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Nonsteroidal Anti-inflammatory Drugs and Cyclooxygenase-2 Inhibitors for Primary Prevention of Colorectal Cancer: A Systematic Review Prepared for the U.S. Preventive Services Task Force

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Purpose: To examine the benefits and harms of nonaspirin (non-ASA) nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX-2) inhibitors for the prevention of colorectal cancer (CRC) and adenoma.

Data Sources: MEDLINE (1966 to 2006), EMBASE (1980 to 2006), Cochrane Central Register of Controlled Trials, Cochrane Collaboration's registry of clinical trials, Cochrane Database of Systematic Reviews.

Study Selection: Randomized, controlled trials and case–control and cohort studies of the effectiveness of NSAIDs for the prevention of CRC and colorectal adenoma were identified by multilevel screening by 2 independent reviewers. Systematic reviews of harms were sought.

Data Extraction: Data abstraction, checking, and quality assessment were completed in duplicate.

Data Synthesis: A single cohort study showed no effect of non-ASA NSAIDs on death due to CRC. Colorectal cancer incidence was reduced with non-ASA NSAIDs in cohort studies (relative risk, 0.61 [95% CI, 0.48 to 0.77]) and case–control studies (relative risk, 0.70 [CI, 0.63 to 0.78]). Colorectal adenoma incidence was also reduced with non-ASA NSAID use in cohort studies (relative risk, 0.64 [CI, 0.48 to 0.85]) and case–control studies (relative risk, 0.54 [CI, 0.4 to 0.74]) and by COX-2 inhibitors in randomized, controlled trials (relative risk, 0.72 [CI, 0.68 to 0.77]). The ulcer complication rate associated with non-ASA NSAIDs is 1.5% per year. Compared with non-ASA NSAIDs, COX-2 inhibitors reduce this risk but, in multiyear use, have a higher ulcer complication rate than placebo. Cyclooxygenase-2 inhibitors and nonnaproxen NSAIDs increase the risk for serious cardiovascular events (relative risk, 1.86 [CI, 1.33 to 2.59] for COX-2 inhibitors vs. placebo).

Limitations: Heterogeneity in the dose, duration and frequency of use necessitated careful grouping for analysis.

Conclusions: Cyclooxygenase-2 inhibitors and NSAIDs reduce the incidence of colonic adenomas. Nonsteroidal anti-inflammatory drugs also reduce the incidence of CRC. However, these agents are associated with important cardiovascular events and gastrointestinal harms. The balance of benefits to risk does not favor chemoprevention in average-risk individuals.

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In the United States, cancer is the second leading cause of death after heart disease and is the leading cause of death in persons younger than 65 years of age. Colorectal cancer (CRC) is the second and third leading cause of cancer-related deaths in men and women, respectively, and overall, is the third most common type of cancer in men and women. In 2006, it was estimated that 148 610 new cases of CRC occurred and that 51 170 patients died of the disease (1, 2).

The U.S