addition to the general risks of developing lung cancer associated with occupational and environmental exposures, some families may have inherited a certain susceptibility to the effects of carcinogens. Diet and pre-existing nonmalignant lung disease also have been associated with the risk for developing lung cancer.

There have been several case control and cohort studies seeking to elucidate associations between NSAID use and lung cancer which have resulted in conflicting results {Rosenberg 1995, Langman 2000, Akhmedkhanov 2002, Muscat 2003, Moysich 2002, Harris 2002, Schreinemachers 1994, Paganini-Hill 1989, Thun 1993}. Although a meta-analysis of those studies {Gonzalez-Perez, 2003} concluded that there is a non-significant reduced risk of lung cancer associated with NSAIDs (RR 0.65, 95%CI 0.34-1.22) and aspirin users (RR, 0.84; 95%CI 0.66-1.07), the results must be interpreted considering the pooled estimates were derived from 8 heterogeneous studies with small sample sizes. In addition, a significant inverse association was detected in high-risk population, smokers, with an estimated 68% risk reduction among regular aspirin-use smokers {Harris 2002}.

The evidence supporting the existence of a dose-response relationship between NSAID use and lung cancer is more consistent. Harris and colleagues suggested the inverse trend of lung cancer risk with increasing NSAID use among cigarette smokers {Harris 2002}. For instance, compared with non-NSAID users, reductions in the risk of lung cancer were 43% and 68% for smokers taking NSAIDs less than one NSAID daily (OR, 0.57; 95% CI, 0.40-0.82) and those taking at least one NSAID daily (OR, 0.32; 95% CI, 0.23-0.44) (trend test, $p<0.01$). A similar trend was also found by Moysich and colleagues; odds ratio of diagnosis of lung cancer were 0.63 (95% CI, 0.44-0.92) in patients taking NSAID 1-10 tablet years (number of daily pills

x duration of use) and 0.45 (95% CI, 0.27-0.77) in those NSAID at least 11 tablet years (trend test, $p<0.01$) {Moysich 2002}. Akhmedkhanov and colleagues found that prolonged duration of aspirin use (at least 5 years) was associated with reduced non-small cell lung cancer risk among women (P for trend, 0.02) {Akhmedkhanov 2002}.

Prostate cancer

Prostate cancer is the most common cancer among American men {American Cancer Society 2003}. Prostate cancer incidence increases with age, especially those over age 65 {Jamel 2003}. It is estimated that 1 in 7 men over age 65 was diagnosed with prostate cancer {Jamel 2003}. Although the exact cause of prostate cancer is unknown, several factors are possibly involved in the development of prostate cancer including diet, i.e. animal fat intake {Kolonel 1999}, sexual activity and frequency of venereal disease {Ross 1987}, history of some benign prostatic disease, including prostatitis {Nelson 2002} and benign prostatic hyperplasia {Hammarsten 2002}, hormones, including testosterone {Ross 1998}.

Evidence for chemoprevention of prostate cancer is controversial. Two case-control {Neugut 1998, Irani 2002} and 4 cohort studies {Leitzmann 2002, Norrish 1998, Paganini-Hill 1989} demonstrated that no association existed between prostate cancer incidence and use of NSAIDs. Some suggested increasing risk {Friis 2003, Langman 2000, Sorensen 2003}. Contrarily, Garcia Rodriguez & Gonzalez-Perez {Garcia Rodriguez & Gonzalez-Perez 2004},Habel et al {Habel 2002} and Nelson & Harris {Nelson 2000} reported a protective effect of NSAIDs. For instance, strong evidence for a chemopreventive role of NSAIDs was described in a hospital-based case-control study, where the decreased risk of prostate cancer was around 65% for both over-the-counter NSAIDs (OR, 0.34; 95% CI, 0.23-0.58) and prescription NSAIDs

(OR, 0.35; 95% CI, 0.15-0.84). Likewise, in a multiracial cohort of the Kaiser Permanente Medical Care Program {Habel 2002}, lower incidence of prostate cancer among men who reported taking high dose of aspirin (RR, 0.76; 95% CI, 0.60-0.98). A nested case-control studies using the UK General Practice Research Database suggested a decreased risk of prostate cancer by 30% in aspirin users (OR, 0.70; 95% CI, 0.61-0.79) {Garcia Rodriguez & Gonzalez-Perez 2004}.

Other cancers

After the protective effect of NSAID use on the risk of colorectal cancer has been documented, many researchers have raced to study the possible effects of NSAID use on the risk of other cancers. Recent Danish population-based cohort studies {Sorensen 2003, Friis 2003} compared cancer incidence among persons prescribed low-dose aspirin (29,470 persons) and other NSAIDs (172,057 persons) with regional cancer rates. While protective associations of non-ASA-NSAIDs against stomach and ovarian cancer were found {Sorensen 2003}, increased risk of cancer of the kidney was observed in persons both prescribed low-dose aspirin and non-aspirin NSAIDs {Sorensen 2003, Friis 2003}. Bosetti and colleagues determined the role of aspirin on the risk of cancers of the upper aerodigestive tract, including oral, esophagus, pharyngeal and laryngeal cancer by using 3 hospital-based case-control studies (1,362 cases and 3036 controls){Bosetti 2003}. Interview-administered questionnaire was used to assess aspirin intake. Although a non-significant risk reduction was reported for persons who regularly used aspirin for at least once a week for more than 6 months, ones exposed to aspirin for at least 5 years were less likely to be diagnosed of cancers of the upper aerodigestive tract (OR,0.33; 95%CI,0.13-0.82) {Bosetti 2003}. A recent meta-analysis of 9 studies (2 cohort, 7 case-control)

by Corley and colleague revealed a significant protective association between any use of NSAIDs and esophageal cancer (OR, 0.57; 95% CI, 0.47-0.71), both intermittent (OR, 0.82; 95% CI, 0.67-0.99) and frequent use (OR,0.54; 95% CI, 0.43-0.67) {Corley 2003}. The greater protection was observed with aspirin use (OR, 0.5; 95% CI, 0.38-0.66) than non-aspirin NSAID use (OR,0.75; 95% CI, 0.54-1.00) {Corley 2003}.

Most studies examining a correlation between NSAID use and incidence of pancreatic cancer reported a lack of association {Friis 2003, Langman 2000, Sorensen 2003, Menezes 2002}. Contrarily, Anderson and colleagues demonstrated a reduced risk for aspirin users in a prospective cohort of 28,283 post-menopausal women who lived in Iowa {Anderson 2002} as well as a decreasing risk with increased weekly aspirin use. It is noted that a non-significant increased risk of pancreatic cancer was reported in women who used only non-aspirin NSAIDs.

The role for NSAID use as probable chemopreventive agents for ovarian cancer have been widely assessed and yielded inconclusive results. While Cramer {Cramer 1998}, Tavani {Tavani 2000} and Akhmedkhanov {Akhmedkhanov 2001} demonstrated roughly a 25-40% non-significant reduction in risk among women who reported aspirin intake for at least 6 months, Lacey {Lacey 2004}, Moysich {Moysich 2001} and Fairfield {Fairfield 2002} found no evidence of reduced risk. A case-control study of 7,870 women with epithelial ovarian cancer by Rosenberg {Rosenberg 2000}, however found a 50% reduction in ones using any NSAIDs at least 4 times per week for at least 5 years.

The Danish population-based cohort studies demonstrated a 20% increased risk of bladder cancer in persons reported having NSAID intake {Friis 2003, Sorensen 2003}. On the contrary, a case-control study by Castelao {Castelao 2000} investigating the relation of chronic

use of OTC and prescription analgesics and bladder cancer risk reported an inverse, dose-dependent association, except for pyrazolon derivative (i.e. phenylbutazone).

Endometrial and cervical cancer is one of the most common cancers among American women {Cancer facts and figure 2004}. Several risk factors have found to be associated with developing endometrial cancer: advanced age, white race, endometrial hyperplasia, hormone replacement therapy, and obesity {cancer.gov}. Cervical cancer risk factors consist of family history, sexually transmitted diseases, e.g. Human papillomavirus and Chlamydia infection, pelvic inflammatory diseases, and oral contraceptives {American Cancer Society 2004b}. A dose-dependent inhibition of endometrial tumor cell growth by aspirin was shown in vitro {Arango 2001}. Similar to that in endometrial tumor cells, aspirin, non-aspirin NSAIDs and COX-2 inhibitors decreased COX-2 expression, angiogenesis, cell proliferation, and colony formation of cervical tumor cell {Ferrandina 2003, Kim 2003}. However, to our knowledge, there are no epidemiological studies determining an association between NSAID use and risk of endometrial cancer or cervical cancer.

Limitation of previous studies

There are several limitations allied with some of the previous studies, particularly for the case control studies. Because NSAID exposure, including dose and duration of use, and diagnosed cancer were often obtained by self-report, they are subject to measurement error and potential recall bias, a limitation not inherent in claims databases. Noting that, unlike aspirin, non-aspirin NSAIDs have been explored in fewer studies. Moreover, the effect of individual non-aspirin NSAIDS on various cancer rates have not been determined due to lack of sample size power. Though some studies attempted to identify dose response relationships between

NSAIDS and incident cancer, conclusive evidence remains lacking. For example, periods after continuous use in which a protective effect of NSAIDs has been significantly observed range from at least 6 months {Garcia-Rodriguez 2001} to at least 20 years {Giovannucci 1995}. Langman et al suggested odds ratio were decreasing while increasing number of aspirin and other NSAID prescriptions use in a period of 13-36months prior to colon cancer diagnosed; trend also was seen in rectal cancer but not statistically significant {Langman 2000}. Similarly, Collet et al reported a trend with dose within certain periods {Collet 1999} . Giovannucci et al found decreasing relative risks when increasing years of use and a trend over time in both colon and rectal cancer, although trend was not statistically significant in rectal cancer {Giovannucci 1995}. Giovannucci et al, however did not find decreasing trend based on dose {Giovannucci 1995}. Some studies did not analyze dose-response trend statistically {Peleg 1994, Smalley 1999}. Yet they showed trend of risk reduction with increasing duration of NSAIDs (both ASP and NA NSAIDs) exposure and cumulative dose.

There exists some evidence suggesting that the benefit of NSAIDs would subside after it is discontinued in a period of 60days {Garcia-Rodriguez 2001} to 1 year {Friedman 1998} for CRC. Pharmacologically, any chemopreventive effect may be reversible due to the reversible inhibition of COX enzymes of most NSAIDS or reproduction of COX enzymes in target tissue when aspirin is used and few studies have addressed this issue.

Adverse Effects of NSAIDs

One of the limitations of the use of NSAIDs as chemoprevention is their adverse effects, which are listed in Table 2.5. The well-documented adverse effects of NSAIDs include gastrointestinal (GI) complications (i.e. GI bleeding, perforation, and ulcer) and renal complications (i.e. acute renal failure).

NSAID related GI complications

NSAID related GI complications are the major concern for NSAID users. There are an estimated 100,000 hospitalizations and 10,000 to 20,000 deaths annually are due to NSAID-related GI complications at an annual cost of 1.6 billion dollars {Fries 1991, Smalley 1996}. There is little doubt that short term NSAID exposure can increase the risk of gastric and duodenal ulcers, GI hemorrhage and perforation. A recent meta-analysis of the risk of NSAID related GI complications, by Ofman et al, reported that NSAID users are 3-5 times more likely to have GI complications than nonusers {Ofman 2002}; this rate was similar to that described by Gabriel and colleagues {Gabriel 1991}. Although an estimation reported by Ofman et al was derived from 1966-1998 English and non-English published and unpublished data {Ofman 2002}, there were insufficient data to investigate confounding due to age, comorbidity, dose or duration. Gabriel and colleagues, contrary to Ofman et al, also examined GI complication risk of NSAID use in various subgroups {Gabriel 1991}. Increased risks for GI complications were found in patients age 60 and over (as much as 3 times higher than non-elderly group), those with a history of GI events, those taking concomitant corticosteroid and those taking NSAID for less than 3 months {Gabriel 1991}.

What is less clear is the impact of long term NSAID use on GI complications. One of the encouraging finding of NSAID induced gastric complications is that gastric mucosal adaptation has been reported in both animal and human studies {Fitzpatrick 1999, Lipscomb 1996}. Additionally, an earlier meta-analysis {Gabriel 1991} and several observational studies {Garcia Rodriguez 1998, Smalley 1995} reported decreasing risk of GI complications when NSAIDs were taken over longer durations. For instance, among current users, the constant risk of GI complications was found during the first year of NSAID use and was roughly 7 times more likely than non-user {Garcia Rodriguez 1998}. The risk of GI complications, however, dropped nearly in half for NSAID exposure >1 year. (RR, 3.5; 95%CI,2.0-6.0) {Garcia Rodriguez 1998}. Possible existence of a dose-response relationship between duration of NSAID exposure and GI complications was shown as decreasing odds ratiofor less than 1 month of exposure, 1-3month, and more than 3 months were 8.00, 3.31 and 1.92, respectively {Gabriel 1991}. Nevertheless, the adaptation is disturbed and abates when H.pylori infection presents {Konturek 1998}. Unlike NSAIDs, selective COX-2 inhibitors have been associated with fewer GI ulcer complications than NSAIDs {Buttgereit 2001}; yet non-ulcer-related GI effects, i.e. abdominal pain, dyspepsia, occurred slightly more often when compared to placebo {Buttgereit 2001}.

NSAID related renal complications

Another major complication of NSAIDs involves deterioration in renal function which typically manifest in acute renal failure which may lead to chronic renal failure and end-stage renal disease, especially in persons with pre-existing renal diseases {Hernandez-Diaz 2001}. For instance, persons with cirrhosis, heart failure, renal disease, diabetes, advanced age, heart failure, hypertension, and those exposed to neprotoxic medications, i.e. diuretics, NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, and some antibiotics are at higher risk of acute renal failure

{Fored 2001, Griffin 2000, Hernandez-Diaz 2001, Perneger 1994, Rexrode 2001, Bailie 1995, Henry 1992}. It is believed that NSAIDs may exacerbate renal insufficiency, hyperkalemia, intestitial nephritis, and acute renal failure by inhibiting renal prostaglandins {Brooks 1998}. Griffin and colleagues reported that persons who currently used NSAIDs were almost 1.6 times more likely to be hospitalized for acute renal failure than ones who never used NSAID (OR,1.58, 95%CI, 1.34-1.86). The highest risk was observed within first 30 days of use, although the risk was similar in those discontinued NSAID use for at least 30 days {Griffin 2000}. Regular use of NSAIDs increased the risk of chronic renal failure 2.5 fold (95%CI, 1.9-3.3) {Fored 2001}, and the risk rises with increasing lifetime cumulative dose of NSAIDs. Similar rising risk of ESRD with cumulative dose of NSAIDs have been reported elsewhere {Perneger 1994}. In contrast to most of the findings previously described, the Physician's Heath Cohort study contrarily showed no association between self-reported cumulative NSAID uses over 14 year and risk of renal dysfunction in men {Rexrode 2001}.

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Table 2.1: Overexpression of COX enzymes in Premalignant and Malignant conditions [Modified from Subbaramaiah 2003]

Organ	Premalignancy	Malignancy
Colon	Adenomatous polyp	Adenocarcinoma
Stomach	Metaplasia	Adenocarcinoma
Esophagus	Barrett's Metaplasia	Adenocarcinoma
		Squamous cell carcinoma
Liver	Chronic hepatitis	Hepatocellular carcinoma
Biliary system	Bile duct hyperplasia	Cholangiocarcinoma
Pancreases	Pancreatic intraepithelial neoplasia	Adenocarcinoma
Head and Neck	Leukoplakia	Squamous cell carcinoma
Lung	Atypical adenomatous hyperplasia	Adenocarcinoma
		Squamous cell carcinoma
Breast	Atypical duct hyperplasia	Invasive ductal carcinoma
		Adenocarcinoma
Bladder	Dysplasia	Transitional cell carcinoma Squamous cell carcinoma
Gynecological	Cervical intraepithelial neoplasia	Squamous cell carcinoma OR Adenocarcinoma of cervix
		Endometrial carcinoma
		Ovary carcinoma {Dore 1998}
Prostate	Prostatic intraepithelial neoplasia {Chaudry 1994}	Prostatic carcinoma {Chaudry 1994}
Skin	Actinic keratoses	Squamous cell carcinoma

Source: Subbaramaiah K, Dannenberg AJ. Cyclooxygenase 2: a molecular target for cancer prevention and treatment. Trends Pharmacol Sci.2003;96-102.

Table 2.2: Factors Influencing the Development of Colorectal Cancer {American Cancer Society 2002} [Modified from Colditz 2000a]

	Relative risk
Family history (first degree relative)	1.8
Physical inactivity (less than 3 hours per week)	1.7
Inflammatory bowel disease (physician diagnosed crohn's disease, ulcerative colotis or pancolitis)	1.5
Obesity	1.5
Red meat	1.5
Smoking	1.5
Alcohol (more than 1 drink/day)	1.4
High vegetable consumption (5 or more servings perday)	0.7
Oral contraceptive use (5 or more years of use)	0.7
Estrogen replacement (5 or more years of use)	0.8
Multivitamin containing folic acid	0.5

Source: American Cancer Society. Cancer Facts & Figures 2002. http://www.cancer.org/downloads/STT/CancerFacts&Figures2002TM.pdf

Table 2.3: Risk factors of Breast Cancer [Modified from Colditz, 2000a]

Risk Factors	Strength of Association (RR)	95% CI
Age at Menarche 15 vs. 11 years	0.69	0.65,0.74
Age at First Births 20's vs. Nulliparous 30's vs. Nulliparous	0.73 1.16	0.63,0.86 0.96,1.41
Type of Menopause Bilateral oophorectomy vs. Natural	0.89	0.80, 0.98
Postmenopausal hormone use Estrogen Replacement Therapy Estrogen and Progesterone Replacement Therapy	1.23 1.67	1.06,1.42 1.18,2.36
Benign Breast Disease	1.57	1.43,1.73
Family History	1.46	1.29,1.67
Alcohol (1 drink/day)	1.07	1.00,1.13

Source: Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: Data from the Nurses' Health Study. Am.J.Epidemiol. 2000;950-64.

Table 2.4: Risk Factors associated with Lung Cancer

Risk Factor	Strength Of Association	Reference
Gender Women vs. Men	RR, 1.5	{American Cancer Society 2004}
Cigarette Smoking	RR, 4-46	{Doll 1976, Freidman 1997, US Department of Health and Human Services 1989}
Cigar Smoking	RR, 2-5; OR, 9	{Boffetta 1999, Iribarren 1999, Shapiro2000}
Environmental Tobacco Smoke	RR, 1.9; Excess Risk 24%	{Cardenas 1997, Hacksaw 2002}
Radon	RR, 1.14	{Lubin 1997}
Asbestos	RR, 6	{Hammond 1979}
Genetic Factors	OR, 2-5	{Bromen 2000, Ooi 1986, Samet 1986, Tokuhata 1963}
Alcohol use	OR, 1.86	{Bandera 2001, Rachtan 2002, Korte2002}
Hypertension	Smokers (RR, 1.17) Non-smokers (RR, 0.98)	{Lindgren 2003}
Lung diseases	Any lung disease (OR, 1.56) Pneumonia (OR, 1.6-1.7) Tuberculosis (OR, 1.6) Asthma (OR, 1.67) Emphysema (OR, 2.7) Chronic bronchitis (OR, 1.60)	{Brenner 2001, Wu 1995, Brownson 2000, Kreuzer 2000}

Table 2.5: Adverse Events Associated with Non-Steroidal Anti-inflammatory Drugs {Brooks 1998}.

System	Side-Effect
Gastrointestinal	Peptic ulceration
	Esophagitis and strictures
	Small and large bowel erosive disease
Renal	Reversible acute renal failure
	Fluid and electrolyte disturbance
	Chronic renal failure and interstitial fibrosis
	Interstitial nephritis
	Nephrotic syndrome
Cardiovascular	Exacerbation of hypertension
	Exacerbation of congestive cardiac failure
	Exacerbation of angina
Hepatic	Elevated transaminases
	Fulminant hepatic failure (rare)
Central nervous system	Headache
	Drowsiness
	Confusion and behavior disturbance
	Aseptic meningitis
Hematologic	Thrombocytopenia
	Hemolytic anemia
	Agranulocytosis and aplastic anemia
Other	Exacerbation of asthma and nasal polyposis
	Skin rash

Source: Brooks P. Use and benefits of nonsteroidal anti-inflammatory drugs. Am.J.Med. 1998;9S-13S.

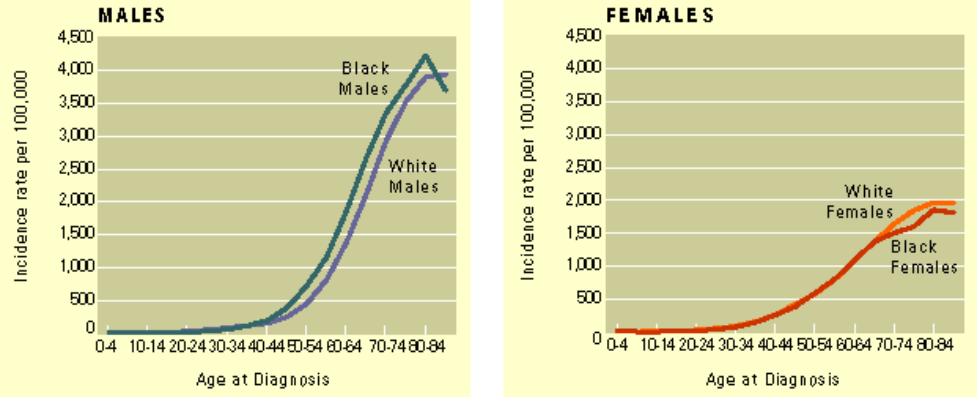

Figure 2.1: Average Annual Age-specific Cancer Incidence Rates, 1987-1991 {National Institute of Health and National Cancer Institute 2003}. Source: National Institute of Health and National Cancer Institute. Cancer Rates and Risks. http://seer.cancer.gov/publications/raterisk/

CHAPTER 3

PRELIMINARY STUDY

We conducted a retrospective cohort study to determine the risk benefit profile of NSAIDs as chemoprevention against colorectal cancer (CRC) by confirming the protective effect of NSAIDs against CRC and to describe the association of NSAID use with renal and gastrointestinal (GI) disease {Koompalum 2003}. A retrospective cohort study of recipients age 50-100, who had at least 2 years continuous eligibility, was conducted using Georgia Medicaid claims. Subjects were recruited between January 1, 1990 and September 30, 1995. We excluded subjects that had any diagnosis of CRC, GI, or renal complications within their first year of eligibility. The cohort was followed through September 30, 1997 (7.75 years). All outcome occurrences were dated and determined by searching for claims with ICD-9-CM codes indicative of outcome events. NSAID exposure was identified by searching the National Drug Code (NDC) in the prescription files. For each NSAID prescription, the strength and prescribed quantifies were converted to ibuprofen equivalent doses. Number of prescriptions per month and cumulative ibuprofen equivalent doses were used to explore a dose-response relationship. Survival Analysis (Cox-Proportional Hazard) technique was used to calculate all relative risks. Sensitivity analyses were also conducted (1) excluding patients with dual Medicare eligibility, and (2) excluding patients dwelling in nursing home more than 1 year.

As a result, there were 186,289 Georgia Medicaid recipients in the cohort and 61.3% were exposed to an NSAID. On average, a subject was followed 5.4 years (1,009,995 person-years). The cohort average age was 69.9 years (s.d. 10.5years); 75.6% were female, 48.3% were

white, 40.6% were non-white, and 11.0% were of unknown race. Incidence rates of CRC, GI and renal complications were 58.6, 529.4, and 311.2 per 100,000 person-years, respectively. After adjustments for age, gender, race, alcoholism, and obesity, subjects exposed to NSAIDs were 35% less likely to have CRC (RR, 0.65; $p<0.0001$), and were 20% less likely to have renal complications (RR, 0.80; $p<0.0001$). There was no difference in GI events based on NSAID exposure. Similar trends were observed in both sensitivity analyses. Figures 3.1-3.3 below present a dose response effect of NSAID exposure on all outcomes.

We confirmed the protective effect of NSAIDs on colorectal cancer. We found 35% risk reduction with NSAID use. Our results suggested not only greater reduction of CRC with higher cumulative exposure of NSAIDs, but also no association with increase risk of renal and GI complications.

Reference

Koompalum D., Niecko TE, Martin BC (2003). The risk benefit profile of non-steroidal anti-inflammatory drugs as chemoprevention of colorectal cancer: a Georgia Medicaid cohort study [abstract]. Pharmacoepidemiol Drug Saf 2003; 12 Suppl 1:S64-S65

Table 3.1: Effect of NSAID Use on Incidence of Colorectal Cancer, GI and Renal Events

Outcome Events	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR* (95% CI)	Multivariate Adjusted RR** (95% CI)
Colorectal Cancer	Any Use	672,722	350	52.03	0.72 (0.62, 0.86)	0.65 (0.55, 0.77)
	None	344,018	246	71.51	Reference	Reference
GI Events	Any Use	659,255	3,662	555.48	1.16 (1.09, 1.23)	0.97 (0.92, 1.03)
	None	343,209	1,645	479.30	Reference	Reference
Renal Events	Any Use	667,385	2,094	313.76	1.02 (0.95, 1.10)	0.80 (0.74, 0.87)
	None	343,398	1,052	306.35	Reference	Reference

* Unadjusted relative risk (RR) and 95% confidence interval (CI) estimated by Mantel-Haenszel Techniques
** Multivariate adjusted RR and 95% CI estimated by Cox-propotional hazard regression model.

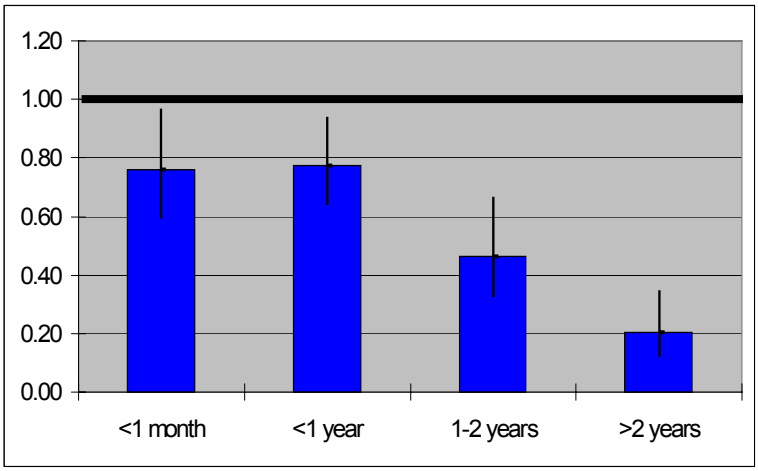

Figure 3.1: Relative Risk of Incident Colorectal Cancer by Cumulative Exposure Amount

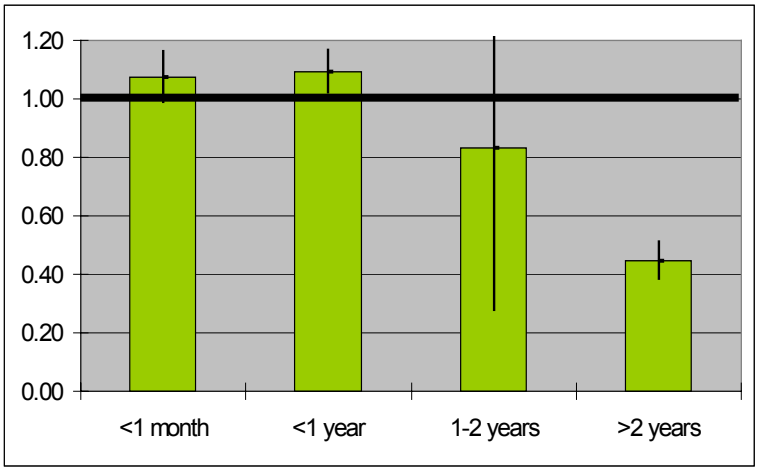

Figure 3.2: Relative Risk of Incident GI Events by Cumulative Exposure Amount

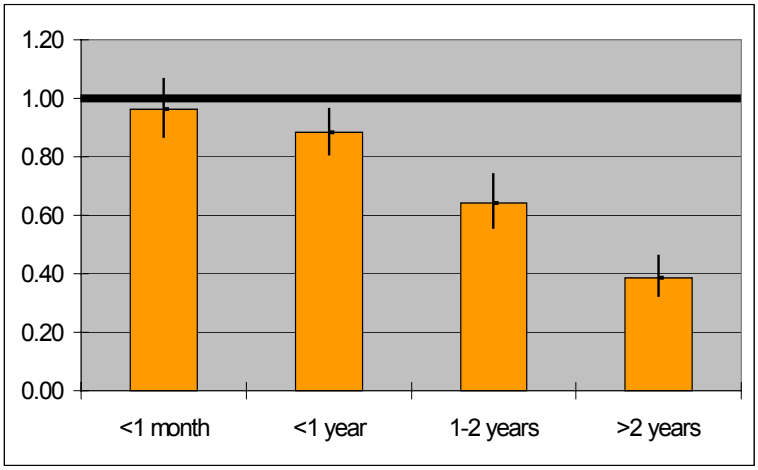

Figure 3.3: Relative Risk of Incident Renal Events by Cumulative Exposure Amount

CHAPTER 4

RESEARCH DESIGN AND METHODS

Research Design

A retrospective longitudinal cohort design was used to determine the relationship between NSAID exposure and incidence of cancer at various sites, as well as incidence of NSAID-related adverse events. A cohort of Georgia Medicaid enrollees aged 50-100 without any history of cancer, GI or renal disease was followed from 1990 to 2001. Georgia Medicaid enrollees with at least 2 years of continuous eligibility were retained. Subjects were followed up until the earliest occurrence of (1) study events of interest (e.g. incident cancer at various sites, GI or renal diseases), (2) loss of eligibility, (3) death, or (4) end of study (December 31,2002). Exposure to NSAIDs was recorded throughout follow-up period (figure 4.1).

To validate the study result, we simultaneously tracked a cohort of North Carolina Medicaid beneficiaries from 1990 to 1998. Like with the Georgia Medicaid cohort, the same inclusion and exclusion criteria were applied in NC Medicaid cohort. All members of NC Medicaid cohort were followed up until the earliest occurrence of (1) study events of interest (e.g. incident cancer at various sites, GI or renal diseases), (2) loss of eligibility, (3) death, or (4) end of study (December 31,1998). Exposure to NSAIDs was also recorded throughout follow-up period.

Data

The administrative claims data capturing all reimbursed medical encounters of Georgia Medicaid recipients is managed by the Georgia Department of Medical Assistance (GDMA). Adults eligible for GA Medicaid benefits include some low-income residents, medically needy individuals, the elderly, and people with disabilities if state and federal guidelines are met. Currently, the Medicaid claims data from 1990-2001, in form of SAS data sets, are housed at the University of Georgia. The GA Medicaid database contains an annual enrollment of approximately 1.2 million eligible persons per year, which provides patient level details on recipient demographics and monthly Medicaid coverage. All Medicaid beneficiaries' non-prescription medical utilization, including inpatient, outpatient, nursing home, and emergency services, are collected in the medical claim file and for encounters between most providers the ICD-9-CM and CPT4 codes are provided. The pharmacy claim file records each reimbursed prescription which includes information describing the date prescriptions are filled, drug name, National Drug Code (NDC), strength, dosage, number of unit dispensed. All three of the files are linked by encrypted recipient identifier allowing the construction of person level analytic files where treatments and ensuing medical encounters can be measured at the patient level.

In addition, the University of Georgia possesses the North Carolina Medicaid claims database. It is an administrative claim data of medical encounters of roughly 3 million North Carolina Medicaid recipients per year. It is managed by the NC Division of Medical assistance. Data from 1990-1998 are converted and stored in form of SAS data sets. Reminiscent of Georgia Medicaid, NC Medicaid data contain patient level details on demographics, monthly coverage, non-prescription medical utilization, and pharmacy claim file, all of which are linked by encrypted recipient identifier.

Several epidemiological and health policy studies have utilized both Georgia and North Carolina Medicaid databases {Martin 2001, Kotzan 2002}. Those studies have shown that both Georgia and North Carolina Medicaid data are valid and coherent with supplied documentation.

Research Subjects

The study cohort consisted of Medicaid Recipients aged 50-100 during the period of 1990-2001 with at least 2 years of continuous eligibility.

Individuals were recruited in the cohort if they meet the following criteria:

Inclusion Criteria

1. Individuals were eligible for Medicaid Benefit continuously for at least 2 years between January 1, 1990 and December 31, 2000. The date subjects were included in the cohort was termed the "index date".

   According to SEER Cancer Statistics Review 1975-2000 {Ries 2003}*, estimated median ages of colorectal cancer (CRC) at diagnosis and at death were 72 and 75, respectively. This implies that median survival time of CRC is 3 years. Therefore, we include Medicaid enrollees who had at least 2-year continuous eligibility so that our cohort would be better generalized to CRC population and to ensure accessibility of 2-year medication history.*

2. Individuals were at least 50 years of age on their index date. Age was calculated at the time subject entered the cohort.

   It is based on substantial increase of cancer risks after age 50 in both males and females {National Institute of Health and National Cancer Institute 2003}.

Exclusion criteria

(1) Individuals with a history of any cancer, GI or renal disease during washout period were excluded. Washout period was defined as 1 year subsequent to their index date.

This criterion was used to assure the chronological relationship that subjects exposed to NSAIDs occurs before incident cancer, GI and renal diseases.

(2) Individuals were older than 100 years of age on their index date.

(3) Individuals with dual eligibility status did not receive full Medicaid benefits.

As a supplemental insurance to Medicare, a person is a "dual eligible" when one is entitled to Medicare and eligible for one of dual eligibility Medicaid benefit categories. In most of the categories, dual eligible beneficiaries do not receive full Medicaid benefits; for instances, Medicaid pays only their Medicare premiums, deductibles and coinsurance. Due to lack of linkage between Medicaid and Medicare, there is no information regarding medical, nor pharmacy record available for these beneficiaries with limited Medicaid benefits; they are likely to be comprised in non-NSAID exposure group. Thus, we excluded those with dual eligibility status and limited Medicaid benefits.

First we search for individuals with dual eligibility status by capturing persons with Aid Category of (1) Qualified Medicare Beneficiary (Aid Category, 60) or (2) Specified Low Income Medicare Beneficiary (Aid Category, 66) or (3) person enrolled Membership Request by Medicare/Medicaid Eligible Recipient (Enrollment Code, 408). All subjects with at least one of the dual eligibility codes after their index date were then searched for types of claim in medical history files: inpatient crossover (Claim Type, 16), outpatient crossover (Claim Type, 17), nursing facility crossover (Claim Type, 18), or other crossover

(e.g. physician, Claim Type, 19). We excluded those individuals with dual eligibility, who have any of the claim types mentioned above.

Each subject in the study cohort was followed up until earliest date among

A. Study Events of Interest (see 'Measurement of Outcomes')
B. Loss of Eligibility
C. Death
D. End of Study: (December 31,2002 for the Georgia Medicaid cohort and December 31, 1998 for the North Carolina Medicaid cohort)

Measurement of Outcomes

The study events of interest consisted of incident cancer at various sites, GI and renal diseases. We measured each of them separately by searching all diagnoses and procedures recorded in the medical claim file. All definitions of the study events of interest were first originated from previous epidemiological studies, and then modified to better capture relevant events of interest. To identify each of the study events, we screened all diagnosis and procedure codes recorded in the cohort's medical history file.

Operational definitions

Cancers

A. Colorectal cancer (CRC)

To identify incident CRC, we first adopted an ICD-9-CM algorithm suggested by Smalley and colleagues {Smalley 1999}. They investigated the association between NSAID exposure and incident CRC in elderly population in the Tennessee Medicaid Program. ICD-9-

CM codes of malignant neoplasm of colon (153.x) and rectum (154.x) were used and found to be consistent with histological findings. To enhance understanding potential role of NSAIDS as a primary prevention of cancer, we then added ICD-9-CM codes of Carcinoma in situ of colon (230.3) and rectum (230.4), as well as benign neoplasms of colon (211.3) and rectum (211.4) {Niecko 2001}. Additionally, secondary ICD-9-CM codes for malignant neoplasm of large intestine and rectum (197.5) were also included.

B. Breast Cancer

To identify incident breast cancer, we first implemented an ICD-9-CM algorithm suggested by Kahn and colleagues {Kahn 1996}. This study has shown that 83% of ICD-9-CM coded information matched "gold standard" tumor registry data. ICD-9-CM codes used in the validation study contained the diagnosis of primary breast cancer (174.x) and breast carcinoma-in-situ (233.0). This definition was modified by incorporating benign breast tumors (217).

C. Lung Cancer

ICD-9-CM codes identifying incident lung cancer included diagnosis of malignant lung cancer (162.x). Several studies have utilized and shown that all codes are coherent with SEER tumor registry data {Whittle 1991, Fedele 1998}. We added ICD-9-CM codes for carcinoma in situ (231.2), benign neoplasms (212.2), and secondary malignant neoplasm (197.0) of lung.

D. Prostate Cancer

To detect individuals with prostate cancer, we used ICD-9-CM codes for malignant neoplasm (185),benign neoplasms(222.2) and carcinoma in situ (233.4), which were found to be consistent with prostate specific antigen (PSA) screening {Skarsgard 2000}.

E. Other cancers

The ICD-9-CM codes for other cancers in table 4.1 stemmed from a study conducted by Thun and colleagues {Thun 1993}. They explored the relationship between aspirin use and risk of cancer death. However, the proposed ICD-9-CM codes captured only malignant neoplasms. Thus, our operational definitions incorporated additional codes for benign neoplasms, carcinoma-in-situ and secondary malignant neoplasms.

GI Events

GI events of interest were defined as upper gastrointestinal bleeding and perforation. To identify GI events, ICD-9-CM codes consisted of gastric ulcer (531.x), duodenal ulcer (532.x), gastrojejunal ulcer (534.x), peptic ulcer (533.x), gastrointestinal hemorrhage (578.xx) {Smalley 1995}. The positive predictive value of these codes were 97%, 84%, 80%, and 59% coherent with hospital clinical records for 531.x-532.x, 534.x, 533.x, and 578.x, respectively {Cattaruzzi 1999}.

Renal Events

Identification of individuals with acute renal failure was listed in table 4.1 below. ICD-9-CM codes were selected based on existing medical literature for potential NSAID-related renal failure {Griffin 2000, Harley 2003, Niecko 2001}.

Measurement of Exposure

We determined NSAID utilization by searching all prescription codes in the pharmacy claims file. Since we measured each study outcome separately, all NSAIDs prescribed between "Index Date" and "End Date" were recorded for each study outcome. We aimed to explore chemopreventive properties of all NSAIDs listed in Table 4.2. Only orally administered NSAIDs were relevant to the study.

Multum's therapeutic categories (MULTUM) and NDC codes were employed to identify aspirin, NSAID and COX-2 inhibitors prescribed

Each subject was classified into two groups, non-NSAID-exposure and NSAID-exposure. A dichotomous variable, NSAIDs (0 if non-exposed, 1 if exposed) were used as an explanatory variable. We then determined protective properties of NSAIDs separately based on their chemical classes and generic groups dependent upon sufficient sample size. Each chemical class and each generic of NSAID exposure was one-by-one compared with to non-NSAID-exposure.

To explore the dose-response relationships between NSAID exposure and incidence of each study outcome, two proxies were used to assess amount of NSAID exposure: cumulative dose and cumulative duration.

Cumulative dose= Σ (number of units dispensed X strength of the drug)

Cumulative duration = Σ (number of prescriptions X number of days supply[**])

[**] Prior to 1998,the number of days supply field was not available in the GA Medicaid data. However, in general, the quantity level limits were set at a month's (31 days). Thus 31 days supply was used as a proxy for each NSAID prescription record filled prior to 1998

For each individual NSAID, we defined low and high daily dose based on minimum and maximum starting doses recommended for treatment of arthritis as noted in the *Physicians' Desk Reference* {Smalley 1999, Niecko 2001}. When the cumulative dose of NSAID exposure was considered as a whole or for each chemical class, all prescribed dose were standardized to ibuprofen-equivalent doses. Based on assumption of equal efficacy among high-dose NSAIDs for the treatment of arthritis, an "ibuprofen weighted" factor is computed. An "ibuprofen weighted" factor equals 2,400 (high daily dose of ibuprofen) divided by the high daily dose recommended for any particular NSAID {Smalley 1999, Niecko 2001}.

Statistical Analysis

Demographic and other clinical characteristics of the NSAID exposure and non-exposure groups, i.e. length of Medicaid coverage, comorbidity, were tabulated and tested for differences using chi-square test for categorical variables and t-test for continuous variables. All statistic analyses were performed using SAS statistical software (Version 8.2).

Unadjusted incidence was calculated by dividing number of new cases by number of person-years in each study event. We computed crude relative risks by dividing the unadjusted incidence rates of NSAID users (e.g. cases per 100,000 person-years) by those of non-users.

Cox proportional hazards model was used to enumerate multivariate rates and relative risks (using PROC PHREG). Model specification and operative definition of all covariates were summarized below. Multivariate adjusted relative risks (RRs) and 95%CI were reported. Effect of cumulative dose and duration of NSAID exposure were entered into the Cox proportional hazard model as time-dependent variables. The proportional hazards assumption was tested by including time-dependent covariates. Effect of interaction among covariates was analyzed.

Model specification

The Cox proportional hazard Model was defined as follows:

$$h(t \mid Z) = h_0(t) * \exp[\ \alpha(\text{NSAID exposure}) + \beta * X + \varepsilon\text{rror}\ ]$$

Where $h(t \mid Z)$: hazard rate at time 't' for an individual with risk vector Z

$h_0(t)$: baseline hazard rate

α : Coefficient for NSAID exposure

X : Matrix of covariates

β : Vector of coefficients corresponding to the matrix of covariates

Dependent variables:

Our major outcomes of interest were the first incidence of diagnosed cancers, and adverse gastrointestinal and renal events; an operational definition of each study event was provided in the "Measurement of Outcomes".

For each study event of interest, a Cox proportional hazard model was fitted based on two dependent variables.

(1) Incidence of each study event: A dichotomous dependent variable was coded as '0' for absence of the outcome, and '1' for presence of the outcome. During study period, subjects who had any diagnosis codes of the study outcome were recoded as '1', otherwise '0'. The ICD-9-CM algorithms used to identify the study outcomes were listed in "Measurement of Outcome"

(2) Time to each study event: A continuous dependent variable was computed, in years, by subtracting the date when a subject entered the cohort (Index Date) from the date when the subject left the cohort (End Date)

Independent variables:

Effect of NSAID exposure was modeled in three sets of separate analyses as follows:

1) NSAID exposure as a class: A dichotomous independent variable coded if a subject prescribed any NSAID.
2) Cumulative exposure of NSAIDs: NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints (less than one month, 1-6 months, 7-12 months, and greater than 12 months)

3) Effects of the use of some specific NSAIDs were analyzed. Based on generic names recorded from each subject's prescriptions, NSAID exposure was classified into 8 groups (see below). There is a high possibility that subjects may be exposed to more than one product or group, so persons could have more than one of the following NSAID variables recorded as exposed. Furthermore, to determine the effect cumulative exposure of each on study endpoints, the cumulative exposure for each generic group was calculated and stratified into 4 categories: less than one month, 1-6 months, 7-12 months, and greater than 12 months.

   a) Aspirin
   b) Selective Cox-2 inhibitors (celecoxib and rofecoxib)
   c) Ibuprofen (commonly prescribed) {Smalley 1999, Niecko 2001}
   d) Naproxen (commonly prescribed) {Smalley 1999, Niecko 2001}
   e) Indomethacin (commonly prescribed)
   f) Fenoprofen (commonly prescribed)
   g) Sulindac (effective in many animal models) {Smalley 1999, Niecko 2001}
   h) Other non-specific NSAIDs

Noting that when effects of NSAIDs were considered as a class or by chemical classes, amount of NSAID exposure was converted to ibuprofen equivalent amount (Measure of Exposure and Table 4.2). A Cox proportional hazard model with time-dependent variables used to further analyze effect of cumulative dose and duration of NSAID exposure.

Covariates

All covariates, which were included in the model, were listed in Table 4.3. Operational definition and the ICD-9-CM codes for each covariate were summarized.

A concern of NSAID-related GI adverse events may also yield increase of health care utilizations, i.e. GI tract testing, other screenings, physician visits, and hospitalizations. This rising trend could augment early cancer diagnoses of NSAID users. As a consequence, the influence of several covariates, listed below, on study outcomes were investigated.

a. Frequency of health care utilizations: Total numbers of patient visits throughout study period were counted using category of service (COS) recorded and date of the visit in medical history files.
b. Frequency of cancer screening: We identify cancer screening by using V-codes for "Special screening for malignant neoplasm" (V-codes: V76.xx). Total numbers of cancer screenings throughout study period were counted.

Sensitivity Analysis

To assess the robustness of the results, two sensitivity analysis were conducted. Firstly, due to potential variation in documenting clinical conditions of patients, who reside in long-term care facilities, may create ascertainment bias. This potential source of bias derives from the coding practices of nursing home staff and many nursing-home patients have several severe comorbidities that may be coded instead of our study outcomes. Therefore, physicians may not always thoroughly code for all of patients' conditions and comorbidities. The exclusion criteria were expanded to exclude persons residing in a nursing home for more than one year. Secondly, subjects whose age were 65 years and greater are eligible for Medicare benefit. The potential of

Medicare to pick up reimbursement for study outcomes procedures is highly likely. Therefore, subjects whose age were 65 years and greater may appear to be at less risk of study outcomes due to a result of Medicare picking up claims, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare

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Table 4.1: List of Study Outcomes of Interest and Their ICD-9-CM Operation Definitions

Study Outcomes of Interest	ICD-9-CM Codes
Cancer	
Colorectal Cancer	153.x, 154.x, 197.5, 211.3-211.4, 230.3-230.6
Breast Cancer	174.x, 175.x, 217, 233.0
Lung Cancer	162.x, 197.0, 212.3, 231.2
Prostate Cancer	185, 222.2, 233.4
Other Cancers	
Cervical Cancer	180, 233.1
Endometrial Cancer	182
Ovarian Cancer	183, 198.6, 220
Esophageal Cancer	150.x, 211.0, 230.1
Gastric Cancer	151.x, 211.1, 230.2
Liver Cancer	155.x, 211.5, 230.8
Pancreatic Cancer	157.x, 211.6, 230.9
Bladder Cancer	188.x, 223.3, 233.7
Kidney Cancer	189.x, 223.0, 223.1
Gastrointestinal Events	531.xx-534.xx, 536.x, 537.xx, 578.x
Renal Events	250.4x, 271.4, 403.xx, 404.xx, 580.xx-589.x, 590.xx, 593.xx, 753.1

Table 4.2: Commonly Available Non-Steroidal Anti-inflammatory Drug (NSAIDs), According to Chemical Class

Chemical Class	Generic	Low daily dose (mg)	High daily dose (mg)	Standardization to Ibuprofen
Nonselective COX inhibitors				
Salicylic acid derivatives	Aspirin (acetylsalicylic acid)	2,400	3,600	0.67
	Salicylate salts (i.e. Choline Magnesium trisalicylate)	2,000	3,000	0.80
	Diflunisal	500	1,000	2.40
	Salsalate	2,000	4,000	0.60
Heteroacrl acetic acids	Diclofenac	100	150	16.00
	Etodolac	800	1,200	2.00
	Ketorolac	10	40	60.00
	Tolmetin	1,200	1,800	1.33
Indole and indene acetic acids	Indomethacin	50	150	16.00
	Sulindac	300	400	6.00
Arylpropionic acids	Fenoprofen	900	2,400	1.00
	Flurbiprofen	200	300	8.00
	Ibuprofen	1,200	2,400	1.00
	Ketoprofen	200	300	8.00
	Naproxen	550	1,100	2.18
	Oxaprozin	1,200	1,800	1.33
Anthranilic acid (Fenamates)	Meclofenamic acid	100	400	6.00
	Mefenamic acid	500	1,000	2.40
Enolic acids				
Pyrazolones	Phenylbutazone	300	400	6.00
Oxicams	Piroxicam	less than 20	20	120.00
Nonacidic agent				
Alkanones	Nabumetone	1,000	2,000	1.20
Selective COX-2 Inhibitors				
Diaryl-substituted furanones	Rofecoxib	12.5	25	96.00
Diaryl-substituted isoxazole	Valdecoxib	10	20	120.00
Diaryl-substituted pyrazoles	Celecoxib	200	400	6.00

Source: (1) Roberts LJ2, Marrow JD. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Good man and Gilman's the pharmacological basis of therapeutics. Columbus: The McGraw-Hill Companies, Inc., 2001;687-731.

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Table 4.3: List of Model Covariates and Their Operational Definitions

Demographics:
Age at entry (years)
Gender (female vs. male)
Race (non-white vs. white)
Frequency of health care utilization: Total number of visits to ambulatory care services, emergency department, long-term care facilities, and acute inpatient services throughout study period
Frequency of cancer screenings: Total numbers of any cancer screenings throughout study period
Risk factors:
Alcohol use and alcohol abuse (ICD-9-CM = 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 {Elixhauser 1998})
Asthma (ICD-9-CM= 493.xx)
Chronic Bronchitis (ICD-9-CM = 491.xx)
Chronic liver infection (ICD-9-CM=070.2,070.3, 070.41, 070.44, 070.51, 070.54)
Chronic Pancreatitis (ICD-9-CM= 577.1)
Cirrhosis (ICD-9-CM = 571.5, 571.6)
Congestive heart failure (ICD-9-CM = 389.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9 {Elixhauser 1998})
Diabetes Melitus (ICD-9-CM = 250.0x-250.3x; 250.5x-250.9x {Elixhauser 1998})
Emphysema (ICD-9-CM = 492.xx)
Endometrial hyperplasia (ICD-9-CM=621.3x) {CDC 2003}
Gastroesophageal reflux disease (GERD)/Barrett's Esophagus (ICD-9-CM= 530.81, 530.85)
H.Pylori infection (ICD-9-CM = 041.86)
Hypertension (ICD-9-CM = 401.xx, 402.xx, 405.xx {Elixhauser 1998})
Liver Failure (ICD-9-CM = 570.xx)
Obesity (ICD-9-CM = 278.x {Elixhauser 1998})
Pelvic inflammatory disease (PID; ICD-9-CM= 614.9)
Pernicious anemia (ICD-9-CM= 281.0)
Pneumonia (ICD-9-CM= 480.xx-486.xx)
Prostatitis (ICD-9-CM=601.x)
Sexually transmitted diseases (STDs)
Gonococcal infection (ICD-9-CM=098.x)
Human immunodeficiency virus disease (HIV)/ acquired immunodeficiency syndrome (AIDS; ICD-9-CM=042, V08)
Human papillomavirus (HPV) infection (ICD-9-CM= 079.4)
Syphilis (ICD-9-CM= 091.x- 097.x)
Tobacco Smoke (ICD-9-CM = 305.1, V15.82 {Romano 1994})
Tuberculosis (ICD-9-CM= 010.xx-018.xx)
Medications:
Anticoagulant use (i.e. heparins, coumarin and indadiones)
Corticosteroids (i.e. prednisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone and hydrocortisone)
Cyclophosphamide
Finasteride
GI protective agents (i.e. Misoprostal, proton pump inhibitors (PPIs), and histamine-2 (H2) receptor antagonists)
Hormone replacement therapy (HRT)
Nephrotoxic Drugs:
Allopurinol
Angiotensin-converting Enzyme (ACE) Inhibitors and Angiotensin-II-receptor antagonist (e.g captopril, enalapril, lisinopril, losartan etc.)
Antibiotics:
Aminoglycosides
Cephalosporins
Vancomycin
Cyclosporine
Diuretics (i.e. loop, potassium-sparing, thiazide diuretics)
Oral contraceptives

Table 4.4: Codes to Identify Cancer Screening

Type of Screening	Operational Definition
Screening for malignant neoplasms of the respiratory organs	V76.0
Screening of the breast {National Committee for Quality Assurance 2001}	Inclusion: V-codes: V76.1x CPT: 76090-76092 Exclusion: CPT- 19180,19200,19220.50,19240
Screening for malignant neoplasms of the cervix routine cervical papanicolaou smear {National Committee for Quality Assurance 2001}	Inclusion: V-codes: V76.2 CPT: 88141-88145, 88147,88148, 88150, 88152, 88156, 88158, 88164-88167 Exclusion: CPT: 51925, 56308, 58150, 58152, 58200, 58210, 58240, 58260, 58262, 58263, 58267, 58270, 58275, 58280, 58285, 58550, 58551, 58951, 59135, 59525
Screening for malignant neoplasms of the bladder	V76.3
Screening for malignant neoplasms of colon and rectum	V76.41, V76.51
Screening for malignant neoplasms of the prostate	V76.44
Special screening for malignant neoplasms of intestine	V76.50, V76.52
Screening for malignant neoplasms of the oral cavity Screening for malignant neoplasms of the skin Screening for malignant neoplasms of the testis Screening for malignant neoplasms of the ovary Screening for malignant neoplasms of the vagina	V76.42 V76.43 V76.45 V76.46 V76.47
Screening for other malignant neoplasms Screening for unspecified malignant neoplasms	V76.8x V76.9

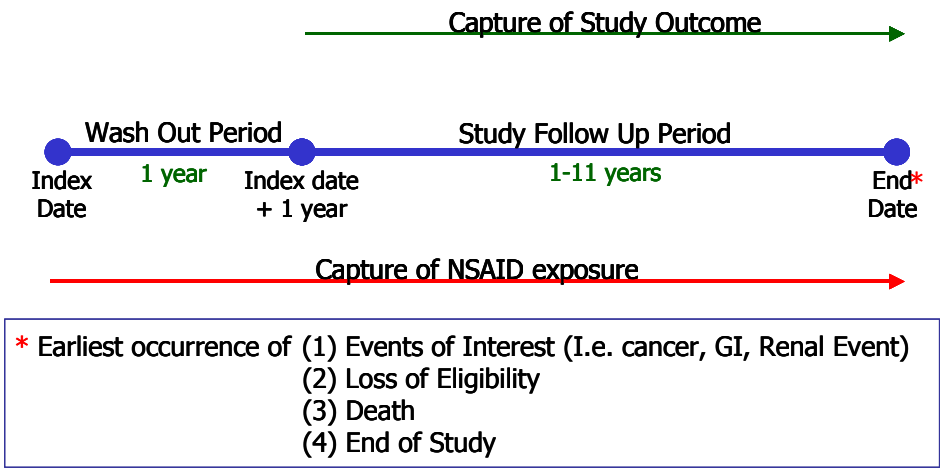

Figure 4.1: Temporal Pattern of Cohort Recruitment

CHAPTER 5

THE RISK-BENEFIT PROFILE OF NSAIDS AS CHEMOPREVENTIVES AGAINST COLORECTAL CANCER.[1]

[1] Koompalum D., Niecko T.E., Vidyashankar A.N., and Martin B.C. Submitted to *Annals Internal Medicines*.

Abstract

Background: Epidemiologic and clinical trials have suggested that non-steroidal anti-inflammatory drug (NSAIDs) exposure reduces the incidence of colorectal cancer (CRC). Since NSAIDs are relatively inexpensive, NSAIDs may offer a possible strategy to reduce the burden of CRC. However, before NSAIDs can be considered as realistic chemopreventives, their potential benefit must be weighed against the risks of gastrointestinal (GI) and renal adverse events

Objective: To establish the risk-benefit profile of NSAIDs as chemopreventives against CRC by confirming the protective effect of NSAIDs against CRC and to describe the relationship of NSAID use with GI and renal adverse events.

Design: Population-based retrospective cohort study.

Setting: Georgia Medicaid, 1990-2001

Subjects: Recipients aged 50-100 years with at least 2-year continuous eligibility without any history of colorectal cancer, GI, or renal diseases.

Measurements: The study outcomes of interest include CRC, GI events (i.e. GI ulcers and GI hemorrhage), and renal events (i.e. renal failure). We searched all medical claims for ICD-9-CM codes indicative of these outcome events

Results: The cohort contained 221,148 subjects and 62% were exposed to an NSAID. Mean follow-up period ranged from 6.2 years in GI cohort to 6.7 years in CRC cohort. The cohort average age was 70 years, 73.5% female, 47.6% white; 39.7% non-white and 12.7% were of unknown race. After multivariate-adjustments, subjects exposed to NSAIDs were 33% (RR,0.67; 95%CI,0.60 to 0.76), 15% (RR,0.85; CI,0.81 to 0.89), and 44% (RR,0.56; CI,0.53 to 0.58) less likely to have CRC, GI and renal events, respectively. The protective effect of against

CRC was greater with Cox-II-inhibitors (RR,0.25; CI,0.21 to 0.30) than non-selective NSAIDs (RR,0.87; CI,0.78 to 1.12). Any exposure to aspirin (RR,0.96; CI,0.83 to1.12) did not significantly influence the relative risk of CRC, however, the protective effects of higher cumulative exposure of aspirin were more pronounced than lower levels of cumulative exposure. We did not find an elevated risk of GI and renal adverse events in nearly all the analyses except small increases in the risk of GI events associated with aspirin (RR,1.13; CI,1.08 to 1.19), fenoprofen (RR,1.14; CI,1.07 to 1.21), and sulindac (RR,1.07; CI,1.00 to 1.15) use. Persons who had more than 1 year of NSAID exposure had relatively fewer GI and renal events than non-NSAID users

Conclusion: This is the first study to assess the risks of GI and renal events with the potential benefits of CRC protection association with NSAIDs in a single study. Our results portray a picture where there is a significant CRC prevention benefit of NSAIDs that is greater with higher levels of NSAID usages and almost no increased risk of renal or GI events especially for those with higher levels of cumulative NSAID use.

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most popular and widely used drugs because of their many therapeutic applications: anti-inflammatory, anti-pyretic, analgesic, possibly Alzheimer's disease protective effects of NSAIDs, and the cardiovascular benefits of aspirin.

The potentially protective effect of NSAIDs, especially aspirin, against the development of adenomatous polyps and colorectal cancer (CRC) has been robustly demonstrated in experimental, epidemiological, and randomized controlled trials in different populations and NSAID exposure measurement (1-18). It is estimated that NSAID users are 33% to 67% less likely to be diagnosed with CRC (1-18). A recent prospective study confirmed that both short-term and long-term regular use of aspirin is inversely associated with risk of colorectal adenoma, especially at higher doses (19). However, before a strategy of widely advocating the use of NSAIDs to prevent CRC can be considered, we need a better understanding of the risk benefit profile of NSAIDs. In other words, the benefit of NSAID usage on CRC must be weighed against the risks of NSAID-induced adverse events.

The well-documented adverse effects of NSAIDs include gastrointestinal (GI) complications (i.e. GI bleeding, perforation, and ulcer) and renal complications (i.e. acute renal failure). There are an estimated 100,000 hospitalizations and 10,000 to 20,000 deaths annually are due to NSAID-related GI complications at an annual cost of 1.6 billion dollars (20-21). There is little doubt that short term NSAID exposure can increase the risk of gastric and duodenal ulcers, GI hemorrhage and perforation. The risk of GI complications is 3-5 times more likely in NSAID users (22).

What is less clear is the impact of long term NSAID use on GI complications. Several studies have shown evidence that the risk for NSAID associated GI events is highest at the initiation of a regimen and then the risk tapers over time (23-25). Several observational studies have similarly reported decreasing risks of GI complications when NSAIDs were taken over longer durations (24-25). For instance, among current users, the constant risk of GI complications was found during the first year of NSAID use and was roughly 7 times more likely

than non-users (24). The risk of GI complications, however, was cut nearly half for NSAID exposure >1 year. (RR, 3.5; 95%CI, 2.0-6.0) (24). Gastric mucosal adaptation has been reported in both animal and human studies and may account for the decreasing risk of NSAID exposure over time (26-27). Gastric mucosal adaptation is described as the phenomenon in which visible gastric mucosal injury lessens or resolves completely despite continued administration of an injurious substance such as aspirin (28-31). Although the mechanism remains unclear, it is suggested that increased cell proliferation and correction of NSAID drug induced reduction in gastric blood flow as possibly being a factor (28).

Acute and chronic renal complications are also a major concern with NSAID use, especially in persons with pre-existing impaired renal function (32). For instance, persons with cirrhosis, heart failure, renal disease, diabetes, advanced age, heart failure, hypertension, and those exposed to nephrotoxic medications, i.e. diuretics, NSAIDs, and some antibiotics are at higher risk of acute renal failure (32-38). Renal injury as a result of NSAID exposure affects approximately 2 persons per 100,000 (36, 39-43). It is believed that NSAIDs may exacerbate renal insufficiency, hyperkalemia, interstitial nephritis, and acute renal failure by inhibiting renal prostaglandins (44). Griffin and colleagues reported that persons who currently used NSAIDs were almost 1.6 times more likely to be hospitalized for acute renal failure than ones who never used NSAID (OR, 1.58, 95%CI, 1.34-1.86). The highest risk was observed within first 30 days of use. Regular use of NSAID increased the risk of chronic renal failure 2.5 fold (95%CI, 1.9-3.3) (33). In contrast to most of the findings previously described, the Physician's Heath Cohort study contrarily showed no association between self-reported cumulative NSAID use over 14 years and the risk of renal dysfunction in men (37).

To our knowledge this is the first study to establish the risk-benefit profile of NSAIDs as chemopreventives against CRC. We aimed to confirm the protective effect of NSAIDs against CRC and to describe the relationship of NSAID use with GI and renal adverse events using a Georgia Medicaid cohort.

Methods

Data Source

Our study utilized the Georgia Medicaid administrative claims data. The administrative claims data capture all reimbursed medical encounters of the Georgia Medicaid recipients. Adults eligible for Georgia Medicaid benefits include some low-income residents, medically needy individuals, the elderly, and people with disabilities if state and federal guidelines are met. The GA Medicaid database contains an annual enrollment of approximately 1.2 million eligible persons per year, which provides patient level details on recipient demographics and monthly Medicaid coverage. All Medicaid beneficiaries' medical utilization, including inpatient, outpatient, nursing home, and emergency services, is collected in the medical claim file. The pharmacy claims file records each reimbursed prescription including information describing the date prescriptions are filled, drug name, National Drug Code (NDC), strength, dosage, and number of units dispensed. All three of the files are linked by encrypted recipient identifier allowing the construction of person level analytic files where treatments and ensuing medical encounters can be measured at the patient level.

Subjects

The study cohort consists of Medicaid Recipients aged 50-100 who had at least 2 years of continuous eligibility between January 1, 1990 and December 31, 1999. We excluded subjects who had any diagnosis of CRC, GI or renal disease within their first year eligibility, and any recipients with dual Medicare eligibility without full Medicaid coverage (figure 5.1). The cohort was followed until the earliest occurrence of: (1) outcomes of interest, namely CRC, GI events (i.e. GI ulcers and GI hemorrhage), and renal events (e.g. renal failure), (2) loss of eligibility, (3) death, or (4) end of study (December 31, 2001).

Identification of Colorectal Cancer, GI And Renal Events

To identify incident CRC, GI and renal events, all diagnoses recorded in the medical claims file were searched. All outcome occurrences were dated and determined by searching for claims with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes indicative of the outcome events described below.

Colorectal Cancer (CRC)

To identify incident CRC, we first adopted an ICD-9-CM algorithm suggested by Smalley and colleagues (12). ICD-9-CM codes of malignant neoplasm of colon (153.x) and rectum (154.x) were used and found to be consistent with histological findings. To enhance understanding potential role of NSAIDS as a primary prevention of cancer, we then added ICD-9-CM codes of Carcinoma in situ of colon (230.3) and rectum (230.4), as well as, secondary ICD-9-CM codes for malignant neoplasm of large intestine and rectum (197.5).

Gastrointestinal (GI) Events

The GI events were defined as upper gastrointestinal bleeding, perforation, or ulcer. A subject with any diagnosis of gastric ulcer (531.x), duodenal ulcer (532.x), gastrojejunal ulcer (534.x), peptic ulcer (533.x), and gastrointestinal hemorrhage (578.x) was identified (25). The positive predictive value of these codes were previously reported as 97%, 84%, 80%, and 59% with hospital clinical records for 531.x-532.x, 534.x, 533.x, and 578.x, respectively (45).

Renal Events

The renal events are diagnosed cases acute renal failure and other impairment of renal function that is associated with NSAID exposure. The ICD-9-CM algorithm to identify cases of renal events was derived from existing medical literature for potential NSAID-related renal failure (34,46-47). The outcome measures identified by ICD-9-CM codes were acute glomerulonephritis (580.x), nephrotic syndrome (581.x), non-specified nephritis and nephropathy (583.x), acute renal failure (584.x), renal failure (586.x), disorder of the kidney (593.9), diabetes with renal manifestations (250.4), and hypertension with renal manifestations (403.x, 404.x).

NSAID Exposure

We determined NSAID utilization by searching all prescription codes in the pharmacy claims file for all NSAIDs listed in table 5.1. Only orally administered NSAIDs are relevant to the study. The NDC codes were employed to identify aspirin, NSAID and COX-II-inhibitors prescribed. For those individuals who were prescribed any NSAID, we recorded the generic name, the chemical class, the strength (in milligrams), and the number of units of drug dispensed for each NSAID prescription.

We define low and high daily dose based on minimum and maximum starting doses recommended for treatment of arthritis as noted in the *Physicians' Desk Reference* (12,47). Cumulative drug exposure was used to determine prescription NSAID exposure in the study cohort and was defined as the number of units of drug dispensed multiplied by the dose of the drug. All study NSAID dosages were standardized and converted to ibuprofen dosage equivalents. Based on the assumption of equal efficacy among high-dose NSAIDs for the treatment of arthritis, an "ibuprofen weighted" factor is computed. An "ibuprofen weighted" factor equals 2,400 (high daily dose of ibuprofen) divided by the high daily dose recommended for any particular NSAID (12,47). Then, NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints. The cumulative exposure was defined as NSAID use equivalent to a period of NSAID use at the highest daily dose: less than one month (ibuprofen equivalents up to 72 grams), 1-6 months (ibuprofen equivalents 72-432 grams), 7-12 months (ibuprofen equivalents 433-876 grams), and greater than 12 months (ibuprofen equivalents more than 876 grams) of use.

Statistical Analysis

Demographic and other clinical characteristics (i.e. age, gender, length of Medicaid coverage, prevalence of selected comorbidities) between the NSAID exposure and non-exposure groups, were tabulated and tested for differences using chi-square test for categorical variables and t-test for continuous variables. All statistic analyses were performed using SAS statistical software (Version 8.2, SAS Institute, Cary, North Carolina). All p-values were 2-sided and significant level set at $p<0.05$.

Unadjusted incidence was calculated by dividing number of new cases of each outcome event by the number of person-years. We computed crude relative risks by dividing the unadjusted incidence rates of NSAID users (e.g. cases per 100,000 person-years) by those of non-users, and confidence intervals (CI) were estimated by Mantel Haenszel techniques (48).

Cox proportional hazards models were used to estimate the multivariate adjusted rates and relative risks (using PROC PHREG of SAS package). Model specification and operative definition of all covariates are summarized below. Multivariate adjusted relative risks (RRs) and 95%CI are reported.

Model Specification

The Cox proportional hazard model was defined as follows:

$$h(t \mid Z) = h_0(t) * \exp[\ \alpha(\text{NSAID exposure}) + \beta * X + \varepsilon\text{rror}\ ]$$

Where $h(t \mid Z)$: hazard rate at time 't' for an individual with risk vector Z

$h_0(t)$: baseline hazard rate

α : Coefficient for NSAID exposure

X : Matrix of covariates

β : Vector of coefficients corresponding to the matrix of covariates

Dependent Variables

Our major outcomes of interest are the first incidence of diagnosed cancers, and adverse gastrointestinal and renal events. Since occurrences or the three outcomes do not depend on one another, we model each outcome separately with specific set of covariates. For each study event of interest, a Cox proportional hazard model was fitted based on:

(1) Incidence of each study event: A dichotomous dependent variable was coded whether or not subjects had any diagnosis codes of the study outcome.

(2) Person-years in study cohort: Number of years each subjects stayed in the cohort is calculated by subtracting the date when a subject entered the cohort from the date when the subject left the cohort.

Independent variables

Effect of NSAID exposure was modeled in four sets of separate analyses as follows:

1) NSAID exposure as a class: A dichotomous independent variable coded if a subject prescribed any NSAID.
2) Cumulative exposure of NSAIDs: NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints (less than one month, 1-6 months, 7-12 months, and greater than 12 months)
3) NSAID exposure was classified into 3 categories: Aspirin, Non-aspirin NSAIDs, and Selective Cox-2 inhibitors.
4) In addition to model 3, the effect of the use of some specific NSAIDs were analyzed. Based on generic names recorded from each subject's prescriptions, NSAID exposure was classified into 8 groups (see below). There is a high possibility that subjects may be exposed to more than one product or group, so persons could have more than one of the following NSAID variables recorded as exposed. Furthermore, to determine the effect cumulative exposure of each on study endpoints, the cumulative exposure for each generic group was calculated and stratified into 4 categories: less than one month, 1-6 months, 7-12 months, and greater than 12 months.
   a) Aspirin
   b) Selective Cox-2 inhibitors (celecoxib and rofecoxib)
   c) Ibuprofen (commonly prescribed) (12,47)
   d) Naproxen (commonly prescribed) (12,47)
   e) Indomethacin (commonly prescribed)
   f) Fenoprofen (commonly prescribed)

g) Sulindac (effective in many animal models) (12,47)

h) Other non-specific NSAIDs

Covariates

All covariates included in the model were listed in table 5.2. Operational definition and the ICD-9-CMcodes for each covariate were summarized in table 5.2.

Results

The study cohort contained 221,148 subjects. On average, the length of follow-up ranged from 6.2 years (s.d. 3.5) in GI event cohort to 6.7 years (s.d. 3.5) in CRC cohort. The cohort average age was 70 years of age (s.d. 11 years); 73.5% were female; 47.6% were white; 39.7% were non-white and 12.7% were of unknown race. Overall, 62% of subjects were prescribed an NSAID. The 9 most commonly prescribed NSAIDs , accounted for 78% of all NSAID usage, were ibuprofen (23%), naproxen (12.5%), celecoxib (9%), aspirin (9%), indomethacin (8%), rofecoxib (6%), fenoprofen (5.5%), and sulindac (5%). Subject's demographic profile by exposure status for each outcome is displayed in Table 5.3. The lengths of follow-up of subjects prescribed NSAIDs were significantly longer than those not prescribed NSAIDs ($p<0.05$). Younger persons, non-whites, and females were more likely to have an NSAID prescription filled than their respective counterparts. Moreover, the NSAID exposure group was more likely to have an ICD-9-CM claim for tobacco use, obesity, and alcohol abuse.

We observed a significant lower risk for CRC (p-value <0.0001), GI (p-value<0.0001) and renal events (p-value<0.0001) among subjects exposed to NSAIDs compared with those not exposed to NSAIDs (Table 5.4). The multivariate-adjusted relative risks were significant, as 0.67 (95%CI, 0.60 to 0.76), 0.85 (95%CI, 0.81-0.89), and 0.56 (95%CI, 0.53-0.58) for CRC, GI and renal events respectively.

Older age groups, both 65 - 75 and >75 age groups, appeared to be at less risk for the three study outcomes than the 50 to 64 age group. Gender did not significantly alter the risk for all three outcomes; however, race was significant in the GI and renal models. While white race were at lower risk for renal events, whites were at higher risk for GI events. In the CRC cohort, obesity, alcoholism and tobacco smoke did not alter risk of CRC, however, obesity and alcoholism increased the risk of GI and renal events. Tobacco use increased the risk of GI events. We found that H. pylori infection and GI protective agents were the most important risk factors for GI events. While H. pylori infection increased risk of GI events by 2.5 times, subjects prescribed GI protective agents were 2.5 times more likely to experience a GI event. Diabetes mellitus and immunosuppressive agents (i.e. cyclosporine, tacrolimus) were the most important risk factors for renal events; subjects with diabetes, cyclosporine prescription, and tacrolimus prescription were 2.3, 3.7 and 3 times more likely to be diagnosed with renal events, respectively.

We considered the possibility that physicians' concern regarding NSAID-related adverse events could increase patients' health services utilization, thus prevent cases of CRC by removing adenomatous polyps. We found that subjects with frequent health services utilization were less likely to be diagnosed with CRC. Moreover, a similar inverse association revealed for GI and renal events.

The impact of specific NSAID exposure on CRC, GI and renal events are summarized in Tables 5.5-5.7. The apparent protective effect of Cox-II-inhibitors against CRC was the most pronounced (RR, 0.25; 95%CI, 0.21 to 0.30). Although the benefit of non-selective Cox inhibitors on CRC was shown as a whole, the benefit of each individual NSAID, including aspirin, against CRC were not significant. Compared with the non-NSAID exposure group, the reduction of GI events risk was found, to be lowest, in subjects prescribed Cox-II-inhibitors. With exception of naproxen (RR, 0.87, 95% CI, 0.83 to 0.91) and ibuprofen (RR, 0.95; 95%CI, 0.91 to 0.99), all non-selective NSAIDs and aspirin slightly increased risk of GI events. We found either no statistically significant increase, i.e. in aspirin (p-value=0.92), fenoprofen (p-value=0.05), and indomethacin group (p-value=0.65), or statistically significant decrease, i.e. ibuprofen (p-value<0.001), naproxen (p-value<0.001), and other NSAIDs (p-value<0.001), in renal events in each of the specific NSAIDs group. However, we found statistically significant increase in renal events in sulindac group (p-value=0.04).

The increased cumulative exposure of NSAIDs was associated with decreased rates of CRC, GI and renal events (figure 5.2). The higher the cumulative exposure, the lower the risk of CRC, GI and renal events. The adjusted RRs associated with more than the equivalent of 1 years of high daily dose were 0.39, 0.59, and 0.32 for CRC, GI and renal events, respectively.

Protective effects of long-term NSAID use against CRC, particularly for non-selective Cox inhibitor groups were showed despite non-significant relative risks of CRC in aspirin and non-selective Cox inhibitor groups. For instance, long-term use of sulindac and other non-specific NSAIDs were significantly associated with 50% and 42% decreased risk of CRC (figure 5.3). In addition, our results demonstrated the risk reduction of GI and renal events in persons who had more than 1 year of aspirin and non-selective Cox inhibitor usage (figures 5.4-5.5).

Because the impact of NSAIDs on GI and Renal events was somewhat surprising, a sensitivity analysis was conducted to explore other potential possible explanations for an apparent protective effect of NSAIDs on these outcomes. It has been noted from previous research with these data that long term care facilities provide relatively fewer ICD-9-CM codes than other providers and if NSAID usage was related to long term care use, that might account for an apparent undercoding and may partially explain the observed finding. To explore this possibility we conducted an analysis excluding all persons admitted to a long-term care facility > 1 year (n=63,326) and re-estimated the multivariate adjusted models on the remaining 157,822 subject (table 5.8).

Discussion

This is the first study to assess the risks of GI and renal events of NSAIDs with the potential benefits of CRC prevention in a single study. Overall, our study confirms that NSAID exposure exhibited a protective effect against CRC, with a reduction in risk of about 33% for any exposure to NSAIDs and greater reductions in relative risks at higher levels of NSAID consumption. This study demonstrated a consistent increasing reduction in CRC risks with increasing cumulative NSAID exposure where persons who had more than 1 years of NSAID usage experienced a 60% reduction in the risk of a CRC diagnosis than did persons who had no exposure. We found that the protective effect of Cox-II-inhibitors was the most apparent and was greater with increasing cumulative exposure. Despite a significant 28% relative risk reduction for any exposure to the non-selective Cox inhibitors as a class, the relative risks of CRC for aspirin and the selected individual non-selective Cox inhibitors trended toward a CRC prevention benefit, however, those associations for the individual NSAID drug were not

significant ($p>0.05$), which is most likely due to smaller samples and corresponding event rates, though collectively. These results were not affected after excluding recipients that were admitted to a long-term care facility for greater than one year.

We did not find an elevated risk of GI and renal adverse events. After multivariate adjustment, NSAID use was associated with a statistically significant reduction in GI and renal adverse events. Similar to the risks of CRC by cumulative NSAID exposure, higher cumulative exposure was associated with decreasing risks of GI and renal events. In others words, the risk of GI and renal adverse events appears to be inversely associated with cumulative amount used. Persons who had more than 1 years of NSAID usage experienced an apparent 40% and 70% decreased risk for GI and renal adverse events than did persons who had no exposure, respectively. Again, the apparent risk reductions observed were the greatest for Cox-II-inhibitors.

Nevertheless, these results must be interpreted with caution, as we required subjects to be free of all outcomes for one year within their first year eligibility. Subsequently, many of the NSAID users able to meet the inclusion criteria and remain in the study might tolerate NSAID therapy better than most typical users. Therefore, these subjects are less likely to be considered naïve to NSAIDs and may demonstrate a lower risk for GI and renal events relative to those persons with NSAID exposure and who don't tolerate therapy as well. In order to be reasonably certain that we could temporally relate NSAID use that precedes the development of our outcome events, it was necessary to exclude persons who experienced events in the first year of the study. These criteria were necessary because it would be unclear if claims occurring in year one represent new diagnoses or ongoing treatment of outcomes that occurred in the periods prior to when we had data available (left censoring). As a result of these exclusion criteria, persons

whom may have had events shortly after an initial exposure to NSAIDs may have been omitted and consequently the GI risks reported in this study may be understated, particularly for low volume NSAID users. The drugs assessed in this study were more inclusive than most other pharmacoepidemiolgic studies of this nature as both NSAIDs and aspirin products were examined. Studies measuring similar endpoints have typically only included either aspirin products or non-aspirin NSAIDs and ordinarily have not measured exposure of both in the same study. The NSAIDs included in this study reflect real life usage patterns more so than other studies that limit exposure to a narrow selection of NSAIDs.

Our results suggest that the risk of GI adverse events is highest at the beginning of NSAID use with decreases as persons consume more NSAIDs. This finding is consistent with studies showing that the initial doses of NSAIDs and not long term NSAID use are most likely to result in GI adverse related events (23-25). This may be explained by gastric mucosal adaptation, which has been reported in both animal and human studies (26,27). The age span of the population studied (age 50 to 100) is broader than other studies of this nature. Many other studies that examine the NSAID and CRC relationship often limit study inclusion criteria to persons age 65 years and greater. Studies have shown that the risk for CRC begins to escalate at age 50, which often leaves a large number of persons at risk unstudied. A breakpoint for age class was conducted at age 65 because of the potential of Medicare to pick up reimbursement for study outcomes procedures. Older age classes, both (65 - 75) and (>75), appeared to be at less risk for the three study outcomes than the 50 to 64 age group, possibly as a result of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare.

There are several potential limitations in this study. Based on inspecting the claims volume over time some issues with the completeness and accuracy of a very small portion of the data may have been detected. First, for one month of the study period (March 1998), the dates of service on the claims may have been errantly recorded for January, February or April 1998 and there was no way to reconcile these dates with source records. Secondly, the total numbers of claims for the period October through December 1997 are noticeably lower than expected. This was despite a re-generation of the claims data obtained from the claims processor. Since these data only affect a small time window in this study and there is no reason to believe that the dates or potentially missing claims were systematically related to exposure or outcome ascertainment, this is not likely to impact any measures of relative risk. As a check, these analyses were replicated where no data after September 1997 were used and none of the main findings reported here were meaningfully affected.

Since we depend on diagnosis (ICD-9-CM) codes to identify the study outcomes and confounders, measurement bias may arise due to coding inconsistencies. This may be of particular concern if there are differences in coding that is related to NSAID exposure. As a check for this potential concern, we conducted a sensitivity analysis excluding recipients with long term care admissions > 1 year and found the results to be generally consistent with the initial analysis. Additionally, detailed information on risk behaviors, i.e. tobacco and alcohol consumption is not specifically recorded in claims data and could only be inferred from diagnostic information. In claims data, clinical measures, i.e. histological type and stage of cancer, are also not available. So the effect of NSAIDs on different histological type and stage of cancer cannot be explored. Despite the fact that Medicaid pays for ASA, ibuprofen, and naproxen, exposure misclassification may still occur as a result of recipients purchasing these

products over-the-counter. This may attenuate the disparity between exposure and non-exposure groups and underestimate relative risk of outcomes.

Since it is well known that NSAIDs are associated with increasing risks of GI and renal events, though perhaps transitory, channeling bias is an inextricable limitation of this study because physicians would be less likely to prescribe non-selective NSAIDs to persons they believe might be prone to GI or renal adverse events. We attended to this limitation by including the use of gastroprotective agents (a potential marker for past GI events) as a covariate in the GI adverse event models, but we recognize that this can only partially describes someone's GI event likelihood. Moreover, physicians may also pay closer attention to those who take NSAIDs, for example, more physician visits, which may lead to earlier diagnosis. Nevertheless, frequency of health care utilization was adjusted in the models in an attempt to attend to this phenomenon. We do not believe that if recipients were randomly assigned to NSAIDs and non-NSAIDs that the same results would be obtained with regard to GI and renal adverse events, however, these data do demonstrate that the NSAID prescribing decisions made in this population are not associated with an increase in GI and Renal events and this finding may better reflect the risks of NSAID prescribing rather than the relative risk of NSAIDs themselves. Though we do believe that channeling bias is an important consideration when interpreting the results of the adverse events, we do not believe channeling bias is a significant concern for the results for the CRC prevention analyses, because it is unlikely that physicians were prescribing NSAIDs for persons whom they thought might be at higher risk of CRC during this study time frame.

Conclusion

Any NSAID exposure was associated with an approximate 30% reduction in the incidence of CRC with greater reductions observed for higher cumulative exposure to NSAIDs and COX-II inhibitors. There were no statistically significant increased rates of GI and renal events associated with NSAID prescribing in this population.

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Table 5.1: Commonly Available Non-Steroidal Anti-inflammatory Drug (NSAIDs), According to Chemical Class

Chemical Class	Generic	Low daily dose (mg)	High daily dose (mg)	Standardization to Ibuprofen
Nonselective COX inhibitors				
Salicylic acid derivatives	Aspirin (acetylsalicylic acid)	2,400	3,600	0.67
	Salicylate salts (i.e. Choline Magnesium trisalicylate)	2,000	3,000	0.80
	Diflunisal	500	1,000	2.40
	Salsalate	2,000	4,000	0.60
Heteroacrl acetic acids	Diclofenac	100	150	16.00
	Etodolac	800	1,200	2.00
	Ketorolac	10	40	60.00
	Tolmetin	1,200	1,800	1.33
Indole and indene acetic acids	Indomethacin	50	150	16.00
	Sulindac	300	400	6.00
Arylpropionic acids	Fenoprofen	900	2,400	1.00
	Flurbiprofen	200	300	8.00
	Ibuprofen	1,200	2,400	1.00
	Ketoprofen	200	300	8.00
	Naproxen	550	1,100	2.18
	Oxaprozin	1,200	1,800	1.33
Anthranilic acid (Fenamates)	Meclofenamic acid	100	400	6.00
	Mefenamic acid	500	1,000	2.40
Enolic acids				
Pyrazolones	Phenylbutazone	300	400	6.00
Oxicams	Piroxicam	less than 20	20	120.00
Nonacidic agent				
Alkanones	Nabumetone	1,000	2,000	1.20
Selective COX-2 Inhibitors				
Diaryl-substituted furanones	Rofecoxib	12.5	25	96.00
Diaryl-substituted isoxazole	Valdecoxib	10	20	120.00
Diaryl-substituted pyrazoles	Celecoxib	200	400	6.00

Source: (1) Roberts LJ2, Marrow JD. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Good man and Gilman's the pharmacological basis of therapeutics. Columbus: The McGraw-Hill Companies, Inc., 2001;687-731.

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Table 5.2: List of Covariates and Their Operational Definitions

Covariates	Outcomes		
	CRC	GI Events	Renal Events
Demographics			
Age (50-65, 65-75 >75)	Yes	Yes	Yes
Gender (Male vs. Female)	Yes	Yes	Yes
Race (White, Non-white, Unknown race)	Yes	Yes	Yes
Alcohol use and alcohol abuse (ICD-9-CM = 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 [49]	Yes	Yes	Yes
Obesity (ICD-9-CM = 278.x [49]	Yes	Yes	Yes
Tobacco Smoke (ICD-9-CM = 305.1, V15.82 [50]	Yes	Yes	Yes
Frequency of health care utilizations * <see footnote>	Yes	Yes	Yes
GI protective agents (i.e. Misoprostal, proton pump inhibitors (PPIs), histamine H2 receptor antagonists)	No	Yes	No
Emphysema (ICD-9-CM = 492.xx)	No	Yes	No
Chronic Bronchitis (ICD-9-CM = 491.xx)	No	Yes	No
H.Pylori infection (ICD-9-CM = 041.86)	No	Yes	No
Corticosteroids (adrenal cortical steroids)	No	Yes	No
Anticoagulant use (i.e. heparins, coumarin and indadiones)	No	Yes	No
Cirrhosis (ICD-9-CM = 571.5, 571.6)	No	No	Yes
Hypertension (ICD-9-CM = 401.xx, 402.xx, 405.xx [49]	No	No	Yes
Diabetes Mellitus (ICD-9-CM = 250.0x-250.3x; 250.5x-250.9x [49]	No	No	Yes
Congestive Heart Failure (ICD-9-CM = 389.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9 [49]	No	No	Yes
Liver Failure (ICD-9-CM = 570.xx)	No	No	Yes

Table 5.2 (continued): List of Covariates and Their Operational Definitions

Covariates	Outcomes		
	CRC	GI Events	Renal Events
Nephrotoxic Drugs:	No	No	Yes
Cardiovascular			
Diuretics	No	No	Yes
ACE inhibitors	No	No	Yes
Propranolol	No	No	Yes
Antimicrobial			
Aminoglycosides	No	No	Yes
Amphotericin B	No	No	Yes
Cephalosporins	No	Yes	Yes
Penicillins (carbenicillin, piperacillin, or ticarcillin)	No	Yes	No
Sulfonamides	No	No	Yes
Vancomycin	No	No	Yes
Rheumatologic			
Allopurinol	No	No	Yes
Gold	No	No	Yes
Sulfinpyrazone	No	Yes	Yes
Neuropsychiatirc			
carbamazepine	No	No	Yes
valproic acid	No	Yes	No
Immunosuppressive			
Cyclosporine	No	No	Yes
Tacrolimus	No	No	Yes
* Total number of visits to ambulatory care services, emergency department, long-term care facilities, and acute inpatient services			

Table 5.3: Study Cohort Characteristics by Drug Exposure Status by Outcome Events

Variables	Colorectal Cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	82,860	138,288	83,962	137,186	83,400	137,748
Follow up period, mean ± SD (yr) [a,b,c]	4.8 ± 2.9	7.3 ± 3.5	4.7 ± 2.9	7.1 ± 3.5	4.8 ± 2.9	7.2 ± 3.5
Prior utilizations, mean ± SD (number of visits) [a,b,c]	132.8±155.5	194.0±178.28	129.9±153.1	187.1±174.3	72.3±99.8	149.8±138.9
Demographics (%)						
Age, mean ± SD (yr) [a,b,c]	72.3 ± 11.8	69.1 ± 11.2	72.1 ± 11.9	69.2 ± 11.2	72.2 ± 11.9	69.0 ± 11.2
Female (%) [a,c]	68.4	76.5	68.3	76.6	68.4	76.6
Race [a,b,c]						
White (%)	54.1	43.6	53.9	43.7	53.9	43.7
Non White (%)	35.7	42.0	35.8	42.0	35.9	41.9
Unknown Race (%)	10.2	14.3	10.2	14.3	10.2	14.3
Risk Factors (%)						
Tobacco Smoke (%) [a,b,c]	1.6	3.1	1.5	2.7	1.5	3.0
Obesity (%) [a,b,c]	0.7	3.2	0.8	2.9	0.7	3.1
Alcohol Abuse (%) [a,b,c]	2.3	3.4	2.4	3.1	2.3	3.3
Cumulative duration of high daily dose ibuprofen, mo (%)						
None	37.5	0	38.0	0	37.7	0
< 1	0	16.1	0	16.3	0	16.3
1-6	0	20.0	0	20.1	0	20.1
7-12	0	9.6	0	9.4	0	9.4
>12	0	16.8	0	16.3	0	16.3

Between group comparisons of age, follow-up period (t-test), gender, race and risk factors (chi-square) were performed for each study outcome; [a] significant at $p<0.05$ for colorectal cancer; [b] significant at $p<0.05$ for GI events; [c] significant at $p<0.05$ for renal events

Table 5.4: Effect of NSAID Use on Incidence of Colorectal Cancer, Gastrointestinal and Renal events

Outcome Events	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR* (95% CI)	Multivariate adjusted RR** (95% CI)
Colorectal Cancer	Any Use	1,010,784	958	94.78	0.72 (0.65-0.80)	0.67 (0.60-0.76)
	None	396,772	521	131.31	Reference	Reference
GI Events	Any Use	975,217	7,748	794.49	0.93 (0.90-0.97)	0.85 (0.81-0.89)
	None	395,195	3,361	850.47	Reference	Reference
Renal Events	Any Use	994,116	5,774	580.82	0.79 (0.76-0.83)	0.56 (0.53-0.58)
	None	394,914	2,890	731.81	Reference	Reference

* Unadjusted relative risk (RR) and 95% confidence interval (CI) estimated by Mantel-Haenszel Techniques.

** Multivariate adjusted RR and 95% CI estimated by Cox-proportional hazard regression model.

Table 5.5: Effect of specific NSAID exposure on the incidence of any CRC event

NSAID exposure	Person-years	Colorectal Cancer Cases	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	258,175	215	83.28	0.63	0.96 (0.83, 1.12)
Non-Selective Cox Inhibitors	939,404	894	95.17	0.72	0.87 (0.78, 0.97)
Fenoprofen	169,604	141	83.14	0.63	0.92 (0.77, 1.10)
Ibuprofen	637,958	601	94.21	0.72	0.94 (0.84, 1.05)
Indomethacin	233,892	195	83.37	0.63	0.91 (0.78, 1.06)
Naproxen	362,741	305	84.08	0.64	0.88 (0.77, 1.01)
Sulindac	143,151	113	78.94	0.60	0.95 (0.78, 1.16)
Others NSAIDs	636,177	477	74.98	0.57	0.93 (0.73, 1.19)
Cox II Inhibitors	350,822	127	36.20	0.28	0.25 (0.21, 0.30)
None	396,772	521	131.31	Reference	Reference

Table 5.6: Effect of specific NSAID exposure on the incidence of any GI event

NSAID exposure	Person-years	GI Event Cases	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	245,571	1,875	763.53	0.90	1.13 (1.08, 1.19)
Non-Selective Cox Inhibitors	905,713	7,261	801.69	0.94	1.01 (0.96, 1.05)
Fenoprofen	161,914	1,317	813.39	0.96	1.14 (1.07, 1.21)
Ibuprofen	612,688	4,695	649.57	0.76	0.95 (0.91, 0.99)
Indomethacin	222,680	1,644	766.30	0.90	1.00 (0.95, 1.06)
Naproxen	342,769	2,523	738.28	0.87	0.87 (0.83, 0.91)
Sulindac	136,925	949	758.00	0.89	1.07 (1.00, 1.15)
Others NSAIDs	621,795	4,266	686.08	0.81	1.04 (0.95, 1.13)
Cox II Inhibitors	323,534	1,054	325.78	0.38	0.27 (0.25, 0.29)
None	395,195	3,361	850.47	Reference	Reference

Table 5.7: Effect of specific NSAID exposure and cumulative exposure on the incidence of any renal event

NSAID exposure	Person-years	Renal Event Cases	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	253,082	1,392	550.02	0.75	0.96 (0.91, 1.02)
Non-Selective Cox Inhibitors	923,774	5,414	586.07	0.80	0.71 (0.68, 0.75)
Fenoprofen	166,663	933	559.81	0.76	0.94 (0.88, 1.01)
Ibuprofen	626,646	3,524	497.05	0.68	0.74 (0.71, 0.78)
Idomethacin	227,443	1,585	562.36	0.77	1.00 (0.94, 1.06)
Naproxen	355,192	1,685	696.88	0.95	0.68 (0.64, 0.72)
Sulindac	139,593	859	450.94	0.62	1.12 (1.04, 1.20)
Others NSAIDs	646,904	2,938	454.16	0.62	0.80 (0.71, 0.89)
Cox II Inhibitors	340,472	738	216.76	0.30	0.22 (0.20, 0.24)
None	394,914	2,890	731.81	Reference	Reference

Table 5.8: Effect of NSAID exposure on Incidence of Colorectal Cancer, Gastrointestinal and Renal events after exclusion of all persons admitted to a long term care facility > 1 year

NSAID exposure	Person-years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Colorectal Cancer					
Aspirin	206,847	172	83.15	0.52	0.93 (0.79, 1.10)
Non-SelectiveCox Inhibitors	744,064	743	99.86	0.62	0.87 (0.77, 0.98)
Cox II Inhibitors	307,225	112	36.46	0.23	0.25 (0.21, 0.31)
None	254,675	409	160.60	Reference	Reference
GI Events					
Aspirin	195,098	1,660	850.86	0.78	1.17 (1.10, 1.23)
Non-Selective Cox Inhibitors	713,219	6,454	904.91	0.83	1.04 (0.99, 1.09)
Cox II Inhibitors	281,698	962	341.50	0.31	0.28 (0.26, 0.29)
None	253,652	2,776	1,094.41	Reference	Reference
Renal Events					
Aspirin	202,363	1,191	588.55	0.63	0.97 (0.91, 1.03)
Non-Selective Cox Inhibitors	730,720	4,575	626.10	0.67	0.68 (0.64, 0.71)
Cox II Inhibitors	298,008	660	221.47	0.24	0.22 (0.20, 0.24)
None	253,242	2,358	931.13	Reference	Reference

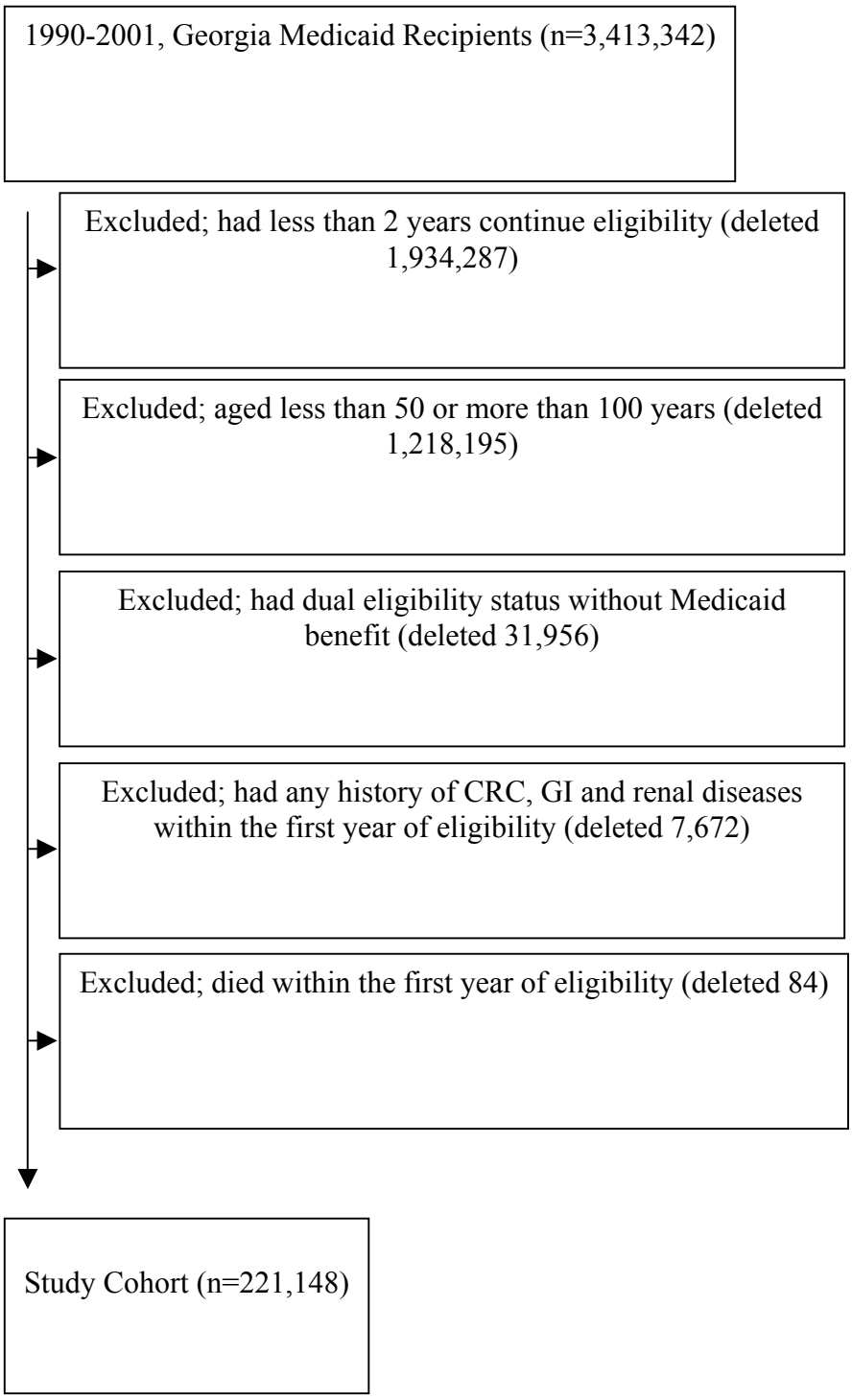

Figure 5.1: Flow Chart of Cohort Subjects

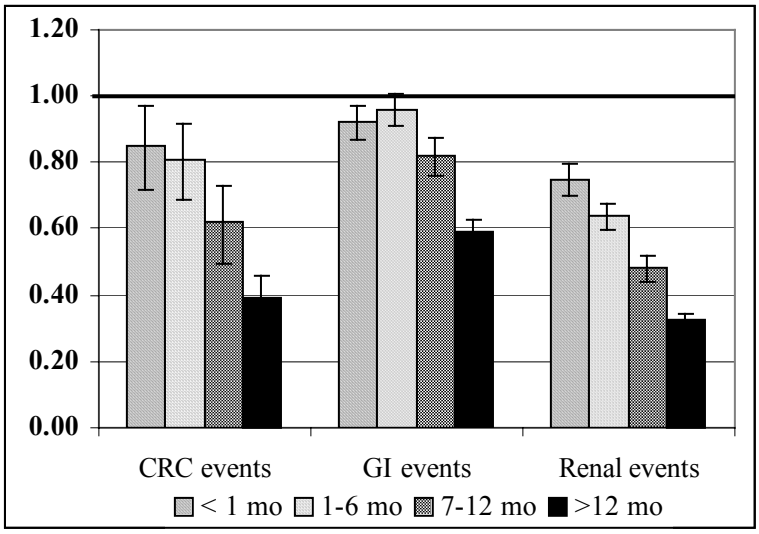

Figure 5.2: Effect of Cumulative NSAID Exposure on the Relative Risks of Colorectal cancer, GI and renal events

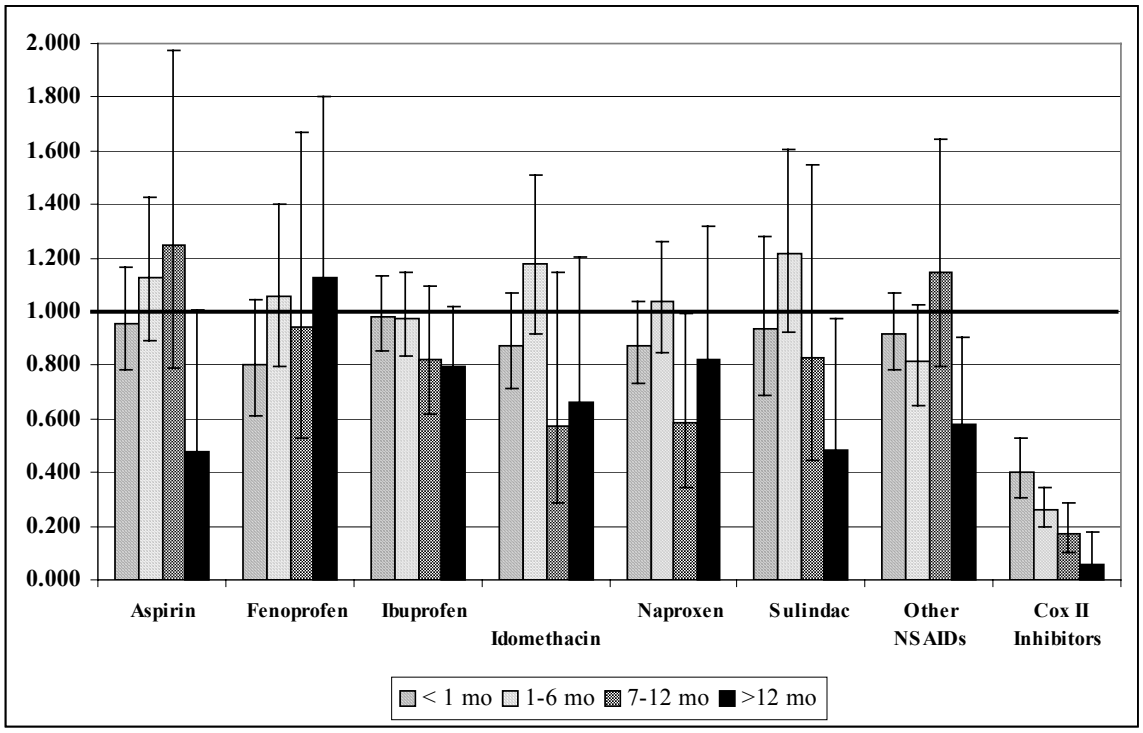

Figure 5.3: Effect of cumulative exposure of specific NSAIDs on the relative risks of any CRC event

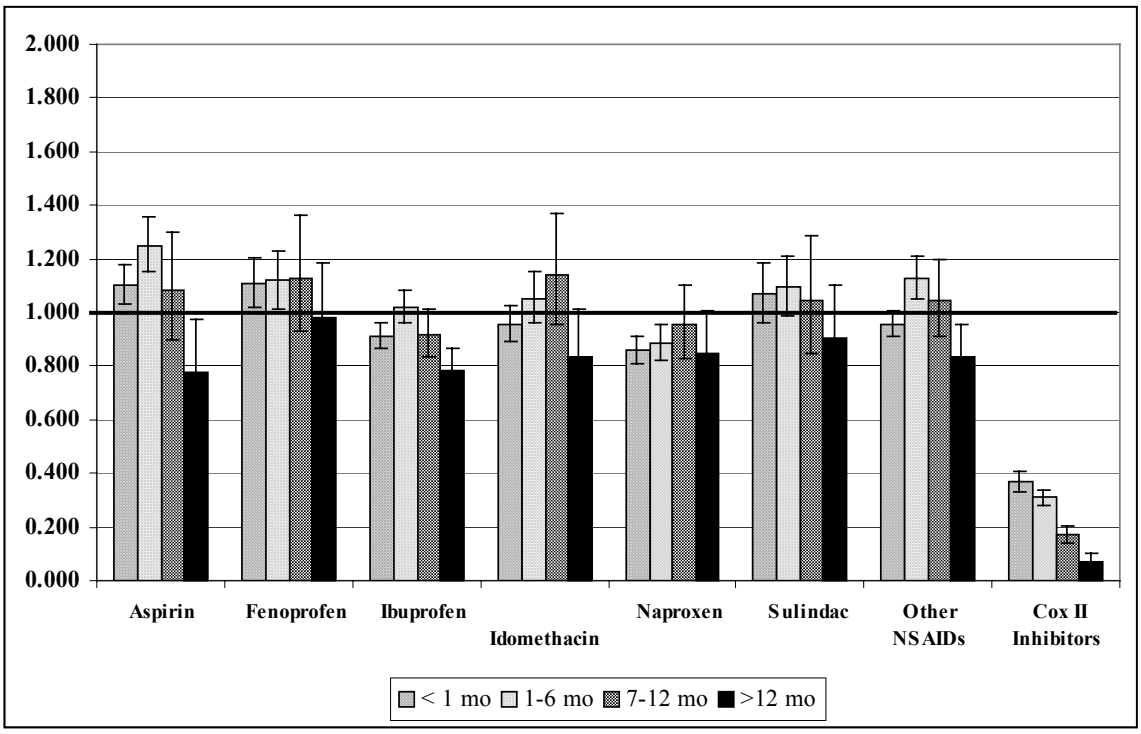

Figure 5.4: Effect of cumulative exposure of specific NSAIDs on the relative risks of any GI event

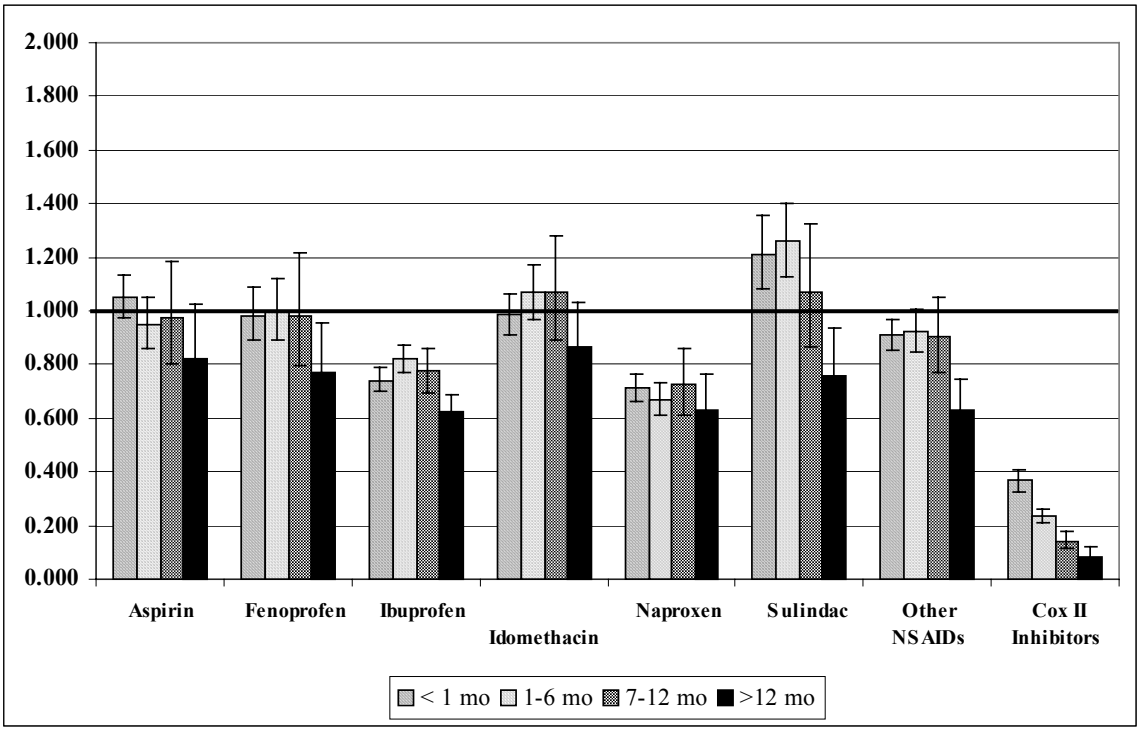

Figure 5.5: Effect of cumulative exposure of specific NSAIDs on the relative risks of any renal event

CHAPTER 6

THE RISK-BENEFIT PROFILE OF NSAIDS AS CHEMOPREVENTIVES AGAINST LUNG CANCER[2]

[2] Koompalum D., Vidyashankar A.N., Dainer P.M., Naeher L.P., Kotzan J.A., and Martin B.C. To be submitted to Journal of the National Cancer Institutes.

Abstract

Background: Several epidemiological studies have suggested that NSAID exposure may reduce the incidence of lung cancer. Since NSAIDs are relatively inexpensive, NSAIDs may offer a possible strategy to reduce the burden of lung cancer. However, before NSAIDs can be considered as chemopreventives, their potential benefit must be weighed against the risks of gastrointestinal (GI) and renal adverse effects.

Objectives: This study sought to determine the risk benefit profile of NSAIDs as chemopreventives by confirming the protective effect of NSAIDs against lung cancer and to describe the association between NSAID use and GI and renal diseases.

Methods: Two retrospective cohort studies were conducted using Georgia (GA) and North Carolina (NC) Medicaid claims. We recruited subjects aged 50-100, who had at least 2 years of continuous eligibility. We excluded subjects that had any diagnosis of lung cancer, GI, or renal diseases within their first year of eligibility. The cohort was followed until the earliest occurrence of: (1) outcomes of interest, namely lung cancer, GI events (i.e. GI Ulcers and GI hemorrhage) and renal events (e.g. renal failure and glomerulonephritis), (2) loss of eligibility, (3) death, or (4) end of study (December 31, 2001 for GA cohort and December 31, 1998 for NC cohort). All outcome occurrences were dated and determined by searching for claims with ICD-9-CM codes indicative of the outcome events. NSAID exposure was identified by searching the National Drug Code (NDC) in the prescription files. For each NSAID prescription, the strength and prescribed quantifies were kept to further explore a dose-response relationship. Survival Analysis (Cox-Proportional Hazard) technique was used to calculate all relative risks.

Results: There were 218,246 Georgia Medicaid recipients in the cohort and 62.3% were exposed to an NSAID. The GA cohort average age was 70.4 years (s.d. 11.5 years); 73.5% were female, 47.6% were white, 39.7% were non-white, and 12.7% were of unknown race. After multivariate-adjustments, subjects exposed to NSAIDs were at lower risk of lung cancer, GI and renal events, as 0.61 (95%CI, 0.56 to 0.67), 0.82 (95%CI, 0.78 to 0.86), and 0.56 (95%CI, 0.53 to 0.59), respectively. Out of 187,273 NC Medicaid recipients in the NC cohort, 43.5% were exposed to an NSAID. The NC cohort average age was 71.6years (s.d.10.9years); 73.1% were female, 53.7% were white, and 46.3% were non-white. After multivariate-adjustments, subjects exposed to NSAIDs were 17% (RR, 0.83; 95%CI, 0.73 to 0.95), 29% (RR, 0.71; 95%CI, 0.67 to 0.75), and 44% (RR, 0.56; 95%CI, 0.52 to 0.60) less likely to have lung cancer, GI and renal events, respectively. The apparent protective effect of Cox-II inhibitors against lung cancer was more pronounced (RR, 0.30; 95%CI 0.26 to 0.34) than aspirin and non-aspirin NSAIDs. We found that subjects prescribed ibuprofen had a significant 15% decrease in the risk of lung cancer; this result was confirmed in NC cohort as significant 21% decreased risk of lung cancer. We did not find an elevated risk of GI and renal events in all analyses. The increased cumulative exposure of NSAIDs was associated with decreased rates of lung cancer, GI and renal events.

Conclusions: Our study confirms the protective effect of NSAIDs on lung cancer and found no increase in renal and GI events.

Background

Lung cancer is one of the most common cancers diagnosed in the United States and the leading cause of cancer death {American Cancer Society 2004}. The incidence of lung cancer in a given population largely reflects its prevailing smoking habit; 87% of all lung cancer deaths are attributable to smoking {American Cancer Society 2004}. Although cigarette smoking is thought to be the primary risk factor for lung cancer, there are several other risk factors contributing to lung cancer including environmental exposures, family history, and history of lung diseases, e.g. tuberculosis.

Numerous studies have shown elevation of cyclooxygenase (COX) expression, especially COX-2 isoform, occurs in cancerous tissues, including adenocarcinoma and squamous cell carcinoma of the lungs {Marks 1999, Subbaramaiah 2003}. The COX enzyme and carcinogenesis have been linked in genetic studies that increased levels of COX-2 and prostaglandins can potentially account for the tumor-promoting effects; prostaglandins could enhance tumor growth and metastasis by stimulating angiogenesis and invasiveness, in addition to inhibiting apoptosis and immune surveillance {Liu 2001, Marks 1999}. Moreover, epidemiologic, experimental, and intervention research suggests that NSAIDs can inhibit COX enzyme increases tumor cell apoptosis {Subbaramaiah 2003, Xu 2002}.

Several case control and cohort studies have sought to elucidate associations between NSAID use and lung cancer {Rosenberg 1995, Langman 2000, Akhmedkhanov 2002, Muscat 2003, Moysich 2002, Harris 2002, Schreinemachers 1994, Paganini-Hill 1989, Thun 1993}. Although a meta-analysis of those studies {Gonzalez-Perez, 2003} concluded a non-significant reduced risk of lung cancer in NSAID (RR 0.65, 95%CI 0.34-1.22) and aspirin users (RR, 0.84; 95%CI 0.66-1.07), its result was derived from 8 heterogeneous studies with small sample sizes.

In addition, a significant inverse association was detected in the high-risk population, smokers. The estimated 68% risk reduction among regular aspirin-use smokers was reported {Harris 2002}.

The notorious adverse effects of NSAIDs include gastrointestinal (GI) complications (i.e. GI bleeding, perforation, and ulcer) and renal complications (i.e. acute renal failure). Increased risk of gastric and duodenal ulcers, GI hemorrhage and perforation shortly after first NSAID exposure are frequently reported {Ofman 2002}. However, the impact of long-term NSAID use on GI complications is somewhat unclear. Evidence has shown that the risk for NSAID associated GI events is highest at the initiation of a regimen and then the risk tapers over time {Gabriel 1991, Garcia Rodriquez 1998, Smalley 1995}. Several observational studies have similarly reported decreasing risks of GI complications when NSAIDs were taken over longer durations {Garcia Rodriquez 1998, Smalley 1995}. For instance, among current users, the constant risk of GI complications was found during the first year of NSAID use and was roughly 7 times more likely than non-users {Garcia Rodriquez 1998}. The risk of GI complications, however, was cut nearly half for NSAID exposure >1 year. (RR, 3.5; 95%CI, 2.0-6.0) {Garcia Rodriquez 1998}. Gastric mucosal adaptation has been reported in both animal and human studies and may account for the decreasing risk of NSAID exposure over time {Fitzpatrick 1999, Lipscomb 1996}. Gastric mucosal adaptation is described as the phenomenon in which visible gastric mucosal injury lessens or resolves completely despite continued administration of an injurious substance such as aspirin {Olivero 1992, Graham 1983, Graham 1988, Graham 1986}. Although the mechanism remains unclear, it is suggested that increased cell proliferation and correction of NSAID drug induced reduction in gastric blood flow as possibly being a factor {Olivero 1992}.

Another major concern with NSAID use is acute and chronic renal complications, especially in persons with pre-existing impaired renal function {Henry 1992}. For instance, persons with cirrhosis, heart failure, renal disease, diabetes, advanced age, heart failure, hypertension, and those exposed to nephrotoxic medications, i.e. diuretics, NSAIDs, and some antibiotics are at higher risk of acute renal failure {Fored 2001, Griffin 2000, Hernandez-Diaz 2001, Perneger 1994, Rexrode 2001, Bailie 1995, Henry 1992}. NSAIDs are believed to exacerbate renal insufficiency, hyperkalemia, interstitial nephritis, and acute renal failure by inhibiting renal prostaglandins {Brooks 1998}. Griffin and colleagues reported that persons who currently used NSAIDs were almost 1.6 times more likely to be hospitalized for acute renal failure than ones who never used NSAIDs (OR, 1.58, 95%CI, 1.34-1.86) {Griffin 2000}. The highest risk was observed within first 30 days of use. Regular use of NSAID increased the risk of chronic renal failure 2.5 fold (95%CI, 1.9-3.3) {Fored 2001}. In contrast to most of the findings previously described, the Physician's Heath Cohort study contrarily showed no association between self-reported cumulative NSAID use over 14 years and the risk of renal dysfunction in men {Rexrode 2001}.

To establish the risk-benefit profile of NSAIDs as chemopreventives against lung cancer, we aimed to confirm the protective effect of NSAIDs against lung cancer and to describe the relationship of NSAID use with GI and renal adverse events using 2 Medicaid cohorts from states of Georgia and North Carolina.

Methods

Data Source

We simultaneously conducted 2 retrospective cohort studies utilizing administrative claims data of the Medicaid program from 2 states: Georgia and North Carolina. The Medicaid, jointly funded by the Federal and State governments, is health insurance that assists certain individuals and families with limited incomes and resources in providing medical and health-related services for those who meet eligibility criteria. Adults eligible for Medicaid benefits include some low-income residents, medically needy individuals, the elderly, and people with disabilities if state and federal guidelines are met.

The Georgia Medicaid administrative claims data capture all reimbursed medical encounters of the Georgia Medicaid recipients. The GA Medicaid database contains an annual enrollment of approximately 1.2 million eligible persons per year, and the enrollment file contains patient level details on recipient demographics, including patient identifier, date of birth, gender, race, date of dead, as well as monthly Medicaid coverage (eligibility information). All Medicaid beneficiaries' medical utilization, including inpatient, outpatient, nursing home, and emergency services, is collected in the medical claims file. The pharmacy claims file records each reimbursed prescription including information describing the date prescriptions are filled, drug name, National Drug Code (NDC), strength, dosage, and number of units dispensed. All three of the files are linked by encrypted recipient identifier allowing the construction of person level analytic files where treatments and ensuing medical encounters can be measured at the patient level.

Similarly, the North Carolina Medicaid claims database is an administrative claim data of the North Carolina Medicaid recipients' medical encounters. There are roughly 1 million North

Carolina Medicaid recipients per year. The NC Medicaid data contain patient level details on demographics, monthly coverage, non-prescription medical utilization, and pharmacy claim file, all of which are linked by encrypted recipient identifier.

Subjects

In both cohorts, the study subjects were between the ages of 50 and 100 years, who had at least 2 years of continuous eligibility. We excluded subjects who had any diagnosis of lung cancer, GI or renal disease within their first year of eligibility, and any recipients with dual Medicare eligibility without full Medicaid coverage (figures 6.1-6.2). The cohort was followed until the earliest occurrence of: (1) outcomes of interest, namely lung cancer, GI events (i.e. GI ulcers and GI hemorrhage), and renal events (e.g. renal failure), (2) loss of eligibility, (3) death, or (4) end of study (figure 6.3).

Identification of Lung Cancer, GI and Renal Events

To identify incident lung cancer, GI, and renal events, all diagnoses recorded in the medical claims file were searched. All outcome occurrences were dated and determined by searching for claims with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes indicative of the outcome events described below.

Lung cancer

ICD-9-CM codes identifying incident lung cancer included diagnosis of malignant lung cancer (162.x). Several studies have utilized and shown that all codes are coherent with SEER

tumor registry data {Whittle 1991, Fedele 1998}. We added ICD-9-CM codes for carcinoma in situ (231.2), benign (212.2), and secondary malignant neoplasms (197.0) of the lungs.

Gastrointestinal (GI) Events

The GI events were defined as upper gastrointestinal bleeding, perforation, or ulcer. A subject with any diagnosis of gastric ulcer (531.x), duodenal ulcer (532.x), gastrojejunal ulcer (534.x), peptic ulcer (533.x), and gastrointestinal hemorrhage (578.x) was identified {Smalley 1995}. The positive predictive value of these codes were previously reported as 97%, 84%, 80%, and 59% with hospital clinical records for 531.x-532.x, 534.x, 533.x, and 578.x, respectively {Cattaruzzi 1999}.

Renal Events

The renal events are diagnosed cases acute renal failure and other impairment of renal function that is associated with NSAID exposure. The ICD-9-CM algorithm to identify cases of renal events was derived from existing medical literature for potential NSAID-related renal failure {Griffin 2000, Harley 2003, Niecko 2001}. The outcome measures identified by ICD-9-CM codes were acute glomerulonephritis (580.x), nephrotic syndrome (581.x), non-specified nephritis and nephropathy (583.x), acute renal failure (584.x), renal failure (586.x), disorder of the kidney (593.9), diabetes with renal manifestations (250.4), and hypertension with renal manifestations (403.x, 404.x).

NSAID Exposure

We determined NSAID utilization by searching all prescription codes in the pharmacy claims file for all NSAIDs listed in table 6.1. Only orally administered NSAIDs are relevant to the study. The NDC codes were employed to identify aspirin, NSAID and COX-2 inhibitors prescribed. For those individuals who were prescribed any NSAID, we recorded the generic name, the chemical class, the strength (in milligrams), and the number of units of drug dispensed for each NSAID prescription. In the NC cohort, we were unable to determine an impact of COX-II-inhibitors on study events due to unavailable data; dates approved by FDA of celecoxib and refecoxib were December 1998 and May 1999 respectively.

We define low and high daily dose based on minimum and maximum starting doses recommended for treatment of arthritis as noted in the *Physicians' Desk Reference* {Smalley 1999, Niecko 2001}. Cumulative drug exposure was used to determine prescription NSAID exposure in the study cohort and was defined as the number of units of drug dispensed multiplied by the dose of the drug. All study NSAID dosages were standardized and converted to ibuprofen dosage equivalents. Based on the assumption of equal efficacy among high-dose NSAIDs for the treatment of arthritis, an "ibuprofen weighted" factor is computed. An "ibuprofen weighted" factor equals 2,400 (high daily dose of ibuprofen) divided by the high daily dose recommended for any particular NSAID {Smalley 1999, Niecko 2001}. Then, NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints. The cumulative exposure was defined as NSAID use equivalent to a period of NSAID use at the highest daily dose: less than one month (ibuprofen equivalents up to 72 grams), 1-6 months (ibuprofen equivalents 72-432 grams), 7-12 months (ibuprofen equivalents 433-876 grams), and greater than 12 months (ibuprofen equivalents more than 876 grams) of use.

Statistical Analysis

Demographic and other clinical characteristics (i.e. age, gender, length of follow up, prevalence of selected comorbidities) between the NSAID exposure and non-exposure groups were tabulated and tested for differences using chi-square test for categorical variables and t-test for continuous variables. All statistic analyses were performed using SAS statistical software (Version 8.2, SAS Institute, Cary, North Carolina). All p-values were 2-sided and the significance level was set at $p<0.05$.

Unadjusted incidence was calculated by dividing number of new cases of each outcome event by the number of person-years. We computed crude relative risks by dividing the unadjusted incidence rates of NSAID users (e.g. cases per 100,000 person-years) by those of non-users.

Cox proportional hazards models were used to estimate the multivariate adjusted rates and relative risks (using PROC PHREG of SAS package). Model specification and operative definition of all covariates are summarized below. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CI) are reported.

Model Specification

The Cox proportional hazard model was defined as follows:

$h(t \mid Z) = h_0(t) * \exp[\ \alpha(\text{NSAID exposure}) + \beta * X + \varepsilon\text{rror}\ ]$

Where $h(t \mid Z)$: hazard rate at time 't' for an individual with risk vector Z

$h_0(t)$: baseline hazard rate

α : Coefficient for NSAID exposure

X : Matrix of covariates

β : Vector of coefficients corresponding to the matrix of covariates

Dependent Variables

Our major outcomes of interest were the first incidence of diagnosed cancers, and adverse gastrointestinal and renal events. Since occurrences of the three outcomes do not depend on one another, we modeled each outcome separately with specific set of covariates. For each study event of interest, a Cox proportional hazard model was fitted based on:

(1) Incidence of each study event: A dichotomous dependent variable was coded whether or not subjects had any diagnosis codes of the study outcomes.

(2) Person-years in study cohort: Number of years each subjects stayed in the cohort is calculated by subtracting the date when a subject entered the cohort from the date when the subject left the cohort, since we obtained NSAID exposure information from the first date when the subject entered the cohort.

Independent variables

Effect of NSAID exposure was modeled in four sets of separate analyses as follows:

1) NSAID exposure as a class: A dichotomous independent variable coded if a subject was prescribed any NSAID.
2) Cumulative exposure of NSAIDs: NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints (less than one month, 1-6 months, 7-12 months, and greater than 12 months)
3) Effects of the use of some specific NSAIDs were analyzed. Based on generic names recorded from each subject's prescriptions, NSAID exposure was classified into 8 groups (see below). There is a high possibility that subjects may be exposed to more than one product or group, so persons could have more than one of the following NSAID variables recorded as exposed. Furthermore, to determine the effect cumulative exposure of each on study endpoints, the cumulative exposure for each generic group was calculated and stratified into 4 categories: less than one month, 1-6 months, 7-12 months, and greater than 12 months.
    a) Aspirin
    b) Selective Cox-2 inhibitors (celecoxib and rofecoxib)
    c) Ibuprofen (commonly prescribed) {Smalley 1999, Niecko 2001}
    d) Naproxen (commonly prescribed) {Smalley 1999, Niecko 2001}
    e) Indomethacin (commonly prescribed)
    f) Fenoprofen (commonly prescribed)
    g) Sulindac (effective in many animal models) {Smalley 1999, Niecko 2001}
    h) Other non-specific NSAIDs

4) In addition determining effect of cumulative NSAID exposure as a fixed variable, we entered NSAID cumulative exposure as time-dependent variables in order to depict possible optimal dose and duration of NSAID exposure as chemopreventives. First, effects of annual cumulative doses were described. We further investigated effects of monthly cumulative doses.

Covariates

All covariates included in the model were listed in table 6.2. Operational definition and the ICD-9-CMcodes for each covariate were summarized in table 6.2.

Results

There were 218,246 Georgia Medicaid recipients in the cohort and 62.3% were exposed to an NSAID. On average, a subject was followed 6.4 years. The cohort average age was 70.4 years (s.d. 11.5 years); 73.5% were female, 47.6% were white, 39.7% were non-white and 12.7% were of unknown race. Incidence rates of lung cancer, GI and renal events were 181.1, 775.4, and 599.5 per 100,000 person-years, respectively.

The NC cohort contained 187,273 NC Medicaid recipients and 43.5% were exposed to an NSAID. On average, a subject was followed 5.1years. The cohort average age was 71.6 years (s.d. 10.9 years); 73.1% were female, 53.7% were white, and 46.3% were non-white. Incidence rates of lung cancer, GI and renal events were 103.0, 576.3, and 327.2 per 100,000 person-years, respectively.

Both GA and NC cohort characteristics by NSAID exposure status is displayed in tables 6.3-6.4. The length of follow up of subjects exposed NSAIDs were significantly longer than those not exposed NSAIDs ($p<0.05$). Younger persons, non-whites and women were more likely to have an NSAID prescription filled than their respective counterparts.

We observed a significantly lower risk for lung cancer, GI and renal events among subjects exposed to NSAIDs compared with those not exposed to NSAIDs (tables 6.5-6.6) after multivariate adjustment, but had mixed results when comparing the unadjusted results obtained from GA and NC. Results from the GA cohort revealed that the multivariate-adjusted relative risks were significant, as the relative risks were 0.61 (95%CI, 0.56 to 0.67), 0.82 (95%CI, 0.78 to 0.86), and 0.56 (95%CI, 0.53 to 0.59) for lung cancer, GI and renal events, respectively for Georgia. Unlike the results obtained from the Georgia Medicaid data, the unadjusted rates for the North Carolina NSAID users were higher with unadjusted relative risks of 1.17 (95%CI, 1.10 to 1.25), 1.60 (95%CI, 1.55 to 1.64), and 1.26 (95%CI, 1.22 to 1.31) for lung cancer, GI, and renal events. The multivariate-adjusted relative risks from the NC cohort, were significant and comparable to the GA estimates, as the relative risks were 0.83 (95%CI, 0.73 to 0.95), 0.71 (95%CI, 0.67 to 0.75), and 0.56 (95%CI, 0.52 to 0.60) for lung cancer, GI and renal events, respectively.

According to both the GA and NC cohorts, effects of covariates on study events of interest were summarized (tables 6.7-6.9). Older age groups, both 65-75 and >75 age groups, appeared to be at less risk for the three study outcomes than the 50-64 age group. Women were at lower risk for all three outcomes. Race was significant in all three outcomes. While whites were at lower risk for renal events, they were at higher risk for lung cancer and GI events. Alcoholism increased the risk of lung cancer, GI and renal events. Tobacco smoke did not alter

risk of renal events; however, tobacco smoke increased the risk of lung cancer and GI events. Obesity did not alter risk of lung cancer and renal events; however, obesity increased the risk of GI events. We found that lung diseases were associated with increased risk of lung cancer. H. pylori infection and GI protective agents were the most important risk factors for GI events. While H. pylori infection increased risk of GI events by 2-4 times, subjects prescribed GI protective agents were 2-6 times more likely to experience a GI event. Diabetes mellitus and immunosuppressive agents (i.e. cyclosporine) were the most important risk factors for renal events; subjects with diabetes and cyclosporine prescription were 2-2.3 and 2-4 times more likely to be diagnosed with renal events, respectively.

We considered the possibility that physicians' concern regarding NSAID-related adverse events could increase patients' health services utilization, thus allow for earlier detection of lung cancer. We found that subjects with more frequent health services utilization were less likely to be diagnosed with lung cancer. Moreover, a similar inverse association revealed for GI and renal events.

The impact of specific NSAID exposure on lung cancer, GI and renal events are summarized in tables 6.10-6.11. The protective effect of Cox-2 inhibitors against lung cancer was the most pronounced benefit. The benefit of aspirin against lung cancer was not significant. In the GA cohort, we found that subjects prescribed ibuprofen and naproxen had a significant 15% decreased risk of lung cancer, although only the benefit of ibuprofen (RR, 0.79; 95%CI 0.68 to 0.93), not naproxen (RR, 0.99; 95%CI 0.84 to 1.17), was confirmed in the NC cohort. Compared with the non-NSAID exposure group, the reduction of GI event risks was found, to be lowest in subjects prescribed Cox-2 inhibitors. With the exception of ibuprofen and naproxen, all non-selective NSAIDs and aspirin slightly increased the risk of GI events in the GA cohort.

However, all non-selective NSAIDs and aspirin insignificantly altered risk of GI events in NC cohort with ibuprofen, naproxen and indomethacin significantly decreased risk of GI events. Consistent results from both GA and NC cohorts showed no increase in renal events in each of the specific NSAID groups, except sulindac. Additionally, we found that ibuprofen and naproxen exposures were inversely associated with risk of renal events.

The increased cumulative exposure of NSAIDs was associated with decreased rates of lung cancer, GI and renal events (figures 6.4-6.5). The higher the cumulative exposure, the lower the risk of lung cancer, GI and renal events. The protective effects of long-term non-aspirin NSAID use against lung cancer were shown despite non-significant relative risks (figures 6.6, 6.9). For instance, long-term use of ibuprofen was associated with a significant 20% decreased risk of lung cancer (figure 6.6). In addition, our results from both GA and NC cohort demonstrated the risk reduction of GI and renal events in persons who had more than 1 year of each specific NSAID exposure (figures 6.7-6.8, 6.10-6.11).

Significant inverse associations were revealed between annual cumulative doses and risk of lung cancer start at year 7 onward in both the GA and NC cohort. One unit increase of ibuprofen-equivalent milligram was associated with the 1.74×10^{-5} (p-value, 0.0413), and 2.33×10^{-5} (p-value, 0.0178) decrease of log relative risk of lung cancer at year 7 in the GA and NC cohort, respectively. One unit increase of ibuprofen-equivalent milligram was associated with the 3.27×10^{-5} (p-value, 0.0021), and 5.35×10^{-5} (p-value, 0.0059) decrease of log relative risk of lung cancer at year 8 in the GA and NC cohort, respectively. The magnitude of reduced risk of lung cancer was more evident at the later year. For example one unit increase of ibuprofen-equivalent milligram was associated with the 12.41×10^{-5} (p-value, <.0001) and 48.59×10^{-5} (p-value, <.0001) decrease of log relative risk of lung cancer at year 11 and year 12 in the GA

cohort, respectively. Furthermore, inverse associations were revealed between monthly cumulative doses and risk of lung cancer in the year 7 and the later years in both the GA and NC cohort. One unit increase of ibuprofen-equivalent milligram was associated with the 19.96×10^{-5} (p-value, 0.0002) decrease of log relative risk of lung cancer at month 12 of the year 7 in the GA cohort. Similarly, one unit increase of ibuprofen-equivalent milligram was significantly associated with the 15.22×10^{-5} (p-value, 0.0486), and 23.48×10^{-5} (p-value, 0.0349) decrease of log relative risk of lung cancer at month 3 and 9 of the year 7 in the NC cohort, respectively.

A sensitivity analysis was conducted to explore other potential possible explanations for an apparent protective effect of NSAIDs on these outcomes, especially on GI and renal events. It has been noted from previous research with these data that long-term care facilities provide relatively fewer ICD-9-CM codes than other providers and if NSAID usage was related to long-term care use, that might account for an apparent undercoding and may partially explain the observed finding. To explore this possibility we conducted an analysis excluding all persons admitted to a long-term care facility more than 1 year and re-estimated the multivariate adjusted models on the remaining subject; we excluded 62,998 and 310 persons admitted to a long-term care facility more than 1 year from GA and NC cohorts, respectively. The results of sensitivity analyses were presented in tables 6.12-6.13.

Moreover, we conducted an additional sensitivity analysis excluding all persons whose age was between 65 and 100 years. Since there are some disagreement with other studies that have shown the risk for lung cancer increased with age, we found that older age classes, both 65-75 and >75, appeared to be at less risk for the three study outcomes than the 50-64 age group. We believe this is possibly a result of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare.

We excluded 150,139 and 141,390 persons whose age was between 65 and 100 years from the GA and NC cohorts, respectively and re-estimated the multivariate adjusted models on the remaining subject. The results of sensitivity analysis were comparable with those reported in the original cohort.

Discussion

Our study found that NSAID exposure exhibited a modest protective effect against lung cancer with a reduction in risk of about 17-39% for any exposure to NSAIDs and greater reductions in relative risks at higher levels of NSAID consumption. A consistent increasing reduction in lung cancer risks with increasing cumulative NSAID exposure where persons who had more than 1 years of NSAID usage experienced more than 50% reduction in the risk of a lung cancer diagnosis than did persons who had no exposure. We found that the protective effect of Cox-2 inhibitors was the most apparent and was greater with increasing cumulative exposure. These results were not affected after excluding recipients that were admitted to long-term care facilities for greater than one year.

We did not find an elevated risk of GI and renal adverse events. After multivariate adjustment, NSAID use was associated with a statistically significant reduction in GI and renal adverse events. Similar to the risks of lung cancer by cumulative NSAID exposure, higher cumulative exposure was associated with decreasing risk of GI and renal events. In other words, the risk of GI and renal adverse events appears to be inversely associated with cumulative amount used. Persons who had more than 1 years of NSAID usage experienced an apparent 46-62% and 68-72% decreased risk for GI and renal adverse events than did persons who had no exposure, respectively.

Nevertheless, these results must be interpreted with caution. Since subjects were required to be free of all outcomes within first year of their eligibility, many of the NSAID users able to meet the inclusion criteria and remain in the study might tolerate NSAID therapy better than most typical users. Therefore, these subjects may demonstrate a lower risk for GI and renal events relative to those persons with NSAID exposure who do not tolerate therapy. However, to be certain about temporal relationship between NSAID use and the development of our outcome events, it was necessary to exclude persons who experienced events in the first year of the study. As a result of this exclusion criterion, persons whom may have had events shortly after an initial exposure to NSAIDs may have been omitted and consequently the GI risks reported in this study may be understated, particularly for low volume NSAID users.

We found a reduction in risk of lung cancer about 17-39% for any exposure to NSAIDs. The magnitude of risk reduction is similar to those reported, though non-significance, in the meta-analysis by Gonzalez-Perez and colleagues {Gonzalez-Perez, 2003} that there are 35% and 16% reduced risk of lung cancer associated with NSAIDs (RR 0.65, 95%CI 0.34-1.22) and aspirin users (RR, 0.84; 95%CI 0.66-1.07). Similar dose-response relationship between NSAID use and lung cancer were observed. It is consistent with the inverse trend of lung cancer risk with increasing NSAID use among cigarette smokers {Harris 2002}. For instance, compared with non-NSAID users, reductions in the risk of lung cancer were 43% and 68% for smokers taking NSAIDs less than one NSAID daily (OR, 0.57; 95% CI, 0.40-0.82) and those taking at least one NSAID daily (OR, 0.32; 95% CI, 0.23-0.44) (trend test, $p<0.01$). A similar trend was also found by Moysich and colleagues; odds ratio of diagnosis of lung cancer were 0.63 (95% CI, 0.44-0.92) in patients taking NSAID 1-10 tablet years (number of daily pills x duration of use) and 0.45 (95% CI, 0.27-0.77) in those NSAID at least 11 tablet years (trend test, $p<0.01$)

{Moysich 2002}. Furthermore, in this study, a reduction in lung cancer was seen among those who exposed to NSAIDs at year 7 onward. In addition to similar reductions in risk observed for 5 or more years of aspirin used (OR, 0.68; 95%CI, 0.31 to 1.51) {Akhmedkhanov 2002}, the lung cancer risk associated with consistent aspirin use for 6 years was slightly inverse (RR, 0.89; 95%CI, 0.47 to 1.67) {Holick 2003}.

Our results suggest that the risk of GI adverse events is highest at the beginning of NSAID use with decreases as persons consume more NSAIDs. This finding is consistent with studies showing that the initial doses of NSAIDs and not long term NSAID use are most likely to result in GI adverse related events {Gabriel 1991, Garcia Rodriquez 1998, Smalley 1995}. This may be explained by gastric mucosal adaptation, which has been reported in both animal and human studies {Fitzpatrick 1999, Lipscomb 1996}.

Despite comparable demographic compositions between the Medicaid cohorts in Georgia and North Carolina, a higher percentage of subjects in the Georgia (62%) were prescribed any NSAID than those in the North Carolina (44%). This discrepancy may be explained by differences in pharmacy services policy, available prescription NSAIDs, and physician's prescribing preferences. Before July 1998, the Georgia Medicaid pharmacy program covered only five prescriptions per recipient per month. After of July 1998, with a written or oral prescription from a physician indicating the need for a drug override to exceed the monthly limits, pharmacists in Georgia are able to do self-approval to exceed these prescription limits {Georgia Department of Community Health 2004}. North Carolina Medicaid has also established monthly prescription limits of six prescriptions per recipient per month. Unlike the Georgia Medicaid program, after July 1998, exemption from the prescription limitation will only be authorized for life threatening illnesses. The recipient's physician must submit a "Six

Prescription Limit Override Form" where he or she justifies the patient's need for a drug override to exceed the monthly prescription limits {North Carolina Division of Medical Assistance 2004}. The possible follow-up period of the Georgia cohort (1990- 2001) was three years longer than that of the North Carolina cohort (1990-1998). The policy of override to exceed the monthly prescription limits under the Georgia Medicaid program was changed. Therefore NSAID prescription rates in Georgia might have increased during that three-year period (1999-2001). Moreover, Cox-2 inhibitors, celecoxib and rofecoxib, were introduced in 1999. Cox-2 inhibitors are covered, without requirement of prior authorization, by Georgia Medicaid, although there are quantity level limits of 34 tablets per 34 days when celecoxib and rofecoxib are prescribed {Georgia Department of Community Health 2004}. Both Georgia and North Carolina Medicaid programs do not cover over-the-counter aspirin. Enteric-coated aspirin is available as a prescription drug and covered by Georgia Medicaid; prescription aspirin is not covered by the North Carolina Medicaid program. Lastly, there may be a difference of NSAID prescribing preferences of physicians in Georgia and North Carolina.

The results obtained from the North Carolina Medicaid data demonstrated the higher unadjusted relative risks than and reversed direction of multivariate adjusted relative risks of all three study outcomes. Generally, in the NC cohort, higher percentages of subjects prescribed NSAIDs had the risk factors we adjusted for in calculating multivariate adjusted relative risks. Some of those risk factors were strongly associated with the risks of the study outcomes; for example ones with pneumonia were 5 times more likely to experience lung cancer. Therefore, the increased unadjusted relative risks may be subsequently due to strongly associated risk factors.

In contrast to other studies that have shown the risk for lung cancer increased with age, we found that older age classes, both 65-75 and >75, appeared to be at less risk for the three study outcomes than the 50-64 age group. This is possibly a result of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare. Therefore, we conducted a sensitivity analysis excluding all persons whose age was between 65 and 100 years. As a result, we observed comparable effects of, not only NSAID exposure, but also all covariates on all study outcomes to those of the original cohort.

There are several potential limitations in this proposed study. Based on inspecting the claims volume over time some issues with the completeness and accuracy of a very small portion of the data may have been detected. First, for one month of the study period (March 1998), the dates of service on the claims may have been errantly recorded for January, February or April 1998 and there was no way to reconcile these dates with source records. Secondly, the total numbers of claims for the period October through December 1997 are noticeably lower than expected. This was despite a re-generation of the claims data obtained from the claims processor. Since these data only affect a small time window in this study and there is no reason to believe that the dates or potentially missing claims were systematically related to exposure or outcome ascertainment, this is not likely to impact any measures of relative risk.

Since we depend on diagnosis (ICD-9-CM) codes to identify the study outcomes and confounders, measurement bias may arise due to coding inconsistencies. This may be of particular concern if there are differences in coding that is related to NSAID exposure. As a check for this potential concern, we conducted a sensitivity analysis excluding recipients with long term care admissions > 1 year and found the results to be generally consistent with the

initial analysis. Additionally, detailed information on risk behaviors, i.e. tobacco and alcohol consumption is not specifically recorded in claims data and could only be inferred from diagnostic information. In claims data, clinical measures, i.e. histological type and stage of cancer, are also not available. So the effect of NSAIDs on different histological type and stage of cancer cannot be explored. Despite the fact that Medicaid pays for aspirin, ibuprofen, and naproxen, exposure misclassification may still occur as a result of recipients purchasing these products over-the-counter. This may attenuate the disparity between exposure and non-exposure groups and underestimate relative risk of outcomes.

Since it is well known that NSAIDs are associated with increasing risks of GI and renal events, though perhaps transitory, channeling bias is an inextricable limitation of this study because physicians would be less likely to prescribe non-selective NSAIDs to persons they believe might be prone to GI or renal adverse events. We attended to this limitation by including the use of gastroprotective agents (a potential marker for past GI events) as a covariate in the GI adverse event models, but we recognize that this can only partially describes someone's GI event likelihood. Moreover, physicians may also pay closer attention to those who take NSAIDs, for example, more physician visits, which may lead to earlier diagnosis. Nevertheless, frequency of health care utilization was adjusted in the models in an attempt to attend to this phenomenon. We do not believe that if recipients were randomly assigned to NSAIDs and non-NSAIDs that the same results would be obtained with regard to GI and renal adverse events, however, these data do demonstrate that the NSAID prescribing decisions made in this population are not associated with an increase in GI and Renal events and this finding may better reflect the risks of NSAID prescribing rather than the relative risk of NSAIDs themselves. Though we do believe that channeling bias is an important consideration when interpreting the results of the adverse

events, we do not believe channeling bias is a significant concern for the results for the lung cancer prevention analyses, because it is unlikely that physicians were prescribing NSAIDs for persons whom they thought might be at higher risk of lung cancer during this study time frame.

Conclusion

Any NSAID exposure was associated with approximates 17-39% reduction in incident lung cancer with greater reductions observed for higher cumulative exposure to NSAIDs and COX-II inhibitors. There were no increased rates of GI and renal events associated with NSAID prescribing in this population. Findings from our study support the hypothesis that there exists the protective effect of NSAIDs against lung cancer. Moreover, NSAID use did not elevate the risk of GI and renal adverse events. Therefore, NSAIDs should be considered to use as chemopreventives against lung cancer. Although the dose-response relationship was modestly revealed and the at least 7 years duration of NSAID use was suggestive to affect the risk of lung cancer, the questions regarding optimal chemopreventive dose and duration of specific NSAIDs are remaining unanswered. Additional large perspective cohort studies with more extended period of follow-up and clinical trails in order to validate and examine biochemical components of NSAIDs. Further research should adopt better measures of NSAID use, and better controls of behavioral risk factors to examine a specific recommendation of NSAID use as chemopreventives against lung cancer.

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Table 6.1: Commonly Available Non-Steroidal Anti-inflammatory Drug (NSAIDs), According to Chemical Class

Chemical Class	Generic	Low daily dose (mg)	High daily dose (mg)	Standardization to Ibuprofen
Nonselective COX inhibitors				
Salicylic acid derivatives	Aspirin (acetylsalicylic acid)	2,400	3,600	0.67
	Salicylate salts (i.e. Choline Magnesium trisalicylate)	2,000	3,000	0.80
	Diflunisal	500	1,000	2.40
	Salsalate	2,000	4,000	0.60
Heteroacrl acetic acids	Diclofenac	100	150	16.00
	Etodolac	800	1,200	2.00
	Ketorolac	10	40	60.00
	Tolmetin	1,200	1,800	1.33
Indole and indene acetic acids	Indomethacin	50	150	16.00
	Sulindac	300	400	6.00
Arylpropionic acids	Fenoprofen	900	2,400	1.00
	Flurbiprofen	200	300	8.00
	Ibuprofen	1,200	2,400	1.00
	Ketoprofen	200	300	8.00
	Naproxen	550	1,100	2.18
	Oxaprozin	1,200	1,800	1.33
Anthranilic acid (Fenamates)	Meclofenamic acid	100	400	6.00
	Mefenamic acid	500	1,000	2.40
Enolic acids				
Pyrazolones	Phenylbutazone	300	400	6.00
Oxicams	Piroxicam	less than 20	20	120.00
Nonacidic agent				
Alkanones	Nabumetone	1,000	2,000	1.20
Selective COX-2 Inhibitors				
Diaryl-substituted furanones	Rofecoxib	12.5	25	96.00
Diaryl-substituted isoxazole	Valdecoxib	10	20	120.00
Diaryl-substituted pyrazoles	Celecoxib	200	400	6.00

Source: (1) Roberts LJ2, Marrow JD. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Good man and Gilman's the pharmacological basis of therapeutics. Columbus: The McGraw-Hill Companies, Inc., 2001;687-731.

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Table 6.2: List of Model Covariates and their Operation Definitions

Covariates	Outcome		
	Lung Cancer	GI Events	Renal Events
Demographics			
Age at entry (years)	Yes	Yes	Yes
Gender (female vs. male)	Yes	Yes	Yes
Race (non-white vs. white)	Yes	Yes	Yes
Frequency of health care utilization: Total number of visits to ambulatory care services, emergency department, long-term care facilities, and acute inpatient services throughout study period	Yes	Yes	Yes
Frequency of cancer screenings: Total numbers of any cancer screenings throughout study period	Yes	Yes	Yes
Alcohol use and alcohol abuse (ICD-9-CM = 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 {Elixhauser 1998})	Yes	Yes	Yes
Obesity (ICD-9-CM = 278.x {Elixhauser 1998})	Yes	Yes	Yes
Tobacco Smoke (ICD-9-CM = 305.1, V15.82 {Romano 1994})	Yes	Yes	Yes
Pneumonia (ICD-9-CM= 480.xx-486.xx)	Yes	No	No
Tuberculosis (ICD-9-CM= 010.xx-018.xx)	Yes	No	No
Asthma (ICD-9-CM= 493.xx)	Yes	No	No
Emphysema (ICD-9-CM = 492.xx)	No	Yes	No
Chronic Bronchitis (ICD-9-CM = 491.xx)	No	Yes	No
H.Pylori infection (ICD-9-CM = 041.86)	No	Yes	No
Cirrhosis (ICD-9-CM = 571.5, 571.6)	No	No	Yes
Hypertension (ICD-9-CM = 401.xx, 402.xx, 405.xx {Elixhauser 1998})	No	No	Yes
Diabetes Melitus (ICD-9-CM = 250.0x-250.3x; 250.5x-250.9x {Elixhauser 1998})	No	No	Yes
Congestive heart failure (ICD-9-CM = 389.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9 {Elixhauser 1998})	No	No	Yes
Liver Failure (ICD-9-CM = 570.xx)	No	No	Yes
GI protective agents (i.e. Misoprostal, proton pump inhibitors (PPIs), and histamine-2 (H2) receptor antagonists)	No	Yes	No
Corticosteroids (i.e. prednisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone and hydrocortisone)	No	Yes	No
Anticoagulant use (i.e. heparins, coumarin and indadiones)	No	Yes	No
Nephrotoxic Drugs:			
Diuretics (i.e. loop, potassium-sparing, thiazide diuretics)	No	No	Yes
Angiotensin-converting Enzyme (ACE) Inhibitors and Angiotensin-II-receptor antagonist (e.g captopril, enalapril, lisinopril, losartan etc.)	No	No	Yes
Aminoglycosides	No	No	Yes
Cephalosporins	No	Yes	Yes
Vancomycin	No	No	Yes
Allopurinol	No	No	Yes
Cyclosporine	No	No	Yes

Table 6.3: Georgia Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Lung Cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	82,194	136,052	83,200	135,046	82,660	135,586
Incidence rate per 100,000 person-years	238.03	158.48	817.42	758.26	697.30	560.25
Follow up period, mean ± SD (yr) [a,b,c]	4.8 ± 2.9	7.3 ± 3.5	4.7 ± 2.9	7.1 ± 3.5	4.7 ± 2.9	7.2 ± 3.5
Demographics (%)						
Female [a,c]	68.5	76.6	68.4	76.7	68.5	76.6
Age, mean ± SD (yr) [a,b,c]	72.4 ± 11.8	69.2 ± 11.1	72.2 ± 11.9	69.3 ± 11.1	72.3 ± 11.8	69.3 ± 11.1
Race [a,b,c]						
White	54.1	43.7	54.0	43.7	53.9	43.8
Non White	35.7	42.0	35.8	42.0	35.9	41.9
Unknown Race	10.2	14.3	10.2	14.3	10.2	14.3
Risk Factors (%)						
Tobacco Smoke [a,b,c]	1.5	2.9	1.5	2.5	1.5	2.8
Obesity [a,b,c]	0.7	3.1	0.7	2.8	0.7	2.9
Alcohol Abuse [a,b,c]	2.3	3.2	2.3	3.0	2.2	3.2
Lung Diseases						
Pneumonia	6.3	9.9	na	na	na	na
Tuberculosis	0.4	0.7	na	na	na	na
Asthma	2.0	5.3	na	na	na	na
Emphysema	1.2	2.1	1.2	1.9	na	na
Chronic Bronchitis	2.7	5.4	2.7	4.9	na	na
H. pylori Infection	na	na	0.1	0.3	na	na
Hypertension	17.0	31.8	na	na	17.1	31.5
Diabetes Mellitus	na	na	na	na	9.0	17.2
Congestive Heart Failure	na	na	na	na	8.0	12.8
Cirrhosis	na	na	na	na	0.4	0.5
Medication exposures						
GI protective agents	na	na	34.8	63.6	na	na
Corticosteroids	na	na	16.0	37.4	na	na
Anticoagulants	na	na	11.1	15.1	na	na
Diuretics	na	na	na	na	39.5	61.1
ACE inhibitors	na	na	na	na	26.3	45.0
Antibiotics						
Aminoglycosides	na	na	na	na	1.7	1.5
Cephalosporines	na	na	47.7	70.1	47.8	70.5
Vancomycins	na	na	na	na	1.1	1.1
Allopurinal	na	na	na	na	2.2	8.1
Cyclosporine	na	na	na	na	0.1	0.1
Frequency of Health Care Utilization, mean ± SD (times) a,b,c	132.5 ± 155.3	193.4 ± 177.8	129.8 ± 153.1	187.1 ± 174.1	130.3 ± 152.9	188.5 ± 172.6
Frequency of Cancer Screening, mean ± SD (times) a,b,c	0.07 ± 0.38	0.22 ± 0.79	0.07 ± 0.42	0.22 ± 0.78	0.06 ± 0.39	0.22 ± 0.79

Between group comparisons of age, follow-up period, frequency of health care utilization, frequency of cancer screening (t-test), gender, race and risk factors (chi-square) were performed for each study outcome; a significant at $p<0.05$ for lung cancer; b significant at $p<0.05$ for GI events; c significant at $p<0.05$ for renal events.

Table 6.4: North Carolina Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Lung Cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	105,805	81,468	106,196	81,077	105,941	81,332
Incidence rate per 100,000 person-years	94.97	111.40	446.57	713.59	289.87	366.23
Follow up period, mean ± SD (yr) [a,b,c]	4.6 ± 2.1	5.7 ± 2.4	4.5 ± 2.1	5.6 ± 2.4	4.6 ± 2.1	5.7 ± 2.4
Demographics (%)						
Female	70.0	77.0	70.0	77.1	70.0	77.1
Age, mean ± SD (yr) [a,b,c]	72.6 ± 10.7	70.3 ± 11.1	72.6 ± 10.7	70.3 ± 11.1	72.6 ± 10.7	70.3 ± 11.1
Race [a,b,c]						
White	57.3	49.0	57.2	49.0	57.3	49.0
Non White	42.7	51.0	42.8	51.0	42.8	51.0
Risk Factors (%)						
Tobacco Smoke [a,b,c]	1.0	2.6	1.1	2.5	1.0	2.6
Obesity [a,b,c]	0.8	2.9	0.8	2.9	0.8	2.9
Alcohol Abuse [a,b,c]	1.7	3.2	1.8	3.0	1.7	3.2
Lung Diseases						
Pneumonia	3.7	5.9	na	na	na	na
Tuberculosis	0.2	0.4	na	na	na	na
Asthma	1.3	3.9	na	na	na	na
Emphysema	0.7	1.6	0.7	1.5	na	na
Chronic Bronchitis	1.1	2.7	1.2	2.7	na	na
H. pylori Infection	na	na	0.0	0.1	na	na
Hypertension	11.1	24.2	na	na	11.2	24.1
Diabetes Mellitus	na	na	na	na	8.0	15.7
Congestive Heart Failure	na	na	na	na	5.8	9.8
Cirrhosis	na	na	na	na	0.2	0.3
Medication exposures						
GI protective agents	na	na	25.7	53.9	na	na
Corticosteroids	na	na	10.5	27.1	na	na
Anticoagulants	na	na	7.5	10.3	na	na
Diuretics	na	na	na	na	30.0	53.2
ACE inhibitors	na	na	na	na	17.0	31.9
Antibiotics						
Aminoglycosides	na	na	na	na	1.0	0.9
Cephalosporines	na	na	34.2	58.0	34.1	58.1
Vancomycins	na	na	na	na	0.6	0.7
Allopurinal	na	na	na	na	1.6	6.2
Cyclosporine	na	na	na	na	0.0	0.1
Frequency of Health Care Utilization, mean ± SD (times) a,b,c	31.8 ± 51.6	57.1 ± 73.8	32.2 ± 52.4	56.8 ± 73.4	31.9 ± 51.9	57.0 ± 73.7
Frequency of Cancer Screening, mean ± SD (times) a,b,c	0.02 ± 0.20	0.07 ± 0.40	0.02 ± 0.20	0.07 ± 0.39	0.02 ± 0.20	0.07 ± 0.39

Between group comparisons of age, follow-up period, frequency of health care utilization, frequency of cancer screening (t-test), gender, race and risk factors (chi-square) were performed for each study outcome; a significant at $p<0.05$ for lung cancer; b significant at $p<0.05$ for GI events; c significant at $p<0.05$ for renal events.

Table 6.5: Effect of NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Lung Cancer	Any Use	994,424	1,576	158.48	0.67	0.61 (0.56, 0.67)
	None	394,901	940	238.03	Reference	Reference
GI Events	Any Use	961,549	7,291	758.26	0.93	0.82 (0.78, 0.86)
	None	393,433	3,216	817.42	Reference	Reference
Renal Events	Any Use	978,851	5,484	560.25	0.8	0.56 (0.53, 0.59)
	None	393,232	2,742	697.30	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 6.6: Effect of NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Lung Cancer	Any Use	465,883	519	111.40	1.17	0.83 (0.73,0.95)
	None	484,385	460	94.97	Reference	Reference
GI Events	Any Use	455,441	3,250	713.59	1.60	0.71 (0.67,0.75)
	None	482,338	2,154	446.57	Reference	Reference
Renal Events	Any Use	462,553	1,694	366.23	1.26	0.56 (0.52, 0.60)
	None	483,323	1,401	289.87	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 6.7: Effect of Various Risk Factors on the Incidence of Lung cancer in the Georgia and North Carolina Medicaid Cohort

Risk Factors	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.4907	0.0437	<.0001	0.61	-0.1822	0.0678	0.0072	0.83
Age groups								
75-100 years old	-1.1145	0.0679	<.0001	0.33	-0.1057	0.1014	<.0001	0.90
65-74 years old	-0.6727	0.0528	<.0001	0.51	-0.5495	0.0893	<.0001	0.58
50-64 years old				Ref				Ref
Genders								
Female	-0.6137	0.0441	<.0001	0.54				Ref
Male				Ref	0.60669	0.07082	<.0001	1.83
Race								
Non-White	-0.2402	0.0452	<.0001	0.79	-0.0430	0.0683	0.5293	0.96
White				Ref				Ref
Frequency of Cancer Screening	0.0347	0.0235	0.1389	1.04	-0.0584	0.0752	0.4375	0.94
Frequency of Health Care Utilization	-0.0040	0.0002	<.0001	1.00	0.0003	0.0004	0.3716	1.00
Risk Factors								
Alcohol Abuse	0.3046	0.0689	<.0001	1.36	0.2767	0.10588	0.009	1.32
Obesity	-0.1566	0.1124	0.1636	0.86	-0.1299	0.1632	0.4261	0.88
Tobacco Smoke	0.3335	0.0733	<.0001	1.40	0.6057	0.1098	<.0001	1.83
Pneumonia	0.9543	0.0516	<.0001	2.60	1.6074	0.0854	<.0001	4.99
Tuberculosis	0.6026	0.1228	<.0001	1.83	0.5885	0.1878	0.0017	1.80
Asthma	0.0815	0.0713	0.2535	1.09	0.1794	0.1132	0.1129	1.20
Emphysema	0.5698	0.0773	<.0001	1.77	0.4540	0.1221	0.0002	1.57
Chronic Bronchitis	0.4973	0.0663	<.0001	1.64	0.4529	0.1178	0.0001	1.57
Hypertension	0.0170	0.0477	0.7212	1.02	0.0550	0.0802	0.4927	1.06

Table 6.8: Effect of Risk Factors on the Incidence of GI events in the Georgia and North Carolina Medicaid Cohort

Risk Factors	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	Standard Error	p-value	Hazard Ratio	Coefficient	Standard Error	p-value	Hazard Ratio
NSAID exposure	-0.1995	0.0234	<.0001	0.82	-0.3528	0.0298	<.0001	0.70
Age groups								
75-100 years old	-1.4839	0.0319	<.0001	0.23	-1.0672	0.0371	<.0001	0.34
65-74 years old	-1.4602	0.0283	<.0001	0.23	-1.6022	0.0459	<.0001	0.20
50-64 years old				Ref				
Genders								
Female	-0.0973	0.0229	<.0001	0.91				
Male				Ref	0.1569	0.0319	<.0001	1.17
Race								
Non-White	-0.0454	0.0221	0.0402	0.96	-0.1062	0.0292	0.0003	0.90
White				Ref				
Frequency of Cancer Screening	0.2018	0.0063	<.0001	1.22	0.1692	0.0179	<.0001	1.18
Frequency of Health Care Utilization	-0.0042	0.0001	<.0001	1.00	0.0030	0.0001	<.0001	1.00
Risk Factors								1.00
Alcohol Abuse	0.6081	0.0347	<.0001	1.84	0.7916	0.0441	<.0001	2.21
Obesity	0.3566	0.0413	<.0001	1.43	0.3771	0.0503	<.0001	1.46
Tobacco Smoke	0.1123	0.0432	0.0094	1.12	0.4563	0.0482	<.0001	1.58
H. pylori Infection	0.8258	0.0887	<.0001	2.28	1.2806	0.1067	<.0001	3.60
Emphysema	0.4759	0.0478	<.0001	1.61	0.2277	0.0616	0.0002	1.26
Chronic Bronchitis	0.2997	0.0369	<.0001	1.35	0.2061	0.0516	<.0001	1.23
GI protective agents	0.6999	0.0228	<.0001	2.01	1.8058	0.0390	<.0001	6.08
Corticosteroids	-0.3591	0.0235	<.0001	0.70	-0.1032	0.0319	0.0012	0.90
Anticoagulants	-0.1007	0.0331	0.0023	0.90	0.0929	0.0409	0.231	1.10
Cephalosporines	-0.2695	0.0222	<.0001	0.76	0.1708	0.0314	<.0001	1.19

Table 6.9: Effect of Covariates on the Incidence of Renal events in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.5761	0.0260	<.0001	0.56	-0.5813	0.0394	<.0001	0.56
Age groups								
75-100 years old	-0.8143	0.0351	<.0001	0.44	-0.4252	0.0522	<.0001	0.65
65-74 years old	-0.7081	0.0306	<.0001	0.49	-0.4895	0.0506	<.0001	0.61
50-64 years old								
Genders								
Female	-0.0818	0.0265	0.002	0.92				
Male					0.2466	0.0426	<.0001	1.28
Race								
Non-White	0.5692	0.0269	<.0001	1.77	-0.6164	0.0376	<.0001	0.54
White								
Frequency of Cancer Screening	-0.0028	0.0111	0.8	1.00	0.1125	0.0330	0.7334	1.12
Frequency of Health Care Utilization	-0.0019	0.0001	<.0001	1.00	0.0012	0.0002	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.2247	0.0462	<.0001	1.25	0.2173	0.0739	0.0033	1.24
Obesity	0.0861	0.0446	0.0537	1.09	-0.1498	0.0697	0.0316	0.86
Tobacco Smoke	-0.0741	0.0546	0.1749	0.93	0.3355	0.0732	<.0001	1.40
Cirrhosis	0.5626	0.0908	<.0001	1.76	0.5367	0.1244	<.0001	1.71
Hypertension	0.4596	0.0274	<.0001	1.58	0.9757	0.0455	<.0001	2.65
Diabetes Melitus	0.8207	0.0263	<.0001	2.27	0.7710	0.0418	<.0001	2.16
Congestive heart failure	0.6508	0.0277	<.0001	1.92	1.0176	0.0438	<.0001	2.77
Liver Failure	0.3768	0.2097	0.0724	1.46	0.7408	0.2366	0.0017	2.10
Diuretics	0.1379	0.0268	<.0001	1.15	0.3104	0.0451	<.0001	1.36
ACE Inhibitors	0.1098	0.0250	<.0001	1.12	0.3063	0.0404	<.0001	1.36
Aminoglycosides	0.1453	0.0973	0.1355	1.16	0.4533	0.1357	0.0008	1.57
Cephalosporins	-0.2975	0.0250	<.0001	0.74	0.2290	0.0405	<.0001	1.26
Vancomycin	0.1953	0.1167	0.0943	1.22	0.7434	0.1308	<.0001	2.10
Allopurinol	0.6047	0.0340	<.0001	1.83	0.8002	0.0556	<.0001	2.23
Cyclosporine	1.4338	0.1841	<.0001	4.19	0.8201	0.3058	0.0073	2.27

Table 6.10: Effect of specific NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort

NSAID exposure	Person-years	Lung Cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	252,878	335	132.48	0.56	0.97 (0.86,1.10)
Non-Selective Cox Inhibitors					
Fenoprofen	166,377	264	158.68	0.67	1.08 (0.95,1.23)
Ibuprofen	628,007	962	153.18	0.64	0.85 (0.78,0.93)
Idomethacin	229,255	309	134.78	0.57	0.88 (0.78,1.00)
Naproxen	355,458	507	142.63	0.60	0.85 (0.76,0.94)
Sulindac	140,835	167	118.58	0.50	0.95 (0.81, 1.12)
Others NSAIDs	429,655	597	138.95	0.58	0.91 (0.82, 1.00)
Cox-2 Inhibitors	343,488	233	67.83	0.28	0.30 (0.26, 0.34)
None	394,901	940	238.03	Reference	Reference

NSAID exposure	Person-years	GI events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	241,526	1,749	724.15	0.89	1.13 (1.07,1.19)
Non-Selective Cox Inhibitors					
Fenoprofen	159,292	1,247	782.84	0.96	1.12 (1.06,1.19)
Ibuprofen	604,577	4,454	736.71	0.90	0.93 (0.89, 0.97)
Idomethacin	219,031	1,546	705.84	0.86	1.00 (0.94,1.06)
Naproxen	337,051	2,380	706.12	0.86	0.86 (0.82,0.91)
Sulindac	134,968	894	662.38	0.81	1.08 (1.00, 1.16)
Others NSAIDs	410,507	2,822	687.44	0.84	0.96 (0.92, 1.01)
Cox-2 Inhibitors	318,367	1,014	318.50	0.39	0.28 (0.26, 0.29)
None	393,433	3,216	817.42	Reference	Reference

NSAID exposure	Person-years	Renal events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	248,123	1,316	530.38	0.76	1.00 (0.94,1.07)
Non-Selective Cox Inhibitors					
Fenoprofen	163,567	882	539.23	0.77	0.97 (0.90,1.04)
Ibuprofen	617,385	3,374	546.50	0.78	0.77 (0.74,0.81)
Idomethacin	223,238	1,511	676.86	0.97	1.02 (0.96, 1.08)
Naproxen	348,335	1,596	458.18	0.66	0.70 (0.66, 0.74)
Sulindac	137,410	823	598.94	0.86	1.15 (1.07,1.24)
Others NSAIDs	422,330	2,005	474.75	0.68	0.87 (0.82, 0.92)
Cox-2 Inhibitors	333,762	695	208.23	0.30	0.24 (0.22, 0.26)
None	393,232	2,742	697.30	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; Cox, cyclo-oxygenase; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 6.11: Effect of specific NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort

NSAID exposure	Person-years	Lung Cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,853	62	95.60	1.01	0.85 (0.65,1.11)
Non-Selective Cox Inhibitors					
Fenoprofen	8,869	15	169.12	1.78	1.29 (0.77,2.16)
Ibuprofen	193,365	215	111.19	1.17	0.79 (0.68,0.93)
Idomethacin	61,077	67	109.70	1.16	0.83 (0.64,1.07)
Naproxen	163,232	196	120.07	1.26	0.99 (0.84,1.17)
Sulindac	33,784	32	94.72	1.00	0.98 (0.69, 1.41)
Others NSAIDs	282,755	289	102.21	1.08	0.80 (0.69, 0.93)
None	484,385	460	94.97	Reference	Reference
NSAID exposure	Person-years	GI events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	62,345	514	824.44	1.85	0.96 (0.88,1.06)
Non-Selective Cox Inhibitors					
Fenoprofen	8,455	96	1,135.36	2.54	1.14 (0.93,1.40)
Ibuprofen	187,769	1,322	704.06	1.58	0.73 (0.68, 0.78)
Idomethacin	59,116	441	745.99	1.67	0.86 (0.77,0.95)
Naproxen	158,285	1,132	715.16	1.60	0.75 (0.70,0.80)
Sulindac	32,963	228	691.68	1.55	0.91 (0.80, 1.05)
Others NSAIDs	275,062	1,952	709.66	1.59	0.76 (0.71, 0.80)
None	482,338	2,154	446.57	Reference	Reference
NSAID exposure	Person-years	Renal events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,182	264	411.33	1.42	0.98 (0.86,1.12)
Non-Selective Cox Inhibitors					
Fenoprofen	8,779	47	535.37	1.85	1.06 (0.79,1.41)
Ibuprofen	191,619	655	341.82	1.18	0.62 (0.57,0.68)
Idomethacin	60,002	366	609.98	2.10	0.96 (0.85, 1.09)
Naproxen	161,974	595	367.34	1.27	0.74 (0.67, 0.81)
Sulindac	33,311	172	516.34	1.78	1.13 (0.97,1.32)
Others NSAIDs	280,618	913	325.35	1.12	0.59 (0.54, 0.64)
None	483,323	1,401	289.87	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal

** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 6.12: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort after excluding 62,998 subjects who resided in LTC for more than 1 year.

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Lung Cancer	Any Use	779,499	1,421	182.30	0.57	0.60 (0.55, 0.66)
	None	252,966	813	321.39	Reference	Reference
GI Events	Any Use	749,726	6,462	861.91	0.82	0.87 (0.82, 0.91)
	None	252,087	2,651	1,051.62	Reference	Reference
Renal Events	Any Use	766,435	4,602	600.44	0.68	0.53 (0.50, 0.56)
	None	251,739	2,237	888.62	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 6.13: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort after excluding 310 subjects who resided in LTC for more than 1 year.

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Lung Cancer	Any Use	465,620	519	111.46	1.17	0.84 (0.73,0.96)
	None	482,976	457	94.62	Reference	Reference
GI Events	Any Use	455,194	3,249	713.76	1.6	0.70 (0.66,0.74)
	None	480,934	2,149	446.84	Reference	Reference
Renal Events	Any Use	462,290	1,694	366.44	1.26	0.55 (0.51.0.59)
	None	481,912	1,400	290.51	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

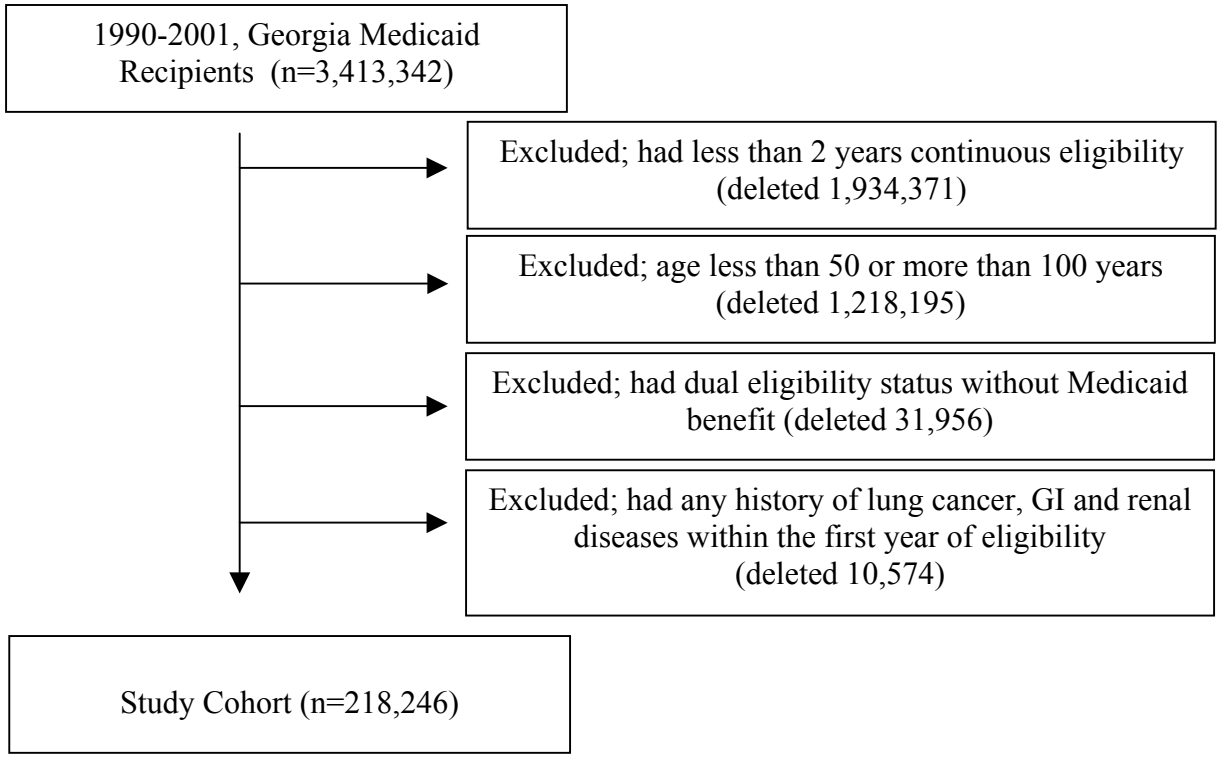

Figure 6.1: Flow chart of Georgia Medicaid cohort subjects

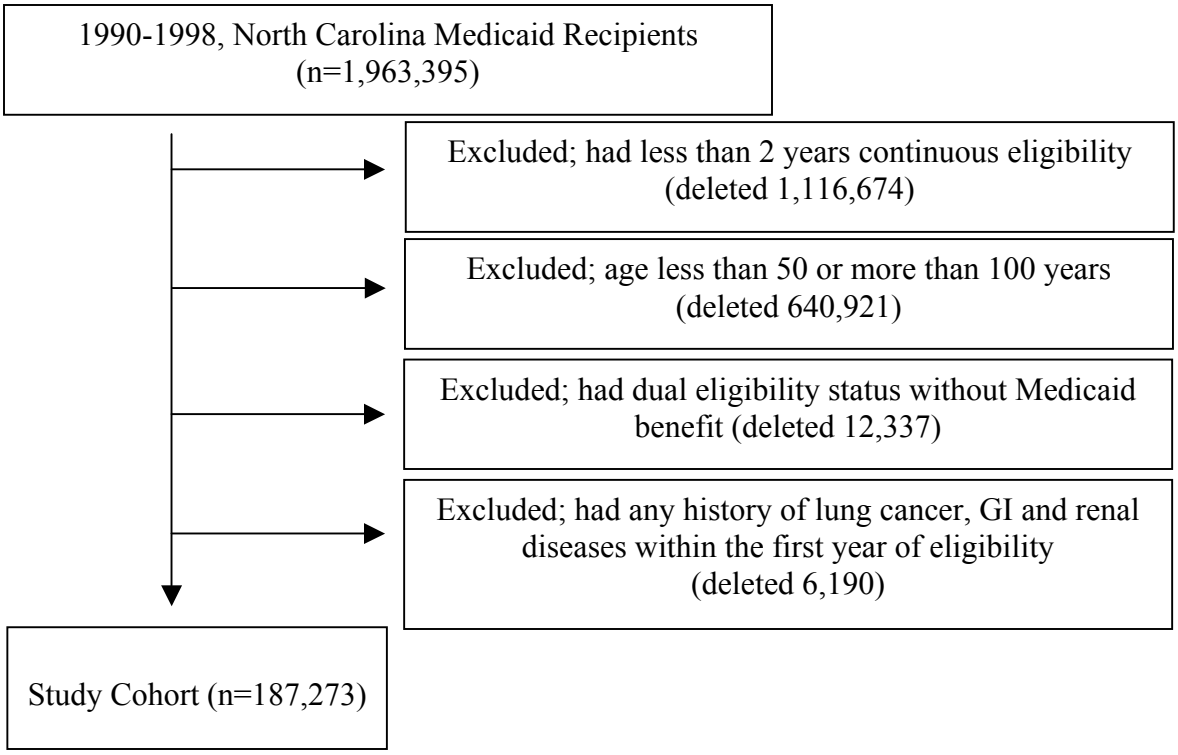

Figure 6.2: Flow chart of North Carolina Medicaid cohort subjects

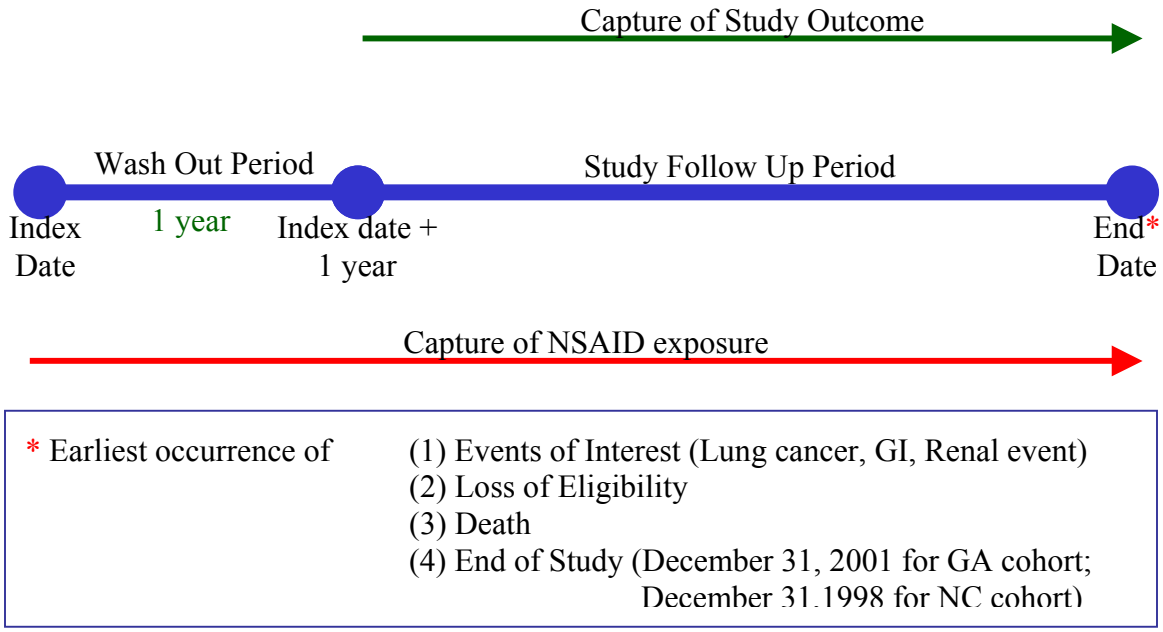

Figure 6.3: Temporal pattern of cohort

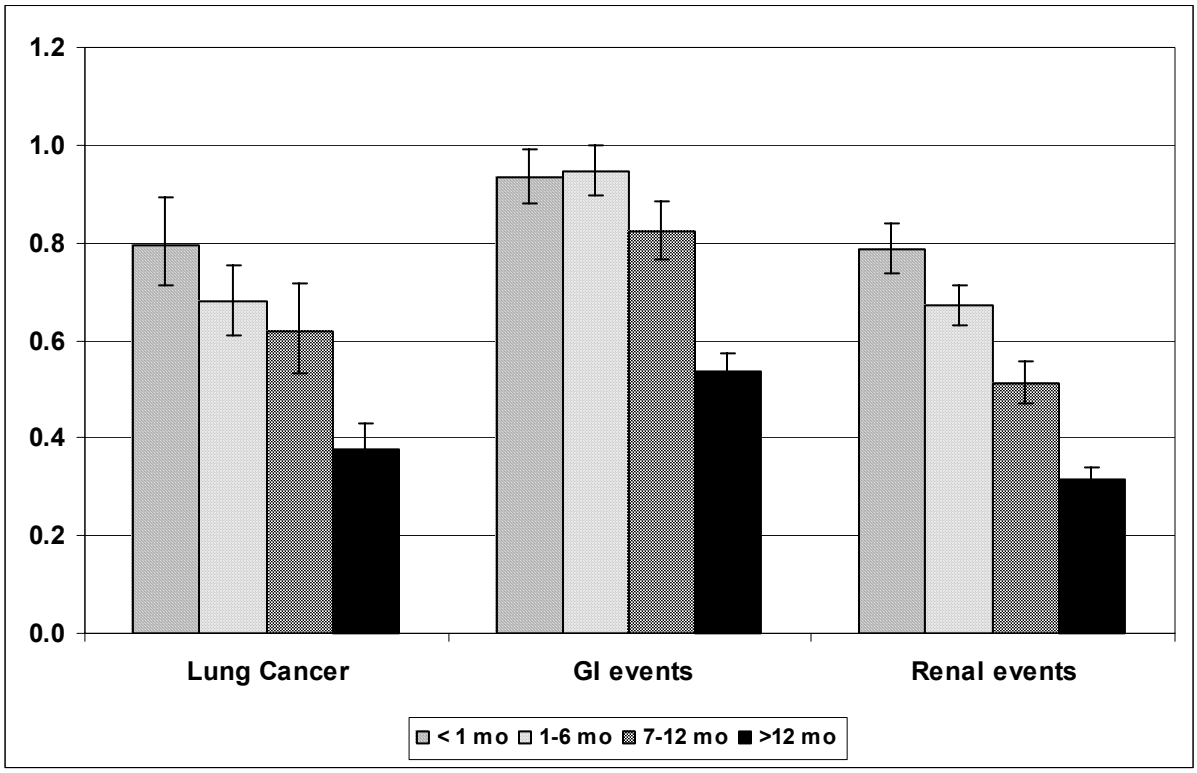

Figure 6.4: Effect of Cumulative NSAID exposure on the Relative Risk of Lung cancer, GI and Renal events in Georgia Cohort

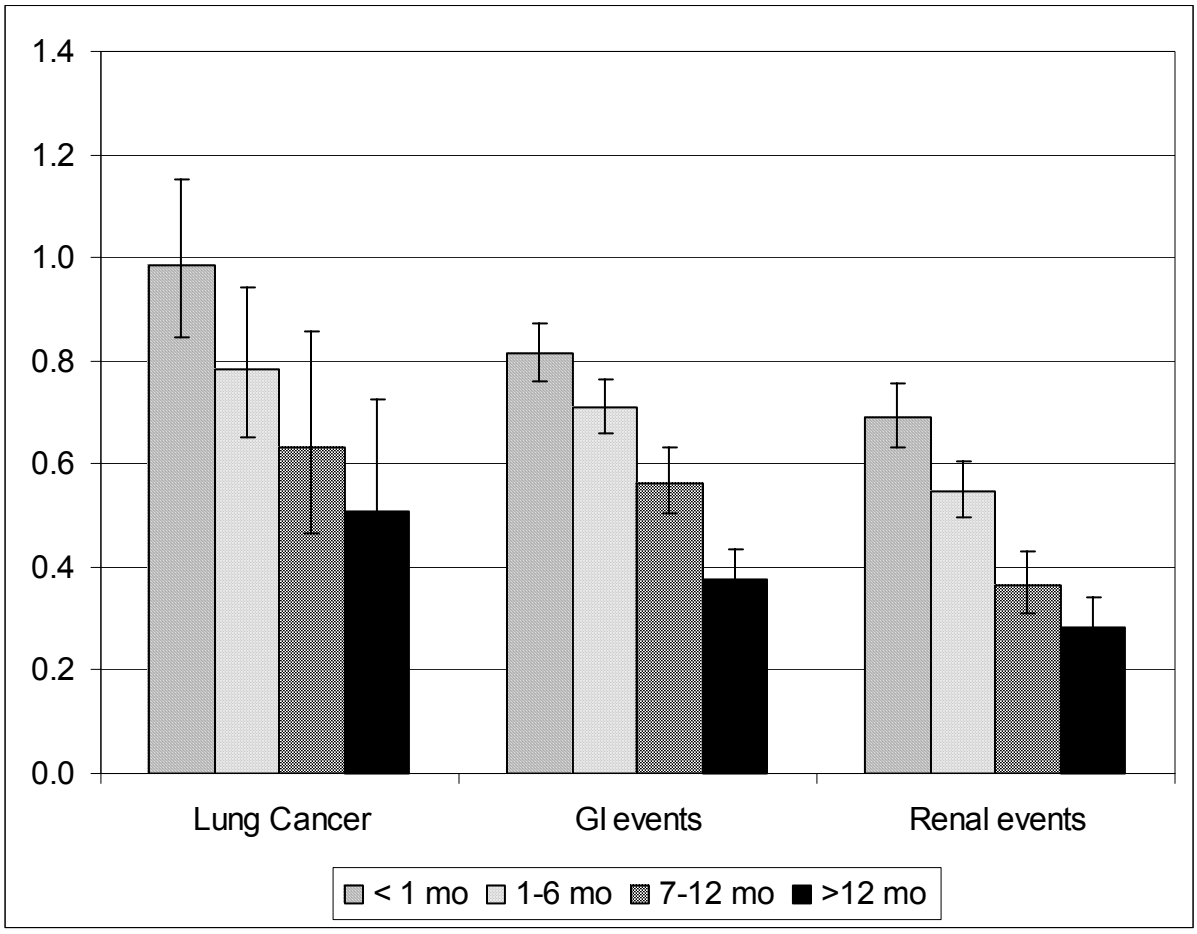

Figure 6.5: Effect of Cumulative NSAID exposure on the Relative Risk of Lung cancer, GI and Renal events in North Carolina Cohort

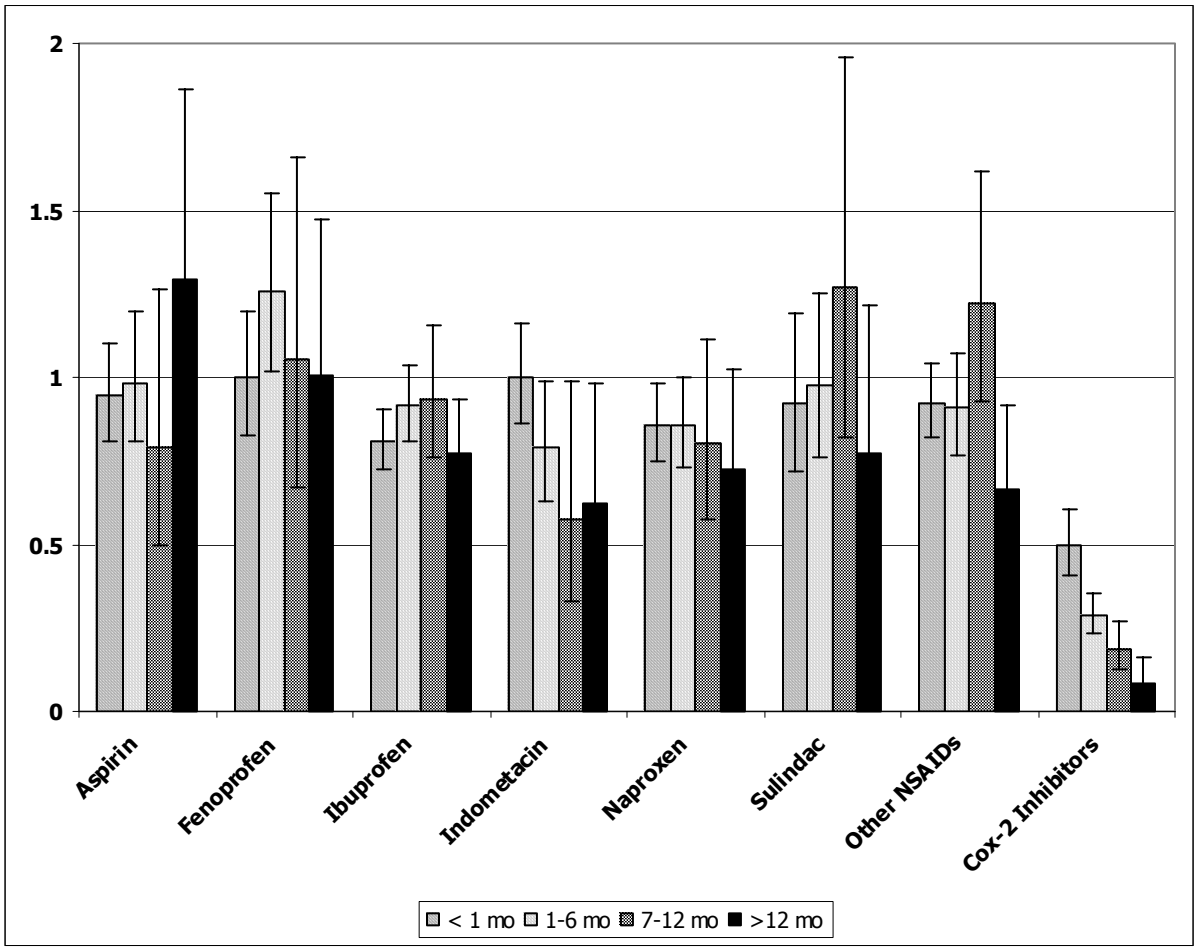

Figure 6.6: Cumulative Exposure Effect of specific NSAIDs on Lung Cancer in Georgia Medicaid Cohort

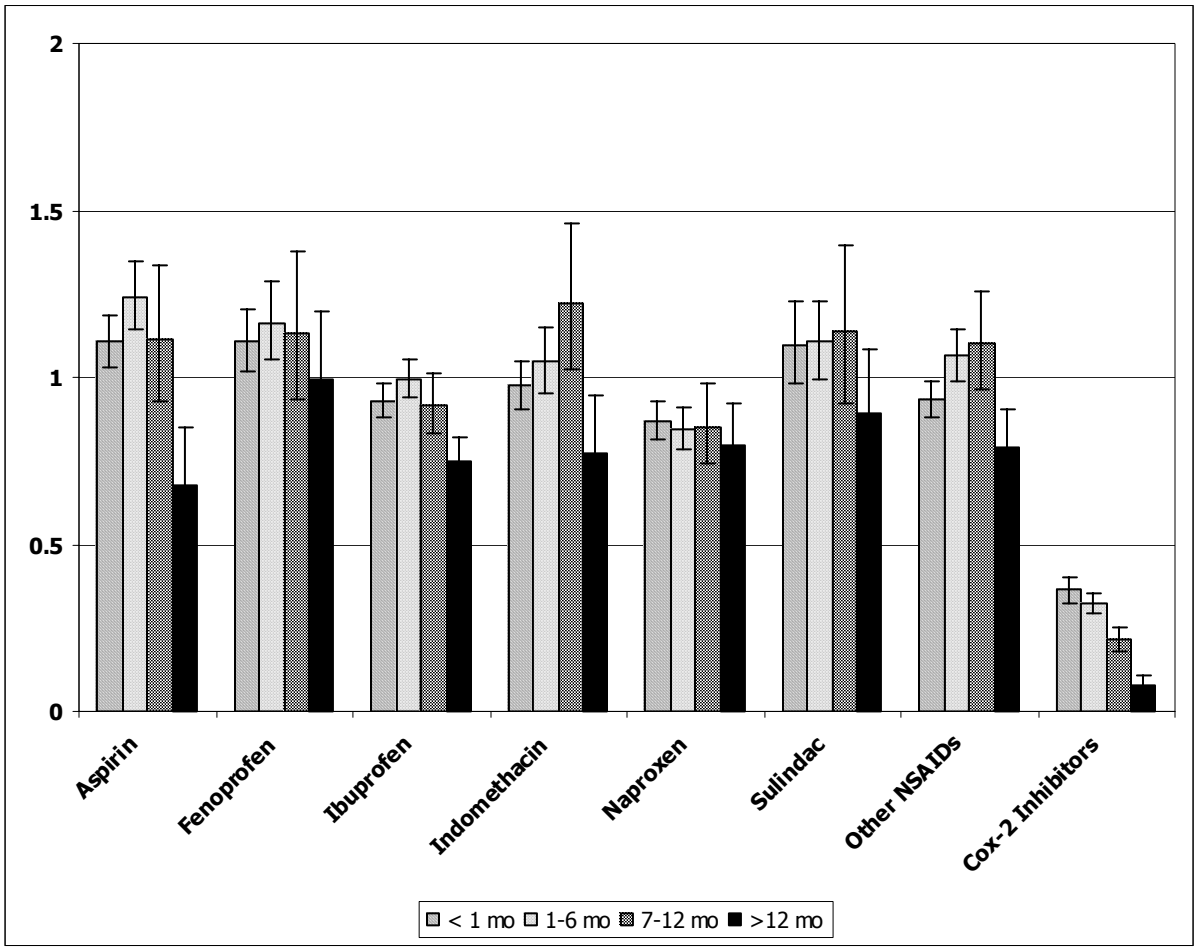

Figure 6.7: Cumulative Exposure Effect of specific NSAIDs on GI events in Georgia Medicaid Cohort

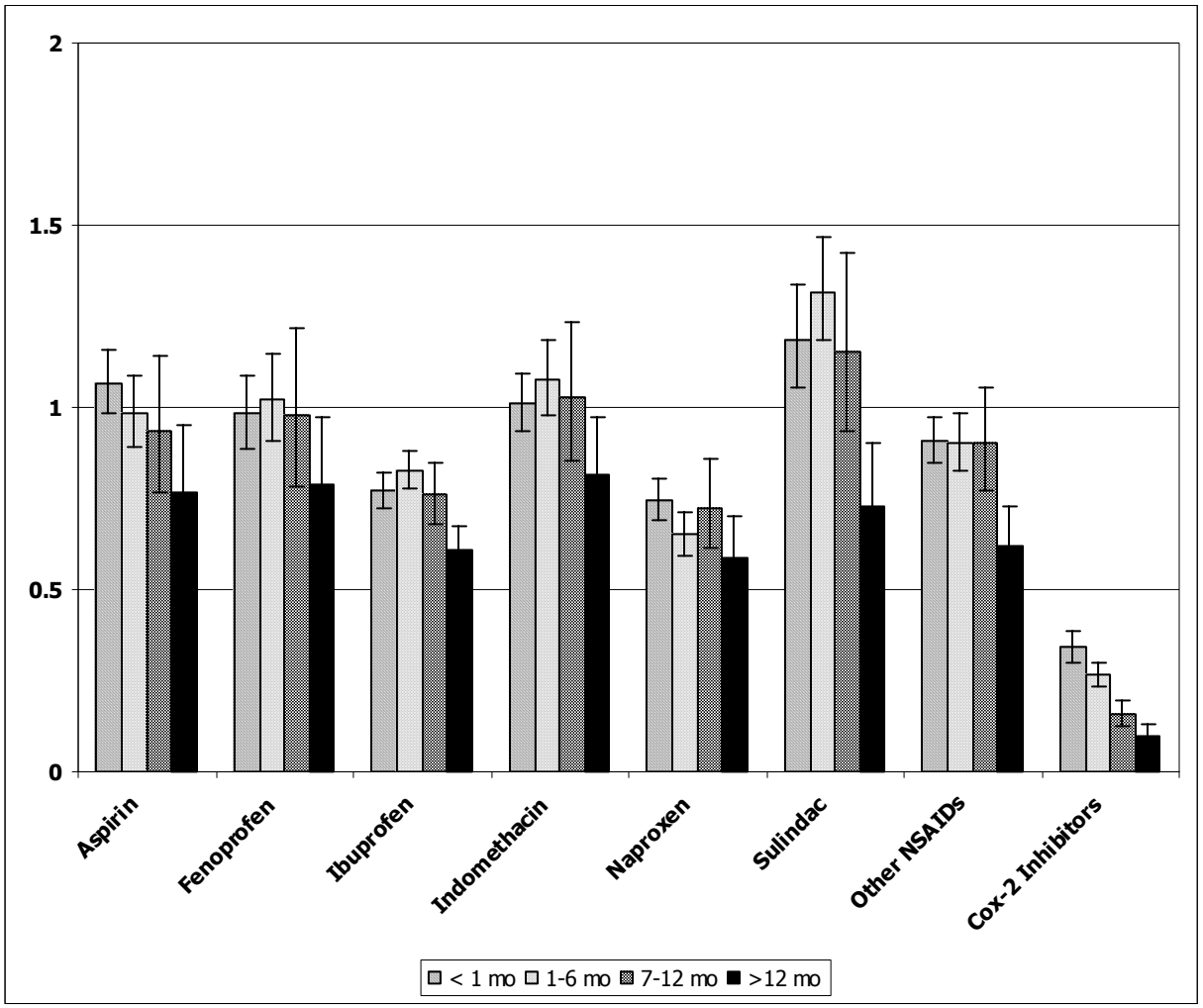

Figure 6.8: Cumulative Exposure Effect of specific NSAIDs on Renal events in Georgia Medicaid Cohort

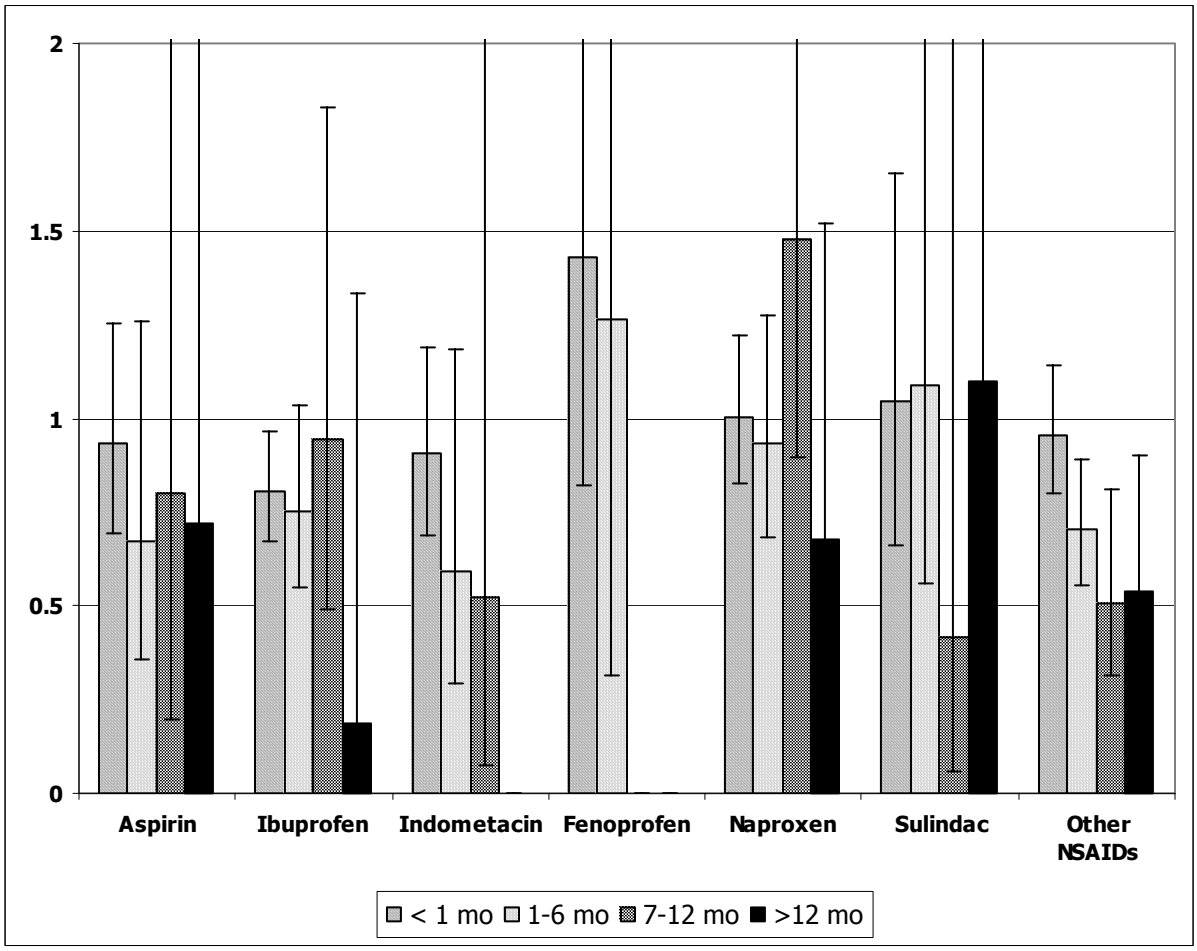

Figure 6.9: Cumulative Exposure Effect of specific NSAIDs on Lung cancer in North Carolina Medicaid Cohort

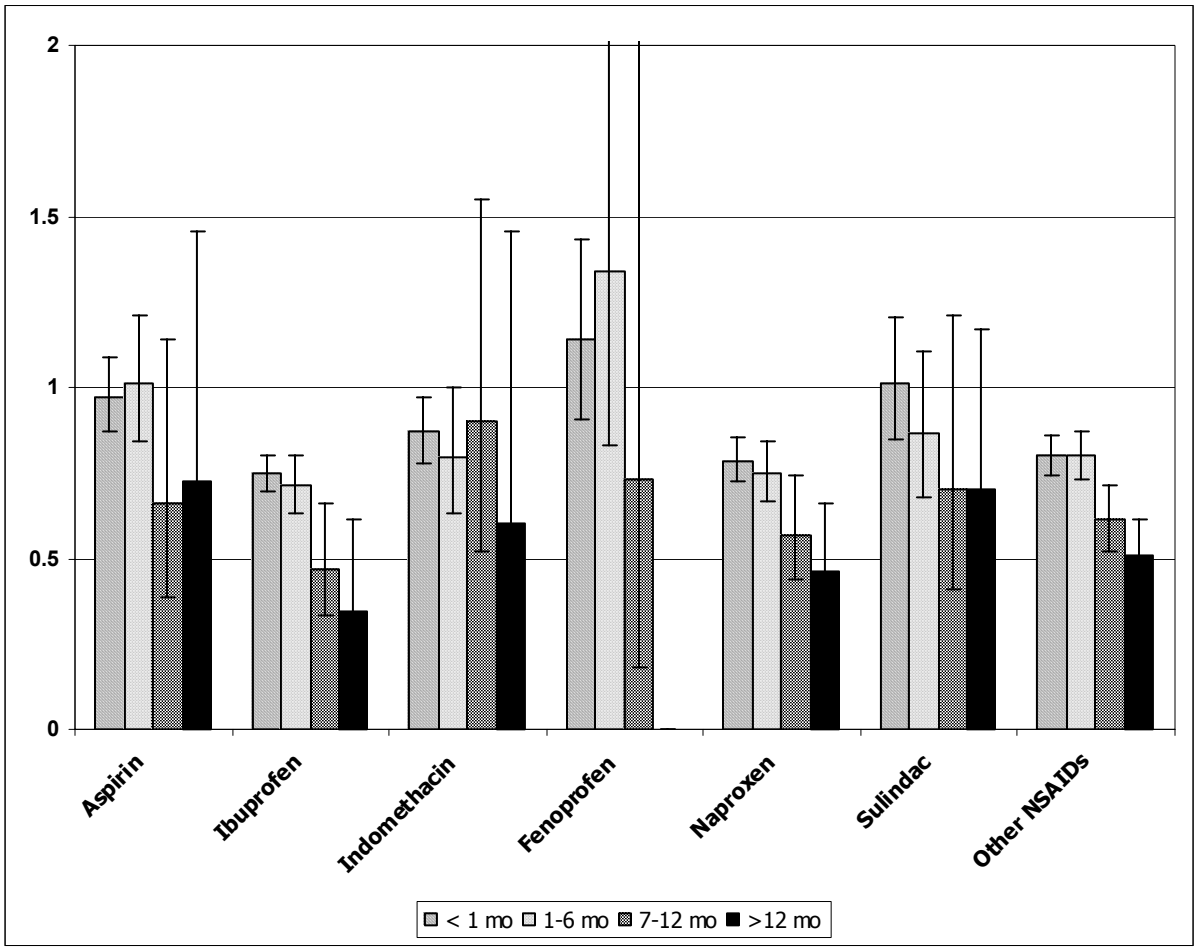

Figure 6.10: Cumulative Exposure Effect of specific NSAIDs on GI events in North Carolina Medicaid Cohort

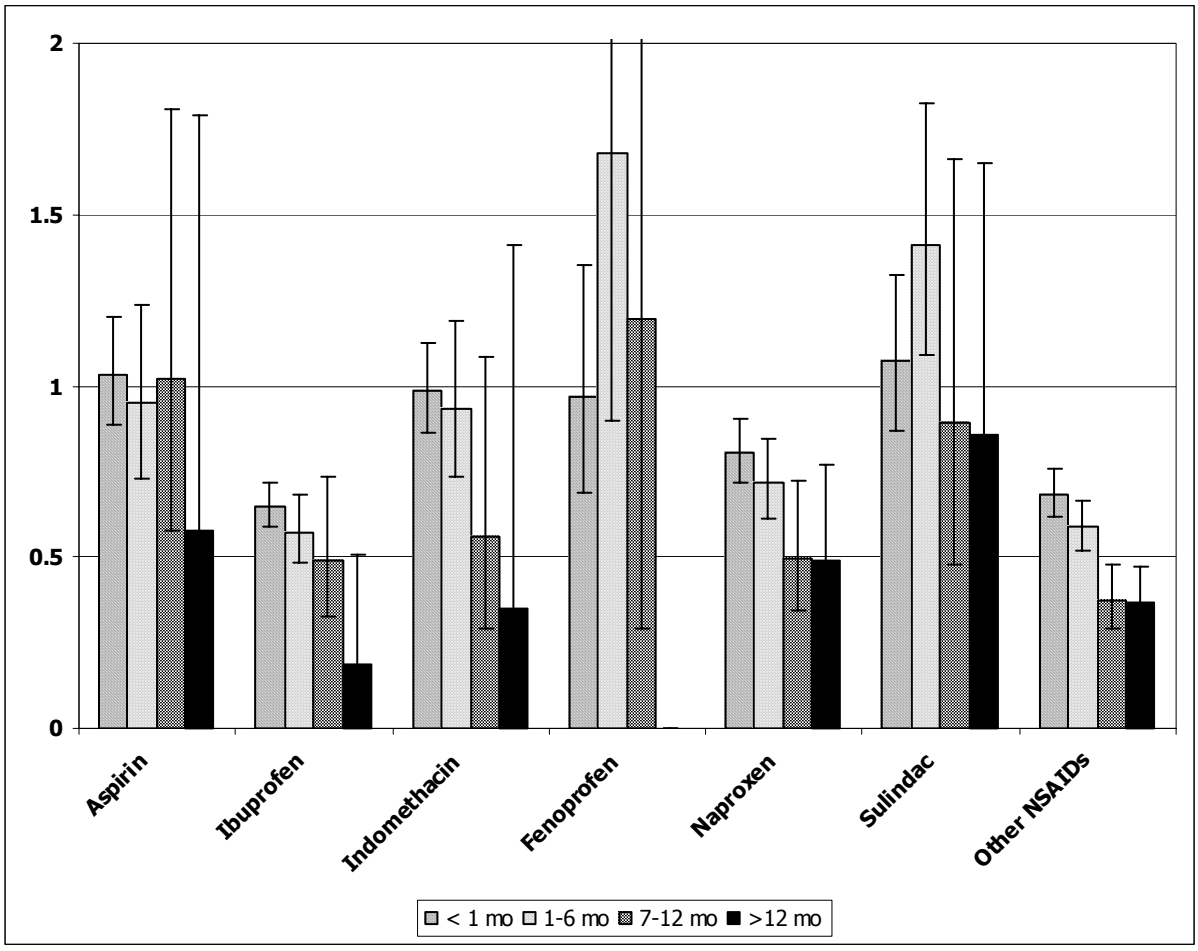

Figure 6.11: Cumulative Exposure Effect of specific NSAIDs on Renal events in North Carolina Medicaid Cohort

CHAPTER 7

THE RISK-BENEFIT PROFILE OF NSAIDS AS CHEMOPREVENTIVES AGAINST PROSTATE CANCER[3]

[3] Koompalum D., Vidyashankar A.N., Dainer P.M., Naeher L.P., Kotzan J.A., and Martin B.C. To be submitted to Cancer Epidemiology Biomarkers and Prevention.

Abstract

Background: Evidence from epidemiological studies has suggested that NSAID exposure may reduce the incidence of prostate cancer. Since NSAIDs are relatively inexpensive, NSAIDs may offer a possible strategy to reduce the burden of prostate cancer. However, before NSAIDs can be considered as chemopreventives, their potential benefit must be weighed against the risks of gastrointestinal (GI) and renal adverse effects.

Objectives: This study sought to determine the risk benefit profile of NSAIDs as chemopreventives by confirming the protective effect of NSAIDs against prostate cancer and to describe the association between NSAID use and GI and renal diseases.

Methods: Two retrospective cohort studies were conducted using Georgia (GA) and North Carolina (NC) Medicaid claims. We recruited men aged 50-100, who had at least 2 years of continuous eligibility. We excluded subjects that had any diagnosis of any cancer, GI, or renal diseases within their first year eligibility. The cohort was followed until the earliest occurrence of: (1) outcomes of interest, namely prostate cancer, GI events (i.e. GI Ulcers and GI hemorrhage) and renal events (e.g. renal failure and glomerulonephritis), (2) loss of eligibility, (3) death, or (4) end of study (December 31, 2001 for GA cohort and December 31, 1998 for NC cohort). All outcome occurrences were dated and determined by searching for claims with ICD-9-CM codes indicative of the outcome events. NSAID exposure was identified by searching the National Drug Code (NDC) in the prescription files. For each NSAID prescription, the strength and prescribed quantifies were kept to further explore a dose-response relationship. Survival Analysis (Cox-Proportional Hazard) technique was used to calculate all relative risks.

Results: There were 56,876 men in the GA Medicaid cohort and 54% were exposed to an NSAID. After multivariate adjustment, we found a significantly lower risk for prostate cancer, GI and renal events among subjects exposed to NSAIDs compared with those not exposed to NSAIDs, relative risk were 0.84 (95%CI, 0.74 to 0.94), 0.53 (95%CI, 0.50 to 0.57), and 0.44 (95%CI, 0.40 to 0.48), respectively. These results were validated in the NC Medicaid cohort; the cohort contained 49,668 men and 37% were exposed to an NSAID. After multivariate-adjustment, subjects prescribed NSAIDs were at 25% (RR, 0.75; 95%CI, 0.63 to 0.89), 35% (RR, 0.65; 95%CI, 0.59 to 0.71), and 44% (RR, 0.56; 95%CI, 0.48 to 0.64) lower risk of prostate cancer, GI and renal events, respectively. The protective effect of Cox-2 inhibitors and aspirin against prostate cancer was reported, despite the non-significant benefit of non-aspirin NSAIDs. We found no increase in risk of NSAID-related adverse events, GI and renal events. In addition to the apparent reduced risk of NSAID-related adverse events in subject exposed Cox-2 inhibitors, all aspirin and non-selective NSAIDs were not associated with increased risk of NSAID-related adverse events. The increased cumulative exposure of NSAIDs was associated with decreased rates of prostate cancer, GI and renal events. Protective effects of long-term NSAID use against prostate cancer, GI and renal events were 42-55%, 54-66%, and 68-79%, respectively.

Conclusions: Our study confirms the protective effect of NSAIDs on prostate cancer and found no increase in NSAID-related adverse events.

Background

Prostate cancer is the most common cancer among American men {American Cancer Society 2003}. Prostate cancer incidence increases with age, especially for those over age 65 {Jamel 2003}. It is estimated that 1 in 7 men over age 60 was diagnosed with prostate cancer {American Cancer Society 2004}. Although the exact cause of prostate cancer is unknown, several factors are possibly involved in the development of prostate cancer including diet, i.e. animal fat intake {Kolonel 1999}, sexual activity and frequency of venereal disease {Ross 1987}, history of benign prostatic disease, including prostatitis {Nelson 2002}, and hormones, such as testosterone {Ross 1998}.

Numerous studies have shown elevation of cyclooxygenase (COX) expression, especially COX-2 isoform, occurs in cancerous tissues, including prostate adenocarcinoma and carcinoma {Chaudry 1994}. The COX enzyme and carcinogenesis have been linked in genetic studies that showed that increased levels of COX-2 and prostaglandins can potentially account for the tumor-promoting effects; prostaglandins could enhance tumor growth and metastasis by stimulating angiogenesis and invasiveness, in addition to inhibiting apoptosis and immune surveillance {Liu 2001, Marks 1999}. Moreover, epidemiologic, experimental, and intervention research suggests that ability of NSAIDs to inhibit COX enzyme increases tumor cell apoptosis {Subbaramaiah 2003, Xu 2002}.

Epidemiological evidence for chemoprevention of prostate cancer is controversial. Two case-control {Neugut 1998, Irani 2002} and 4 cohort studies {Leitzmann 2002, Norrish 1998, Paganini-Hill 1989} demonstrated that no association existed between prostate cancer incidence and use of NSAIDs. Some suggested increasing risk {Friis 2003, Langman 2000, Sorensen 2003}. Contrarily, Garcia Rodriguez & Gonzalez-Perez {Garcia Rodriguez & Gonzalez-Perez

2004}, Habel et al {Habel 2002} and Nelson & Harris {Nelson 2000} reported a protective effect of NSAIDs. For instance, strong evidence for a chemopreventive role of NSAIDs was described in a hospital-based case-control study, where the decreased risk of prostate cancer was around 65% for both over-the-counter NSAIDs (OR, 0.34; 95% CI, 0.23-0.58) and prescription NSAIDs (OR, 0.35; 95% CI, 0.15-0.84). Likewise, in a multiracial cohort of the Kaiser Permanente Medical Care Program {Habel 2002}, lower incidence of prostate cancer among men who reported taking high dose of aspirin (RR, 0.76; 95% CI, 0.60-0.98). A nested case-control studies using the UK General Practice Research Database suggested a decreased risk of prostate cancer by 30% in aspirin users (OR, 0.70; 95% CI, 0.61-0.79) {Garcia Rodriguez & Gonzalez-Perez 2004}.

The well-documented adverse effects of NSAIDs include gastrointestinal (GI) complications (i.e. GI bleeding, perforation, and ulcer) and renal complications (i.e. acute renal failure). There are an estimated 100,000 hospitalizations and 10,000 to 20,000 deaths annually are due to NSAID-related GI complications at an annual cost of 1.6 billion dollars {Fries 1991, Smalley1996}. There is little doubt that short term NSAID exposure can increase the risk of gastric and duodenal ulcers, GI hemorrhage and perforation. The risk of GI complications is 3-5 times more likely in NSAID users {Ofman 2002}.

What is less clear is the impact of long term NSAID use on GI complications. Several studies have shown evidence that the risk for NSAID associated GI events is highest at the initiation of a regimen and then the risk tapers over time {Gabriel 1991, Garcia Rodriquez 1998, Smalley 1995}. Several observational studies have similarly reported decreasing risks of GI complications when NSAIDs were taken over longer durations {Garcia Rodriquez 1998, Smalley 1995}. For instance, among current users, the constant risk of GI complications during the first

year of NSAID use and was roughly 7 times more likely than non-users {Garcia Rodriquez 1998}. The risk of GI complications, however, was cut nearly half for NSAID exposure >1 year. (RR, 3.5; 95%CI, 2.0-6.0) {Garcia Rodriquez 1998}. Gastric mucosal adaptation has been reported in both animal and human studies and may account for the decreasing risk of NSAID exposure over time {Fitzpatrick 1999, Lipscomb 1996}. Gastric mucosal adaptation is described as the phenomenon in which visible gastric mucosal injury lessens or resolves completely despite continued administration of an injurious substance such as aspirin {Olivero 1992, Graham 1988, Graham 1983}. Although the mechanism remains unclear, it is suggested that increased cell proliferation and correction of NSAID drug induced reduction in gastric blood flow as possibly being a factor {Olivero 1992}.

Acute and chronic renal complications are also a major concern with NSAID use, especially in persons with pre-existing impaired renal function {Hernandez-Diaz 2001}. For instance, persons with cirrhosis, heart failure, renal disease, diabetes, advanced age, heart failure, hypertension, and those exposed to nephrotoxic medications, i.e. diuretics, NSAIDs, and some antibiotics are at higher risk of acute renal failure {Fored 2001, Griffin 2000, Hernandez-Diaz 2001, Perneger 1994, Rexrode 2001, Bailie 1995, Henry 1992}. Renal injury as a result of NSAID exposure affects approximately 2 persons per 100,000 {Perneger 1994}. It is believed that NSAIDs may exacerbate renal insufficiency, hyperkalemia, interstitial nephritis, and acute renal failure by inhibiting renal prostaglandins {Brooks 1998} Griffin and colleagues reported that persons who currently used NSAIDs were almost 1.6 times more likely to be hospitalized for acute renal failure than ones who never used NSAIDs (OR, 1.58, 95%CI, 1.34-1.86). The highest risk was observed within first 30 days of use. Regular use of NSAIDs increased the risk of chronic renal failure 2.5 fold (95%CI, 1.9-3.3) {Fored 2001}. In contrast to most of the

findings previously described, the Physician's Heath Cohort study contrarily showed no association between self-reported cumulative NSAID use over 14 years and the risk of renal dysfunction in men {Rexrode 2001}.

The objective of this study was to establish the risk-benefit profile of NSAIDs as chemopreventives against prostate cancer; we aimed to determined if there is a protective effect of NSAIDs against prostate cancer and to describe the relationship of NSAID use with GI and renal adverse events using two Medicaid databases: Georgia and North Carolina Medicaid.

Methods

Data Source

We simultaneously conducted 2 retrospective cohort studies utilizing administrative claims data of the Medicaid program from 2 states: Georgia and North Carolina. The Medicaid, jointly funded by the Federal and State governments, is health insurance that assists certain individuals and families with low incomes and resources in providing medical and health-related services for people with limited income, who meet eligibility criteria. Adults eligible for Medicaid benefits include some low-income residents, medically needy individuals, the elderly, and people with disabilities if state and federal guidelines are met.

The Georgia Medicaid administrative claims data capture all reimbursed medical encounters of the Georgia Medicaid recipients. The GA Medicaid database contains an annual enrollment of approximately 1.2 million eligible persons per year, and the enrollment file contains patient level details on recipient demographics, including patient identifier, date of birth, gender, race, date of dead, as well as monthly Medicaid coverage (eligibility information). All Medicaid beneficiaries' medical utilization, including inpatient, outpatient, nursing home,

and emergency services, is collected in the medical claims file. The pharmacy claims file records each reimbursed prescription including information describing the date prescriptions are filled, drug name, National Drug Code (NDC), strength, dosage, and number of units dispensed. All three of the files are linked by encrypted recipient identifier allowing the construction of person level analytic files where treatments and ensuing medical encounters can be measured at the patient level.

Similarly, the North Carolina Medicaid claims database is an administrative claims database of the North Carolina Medicaid recipients' medical encounters. There are roughly 1 million North Carolina Medicaid recipients per year. The NC Medicaid data contain patient level details on demographics, monthly coverage, non-prescription medical utilization, and pharmacy claim file, all of which are linked by encrypted recipient identifier.

Subjects

In both cohorts, the study subjects were between the ages of 50 and 100 years, who had at least 2 years of continuous eligibility. We excluded subjects who had any diagnosis of any cancer, GI or renal disease within their first year eligibility, and any recipients with dual Medicare eligibility without full Medicaid coverage (figures 7.1-7.2). The cohort was followed until the earliest occurrence of: (1) outcomes of interest, namely prostate cancer, GI events (i.e. GI ulcers and GI hemorrhage), and renal events (e.g. renal failure), (2) loss of eligibility, (3) death, or (4) end of study (figure 7.3).

Identification of Prostate cancer, GI and Renal Events

To identify incident prostate cancer, GI and renal events, all diagnoses recorded in the medical claims file were searched. All outcome occurrences were dated and determined by searching for claims with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes indicative of the outcome events described below.

Prostate cancer

To detect individuals with prostate cancer, we used ICD-9-CM codes for malignant neoplasm (185), benign neoplasms (222.2) and carcinoma in situ (233.4), which were found to be consistent with prostate specific antigen (PSA) screening {Skarsgard 2000}.

Gastrointestinal (GI) Events

The GI events were defined as upper gastrointestinal bleeding, perforation, or ulcer. A subject with any diagnosis of gastric ulcer (531.x), duodenal ulcer (532.x), gastrojejunal ulcer (534.x), peptic ulcer (533.x), and gastrointestinal hemorrhage (578.x) was identified {Smalley 1995}. The positive predictive value of these codes were previously reported as 97%, 84%, 80%, and 59% with hospital clinical records for 531.x-532.x, 534.x, 533.x, and 578.x, respectively {Cattaruzzi 1999}.

Renal Events

The renal events are diagnosed cases acute renal failure and other impairment of renal function that is associated with NSAID exposure. The ICD-9-CM algorithm to identify cases of renal events was derived from existing medical literature for potential NSAID-related renal

failure {Griffin 2000, Harley 2003, Niecko 2001}. The outcome measures identified by ICD-9-CM codes were acute glomerulonephritis (580.x), nephrotic syndrome (581.x), non-specified nephritis and nephropathy (583.x), acute renal failure (584.x), renal failure (586.x), disorder of the kidney (593.9), diabetes with renal manifestations (250.4), and hypertension with renal manifestations (403.x, 404.x).

NSAID Exposure

We determined NSAID utilization by searching all prescription codes in the pharmacy claims file for all NSAIDs listed in table 7.1. Only orally administered NSAIDs are relevant to the study. The NDC codes were employed to identify aspirin, NSAID and COX-2 inhibitors prescribed. For those individuals who were prescribed any NSAID, we recorded the generic name, the chemical class, the strength (in milligrams), and the number of units of drug dispensed for each NSAID prescription. In the NC cohort, we were unable to determine an impact of COX-2 inhibitors on study events due to unavailable data; dates approved by FDA of celecoxib and refecoxib were December 1998 and May 1999 respectively.

We define low and high daily dose based on minimum and maximum starting doses recommended for treatment of arthritis as noted in the *Physicians' Desk Reference* {Smalley 1999, Niecko 2001}. Cumulative drug exposure was used to determine prescription NSAID exposure in the study cohort and was defined as the number of units of drug dispensed multiplied by the dose of the drug. All study NSAID dosages were standardized and converted to ibuprofen dosage equivalents. Based on the assumption of equal efficacy among high-dose NSAIDs for the treatment of arthritis, an "ibuprofen weighted" factor is computed. An "ibuprofen weighted" factor equals 2,400 (high daily dose of ibuprofen) divided by the high daily dose recommended

for any particular NSAID {Smalley 1999, Niecko 2001}. Then, NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints. The cumulative exposure was defined as NSAID use equivalent to a period of NSAID use at the highest daily dose: less than one month (ibuprofen equivalents up to 72 grams), 1-6 months (ibuprofen equivalents 72-432 grams), 7-12 months (ibuprofen equivalents 433-876 grams), and greater than 12 months (ibuprofen equivalents more than 876 grams) of use.

Statistical Analysis

Demographic and other clinical characteristics (i.e. age, gender, length of follow up, prevalence of selected comorbidities) between the NSAID exposure and non-exposure groups, were tabulated and tested for differences using chi-square test for categorical variables and t-test for continuous variables. All statistic analyses were performed using SAS statistical software (Version 8.2, SAS Institute, Cary, North Carolina). All p-values were 2-sided and the significance level was set at $p<0.05$.

Unadjusted incidence was calculated by dividing number of new cases of each outcome event by the number of person-years. We computed crude relative risks by dividing the unadjusted incidence rates of NSAID users (e.g. cases per 100,000 person-years) by those of non-users.

Cox proportional hazards models were used to estimate the multivariate adjusted rates and relative risks (using PROC PHREG of SAS package). Model specification and operative definition of all covariates are summarized below. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CI) are reported.

Model Specification

The Cox proportional hazard model was defined as follows:

$$h(t \mid Z) = h_0(t) * \exp[\ \alpha(\text{NSAID exposure}) + \beta * X + \varepsilon\text{rror}\ ]$$

Where $h(t \mid Z)$: hazard rate at time 't' for an individual with risk vector Z

$h_0(t)$: baseline hazard rate

α : Coefficient for NSAID exposure

X : Matrix of covariates

β : Vector of coefficients corresponding to the matrix of covariates

Dependent Variables

Our major outcomes of interest are the first incidence of diagnosed prostate cancer, and adverse gastrointestinal and renal events. Since occurrences of the three outcomes do not depend on one another, we modeled each outcome separately with specific set of covariates. For each study event of interest, a Cox proportional hazard model was fitted based on:

(1) Incidence of each study event: A dichotomous dependent variable was coded whether or not subjects had any diagnosis codes of the study outcome.

(2) Person-years in study cohort: Number of years each subjects stayed in the cohort is calculated by subtracting the date when a subject entered the cohort from the date when the subject left the cohort.

Independent variables

Effect of NSAID exposure was modeled in three sets of separate analyses as follows:

1) NSAID exposure as a class: A dichotomous independent variable coded if a subject prescribed any NSAID.
2) Cumulative exposure of NSAIDs: NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints (less than one month, 1-6 months, 7-12 months, and greater than 12 months)
3) Effect of the use of some specific NSAIDs was analyzed. Based on generic names recorded from each subject's prescriptions, NSAID exposure was classified into 8 groups (see below). There is a high possibility that subjects may be exposed to more than one product or group, so persons could have more than one of the following NSAID variables recorded as exposed. Furthermore, to determine the effect cumulative exposure of each on study endpoints, the cumulative exposure for each generic group was calculated and stratified into 4 categories: less than one month, 1-6 months, 7-12 months, and greater than 12 months.
    a) Aspirin
    b) Selective Cox-2 inhibitors (celecoxib and rofecoxib)
    c) Ibuprofen (commonly prescribed) {Smalley 1999, Niecko 2001}
    d) Naproxen (commonly prescribed) {Smalley 1999, Niecko 2001}
    e) Indomethacin (commonly prescribed)
    f) Fenoprofen (commonly prescribed)
    g) Sulindac (effective in many animal models) {Smalley 1999, Niecko 2001}
    h) Other non-specific NSAIDs

Covariates

All covariates included in the model were listed in table 7.2. Operational definition and the ICD-9-CMcodes for each covariate were summarized in table 7.2.

Results

There were 56,876 eligible men in the GA Medicaid cohort and 54% were exposed to an NSAID. On average, subjects were followed for 3.3 years (s.d., 1.0). Their average age was 67.4 years (s.d. 11.1 years); 45.2% were white, 42.1% were non-white and 12.7% were of unknown race. Incidence rates of prostate cancer, GI and renal events were 377.6, 1021.1, and 703.7 per 100,000 person-years, respectively.

The NC Medicaid cohort contained 49,668 men and 37% were exposed to an NSAID. On average, subjects were followed for 4.7 years (s.d., 2.2). The cohort mean age was 68.9 years (s.d. 10.8 years); 50.3% were white, and 49.7% were non-white. Incidence rates of prostate cancer, GI and renal events were 258.3, 762.0, and 394.2 per 100,000 person-years, respectively.

Both GA and NC cohort characteristics by NSAID exposure status is displayed in tables 7.3-7.4. The length of follow up of subjects exposed NSAIDs were significantly longer than those not exposed NSAIDs ($p<0.05$). Younger persons and non-whites were more likely to have an NSAID prescription filled than their respective counterparts.

We observed a significantly lower risk for prostate cancer, GI and renal events among subjects exposed to NSAIDs compared with those not exposed to NSAIDs (tables 7.5-7.6) after multivariate adjustment; however there were some discrepancies in results between the unadjusted and the multivariate adjusted rates. The unadjusted rates of the GA cohort were 1.10 (95%CI, 1.03 to 1.16), 0.90 (95%CI, 0.87 to 0.94), 0.75 (95%CI, 0.72 to 0.78) for prostate

cancer, GI and renal events, respectively. After adjusting for several covariates, the relative risks became significant, with relative risks of 0.84 (95%CI, 0.74 to 0.94), 0.53 (95%CI, 0.50 to 0.57), and 0.44 (95%CI, 0.40 to 0.48) for prostate cancer, GI and renal events, respectively. Comparing the adjusted results obtained from the NC cohort, the unadjusted rates for the North Carolina NSAID users were higher with unadjusted risks of 1.01 (95%CI, 0.93 to 1.09), 1.41 (95%CI, 1.34 to 1.48), 1.22 (95%CI, 1.15 to 1.31), for prostate cancer, GI and renal events respectively. The multivariate-adjusted relative risks, from the NC cohort, showed to be significant, as the relative risks were 0.75 (95%CI, 0.63 to 0.89), 0.65 (95%CI, 0.59 to 0.71), and 0.56 (95%CI, 0.48 to 0.64) for prostate cancer, GI and renal events, respectively.

The effects of covariates on study events of interest were summarized (table 7.7-7.9). Compared with the 50 to 64 age group, the older age groups, >75 age groups, appeared to be at higher risk for prostate cancer, although both 65-75 and >75 age groups appeared to be at lower risk for GI and renal events. Being non-white, being alcoholic, and smoking tobacco increased the risk for all three outcomes. Even though the prostate cancer and renal event risks were similar in obese and non-obese persons, obesity increased the risk of GI events. We found that prostatitis was associated with 5-fold increased risk of prostate cancer. H. pylori infection and GI protective agents were the most important risk factors for GI events; while H. pylori infection increased risk of GI events by 3.5-4.5 times, subjects prescribed GI protective agents were 4-5 times more likely to experience a GI event. Hypertension, congestive heart failure, diabetes mellitus and immunosuppressive agents (i.e. cyclosporine) were the most important risk factors for renal events; subjects with hypertension, congestive heart failure, diabetes, and cyclosporine prescription were 2-3, 2-3, 1.5-2, and 3.5-6 times more likely to be diagnosed with renal events, respectively.

The impact of specific NSAID exposure on prostate cancer, GI and renal events are summarized in tables 7.10-7.11. The protective effect of Cox-2 inhibitors against prostate cancer was the most pronounced. Despite the significant benefit of aspirin against prostate cancer, non-aspirin NSAIDs were not significant. With exception of ibuprofen, in NC cohort, we found that subjects prescribed ibuprofen had significant 23% decreased risk of prostate cancer. Compared with the non-NSAID exposure group, the reduced risk of NSAID-related adverse events was lowest in subject prescribed Cox-2 inhibitors. In addition, all non-selective NSAIDs and aspirin were either insignificantly altered or significantly decreased risk of both NSAID-related adverse events; subject prescribed ibuprofen and naproxen were at lower risk of GI and renal events.

The increased cumulative exposure of NSAIDs was associated with decreased rates of prostate cancer, GI and renal events (figures 7.4-7.5). Protective effects of long-term NSAID use against prostate cancer were shown for some specific NSAIDs (figures 7.6, 7.9). For instance, long-term use of ibuprofen and naproxen, in GA cohort, were significantly associated with 24% and 53% decreased risk of prostate cancer (figure 7.6). In addition, our results from the GA cohort demonstrated the risk reduction of GI and renal events in persons who had more than 1 year of each specific NSAID exposure, except fenoprofen and sulindac (figure 7.7-7.8).

To explore a possible explanation for an apparent protective effect of NSAIDs on renal and GI study outcomes, we conducted a sensitivity analysis excluding all persons admitted to a long-term care facility more than 1 year and re-estimated the multivariate adjusted models on the remaining subjects. With this additional exclusion criterion, we excluded 14,412 and 140 persons admitted to a long-term care facility more than 1 year from GA and NC cohorts, respectively. The results of sensitivity analyses are presented in tables 7.12-7.13 and this sensitivity analysis had little bearing on the main findings previously reported.

Discussion

Our study showed that NSAID exposure exhibited a modest protective effect against prostate cancer with a reduction in risk of about 16-25% for any exposure to NSAIDs and greater reductions in relative risks at higher levels of NSAID consumption. We found that the protective effect of Cox-2 inhibitors was the most apparent and was greater with increasing cumulative exposure. These results were not affected after excluding recipients that were admitted to long-term care facilities for greater than one year.

Evidence from previous epidemiologic studies of NSAID use and the risk of prostate cancer have been mixed. However, in a recent case-control studies using the UK General Practice Research Database, a reduction in prostate cancer risk (OR, 0.70; 95% CI, 0.61-0.79) was reported among aspirin users {Garcia Rodriguez & Gonzalez-Perez 2004}. Similar reduction, were described in those exposed to prescription NSAIDs (OR, 0.35; 95% CI, 0.15-0.84) in a hospital-based case-control study {Nelson 2000} and in those took high dose of aspirin (RR, 0.76; 95% CI, 0.60-0.98) in a multiracial cohort of the Kaiser Permanente Medical Care Program {Habel 2002}.

We did not find an elevated risk of GI and renal adverse events. After multivariate adjustment, NSAID use was associated with a statistically significant reduction in GI and renal adverse events. Similar to the risks of prostate cancer by cumulative NSAID exposure, the risk of GI and renal adverse events appears to be inversely associated with cumulative amount used. Persons who had more than 1 years of NSAID usage experienced an apparent 54-66% and 68-79% decreased risk for GI and renal adverse events than did persons who had no exposure, respectively.

Nevertheless, these results must be interpreted with caution. Since subjects were required to be free of all outcomes within their first year eligibility, many of the NSAID users able to meet the inclusion criteria and remain in the study might tolerate NSAID therapy better than most typical users. Therefore, these subjects may demonstrate a lower risk for GI and renal events relative to those persons with NSAID exposure who do not tolerate therapy.

Our results suggest that the risk of GI adverse events decreases as persons consume more NSAIDs, which is consistent with previous studies showing that the initial doses of NSAIDs and not long term NSAID use are most likely to result in GI adverse related events {Gabriel 1991, Garcia Rodriquez 1998, Smalley 1995}. This may be explained by gastric mucosal adaptation, which has been reported in both animal and human studies {Fitzpatrick 1999, Lipscomb 1996}.

Despite comparable demographic compositions between the Medicaid cohorts in Georgia and North Carolina, a higher percentage of subjects in the Georgia (54%) were prescribed any NSAID than those in the North Carolina (37%). This discrepancy may be explained by differences in pharmacy services policy, available prescription NSAIDs, and physician's prescribing preferences. Before July 1998, the Georgia Medicaid pharmacy program covered only five prescriptions per recipient per month. After of July 1998, with a written or oral prescription from a physician indicating the need for a drug override to exceed the monthly limits, pharmacists in Georgia are able to do self-approval to exceed these prescription limits {Georgia Department of Community Health 2004}. North Carolina Medicaid has also established monthly prescription limits of six prescriptions per recipient per month. Unlike the Georgia Medicaid program, after July 1998, exemption from the prescription limitation will only be authorized for life threatening illnesses. The recipient's physician must submit a "Six Prescription Limit Override Form" where he or she justifies the patient's need for a drug

override to exceed the monthly prescription limits {North Carolina Division of Medical Assistance 2004}. The possible follow-up period of the Georgia cohort (1990- 2001) was three years longer than that of the North Carolina cohort (1990-1998). The policy of override to exceed the monthly prescription limits under the Georgia Medicaid program was changed. Therefore NSAID prescription rates in Georgia might have increased during that three-year period (1999-2001). Moreover, Cox-2 inhibitors, celecoxib and rofecoxib, were introduced in 1999. Cox-2 inhibitors are covered, without requirement of prior authorization, by Georgia Medicaid, although there are quantity level limits of 34 tablets per 34 days when celecoxib and rofecoxib are prescribed {Georgia Department of Community Health 2004}. Both Georgia and North Carolina Medicaid programs do not cover over-the-counter aspirin. Enteric-coated aspirin is available as a prescription drug and covered by Georgia Medicaid; prescription aspirin is not covered by the North Carolina Medicaid program. Lastly, there may be a difference of NSAID prescribing preferences of physicians in Georgia and North Carolina.

Some inconsistent results between unadjusted and multivariate adjusted relative risks obtained from both Georgia and North Carolina Medicaid data. We found the higher unadjusted relative risks than and reversed direction of multivariate adjusted relative risks of all three study outcomes. NSAID users had higher percentages of risk factors we adjusted in calculating multivariate adjusted relative risks. Some of those risk factors were strongly associated with the risks of the study outcomes; for example ones diagnosed with prostatitis were associated with 5-fold increased risk of prostate cancer. Therefore, the increased unadjusted relative risks may be subsequently due to these strongly associated risk factors.

We found that person aged >75 were at higher risk for prostate cancer than those aged between 50 and 64; this is coherent with increased risk of prostate cancer at advanced age. However, older age classes, both 65-75 and >75 age group, appeared to be at lower risk for NSAID-related adverse events than the 50 to 64 age group; this may be a subsequence of Medicare picking up claims for those aged 65 and greater.

There are several potential limitations in this proposed study. Based on inspecting the claims volume over time, some issues with the completeness and accuracy of a very small portion of the data may have been detected. First, for one month of the study period (March 1998), the dates of service on the claims may have been errantly recorded for January, February or April 1998 and there was no way to reconcile these dates with source records. Secondly, the total numbers of claims for the period October through December 1997 are noticeably lower than expected. This was despite a re-generation of the claims data obtained from the claims processor. Since these data only affect a small time window in this study and there is no reason to believe that the dates or potentially missing claims were systematically related to exposure or outcome ascertainment, this is not likely to impact any measures of relative risk. As a check, these analyses were replicated where no data after September 1997 were used and none of the main findings reported here were meaningfully affected.

We depend solely on diagnosis (ICD-9-CM) codes to identify the study outcomes and confounders. Measurement bias may arise due to coding inconsistencies. This may be of particular concern if there are differences in coding that is related to NSAID exposure. As a check for this potential concern, we conducted a sensitivity analysis excluding recipients with long term care admissions > 1 year and found the results to be generally consistent with the initial analysis. Additionally, detailed information on risk behaviors, i.e. tobacco and alcohol

consumption is not specifically recorded in claims data and could only be inferred from diagnostic information. In claims data, clinical measures, i.e. histological type and stage of cancer, are also not available. So the effect of NSAIDs on different histological type and stage of cancer cannot be explored. Despite the fact that Medicaid pays for aspirin, ibuprofen, and naproxen, exposure misclassification may still occur as a result of recipients purchasing these products over-the-counter. This may attenuate the disparity between exposure and non-exposure groups and underestimate relative risk of outcomes.

Since it is well known that NSAIDs are associated with increasing risks of GI and renal events, though perhaps transitory, channeling bias is an inextricable limitation of this study because physicians would be less likely to prescribe non-selective NSAIDs to persons they believe might be prone to GI or renal adverse events. We attended to this limitation by including the use of gastroprotective agents (a potential marker for past GI events) as a covariate in the GI adverse event models, but we recognize that this can only partially describes someone's GI event likelihood. Moreover, physicians may also pay closer attention to those who take NSAIDs, for example, more physician visits, which may lead to earlier diagnosis. Nevertheless, frequency of health care utilization was adjusted in the models in an attempt to attend to this phenomenon. We do not believe that if recipients were randomly assigned to NSAIDs and non-NSAIDs that the same results would be obtained with regard to GI and renal adverse events, however, these data do demonstrate that the NSAID prescribing decisions made in this population are not associated with an increase in GI and Renal events and this finding may better reflect the risks of NSAID prescribing rather than the relative risk of NSAIDs themselves. Though we do believe that channeling bias is an important consideration when interpreting the results of the adverse events, we do not believe channeling bias is a significant concern for the results for the prostate

cancer prevention analyses, because it is unlikely that physicians were prescribing NSAIDs for persons whom they thought might be at higher risk of prostate cancer during this study time frame.

Conclusion

Any NSAID exposure was associated with approximates 16-25% reduction in incident prostate cancer with greater reductions observed for higher cumulative exposure to NSAIDs and COX-2 inhibitors. There were no increased rates of GI and renal events associated with NSAID prescribing in this population. Findings from our study support the hypothesis that there exists the protective effect of NSAIDs against prostate cancer. Moreover, NSAID use did not elevate the risk of GI and renal adverse events. Therefore, NSAIDs could be considered to use as chemopreventives against prostate cancer. Although the dose-response relationship was modestly revealed, the questions regarding optimal chemopreventive dose and duration of NSAIDs are remaining unanswered. Additional large perspective cohort studies with more extended period of follow-up and clinical trails in order to validate and examine biochemical components of NSAIDs. Further research should adopt better measures of NSAID use, and better controls of behavioral risk factors to examine a specific recommendation of NSAID use as chemopreventives against prostate cancer.

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Table 7.1: Commonly Available Non-Steroidal Anti-inflammatory Drug (NSAIDs), According to Chemical Class

Chemical Class	Generic	Low daily dose (mg)	High daily dose (mg)	Standardization to Ibuprofen
Nonselective COX inhibitors				
Salicylic acid derivatives	Aspirin (acetylsalicylic acid)	2,400	3,600	0.67
	Salicylate salts (i.e. Choline Magnesium trisalicylate)	2,000	3,000	0.80
	Diflunisal	500	1,000	2.40
	Salsalate	2,000	4,000	0.60
Heteroacrl acetic acids	Diclofenac	100	150	16.00
	Etodolac	800	1,200	2.00
	Ketorolac	10	40	60.00
	Tolmetin	1,200	1,800	1.33
Indole and indene acetic acids	Indomethacin	50	150	16.00
	Sulindac	300	400	6.00
Arylpropionic acids	Fenoprofen	900	2,400	1.00
	Flurbiprofen	200	300	8.00
	Ibuprofen	1,200	2,400	1.00
	Ketoprofen	200	300	8.00
	Naproxen	550	1,100	2.18
	Oxaprozin	1,200	1,800	1.33
Anthranilic acid (Fenamates)	Meclofenamic acid	100	400	6.00
	Mefenamic acid	500	1,000	2.40
Enolic acids				
Pyrazolones	Phenylbutazone	300	400	6.00
Oxicams	Piroxicam	less than 20	20	120.00
Nonacidic agent				
Alkanones	Nabumetone	1,000	2,000	1.20
Selective COX-2 Inhibitors				
Diaryl-substituted furanones	Rofecoxib	12.5	25	96.00
Diaryl-substituted isoxazole	Valdecoxib	10	20	120.00
Diaryl-substituted pyrazoles	Celecoxib	200	400	6.00

Source: (1) Roberts LJ2, Marrow JD. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Good man and Gilman's the pharmacological basis of therapeutics. Columbus: The McGraw-Hill Companies, Inc., 2001;687-731.

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Table 7.2: List of Model Covariates and their Operational Definitions

Covariates	Outcome		
	Prostate cancer	GI events	Renal events
Demographics			
Age at entry (years)	Yes	Yes	Yes
Gender (female vs. male)	Yes	Yes	Yes
Race (non-white vs. white)	Yes	Yes	Yes
Frequency of health care utilization: Total number of visits to ambulatory care services, emergency department, long-term care facilities, and acute inpatient services throughout study period	Yes	Yes	Yes
Frequency of cancer screenings: Total numbers of any cancer screenings throughout study period	Yes	Yes	Yes
Alcohol use and alcohol abuse (ICD-9-CM = 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 {Elixhauser 1998})	Yes	Yes	Yes
Obesity (ICD-9-CM = 278.x {Elixhauser 1998})	Yes	Yes	Yes
Tobacco Smoke (ICD-9-CM = 305.1, V15.82 {Romano 1994})	Yes	Yes	Yes
Prostatitis (ICD-9-CM=601.x)	Yes	No	No
Sexually transmitted diseases (STDs)	Yes	No	No
Human immunodeficiency virus disease (HIV)/ acquired immunodeficiency syndrome (AIDS; ICD-9-CM=042, V08)	Yes	No	No
Syphilis (ICD-9-CM= 091.x- 097.x)	Yes	No	No
Gonococcal infection (ICD-9-CM=098.x)	Yes	No	No
Human papillomavirus (HPV) infection (ICD-9-CM= 079.4)	Yes	No	No
Emphysema (ICD-9-CM = 492.xx)	No	Yes	No
Chronic Bronchitis (ICD-9-CM = 491.xx)	No	Yes	No
H.Pylori infection (ICD-9-CM = 041.86)	No	Yes	No
Cirrhosis (ICD-9-CM = 571.5, 571.6)	No	No	Yes
Hypertension (ICD-9-CM = 401.xx, 402.xx, 405.xx {Elixhauser 1998})	No	No	Yes
Diabetes Melitus (ICD-9-CM = 250.0x-250.3x; 250.5x-250.9x {Elixhauser 1998})	No	No	Yes
Congestive heart failure (ICD-9-CM = 389.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9 {Elixhauser 1998})	No	No	Yes
Liver Failure (ICD-9-CM = 570.xx)	No	No	Yes
Finasteride	Yes	No	No
GI protective agents (i.e. Misoprostal, proton pump inhibitors (PPIs), and histamine-2 (H2) receptor antagonists)	No	Yes	No
Corticosteroids (i.e. prednisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone and hydrocortisone)	No	Yes	No
Anticoagulant use (i.e. heparins, coumarin and indadiones)	No	Yes	No
Nephrotoxic Drugs:	No		
Diuretics (i.e. loop, potassium-sparing, thiazide diuretics)	No	No	Yes
Angiotensin-converting Enzyme (ACE) Inhibitors and Angiotensin-II-receptor antagonist (e.g captopril, enalapril, lisinopril, losartan etc.)	No	No	Yes
Aminoglycosides	No	No	Yes
Cephalosporins	No	Yes	Yes
Vancomycin	No	No	Yes
Allopurinol	No	No	Yes
Cyclosporine	No	No	Yes

Table 7.3: Georgia Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Prostate Cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	25,866	31,010	26,171	30,705	25,948	30,928
Incidence rate per 100,000 person-years	355.70	390.39	1086.69	981.83	834.54	627.50
Follow up period, mean ± SD (yr)	4.7 ± 2.9	6.7 ± 3.4	4.6 ± 2.9	6.6 ± 3.4	4.6 ± 2.9	6.7 ± 3.4
Demographics (%)						
Age, mean ± SD (yr)	68.1 ± 11.5	66.7 ± 10.7	67.9 ± 11.5	66.9 ± 10.7	68.0 ± 11.5	66.8 ± 10.7
Race						
White	48.6	42.4	48.6	42.4	48.5	42.5
Non White	41.2	43.0	41.2	43.0	41.3	42.9
Unknown Race	10.3	14.6	10.3	14.7	10.3	14.7
Risk Factors (%)						
Tobacco Smoke	2.8	5.6	3.1	5.4	2.9	5.6
Obesity	0.5	1.6	0.6	1.5	0.6	1.5
Alcohol Abuse	5.1	8.6	5.5	8.3	5.1	8.6
Prostatitis	1.3	4.1	na	na	na	na
STDs						
HIV/AIDS	0.5	0.5	na	na	na	na
Gonoccoccal Infection	0.1	0.3	na	na	na	na
Syphillis	0.3	0.5	na	na	na	na
Emphysema	na	na	2.4	3.9	na	na
Chronic Bronchitis	na	na	4.2	7.5	na	na
H. pylori Infection	na	na	0.2	0.4	na	na
Hypertension	na	na	na	na	18.1	30.5
Diabetes Mellitus	na	na	na	na	8.8	14.0
Congestive Heart Failure	na	na	na	na	8.7	12.1
Cirrhosis	na	na	na	na	0.7	0.8
Medication exposures						
Finasteride	1.8	4.1	na	na	na	na
GI protective agents	na	na	35.0	61.2	na	na
Corticosteroids	na	na	16.4	19.5	na	na
Anticoagulants	na	na	10.5	14.2	na	na
Diuretics	na	na	na	na	33.3	50.5
ACE inhibitors	na	na	na	na	24.3	38.7
Antibiotics						
Aminoglycosides	na	na	na	na	1.6	1.6
Cephalosporines	na	na	43.8	68.2	43.6	68.1
Vancomycins	na	na	na	na	1.1	1.1
Allopurinal	na	na	na	na	2.6	10.2
Cyclosporine	na	na	na	na	0.1	0.1
Frequency of Health Care Utilization, mean ± SD (times)	119.9 ± 154.6	174.0 ± 171.9	121.1 ± 156.9	173.5 ± 170.6	120.7 ± 155.8	173.4 ± 171.2
Frequency of Cancer Screening, mean ± SD (times)	0.005 ± 0.09	0.013 ± 0.13	0.006 ± 0.10	0.013 ± 0.13	0.005 ± 0.09	0.013 ± 0.14

Table 7.4: North Carolina Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Prostate Cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	31,390	18,278	31,497	18,171	31,385	18,283
Incidence rate per 100,000 person-years	257.42	259.54	651.62	918.15	360.48	440.90
Follow up period, mean ± SD (yr)	4.3 ± 2.1	5.4 ± 2.4	4.3 ± 2.1	5.3 ± 2.4	4.3 ± 2.1	5.4 ± 2.4
Demographics (%)						
Age, mean ± SD (yr)	69.7 ± 10.7	67.5 ± 10.9	69.7 ± 10.7	67.6 ± 10.8	69.7 ± 10.7	67.5 ± 10.9
Race						
White	52.3	47.0	52.4	46.9	52.3	47.0
Non White	47.7	53.0	47.7	53.1	47.7	53.0
Risk Factors (%)						
Tobacco Smoke	2.0	5.0	2.1	4.8	2.0	5.0
Obesity	0.5	1.7	0.6	1.7	0.6	1.6
Alcohol Abuse	4.2	9.0	4.4	8.7	4.2	9.0
Prostatitis	0.7	2.6	na	na	na	na
STDs						
HIV/AIDS	0.1	0.3	na	na	na	na
Gonoccoccal Infection	0.02	0.09	na	na	na	na
Syphillis	0.2	0.5	na	na	na	na
Emphysema	na	na	1.3	3.0	na	na
Chronic Bronchitis	na	na	1.8	3.9	na	na
H. pylori Infection	na	na	0.04	0.19	na	na
Hypertension	na	na	na	na	10.8	22.6
Diabetes Mellitus	na	na	na	na	7.0	12.2
Congestive Heart Failure	na	na	na	na	5.4	9.2
Cirrhosis	na	na	na	na	0.4	0.6
Medication exposures						
Finasteride	0.9	1.8	na	na	na	na
GI protective agents	na	na	26.2	51.2	na	na
Corticosteroids	na	na	10.6	25.9	na	na
Anticoagulants	na	na	7.0	9.9	na	na
Diuretics	na	na	na	na	25.6	43.5
ACE inhibitors	na	na	na	na	14.8	27.0
Antibiotics						
Aminoglycosides	na	na	na	na	1.1	1.1
Cephalosporines	na	na	33.0	56.8	32.9	56.9
Vancomycins	na	na	na	na	0.6	0.8
Allopurinal	na	na	na	na	2.0	8.4
Cyclosporine	na	na	na	na	0.04	0.03
Frequency of Health Care Utilization, mean ± SD (times)	31.1 ± 52.0	54.4 ± 69.5	31.5 ± 52.7	53.8 ± 68.9	31.2 ± 52.1	54.3 ± 69.4
Frequency of Cancer Screening, mean ± SD (times)	0.002 ± 0.04	0.005 ± 0.09	0.002 ± 0.05	0.004 ± 0.08	0.002 ± 0.04	0.005 ± 0.09

Table 7.5: Effect of NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Prostate Cancer	Any Use	208,507	814	390.39	1.10	0.84 (0.74, 0.94)
	None	121,170	431	355.70	Reference	Reference
GI Events (male only)	Any Use	201,358	1,977	981.83	0.9	0.53 (0.50, 0.57)
	None	120,365	1,308	1,086.69	Reference	Reference
Renal Events (male only)	Any Use	206,854	1,298	627.50	0.75	0.44 (0.40, 0.48)
	None	120,545	1,006	834.54	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 7.6: Effect of NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Prostate Cancer	Any Use	98,636	256	259.54	1.01	0.75 (0.63, 0.89)
	None	136,740	352	257.42	Reference	Reference
GI Events (male only)	Any Use	96,172	883	918.15	1.41	0.65 (0.59, 0.71)
	None	135,969	886	651.62	Reference	Reference
Renal Events (male only)	Any Use	98,434	434	440.90	1.22	0.56 (0.48, 0.64)
	None	136,484	492	360.48	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 7.7: Effect of Covariates on the Incidence of Prostate cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.1781	0.0618	0.004	0.84	-0.2892	0.0863	0.0008	0.75
Age groups								
75-100 years old	0.5034	0.0795	<.0001	1.65	0.9390	0.1079	<.0001	2.56
65-74 years old	0.3203	0.0721	<.0001	1.38	-0.1646	0.1298	0.2046	0.85
50-64 years old								
Race								
Non-White	0.6934	0.0656	<.0001	2.00	0.4648	0.0845	<.0001	1.59
White								
Frequency of Cancer Screening	0.4673	0.1106	<.0001	1.60	0.3049	0.2452	0.2137	1.36
Frequency of Health Care Utilization	-0.0002	0.0001	0.2863	1.00	0.0025	0.0004	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.0851	0.1036	0.4117	1.09	0.5044	0.1442	0.0005	1.66
Obesity	0.1486	0.2074	0.4736	1.16	0.3036	0.2746	0.2689	1.36
Tobacco Smoke	0.4927	0.1151	<.0001	1.64	0.7311	0.1648	<.0001	2.08
Prostatitis	1.6573	0.0864	<.0001	5.25	1.6424	0.1582	<.0001	5.17
STDs								
HIV/AIDS	0.2418	0.3374	0.4736	1.27	-0.1084	1.0067	0.9142	0.90
Gonoccoccal Infection	-1.7665	1.0018	0.0778	0.17	0.4822	0.7253	0.5061	1.62
Syphillis	0.4002	0.2920	0.1706	1.49	0.0171	0.5830	0.9766	1.02
Medication exposures								
Finasteride	0.2581	0.1195	0.0309	1.29	0.0990	0.2827	0.7262	1.10

Table 7.8: Effect of Covariates on the Incidence of GI events (male only) cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.6287	0.0377	<.0001	0.53				
Age groups								
75-100 years old	-1.4064	0.0680	<.0001	0.25	-0.9533	0.0732	<.0001	0.39
65-74 years old	-1.1591	0.0531	<.0001	0.31	-1.4167	0.0832	<.0001	0.24
50-64 years old								
Race								
Non-White	0.1519	0.0391	0.0001	1.16	0.1237	0.0485	0.0108	1.13
White								
Frequency of Cancer Screening	0.2906	0.0705	<.0001	1.34	0.3589	0.1241	0.0038	1.43
Frequency of Health Care Utilization	0.0000	0.0001	0.8726	1.00	0.0033	0.0002	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.7626	0.0440	<.0001	2.14	0.8428	0.0603	<.0001	2.32
Obesity	0.3120	0.0910	0.0006	1.37	0.3546	0.1173	0.0025	1.43
Tobacco Smoke	0.6001	0.0519	<.0001	1.82	0.5760	0.0700	<.0001	1.78
Emphysema	0.3643	0.0593	<.0001	1.44	0.1159	0.0890	0.1929	1.12
Chronic Bronchitis	0.3739	0.0521	<.0001	1.45	0.3600	0.0803	<.0001	1.43
H. pylori Infection	1.2751	0.1001	<.0001	3.58	1.4958	0.1787	<.0001	4.46
Medication exposures								
GI protective agents	1.4786	0.0504	<.0001	4.39	1.6847	0.0636	<.0001	5.39
Corticosteroids	0.0303	0.0392	0.4389	1.03	-0.1528	0.0586	0.0091	0.86
Anticoagulants	0.1276	0.0464	0.0059	1.14	0.0842	0.0743	0.2573	1.09
Cephalosporines	-0.0767	0.0416	0.0654	0.93	0.1923	0.0540	0.0004	1.21

Table 7.9: Effect of Covariates on the Incidence of Renal events (male only) cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.8227	0.0456	<.0001	0.44	-0.5880	0.0715	<.0001	0.56
Age groups								
75-100 years old	-0.3938	0.0699	<.0001	0.67	-0.3895	0.0963	<.0001	0.68
65-74 years old	-0.4007	0.0599	<.0001	0.67	-0.4410	0.0976	<.0001	0.64
50-64 years old								
Race								
Non-White	0.6469	0.0495	<.0001	1.91	0.5675	0.0723	<.0001	1.76
White								
Frequency of Cancer Screening	-0.0119	0.1215	0.922	0.99	0.2875	0.1693	0.0895	1.33
Frequency of Health Care Utilization	0.0004	0.0001	<.0001	1.00	0.0015	0.0003	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.2720	0.0594	<.0001	1.31	0.3223	0.0969	0.0009	1.38
Obesity	0.1327	0.0980	0.1758	1.14	-0.2616	0.1648	0.1124	0.77
Tobacco Smoke	0.3073	0.0673	<.0001	1.36	0.2488	0.1090	0.0225	1.28
Hypertension	0.7657	0.0527	<.0001	2.15	0.9700	0.0836	<.0001	2.64
Diabetes Mellitus	0.6826	0.0486	<.0001	1.98	0.6059	0.0778	<.0001	1.83
Congestive Heart Failure	0.6857	0.0506	<.0001	1.99	1.0850	0.0821	<.0001	2.96
Cirrhosis	0.7173	0.1189	<.0001	2.05	0.2269	0.1942	0.2425	1.26
Medication exposures								
Diuretics	0.2408	0.0512	<.0001	1.27	0.3909	0.0799	<.0001	1.48
ACE inhibitors	0.4054	0.0485	<.0001	1.50	0.1494	0.0750	0.0462	1.16
Antibiotics								
Aminoglycosides	0.1834	0.1313	0.1624	1.20	0.2956	0.2647	0.2642	1.34
Cephalosporines	0.0145	0.0493	0.769	1.02	0.2752	0.0738	0.0002	1.32
Vancomycins	0.5232	0.1381	0.0002	1.69	0.3696	0.2937	0.2081	1.45
Allopurinal	0.5513	0.0596	<.0001	1.74	1.0022	0.0948	<.0001	2.72
Cyclosporine	1.2560	0.2597	<.0001	3.51	1.8320	0.4535	<.0001	6.25

Table 7.10: Effect of specific NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort

NSAID exposure	Person-years	Prostate cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	42,586	135	317.00	0.89	0.76 (0.63, 0.92)
Non-Selective Cox Inhibitors	192,851	755	391.49	1.10	
Fenoprofen	29,356	112	381.52	1.07	0.95 (0.77, 1.16)
Ibuprofen	129,154	495	383.26	1.08	0.89 (0.79, 1.00)
Idomethacin	49,521	209	422.04	1.19	1.07 (0.91, 1.25)
Naproxen	66,900	249	372.20	1.05	0.95 (0.81, 1.10)
Sulindac	22,209	87	391.73	1.10	1.02 (0.82, 1.28)
Others NSAIDs	74,972	265	353.46	0.99	0.92 (0.79, 1.07)
Cox-2 Inhibitors	57,692	134	232.27	0.65	0.46 (0.38, 0.55)
None	121,170	431	355.70	Reference	Reference
NSAID exposure	Person-years	GI events (male only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	40,710	372	913.78	0.84	0.85 (0.76, 0.95)
Non-Selective Cox Inhibitors	186,160	1,847	992.16	0.91	
Fenoprofen	28,269	254	898.52	0.83	0.85 (0.75, 0.97)
Ibuprofen	124,414	1,154	927.55	0.85	0.70 (0.65, 0.76)
Idomethacin	47,696	393	823.96	0.76	0.78 (0.70, 0.87)
Naproxen	63,513	571	899.03	0.83	0.82 (0.74, 0.89)
Sulindac	21,230	194	913.80	0.84	1.02 (0.88, 1.19)
Others NSAIDs	71,642	657	917.06	0.84	0.87 (0.79, 0.95)
Cox-2 Inhibitors	53,566	247	461.11	0.42	0.32 (0.28, 0.36)
None	120,365	1,308	1,086.69	Reference	Reference
NSAID exposure	Person-years	Renal Events (male only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	42,106	240	570.00	0.68	0.78 (0.68, 0.90)
Non-Selective Cox Inhibitors	191,390	1,200	626.99	0.75	
Fenoprofen	29,157	169	579.62	0.69	0.87 (0.74, 1.03)
Ibuprofen	128,217	754	588.06	0.70	0.64 (0.59, 0.71)
Idomethacin	48,904	360	736.14	0.88	0.84 (0.74, 0.95)
Naproxen	66,434	300	451.58	0.54	0.61 (0.54, 0.70)
Sulindac	21,998	136	618.23	0.74	0.99 (0.83, 1.18)
Others NSAIDs	74,449	377	506.39	0.61	0.78 (0.69, 0.87)
Cox-2 Inhibitors	57,339	157	273.81	0.33	0.30 (0.25, 0.35)
None	120,545	1,006	834.54	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; Cox, cyclo-oxygenase; RR,relative risk; GI, gastrointestinal

** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 7.11: Effect of specific NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort

NSAID exposure	Person-years	Prostate cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	10,584	27	255.11	0.99	0.90 (0.61, 1.33)
Non-Selective Cox Inhibitors	95,995	248	258.35	1.00	
Fenoprofen	1,742	4	229.67	0.89	0.69 (0.26, 1.86)
Ibuprofen	43,700	112	256.29	1.00	0.77 (0.62, 0.95)
Idomethacin	16,725	41	245.15	0.95	0.82 (0.59, 1.13)
Naproxen	31,990	86	268.84	1.04	0.92 (0.72, 1.18)
Sulindac	5,125	12	234.13	0.91	0.83 (0.47, 1.48)
Others NSAIDs	51,001	135	264.70	1.03	0.87 (0.71, 1.07)
None	136,740	352	257.42	Reference	Reference
NSAID exposure	Person-years	GI events (male only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	10,092	108	1,070.19	1.64	1.04 (0.86, 1.27)
Non-Selective Cox Inhibitors	93,593	859	917.80	1.41	
Fenoprofen	1,632	18	1,102.66	1.69	0.90 (0.56, 1.43)
Ibuprofen	42,322	379	895.51	1.37	0.69 (0.61, 0.78)
Idomethacin	16,274	148	909.43	1.40	0.87 (0.73, 1.03)
Naproxen	30,935	270	872.81	1.34	0.70 (0.61, 0.80)
Sulindac	4,962	39	785.90	1.21	0.73 (0.53, 1.01)
Others NSAIDs	49,317	475	963.15	1.48	0.80 (0.72, 0.90)
None	135,969	886	651.62	Reference	Reference
NSAID exposure	Person-years	Renal Events (male only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	10,560	44	416.68	1.16	0.97 (0.85, 1.11)
Non-Selective Cox Inhibitors	95,788	422	440.56	1.22	
Fenoprofen	1,727	13	752.63	2.09	1.01 (0.75, 1.37)
Ibuprofen	43,654	153	350.48	0.97	0.52 (0.43, 0.62)
Idomethacin	16,524	129	780.69	2.17	0.95 (0.77, 1.17)
Naproxen	31,952	133	416.25	1.15	0.74 (0.61, 0.90)
Sulindac	5,063	37	730.75	2.03	1.22 (0.87, 1.71)
Others NSAIDs	50,913	218	428.18	1.19	0.72 (0.61, 0.85)
None	136,484	492	360.48	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal

** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 7.12: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort after excluding 14,412 persons admitted to LTC >1 year

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Prostate Cancer	Any Use	167,516	667	398.17	0.99	0.72 (0.63, 0.83)
	None	85,612	343	400.64	Reference	Reference
GI Events (male only)	Any Use	160,842	1,790	1,112.89	0.87	0.51 (0.47, 0.55)
	None	85,078	1,086	1,276.47	Reference	Reference
Renal Events (male only)	Any Use	166,017	1,077	648.73	0.68	0.38 (0.35, 0.42)
	None	85,207	818	960.02	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 7.13: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort after excluding 140 persons admitted to LTC >1 year

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Prostate Cancer	Any Use	98,520	256	259.85	1.01	0.75 (0.63, 0.89)
	None	136,138	349	256.36	Reference	Reference
GI Events (male only)	Any Use	96,056	881	917.17	1.41	0.65 (0.59, 0.71)
	None	135,370	883	652.29	Reference	Reference
Renal Events (male only)	Any Use	98,318	434	441.43	1.22	0.55 (0.48, 0.64)
	None	135,878	492	362.09	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

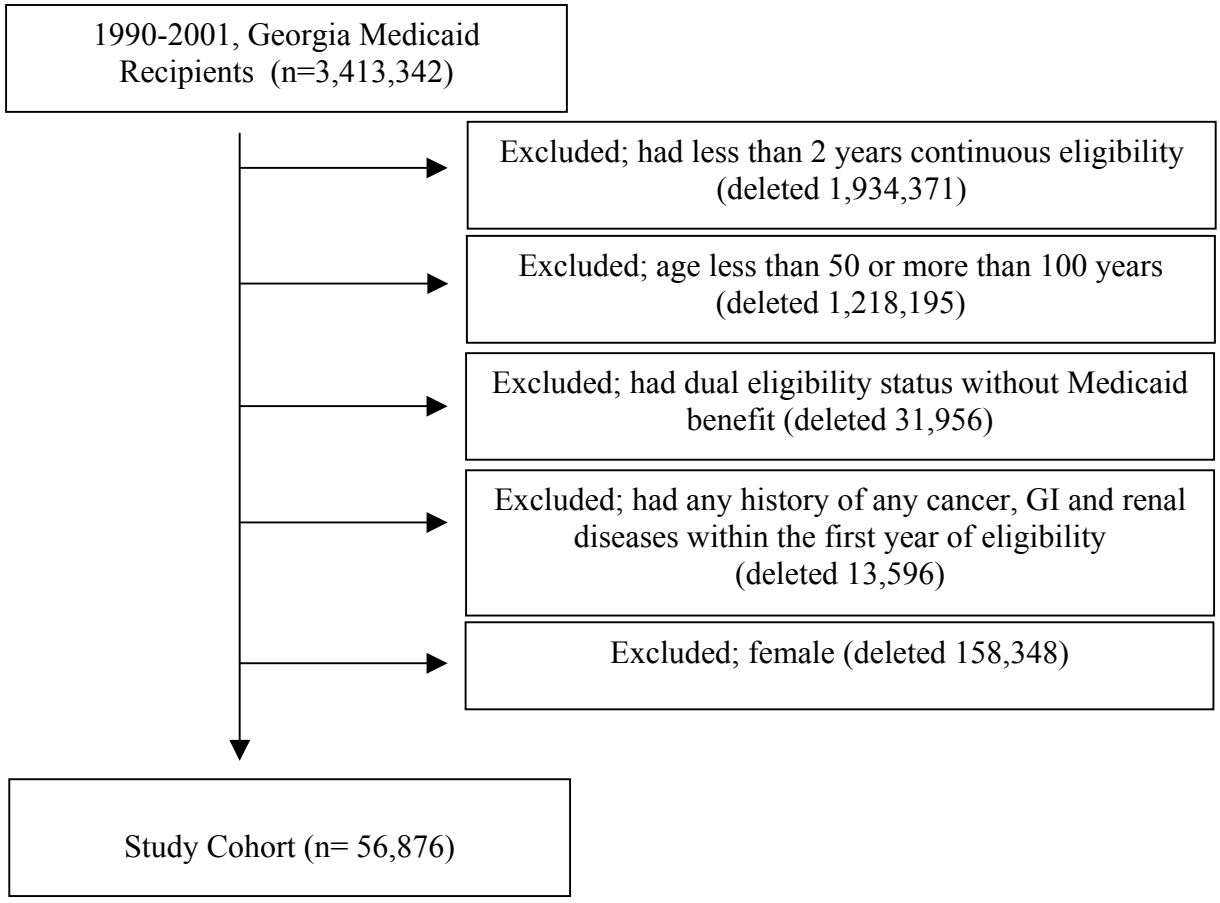

Figure 7.1: Flow chart of Georgia Medicaid cohort subjects

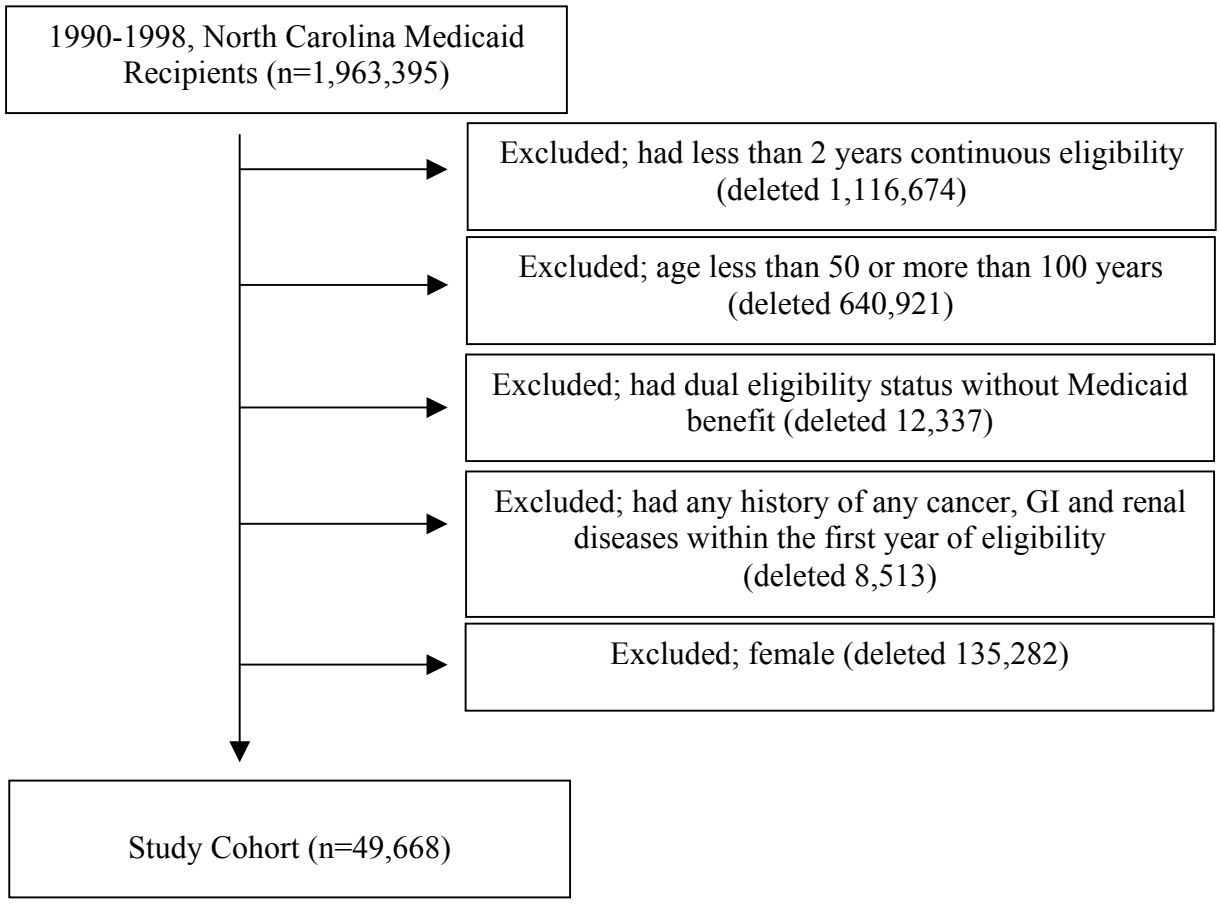

Figure 7.2: Flow chart of North Carolina Medicaid cohort subjects

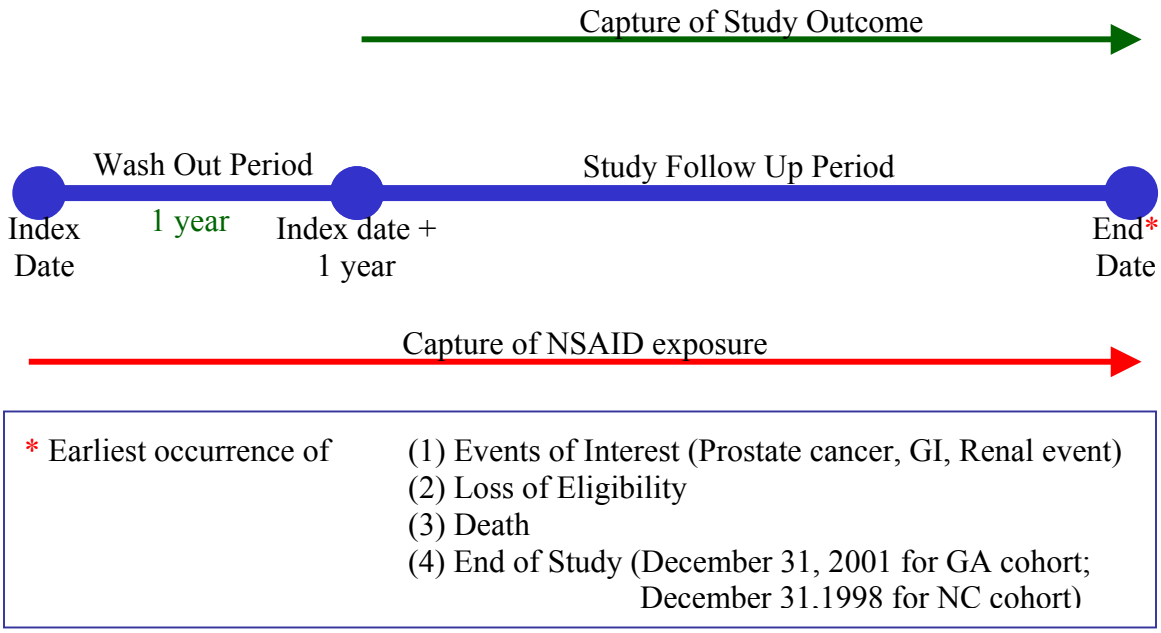

Figure 7.3: Temporal pattern of cohort

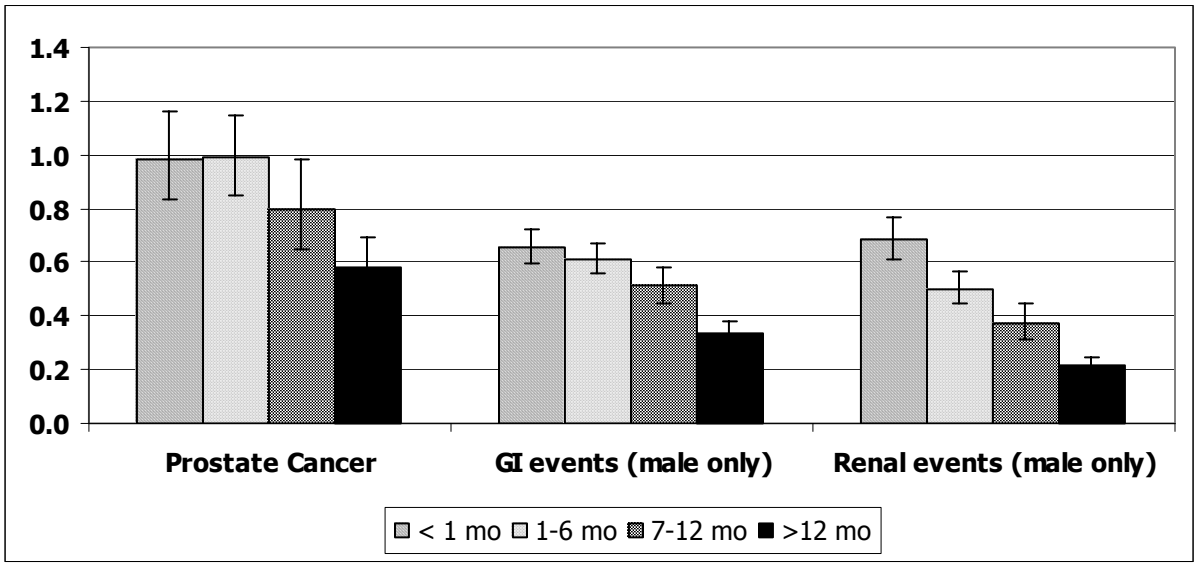

Figure 7.4: Effect of Cumulative NSAID exposure on the Relative Risk of Prostate cancer, GI and Renal events in Georgia Cohort.

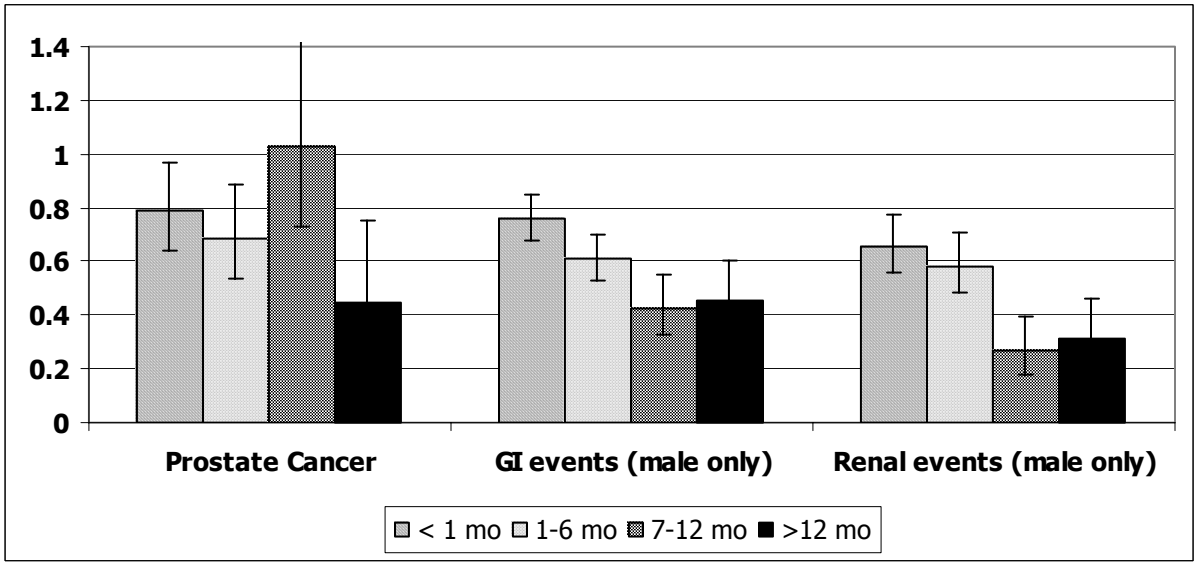

Figure 7.5: Effect of Cumulative NSAID exposure on the Relative Risk of Prostate cancer, GI and Renal events in North Carolina Cohort

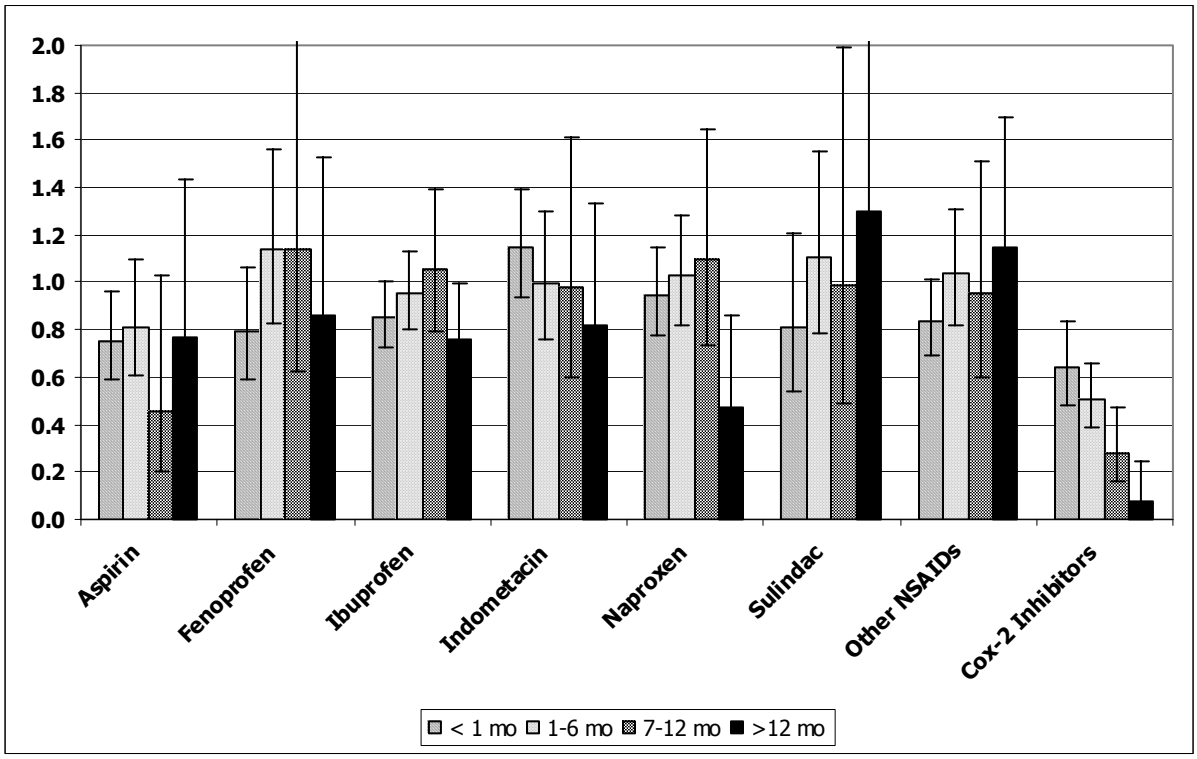

Figure 7.6: Cumulative Exposure Effect of specific NSAIDs on Prostate cancer in Georgia Medicaid Cohort

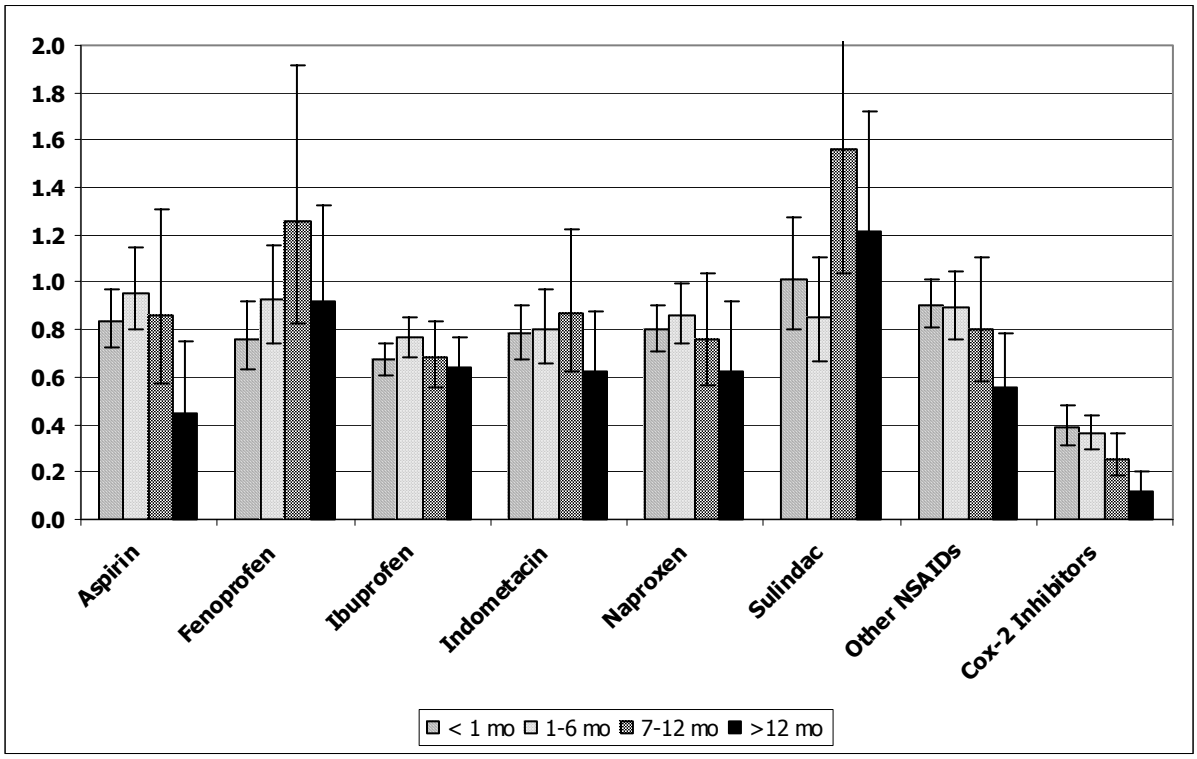

Figure 7.7: Cumulative Exposure Effect of specific NSAIDs on GI events in Georgia Medicaid Cohort

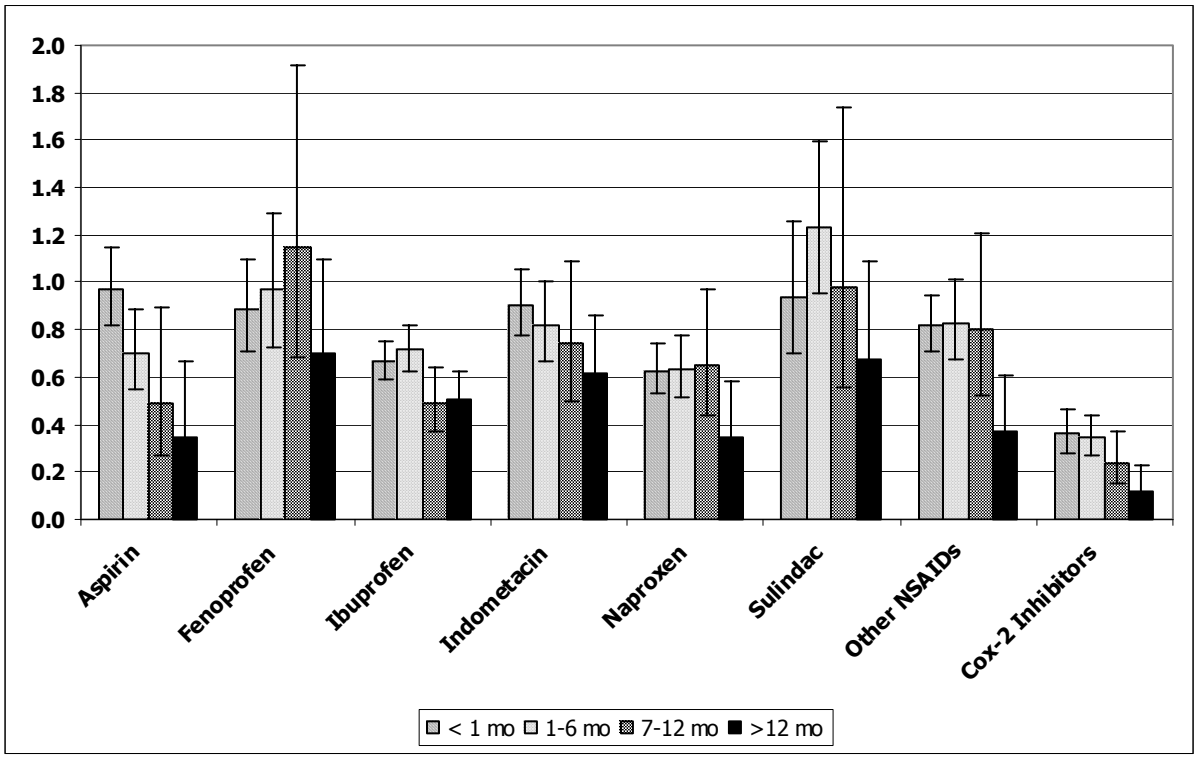

Figure 7.8: Cumulative Exposure Effect of specific NSAIDs on Renal events in Georgia Medicaid Cohort

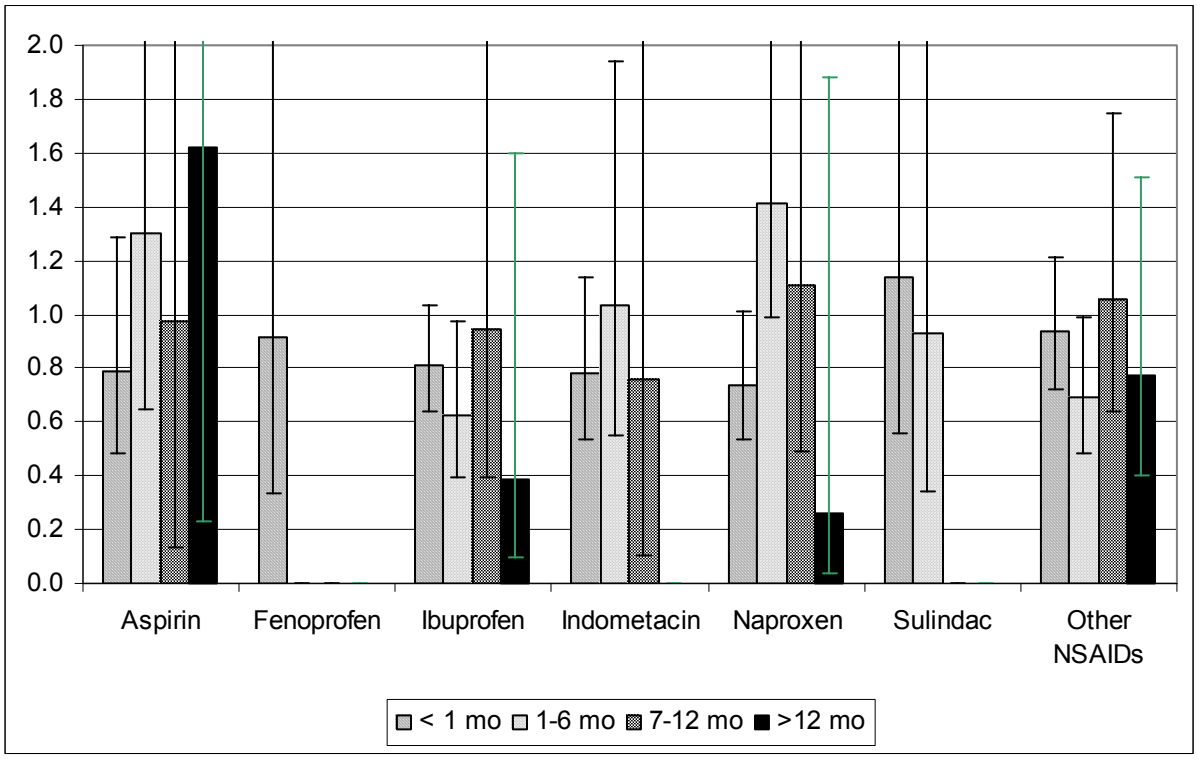

Figure 7.9: Cumulative Exposure Effect of specific NSAIDs on Prostate cancer in North Carolina Medicaid Cohort

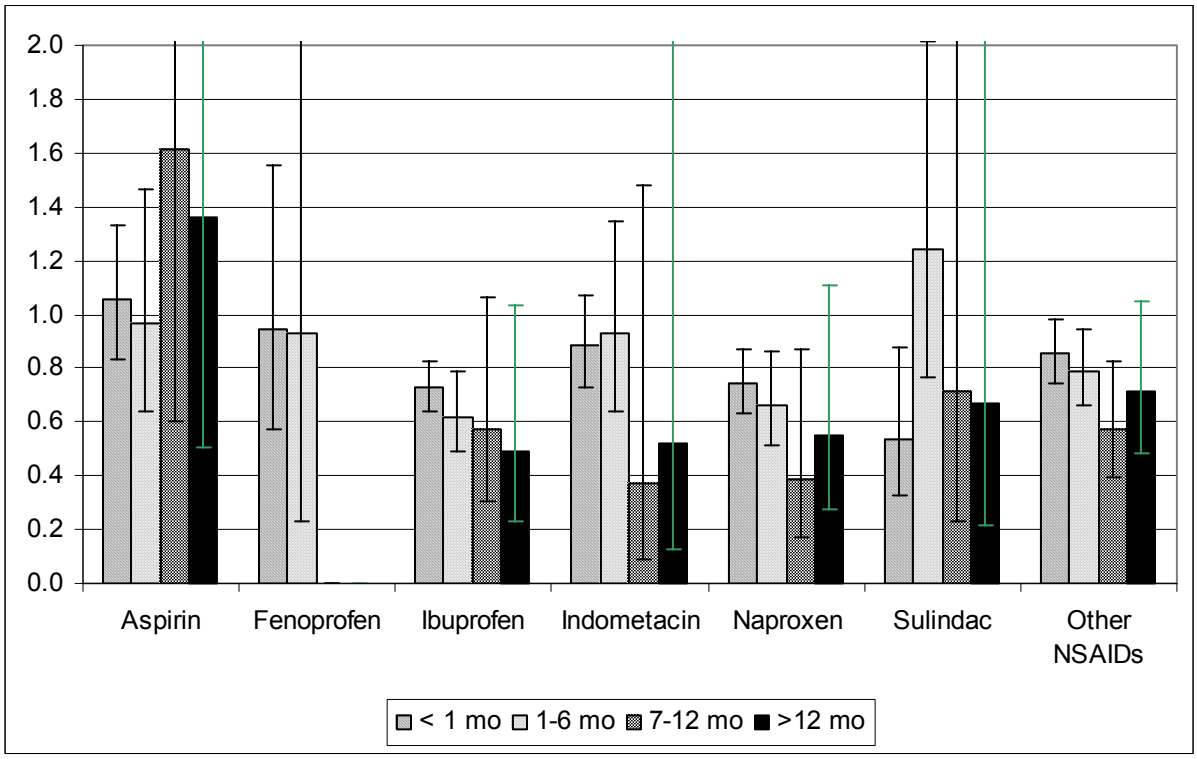

Figure 7.10: Cumulative Exposure Effect of specific NSAIDs on GI events in North Carolina Medicaid Cohort

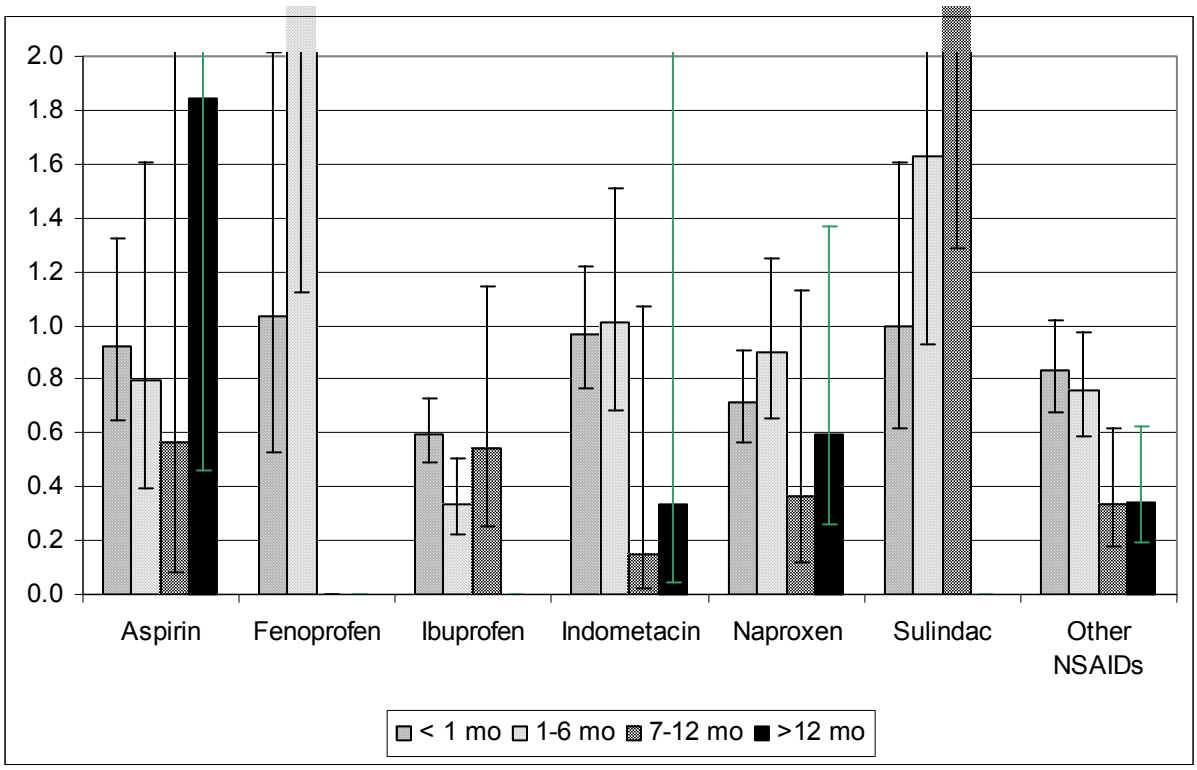

Figure 7.11: Cumulative Exposure Effect of specific NSAIDs on Renal events in North Carolina Medicaid Cohort

CHAPTER 8

THE RISK-BENEFIT PROFILE OF NSAIDS AS CHEMOPREVENTIVES AGAINST BREAST AND GYNECOLOGIC CANCERS[4]

[4] Koompalum D., Vidyashankar A.N., Dainer P.M., Naeher L.P., Kotzan J.A., and Martin B.C. To be submitted to Journal of the National Cancer Institutes.

Abstract

Background: Several experimental and epidemiological studies have suggested that NSAID exposure may reduce the incidence of breast and gynecologic cancers. Since NSAIDs are relatively inexpensive, NSAIDs may offer a possible strategy to reduce the burden of these cancers. However, before NSAIDs can be considered as chemopreventives, their potential benefit must be weighed against the risks of gastrointestinal (GI) and renal adverse effects.

Objectives: This study sought to determine the risk benefit profile of NSAIDs as chemopreventives by determining the possibly protective effect of NSAIDs against breast cancer, cervical cancer, endometrial cancer, and ovarian cancer and by describing the association of NSAID use with GI and renal diseases.

Methods: Two retrospective cohort studies were conducted using Georgia (GA) and North Carolina (NC) Medicaid claims. Women aged 50-100, who had at least 2 years of continuous eligibility, were analyzed. We excluded subjects that had any diagnoses of cancer, GI, or renal diseases within their first year of eligibility. The cohort was followed until the earliest occurrence of: (1) outcomes of interest, namely breast cancer, cervical cancer, endometrial cancer, and ovarian cancer, GI events (i.e. GI Ulcers and GI hemorrhage) and renal events (e.g. renal failure and glomerulonephritis), (2) loss of eligibility, (3) death, or (4) end of study (December 31, 2001 for GA cohort and December 31, 1998 for NC cohort). All outcome occurrences were dated and determined by searching for claims with ICD-9-CM codes indicative of the outcome events. NSAID exposure was identified by searching the National Drug Code (NDC) in the prescription files. For each NSAID prescription, the strength and prescribed quantifies were kept to further explore a dose-response relationship. Survival Analysis (Cox-Proportional Hazard) technique was used to calculate all relative risks.

Results: There were 158,348 women in the GA Medicaid cohort and 64% were exposed to an NSAID. After adjusting for several covariates, the relative risks were significant, as 0.55 (95%CI, 0.50 to 0.61), 0.51 (95%CI, 0.40 to 0.64), 0.45 (95%CI, 0.34 to 0.61), 0.56 (95%CI, 0.44 to 0.71), 0.46 (95%CI, 0.43 to 0.49), and 0.39 (95%CI, 0.36 to 0.41) for breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal, respectively. The NC Medicaid cohort contained 135,282 women and 46% were exposed to an NSAID. While those of breast cancer 0.90 (95%CI, 0.78 to 1.04), cervical cancer 0.87 (95%CI, 0.61 to 1.25), and ovarian cancer 0.91 (95%CI, 0.63 to 1.32) were not significant, the multivariate-adjusted relative risks of endometrial cancer, GI and renal events were significant, as 0.64 (95%CI, 0.43 to 0.97), 0.71 (95%CI, 0.66 to 0.77), and 0.54 (95%CI, 0.48 to 0.58), respectively. The protective effect of Cox-2 inhibitors against breast cancer, cervical cancer, endometrial cancer, ovarian cancer was the most prominent, in addition to the reduced risk of NSAID-related adverse events. All non-selective NSAIDs were not increased risk of the NSAID-related adverse events. The inversed association was found between cumulative exposure of NSAIDs and the rates of breast cancer, gynecologic cancers, GI and renal events.

Conclusions: Without increasing risk of NSAID-related adverse events, renal and GI events, the protective effect of NSAIDs on endometrial cancer was confirmed. The potential benefit of NSAIDs on breast cancer, cervical cancer, and ovarian cancer was revealed in the Georgia Medicaid cohort, although it was not validated in the North Carolina cohort.

Background

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are among the most popular and widely use drugs because of their many therapeutic applications: anti-inflammatory, anti-pyretic, analgesic, possibly Alzheimer's disease protective effects of NSAIDs and the cardiovascular benefits of aspirin. There is growing evidence that NSAIDs may reduce the incidence of some cancers; the protective effect of NSAIDs against colorectal cancer has been extensively demonstrated.

Numerous studies have shown elevation of cyclooxygenase (COX) expression, both COX-1 and COX-2 isoforms, occurs in cancerous tissues, including breast adenocarcinoma, cervical adenocarcinoma, endometrial carcinoma, and ovary carcinoma {Dore 1998, Subbaramaiah 2003}. The COX enzyme and carcinogenesis have been linked in genetic studies that increased levels of COX enzymes and prostaglandins can potentially account for the tumor-promoting effects; prostaglandins could enhance tumor growth and metastasis by stimulating angiogenesis and invasiveness, in addition to inhibiting apoptosis and immune surveillance {Liu 2001, Marks 1999}. Moreover, epidemiologic, experimental, and intervention research suggests that ability NSAIDs to inhibit COX enzyme increases tumor cell apoptosis {Subbaramaiah 2003, Xu 2002}.

Breast cancer is the most common cancer among American women {Jemal 2003}. Risk factors of developing breast cancer include family history, reproductive events, i.e. early age at menarche, late menopause, older age at first birth, and nulliparous, hormone replacement therapy {Colditz 2000}. Despite promising findings of NSAIDs' protective effect against colorectal cancer, a weaker association between NSAID use and breast cancer has been reported. Khuder and colleagues conducted a meta-analysis of 14 studies to examine the chemopreventive property

of NSAIDs against breast cancer {Khuder 2001}. The meta-analysis included 7 studies that showed no effect and 7 studies that did. As a result, it concluded that the risk of breast cancer is reduced by nearly 20% (OR, 0.82; 95% CI, 0.75-0.89). Aspirin use was associated with a 20-30% risk reduction on breast cancer; the estimates of odd ratios were 0.79 (95% CI, 0.59-1.06) for cohort, and 0.70 (95% CI, 0.61-0.81) for case-control studies. A connection between non-aspirin NSAID use and risk of breast cancer was not reported in the meta-analysis. Consistent with the meta-analysis, the Iowa Women's Health Cohort study (RR, 0.80; 95% CI, 0.67-0.95) and the Long Island population-based case-control study (RR, 0.80; 95% CI, 0.66-0.97), not included in the meta-analysis, confirmed the modest protective property of NSAIDs against breast cancer {Johnson 2002, Terry 2004}.

Endometrial and cervical cancer is one of the most common cancers among American women {American Cancer Society 2004}. Several risk factors have found to be associated with developing endometrial cancer: advanced age, white race, endometrial hyperplasia, hormone replacement therapy, and obesity {cancer.gov}. Cervical risk factors consist of family history, sexually transmitted diseases, e.g. Human papillomavirus and Chlamydia infection, pelvic inflammatory diseases, and oral contraceptives {American Cancer Society 2004}. Inhibition of endometrial tumor cell growth by aspirin was shown in vitro in a dose-dependent relationship {Arango 2001}. Similar to that in endometrial tumor cells, aspirin, non-aspirin NSAIDs and COX-2 inhibitors decreased COX-2 expression, angiogenesis, cell proliferation, and colony formation of cervical tumor cell {Ferrandina 2003, Kim 2003}. However, to our knowledge, there are no epidemiological studies determining an association between NSAID use and risk of endometrial cancer or cervical cancer.

Ovarian cancer is one of the most leading causes of death in women. Women who have a family history of ovarian cancer, have never had children, or use hormone replacement therapy are at higher risk of ovarian cancer. The role for NSAID use as probable chemopreventive agents for ovarian cancer have been widely assessed and yielded inconclusive results. While Cramer {Cramer 1998}, Tavani {Tavani 2000} and Akhmedkhanov {Akhmedkhanov 2001} demonstrated a 25-40% non-significant reduction in risk among women who reported aspirin intake for at least 6 months, Lacey {Lacey 2004}, Moysich {Moysich 2001} and Fairfield {Fairfield 2002} found no evidence of reduced risk. A case-control study of 7,870 women with epithelial ovarian cancer by Rosenberg {Rosenberg 2000}, however, found a 50% reduction in ones using any NSAIDs at least 4 times per week for at least 5 years.

The well-documented adverse effects of NSAIDs include gastrointestinal (GI) complications (i.e. GI bleeding, perforation, and ulcer) and renal complications (i.e. acute renal failure). There are an estimated 100,000 hospitalizations and 10,000 to 20,000 deaths annually are due to NSAID-related GI complications at an annual cost of 1.6 billion dollars {Fries 1991, Smalley 1996}. There is little doubt that short term NSAID exposure can increase the risk of gastric and duodenal ulcers, GI hemorrhage and perforation. The risk of GI complications is 3-5 times more likely in NSAID users {Ofman 2002 }

What is less clear is the impact of long term NSAID use on GI complications. Several studies have shown evidence that the risk for NSAID associated GI events is highest at the initiation of a regimen and then the risk tapers over time {Garcia Rodriguez 1998, Smalley 1995, Griffin 1991}. Several observational studies have similarly reported decreasing risks of GI complications when NSAIDs were taken over longer durations {Garcia Rodriguez 1998, Smalley 1995}. For instance, among current users, the constant risk of GI complications was found

during the first year of NSAID use and was roughly 7 times more likely than non-users {Garcia Rodriguez 1998}. The risk of GI complications, however, was cut nearly half for NSAID exposure >1 year. (RR, 3.5; 95%CI, 2.0-6.0) {Garcia Rodriguez 1998}. Gastric mucosal adaptation has been reported in both animal and human studies and may account for the decreasing risk of NSAID exposure over time {Fitzpatrick 1999, Lipscomb 1996}. Gastric mucosal adaptation is described as the phenomenon in which visible gastric mucosal injury lessens or resolves completely despite continued administration of an injurious substance such as aspirin {Olivero 1992, Graham 1988, Graham 1983}. Although the mechanism remains unclear, it is suggested that increased cell proliferation and correction of NSAID drug induced reduction in gastric blood flow as possibly being a factor {Olivero 1992}.

Acute and chronic renal complications are also a major concern with NSAID use, especially in persons with pre-existing impaired renal function {Hernandez-Diaz 2001}. For instance, persons with cirrhosis, heart failure, renal disease, diabetes, advanced age, heart failure, hypertension, and those exposed to nephrotoxic medications, i.e. diuretics, NSAIDs, and some antibiotics are at higher risk of acute renal failure {Fored 2001, Griffin 2000, Hernandez-Diaz 2001, Perneger 1994, Rexrode 2001, Bailie 1995, Henry 1992}. Renal injury as a result of NSAID exposure affects approximately 2 persons per 100,000 {Perneger 1994}. It is believed that NSAIDs may exacerbate renal insufficiency, hyperkalemia, interstitial nephritis, and acute renal failure by inhibiting renal prostaglandins {Brooks 1998}. Griffin and colleagues reported that persons who currently used NSAIDs were almost 1.6 times more likely to be hospitalized for acute renal failure than ones who never used NSAID (OR, 1.58, 95%CI, 1.34-1.86). The highest risk was observed within first 30 days of use. Regular use of NSAID increased the risk of chronic renal failure 2.5 fold (95%CI, 1.9-3.3) {Griffin 2000}. In contrast to most of the

findings previously described, the Physician's Heath Cohort study contrarily showed no association between self-reported cumulative NSAID uses over 14 years and the risk of renal dysfunction in men {Rexrode 2001}.

Before NSAIDs can be considered as chemopreventives for women, we need a better understanding of the risk-benefit profile of NSAIDs. In this study, we aimed to describe the relationship of NSAIDs with breast cancer, cervical cancer, endometrial and ovarian cancer, as well as NSAID-related GI and renal adverse events using two Medicaid cohorts: Georgia and North Carolina Medicaid.

Methods

Data Source

We simultaneously conducted 2 retrospective cohort studies utilizing administrative claims data of the Medicaid program from 2 states: Georgia and North Carolina. The Medicaid, jointly funded by the Federal and State governments, is health insurance that assists certain individuals and families with low incomes and resources in providing medical and health-related services for people with limited income, who meet eligibility criteria. Adults eligible for Medicaid benefits include some low-income residents, medically needy individuals, the elderly, and people with disabilities if state and federal guidelines are met.

The Georgia Medicaid administrative claims data capture all reimbursed medical encounters of the Georgia Medicaid recipients. The GA Medicaid database contains an annual enrollment of approximately 1.2 million eligible persons per year, which provides patient level details on recipient demographics, including patient identifier, date of birth, gender, race, date of dead, as well as monthly Medicaid coverage (eligibility information). All Medicaid

beneficiaries' medical utilization, including inpatient, outpatient, nursing home, and emergency services, is collected in the medical claim file. The pharmacy claims file records each reimbursed prescription including information describing the date prescriptions are filled, drug name, National Drug Code (NDC), strength, dosage, and number of units dispensed. All three of the files are linked by encrypted recipient identifier allowing the construction of person level analytic files where treatments and ensuing medical encounters can be measured at the patient level.

Similarly, the North Carolina Medicaid claims database is an administrative claim data of the North Carolina Medicaid recipients' medical encounters. There are roughly 1 million North Carolina Medicaid recipients per year. NC Medicaid data contain patient level details on demographics, monthly coverage, non-prescription medical utilization, and pharmacy claim file, all of which are linked by encrypted recipient identifier.

Subjects

In both cohorts, the study subjects were between the ages of 50 and 100 years, who had at least 2 years of continuous eligibility. We excluded subjects who had any diagnosis of cancer, GI or renal disease within their first year of eligibility and any recipients with dual Medicare eligibility without full Medicaid coverage (figures 8.1-8.2). The cohort was followed until the earliest occurrence of: (1) outcomes of interest, namely breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI events (i.e. GI ulcers and GI hemorrhage), and renal events (e.g. renal failure), (2) loss of eligibility, (3) death, or (4) end of study (figure 8.3).

Identification of Breast cancer, Gynecologic Cancers, GI and Renal Events

To identify incident breast cancer, gynecologic cancers, GI and renal events, all diagnoses recorded in the medical claims file were searched. All outcome occurrences were dated and determined by searching for claims with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes indicative of the outcome events described below.

Breast cancer

To identify incident breast cancer, we first implemented an ICD-9-CM algorithm suggested by Kahn and colleagues {Kahn 1996}. This study has shown that 83% of ICD-9-CM coded information matched "gold standard" tumor registry data. ICD-9-CM codes used in the validation study contained the diagnosis of primary breast cancer (174.x) and breast carcinoma-in-situ (233.0). This definition was modified by incorporating benign (217) and secondary malignant neoplasm of breast (198.81).

Gynecologic cancers

In this study, we aimed to determine associations between NSAID exposure and most common gynecologic cancers: cervical, endometrial, and ovarian cancers.

Cervical cancer

To detect individuals with cervical cancer, we used ICD-9-CM codes for malignant neoplasm (180) {Thun 1993} and carcinoma in situ (233.1).

Endometrial cancer

We identify incident endometrial cancer; we searched for ICD-9-CM codes for malignant neoplasm of body of uterus (182) {Thun 1993, The National Cancer Institute 1997}.

Ovarian cancer

To identify individuals with ovarian cancer, we used ICD-9-CM codes for malignant neoplasm (183) {Thun 1993, The National Cancer Institute 1997}, benign neoplasms (220) and secondary malignant neoplasm of ovary (198.6).

Gastrointestinal (GI) Events

The GI events were defined as upper gastrointestinal bleeding, perforation, or ulcer. A subject with any diagnosis of gastric ulcer (531.x), duodenal ulcer (532.x), gastrojejunal ulcer (534.x), peptic ulcer (533.x), and gastrointestinal hemorrhage (578.x) was identified {Smalley 1995}. The positive predictive value of these codes were previously reported as 97%, 84%, 80%, and 59% with hospital clinical records for 531.x-532.x, 534.x, 533.x, and 578.x, respectively {Cattaruzzi 1999}.

Renal Events

The renal events are diagnosed cases acute renal failure and other impairment of renal function that is associated with NSAID exposure. The ICD-9-CM algorithm to identify cases of renal events was derived from existing medical literature for potential NSAID-related renal failure {Griffin 2000, Harley 2003, Niecko 2001}. The outcome measures identified by ICD-9-CM codes were acute glomerulonephritis (580.x), nephrotic syndrome (581.x), non-specified nephritis and nephropathy (583.x), acute renal failure (584.x), renal failure (586.x), disorder of the kidney (593.9), diabetes with renal manifestations (250.4), and hypertension with renal manifestations (403.x, 404.x).

NSAID Exposure

We determined NSAID utilization by searching all prescription codes in the pharmacy claims file for all NSAIDs listed in table 8.1. Only orally administered NSAIDs are relevant to the study. The NDC codes were employed to identify aspirin, NSAID and COX-2-inhibitors prescribed. For those individuals who were prescribed any NSAID, we recorded the generic name, the chemical class, the strength (in milligrams), and the number of units of drug dispensed for each NSAID prescription. In NC cohort, we were unable to determine an impact of COX-2-inhibitors on study events due to unavailable data; dates approved by FDA of celecoxib and refecoxib were December 1998 and May 1999 respectively.

We define low and high daily dose based on minimum and maximum starting doses recommended for treatment of arthritis as noted in the *Physicians' Desk Reference* {Niecko 2001, Smalley 1999}. Cumulative drug exposure was used to determine prescription NSAID exposure in the study cohort and was defined as the number of units of drug dispensed multiplied

by the dose of the drug. All study NSAID dosages were standardized and converted to ibuprofen dosage equivalents. Based on the assumption of equal efficacy among high-dose NSAIDs for the treatment of arthritis, an "ibuprofen weighted" factor is computed. An "ibuprofen weighted" factor equals 2,400 (high daily dose of ibuprofen) divided by the high daily dose recommended for any particular NSAID {Niecko 2001, Smalley 1999}. Then, NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints. The cumulative exposure was defined as NSAID use equivalent to a period of NSAID use at the highest daily dose: less than one month (ibuprofen equivalents up to 72 grams), 1-6 months (ibuprofen equivalents 72-432 grams), 7-12 months (ibuprofen equivalents 433-876 grams), and greater than 12 months (ibuprofen equivalents more than 876 grams) of use.

Statistical Analysis

Demographic and other clinical characteristics (i.e. age, gender, length of Medicaid coverage, prevalence of selected comorbidities) between the NSAID exposure and non-exposure groups, were tabulated and tested for differences using chi-square test for categorical variables and t-test for continuous variables. All statistic analyses were performed using SAS statistical software (Version 8.2, SAS Institute, Cary, North Carolina). All p-values were 2-sided and significant level set at $p<0.05$.

Unadjusted incidence was calculated by dividing number of new cases of each outcome event by the number of person-years. We computed crude relative risks by dividing the unadjusted incidence rates of NSAID users (e.g. cases per 100,000 person-years) by those of non-users.

Cox proportional hazards models were used to estimate the multivariate adjusted rates and relative risks (using PROC PHREG of SAS package). Model specification and operative definition of all covariates are summarized below. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CI) are reported.

Model Specification

The Cox proportional hazard model was defined as follows:

$h(t \mid Z) = h_0(t) * \exp[\ \alpha(\text{NSAID exposure}) + \beta * X + \varepsilon\text{rror}\ ]$

Where $h(t \mid Z)$: hazard rate at time 't' for an individual with risk vector Z

$h_0(t)$: baseline hazard rate

α : Coefficient for NSAID exposure

X : Matrix of covariates

β : Vector of coefficients corresponding to the matrix of covariates

Dependent Variables

Our major outcomes of interest are the first incidence of diagnosed breast cancer, gynecologic cancers, and adverse gastrointestinal and renal events. Since percents of cases diagnosed with other cancers before the studied cancers were low, we modeled each outcome separately with specific set of covariates; percents of cases diagnosed with other cancers before breast, cervical, endometrial, and ovarian cancers were 6%, 13%, 15%, and 24%, respectively.

For each study event of interest, a Cox proportional hazard model was fitted based on:

(1) Incidence of each study event: A dichotomous dependent variable was coded whether or not subjects had any diagnosis codes of the study outcome.

(2) Person-years in study cohort: Number of years each subjects stayed in the cohort is calculated by subtracting the date when a subject entered the cohort from the date when the subject left the cohort.

Independent variables

Effect of NSAID exposure was modeled in three sets of separate analyses as follows:

1) NSAID exposure as a class: A dichotomous independent variable coded if a subject prescribed any NSAID.
2) Cumulative exposure of NSAIDs: NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints (less than one month, 1-6 months, 7-12 months, and greater than 12 months)
3) Effect of the use of some specific NSAIDs was analyzed. Based on generic names recorded from each subject's prescriptions, NSAID exposure was classified into 8 groups (see below). There is a high possibility that subjects may be exposed to more than one product or group, so persons could have more than one of the following NSAID variables recorded as exposed. Furthermore, to determine the effect cumulative exposure of each on study endpoints, the cumulative exposure for each generic group was calculated and stratified into 4 categories: less than one month, 1-6 months, 7-12 months, and greater than 12 months.
    a) Aspirin
    b) Selective Cox-2 inhibitors (celecoxib and rofecoxib)

c) Ibuprofen (commonly prescribed) {Niecko 2001, Smalley 1999}.

d) Naproxen (commonly prescribed) {Niecko 2001, Smalley 1999}.

e) Indomethacin (commonly prescribed)

f) Fenoprofen (commonly prescribed)

g) Sulindac (effective in many animal models) {Niecko 2001, Smalley 1999}.

h) Other non-specific NSAIDs

Covariates

All covariates included in the model were listed in table 8.2. Operational definition and the ICD-9-CMcodes for each covariate were summarized in table 8.2.

Results

There were 158,348 women in the GA Medicaid cohort and 64% were exposed to an NSAID. On average, the length of follow-up ranged from 6.5 years (s.d., 3.5) in GI event cohort to 6.6 years (s.d., 3.6) in endometrial cancer cohort. The cohort average age was 71.5 years (s.d., 11.6 years); 48.2% were white, 39.0% were non-white and 12.8% were of unknown race. Incidence rates of breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events were 205.8, 35.4, 22.7, 35.3, 678.0, and 561.9 per 100,000 person-years, respectively.

The NC Medicaid cohort contained 135,282 women and 46% were exposed to an NSAID. On average, the length of follow-up ranged from 5.1 years (s.d., 2.4) in GI event cohort

to 5.2 years (s.d., 2.4) in endometrial cancer cohort. The cohort average age was 72.8 years (s.d., 10.8 years); 54.9% were white, and 45.1% were non-white. Incidence rates of breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events were 120.9, 19.7, 15.5, 19.2, 498.8, and 303.1 per 100,000 person-years, respectively.

Both GA and NC cohort characteristics by NSAID exposure status is displayed in table 3-4. The length of follow up of subjects exposed NSAIDs were significantly longer than those not exposed NSAIDs ($p<0.05$). Younger persons and non-white were more likely to have an NSAID prescription filled than their respective counterparts.

We observed significant lower multivariate-adjusted risks for breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events among subjects exposed to NSAIDs compared with those not exposed to NSAIDs (tables 8.5-8.6). Apart from discrepancy between unadjusted and multivariate-adjusted relative risks of GI event, in GA cohort, both unadjusted and multivariate-adjusted relative risks were significant (table 8.5). After adjusting for several covariates, the relative risks were significant, as 0.55 (95%CI, 0.50 to 0.61), 0.51 (95%CI, 0.40 to 0.64), 0.45 (95%CI, 0.34 to 0.61), 0.56 (95%CI, 0.44 to 0.71), 0.46 (95%CI, 0.43 to 0.49), and 0.39 (95%CI, 0.36 to 0.41) for breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal, respectively; unadjusted relative risk of GI event was 1.04 (95%CI, 1.01 to 1.07). Comparing with the adjusted results obtained from the NC cohort, the unadjusted rates for the North Carolina NSAID users were higher with unadjusted risks of 1.29 (95%CI, 1.20 to 1.38), 1.29 (95%CI, 1.09 to 1.54), 1.21 (95%CI, 1.00 to 1.47), 1.57 (95%CI, 1.32 to 1.88), 1.79 (95%CI, 1.73 to 1.86), and 1.29 (95%CI, 1.24 to 1.35) for breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal, respectively. However, from the NC cohort, the multivariate-adjusted relative risks of endometrial cancer, GI and renal events

were found to be significant, as 0.64 (95%CI, 0.43 to 0.97), 0.71 (95%CI, 0.66 to 0.77), and 0.54 (95%CI, 0.48 to 0.58), respectively; those of breast cancer 0.90 (95%CI, 0.78 to 1.04), cervical cancer 0.87 (95%CI, 0.61 to 1.25), and ovarian cancer 0.91 (95%CI, 0.63 to 1.32) were not significant.

According to both GA and NC cohort, effects of covariates on study events of interest were summarized (tables 8.7-8.11). Compared with the 50 to 64 age group, older age groups, both 65-75 and >75 age groups, appeared to be at lower risk for breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events. Non-white race, alcoholism, obesity and tobacco smoke increased the risk for breast cancer. We did not find significant association between exposure to hormone replacement therapy or oral contraceptive and risk of breast cancer. Alcoholism, obesity, tobacco smoke, pelvic inflammatory disease, and Human Papillomavirus (HPV) infection increased the risk for cervical cancer. In addition to a 6-8 fold increased risk of endometrial cancer by endometrial hyperplasia, subjects, who were obese, had hypertension and diabetes, were 2-3 times more likely to be diagnosed with endometrial cancer. We found that white race, obesity, and hormone replacement therapy use increased risk of ovarian cancer. Whites, alcoholics, obese persons and tobacco smokers were at higher risk of NSAID-related adverse events, GI and renal events. Moreover, we found that H. pylori infection and taking GI protective agents were the most important risk factors for GI events; H. pylori infection increased risk of GI events by 3-4 folds; subjects prescribed GI protective agents were 5-7 times more likely to experience a GI event. Hypertension, congestive heart failure, diabetes mellitus and cirrhosis were the most important risk factors for renal events; subjects with hypertension, congestive heart failure, diabetes, and cyclosporine prescription were 2-3, 2-2.3, 2-3, and 2-2.5 times more likely to be diagnosed with renal events, respectively.

We considered the possibility that physicians' concern regarding NSAID-related adverse events could increase patients' health services utilization, thus detect cases of cancers. We found that frequency of health services utilization was not associated with chance of diagnosed with all study outcomes.

The impact of specific NSAID exposure on breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events are summarized in tables 8.13-8.14. The apparent protective effect of Cox-2 inhibitors against breast cancer, cervical cancer, endometrial cancer, and ovarian cancer was the most pronounced. Despite the non-significant benefit of aspirin against breast cancer, cervical cancer, and endometrial cancer, subjects prescribed aspirin were at 30% lower risk of ovarian cancer (RR 0.70; 95%CI 0.51, 0.94); however, the protective effect of aspirin on ovarian cancer was not found in the NC cohort (RR 0.95; 95%CI 0.53, 1.70). The associations between non-aspirin NSAID exposure and the risks of breast cancer, cervical cancer, endometrial cancer, and ovarian cancer were either non-significant or showed a significant increase in the risk of these cancers. With the exception of fenoprofen and indomethacin, in NC cohort, we found that subjects prescribed fenoprofen and indomethacin had significant 3 and 1.8 times increased risk of cervical cancer and endometrial cancer, respectively. Compared with the non-NSAID exposure group, the reduced risk of NSAID-related adverse events, GI and renal events, was found to be lowest, in subject prescribed Cox-2 inhibitors. In addition, all non-selective NSAIDs and aspirin were not at increased risk of both NSAID-related adverse events; subjects prescribed ibuprofen and naproxen were at lower risk of GI and renal events.

The increased cumulative exposure of NSAIDs was associated with decreased rates of breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events (figures 8.4-8.5). The higher the cumulative exposure, the lower the risk of breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events. Effects of long-term NSAID use against breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events were shown (figures 8.6-8.17). The apparent dose-response protective effect of Cox-2 inhibitors use against all outcomes was found; the higher the cumulative exposure of Cox-2 inhibitors, the lower the risk of breast cancer, cervical cancer, endometrial cancer, ovarian cancer, GI and renal events. We found a non-significant relationship between long-term use of non-selective NSAIDs and risk of breast cancer, cervical cancer, endometrial cancer, ovarian cancer. While long-term indomethacin use in the NC cohort, showed a significant 11-fold increased risk of endometrial cancer (figure 8.14), long-term use of aspirin and ibuprofen, in GA cohort, were significantly associated with 42% and 43% decreased risk of breast cancer (figure 8.6). In addition, our results from, both cohorts, did not demonstrate an increased risk of GI and renal events in persons who had more than 1 year of each specific NSAID exposure (figures 8.10-8.11, 8.16-8.17).

Because the impact of NSAIDs on GI and renal events were somewhat surprising, a sensitivity analysis was conducted to explore other potential possible explanations for an apparent protective effect of NSAIDs on these outcomes. It has been noted from previous research with these data that long-term care facilities provide relatively fewer ICD-9-CM codes than other providers and if NSAID usage was related to long-term care use, that might account for an apparent undercoding and may partially explain the observed finding. To explore this possibility we conducted an analysis excluding all persons admitted to a long-term care facility

more than 1 year and re-estimated the multivariate adjusted models on the remaining subject; we excluded 62,086 and 307 persons admitted to a long-term care facility more than 1 year from GA and NC cohorts, respectively. The results of sensitivity analyses were presented in tables 8.15-8.16.

Moreover, we conducted an additional sensitivity analysis excluding all persons whose age was between 65 and 100 years. Since there are some disagreement with other studies that have shown the risk for breast and gynecological cancer increased with age, we found that older age classes, both 65-75 and >75, appeared to be at less risk for the three study outcomes than the 50-64 age group. We believe this is possibly a result of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare. After we excluded persons whose age was between 65 and 100 years from the GA and NC cohorts, we re-estimated the multivariate adjusted models on the remaining subject. The effects of NSAID use and covariates on the risk of study outcomes were comparable with original cohorts.

Discussion

To our knowledge this is the first epidemiologic study to demonstrate a protective effect of NSAIDs against endometrial cancer; the reduction in risk of endometrial cancer about 36-55% was revealed for any exposure to NSAIDs after multivariate adjustment. The results for breast cancer, cervical cancer, and ovarian cancer were mixed as a significant reductions were reported in the Georgia Medicaid population with reductions in the risk of breast cancer (45%), cervical cancer (49%) and ovarian cancer (44%); however, no significant associations were demonstrated in the NC cohort. In addition, we found that the protective effects of Cox-2 inhibitors was the

most apparent and was greater with increasing cumulative exposure in the Georgia Medicaid cohort. The greater reductions in relative risks at higher levels of NSAID consumption were observed. Persons who had more than 1 years of NSAID usage experienced 60% reduction in the risks of breast cancer, cervical cancer, endometrial cancer, and ovarian cancer than did persons who had no exposure in the Georgia Medicaid population. These results were robust and were not affected after excluding recipients that were admitted to long-term care facilities for greater than one year.

Despite comparable demographic compositions between the Medicaid cohorts in Georgia and North Carolina, a higher percentage of subjects in the Georgia (64%) were prescribed any NSAID than those in the North Carolina (46%). This discrepancy may be explained by differences in pharmacy services policy, available prescription NSAIDs, and physician's prescribing preferences. Before July 1998, the Georgia Medicaid pharmacy program covered only five prescriptions per recipient per month. After of July 1998, with a written or oral prescription from a physician indicating the need for a drug override to exceed the monthly limits, pharmacists in Georgia are able to do self-approval to exceed these prescription limits {Georgia Department of Community Health 2004}. North Carolina Medicaid has also established monthly prescription limits of six prescriptions per recipient per month. Unlike the Georgia Medicaid program, after July 1998, exemption from the prescription limitation will only be authorized for life threatening illnesses. The recipient's physician must submit a "Six Prescription Limit Override Form" where he or she justifies the patient's need for a drug override to exceed the monthly prescription limits {North Carolina Division of Medical Assistance 2004}. The possible follow-up period of the Georgia cohort (1990- 2001) was three years longer than that of the North Carolina cohort (1990-1998). The policy of override to

exceed the monthly prescription limits under the Georgia Medicaid program was changed. Therefore NSAID prescription rates in Georgia might have increased during that three-year period (1999-2001). Moreover, Cox-2 inhibitors, celecoxib and rofecoxib, were introduced in 1999. Cox-2 inhibitors are covered, without requirement of prior authorization, by Georgia Medicaid, although there are quantity level limits of 34 tablets per 34 days when celecoxib and rofecoxib are prescribed {Georgia Department of Community Health 2004}. Both Georgia and North Carolina Medicaid programs do not cover over-the-counter aspirin. Enteric-coated aspirin is available as a prescription drug and covered by Georgia Medicaid; prescription aspirin is not covered by the North Carolina Medicaid program. Lastly, there may be a difference of NSAID prescribing preferences of physicians in Georgia and North Carolina.

There are some inconsistent results between unadjusted and multivariate adjusted relative risks from both Georgia and North Carolina Medicaid cohorts. Mainly, we found the higher unadjusted relative risks than and sometimes reversed direction of multivariate adjusted relative risks of all study outcomes. Since more persons in NSAID exposure group experienced risk factors of the study outcomes than ones in non-exposure group. While extents to which some risk factors affects on developing breast cancer, gynecological cancers, and NSAID-related adverse events are small, others are strongly associated with the risks of the study outcomes. Therefore, the increased unadjusted relative risks may be subsequently due to these highly associated risk factors and the calculated relative risks attenuated after adjusting for such risk factors.

We found that the Georgia Medicaid women prescribed NSAIDs were 45% less likely to experience breast cancer after multivariate adjustment. This protective effect of NSAIDs is in agreement with the 20% reduced risk of breast cancer that has been previously associated with

NSAID usage {Khun 2002, Johnson 2002, Terry 2004}. However, the benefit of any NSAID use was marginally non-significant in the North Carolina women. Despite the comparable demographic composition and selected comorbidities of women, as well as mean length of follow up of those in non-NSAID exposure group, women prescribed an NSAID in the GA cohort, on average, remained in the cohort longer than those in the NC cohort. Therefore, in my opinion, the potential protective effect of NSAID use may be more apparent when extend period of follow up. Additionally, we found that the long-term use of NSAIDs was associated with reduced risk of breast cancer: 43-70% reduction in the risks of breast cancer.

Similar to breast cancer, the conflicting results were found in determining an association between incident ovarian cancer and NSAID usage. While we demonstrated 9% non-significant reduction in risk among the North Carolina Medicaid women prescribed NSAIDs, a 44% reduction was revealed in the Georgia Medicaid women. However, women who had more than 1 years of NSAID usage were 63-71% less likely to have ovarian cancer. Consistent with a case-control study by Rosenberg {Rosenberg 2000}, it was estimated a 50% reduction in ones using any NSAIDs at least 4 times per week for at least 5 years.

We did not find an elevated risk of GI and renal adverse events. After multivariate adjustment, NSAID use was associated with a statistically significant reduction in GI and renal adverse events. Higher cumulative exposure was associated with decreasing risk of GI and renal events. In other words, the risk of GI and renal adverse events appears to be inversely associated with cumulative amount used. Persons who had more than 1 years of NSAID usage experienced an apparent 65-75% and 73-80% decreased risk for GI and renal adverse events than did persons who had no exposure, respectively.

Nevertheless, these results must be interpreted with caution. Since subjects were required to be free of all outcomes within their first year eligibility, many of the NSAID users able to meet the inclusion criteria and remain in the study might tolerate NSAID therapy better than most typical users. Therefore, these subjects may demonstrate a lower risk for GI and renal events relative to those persons with NSAID exposure who don't tolerate therapy. However, to be certain about temporal relationship between NSAID use and the development of our outcome events, it was necessary to exclude persons who experienced events in the first year of the study. As a result of this exclusion criterion, persons whom may have had events shortly after an initial exposure to NSAIDs may have been omitted and consequently the GI risks reported in this study may be understated, particularly for low volume NSAID users.

Our results suggest that the risk of GI adverse events is highest at the beginning of NSAID use with decreases as persons consume more NSAIDs. This finding is consistent with studies showing that the initial doses of NSAIDs and not long term NSAID use are most likely to result in GI adverse related events {Gabriel 1991, Garcia Rodriguez 1998, Smalley 1995}. This may be explained by gastric mucosal adaptation, which has been reported in both animal and human studies {Fitzpatrick 1999, Lipscomb 1996}.

Studies have shown that the risk of breast cancer, cervical cancer, endometrial cancer and ovarian cancer increased with age. However we found that older age classes, both 65-75 and >75 age group, appeared to be at less risk for the three study outcomes than the 50 to 64 age group. This may be a subsequence of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare.

We conducted a sensitivity analysis excluding those whose age were between 65 and 100, however; as the results, the effects of NSAID use and covariates on the study outcomes were comparable to the original cohort.

There are several potential limitations in this proposed study. Since we depend on diagnosis (ICD-9-CM) codes to identify the study outcomes and confounders, measurement bias may arise due to coding inconsistencies. This may be of particular concern if there are differences in coding that is related to NSAID exposure. As a check for this potential concern, we conducted a sensitivity analysis excluding recipients with long term care admissions > 1 year and found the results to be generally consistent with the initial analysis. Additionally, detailed information on risk behaviors, i.e. tobacco and alcohol consumption is not specifically recorded in claims data and could only be inferred from diagnostic information. In claims data, clinical measures, i.e. histological type and stage of cancer, are also not available. So the effect of NSAIDs on different histological type and stage of cancer cannot be explored. Despite the fact that Medicaid pays for ASA, ibuprofen, and naproxen, exposure misclassification may still occur as a result of recipients purchasing these products over-the-counter. This may attenuate the disparity between exposure and non-exposure groups and underestimate relative risk of outcomes.

Since it is well known that NSAIDs are associated with increasing risks of GI and renal events, though perhaps transitory, channeling bias is an inextricable limitation of this study because physicians would be less likely to prescribe non-selective NSAIDs to persons they believe might be prone to GI or renal adverse events. We attended to this limitation by including the use of gastroprotective agents (a potential marker for past GI events) as a covariate in the GI adverse event models, but we recognize that this can only partially describes someone's GI event

likelihood. Moreover, physicians may also pay closer attention to those who take NSAIDs, for example, more physician visits, which may lead to earlier diagnosis. Nevertheless, frequency of health care utilization was adjusted in the models in an attempt to attend to this phenomenon. We do not believe that if recipients were randomly assigned to NSAIDs and non-NSAIDs that the same results would be obtained with regard to GI and renal adverse events, however, these data do demonstrate that the NSAID prescribing decisions made in this population are not associated with an increase in GI and Renal events and this finding may better reflect the risks of NSAID prescribing rather than the relative risk of NSAIDs themselves. Though we do believe that channeling bias is an important consideration when interpreting the results of the adverse events, we do not believe channeling bias is a significant concern for the results for cancer prevention analyses, because it is unlikely that physicians were prescribing NSAIDs for persons whom they thought might be at higher risk of the cancers during this study time frame.

Conclusion

Any NSAID exposure was associated with an approximate 36-55% reduction in incident endometrial cancer. There were no increased rates of GI and renal events associated with NSAID prescribing in this population. We identified an inverse association between use of NSAIDs and endometrial cancer from epidemiological study. We believe this to be the first report of such an association these finding will need to be replicated. Future analyses should examine relationships between specific NSAIDs in relation to endometrial risk over more extended periods of time, better measures of NSAID exposure, and better controls of behavioral risk factors.

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Table 8.1: Commonly Available Non-Steroidal Anti-inflammatory Drug (NSAIDs), According to Chemical Class

Chemical Class	Generic	Low daily dose (mg)	High daily dose (mg)	Standardization to Ibuprofen
Nonselective COX inhibitors				
Salicylic acid derivatives	Aspirin (acetylsalicylic acid)	2,400	3,600	0.67
	Salicylate salts (i.e. Choline Magnesium trisalicylate)	2,000	3,000	0.80
	Diflunisal	500	1,000	2.40
	Salsalate	2,000	4,000	0.60
Heteroacrl acetic acids	Diclofenac	100	150	16.00
	Etodolac	800	1,200	2.00
	Ketorolac	10	40	60.00
	Tolmetin	1,200	1,800	1.33
Indole and indene acetic acids	Indomethacin	50	150	16.00
	Sulindac	300	400	6.00
Arylpropionic acids	Fenoprofen	900	2,400	1.00
	Flurbiprofen	200	300	8.00
	Ibuprofen	1,200	2,400	1.00
	Ketoprofen	200	300	8.00
	Naproxen	550	1,100	2.18
	Oxaprozin	1,200	1,800	1.33
Anthranilic acid (Fenamates)	Meclofenamic acid	100	400	6.00
	Mefenamic acid	500	1,000	2.40
Enolic acids				
Pyrazolones	Phenylbutazone	300	400	6.00
Oxicams	Piroxicam	less than 20	20	120.00
Nonacidic agent				
Alkanones	Nabumetone	1,000	2,000	1.20
Selective COX-2 Inhibitors				
Diaryl-substituted furanones	Rofecoxib	12.5	25	96.00
Diaryl-substituted isoxazole	Valdecoxib	10	20	120.00
Diaryl-substituted pyrazoles	Celecoxib	200	400	6.00

Source: (1) Roberts LJ2, Marrow JD. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Good man and Gilman's the pharmacological basis of therapeutics. Columbus: The McGraw-Hill Companies, Inc., 2001;687-731.

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Table 8.2: List of Model Covariates and their Operational Definitions

Covariates	Outcome					
	Breast cancer	Cervical cancer	Endometrial cancer	Ovarian cancer	GI events	Renal events
Demographics						
Age at entry (years)	Yes	Yes	Yes	Yes	Yes	Yes
Gender (female vs. male)	Yes	Yes	Yes	Yes	Yes	Yes
Race (non-white vs. white)	Yes	Yes	Yes	Yes	Yes	Yes
Frequency of health care utilization: Total number of visits to ambulatory care services, emergency department, long-term care facilities, and acute inpatient services throughout study period	Yes	Yes	Yes	Yes	Yes	Yes
Frequency of cancer screenings: Total numbers of any cancer screenings throughout study period	Yes	Yes	Yes	Yes	Yes	Yes
Alcohol use and alcohol abuse (ICD-9-CM = 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 {Elixhauser 1998})	Yes	Yes	Yes	Yes	Yes	Yes
Obesity (ICD-9-CM = 278.x {Elixhauser 1998})	Yes	Yes	Yes	Yes	Yes	Yes
Tobacco Smoke (ICD-9-CM = 305.1, V15.82 {Romano 1994})	Yes	Yes	Yes	Yes	Yes	Yes
Pelvic inflammatory disease (PID; ICD-9-CM= 614.9)	No	Yes	No	No		
Sexually transmitted diseases (STDs)	No	Yes	No	No	No	No
Human immunodeficiency virus disease (HIV)/ acquired immunodeficiency syndrome (AIDS; ICD-9-CM=042, V08)	No	Yes	No	No	No	No
Syphilis (ICD-9-CM= 091.x- 097.x)	No	Yes	No	No	No	No
Gonococcal infection (ICD-9-CM=098.x)	No	Yes	No	No	No	No
Human papillomavirus (HPV) infection (ICD-9-CM= 079.4)	No	Yes	No	No	No	No
Endometrial hyperplasia (ICD-9-CM=621.3x) {CDC 2003}	No	No	Yes	No	No	No
Emphysema (ICD-9-CM = 492.xx)	No	No	No	No	Yes	No
Chronic Bronchitis (ICD-9-CM = 491.xx)	No	No	No	No	Yes	No
H.Pylori infection (ICD-9-CM = 041.86)	No	No	No	No	Yes	No
Cirrhosis (ICD-9-CM = 571.5, 571.6)	No	No	No	No	No	Yes
Hypertension (ICD-9-CM = 401.xx, 402.xx, 405.xx {Elixhauser 1998})	No	No	No	No	No	Yes
Diabetes Melitus (ICD-9-CM = 250.0x-250.3x; 250.5x-250.9x {Elixhauser 1998})	No	No	No	No	No	Yes
Congestive heart failure (ICD-9-CM = 389.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9 {Elixhauser 1998})	No	No	No	No	No	Yes
Liver Failure (ICD-9-CM = 570.xx)	No	No	No	No	No	Yes
Oral contraceptives	Yes	No	Yes	Yes	No	No
Hormone replacement therapy (HRT)	Yes	No	No	Yes	No	No
GI protective agents (i.e. Misoprostal, proton pump inhibitors (PPIs), and histamine-2 (H2) receptor antagonists)	No	No	No	No	Yes	No
Corticosteroids (i.e. prednisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone and hydrocortisone)	No	No	No	No	Yes	No
Anticoagulant use (i.e. heparins, coumarin and indadiones)	No	No	No	No	Yes	No
Nephrotoxic Drugs:	No	No	No	No		
Diuretics (i.e. loop, potassium-sparing, thiazide diuretics)	No	No	No	No	No	Yes
Angiotensin-converting Enzyme (ACE) Inhibitors and Angiotensin-II-receptor antagonist (e.g captopril, enalapril, lisinopril, losartan etc.)	No	No	No	No	No	Yes
Aminoglycosides	No	No	No	No	No	Yes
Cephalosporins	No	No	No	No	Yes	Yes
Vancomycin	No	No	No	No	No	Yes
Allopurinol	No	No	No	No	No	Yes
Cyclosporine	No	No	No	No	No	Yes

Table 8.3: Georgia Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Breast Cancer		Cervical Cancer		Endometrial Cancer	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	56,675	101,673	56,467	101,881	56,450	101,898
Incidence rate per 100,000 person-years	241.49	192.82	42.24	32.97	25.42	21.75
Follow up period, mean ± SD (yr)	4.9 ± 3.0	7.5 ± 3.5	5.0 ± 3.0	7.5 ± 3.5	4.9 ± 3.0	7.5 ± 3.5
Demographics (%)						
Age, mean ± SD (yr)	73.9 ± 12.1	70.1 ± 11.1	74.0 ± 12.1	70.1 ± 11.1	74.0 ± 12.1	70.1 ± 11.1
Race						
White	56.0	43.8	56.1	43.8	56.1	43.8
Non White	33.8	42.0	33.7	42.0	33.7	42.0
Unknown Race	10.2	14.3	10.2	14.3	10.2	14.3
Risk Factors (%)						
Tobacco Smoke	0.9	2.1	0.9	2.1	0.8	2.1
Obesity	0.8	3.4	0.7	3.4	0.7	3.4
Alcohol Abuse	0.9	1.6	0.9	1.6	0.9	1.6
STDs						
HIV/AIDS	na	na	0.1	0.1	na	na
Gonococcal Infection	na	na	0.02	0.07	na	na
Syphillis	na	na	0.1	0.3	na	na
PID	na	na	0.04	0.26	na	na
Endometrial hyperplasia	na	na	na	na	0.04	0.22
Emphysema	na	na	na	na	na	na
Chronic Bronchitis	na	na	na	na	na	na
H. pylori Infection	na	na	na	na	na	na
Hypertension	na	na	na	na	15.7	31.5
Diabetes Mellitus	na	na	na	na	8.7	18.3
Congestive Heart Failure	na	na	na	na	na	na
Cirrhosis	na	na	na	na	na	na
Medication exposures						
Oral contraceptives	0.1	0.3	na	na	0.1	0.3
HRT	7.5	19.4	na	na	7.4	19.5
GI protective agents	na	na	na	na	na	na
Corticosteroids	na	na	na	na	na	na
Anticoagulants	na	na	na	na	na	na
Diuretics	na	na	na	na	na	na
ACE inhibitors	na	na	na	na	na	na
Antibiotics						
Aminoglycosides	na	na	na	na	na	na
Cephalosporines	na	na	na	na	na	na
Vancomycins	na	na	na	na	na	na
Allopurinal	na	na	na	na	na	na
Cyclosporine	na	na	na	na	na	na
Frequency of Health Care Utilization, mean ± SD (times)	138.7 ± 158.6	204.5 ± 182.9	138.4 ± 158.3	204.6 ± 182.9	138.4 ± 158.2	204.6 ± 183.0
Frequency of Cancer Screening, mean ± SD (times)	0.092 ± 0.46	0.269 ± 0.86	0.089 ± 0.44	0.270 ± 0.86	0.088 ± 0.43	0.271 ± 0.86

Table 8.3 (continue): Georgia Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Ovarian Cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	56,454	101,894	57,148	101,200	56,849	101,499
Incidence rate per 100,000 person-years	39.38	33.87	660.10	684.75	619.55	540.67
Follow up period, mean ± SD (yr)	4.9 ± 3.0	7.5 ± 3.5	4.9 ± 3.0	7.3 ± 3.5	4.9 ± 3.0	7.4 ± 3.5
Demographics (%)						
Age, mean ± SD (yr)	74.0 ± 12.1	70.1 ± 11.1	73.8 ± 12.2	70.2 ± 11.1	73.9 ± 12.1	70.2 ± 11.1
Race						
White	56.1	43.7	55.9	43.8	55.9	43.8
Non White	33.7	42.0	33.9	42.0	34.0	41.9
Unknown Race	10.2	14.3	10.2	14.3	10.2	14.3
Risk Factors (%)						
Tobacco Smoke	0.8	2.1	1.0	2.0	0.9	2.1
Obesity	0.7	3.4	0.9	3.4	0.8	3.4
Alcohol Abuse	0.9	1.6	1.0	1.5	0.9	1.5
STDs						
HIV/AIDS	na	na	na	na	na	na
Gonococcal Infection	na	na	na	na	na	na
Syphillis	na	na	na	na	na	na
PID	na	na	na	na	na	na
Endometrial hyperplasia	na	na	na	na	na	na
Emphysema	na	na	0.8	1.5	na	na
Chronic Bronchitis	na	na	2.3	4.6	na	na
H. pylori Infection	na	na	0.1	0.4	na	na
Hypertension	na	na	na	na	16.1	31.4
Diabetes Mellitus	na	na	na	na	9.0	18.1
Congestive Heart Failure	na	na	na	na	7.9	13.5
Cirrhosis	na	na	na	na	0.3	0.4
Medication exposures						
Oral contraceptives	0.1	0.3	na	na	na	na
HRT	7.4	19.5	na	na	na	na
GI protective agents	na	na	35.1	65.6	na	na
Corticosteroids	na	na	15.8	39.0	na	na
Anticoagulants	na	na	11.4	16.0	na	na
Diuretics	na	na	na	na	41.8	65.0
ACE inhibitors	na	na	na	na	27.3	47.8
Antibiotics						
Aminoglycosides	na	na	na	na	1.7	1.5
Cephalosporines	na	na	49.4	71.9	49.2	72.0
Vancomycins	na	na	na	na	1.1	1.1
Allopurinal	na	na	na	na	2.0	7.7
Cyclosporine	na	na	na	na	0.1	0.1
Frequency of Health Care Utilization, mean ± SD (times)	138.4 ± 158.2	204.6 ± 182.9	139.7 ± 159.1	204.3 ± 182.9	139.8 ± 160.2	204.1 ± 182.3
Frequency of Cancer Screening, mean ± SD (times)	0.088 ± 0.43	0.270 ± 0.86	0.099 ± 0.48	0.266 ± 0.85	0.091 ± 0.44	0.270 ± 0.86

Table 8.4: North Carolina Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Breast Cancer		Cervical Cancer		Endometrial Cancer	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	73,570	61,712	73,508	61,774	73,501	61,781
Incidence rate per 100,000 person-years	105.27	135.91	17.15	22.19	13.95	16.92
Follow up period, mean ± SD (yr)	4.7 ± 2.2	5.8 ± 2.4	4.7 ± 2.2	5.8 ± 2.4	4.7 ± 2.2	5.8 ± 2.4
Demographics (%)						
Age, mean ± SD (yr)	74.1 ± 10.5	71.3 ± 10.9	74.1 ± 10.5	71.3 ± 10.9	74.1 ± 10.5	71.3 ± 11.0
Race						
White	59.4	49.5	59.4	49.5	59.4	49.5
Non White	40.7	50.5	40.7	50.5	40.7	50.5
Risk Factors (%)						
Tobacco Smoke	0.5	1.7	0.5	1.7	0.5	1.7
Obesity	0.8	3.2	0.8	3.2	0.8	3.2
Alcohol Abuse	0.6	1.3	0.6	1.3	0.6	1.3
STDs						
HIV/AIDS	na	na	0.04	0.08	na	na
Gonococcal Infection	na	na	0.01	0.04	na	na
Syphillis	na	na	0.1	0.2	na	na
PID	na	na	0.02	0.15	na	na
Endometrial hyperplasia	na	na	na	na	0.03	0.13
Emphysema	na	na	na	na	na	na
Chronic Bronchitis	na	na	na	na	na	na
H. pylori Infection	na	na	na	na	na	na
Hypertension	na	na	na	na	11.0	24.1
Diabetes Mellitus	na	na	na	na	8.1	16.5
Congestive Heart Failure	na	na	na	na	na	na
Cirrhosis	na	na	na	na	na	na
Medication exposures						
Oral contraceptives	0.03	0.06	na	na	4.6	13.2
HRT	4.6	13.2	na	na	0.03	0.06
GI protective agents	na	na	na	na	na	na
Corticosteroids	na	na	na	na	na	na
Anticoagulants	na	na	na	na	na	na
Diuretics	na	na	na	na	na	na
ACE inhibitors	na	na	na	na	na	na
Antibiotics						
Aminoglycosides	na	na	na	na	na	na
Cephalosporines	na	na	na	na	na	na
Vancomycins	na	na	na	na	na	na
Allopurinal	na	na	na	na	na	na
Cyclosporine	na	na	na	na	na	na
Frequency of Health Care Utilization, mean ± SD (times)	31.6 ± 51.0	57.0 ± 74.5	31.5 ± 50.9	57.0 ± 74.5	31.5 ± 50.9	57.0 ± 74.6
Frequency of Cancer Screening, mean ± SD (times)	0.025 ± 0.21	0.089 ± 0.41	0.025 ± 0.21	0.089 ± 0.41	0.025 ± 0.21	0.089 ± 0.41

Table 8.4 (continue): North Carolina Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Ovarian Cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	73,504	61,778	73,756	61,526	73,631	61,651
Incidence rate per 100,000 person-years	14.82	23.30	355.71	637.69	263.53	341.12
Follow up period, mean ± SD (yr)	4.7 ± 2.2	5.8 ± 2.4	4.7 ± 2.2	5.7 ± 2.4	4.7 ± 2.2	5.8 ± 2.4
Demographics (%)						
Age, mean ± SD (yr)	74.1 ± 10.5	71.3 ± 11.0	74.0 ± 10.5	71.3 ± 10.9	74.0 ± 10.5	71.3 ± 10.9
Race						
White	59.3	49.5	59.3	49.5	59.3	49.6
Non White	40.7	50.5	40.7	50.5	40.7	50.5
Risk Factors (%)						
Tobacco Smoke	0.5	1.7	0.6	1.6	0.5	1.7
Obesity	0.8	3.2	0.9	3.2	0.9	3.2
Alcohol Abuse	0.6	1.3	0.7	1.3	0.6	1.3
STDs						
HIV/AIDS	na	na	na	na	na	na
Gonococcal Infection	na	na	na	na	na	na
Syphillis	na	na	na	na	na	na
PID	na	na	na	na	na	na
Endometrial hyperplasia	na	na	na	na	na	na
Emphysema	na	na	0.4	1.0	na	na
Chronic Bronchitis	na	na	0.9	2.2	na	na
H. pylori Infection	na	na	0.03	0.13	na	na
Hypertension	na	na	na	na	11.1	24.0
Diabetes Mellitus	na	na	na	na	8.2	16.5
Congestive Heart Failure	na	na	na	na	6.0	10.0
Cirrhosis	na	na	na	na	0.1	0.2
Medication exposures						
Oral contraceptives	0.03	0.06	na	na	na	na
HRT	4.6	13.2	na	na	na	na
GI protective agents	na	na	25.4	54.7	na	na
Corticosteroids	na	na	10.3	27.1	na	na
Anticoagulants	na	na	7.6	10.4	na	na
Diuretics	na	na	na	na	31.9	56.3
ACE inhibitors	na	na	na	na	17.9	33.5
Antibiotics						
Aminoglycosides	na	na	na	na	1.0	0.9
Cephalosporines	na	na	34.5	58.4	34.4	58.4
Vancomycins	na	na	na	na	0.6	0.7
Allopurinal	na	na	na	na	1.4	5.6
Cyclosporine	na	na	na	na	0.04	0.06
Frequency of Health Care Utilization, mean ± SD (times)	31.5 ± 51.0	57.0 ± 74.5	31.9 ± 51.6	56.7 ± 74.2	31.7 ± 51.3	56.9 ± 74.4
Frequency of Cancer Screening, mean ± SD (times)	0.025 ± 0.21	0.089 ± 0.41	0.026 ± 0.22	0.088 ± 0.41	0.025 ± 0.21	0.089 ± 0.41

Table 8.5: Effect of NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Breast Cancer	Any Use	761,859	1,469	192.82	0.8	0.55 (0.50, 0.61)
	None	276,200	667	241.49	Reference	Reference
Cervical Cancer	Any Use	767,407	253	32.97	0.78	0.51 (0.40, 0.64)
	None	279,323	118	42.24	Reference	Reference
Endometrial Cancer	Any Use	767,844	167	21.75	0.86	0.45 (0.34, 0.61)
	None	279,321	71	25.42	Reference	Reference
Ovarian Cancer	Any Use	767,607	260	33.87	0.86	0.56 (0.44, 0.71)
	None	279,296	110	39.38	Reference	Reference
GI Events (female only)	Any Use	743,195	5,089	684.75	1.04	0.46 (0.43, 0.49)
	None	278,596	1,839	660.10	Reference	Reference
Renal Events (female only)	Any Use	754,439	4,079	540.67	0.87	0.39 (0.36, 0.41)
	None	278,104	1,723	619.55	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 8.6: Effect of NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Breast Cancer	Any Use	359,070	488	135.91	1.29	0.90 (0.78, 1.04)
	None	343,881	362	105.27	Reference	Reference
Cervical Cancer	Any Use	360,463	80	22.19	1.29	0.87 (0.61, 1.25)
	None	344,122	59	17.15	Reference	Reference
Endometrial Cancer	Any Use	360,549	61	16.92	1.21	0.64 (0.43, 0.97)
	None	344,115	48	13.95	Reference	Reference
Ovarian Cancer	Any Use	360,469	84	23.30	1.57	0.91 (0.63, 1.32)
	None	344,139	51	14.82	Reference	Reference
GI Events (female only)	Any Use	353,151	2,252	637.69	1.79	0.71 (0.66, 0.77)
	None	342,979	1,220	355.71	Reference	Reference
Renal Events (female only)	Any Use	357,642	1,220	341.12	1.29	0.54 (0.48, 0.58)
	None	343,412	905	263.53	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 8.7: Effect of Covariates on the Incidence of Breast cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.5949	0.0494	<.0001	0.55	-0.1053	0.0737	0.1531	0.90
Age groups								
75-100 years old	-1.2770	0.0638	<.0001	0.28	-0.9383	0.0890	<.0001	0.39
65-74 years old	-0.9137	0.0566	<.0001	0.40	-1.1247	0.0979	<.0001	0.33
50-64 years old								
Race								
Non-White	0.1377	0.0485	0.0045	1.15	-0.0152	0.0699	0.8275	0.99
White								
Frequency of Cancer Screening	0.1859	0.0121	<.0001	1.20	0.3083	0.0406	<.0001	1.36
Frequency of Health Care Utilization	0.0002	0.0001	0.0816	1.00	0.0031	0.0003	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.2395	0.1122	0.0328	1.27	0.2329	0.1935	0.2289	1.26
Obesity	0.3864	0.0790	<.0001	1.47	0.4245	0.1280	0.0009	1.53
Tobacco Smoke	0.5779	0.0913	<.0001	1.78	0.3631	0.1600	0.0232	1.44
Medication exposures								
Oral contraceptives	-1.0561	0.5782	0.0678	0.35	Not Enough Sample Size to Analyze its Effect			
HRT	-0.0474	0.0548	0.3874	0.95	-0.1615	0.1051	0.1242	0.85

Table 8.8: Effect of Covariates on the Incidence of Cervical cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.6752	0.1172	<.0001	0.51	-0.1366	0.1820	0.4527	0.87
Age groups								
75-100 years old	-1.1060	0.1535	<.0001	0.33	-1.0888	0.2268	<.0001	0.34
65-74 years old	-0.5924	0.1318	<.0001	0.55	-1.1966	0.2445	<.0001	0.30
50-64 years old								
Race								
Non-White	0.0484	0.1163	0.6771	1.05	-0.2103	0.1734	0.2251	0.81
White								
Frequency of Cancer Screening	0.1852	0.0282	<.0001	1.20	0.3779	0.0848	<.0001	1.46
Frequency of Health Care Utilization	0.0004	0.0002	0.1219	1.00	0.0013	0.0008	0.1144	1.00
Risk Factors								
Alcohol Abuse	0.6667	0.2278	0.0034	1.95	1.0584	0.3403	0.0019	2.88
Obesity	0.1314	0.2101	0.5319	1.14	0.5897	0.2944	0.0451	1.80
Tobacco Smoke	0.7371	0.2062	0.0003	2.09	0.9393	0.3113	0.0025	2.56
STDs								
HIV/AIDS	0.9119	0.6285	0.1468	2.49	Not Enough Sample Size to Analyze its effect			
Gonococcal Infection	-0.0685	1.0097	0.9459	0.93	Not Enough Sample Size to Analyze its effect			
HPVs	2.0295	0.9099	0.0257	7.61	Not Enough Sample Size to Analyze its effect			
Syphillis	0.9212	0.4171	0.0272	2.51	Not Enough Sample Size to Analyze its effect			
PID	1.1971	0.3896	0.0021	3.31	0.5373	1.0131	0.5959	1.71

Table 8.9: Effect of Covariates on the Incidence of Endometrial cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgai Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.7901	0.1507	<.0001	0.45	-0.4408	0.2090	0.035	0.64
Age groups								
75-100 years old	-1.4562	0.2395	<.0001	0.23	-0.7008	0.2761	0.0112	0.50
65-74 years old	-0.5277	0.1745	0.0025	0.59	-0.6886	0.2840	0.0153	0.50
50-64 years old								
Race								
Non-White	-0.0870	0.1442	0.5459	0.92	-0.4426	0.1988	0.026	0.64
White								
Frequency of Cancer Screening	0.1110	0.0406	0.0062	1.12	0.4075	0.0922	<.0001	1.50
Frequency of Health Care Utilization	-0.0006	0.0003	0.0744	1.00	-0.0015	0.0011	0.1926	1.00
Risk Factors								
Alcohol Abuse	0.0032	0.3670	0.9931	1.00	-13.1992	386.7136	0.9728	0.00
Obesity	0.6085	0.1983	0.0021	1.84	1.0498	0.2767	0.0001	2.86
Tobacco Smoke	-0.1336	0.3336	0.6888	0.88	0.7358	0.3758	0.0502	2.09
Endometrial hyperplasia	2.0791	0.3076	<.0001	8.00	1.7626	0.5393	0.0011	5.83
Hypertension	0.7229	0.1650	<.0001	2.06	1.1337	0.2495	<.0001	3.11
Diabetes Mellitus	0.5413	0.1542	0.0004	1.72	1.0419	0.2282	<.0001	2.83
Medication exposures								
Oral contraceptives	0.6403	0.5984	0.2847	1.90	-14.3677	4159.0000	0.9972	0.00
HRT	-0.2048	0.1645	0.2131	0.82	-0.6513	0.3132	0.0376	0.52

Table 8.10: Effect of Covariates on the Incidence of Ovarian cancer in the Georgia and North Carolina Medicaid Cohort

	The Georgia Cohort				The North Carolina Cohort			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.5802	0.1211	<.0001	0.56	-0.0949	0.1898	0.6172	0.91
Age groups								
75-100 years old	-1.2260	0.1628	<.0001	0.29	-1.1231	0.2412	<.0001	0.33
65-74 years old	-0.6116	0.1311	<.0001	0.54	-1.2227	0.2546	<.0001	0.29
50-64 years old								
Race								
Non-White	-0.2538	0.1154	0.0278	0.78	-0.1091	0.1758	0.5348	0.90
White								
Frequency of Cancer Screening	0.1978	0.0271	<.0001	1.22	0.3285	0.0833	<.0001	1.39
Frequency of Health Care Utilization	-0.0004	0.0003	0.1447	1.00	0.0025	0.0007	0.0002	1.00
Risk Factors								
Alcohol Abuse	0.3095	0.2815	0.2715	1.36	0.9126	0.3628	0.0119	2.49
Obesity	0.5459	0.1851	0.0032	1.73	0.9450	0.2590	0.0003	2.57
Tobacco Smoke	0.2561	0.2373	0.2804	1.29	-0.2242	0.4118	0.5861	0.80
Medication exposures								
Oral contraceptives	-0.5346	1.0030	0.594	0.59	1.6789	1.0150	0.0981	5.36
HRT	0.4058	0.1218	0.0009	1.50	0.4724	0.2160	0.0287	1.60

Table 8.11: Effect of Covariates on the Incidence of GI events (female only) in the Georgia and North Carolina Medicaid Cohort

	The Georgia Cohort				The North Carolina Cohort			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.7796	0.0295	<.0001	0.46	-0.3417	0.0384	<.0001	0.71
Age groups								
75-100 years old	-1.4917	0.0373	<.0001	0.23	-1.0816	0.0438	<.0001	0.34
65-74 years old	-1.3094	0.0346	<.0001	0.27	-1.6439	0.0556	<.0001	0.19
50-64 years old								
Race								
Non-White	0.2075	0.0277	<.0001	1.23	0.1031	0.0351	0.0033	1.11
White								
Frequency of Cancer Screening	0.1429	0.0070	<.0001	1.15	0.1815	0.0204	<.0001	1.20
Frequency of Health Care Utilization	0.0004	0.0001	<.0001	1.00	0.0030	0.0001	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.6100	0.0496	<.0001	1.84	0.7395	0.0714	<.0001	2.10
Obesity	0.4832	0.0384	<.0001	1.62	0.3950	0.0575	<.0001	1.48
Tobacco Smoke	0.4590	0.0469	<.0001	1.58	0.3944	0.0701	<.0001	1.48
Emphysema	0.3309	0.0548	<.0001	1.39	0.2840	0.0910	0.0018	1.33
Chronic Bronchitis	0.3634	0.0393	<.0001	1.44	0.0522	0.0707	0.4608	1.05
H. pylori Infection	1.2035	0.0700	<.0001	3.33	1.3858	0.1266	<.0001	4.00
Medication exposures								
GI protective agents	1.5576	0.0400	<.0001	4.75	1.9040	0.0511	<.0001	6.71
Corticosteroids	0.0327	0.0263	0.2135	1.03	-0.0631	0.0389	0.1044	0.94
Anticoagulants	0.0917	0.0313	0.0034	1.10	0.1036	0.0499	0.038	1.11
Cephalosporines	0.0447	0.0314	0.1537	1.05	0.1784	0.0395	<.0001	1.20

Table 8.12: Effect of Covariates on the Incidence of Renal events (female only) in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgai Cohort				The North Carolina Cohort			
	Coefficient	Standard Error	p-value	Hazard Ratio	Coefficient	Standard Error	p-value	Hazard Ratio
NSAID exposure	-0.9532	0.0314	<.0001	0.39	-0.6336	0.0479	<.0001	0.53
Age groups								
75-100 years old	-0.8900	0.0414	<.0001	0.41	-0.5045	0.0599	<.0001	0.60
65-74 years old	-0.5860	0.0365	<.0001	0.56	-0.5189	0.0621	<.0001	0.60
50-64 years old								
Race								
Non-White	0.6675	0.0324	<.0001	1.95	0.5710	0.0483	<.0001	1.77
White								
Frequency of Cancer Screening	-0.0473	0.0120	<.0001	0.95	-0.0251	0.0378	0.5069	0.98
Frequency of Health Care Utilization	0.0010	0.0001	<.0001	1.00	0.0011	0.0002	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.2842	0.0652	<.0001	1.33	0.0806	0.1249	0.5184	1.08
Obesity	0.1487	0.0435	0.0006	1.16	-0.0904	0.0777	0.2443	0.91
Tobacco Smoke	0.2408	0.0589	<.0001	1.27	0.2673	0.1057	0.0114	1.31
Hypertension	0.4700	0.0334	<.0001	1.60	0.9943	0.0549	<.0001	2.70
Diabetes Mellitus	0.6892	0.0311	<.0001	1.99	0.8449	0.0505	<.0001	2.33
Congestive Heart Failure	0.7950	0.0304	<.0001	2.21	0.9944	0.0523	<.0001	2.70
Cirrhosis	0.5839	0.1037	<.0001	1.79	0.8793	0.1713	<.0001	2.41
Medication exposures								
Diuretics	0.2582	0.0364	<.0001	1.30	0.3185	0.0558	<.0001	1.38
ACE inhibitors	0.4873	0.0322	<.0001	1.63	0.3451	0.0488	<.0001	1.41
Antibiotics								
Aminoglycosides	0.2570	0.0861	0.0028	1.29	0.6238	0.1503	<.0001	1.87
Cephalosporines	0.0551	0.0337	0.1017	1.06	0.2043	0.0489	<.0001	1.23
Vancomycins	0.3874	0.0932	<.0001	1.47	0.8932	0.1504	<.0001	2.44
Allopurinal	0.6965	0.0358	<.0001	2.01	0.7142	0.0694	<.0001	2.04
Cyclosporine	1.4650	0.2014	<.0001	4.33	0.4276	0.3684	0.2459	1.53

Table 8.13: Effect of specific NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort

NSAID exposure	Person-years	Breast cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	205,092	360	175.53	0.73	0.91 (0.81, 1.03)
Non-Selective Cox Inhibitors	709,910	1,383	194.81	0.82	
Fenoprofen	134,015	271	202.22	0.85	1.07 (0.93, 1.22)
Ibuprofen	483,403	909	188.04	0.79	0.79 (0.72, 0.87)
Idomethacin	174,571	281	160.97	0.67	0.80 (0.71, 0.87)
Naproxen	278,530	513	184.18	0.77	0.87 (0.78, 0.97)
Sulindac	115,236	196	170.09	0.71	0.97 (0.83, 1.13)
Others NSAIDs	343,881	588	170.99	0.72	0.87 (0.78, 0.96)
Cox-2 Inhibitors	273,964	236	86.14	0.36	0.26 (0.23, 0.30)
None	279,200	667	238.90	Reference	Reference
NSAID exposure	Person-years	Cervical cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	206,782	56	27.08	0.64	0.79 (0.49, 1.07)
Non-Selective Cox Inhibitors	715,174	243	33.98	0.80	
Fenoprofen	135,085	50	37.01	0.88	1.22 (0.89, 1.166)
Ibuprofen	487,324	167	34.27	0.81	0.91 (0.74, 1.14)
Idomethacin	176,238	38	21.56	0.51	0.60 (0.42, 0.85)
Naproxen	281,664	76	26.98	0.64	0.71 (0.54, 0.93)
Sulindac	116,342	33	28.36	0.67	0.98 (0.68, 1.42)
Others NSAIDs	346,974	101	29.11	0.69	0.90 (0.70, 1.16)
Cox-2 Inhibitors	278,298	33	11.86	0.28	0.21 (0.15, 0.31)
None	279,323	118	42.24	Reference	Reference
NSAID exposure	Person-years	Endometrial Cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	206,902	36	17.40	0.68	0.69 (0.48, 1.00)
Non-Selective Cox Inhibitors	715,556	160	22.36	0.88	
Fenoprofen	135,226	29	21.45	0.84	0.97 (0.65, 1.45)
Ibuprofen	487,554	123	25.23	0.99	1.07 (0.82, 1.40)
Idomethacin	176,232	41	23.26	0.92	1.00 (0.70, 1.43)
Naproxen	281,832	49	17.39	0.68	0.56 (0.40, 0.78)
Sulindac	116,375	31	26.64	1.05	1.37 (0.92, 2.02)
Others NSAIDs	347,192	67	19.30	0.76	0.84 (0.62, 1.14)
Cox-2 Inhibitors	278,599	23	8.26	0.32	0.20 (0.13, 0.32)
None	279,321	71	25.42	Reference	Reference

Table 8.13 (continue): Effect of specific NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort

NSAID exposure	Person-years	Ovarian cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	206,881	53	25.62	0.65	0.70 (0.51, 0.94)
Non-Selective Cox Inhibitors	715,300	245	34.25	0.87	
Fenoprofen	135,157	41	30.34	0.77	0.88 (0.63, 1.23)
Ibuprofen	487,342	165	33.86	0.86	0.86 (0.69, 1.08)
Idomethacin	176,169	48	27.25	0.69	0.80 (0.58, 1.10)
Naproxen	281,668	108	38.34	0.97	1.11 (0.87, 1.42)
Sulindac	116,375	23	19.76	0.50	0.60 (0.39, 0.92)
Others NSAIDs	346,995	117	33.72	0.86	1.00 (0.79, 1.27)
Cox-2 Inhibitors	278,337	50	17.96	0.46	0.30 (0.22, 0.41)
None	279,296	110	39.38	Reference	Reference
NSAID exposure	Person-years	GI events (female only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	197,371	1,362	690.07	1.05	0.91 (0.85, 0.96)
Non-Selective Cox Inhibitors	692,170	4,787	691.59	1.05	
Fenoprofen	129,329	965	746.16	1.13	1.00 (0.93, 1.07)
Ibuprofen	469,885	3,125	665.06	1.01	0.73 (0.69, 0.77)
Idomethacin	168,199	1,138	676.58	1.02	0.89 (0.83, 0.95)
Naproxen	267,386	1,734	648.50	0.98	0.75 (0.71, 0.80)
Sulindac	111,730	675	604.14	0.92	0.87 (0.80, 0.95)
Others NSAIDs	331,731	2,116	637.87	0.97	0.81 (0.76, 0.85)
Cox-2 Inhibitors	258,343	723	279.86	0.42	0.22 (0.21, 0.24)
None	278,596	1,839	660.09	Reference	Reference
NSAID exposure	Person-years	Renal Events (female only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	202,680	1,060	522.99	0.84	0.85 (0.79, 0.91)
Non-Selective Cox Inhibitors	702,942	3,846	547.13	0.88	
Fenoprofen	132,691	720	542.61	0.88	0.88 (0.82, 0.96)
Ibuprofen	478,279	2,507	524.17	0.85	0.65 (0.61, 0.68)
Idomethacin	171,072	1,131	661.12	1.07	0.90 (0.84, 0.97)
Naproxen	275,457	1,260	457.42	0.74	0.68 (0.64, 0.73)
Sulindac	113,179	684	604.35	0.98	1.03 (0.95, 1.12)
Others NSAIDs	340,582	1,606	471.55	0.76	0.81 (0.76, 0.86)
Cox-2 Inhibitors	269,773	519	192.38	0.31	0.21 (0.19, 0.23)
None	278,104	1,723	619.55	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; Cox, cyclo-oxygenase; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 8.14: Effect of specific NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort

NSAID exposure	Person-years	Breast cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	53,198	63	118.43	1.12	0.79 (0.61, 1.03)
Non-Selective Cox Inhibitors	348,952	477	136.70	1.30	
Fenoprofen	6,927	13	187.67	1.78	1.21 (0.70, 2.11)
Ibuprofen	145,548	196	134.66	1.28	0.81 (0.69, 0.96)
Idomethacin	43,385	60	138.30	1.31	0.93 (0.71, 1.22)
Naproxen	127,745	186	145.60	1.38	0.95 (0.80, 1.14)
Sulindac	28,123	32	113.78	1.08	0.88 (0.61, 1.25)
Others NSAIDs	226,379	288	127.22	1.21	0.83 (0.71, 0.97)
None	343,881	362	105.27	Reference	Reference
NSAID exposure	Person-years	Cervical cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	53,532	13	24.28	1.42	1.04 (0.57, 1.89)
Non-Selective Cox Inhibitors	350,324	77	21.98	1.28	
Fenoprofen	6,973	6	86.05	5.02	3.34 (1.44, 7.77)
Ibuprofen	146,349	33	22.55	1.32	0.81 (0.53, 1.24)
Idomethacin	43,547	8	18.37	1.07	0.75 (0.36, 1.56)
Naproxen	128,429	31	24.14	1.41	0.98 (0.63, 1.52)
Sulindac	28,244	5	17.70	1.03	0.85 (0.34, 2.12)
Others NSAIDs	227,327	43	18.92	1.10	0.65 (0.43, 0.97)
None	344,122	59	17.15	Reference	Reference
NSAID exposure	Person-years	Endometrial Cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	53,549	8	14.94	1.07	0.71 (0.34, 1.50)
Non-Selective Cox Inhibitors	350,406	61	17.41	1.25	
Fenoprofen	6,991	2	28.61	2.05	0.97 (0.22, 4.17)
Ibuprofen	146,385	31	21.18	1.52	0.95 (0.61, 1.49)
Idomethacin	43,569	15	34.43	2.47	1.79 (1.01, 3.16)
Naproxen	128,549	21	16.34	1.17	0.61 (0.36, 1.02)
Sulindac	28,265	6	21.23	1.52	1.15 (0.49, 2.68)
Others NSAIDs	227,364	40	17.59	1.26	0.79 (0.51, 1.21)
None	344,115	48	13.95	Reference	Reference
NSAID exposure	Person-years	Ovarian cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	53,529	14	26.15	1.76	0.95 (0.53, 1.70)
Non-Selective Cox Inhibitors	350,331	82	23.41	1.58	
Fenoprofen	6,959	5	71.85	4.85	2.37 (0.94, 5.93)
Ibuprofen	146,318	45	30.75	2.08	1.19 (0.81, 1.76)
Idomethacin	43,586	10	22.94	1.55	0.82 (0.42, 1.60)
Naproxen	128,481	30	23.35	1.58	0.75 (0.48, 1.16)
Sulindac	28,256	9	31.85	2.15	1.44 (0.72, 2.87)
Others NSAIDs	227,287	50	22.00	1.48	0.75 (0.50, 1.11)
None	344,139	51	14.82	Reference	Reference

Table 8.14 (continue); Effect of specific NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort

NSAID exposure	Person-years	GI events (female only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	51,607	397	769.27	2.16	0.94 (0.84, 1.05)
Non-Selective Cox Inhibitors	343,112	2,192	638.86	1.80	
Fenoprofen	6,724	75	1,115.42	3.14	1.21 (0.96, 1.53)
Ibuprofen	142,499	910	638.60	1.80	0.76 (0.70, 0.82)
Idomethacin	42,188	282	668.44	1.88	0.85 (0.75, 0.96)
Naproxen	124,893	822	658.17	1.85	0.75 (0.69, 0.82)
Sulindac	27,679	180	650.30	1.83	0.93 (0.80, 1.08)
Others NSAIDs	221,762	1,403	632.66	1.78	0.73 (0.68, 0.78)
None	342,979	1,220	355.71	Reference	Reference
NSAID exposure	Person-years	Renal events (female only)	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	52,905	214	404.50	1.53	0.97 (0.85, 1.11)
Non-Selective Cox Inhibitors	347,554	1,179	339.23	1.29	
Fenoprofen	6,912	30	434.03	1.65	1.01 (0.75, 1.37)
Ibuprofen	144,855	484	334.13	1.27	0.65 (0.58, 0.72)
Idomethacin	42,780	233	544.65	2.07	0.98 (0.84, 1.13)
Naproxen	127,371	447	350.94	1.33	0.73 (0.65, 0.81)
Sulindac	27,910	135	483.70	1.84	1.10 (0.92, 1.31)
Others NSAIDs	225,437	669	296.76	1.13	0.54 (0.49, 0.60)
None	343,412	905	263.53	Reference	Reference

NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal

** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 8.15: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort after excluding 47,674 persons admitted to LTC >1 year.

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Breast Cancer	Any Use	591,685	1,296	219.04	0.67	0.48 (0.43, 0.54)
	None	174,282	567	325.33	Reference	Reference
Cervical Cancer	Any Use	596,612	221	37.04	0.63	0.43 (0.34, 0.55)
	None	174,401	103	59.06	Reference	Reference
Endometrial Cancer	Any Use	597,005	154	25.80	0.73	0.42 (0.31, 0.58)
	None	174,406	62	35.55	Reference	Reference
Ovarian Cancer	Any Use	596,771	238	39.88	0.73	0.49 (0.38, 0.63)
	None	174,375	95	54.48	Reference	Reference
GI Events (female only)	Any Use	574,714	4,461	776.21	0.90	0.41 (0.39, 0.44)
	None	174,031	1,494	858.47	Reference	Reference
Renal Events (female only)	Any Use	585,731	3,422	584.23	0.73	0.32 (0.30, 0.35)
	None	173,464	1,396	804.78	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 8.16: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort after excluding 167 persons admitted to LTC >1 year.

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Breast Cancer	Any Use	358,923	488	135.96	1.29	0.90 (0.78, 1.04)
	None	343,090	361	105.22	Reference	Reference
Cervical Cancer	Any Use	360,316	80	22.20	1.29	0.87 (0.61, 1.24)
	None	343,329	59	17.18	Reference	Reference
Endometrial Cancer	Any Use	360,403	61	16.93	1.21	0.64 (0.43, 0.97)
	None	343,322	48	13.98	Reference	Reference
Ovarian Cancer	Any Use	360,323	84	23.31	1.57	0.91 (0.63, 1.32)
	None	343,346	51	14.85	Reference	Reference
GI Events (female only)	Any Use	353,013	2,252	637.94	1.79	0.71 (0.66, 0.77)
	None	342,185	1,217	355.66	Reference	Reference
Renal Events (female only)	Any Use	357,496	1,220	341.26	1.29	0.53 (0.48, 0.58)
	None	342,620	904	263.85	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

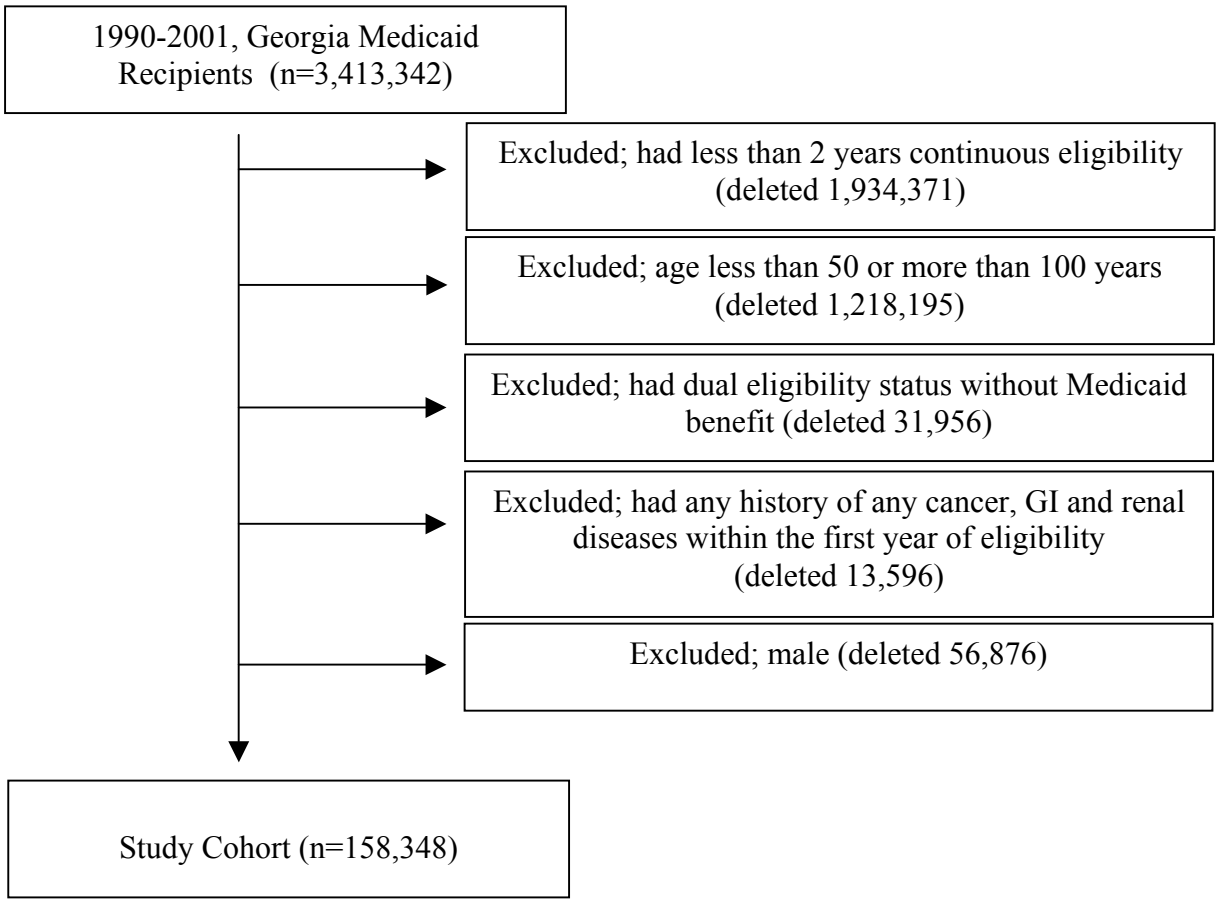

Figure 8.1: Flow chart of Georgia Medicaid cohort subjects

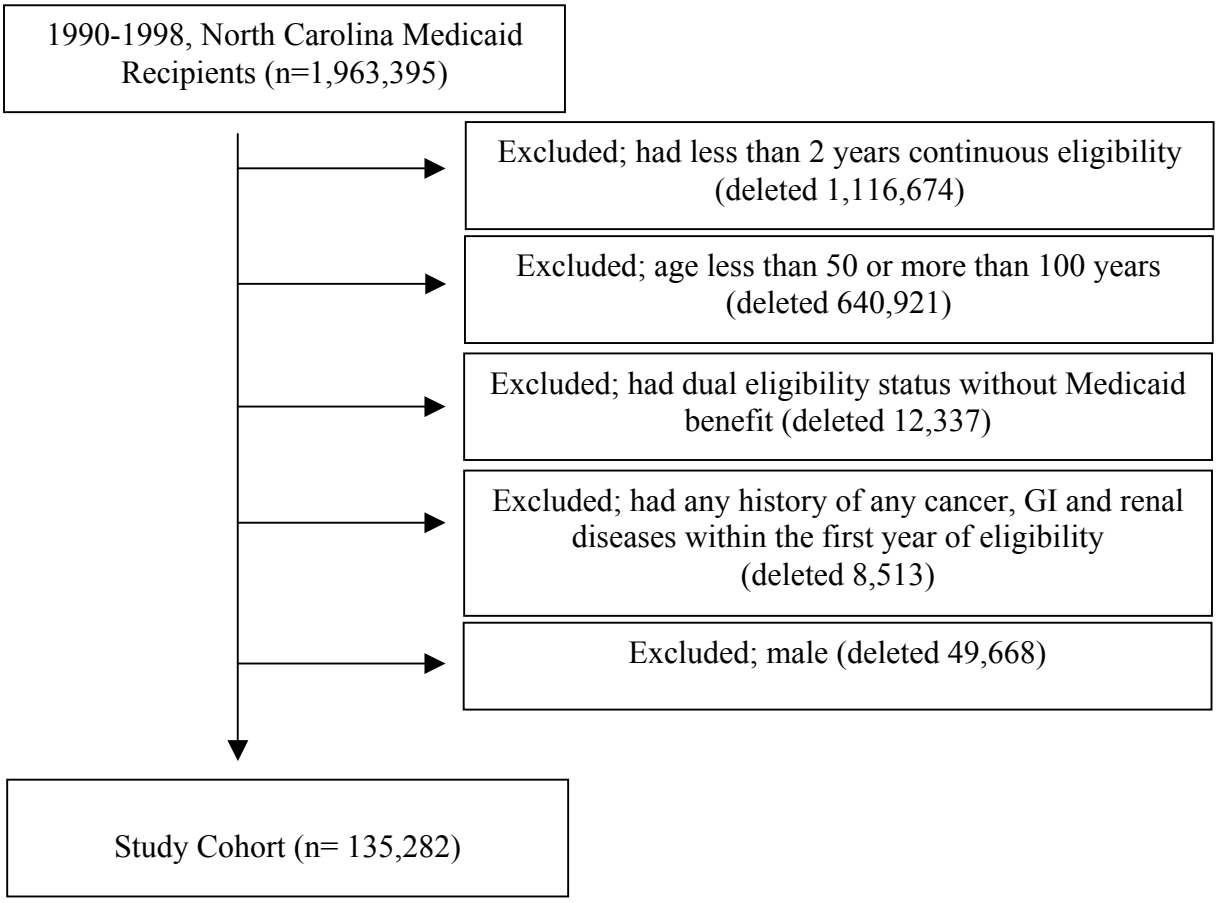

Figure 8.2: Flow chart of North Carolina Medicaid cohort subjects

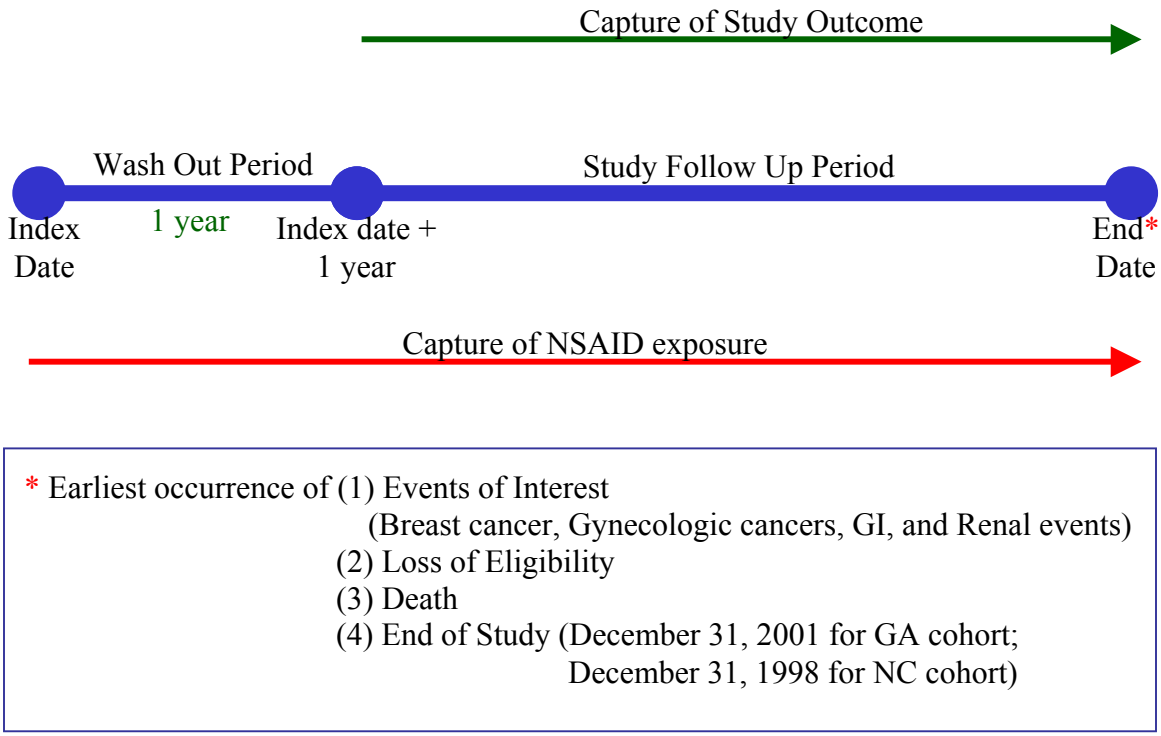

Figure 8.3: Temporal pattern of cohort

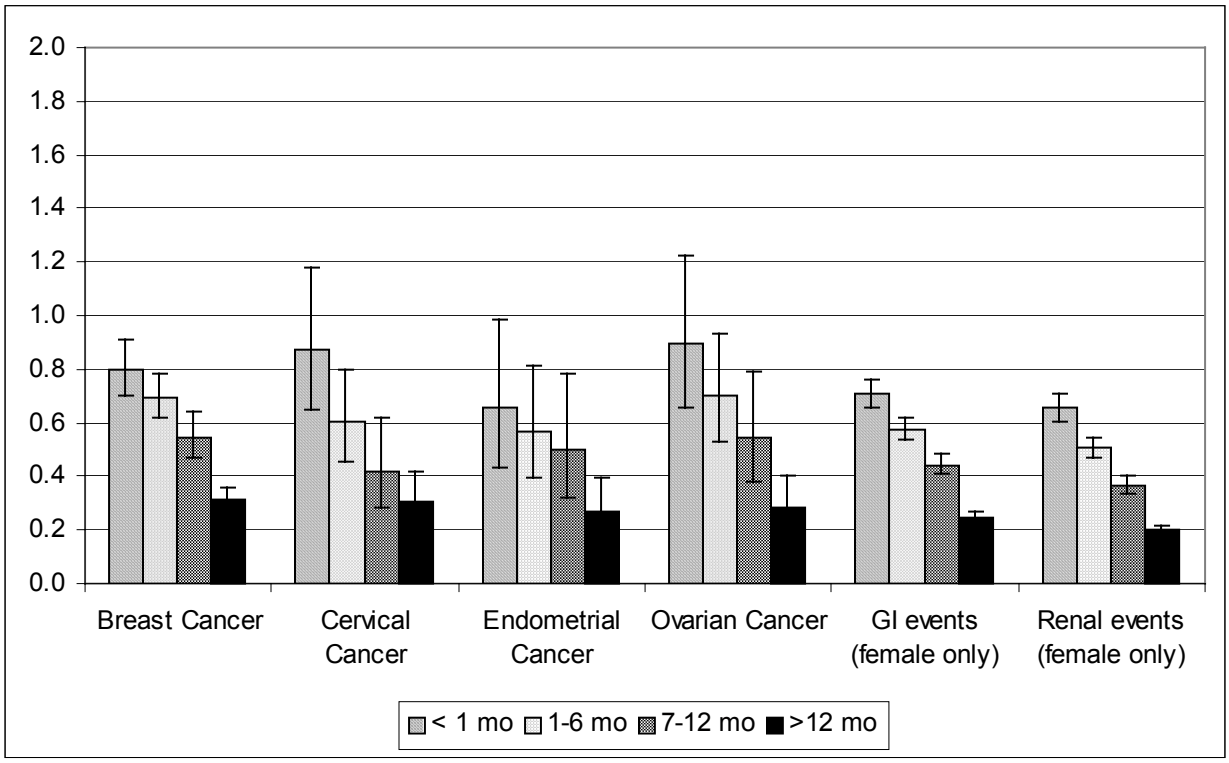

Figure 8.4: Effect of Cumulative NSAID exposure on the Relative Risk of Breast cancer, Gynecologic cancers, GI and Renal events in Georgia Cohort.

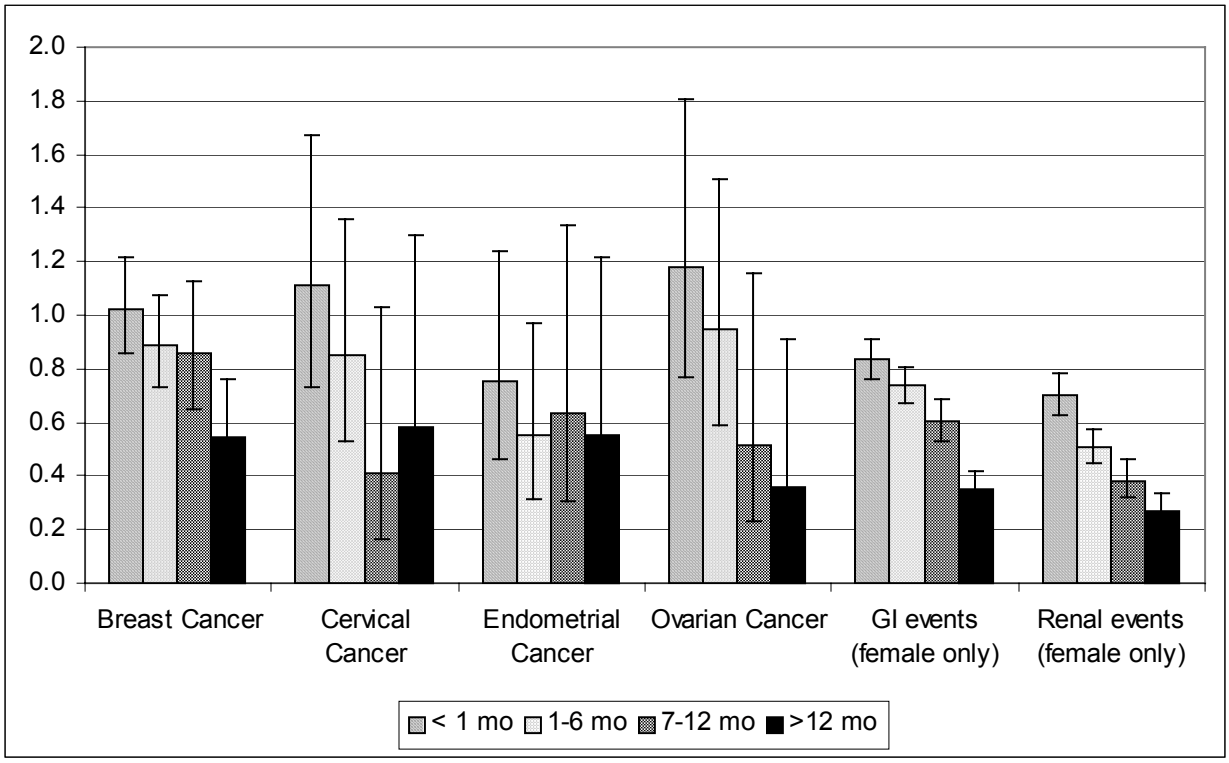

Figure 8.5: Effect of Cumulative NSAID exposure on the Relative Risk of Breast cancer, Gynecologic cancers, GI and Renal events in North Carolina Cohort.

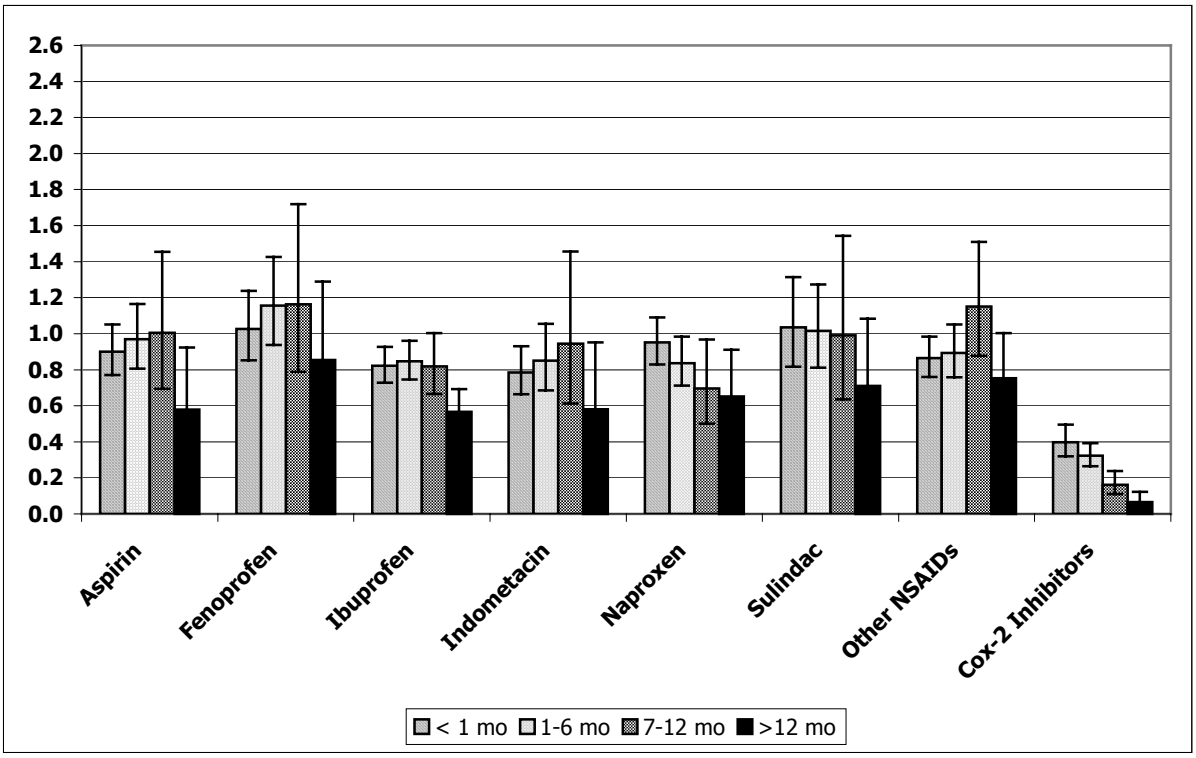

Figure 8.6: Cumulative Exposure Effect of specific NSAIDs on Breast Cancer in Georgia Medicaid Cohort

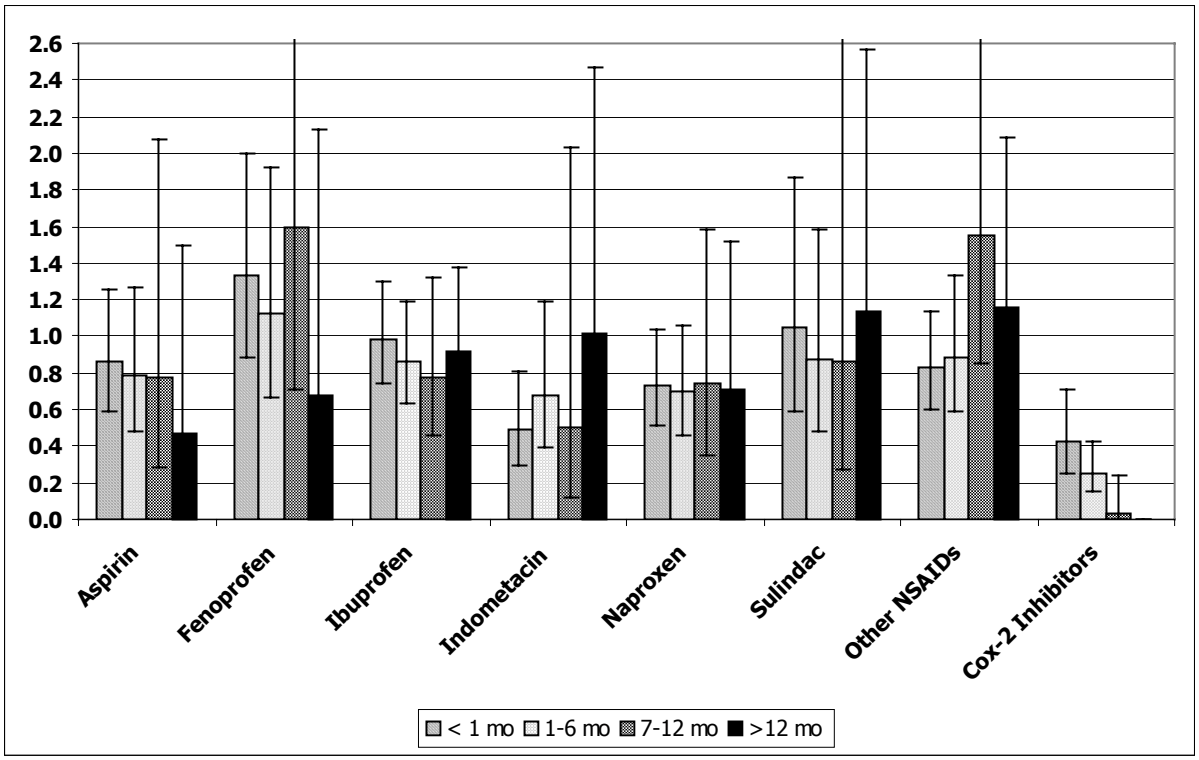

Figure 8.7: Cumulative Exposure Effect of specific NSAIDs on Cervical Cancer in Georgia Medicaid Cohort

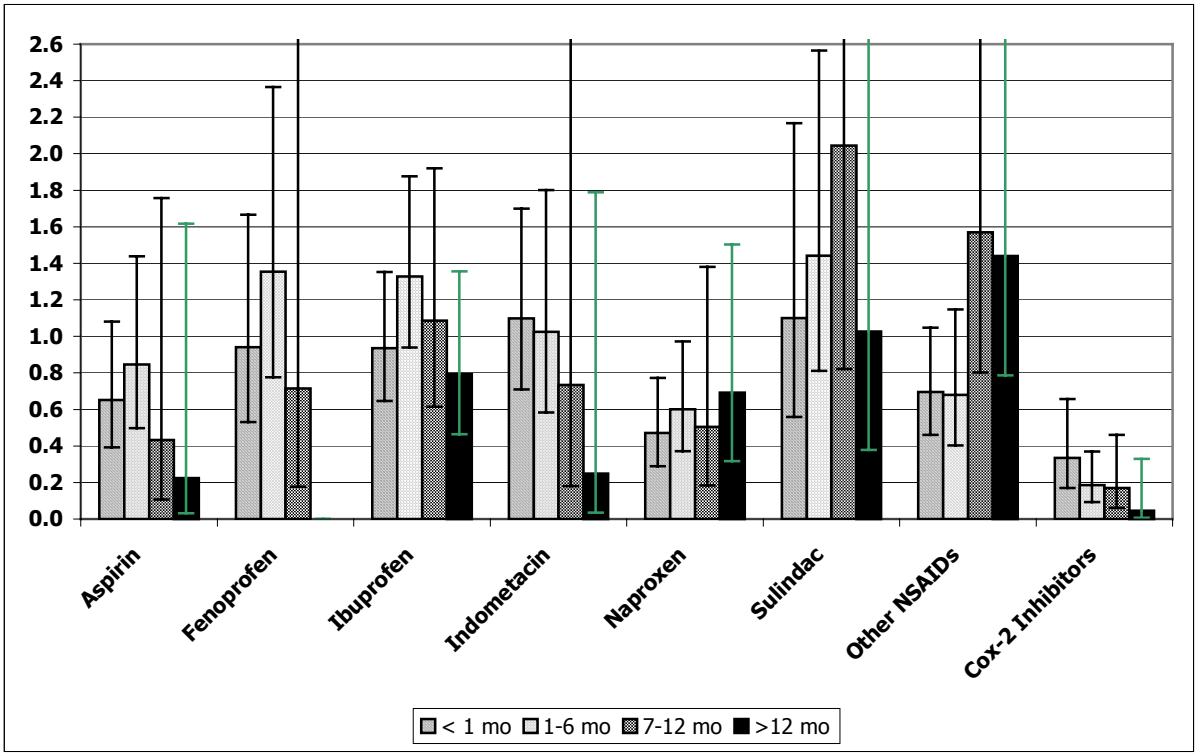

Figure 8.8: Cumulative Exposure Effect of specific NSAIDs on Endometrial cancer in Georgia Medicaid Cohort

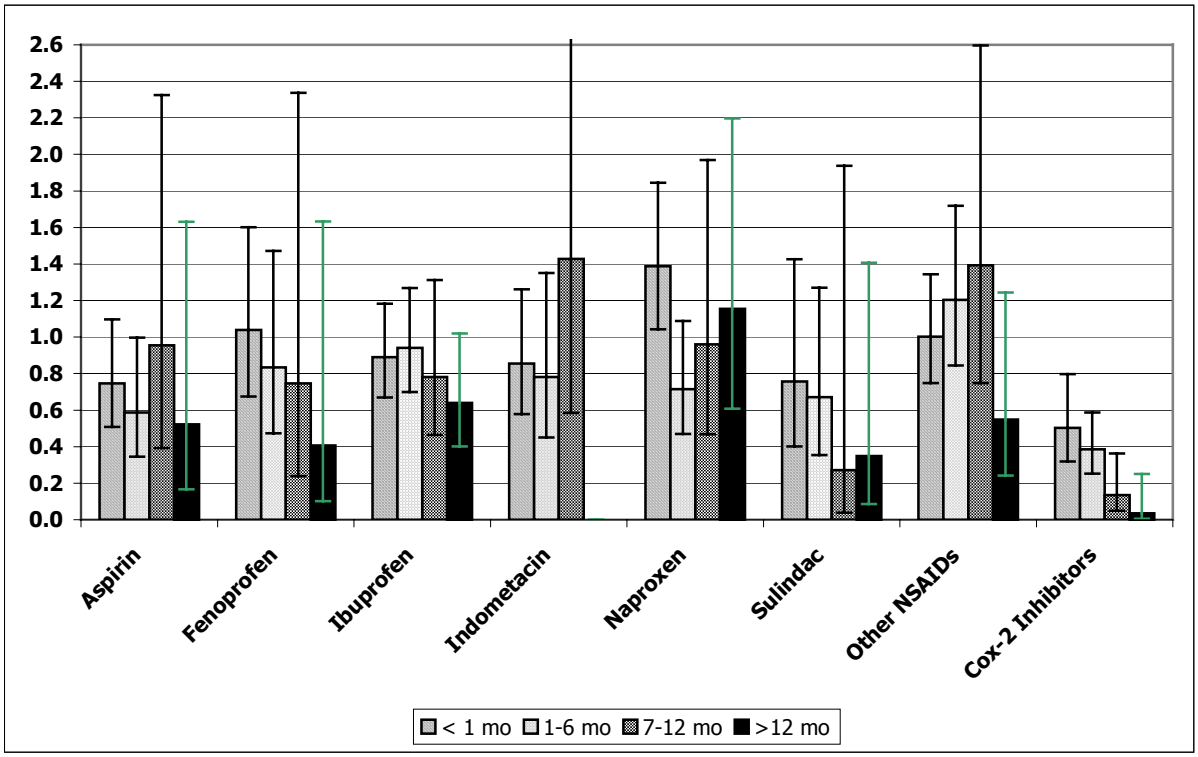

Figure 8.9: Cumulative Exposure Effect of specific NSAIDs on Ovarian Cancer in Georgia Medicaid Cohort

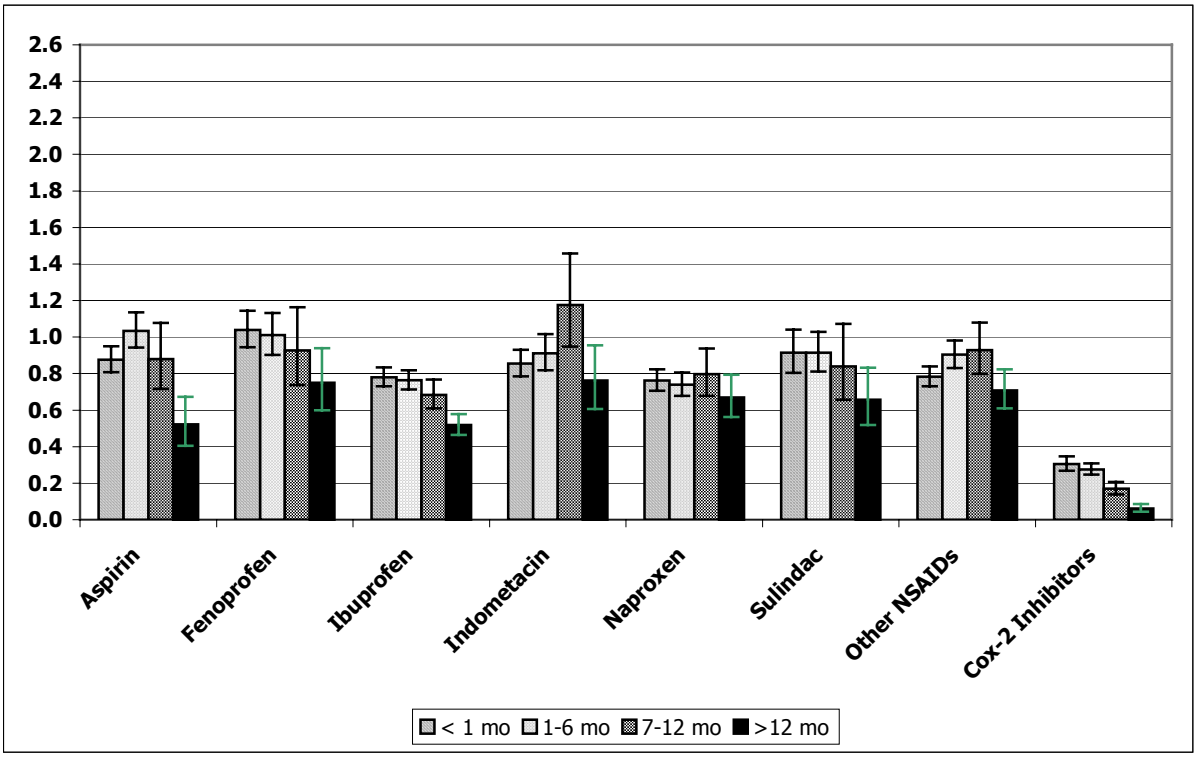

Figure 8.10: Cumulative Exposure Effect of specific NSAIDs on GI events in Georgia Medicaid Cohort

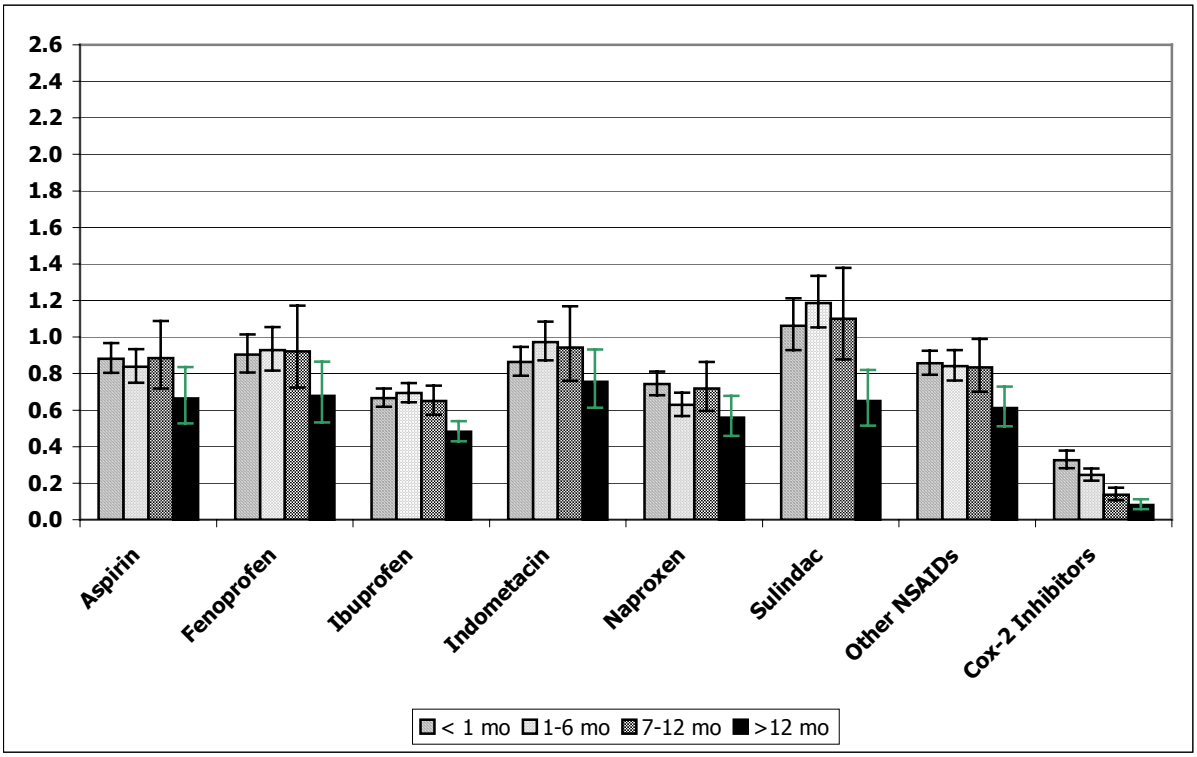

Figure 8.11: Cumulative Exposure Effect of specific NSAIDs on Renal events in Georgia Medicaid Cohort

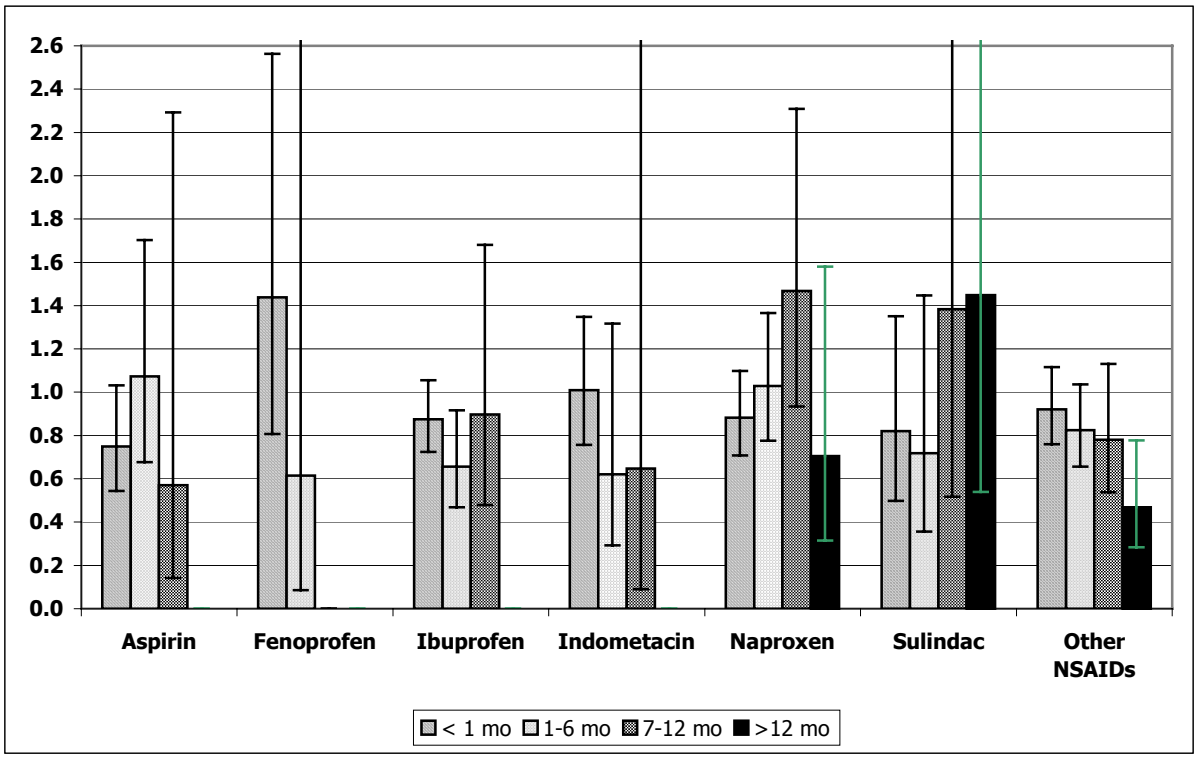

Figure 8.12: Cumulative Exposure Effect of specific NSAIDs on Breast Cancer in North Carolina Medicaid Cohort

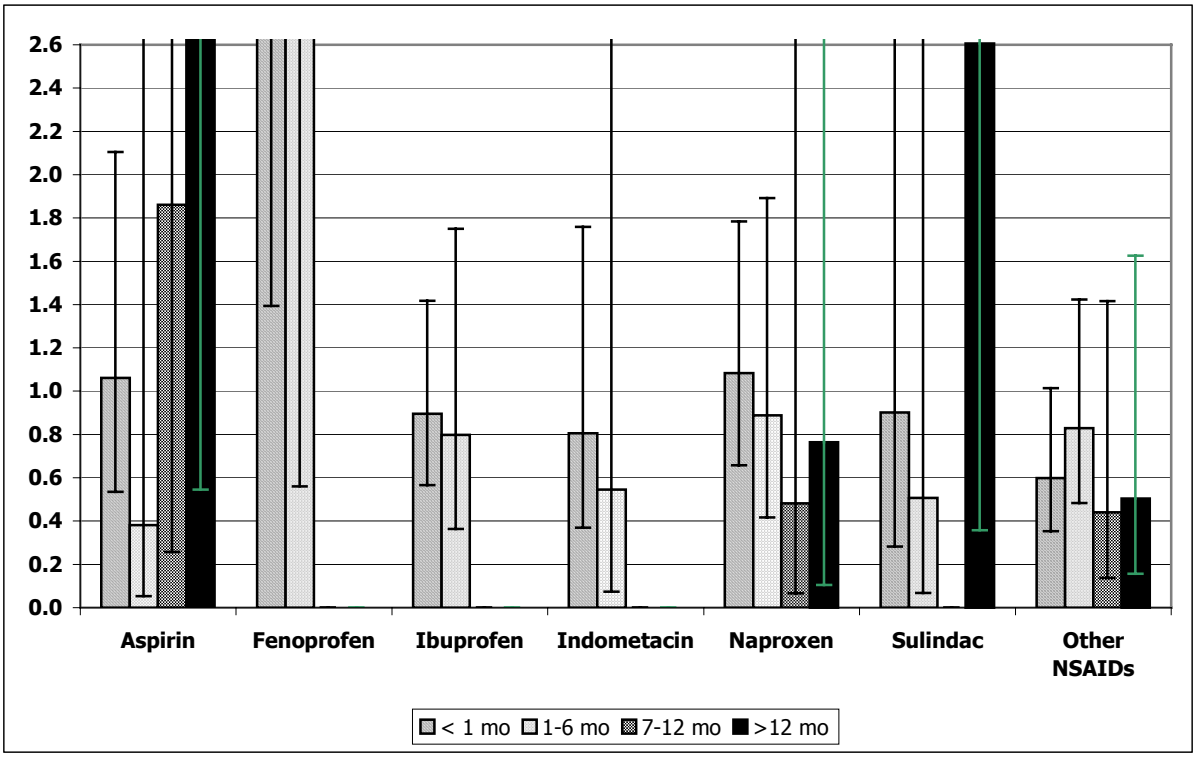

Figure 8.13: Cumulative Exposure Effect of specific NSAIDs on Cervical Cancer in North Carolina Medicaid Cohort

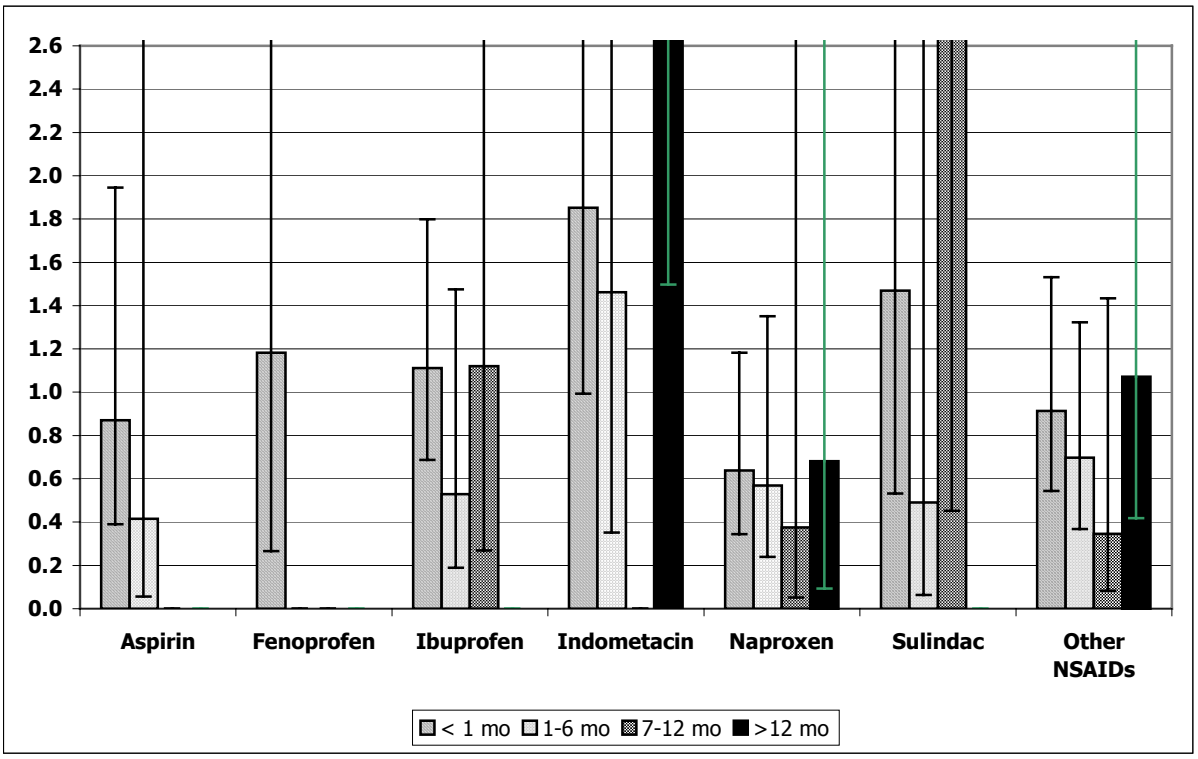

Figure 8.14: Cumulative Exposure Effect of specific NSAIDs on Endometrial Cancer in North Carolina Medicaid Cohort

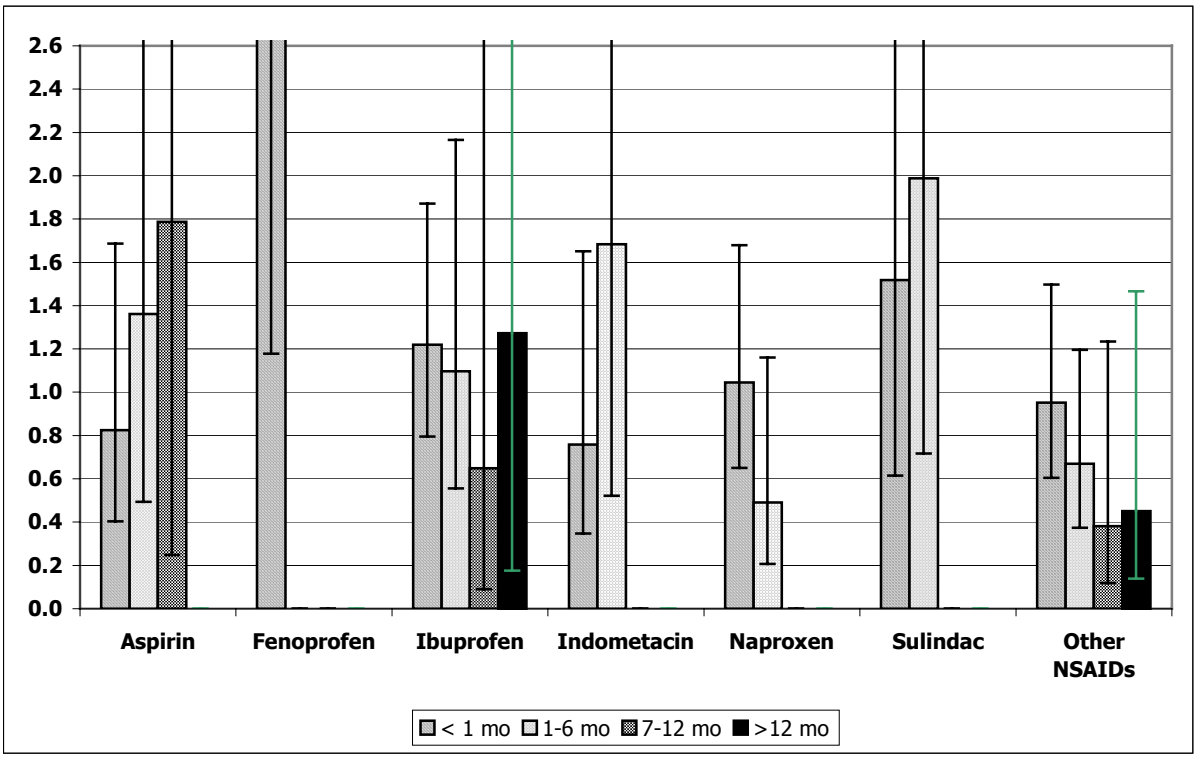

Figure 8.15: Cumulative Exposure Effect of specific NSAIDs on Ovarian Cancer in North Carolina Medicaid Cohort

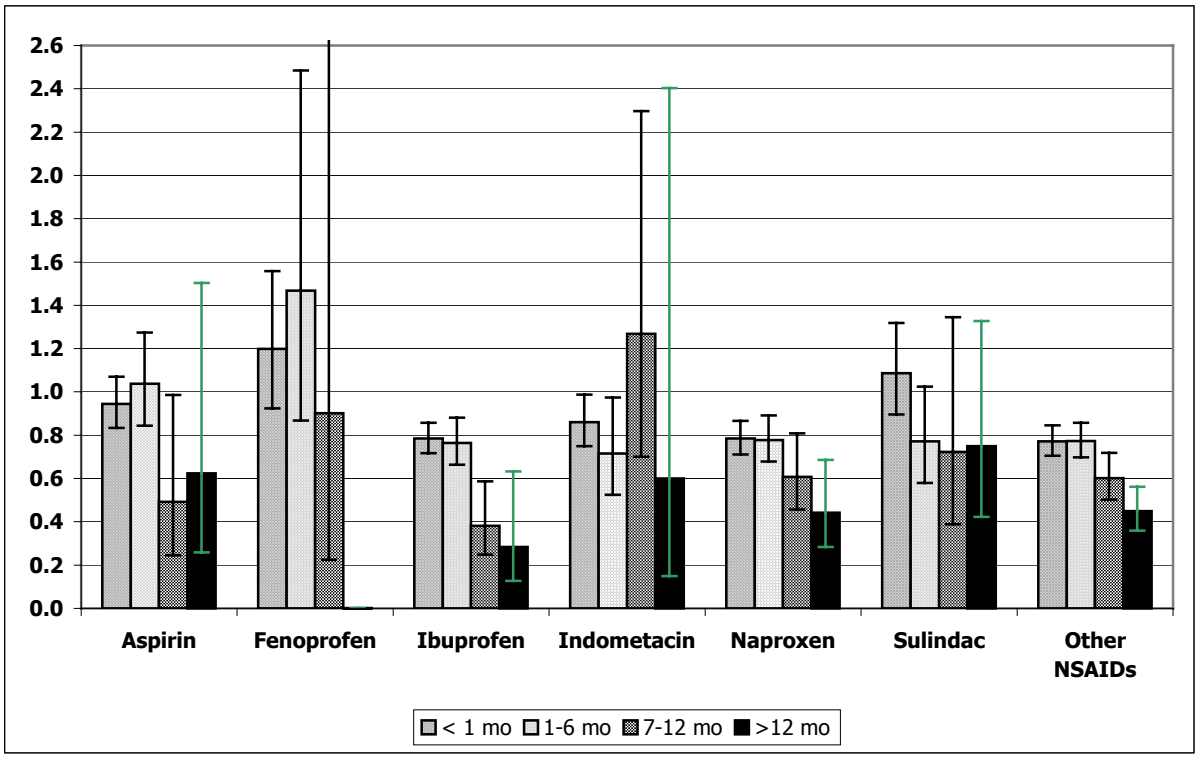

Figure 8.16: Cumulative Exposure Effect of specific NSAIDs on GI events in North Carolina Medicaid Cohort

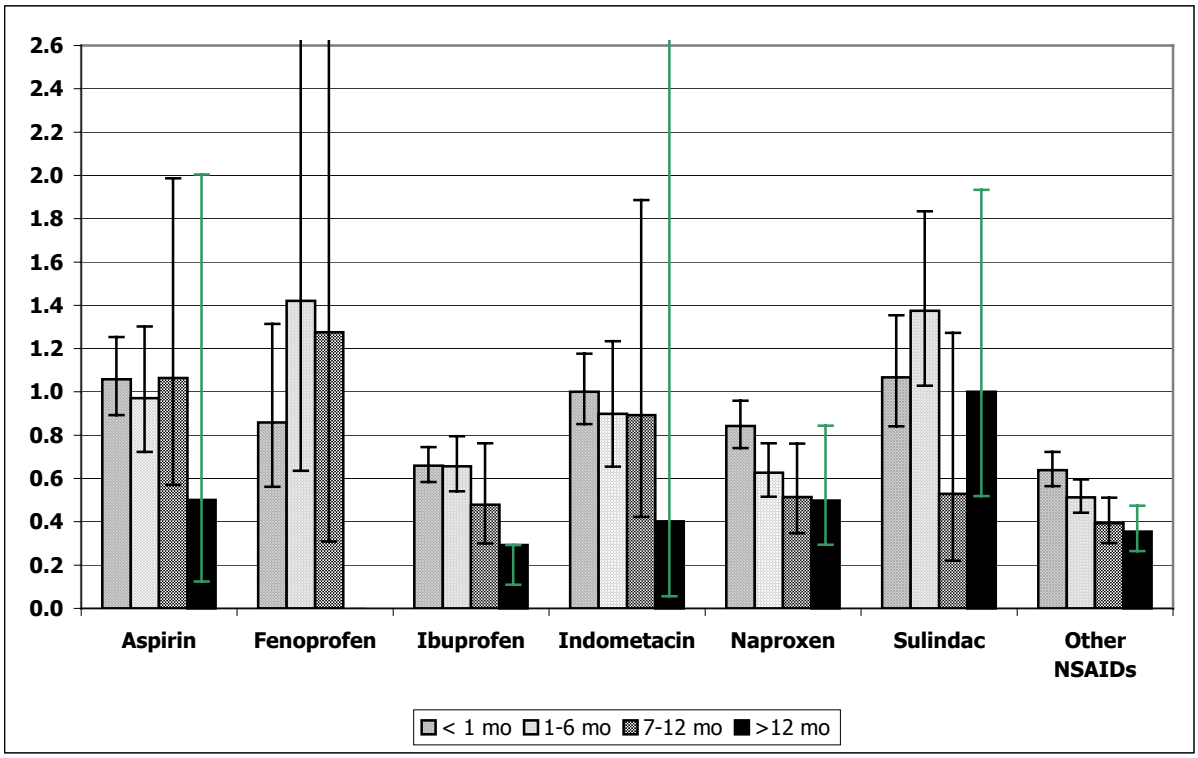

Figure 8.17: Cumulative Exposure Effect of specific NSAIDs on Renal events in North Carolina Medicaid Cohort

CHAPTER 9

THE RISK-BENEFIT PROFILE OF NSAIDS AS CHEMOPREVENTIVES AGAINST DIGESTIVE AND URINARY TRACT CANCERS [5]

[5] Koompalum D., Vidyashankar A.N., Dainer P.M., Naeher L.P., Kotzan J.A., and Martin B.C. To be submitted to Cancer Epidemiology Biomarkers and Prevention.

Abstract

Background: Since the protective effect of NSAID use on the risk of colorectal cancer has been documented, many researchers have raced to study the possible effects of NSAID use on the risk of other cancers and some found supportive evidence. However, before the use of NSAIDs to prevent various cancers can be considered, we need a better understanding of the risk-benefit profile of NSAIDs. The potential benefit of NSAID usage on many types of cancers must be weighed against the risks of NSAID-induced adverse events, which primarily include gastrointestinal (GI) and renal impairments

Objective: This study sought to identify any association between NSAID usage and incidence of digestive and urinary tract cancers, as well as NSAID-related adverse events, GI and renal events.

Methods: Two retrospective cohort studies were conducted using Georgia (GA) and North Carolina (NC) Medicaid claims. Subjects aged 50-100, who had at least 2 years of continuous eligibility, were analyzed. We excluded subjects that had any diagnoses of cancer, GI, or renal diseases within their first year eligibility. Each cohort was followed until the earliest occurrence of: (1) outcomes of interest: digestive cancers, urinary tract cancers, GI events (i.e. GI Ulcers and GI hemorrhage) and renal events (e.g. renal failure and glomerulonephritis), (2) loss of eligibility, (3) death, or (4) end of study (December 31, 2001 for GA cohort and December 31, 1998 for NC cohort). All outcome occurrences were dated and determined by searching for claims with ICD-9-CM codes indicative of the outcome events. NSAID exposure was identified by searching the National Drug Code (NDC) in the prescription files. For each NSAID prescription, the strength and prescribed quantifies were kept to further explore a dose-response relationship. Survival Analysis (Cox-Proportional Hazard) technique was used to calculate all

relative risks.

Results: Out of 215,224 Medicaid recipients in the GA cohort, 62% were exposed to an NSAID. The risks of digestive cancers, urinary tract cancers and NSAID-related adverse events were inversely correlated with any NSAID exposure; after adjusting for several covariates, the relative risks were 0.60 (95%CI, 0.53 to 0.67), 0.40 (95%CI, 0.32 to 0.50), 0.56 (95%CI, 0.47 to 0.67), 0.60 (95%CI, 0.51 to 0.72), 0.92 (95%CI, 0.71 to 1.20), 0.61 (95%CI, 0.49 to 0.75), 0.71 (95%CI, 0.54 to 0.92), 0.49 (95%CI, 0.47 to 0.51), and 0.40 (95%CI, 0.38 to 0.42) for colorectal cancer, esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events, respectively. The NC Medicaid cohort contained 184,950 beneficiary and 43% were exposed to an NSAID. The multivariate-adjusted relative risks of colorectal cancer, esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events were 0.73 (95%CI, 0.62 to 0.86), 0.49 (95%CI, 0.34 to 0.71), 0.77 (95%CI, 0.58 to 1.03), 0.83 (95%CI, 0.64 to 1.09), 0.68 (95%CI, 0.47 to 1.40), 0.80 (95%CI, 0.55 to 1.16), 0.69 (95%CI, 0.65 to 0.73), and 0.54 (95%CI, 0.50 to 0.58), respectively. Persons prescribed Cox-2 inhibitors were at the lowest risks of digestive cancers, urinary tract cancers, and NSAID-related adverse effects. While there was no association between aspirin exposure and risks of all digestive and urinary tract cancers, the benefit of ibuprofen against gastric cancer was revealed, 30% reduced risk of gastric cancer. NSAIDs did not increase risk of both NSAID-related adverse events in this study. The increased cumulative exposure of NSAIDs was associated with decreased rates of digestive cancer, urinary tract cancer, GI and renal events. The protective effects of long-term NSAID use against digestive cancer, urinary tract cancer, GI and renal events were confirmed, besides bladder cancer.

Conclusion: the protective effects of NSAID use on the risk of colorectal and esophageal cancer was established. Whether or not persons exposed to NSAIDs did not impact the chance of developing pancreatic cancer. An increase in risk of NSAID-related adverse events was not associated with NSAID usage.

Background

Since the protective effect of NSAID use on the risk of colorectal cancer has been documented, many researchers have raced to study the possible effects of NSAID use on the risk of other cancers. Recent Danish population-based cohort studies {Sorensen 2003, Friis 2003} compared cancer incidence among persons prescribed low-dose aspirin (29,470 persons) and other NSAIDs (172,057 persons) with regional cancer rates. While protective associations of non-ASA-NSAIDs against stomach and ovarian cancer were found {Sorensen 2003}, increased risk of cancer of the kidney was observed in persons both prescribed low-dose aspirin and non-aspirin NSAIDs {Sorensen 2003, Friis 2003}. Bosetti and colleagues determined the role of aspirin on the risk of cancers of the upper aerodigestive tract, including oral, esophagus, pharyngeal and laryngeal cancer by using 3 hospital-based case-control studies (1,362 cases and 3036 controls){Bosetti 2003}. Interview-administered questionnaire was used to assess aspirin intake. Although non-significant risk reduction reported in persons who regularly used aspirin for at least once a week for more than 6 months, ones exposed to aspirin for at least 5 years were less likely to be diagnosed of cancers of the upper aerodigestive tract (OR,0.33; 95%CI,0.13-0.82) {Bosetti 2003}. A recent meta-analysis of 9 studies (2 cohort, 7 case-control) by Corley and colleague revealed a significant protective association between any use of NSAIDs and esophageal cancer (OR, 0.57; 95% CI, 0.47-0.71), both intermittent (OR, 0.82; 95% CI, 0.67-

0.99) and frequent use (OR, 0.54; 95% CI, 0.43-0.67) {Corley 2003}. The greater protection was observed with aspirin use (OR, 0.5; 95% CI, 0.38-0.66) than non-aspirin NSAID use (OR, 0.75; 95% CI, 0.54-1.00) {Corley 2003}.

A systemic review and meta-analysis of published studies up to January 2003 to evaluate the association between use of NSAIDs and the risk of gastric cancer {Wang 2003}. Based on 9 studies (8 case-control, 1 cohort) with a total of 2831 gastric cancer cases, NSAID use was associated with a reduced risk of gastric cancer, with summary odd ratio of 0.78 (95%CI 0.69 to 0.87). Users of aspirin (OR 0.57; 95%CI 0.63-0.86) and non-aspirin NSAIDs (0.74; 0.55-1.00) experienced similar magnitudes of risk reduction.

Most studies examining a correlation between NSAID use and incidence of pancreatic cancer reported a lack of association {Friis 2003, Langman 2000, Sorensen 2003, Menezes 2002, Schernhammer 2004}. Contrarily, Anderson and colleagues demonstrated a reduced risk for aspirin users in a prospective cohort of 28,283 post-menopausal women who lived in Iowa {Anderson 2002} as well as a decreasing risk with increased weekly aspirin use. It is noted that a non-significant increased risk of pancreatic cancer was reported in women who used only non-aspirin NSAIDs. Increasing duration of regular aspirin use, compared with non-use, was associated with a statistically significant increase in risk in another more recent prospective cohort of 88,378 women. Women who reported more than 20 years of regular aspirin use had an increased risk of pancreatic cancer (RR 1,58; 95%CI 1.03-2.43; p[trend] =0.01). Among women who reported aspirin use on at least 2 of 3 consecutive biennial questionnaires compared with consistent non-users of aspirin, the risk increased with dose. Extended periods of regular aspirin use appear to be associated with a significantly increased risk of pancreatic cancer among women { Schernhammer 2004}.

The Danish population-based cohort studies demonstrated 20% increased risk of bladder cancer in persons reported having NSAID intake {Friis 2003, Sorensen 2003}. On the contrary, a case-control study by Castelao {Castelao 2000} investigating the relation of chronic use of OTC and prescription analgesics and bladder cancer risk reported an inverse, dose-dependent association, except for pyrazolon derivative (i.e. phenylbutazone).

Adverse effects of NSAIDs including GI complications (i.e. GI bleeding, perforation, and ulcer) and renal complications (i.e. acute renal failure) are a major limitation of the use of NSAIDs as chemopreventives. NSAID related GI complications are the major concern for NSAID users. A recent meta-analysis of the risk of NSAID related GI complications, by Ofman et al, reported that NSAID users are 3-5 times more likely to have GI complications than nonusers {Ofman 2002, Gabriel 1991}. However, what is less clear is the impact of long term NSAID use on GI complications, since an earlier meta-analysis {Gabriel 1991} and several observational studies {Garcia Rodriguez 1998, Smalley 1995} reported decreasing risk of GI complications when NSAIDs were taken over longer durations. For instance, among current users, the constant risk of GI complications was found during the first year of NSAID use and was roughly 7 times more likely than non-user {Garcia Rodriguez 1998}. The risk of GI complications, however, drop nearly half for NSAID exposure >1 year. (RR, 3.5; 95%CI, 2.0 to 6.0) {Garcia Rodriguez 1998}.

Another major complication of NSAIDs involves deterioration in renal function which typically manifest in acute renal failure which may lead to chronic renal failure and end-stage renal disease, especially in persons with pre-existing renal diseases {Hernandez-Diaz 2001}. For instance, persons with cirrhosis, heart failure, renal disease, diabetes, advanced age, heart failure, hypertension, and those exposed to neprotoxic medications, i.e. diuretics, NSAIDs, angiotensin-

converting enzyme (ACE) inhibitors, and some antibiotics are at higher risk of acute renal failure {Fored 2001, Griffin 2000, Hernandez-Diaz 2001, Perneger 1994, Rexrode 2001, Bailie 1995Hernandez-Diaz 2001, Henry 1992}. Griffin and colleagues reported that persons who currently used NSAIDs were almost 1.6 times more likely to be hospitalized for acute renal failure than ones who never used NSAID (OR,1.58, 95%CI, 1.34-1.86). The highest risk was observed within first 30 days of use, although the risk was similar in those discontinued NSAID use for at least 30 days {Griffin 2000}. Regular use of NSAID increased the risk of chronic renal failure 2.5 fold (95%CI, 1.9-3.3) {Fored 2001}, and the risk rises with increasing lifetime cumulative dose of NSAIDs. Similar rising risk of ESRD with cumulative dose of NSAIDs have been reported elsewhere {Perneger 1994}. In contrast to most of the findings previously described, the Physician's Heath Cohort study contrarily showed no association between self-reported cumulative NSAID uses over 14 year and risk of renal dysfunction in men {Rexrode 2001}.

Before NSAIDs can be considered as chemopreventives, we need a better understanding of the risk-benefit profile of NSAIDs. In this study, we aimed to describe the relationship of NSAIDs with the risks of digestive and urinary tract cancers, as well as NSAID-related GI and renal adverse events using two Medicaid cohorts: Georgia and North Carolina Medicaid.

Methods

Data Source

We simultaneously conducted 2 retrospective cohort studies utilizing administrative claims data of the Medicaid program from 2 states: Georgia and North Carolina. The Medicaid, jointly funded by the Federal and State governments, is health insurance that assists certain

individuals and families with low incomes and resources in providing medical and health-related services for people with limited income, who meet eligibility criteria. Adults eligible for Medicaid benefits include some low-income residents, medically needy individuals, the elderly, and people with disabilities if state and federal guidelines are met.

The Georgia Medicaid administrative claims data capture all reimbursed medical encounters of the Georgia Medicaid recipients. The GA Medicaid database contains an annual enrollment of approximately 1.2 million eligible persons per year, which provides patient level details on recipient demographics, including patient identifier, date of birth, gender, race, date of dead, as well as monthly Medicaid coverage (eligibility information). All Medicaid beneficiaries' medical utilization, including inpatient, outpatient, nursing home, and emergency services, is collected in the medical claim file. The pharmacy claims file records each reimbursed prescription including information describing the date prescriptions are filled, drug name, National Drug Code (NDC), strength, dosage, and number of units dispensed. All three of the files are linked by encrypted recipient identifier allowing the construction of person level analytic files where treatments and ensuing medical encounters can be measured at the patient level.

Similarly, the North Carolina Medicaid claims database is an administrative claim data of the North Carolina Medicaid recipients' medical encounters. There are roughly 1 million North Carolina Medicaid recipients per year. NC Medicaid data contain patient level details on demographics, monthly coverage, non-prescription medical utilization, and pharmacy claim file, all of which are linked by encrypted recipient identifier.

Subjects

In both cohorts, the study subjects were between the ages of 50 and 100 years, who had at least 2 years of continuous eligibility. We excluded subjects who had any diagnosis of cancer, GI or renal disease within their first year eligibility, and any recipients with dual Medicare eligibility without full Medicaid coverage (figures 9.1-9.2). The cohort was followed until the earliest occurrence of: (1) outcomes of interest, digestive cancers, urinary tract cancers, GI events (i.e. GI ulcers and GI hemorrhage), and renal events (e.g. renal failure), (2) loss of eligibility, (3) death, or (4) end of study (figure 9.3).

Identification of Digestive Cancers, Urinary Tract Cancers, GI and Renal Events

To identify incident digestive cancers, urinary tract cancers, GI and renal events, all diagnoses recorded in the medical claims file were searched. All outcome occurrences were dated and determined by searching for claims with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes indicative of the outcome events described below.

Digestive cancers

Digestive cancers determined in the study consisted of esophageal, gastric, colorectal, liver, and pancreatic cancers. To identify incident digestive cancers, the following ICD-9-CM codes were searched: malignant neoplasms of esophagus (150.x), stomach (151.x), colon (153.x), rectum (154.x), liver (155.x) and pancreas (157.x); secondary malignant neoplasms of liver (197.7), colon and rectum (197.5); benign neoplasms of esophagus (211.0), stomach

(211.1), colon (211.3), rectum (211.4), liver (211.5), and pancreas (211.6) ; carcinoma in situ of esophagus (230.1), stomach (230.2), colon (230.3), rectum (230.4), liver (230.8) and pancreas (230.9) {Thun 1993, the National Cancer Institutes 1997}.

Urinary tract cancers

Two urinary tract cancers were included in this study: bladder and kidney cancer. We used ICD-9-CM codes of carcinoma in situ (233.7), benign (223.3), malignant neoplasms (188.x) of bladder, as well as benign (223.0, 223.1), malignant neoplasms (189.x) of kidney {Thun 1993, the National Cancer Institutes 1997}.

Gastrointestinal (GI) Events

The GI events were defined as upper gastrointestinal bleeding, perforation, or ulcer. A subject with any diagnosis of gastric ulcer (531.x), duodenal ulcer (532.x), gastrojejunal ulcer (534.x), peptic ulcer (533.x), and gastrointestinal hemorrhage (578.x) was identified { Smalley 1995}. The positive predictive value of these codes were previously reported as 97%, 84%, 80%, and 59% with hospital clinical records for 531.x-532.x, 534.x, 533.x, and 578.x, respectively {Cattaruzzi 1999}.

Renal Events

The renal events are diagnosed cases acute renal failure and other impairment of renal function that is associated with NSAID exposure. The ICD-9-CM algorithm to identify cases of renal events was derived from existing medical literature for potential NSAID-related renal failure {Griffin 2000, Harley 2003, Niecko 2001}. The outcome measures identified by ICD-9-

CM codes were acute glomerulonephritis (580.x), nephrotic syndrome (581.x), non-specified nephritis and nephropathy (583.x), acute renal failure (584.x), renal failure (586.x), disorder of the kidney (593.9), diabetes with renal manifestations (250.4), and hypertension with renal manifestations (403.x, 404.x).

NSAID Exposure

We determined NSAID utilization by searching all prescription codes in the pharmacy claims file for all NSAIDs listed in table 9.1. Only orally administered NSAIDs are relevant to the study. The NDC codes were employed to identify aspirin, NSAID and COX-2 inhibitors prescribed. For those individuals who were prescribed any NSAID, we recorded the generic name, the chemical class, the strength (in milligrams), and the number of units of drug dispensed for each NSAID prescription. In NC cohort, we were unable to determine an impact of Cox-2 inhibitors on study events due to unavailable data; dates approved by FDA of celecoxib and refecoxib were December 1998 and May 1999 respectively.

We define low and high daily dose based on minimum and maximum starting doses recommended for treatment of arthritis as noted in the *Physicians' Desk Reference* {Niecko 2001, Smalley 1999}. Cumulative drug exposure was used to determine prescription NSAID exposure in the study cohort and was defined as the number of units of drug dispensed multiplied by the dose of the drug. All study NSAID dosages were standardized and converted to ibuprofen dosage equivalents. Based on the assumption of equal efficacy among high-dose NSAIDs for the treatment of arthritis, an "ibuprofen weighted" factor is computed. An "ibuprofen weighted" factor equals 2,400 (high daily dose of ibuprofen) divided by the high daily dose recommended for any particular NSAID {Niecko 2001, Smalley 1999}. Then, NSAID use was stratified into

four categories to determine the effect of cumulative exposure on study endpoints. The cumulative exposure was defined as NSAID use equivalent to a period of NSAID use at the highest daily dose: less than one month (ibuprofen equivalents up to 72 grams), 1-6 months (ibuprofen equivalents 72-432 grams), 7-12 months (ibuprofen equivalents 433-876 grams), and greater than 12 months (ibuprofen equivalents more than 876 grams) of use.

Statistical Analysis

Demographic and other clinical characteristics (i.e. age, gender, length of Medicaid coverage, prevalence of selected comorbidities) between the NSAID exposure and non-exposure groups were tabulated and tested for differences using chi-square test for categorical variables and t-test for continuous variables. All statistic analyses were performed using SAS statistical software (Version 8.2, SAS Institute, Cary, North Carolina). All p-values were 2-sided and the significance level was set at $p<0.05$.

Unadjusted incidence was calculated by dividing number of new cases of each outcome event by the number of person-years. We computed crude relative risks by dividing the unadjusted incidence rates of NSAID users (e.g. cases per 100,000 person-years) by those of non-users.

Cox proportional hazards models were used to estimate the multivariate adjusted rates and relative risks (using PROC PHREG of SAS package). Model specification and operative definition of all covariates are summarized below. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CI) are reported.

Model Specification

The Cox proportional hazard model was defined as follows:

$$h(t \mid Z) = h_0(t) * \exp[\ \alpha(\text{NSAID exposure}) + \beta * X + \varepsilon\text{rror}\ ]$$

Where $h(t \mid Z)$: hazard rate at time 't' for an individual with risk vector Z

$h_0(t)$: baseline hazard rate

α : Coefficient for NSAID exposure

X : Matrix of covariates

β : Vector of coefficients corresponding to the matrix of covariates

Dependent Variables

Our major outcomes of interest are the first incidence of diagnosed cancers, and adverse gastrointestinal and renal events. We modeled each outcome separately with specific set of covariates. Although correlation among incident studied cancers was found, percentage of cases diagnosed with other cancer before the studied cancers was small. For each study event of interest, a Cox proportional hazard model was fitted based on:

(1) Incidence of each study event: A dichotomous dependent variable was coded whether or not subjects had any diagnosis codes of the study outcome.

(2) Person-years in study cohort: Number of years each subjects stayed in the cohort is calculated by subtracting the date when a subject entered the cohort from the date when the subject left the cohort.

Independent variables

Effect of NSAID exposure was modeled in three sets of separate analyses as follows:

1) NSAID exposure as a class: A dichotomous independent variable coded if a subject prescribed any NSAID.
2) Cumulative exposure of NSAIDs: NSAID use was stratified into four categories to determine the effect of cumulative exposure on study endpoints (less than one month, 1-6 months, 7-12 months, and greater than 12 months)
3) Effects of the use of some specific NSAIDs were analyzed. Based on generic names recorded from each subject's prescriptions, NSAID exposure was classified into 8 groups (see below). There is a high possibility that subjects may be exposed to more than one product or group, so persons could have more than one of the following NSAID variables recorded as exposed. Furthermore, to determine the effect cumulative exposure of each on study endpoints, the cumulative exposure for each generic group was calculated and stratified into 4 categories: less than one month, 1-6 months, 7-12 months, and greater than 12 months.
   a) Aspirin
   b) Selective Cox-2 inhibitors (celecoxib and rofecoxib)
   c) Ibuprofen (commonly prescribed) {Niecko 2001, Smalley 1999}
   d) Naproxen (commonly prescribed) {Niecko 2001, Smalley 1999}
   e) Indomethacin (commonly prescribed)
   f) Fenoprofen (commonly prescribed)
   g) Sulindac (effective in many animal models) {Niecko 2001, Smalley 1999}
   h) Other non-specific NSAIDs

Covariates

All covariates included in the model were listed in table 9.2. Operational definition and the ICD-9-CMcodes for each covariate were summarized in table 9.2.

Results

There were 215,224 recipients in the GA Medicaid cohort and 62% were exposed to an NSAID. On average, the length of follow-up ranged from 6.2 years (s.d., 3.5) in GI event cohort to 6.4 years (s.d., 3.5) in pancreatic cancer cohort. The cohort average age was 70.4 years (s.d., 11.6 years); 73.6% were female, 47.4% were white, 39.8% were non-white and 12.8% were of unknown race. Incidence rates of colorectal cancer, esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events were 96.9, 27.8, 45.2, 44.8, 23.1, 30.4, 20.7, 760.2, and 596.1 per 100,000 person-years, respectively.

The NC Medicaid cohort contained 184,950 beneficiary and 43% were exposed to an NSAID. On average, the length of follow-up ranged from 5.0 years (s.d., 2.3) in GI event cohort to 5.1 years (s.d., 2.3) in pancreatic cancer cohort. The cohort average age was 71.7 years (s.d., 10.9 years); 73.2% were female, 53.7% were white, and 46.3% were non-white. Incidence rates of colorectal cancer, esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events were 70.3, 13.5, 24.2, 25.6, 12.5, 17.4, 13.5, 564.6, and 326.0 per 100,000 person-years, respectively.

Both GA and NC cohort characteristics by NSAID exposure status is displayed in tables 9.3-9.5. The length of follow up of subjects exposed NSAIDs were significantly longer than those not exposed NSAIDs ($p<0.05$). Younger persons, women and non-whites were more likely to have an NSAID prescription filled than their respective counterparts.

Except pancreatic cancer, we observed a significant lower risk for all digestive cancer, urinary tract cancer, GI and renal events among subjects exposed to NSAIDs compared with those not exposed to NSAIDs, after multivariate adjustment, in GA cohort (tables 9.6-9.7). However there were some discrepancies in results between the unadjusted and the multivariate adjusted rates of gastric, pancreatic and kidney cancer. The unadjusted rates of the GA cohort were 0.77 (95%CI, 0.73 to 0.81), 0.72 (95%CI, 0.65 to 0.80), 0.95 (95%CI, 0.87 to 1.03), 0.82 (95%CI, 0.75 to 0.89), 1.22 (95%CI, 1.07 to 1.39), 0.74 (95%CI, 0.67 to 0.82), 1.00 (95%CI, 0.87 to 1.13), 0.95 (95%CI, 0.93 to 0.97), and 0.82 (95%CI, 0.80 to 0.84) for colorectal cancer, esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events, respectively. After adjusting for several covariates, the relative risks were significant, as 0.60 (95%CI, 0.53 to 0.67), 0.40 (95%CI, 0.32 to 0.50), 0.56 (95%CI, 0.47 to 0.67), 0.60 (95%CI, 0.51 to 0.72), 0.92 (95%CI, 0.71 to 1.20), 0.61 (95%CI, 0.49 to 0.75), 0.71 (95%CI, 0.54 to 0.92), 0.49 (95%CI, 0.47 to 0.51), and 0.40 (95%CI, 0.38 to 0.42) for colorectal cancer, esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events, respectively. We only found, from the NC cohort (table 9.7), the multivariate-adjusted relative risks of colorectal cancer, esophageal cancer, GI and renal events to be significant. Like in the GA cohort, disagreement in results between the unadjusted and the multivariate adjusted rates of all outcomes, except colorectal cancer and pancreatic cancer, was observed. Comparing with the adjusted results obtained from the NC cohort, the unadjusted rates for the North Carolina NSAID users were higher with unadjusted risks of 0.91 (95%CI, 0.84 to 0.98), 1.03 (95%CI, 0.86 to 1.23), 1.44 (95%CI, 1.26 to 1.64), 1.18 (95%CI, 1.04 to 1.35), 0.98 (95%CI, 0.81 to 1.17), 1.18 (95%CI, 1.01 to 1.38), 1.41 (95%CI, 1.18 to 1.69), 1.59 (95%CI, 1.54 to 1.63), and 1.25 (95%CI, 1.20 to 1.29) for colorectal cancer, esophageal cancer,

gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events, respectively. The multivariate-adjusted relative risks were 0.73 (95%CI, 0.62 to 0.86), 0.49 (95%CI, 0.34 to 0.71), 0.77 (95%CI, 0.58 to 1.03), 0.83 (95%CI, 0.64 to 1.09), 0.68 (95%CI, 0.47 to 1.00), 1.02 (95%CI, 0.74 to 1.40), 0.80 (95%CI, 0.55 to 1.16), 0.69 (95%CI, 0.65 to 0.73), and 0.54 (95%CI, 0.50 to 0.58) for colorectal cancer, esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, bladder cancer, kidney cancer, GI and renal events, respectively.

According to both GA and NC cohort, effects of covariates on study events of interest were summarized (table 9.8-9.16). Except pancreatic cancer cohort, compared with the 50 to 64 age group, older age groups, both 65-75 and >75 age groups, appeared to be at lower risk for digestive cancer, urinary tract cancer and NSAID-related adverse events. While gender and race did not alternate risk of colorectal, liver and pancreatic cancer, men and non-whites were at higher risk for esophageal and gastric cancer. Alcohol and tobacco use increased the risk of digestive cancers. We found that subjects with GERD were at least 3 times increased risk of esophageal and gastric cancer. We did not find association between H. pylori infection and digestive cancers, except in gastric cancer. The risk of pancreatic cancer increased 13 folds in persons with chronic pancreatitis. Persons with chronic liver infection were at 4-times higher risk of liver cancer. We found that men were more likely to be diagnosed with urinary tract cancer. White race was associated with increased risk of bladder cancer, not kidney cancer. Subjects prescribed cyclophosphamide were 6-8 folds more likely to have bladder cancer. Hypertension increased risk of kidney cancer. The risk of NSAID-related adverse events, both GI and renal events, increased in non-whites, alcoholics, obese persons and tobacco smokers. Moreover, we found that H. pylori infection and taking GI protective agents were the most

important risk factors for GI events; H. pylori infection increased risk of GI events by 3-4 folds; subjects prescribed GI protective agents were 5-6 times more likely to experience a GI event. Hypertension, congestive heart failure, diabetes mellitus and cirrhosis, uses of nephrotoxic drugs were the important risk factors for renal events.

The impact of specific NSAID exposure on digestive cancer, urinary tract cancer, GI and renal events are summarized in tables 9.17-9.20. The protective effect of Cox-2 inhibitors was apparent and pronounced in both digestive cancers and urinary tract cancers. Furthermore, uses of Cox-2 inhibitors decreased risk of NSAID-related adverse effects. Aspirin exposure was not associated with risks of all digestive and urinary tract cancers. Apart from inconclusive effects of non-aspirin NSAIDs on risks of digestive and urinary cancers, the benefit of ibuprofen against gastric cancer was confirmed; subjects prescribed ibuprofen were 30% lower risk of gastric cancer (tables 9.19-9.20). Compared with the non-NSAID exposure group, non-selective NSAIDs including aspirin were not increased risk of both NSAID-related adverse events; subjects prescribed ibuprofen, naproxen and other NSAIDs had significantly lower risk of GI and renal events.

The increased cumulative exposure of NSAIDs was associated with decreased rates of digestive cancer, urinary tract cancer, GI and renal events (figures 9.4-9.5). The higher the cumulative exposure, the lower the risk of digestive cancer, urinary tract cancer, GI and renal events. The protective effects of long-term NSAID use against digestive cancer, urinary tract cancer, GI and renal events were confirmed, besides bladder cancer (figures 9.4-9.5). The apparent dose-response protective effect of Cox-II inhibitors use against all outcomes was found; the higher the cumulative exposure of Cox-II inhibitors, the lower the risk of digestive cancer, urinary tract cancer, GI and renal events. Although there was non-significant relationship

between long-term use of non-selective NSAIDs and risk of digestive and urinary tract cancer, long-term use of ibuprofen, in GA cohort, were significantly reduced risks of digestive cancers, as 0.70 (95% CI, 0.54 to 0.89), 0.35 (95% CI, 0.20 to 0.64), 0.53 (95% CI, 0.37 to 0.77), 0.66 (95% CI, 0.45 to 0.96), and 0.55 (95% CI, 0.31 to 0.98) for colorectal, esophageal, gastric, liver, and pancreatic cancers, respectively. The results, from both cohorts, did not demonstrated the increased risk of GI and renal events in persons who had more than 1 year of each specific NSAID exposure, but we found only in NC cohort that the risk of renal events increased 3 times in persons taking long-term sulindac.

Because the impact of NSAIDs on GI and renal events were somewhat surprising, a sensitivity analysis was conducted to explore other potential possible explanations for an apparent protective effect of NSAIDs on these outcomes. It has been noted from previous research with these data that long-term care facilities provide relatively fewer ICD-9-CM codes than other providers and if NSAID usage was related to long-term care use, that might account for an apparent undercoding and may partially explain the observed finding. To explore this possibility we conducted an analysis excluding all persons admitted to a long-term care facility more than 1 year and re-estimated the multivariate adjusted models on the remaining subject; we excluded 62,086 and 307 persons admitted to a long-term care facility more than 1 year from GA and NC cohorts, respectively. The results of sensitivity analyses were presented in tables 9.21-9.22.

Moreover, we conducted an additional sensitivity analysis excluding all persons whose age was between 65 and 100 years. Since there are some disagreement with other studies that have shown the risk for digestive and urinary tract cancers increased with age, we found that older age classes, both 65-75 and >75, appeared to be at less risk for the three study outcomes

than the 50-64 age group. We believe this is possibly a result of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare. After we excluded persons whose age was between 65 and 100 years from the GA and NC cohorts, we re-estimated the multivariate adjusted models on the remaining subject. The effects of NSAID use and covariates on the risk of study outcomes were comparable with original cohorts.

Discussion

NSAID exposure was significantly associated with 27-40% and 51-60% reduced risk of colorectal and esophageal cancers, respectively. Although risks decreased non-significantly in NC cohort, the significantly reduced risks of gastric cancer (44%), liver cancer (40%), bladder cancer (39%) and kidney cancer (29%) were demonstrated in GA cohort. The greater reductions in relative risks at higher levels of NSAID consumption were observed. Persons who had more than 1 years of NSAID usage were less likely to experience all digestive and urinary tract cancer, except bladder cancer, than did persons who had no exposure. We found that the protective effects of Cox-2 inhibitors was the most substantial and was greater with increasing cumulative exposure. These results were not affected after excluding recipients that were admitted to long-term care facilities for greater than one year.

Despite comparable demographic compositions between the Medicaid cohorts in Georgia and North Carolina, a higher percentage of subjects in the Georgia (62%) were prescribed any NSAID than those in the North Carolina (43%). This discrepancy may be explained by differences in pharmacy services policy, available prescription NSAIDs, and physician's prescribing preferences. Before July 1998, the Georgia Medicaid pharmacy program covered

only five prescriptions per recipient per month. After of July 1998, with a written or oral prescription from a physician indicating the need for a drug override to exceed the monthly limits, pharmacists in Georgia are able to do self-approval to exceed these prescription limits {Georgia Department of Community Health 2004}. North Carolina Medicaid has also established monthly prescription limits of six prescriptions per recipient per month. Unlike the Georgia Medicaid program, after July 1998, exemption from the prescription limitation will only be authorized for life threatening illnesses. The recipient's physician must submit a "Six Prescription Limit Override Form" where he or she justifies the patient's need for a drug override to exceed the monthly prescription limits {North Carolina Division of Medical Assistance 2004}. The possible follow-up period of the Georgia cohort (1990- 2001) was three years longer than that of the North Carolina cohort (1990-1998). The policy of override to exceed the monthly prescription limits under the Georgia Medicaid program was changed. Therefore NSAID prescription rates in Georgia might have increased during that three-year period (1999-2001). Moreover, Cox-2 inhibitors, celecoxib and rofecoxib, were introduced in 1999. Cox-2 inhibitors are covered, without requirement of prior authorization, by Georgia Medicaid, although there are quantity level limits of 34 tablets per 34 days when celecoxib and rofecoxib are prescribed {Georgia Department of Community Health 2004}. Both Georgia and North Carolina Medicaid programs do not cover over-the-counter aspirin. Enteric-coated aspirin is available as a prescription drug and covered by Georgia Medicaid; prescription aspirin is not covered by the North Carolina Medicaid program. Lastly, there may be a difference of NSAID prescribing preferences of physicians in Georgia and North Carolina.

There are some inconsistent results between unadjusted and multivariate adjusted relative risks from both Georgia and North Carolina Medicaid cohorts. Mainly, we found the higher unadjusted relative risks than and sometimes reversed direction of multivariate adjusted relative risks of all study outcomes. Since more persons in NSAID exposure group experienced risk factors of the study outcomes than ones in non-exposure group. While extents to which some risk factors affects on developing digestive cancers, urinary tract cancers, and NSAID-related adverse events are small, others are strongly associated with the risks of the study outcomes; for examples the risk of pancreatic cancer increased 13 folds in persons with chronic pancreatitis; persons prescribed cyclophosphamide were 6-8 folds more likely to have bladder cancer. Therefore, the increased unadjusted relative risks may be subsequently due to these highly associated risk factors.

Our study confirms the protective effect of NSAID use on the risk of colorectal cancer that has been robustly documented in epidemiologic studies and clinical trials. Moreover, we confirm a strong protective effect of NSAID use against esophageal cancers, which is coherent with a meta-analysis of 9 studies by Corley and colleague {Corley 2003}; a significant protective association between any use of NSAIDs and esophageal cancer (OR, 0.57; 95% CI, 0.47-0.71) were reported {Corley 2003}.

An inverse association between use of NSAIDs and the risk of gastric cancer has been evident in a meta-analysis of 9 published studies, as the odd ratio was 0.78 (95%CI 0.69 to 0.87) {Wang 2003}. The results of this study also suggest that NSAID exposure was inversely related to the risks of developing gastric cancer. The association estimated from the Georgia Medicaid data (RR, 0.56; 95%CI, 0.47 to 0.67) was stronger than one estimated from the North Carolina Medicaid data (RR, 0.77; 95%CI, 0.58 to 1.03); however the latter finding was non-significant.

One possible explanation for this inconsistent result is insufficient follow-up period. The comparable demographic composition, percents of selected comorbidities in both NSAID users and non-users, and average length of follow up of those in non-NSAID exposure group were seen in both of the Georgia and North Carolina cohorts. Nonetheless, persons prescribed an NSAID in the GA cohort, on average, remained in the cohort longer than those in the NC cohort. Therefore, in my opinion, the potential protective effect of NSAID use may be more apparent when extend period of follow up. Additionally, we found that the long-term use of NSAIDs was associated with reduced risk of gastric cancer.

In agreement with most studies examining a correlation between NSAID use and incidence of pancreatic cancer {Friis 2003, Langman 2000, Sorensen 2003, Menezes 2002, Schernhammer 2004}, a lack of association was observed. We demonstrated that the long-term use of NSAIDs was associated with reduced risk of pancreatic cancer; a prospective cohort of 88,378 women {Schernhammer 2004} suggested that an increased duration of regular aspirin use was associated with an increase in pancreatic cancer risk, as women exposed to more than 20 years of regular aspirin use had an increased risk of pancreatic cancer (RR 1.58; 95%CI 1.03 to 2.43) {Schernhammer 2004}.

Several animal studies have correlated the over-expression of COX-2 with the differentiation grade of hepatocellular carcinomas and that COX-2 enzymes and prostaglandins plays a role in liver carcinogenesis {Abiru 2002, Bae 2001, Rahman 2000}. In addition, the inhibition of COX-2 can induce liver carcinoma apoptosis {Bae 2001}, decrease hepatocellular carcinoma cell proliferation {Rahman 2000}, and inhibit carcinoma invasiveness {Abiru 2002}. To date, there is no epidemiological study examining potential chemopreventive effects of NSAIDs against liver cancer. This study is the first to demonstrate that a significantly inversed

association between NSAID exposure and the risk of liver cancer (RR, 0.60; 95%CI, 0.51 to 0.72) in the GA cohort; however the inversed relationship was not validated in the NC cohort, as the risk decreased non-significantly (RR, 0.83; 95%CI, 0.64 to 1.09).

Effects of NSAID use on the risk of bladder cancer have been mixed. While the 20% increased risk of bladder cancer in persons having NSAID intake {Friis 2003, Sorensen 2003} has been reported, an inversed dose-dependent association is evident in a case-control study by Castelao {Castelao 2000}. Our study reveals also conflicting results. Whereas an non-significantly increased risk was seen in the NC cohort (RR, 1.02; 95%CI, 0.74 to 1.40), the significantly reduced risk of bladder cancer (RR, 0.61; 95%CI, 0.49 to 0.75) were demonstrated in the GA cohort.

Experimental evidence of the role of carcinogenesis in renal cell carcinoma has been reported increased levels of PGs and increased PG binding sites in renal cell carcinomas {Castilla 2002, Chen 2002}. Moreover, the possible therapeutic benefit of COX-2 inhibitors in kidney cancer has been demonstrated {Sato 2002}; apoptosis of renal cell carcinomas occurred when Cox-2 inhibitors were presented. Despite promising scientific rationale for the NSAID use in kidney cancer, currently there are no epidemiological studies evaluating the role of NSAIDs in kidney cancer. This study is the first epidemiological study to determine relationships between NSAID usage and incidences of, not only, kidney cancer, but also NSAID-related adverse effects. We are able to exhibit the significantly reduced risk of kidney cancer (RR, 0.71; 95%CI, 0.54 to 0.92) in persons prescribed NSAIDs in GA cohort, although the result obtained from the NC cohort suggest non-significantly decreased risk (RR, 0.80; 95%CI, 0.55 to 1.16).

We did not find an elevated risk of GI and renal adverse events. After multivariate adjustment, NSAID use was associated with a statistically significant reduction in GI and renal

adverse events. Higher cumulative exposure was associated with decreasing risk of GI and renal events.

Nevertheless, these results must be interpreted with caution. Since subjects were required to be free of all outcomes within their first year eligibility, many of the NSAID users able to meet the inclusion criteria and remain in the study might tolerate NSAID therapy better than most typical users. Therefore, these subjects may demonstrate a lower risk for GI and renal events relative to those persons with NSAID exposure who do not tolerate therapy. Therefore, the NSAID-related adverse event risks reported in this study may be understated.

Our results suggest that the risk of GI adverse events is highest at the beginning of NSAID use with decreases as persons consume more NSAIDs. This finding is consistent with studies showing that the initial doses of NSAIDs and not long term NSAID use are most likely to result in GI adverse related events {Gabriel 1991, Garcia Rodriguez 1998, Smalley 1995}. This may be explained by gastric mucosal adaptation, which has been reported in both animal and human studies {Fitzpatrick 1999, Lipscomb 1996}.

Most studies have shown that the risk of cancers increased with age. However we found that older age classes, both 65-75 and >75 age group, appeared to be at lower risk for the study outcomes than the 50 to 64 age group. This may be a subsequence of Medicare picking up claims for those aged 65 and greater, although Medicaid frequently covers the billing of procedures not paid for entirely by Medicare.

There are several potential limitations in this proposed study. Since we depend on diagnosis (ICD-9-CM) codes to identify the study outcomes and confounders, measurement bias may arise due to coding inconsistencies. This may be of particular concern if there are differences in coding that is related to NSAID exposure. As a check for this potential concern,

we conducted a sensitivity analysis excluding recipients with long term care admissions > 1 year and found the results to be generally consistent with the initial analysis. Additionally, detailed information on risk behaviors, i.e. tobacco and alcohol consumption is not specifically recorded in claims data and could only be inferred from diagnostic information. In claims data, clinical measures, i.e. histological type and stage of cancer, are also not available. So the effect of NSAIDs on different histological type and stage of cancer cannot be explored. Despite the fact that Medicaid pays for ASA, ibuprofen, and naproxen, exposure misclassification may still occur as a result of recipients purchasing these products over-the-counter. This may attenuate the disparity between exposure and non-exposure groups and underestimate relative risk of outcomes.

Since it is well known that NSAIDs are associated with increasing risks of GI and renal events, though perhaps transitory, channeling bias is an inextricable limitation of this study because physicians would be less likely to prescribe non-selective NSAIDs to persons they believe might be prone to GI or renal adverse events. We attended to this limitation by including the use of gastroprotective agents (a potential marker for past GI events) as a covariate in the GI adverse event models, but we recognize that this can only partially describes someone's GI event likelihood. Moreover, physicians may also pay closer attention to those who take NSAIDs, for example, more physician visits, which may lead to earlier diagnosis. Nevertheless, frequency of health care utilization was adjusted in the models in an attempt to attend to this phenomenon. We do not believe that if recipients were randomly assigned to NSAIDs and non-NSAIDs that the same results would be obtained with regard to GI and renal adverse events, however, these data do demonstrate that the NSAID prescribing decisions made in this population are not associated with an increase in GI and Renal events and this finding may better reflect the risks of

NSAID prescribing rather than the relative risk of NSAIDs themselves. Though we do believe that channeling bias is an important consideration when interpreting the results of the adverse events, we do not believe channeling bias is a significant concern for the results for cancer prevention analyses, because it is unlikely that physicians were prescribing NSAIDs for persons whom they thought might be at higher risk of the cancers.

Conclusion

Any NSAID exposure was associated with 27-40% and 51-60% reduction in incident colorectal and esophageal cancer. There were no increased rates of GI and renal events associated with NSAID prescribing in this population. The results of this study support the hypothesis that NSAIDs have chemopreventive value against colorectal and esophageal cancer. Although the dose-response characteristic was seen, the questions regarding optimal chemopreventive dose and duration of NSAIDs are remaining unanswered. Therefore, additional large perspective cohort studies with more extended period of follow-up and clinical trails are needed in order to validate and examine biochemical components of NSAIDs. Further research in this area with better measures of NSAID use and better controls of behavioral risk factors is needed to examine optimal chemopreventive dose and duration of NSAIDs. This would consequently advice on specific recommendation of NSAID use as chemopreventives.

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Table 9.1: Commonly Available Non-Steroidal Anti-inflammatory Drug (NSAIDs), According to Chemical Class

Chemical Class	Generic	Low daily dose (mg)	High daily dose (mg)	Standardization to Ibuprofen
Nonselective COX inhibitors				
Salicylic acid derivatives	Aspirin (acetylsalicylic acid)	2,400	3,600	0.67
	Salicylate salts (i.e. Choline Magnesium trisalicylate)	2,000	3,000	0.80
	Diflunisal	500	1,000	2.40
	Salsalate	2,000	4,000	0.60
Heteroacrl acetic acids	Diclofenac	100	150	16.00
	Etodolac	800	1,200	2.00
	Ketorolac	10	40	60.00
	Tolmetin	1,200	1,800	1.33
Indole and indene acetic acids	Indomethacin	50	150	16.00
	Sulindac	300	400	6.00
Arylpropionic acids	Fenoprofen	900	2,400	1.00
	Flurbiprofen	200	300	8.00
	Ibuprofen	1,200	2,400	1.00
	Ketoprofen	200	300	8.00
	Naproxen	550	1,100	2.18
	Oxaprozin	1,200	1,800	1.33
Anthranilic acid (Fenamates)	Meclofenamic acid	100	400	6.00
	Mefenamic acid	500	1,000	2.40
Enolic acids				
Pyrazolones	Phenylbutazone	300	400	6.00
Oxicams	Piroxicam	less than 20	20	120.00
Nonacidic agent				
Alkanones	Nabumetone	1,000	2,000	1.20
Selective COX-2 Inhibitors				
Diaryl-substituted furanones	Rofecoxib	12.5	25	96.00
Diaryl-substituted isoxazole	Valdecoxib	10	20	120.00
Diaryl-substituted pyrazoles	Celecoxib	200	400	6.00

Source: (1) Roberts LJ2, Marrow JD. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Good man and Gilman's the pharmacological basis of therapeutics. Columbus: The McGraw-Hill Companies, Inc., 2001;687-731.

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Table 9.2: List of Model Covariates and their Operation Definitions

Covariates	Outcome								
	Colorectal cancer	Esophageal cancer	Gastric cancer	Liver cancer	Pancreatic cancer	Bladder cancer	Kidney cancer	GI event	Renal events
Demographics									
Age at entry (years)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gender (female vs. male)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Race (non-white vs. white)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Frequency of health care utilization: Total number of visits to ambulatory care services, emergency department, long-term care facilities, and acute inpatient services throughout study period	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Frequency of cancer screenings: Total numbers of any cancer screenings throughout study period	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Alcohol use and alcohol abuse (ICD-9-CM = 291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93, 305.00-305.03, V11.3 {Elixhauser 1998})	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Obesity (ICD-9-CM = 278.x {Elixhauser 1998})	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tobacco Smoke (ICD-9-CM = 305.1, V15.82 {Romano 1994})	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gastroesophageal reflux disease (GERD)/Barrett's Esophagus (ICD-9-CM= 530.81, 530.85)	No	Yes	Yes	No	No	No	No	No	No
Pernicious anemia (ICD-9-CM= 281.0)	No	No	Yes	No	No	No	No	No	No
Chronic liver infection (ICD-9-CM=070.2,070.3, 070.41, 070.44, 070.51, 070.54)	No	No	No	Yes	No	No	No	No	No
Chronic Pancreatitis (ICD-9-CM= 577.1)	No	No	No	No	Yes	No	No	No	No
Emphysema (ICD-9-CM = 492.xx)	No	No	No	No	No	No	No	Yes	No
Chronic Bronchitis (ICD-9-CM = 491.xx)	No	No	No	No	No	No	No	Yes	No
H.Pylori infection (ICD-9-CM = 041.86)	No	Yes	Yes	Yes	Yes	No	No	Yes	No
Cirrhosis (ICD-9-CM = 571.5, 571.6)	No	No	No	Yes	Yes	No	No	No	Yes
Hypertension (ICD-9-CM = 401.xx, 402.xx, 405.xx {Elixhauser 1998})	No	No	No	No	No	No	Yes	No	Yes
Diabetes Melitus (ICD-9-CM = 250.0x-250.3x; 250.5x-250.9x {Elixhauser 1998})	No	No	No	Yes	Yes	No	No	No	Yes
Congestive heart failure (ICD-9-CM = 389.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9 {Elixhauser 1998})	No	No	No	No	No	No	No	No	Yes
Liver Failure (ICD-9-CM = 570.xx)	No	No	No	No	No	No	No	No	Yes
Cyclophosphamide	No	No	No	No	No	Yes	No	No	No
GI protective agents (i.e. Misoprostal, proton pump inhibitors (PPIs), and histamine-2 (H2) receptor antagonists)	No	Yes	No	No	No	No	No	Yes	No
Corticosteroids (i.e. prednisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone and hydrocortisone)	No	No	No	No	No	No	No	Yes	No
Anticoagulant use (i.e. heparins, coumarin and indadiones)	No	No	No	No	No	No	No	Yes	No
Nephrotoxic Drugs:	No	No	No	No	No	No	No		
Diuretics (i.e. loop, potassium-sparing, thiazide diuretics)	No	No	No	No	No	No	No	No	Yes
Angiotensin-converting Enzyme (ACE) Inhibitors and Angiotensin-II-receptor antagonist (e.g captopril, enalapril, lisinopril, losartan etc.)	No	No	No	No	No	No	No	No	Yes
Aminoglycosides	No	No	No	No	No	No	No	No	Yes
Cephalosporins	No	No	No	No	No	No	No	Yes	Yes
Vancomycin	No	No	No	No	No	No	No	No	Yes
Allopurinol	No	No	No	No	No	No	No	No	Yes
Cyclosporine	No	No	No	No	No	No	No	No	Yes

Table 9.3: Colorectal Cancer Cohort Characteristics by Drug Exposure

Variables	Georgia Cohort		North Carolina Cohort	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	82,286	132,938	104,855	80,095
Incidence rate per 100,000 person-years	115.87	89.16	73.62	66.83
Follow up period, mean ± SD (yr)	4.9 ± 3.0	7.3 ± 3.5	4.6 ± 2.1	5.7 ± 2.4
Demographics (%)				
Age, mean ± SD (yr)	72.1 ± 12.2	69.3 ± 11.1	72.8 ± 10.7	70.3 ± 11.0
Female	68.7	76.6	70.1	77.1
Race				
White	53.8	43.4	57.3	48.9
Non White	36.1	42.2	42.8	51.1
Unknown race	10.2	14.4	na	na
Risk Factors (%)				
Tobacco Smoke	1.5	2.9	1.0	2.4
Obesity	0.7	3.0	0.7	2.9
Alcohol Abuse	2.2	3.2	1.7	3.1
GERD/Barrett's Esophagus	na	na	na	na
Pernicious anemia	na	na	na	na
Chronic liver infection	na	na	na	na
Chronic Pancreatitis	na	na	na	na
Emphysema	na	na	na	na
Chronic Bronchitis	na	na	na	na
H. pylori Infection	na	na	na	na
Hypertension	na	na	na	na
Diabetes Mellitus	na	na	na	na
Congestive Heart Failure	na	na	na	na
Cirrhosis	na	na	na	na
Medication exposures				
Cyclophosphamide	na	na	na	na
GI protective agents	na	na	na	na
Corticosteroids	na	na	na	na
Anticoagulants	na	na	na	na
Diuretics	na	na	na	na
ACE inhibitors	na	na	na	na
Antibiotics				
Aminoglycosides	na	na	na	na
Cephalosporines	na	na	na	na
Vancomycins	na	na	na	na
Allopurinal	na	na	na	na
Cyclosporine	na	na	na	na
Frequency of Health Care Utilization, mean ± SD (times)	132.6 ± 157.4	197.4 ± 180.9	31.4 ± 51.2	56.4 ± 73.5
Frequency of Cancer Screening, mean ± SD (times)	0.062 ± 0.37	0.210 ± 0.76	0.018 ± 0.18	0.070 ± 0.37

Table 9.4: Georgia Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Esophageal cancer		Gastric cancer		Liver cancer		Pancreatic cancer	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	82,200	133,024	82,216	133,008	82,211	133,013	82,179	133,045
Incidence rate per 100,000 person-years	34.70	25.03	46.93	44.47	51.41	42.08	19.97	24.40
Follow up period, mean ± SD (yr)	4.9 ± 3.0	7.4 ± 3.5	4.9 ± 3.0	7.4 ± 3.5	4.9 ± 3.0	7.4 ± 3.5	4.9 ± 3.0	7.4 ± 3.5
Demographics (%)								
Age, mean ± SD (yr)	72.1 ± 12.2	69.3 ± 11.1	72.1 ± 12.2	69.3 ± 11.1	72.1 ± 12.2	69.3 ± 11.1	72.1 ± 12.2	69.3 ± 11.1
Female (%)	68.7	76.6	68.7	76.6	68.7	76.6	68.7	76.6
Race								
White (%)	53.8	43.4	53.8	43.4	53.8	43.4	53.8	43.4
Non White (%)	36.0	42.2	36.1	42.2	36.1	42.2	36.0	42.2
Unknown Race (%)	10.2	14.4	10.2	14.4	10.2	14.4	10.2	14.4
Risk Factors								
Tobacco Smoke (%)	1.4	2.9	1.5	2.9	1.5	2.9	1.4	2.9
Obesity (%)	0.7	3.0	0.7	3.0	0.7	3.0	0.7	3.0
Alcohol Abuse (%)	2.2	3.2	2.2	3.2	2.2	3.2	2.2	3.2
GERD/Barrett's Esophagus (%)	1.2	3.9	1.2	3.9	na	na	1.2	3.9
Pernicious anemia(%)	na	na	0.3	0.8	na	na	na	na
Chronic liver infection (%)	na	na	na	na	0.2	0.3	na	na
Chronic Pancreatitis (%)	na	na	na	na	na	na	0.2	0.3
Emphysema (%)	na	na	na	na	na	na	na	na
Chronic Bronchitis (%)	na	na	na	na	na	na	na	na
H. pylori Infection (%)	0.1	0.4	0.1	0.4	0.1	0.4	0.1	0.4
Hypertension (%)	na	na	na	na	na	na	na	na
Diabetes Mellitus (%)	na	na	na	na	8.6	17.3	8.6	17.3
Congestive Heart Failure (%)	na	na	na	na	na	na	na	na
Cirrhosis (%)	na	na	na	na	0.4	0.5	0.4	0.5
Medication exposures								
Cyclophosphamide (%)	na	na	na	na	na	na	na	na
GI protective agents (%)	34.3	64.8	34.3	64.8	na	na	na	na
Corticosteroids (%)	na	na	na	na	na	na	na	na
Anticoagulants (%)	na	na	na	na	na	na	na	na
Diuretics (%)	na	na	na	na	na	na	na	na
ACE inhibitors (%)	na	na	na	na	na	na	na	na
Antibiotics (%)								
Aminoglycosides (%)	na	na	na	na	na	na	na	na
Cephalosporines (%)	na	na	na	na	na	na	na	na
Vancomycins (%)	na	na	na	na	na	na	na	na
Allopurinal (%)	na	na	na	na	na	na	na	na
Cyclosporine (%)	na	na	na	na	na	na	na	na
Frequency of Health Care Utilization, mean ± SD (times)	132.5 ± 157.43	197.4 ± 180.9	132.5 ± 157.3	197.4 ± 180.9	132.5 ± 157.3	197.4 ± 180.9	132.5 ± 157.3	197.5 ± 180.9
Frequency of Cancer Screening, mean ± SD (times)	0.062 ± 0.36	0.210 ± 0.77	0.062 ± 0.36	0.210 ± 0.76	0.062 ± 0.36	0.210 ± 0.77	0.061 ± 0.36	0.210 ± 0.77

Table 9.4 (continous): Georgia Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Bladder cancer		Kidney cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	82,217	133,007	82,200	133,024	83,319	131,905	82,797	132,427
Incidence rate per 100,000 person-years	37.19	27.59	20.71	20.63	788.80	748.08	684.56	559.35
Follow up period, mean ± SD (yr)	4.9 ± 3.0	7.4 ± 3.5	4.9 ± 3.0	7.4 ± 3.5	4.8 ± 2.9	7.2 ± 3.5	4.8 ± 3.0	7.3 ± 3.5
Demographics (%)								
Age, mean ± SD (yr)	72.1 ± 12.2	69.3 ± 11.1	72.1 ± 12.2	69.3 ± 11.1	72.0 ± 12.3	69.4 ± 11.1	72.0 ± 12.2	69.4 ± 11.1
Female (%)	68.7	76.6	68.7	76.6	68.6	76.7	68.7	76.7
Race								
White (%)	53.8	43.4	53.8	43.4	53.6	43.5	53.5	43.5
Non White (%)	36.1	42.2	36.1	42.2	36.2	42.2	36.3	42.1
Unknown Race (%)	10.2	14.4	10.2	14.4	10.3	14.4	10.2	14.4
Risk Factors								
Tobacco Smoke (%)	1.5	2.9	1.4	2.9	1.7	2.8	1.5	2.9
Obesity (%)	0.7	3.0	0.7	3.0	0.8	2.9	0.7	3.0
Alcohol Abuse (%)	2.2	3.2	2.2	3.2	2.4	3.1	2.2	3.2
GERD/Barrett's Esophagus (%)	na	na	na	na	na	na	na	na
Pernicious anemia(%)	na	na	na	na	na	na	na	na
Chronic liver infection (%)	na	na	na	na	na	na	na	na
Chronic Pancreatitis (%)	na	na	na	na	na	na	na	na
Emphysema (%)	na	na	na	na	1.3	2.1	na	na
Chronic Bronchitis (%)	na	na	na	na	2.9	5.2	na	na
H. pylori Infection (%)	na	na	na	na	0.2	0.4	na	na
Hypertension (%)	na	na	16.3	31.3	na	na	16.7	31.2
Diabetes Mellitus (%)	na	na	na	na	na	na	8.9	17.2
Congestive Heart Failure (%)	na	na	na	na	na	na	8.1	8.1
Cirrhosis (%)	na	na	na	na	na	na	0.4	0.5
Medication exposures								
Cyclophosphamide (%)	0.05	0.10	na	na	na	na	na	na
GI protective agents (%)	na	na	na	na	35.1	64.6	na	na
Corticosteroids (%)	na	na	na	na	16.0	38.3	na	na
Anticoagulants (%)	na	na	na	na	11.1	15.6	na	na
Diuretics (%)	na	na	na	na	na	na	39.1	61.6
ACE inhibitors (%)	na	na	na	na	na	na	26.3	45.7
Antibiotics (%)								
Aminoglycosides (%)	na	na	na	na	na	na	1.7	1.5
Cephalosporines (%)	na	na	na	na	47.6	71.0	47.5	71.1
Vancomycins (%)	na	na	na	na	na	na	1.1	1.1
Allopurinal (%)	na	na	na	na	na	na	2.2	8.3
Cyclosporine (%)	na	na	na	na	na	na	0.09	0.06
Frequency of Health Care Utilization, mean ± SD (times)	132.5 ± 157.4	197.4 ± 180.9	132.5 ± 157.4	197.4 ± 180.9	133.9 ± 158.7	197.1 ± 180.5	133.8 ± 159.1	196.9 ± 180.2
Frequency of Cancer Screening, mean ± SD (times)	0.062 ± 0.36	0.210 ± 0.77	0.061 ± 0.36	0.210 ± 0.77	0.069 ± 0.40	0.207 ± 0.76	0.064 ± 0.37	0.210 ± 0.76

Table 9.5: North Carolina Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Esophageal cancer		Gastric cancer		Liver cancer		Pancreatic cancer	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	104,817	80,133	104,822	80,128	104,821	80,129	104,811	80,139
Incidence rate per 100,000 person-years	13.30	13.69	19.96	28.70	23.49	27.82	12.68	12.39
Follow up period, mean ± SD (yr)	4.6 ± 2.1	5.7 ± 2.4	4.6 ± 2.1	5.7 ± 2.4	4.6 ± 2.1	5.7 ± 2.4	4.6 ± 2.1	5.7 ± 2.4
Demographics								
Age, mean ± SD (yr)	72.8 ± 10.7	70.4 ± 11.0	72.8 ± 10.7	70.4 ± 11.0	72.8 ± 10.7	70.4 ± 11.0	72.8 ± 10.7	70.4 ± 11.0
Female (%)	70.1	77.1	70.1	77.1	70.1	77.1	70.1	77.1
Race								
White (%)	57.3	48.9	57.3	48.9	57.3	48.9	57.3	48.9
Non White (%)	42.7	51.1	42.7	51.1	42.7	51.1	42.7	51.1
Risk Factors								
Tobacco Smoke (%)	1.0	2.4	1.0	2.4	1.0	2.4	1.0	2.4
Obesity (%)	0.7	2.9	0.8	2.8	0.8	2.9	0.8	2.9
Alcohol Abuse (%)	1.7	3.1	1.7	3.1	1.7	3.1	1.7	3.1
GERD/Barrett's Esophagus (%)	0.5	1.9	0.5	1.9	na	na	na	na
Pernicious anemia(%)	na	na	0.5	0.8	na	na	na	na
Chronic liver infection (%)	na	na	na	na	0.06	0.11	na	na
Chronic Pancreatitis (%)	na	na	na	na	na	na	0.1	0.3
Emphysema (%)	na	na	na	na	na	na	na	na
Chronic Bronchitis (%)	na	na	na	na	na	na	na	na
H. pylori Infection (%)	0.03	0.15	0.03	0.15	0.03	0.15	0.03	0.15
Hypertension (%)	na	na	na	na	na	na	na	na
Diabetes Mellitus (%)	na	na	na	na	7.8	15.6	7.8	15.6
Congestive Heart Failure (%)	na	na	na	na	na	na	na	na
Cirrhosis (%)	na	na	na	na	0.2	0.3	0.2	0.3
Medication exposures								
Cyclophosphamide (%)	na	na	na	na	na	na	na	na
GI protective agents (%)	25.4	54.1	25.4	54.0	na	na	na	na
Corticosteroids (%)	na	na	na	na	na	na	na	na
Anticoagulants (%)	na	na	na	na	na	na	na	na
Diuretics (%)	na	na	na	na	na	na	na	na
ACE inhibitors (%)	na	na	na	na	na	na	na	na
Antibiotics (%)								
Aminoglycosides (%)	na	na	na	na	na	na	na	na
Cephalosporines (%)	na	na	na	na	na	na	na	na
Vancomycins (%)	na	na	na	na	na	na	na	na
Allopurinal (%)	na	na	na	na	na	na	na	na
Cyclosporine (%)	na	na	na	na	na	na	na	na
Frequency of Health Care Utilization, mean ± SD (times)	31.4 ± 51.2	56.4 ± 73.4	31.4 ± 51.2	56.4 ± 73.4	31.4 ± 51.2	56.4 ± 73.5	31.4 ± 51.2	56.4 ± 73.5
Frequency of Cancer Screening, mean ± SD (times)	0.018 ± 0.18	0.070 ± 0.37	0.018 ± 0.18	0.070 ± 0.37	0.018 ± 0.18	0.070 ± 0.37	0.018 ± 0.18	0.070 ± 0.37

Table 9.5 (continue): North Carolina Medicaid Cohort Characteristics by Drug Exposure Status

Variables	Bladder cancer		Kidney cancer		GI events		Renal Events	
	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure	Non NSAID exposure	NSAID exposure
No. Patients	104,814	80,136	104,815	80,135	105,253	79,697	105,016	79,934
Incidence rate per 100,000 person-years	16.01	18.91	11.23	15.87	439.71	697.72	291.10	362.66
Follow up period, mean ± SD (yr)	4.6 ± 2.1	5.7 ± 2.4	4.6 ± 2.1	5.7 ± 2.4	4.6 ± 2.1	5.6 ± 2.4	4.6 ± 2.1	5.7 ± 2.4
Demographics								
Age, mean ± SD (yr)	72.8 ± 10.7	70.4 ± 11.1	72.8 ± 10.7	70.4 ± 11.1	72.7 ± 10.8	70.5 ± 11.0	72.8 ± 10.8	70.4 ± 11.0
Female (%)	70.1	77.1	70.1	77.1	70.1	77.2	70.1	77.1
Race								
White (%)	57.3	48.9	57.3	48.9	57.2	48.9	57.2	49.0
Non White (%)	42.7	51.1	42.7	51.1	42.8	51.1	42.8	51.0
Risk Factors								
Tobacco Smoke (%)	1.0	2.4	1.0	2.4	1.0	2.4	1.0	2.4
Obesity (%)	0.7	2.9	0.7	2.9	0.8	2.8	0.8	2.8
Alcohol Abuse (%)	1.7	3.1	1.7	3.1	1.8	3.0	1.7	3.1
GERD/Barrett's Esophagus (%)	na	na	na	na				
Pernicious anemia(%)	na	na	na	na	na	na	na	na
Chronic liver infection (%)	na	na	na	na	na	na	na	na
Chronic Pancreatitis (%)	na	na	na	na	na	na	na	na
Emphysema (%)	na	na	na	na	0.7	1.5	na	na
Chronic Bronchitis (%)	na	na	na	na	1.1	2.6	na	na
H. pylori Infection (%)	na	na	na	na	0.03	0.14	na	na
Hypertension (%)	na	na	10.9	23.8	na	na	11.0	23.7
Diabetes Mellitus (%)	na	na	na	na	na	na	7.9	15.5
Congestive Heart Failure (%)	na	na	na	na	na	na	5.8	9.9
Cirrhosis (%)	na	na	na	na	na	na	0.2	0.3
Medication exposures								
Cyclophosphamide (%)	0.05	0.09	na	na	na	na	na	Na
GI protective agents (%)	na	na	na	na	25.6	53.9	na	Na
Corticosteroids (%)	na	na	na	na	10.4	26.9	na	na
Anticoagulants (%)	na	na	na	na	7.4	10.3	na	na
Diuretics (%)	na	na	na	na	na	na	30.0	53.4
ACE inhibitors (%)	na	na	na	na	na	na	17.0	32.0
Antibiotics (%)								
Aminoglycosides (%)	na	na	na	na	na	na	1.0	0.9
Cephalosporines (%)	na	na	na	na	34.0	58.0	34.0	58.0
Vancomycins (%)	na	na	na	na	na	na	0.6	0.7
Allopurinal (%)	na	na	na	na	na	na	1.6	6.2
Cyclosporine (%)	na	na	na	na	na	na	0.04	0.05
Frequency of Health Care Utilization, mean ± SD (times)	31.4 ± 51.2	56.4 ± 73.5	31.4 ± 51.2	56.4 ± 73.5	31.8 ± 51.9	56.0 ± 73.0	31.5 ± 51.5	56.2 ± 73.2
Frequency of Cancer Screening, mean ± SD (times)	0.018 ± 0.18	0.070 ± 0.37	0.018 ± 0.18	0.070 ± 0.37	0.019 ± 0.18	0.070 ± 0.36	0.018 ± 0.18	0.069 ± 0.36

Table 9.6: Effect of NSAID use on Incidence of Digestive cancers, Urinary tract cancers, and NSAID-related adverse events in Georgia Medicaid cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR* (95% CI)	Adjusted RR** (95% CI)
Colorectal Cancer	Any Use	976,924	871	89.16	0.77	0.60 (0.53, 0.67)
	None	400,440	464	115.87	Reference	Reference
Esophageal Cancer	Any Use	978,973	245	25.03	0.72	0.40 (0.32, 0.50)
	None	400,623	139	34.70	Reference	Reference
Gastric Cancer	Any Use	978,282	435	44.47	0.95	0.56 (0.47, 0.67)
	None	400,581	188	46.93	Reference	Reference
Liver Cancer	Any Use	979,004	412	42.08	0.82	0.60 (0.51, 0.72)
	None	400,675	206	51.41	Reference	Reference
Pancreatic Cancer	Any Use	979,368	239	24.40	1.22	0.92 (0.71, 1.20)
	None	400,664	80	19.97	Reference	Reference
Bladder Cancer	Any Use	978,624	270	27.59	0.74	0.61 (0.49, 0.75)
	None	400,666	149	37.19	Reference	Reference
Kidney Cancer	Any Use	978,989	202	20.63	1.00	0.71 (0.54, 0.92)
	None	400,681	83	20.71	Reference	Reference
GI Events	Any Use	944,553	7,066	748.08	0.95	0.49 (0.47, 0.51)
	None	398,962	3,147	788.80	Reference	Reference
Renal Events	Any Use	961,293	5,377	559.35	0.82	0.40 (0.38, 0.42)
	None	398,649	2,729	684.56	Reference	Reference

Table 9.7: Effect of NSAID use on Incidence of Digestive cancers, Urinary tract cancers, and NSAID-related adverse events in North Carolina Medicaid cohort

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Colorectal Cancer	Any Use	459,389	307	66.83	0.91	0.73 (0.62, 0.86)
	None	480,846	354	73.62	Reference	Reference
Esophagus Cancer	Any Use	460,128	63	13.69	1.03	0.49 (0.34, 0.71)
	None	481,092	64	13.30	Reference	Reference
Gastric Cancer	Any Use	459,950	132	28.70	1.44	0.77 (0.58, 1.03)
	None	481,046	96	19.96	Reference	Reference
Liver Cancer	Any Use	460,127	128	27.82	1.18	0.83 (0.64, 1.09)
	None	481,096	113	23.49	Reference	Reference
Pancreatic Cancer	Any Use	460,228	57	12.39	0.98	0.68 (0.47, 1.00)
	None	481,081	61	12.68	Reference	Reference
Bladder Cancer	Any Use	460,097	87	18.91	1.18	1.02 (0.74, 1.40)
	None	481,011	77	16.01	Reference	Reference
Kidney Cancer	Any Use	460,053	73	15.87	1.41	0.80 (0.55, 1.16)
	None	481,069	54	11.23	Reference	Reference
GI Events	Any Use	449,323	3,135	697.72	1.59	0.69 (0.65, 0.73)
	None	478,948	2,106	439.71	Reference	Reference
Renal Events	Any Use	456,076	1,654	362.66	1.25	0.54 (0.50, 0.58)
	None	479,896	1,397	291.10	Reference	Reference

Table 9.8: Effect of Covariates on the Incidence of Colorectal cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.5123	0.0602	<.0001	0.60	-0.3105	0.0816	0.0001	0.73
Age groups								
75-100 years old	-0.3089	0.0729	<.0001	0.73	0.1436	0.1038	0.1665	1.15
65-74 years old	-0.3730	0.0710	<.0001	0.69	-0.4197	0.1172	0.0003	0.66
50-64 years old								
Genders								
Female	-0.0648	0.0659	0.3259	0.94	-0.1223	0.0917	0.1821	0.89
Male								
Race								
Non-White	0.1334	0.0600	0.0263	1.14	-0.0059	0.0787	0.9399	0.99
White								
Frequency of Cancer Screening	0.0629	0.0286	0.0279	1.07	0.1619	0.0843	0.0547	1.18
Frequency of Health Care Utilization	0.0000	0.0001	0.7328	1.00	0.0031	0.0004	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.3110	0.1265	0.0139	1.37	0.7010	0.1716	<.0001	2.02
Obesity	0.2738	0.1385	0.048	1.32	-0.0298	0.2356	0.8993	0.97
Tobacco Smoke	0.6171	0.1263	<.0001	1.85	0.6684	0.1886	0.0004	1.95

Table 9.9: Effect of Covariates on the Incidence of Esophageal cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.9148	0.1142	<.0001	0.40	-0.7116	0.1889	0.0002	0.49
Age groups								
75-100 years old	-1.5501	0.1920	<.0001	0.21	-1.7500	0.3311	<.0001	0.17
65-74 years old	-1.0374	0.1468	<.0001	0.35	-0.9439	0.2562	0.0002	0.39
50-64 years old								
Genders								
Female	-0.6284	0.1162	<.0001	0.53	-0.4698	0.2010	0.0194	0.63
Male								
Race								
Non-White	0.6420	0.1188	<.0001	1.90	0.3467	0.1833	0.0586	1.41
White								
Frequency of Cancer Screening	0.0379	0.0492	0.4406	1.04	-0.1849	0.2362	0.4337	0.83
Frequency of Health Care Utilization	-0.0004	0.0003	0.1758	1.00	0.0034	0.0007	<.0001	1.00
Risk Factors								
Alcohol Abuse	1.0431	0.1391	<.0001	2.84	1.7042	0.2280	<.0001	5.50
Obesity	0.0314	0.2185	0.8856	1.03	-1.0201	0.5989	0.0885	0.36
Tobacco Smoke	0.7898	0.1515	<.0001	2.20	0.3288	0.2641	0.213	1.39
GERD/Barrett's Esophagus	1.0356	0.1436	<.0001	2.82	1.0205	0.2760	0.0002	2.77
H. pylori Infection	0.1768	0.3866	0.6475	1.19	Not Enough Sample Size to Analyze its Effect			
Medication exposures								
GI protective agents	0.9821	0.1372	<.0001	2.67	1.1899	0.2176	<.0001	3.29

Table 9.10: Effect of Covariates on the Incidence of Gastric cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.5790	0.0927	<.0001	0.56	-0.2558	0.1442	0.0762	0.77
Age groups								
75-100 years old	-1.1480	0.1334	<.0001	0.32	-1.2017	0.1892	<.0001	0.30
65-74 years old	-0.7000	0.1083	<.0001	0.50	-1.7452	0.2354	<.0001	0.18
50-64 years old								
Genders								
Female	-0.2629	0.0948	0.0055	0.77	-0.1050	0.1534	0.4936	0.90
Male								
Race								
Non-White	0.2035	0.0915	0.0261	1.23	0.5077	0.1403	0.0003	1.66
White								
Frequency of Cancer Screening	0.0990	0.0283	0.0005	1.10	-0.0062	0.1139	0.957	0.99
Frequency of Health Care Utilization	0.0001	0.0002	0.583	1.00	0.0035	0.0005	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.6514	0.1331	<.0001	1.92	0.9902	0.1934	<.0001	2.69
Obesity	0.8092	0.1294	<.0001	2.25	0.3184	0.2371	0.1792	1.38
Tobacco Smoke	0.4529	0.1364	0.0009	1.57	0.0545	0.2363	0.8178	1.06
GERD/Barrett's Esophagus	1.2626	0.1139	<.0001	3.53	1.2423	0.2076	<.0001	3.46
Pernicious anemia	0.7689	0.2124	0.0003	2.16	0.6096	0.3508	0.0823	1.84
H. pylori Infection	0.8519	0.2295	0.0002	2.34	2.0558	0.3235	<.0001	7.81

Table 9.11: Effect of Covariates on the Incidence of Liver cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.5073	0.0895	<.0001	0.60	-0.1819	0.1359	0.1809	0.83
Age groups								
75-100 years old	-1.1329	0.1280	<.0001	0.32	-1.3204	0.1882	<.0001	0.27
65-74 years old	-0.8741	0.1088	<.0001	0.42	-1.1223	0.1761	<.0001	0.33
50-64 years old								
Genders								
Female	-0.1360	0.0939	0.1473	0.87	-0.1692	0.1462	0.2472	0.84
Male								
Race								
Non-White	0.0964	0.0906	0.2875	1.10	0.0783	0.1311	0.5505	1.08
White								
Frequency of Cancer Screening	0.0447	0.0381	0.2409	1.05	-0.1359	0.1597	0.3946	0.87
Frequency of Health Care Utilization	-0.0015	0.0003	<.0001	1.00	0.0014	0.0007	0.0451	1.00
Risk Factors								
Alcohol Abuse	0.5052	0.1400	0.0003	1.66	0.5740	0.2289	0.0121	1.78
Obesity	0.0327	0.1821	0.8574	1.03	0.2375	0.2870	0.408	1.27
Tobacco Smoke	0.9066	0.1344	<.0001	2.48	0.9406	0.2275	<.0001	2.56
Chronic liver infection	1.3576	0.2340	<.0001	3.89	1.3729	0.5334	0.0101	3.95
H. pylori Infection	-0.1373	0.4521	0.7613	0.87	0.9341	0.7161	0.1921	2.55
Diabetes Mellitus	0.4175	0.0976	<.0001	1.52	0.2083	0.1708	0.2226	1.23
Cirrhosis	1.6153	0.1876	<.0001	5.03	1.0435	0.3801	0.006	2.84

Table 9.12: Effect of Covariates on the Incidence of Pancreatic cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.0836	0.1346	0.5346	0.92				
Age groups								
75-100 years old	-0.1241	0.1568	0.4286	0.88	0.2618	0.2537	0.302	1.30
65-74 years old	-0.2725	0.1502	0.0696	0.76	-0.2908	0.2768	0.2935	0.75
50-64 years old								
Genders								
Female	0.0854	0.1379	0.5357	1.09	-0.0670	0.2212	0.7619	0.94
Male								
Race								
Non-White	0.0012	0.1257	0.9924	1.00	0.3780	0.1923	0.0494	1.46
White								
Frequency of Cancer Screening	-0.3311	0.1142	0.0038	0.72	-0.0497	0.2547	0.8453	0.95
Frequency of Health Care Utilization	-0.0014	0.0003	<.0001	1.00	-0.0020	0.0013	0.1396	1.00
Risk Factors								
Alcohol Abuse	0.5515	0.2346	0.0187	1.74	0.2986	0.4694	0.5247	1.35
Obesity	0.0222	0.3077	0.9424	1.02	0.9462	0.3685	0.0102	2.58
Tobacco Smoke	0.4850	0.2424	0.0454	1.62	0.4809	0.4642	0.3003	1.62
Chronic Pancreatitis	2.5857	0.2593	<.0001	13.27	2.5450	0.5092	<.0001	12.74
H. pylori Infection	0.3010	0.5869	0.608	1.35	1.1996	1.0298	0.2441	3.32
Diabetes Mellitus	0.7189	0.1365	<.0001	2.05	1.3882	0.2149	<.0001	4.01
Cirrhosis	0.4423	0.4057	0.2756	1.56	1.3547	0.5804	0.0196	3.88

Table 9.13: Effect of Covariates on the Incidence of Bladder cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.4948	0.1068	<.0001	0.61	0.0168	0.1640	0.9183	1.02
Age groups								
75-100 years old	-0.4460	0.1349	0.0009	0.64	-0.1840	0.1970	0.3503	0.83
65-74 years old	-0.3090	0.1244	0.013	0.73	-0.9141	0.2394	0.0001	0.40
50-64 years old								
Genders								
Female	-0.7376	0.1071	<.0001	0.48	-1.0103	0.1679	<.0001	0.36
Male								
Race								
Non-White	-0.2278	0.1097	0.0379	0.80	-0.5558	0.1634	0.0007	0.57
White								
Frequency of Cancer Screening	0.1400	0.0433	0.0012	1.15	-0.0325	0.2105	0.8772	0.97
Frequency of Health Care Utilization	0.0004	0.0002	0.1057	1.00	0.0031	0.0007	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.2752	0.2029	0.1749	1.32	0.2320	0.3173	0.4646	1.26
Obesity	0.2794	0.2420	0.2482	1.32	0.7157	0.3416	0.0362	2.05
Tobacco Smoke	0.7876	0.1923	<.0001	2.20	0.7020	0.3141	0.0254	2.02
Medication exposures								
Cyclophosphamide	1.8513	0.7091	0.009	6.37	2.1320	1.0039	0.0337	8.43

Table 9.14: Effect of Covariates on the Incidence of Kidney cancer in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.3483	0.1366	0.0108	0.71	-0.2252	0.1917	0.2401	0.80
Age groups								
75-100 years old	-0.7543	0.1860	<.0001	0.47	-0.2186	0.2429	0.3682	0.80
65-74 years old	-0.3481	0.1553	0.025	0.71	-0.4274	0.2654	0.1073	0.65
50-64 years old								
Genders								
Female	-0.6516	0.1326	<.0001	0.52	-0.5125	0.2012	0.0109	0.60
Male								
Race								
Non-White	-0.0945	0.1295	0.4655	0.91	0.2383	0.1841	0.1956	1.27
White								
Frequency of Cancer Screening	0.1047	0.0484	0.0304	1.11	0.1199	0.1420	0.3982	1.13
Frequency of Health Care Utilization	-0.0001	0.0003	0.8543	1.00	0.0033	0.0007	<.0001	1.00
Risk Factors								
Alcohol Abuse	-0.0984	0.2494	0.6931	0.91	0.0803	0.3485	0.8177	1.08
Obesity	0.3980	0.2319	0.0861	1.49	0.5834	0.3051	0.0558	1.79
Tobacco Smoke	0.5270	0.2208	0.017	1.69	0.5148	0.3258	0.1141	1.67
Hypertension	0.8956	0.1384	<.0001	2.45	1.3754	0.2135	<.0001	3.96

Table 9.15: Effect of Covariates on the Incidence of GI events in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	**Standard Error**	**p-value**	**Hazard Ratio**	**Coefficient**	**Standard Error**	**p-value**	**Hazard Ratio**
NSAID exposure	-0.7199	0.0233	<.0001	0.49	-0.3739	0.0304	<.0001	0.69
Age groups								
75-100 years old	-1.4642	0.0325	<.0001	0.23	-1.0437	0.0374	<.0001	0.35
65-74 years old	-1.2685	0.0289	<.0001	0.28	-1.5771	0.0462	<.0001	0.21
50-64 years old								
Genders								
Female	-0.1793	0.0234	<.0001	0.84	-0.1653	0.0323	<.0001	0.85
Male								
Race								
Non-White	0.1881	0.0225	<.0001	1.21	0.1173	0.0283	<.0001	1.12
White								
Frequency of Cancer Screening	0.1434	0.0069	<.0001	1.15	0.1829	0.0199	<.0001	1.20
Frequency of Health Care Utilization	0.0003	0.0000	<.0001	1.00	0.0030	0.0001	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.7025	0.0320	<.0001	2.02	0.8172	0.0444	<.0001	2.26
Obesity	0.4575	0.0352	<.0001	1.58	0.3751	0.0514	<.0001	1.46
Tobacco Smoke	0.5233	0.0346	<.0001	1.69	0.4887	0.0491	<.0001	1.63
Emphysema	0.3429	0.0401	<.0001	1.41	0.2005	0.0633	0.0015	1.22
Chronic Bronchitis	0.3665	0.0314	<.0001	1.44	0.1887	0.0527	0.0003	1.21
H. pylori Infection	1.2327	0.0573	<.0001	3.43	1.4385	0.1028	<.0001	4.21
GI protective agents	1.5263	0.0313	<.0001	4.60	1.8206	0.0398	<.0001	6.18
Corticosteroids	0.0338	0.0218	0.1209	1.03	-0.0940	0.0324	0.0037	0.91
Anticoagulants	0.1044	0.0259	<.0001	1.11	0.1044	0.0414	0.0117	1.11
Cephalosporines	-0.0024	0.0250	0.9221	1.00	0.1840	0.0319	<.0001	1.20

Table 9.16: Effect of Covariates on the Incidence of Renal events in the Georgia and North Carolina Medicaid Cohort

Variable	The Georgia Cohort				The North Carolina Cohort			
	Coefficient	Standard Error	p-value	Hazard Ratio	Coefficient	Standard Error	p-value	Hazard Ratio
NSAID exposure	-0.9097	0.0259	<.0001	0.40	-0.6168	0.0397	<.0001	0.54
Age groups								
75-100 years old	-0.7654	0.0356	<.0001	0.47	-0.4806	0.0507	<.0001	0.62
65-74 years old	-0.5287	0.0311	<.0001	0.59	-0.4951	0.0523	<.0001	0.61
50-64 years old								
Genders								
Female	-0.1509	0.0270	<.0001	0.86	-0.2518	0.0428	<.0001	0.78
Male								
Race								
Non-White	0.6638	0.0270	<.0001	1.94	0.5751	0.0400	<.0001	1.78
White								
Frequency of Cancer Screening	-0.0440	0.0117	0.0002	0.96	-0.0040	0.0364	0.913	1.00
Frequency of Health Care Utilization	0.0008	0.0000	<.0001	1.00	0.0012	0.0002	<.0001	1.00
Risk Factors								
Alcohol Abuse	0.2607	0.0432	<.0001	1.30	0.2305	0.0744	0.0019	1.26
Obesity	0.1574	0.0396	<.0001	1.17	-0.1293	0.0697	0.0637	0.88
Tobacco Smoke	0.2717	0.0440	<.0001	1.31	0.2405	0.0752	0.0014	1.27
Hypertension	0.5521	0.0281	<.0001	1.74	0.9890	0.0458	<.0001	2.69
Diabetes Mellitus	0.6914	0.0262	<.0001	2.00	0.7742	0.0421	<.0001	2.17
Congestive Heart Failure	0.7698	0.0261	<.0001	2.16	1.0203	0.0441	<.0001	2.77
Cirrhosis	0.6454	0.0778	<.0001	1.91	0.5094	0.1274	<.0001	1.66
Medication exposures								
Diuretics	0.2442	0.0295	<.0001	1.28	0.3450	0.0457	<.0001	1.41
ACE inhibitors	0.4617	0.0267	<.0001	1.59	0.2863	0.0407	<.0001	1.33
Antibiotics								
Aminoglycosides	0.2274	0.0719	0.0016	1.26	0.5292	0.1305	<.0001	1.70
Cephalosporines	0.0390	0.0277	0.1595	1.04	0.2241	0.0407	<.0001	1.25
Vancomycins	0.4268	0.0772	<.0001	1.53	0.7378	0.1337	<.0001	2.09
Allopurinal	0.6582	0.0307	<.0001	1.93	0.8028	0.0556	<.0001	2.23
Cyclosporine	1.3551	0.1585	<.0001	3.88	0.8382	0.2846	0.0032	2.31

Table 9.17: Effect of specific NSAID use on Incidence of Colorectal cancer in Georgia Medicaid cohort

NSAID exposure	Person-years	Colorectal cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	249,536	197	78.95	0.68	0.90 (0.76, 1.05)
Non-Selective Cox Inhibitors	336,748	112	33.26	0.29	
Fenoprofen	908,981	814	89.55	0.77	0.89 (0.74, 1.08)
Ibuprofen	164,606	130	78.98	0.68	0.85 (0.76, 0.96)
Idomethacin	617,063	543	88.00	0.76	0.89 (0.75, 1.04)
Naproxen	226,044	178	78.75	0.68	0.90 (0.78, 1.04)
Sulindac	348,875	278	79.68	0.69	0.91 (0.74, 1.11)
Others NSAIDs	138,543	104	75.07	0.65	0.90 (0.78, 1.03)
Cox-2 Inhibitors	422,290	325	76.96	0.66	0.25 (0.20, 0.30)
None	400,440	464	115.87	Reference	Reference

Table 9.18: Effect of specific NSAID use on Incidence of Colorectal cancer in North Carolina Medicaid Cohort

NSAID exposure	Person-years	Colorectal cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,132	45	70.17	0.95	1.02 (0.74, 1.39)
Non-Selective Cox Inhibitors	446,612	292	65.38	0.89	
Fenoprofen	8,724	6	68.78	0.93	0.99 (0.44, 2.22)
Ibuprofen	190,166	127	66.78	0.91	0.84 (0.69, 1.03)
Idomethacin	60,420	36	59.58	0.81	0.84 (0.60, 1.18)
Naproxen	160,601	87	54.17	0.74	0.69 (0.54, 0.87)
Sulindac	33,403	19	56.88	0.77	0.83 (0.52, 1.31)
Others NSAIDs	278,446	165	59.26	0.80	0.75 (0.62, 0.91)
None	480,846	354	73.62	Reference	Reference

Table 9.19: Effect of specific NSAID use on Incidence of Study Outcomes in Georgia cohort

NSAID exposure	Person-years	Esophageal cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	249,925	60	24.01	0.69	0.92 (0.69, 1.23)
Non-Selective Cox Inhibitors	910,832	229	25.14	0.72	
Fenoprofen	164,954	36	21.82	0.63	0.83 (0.58, 1.19)
Ibuprofen	618,441	149	24.09	0.69	0.66 (0.53, 0.82)
Idomethacin	226,597	60	26.48	0.76	0.95 (0.72, 1.27)
Naproxen	349,917	72	20.58	0.59	0.63 (0.48, 0.83)
Sulindac	138,901	32	23.04	0.66	1.09 (0.75, 1.58)
Others NSAIDs	423,307	94	22.21	0.64	0.89 (0.69, 1.15)
Cox-2 Inhibitors	338,067	33	9.76	0.28	0.21 (0.14, 0.30)
None	400,623	139	34.70	Reference	Reference
NSAID exposure	Person-years	Gastric cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	249,736	114	45.65	0.97	0.92 (0.74, 1.14)
Non-Selective Cox Inhibitors	910,153	413	45.38	0.97	
Fenoprofen	164,763	85	51.59	1.10	1.07 (0.84, 1.37)
Ibuprofen	617,942	264	42.72	0.91	0.71 (0.60, 0.84)
Idomethacin	226,277	116	51.26	1.09	1.05 (0.84, 1.30)
Naproxen	349,402	162	46.36	0.99	0.85 (0.70, 1.04)
Sulindac	138,779	62	44.68	0.95	1.05 (0.80, 1.38)
Others NSAIDs	422,907	204	48.24	1.03	1.08 (0.90, 1.31)
Cox-2 Inhibitors	337,251	82	24.31	0.52	0.27 (0.21, 0.35)
None	400,581	188	46.93	Reference	Reference
NSAID exposure	Person-years	Liver cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	250,098	76	30.39	0.59	0.73 (0.57, 0.94)
Non-Selective Cox Inhibitors	910,902	389	42.70	0.83	
Fenoprofen	164,991	74	44.85	0.87	1.17 (0.90, 1.50)
Ibuprofen	618,567	251	40.58	0.79	0.82 (0.69, 0.97)
Idomethacin	226,587	74	32.66	0.64	0.74 (0.58, 0.96)
Naproxen	349,957	145	41.43	0.81	0.96 (0.79, 1.18)
Sulindac	138,928	52	37.43	0.73	1.09 (0.81, 1.46)
Others NSAIDs	423,402	153	36.14	0.70	0.89 (0.73, 1.08)
Cox-2 Inhibitors	338,159	54	15.97	0.31	0.24 (0.18, 0.32)
None	400,675	206	51.41	Reference	Reference
NSAID exposure	Person-years	Pancreatic cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	250,144	62	24.79	1.24	1.04 (0.78, 1.40)
Non-Selective Cox Inhibitors	911,196	227	24.91	1.25	
Fenoprofen	165,003	40	24.24	1.21	0.96 (0.68, 1.35)
Ibuprofen	618,687	155	25.05	1.25	1.01 (0.80, 1.28)
Idomethacin	226,633	56	24.71	1.24	1.01 (0.75, 1.37)
Naproxen	350,058	90	25.71	1.29	1.13 (0.87, 1.48)
Sulindac	138,979	43	30.94	1.55	1.39 (1.00, 1.95)
Others NSAIDs	423,497	100	23.61	1.18	1.04 (0.80, 1.35)
Cox-2 Inhibitors	338,356	30	8.87	0.44	0.23 (0.15, 0.34)
None	400,664	80	19.97	Reference	Reference

Table 9.19 (cont.): Effect of specific NSAID use on Incidence of Study Outcomes in GA cohort

NSAID exposure	Person-years	Bladder cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	249,920	67	26.81	0.72	1.04 (0.79, 1.37)
Non-Selective Cox Inhibitors	910,568	252	27.68	0.74	
Fenoprofen	164,854	40	24.26	0.65	0.91 (0.65, 1.27)
Ibuprofen	618,322	158	25.55	0.69	0.78 (0.63, 0.96)
Idomethacin	226,546	42	18.54	0.50	0.64 (0.46, 0.89)
Naproxen	349,833	75	21.44	0.58	0.72 (0.55, 0.94)
Sulindac	138,909	32	23.04	0.62	0.95 (0.66, 1.38)
Others NSAIDs	423,150	111	26.23	0.71	1.07 (0.84, 1.36)
Cox-2 Inhibitors	337,916	46	13.61	0.37	0.35 (0.26, 0.49)
None	400,666	149	37.19	Reference	Reference
NSAID exposure	Person-years	Kidney cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	250,029	50	20.00	0.97	1.02 (0.74, 1.41)
Non-Selective Cox Inhibitors	910,823	191	20.97	1.01	
Fenoprofen	164,934	22	13.34	0.64	0.59 (0.38, 0.92)
Ibuprofen	618,521	129	20.86	1.01	0.93 (0.72, 1.19)
Idomethacin	226,589	43	18.98	0.92	0.89 (0.64, 1.25)
Naproxen	349,936	63	18.00	0.87	0.78 (0.57, 1.05)
Sulindac	138,866	20	14.40	0.70	0.74 (0.46, 1.17)
Others NSAIDs	423,242	95	22.45	1.08	1.39 (1.06, 1.82)
Cox-2 Inhibitors	338,112	33	9.76	0.47	0.30 (0.20, 0.43)
None	400,681	83	20.71	Reference	Reference
NSAID exposure	Person-years	GI events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	238,081	1,734	728.32	0.92	0.90 (0.85, 0.95)
Non-Selective Cox Inhibitors	878,330	6,634	755.30	0.96	
Fenoprofen	157,598	1,219	773.49	0.98	0.96 (0.91, 1.03)
Ibuprofen	594,300	4,279	720.01	0.91	0.72 (0.69, 0.75)
Idomethacin	215,895	1,531	709.14	0.90	0.86 (0.81, 0.91)
Naproxen	330,899	2,305	696.59	0.88	0.77 (0.74, 0.81)
Sulindac	132,960	869	653.58	0.83	0.91 (0.85, 0.98)
Others NSAIDs	403,373	2,773	687.45	0.87	0.83 (0.79, 0.87)
Cox-2 Inhibitors	311,908	970	310.99	0.39	0.25 (0.23, 0.26)
None	398,962	3,147	788.80	Reference	Reference
NSAID exposure	Person-years	Renal Events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	244,786	1,300	531.08	0.78	0.83 (0.78, 0.89)
Non-Selective Cox Inhibitors	894,332	5,046	564.22	0.82	
Fenoprofen	161,848	889	549.28	0.80	0.88 (0.82, 0.95)
Ibuprofen	606,496	3,261	537.68	0.79	0.65 (0.62, 0.68)
Idomethacin	219,976	1,491	677.80	0.99	0.88 (0.83, 0.94)
Naproxen	341,891	1,560	456.29	0.67	0.67 (0.63, 0.71)
Sulindac	135,177	820	606.61	0.89	1.04 (0.96, 1.12)
Others NSAIDs	415,031	1,983	477.80	0.70	0.81 (0.77, 0.85)
Cox-2 Inhibitors	327,113	676	206.66	0.30	0.23 (0.21, 0.25)
None	398,649	2,729	684.56	Reference	Reference

Table 9.20: Effect of specific NSAID use on Incidence of Study Outcomes in North Carolina cohort

NSAID exposure	Person-years	Esophagus cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,285	5	7.78	0.58	0.50 (0.20, 1.25)
Non-Selective Cox Inhibitors	447,335	62	13.86	1.04	
Fenoprofen	8,752	2	22.85	1.72	1.31 (0.32, 5.33)
Ibuprofen	190,614	33	17.31	1.30	0.87 (0.57, 1.31)
Idomethacin	60,527	5	8.26	0.62	0.38 (0.16, 0.95)
Naproxen	160,902	25	15.54	1.17	0.93 (0.58, 1.47)
Sulindac	33,456	5	14.94	1.12	1.30 (0.52, 3.23)
Others NSAIDs	278,913	27	9.68	0.73	0.40 (0.25, 0.63)
None	481,092	64	13.30	Reference	Reference
NSAID exposure	Person-years	Gastric cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,228	19	29.58	1.48	0.82 (0.50, 1.35)
Non-Selective Cox Inhibitors	447,157	130	29.07	1.46	
Fenoprofen	8,743	3	34.31	1.72	0.78 (0.24, 2.48)
Ibuprofen	190,491	58	30.45	1.53	0.69 (0.50, 0.96)
Idomethacin	60,461	23	38.04	1.91	0.96 (0.61, 1.51)
Naproxen	160,771	56	34.83	1.75	0.99 (0.71, 1.37)
Sulindac	33,428	8	23.93	1.20	0.84 (0.41, 1.72)
Others NSAIDs	278,774	85	30.49	1.53	0.93 (0.69, 1.26)
None	481,046	96	19.96	Reference	Reference
NSAID exposure	Person-years	Liver cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,285	19	29.56	1.26	1.07 (0.65, 1.74)
Non-Selective Cox Inhibitors	447,329	124	27.72	1.18	
Fenoprofen	8,753	4	45.70	1.95	1.37 (0.50, 3.72)
Ibuprofen	190,629	59	30.95	1.32	0.91 (0.67, 1.25)
Idomethacin	60,532	18	29.74	1.27	0.90 (0.55, 1.48)
Naproxen	160,883	52	32.32	1.38	1.09 (0.78, 1.52)
Sulindac	33,454	5	14.95	0.64	0.55 (0.22, 1.34)
Others NSAIDs	278,926	67	24.02	1.02	0.70 (0.51, 0.95)
None	481,096	113	23.49	Reference	Reference
NSAID exposure	Person-years	Pancreatic cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,302	9	14.00	1.10	1.09 (0.54, 2.19)
Non-Selective Cox Inhibitors	447,425	54	12.07	0.95	
Fenoprofen	8,753	0	0.00	0.00	na
Ibuprofen	190,675	24	12.59	0.99	0.79 (0.49, 1.27)
Idomethacin	60,528	7	11.56	0.91	0.67 (0.31, 1.48)
Naproxen	160,930	18	11.18	0.88	0.73 (0.43, 1.25)
Sulindac	33,464	7	20.92	1.65	1.59 (0.73, 3.49)
Others NSAIDs	279,002	35	12.54	0.99	0.82 (0.54, 1.27)
None	481,081	61	12.68	Reference	Reference

Table 9.20 (continue):Effect of specific NSAID use on Incidence of Study Outcomes in North Carolina cohort

NSAID exposure	Person-years	Bladder cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,276	16	24.89	1.56	1.40 (0.81, 2.40)
Non-Selective Cox Inhibitors	447,299	83	18.56	1.16	
Fenoprofen	8,742	4	45.76	2.86	2.17 (0.79, 5.92)
Ibuprofen	190,622	34	17.84	1.11	0.84 (0.56, 1.26)
Idomethacin	60,504	9	14.88	0.93	0.74 (0.37, 1.47)
Naproxen	160,875	31	19.27	1.20	1.01 (0.66, 1.54)
Sulindac	33,458	2	5.98	0.37	0.33 (0.08, 1.34)
Others NSAIDs	278,872	49	17.57	1.10	0.93 (0.64, 1.35)
None	481,011	77	16.01	Reference	Reference
NSAID exposure	Person-years	Kidney cancer	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	64,280	10	15.56	1.39	0.79 (0.40, 1.55)
Non-Selective Cox Inhibitors	447,250	73	16.32	1.45	
Fenoprofen	8,735	5	57.24	5.10	3.07 (1.23, 7.64)
Ibuprofen	190,588	27	14.17	1.26	0.60 (0.38, 0.94)
Idomethacin	60,503	12	19.83	1.77	0.94 (0.51, 1.75)
Naproxen	160,833	32	19.90	1.77	1.10 (0.71, 1.72)
Sulindac	33,439	7	20.93	1.86	1.28 (0.59, 2.78)
Others NSAIDs	278,816	44	15.78	1.41	0.83 (0.55, 1.24)
None	481,069	54	11.23	Reference	Reference
NSAID exposure	Person-years	GI events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	61,699	505	818.49	1.86	0.97 (0.88, 1.06)
Non-Selective Cox Inhibitors	436,705	3,051	698.64	1.59	
Fenoprofen	8,356	93	1,112.93	2.53	1.14 (0.92, 1.40)
Ibuprofen	184,821	1,289	697.43	1.59	0.74 (0.69, 0.79)
Idomethacin	58,462	430	735.52	1.67	0.85 (0.77, 0.94)
Naproxen	155,827	1,092	700.78	1.59	0.74 (0.69, 0.80)
Sulindac	32,642	219	670.92	1.53	0.89 (0.78, 1.02)
Others NSAIDs	271,079	1,878	692.79	1.58	0.75 (0.71, 0.80)
None	478,948	2,106	439.71	Reference	Reference
NSAID exposure	Person-years	Renal Events	Rate per 100,000 Person-Years	Unadjusted RR	Multivariate adjusted RR (95% CI)
Aspirin	63,465	258	406.53	1.40	0.97 (0.85, 1.11)
Non-Selective Cox Inhibitors	443,341	1,601	361.12	1.24	
Fenoprofen	8,639	43	497.73	1.71	1.01 (0.75, 1.37)
Ibuprofen	188,509	637	337.91	1.16	0.61 (0.56, 0.67)
Idomethacin	59,303	362	610.42	2.10	0.96 (0.85, 1.08)
Naproxen	159,323	580	364.04	1.25	0.73 (0.66, 0.81)
Sulindac	32,973	172	521.64	1.79	1.14 (0.97, 1.33)
Others NSAIDs	276,350	887	320.97	1.10	0.59 (0.54, 0.64)
None	479,896	1,397	291.10	Reference	Reference

Table 9.21: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in Georgia Medicaid Cohort after excluding 62,086 persons admitted to LTC >1 year

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Colorectal Cancer	Any Use	765,010	715	93.46	0.00	0.53 (0.46, 0.61)
	None	260,057	358	137.66	Reference	Reference
Esophageal cancer	Any Use	766,709	222	28.95	0.61	0.35 (0.28, 0.45)
	None	260,110	123	47.29	Reference	Reference
Gastric Cancer	Any Use	766,066	400	52.21	0.88	0.54 (0.44, 0.65)
	None	260,080	155	59.60	Reference	Reference
Liver Cancer	Any Use	766,743	374	48.78	0.67	0.53 (0.44, 0.64)
	None	260,148	188	72.27	Reference	Reference
Pancreatic Cancer	Any Use	767,086	204	26.59	1.03	0.83 (0.62, 1.11)
	None	260,135	67	25.76	Reference	Reference
Bladder Cancer	Any Use	766,425	226	29.49	0.63	0.53 (0.42, 0.67)
	None	260,156	121	46.51	Reference	Reference
Kidney Cancer	Any Use	766,728	176	22.95	0.81	0.57 (0.43, 0.76)
	None	260,153	74	28.44	Reference	Reference
GI Events	Any Use	735,556	6,251	849.83	0.85	0.45 (0.43, 0.47)
	None	259,109	2,580	995.72	Reference	Reference
Renal Events	Any Use	751,748	4,499	598.47	0.70	0.34 (0.32, 0.36)
	None	258,671	2,214	855.91	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

Table 9.22: Sensitivity Analysis: Effect of NSAID Use on Incidence of Study Events of Interest in North Carolina Medicaid Cohort after excluding 307 persons admitted to LTC >1 year

Study Events of Interest	NSAIDs	Person-Years	Cases	Rate per 100,000 Person-Years	Unadjusted RR	Adjusted RR** (95% CI)
Colorectal Cancer	Any Use	459,126	307	66.87	0.91	0.74 (0.63, 0.86)
	None	479,448	352	73.42	Reference	Reference
Esophagus Cancer	Any Use	459,865	63	13.70	1.03	0.49 (0.34, 0.71)
	None	479,693	64	13.34	Reference	Reference
Gastric Cancer	Any Use	459,687	132	28.72	1.43	0.77 (0.58, 1.03)
	None	479,647	96	20.01	Reference	Reference
Liver Cancer	Any Use	459,864	128	27.83	1.18	0.83 (0.64, 1.09)
	None	479,697	113	23.56	Reference	Reference
Pancreatic Cancer	Any Use	459,965	57	12.39	0.97	0.68 (0.47, 1.00)
	None	479,682	61	12.72	Reference	Reference
Bladder Cancer	Any Use	459,834	87	18.92	1.18	1.01 (0.74, 1.40)
	None	479,612	77	16.05	Reference	Reference
Kidney Cancer	Any Use	459,790	73	15.88	1.41	0.80 (0.55, 1.16)
	None	479,670	54	11.26	Reference	Reference
GI Events	Any Use	449,069	3,133	697.67	1.59	0.69 (0.65, 0.73)
	None	477,555	2,100	439.74	Reference	Reference
Renal Events	Any Use	455,813	1,654	362.87	1.24	0.54 (0.50, 0.58)
	None	478,498	1,396	291.75	Reference	Reference

LTC, long-term care facilities; NSAIDs, non-steroidal anti-inflammatory drugs; RR,relative risk; GI, gastrointestinal
** Adjusted Relative Risk and 95% CI estimated by Cox-proportional hazard regression model including covariates, e.g. age, gender, race, alcoholism, obesity

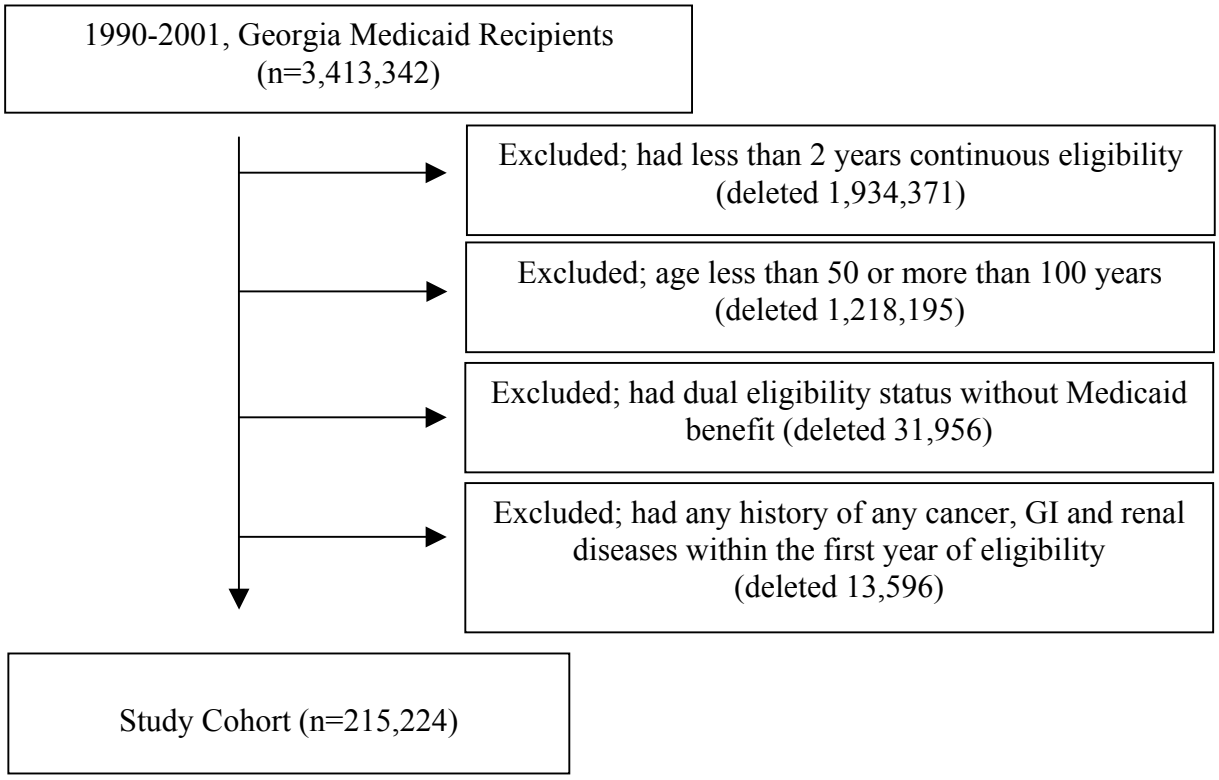

Figure 9.1: Flow chart of Georgia Medicaid cohort subjects

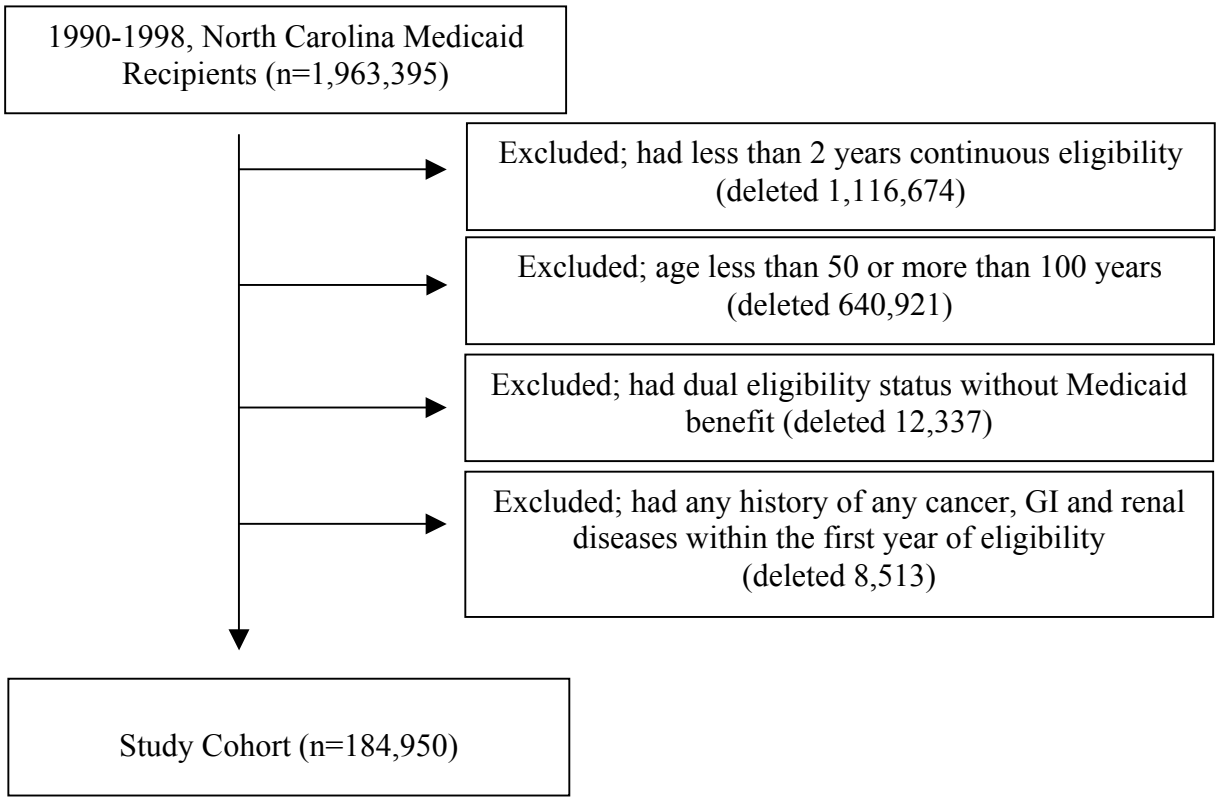

Figure 9.2: Flow chart of North Carolina Medicaid cohort subjects

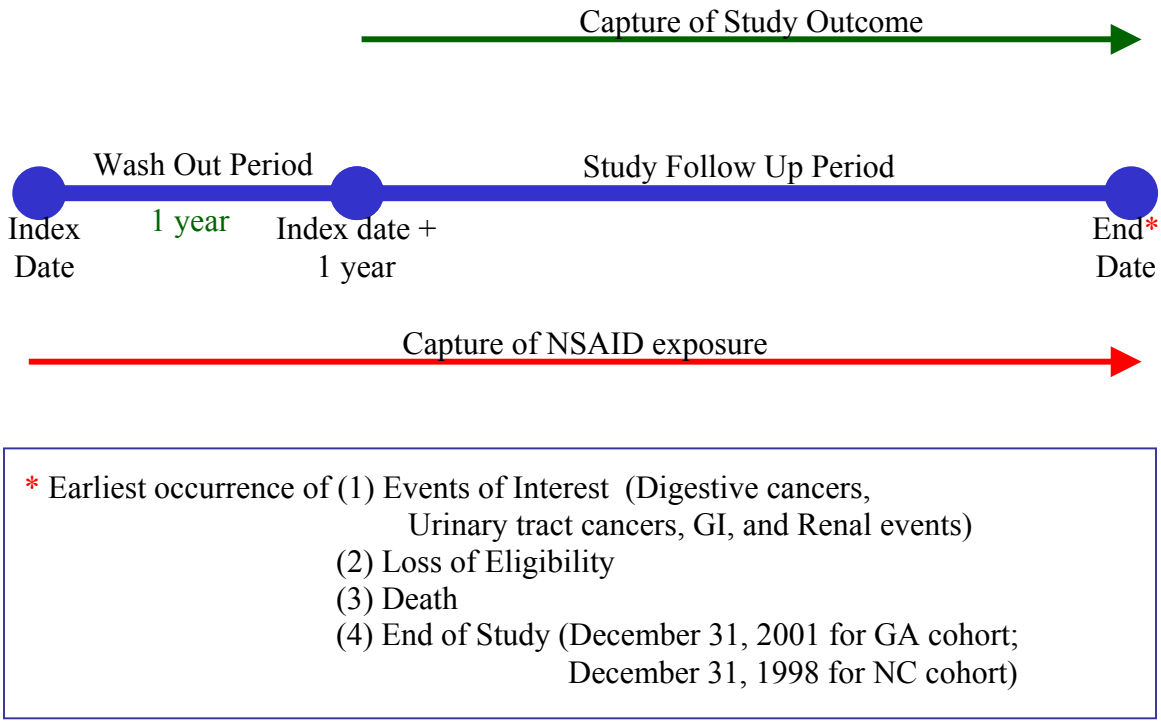

Figure 9.3: Temporal pattern of cohort

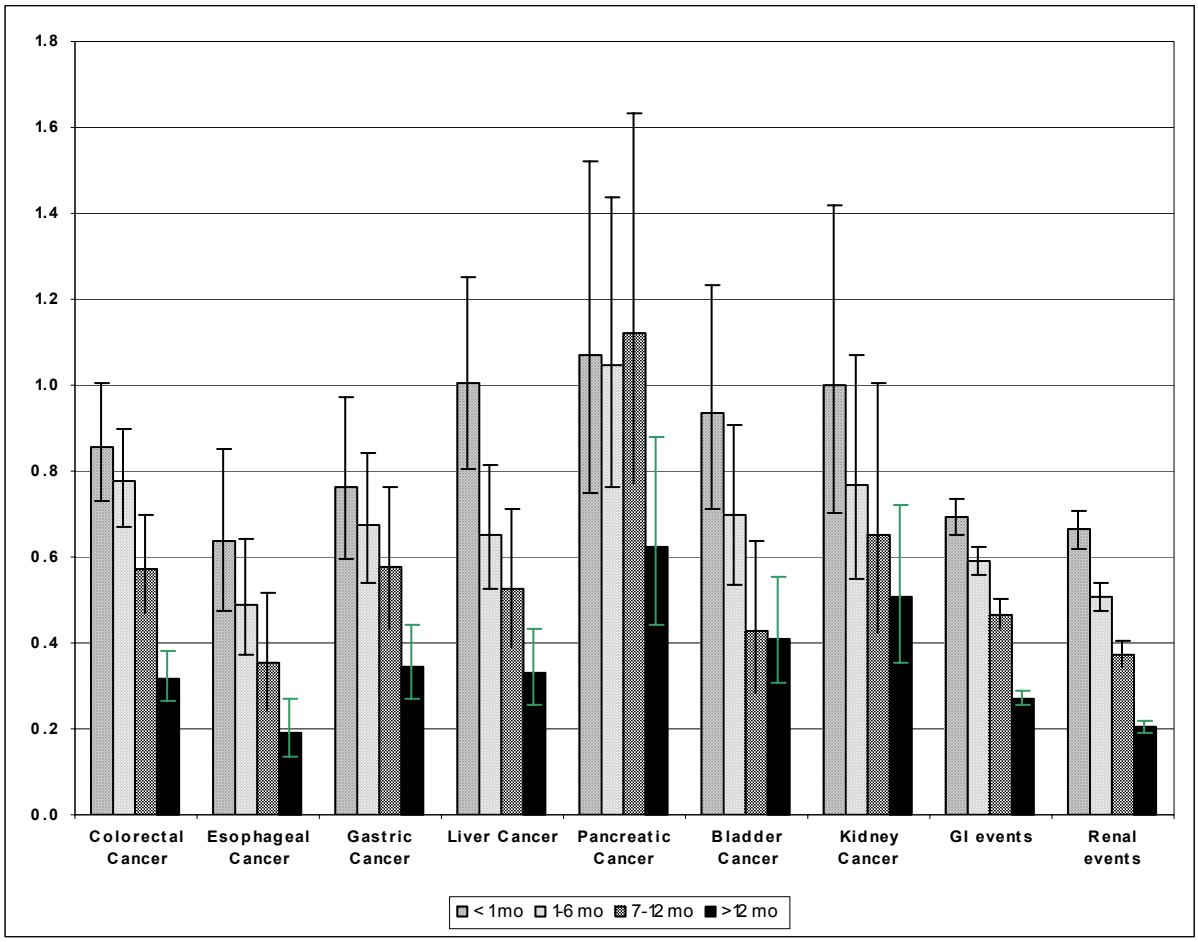

Figure 9.4: Effect of Cumulative NSAID exposure on the Relative Risk of Digestive cancers, Urinary tract cancers, GI and Renal events in Georgia Cohort.

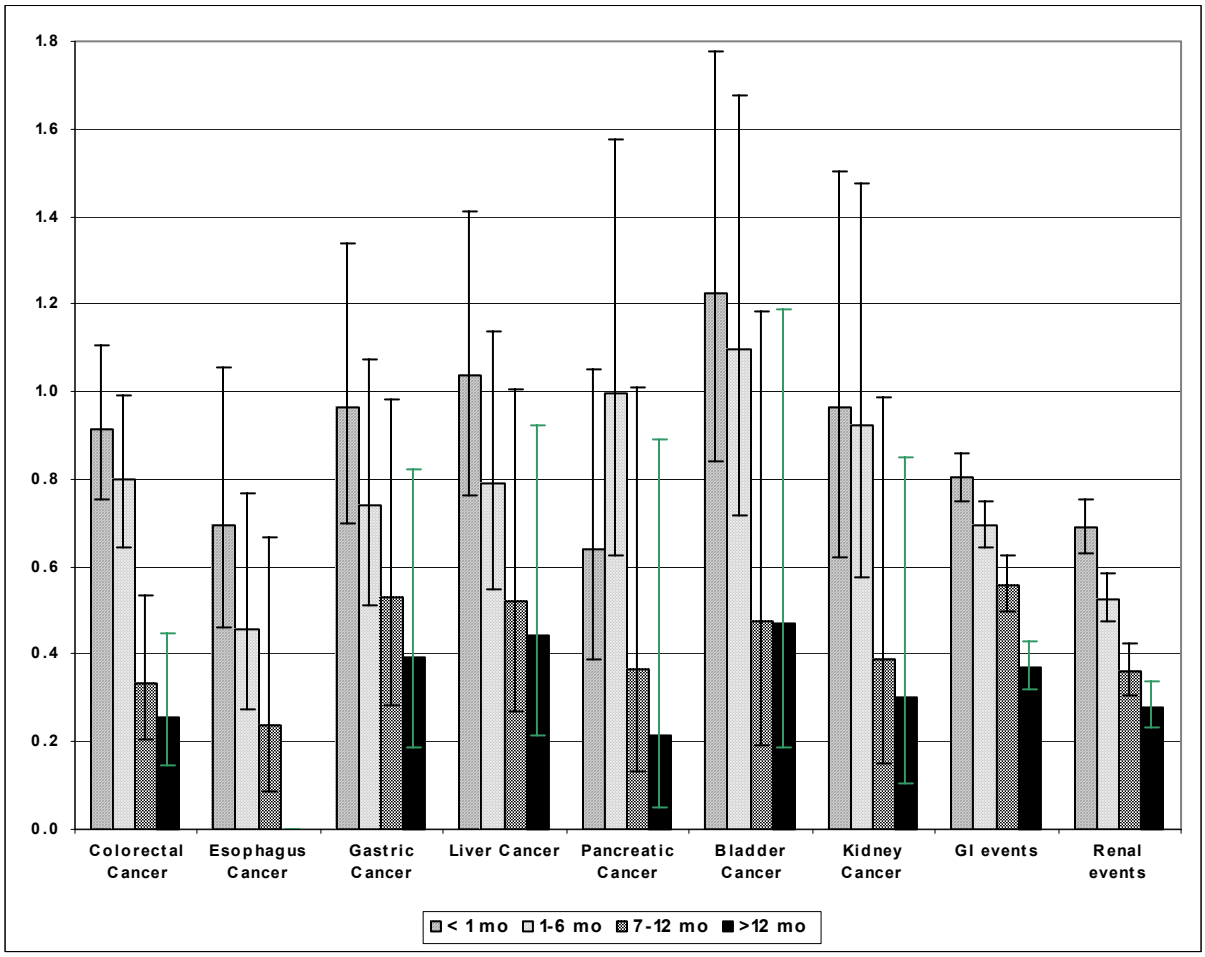

Figure 9.5: Effect of Cumulative NSAID exposure on the Relative Risk of Digestive cancers, Urinary tract cancers, GI and Renal events in North Carolina cohort

CHAPTER 10

CONCLUSION

The significant chemopreventive benefit of NSAIDs was established against colorectal, esophageal, lung, prostate, and endometrial cancer. Besides no correlation between incidence rate of pancreatic cancer and NSAID usage, any NSAID exposure was possibly associated with the risk reduction in breast, lung, digestive, gynecologic and urinary tract cancers. Moreover, there was no increased risk of NSAID-related adverse effects with NSAID prescribing in the Medicaid population. We found that the benefit of Cox-2 inhibitors was the most substantial; persons prescribed Cox-2 inhibitors were not only 70% less likely to be diagnosed with cancers, but 75% less likely to experience NSAID-related adverse events as well.

The dose-response relationship between NSAID use and incident cancer, as well as their common adverse events was delineated. The higher the cumulative exposure, the lower the incident cancer and NSAID-related adverse event risks. For instance, multivariate-adjusted incidence cancer and NSAID-related adverse events rates of ones who had more than 1 years of NSAID exposure were lower than those of ones who had no exposure.

The results of this study support the hypothesis that NSAIDs have chemopreventive value against cancer, especially colorectal, esophageal, lung, prostate, and endometrial cancer. Therefore, we would urge additional large perspective cohort studies with more extended period of follow-up and clinical trails in order to validate and examine biochemical components of NSAIDs. Moreover, the questions regarding optimal chemopreventive dose and duration of

NSAIDs are remaining unanswered. Further research in this area with better measures of NSAID use and better controls of behavioral risk factors is needed to examine optimal chemopreventive dose and duration of NSAIDs . This would consequently advice on specific recommendation of NSAID use as chemopreventives.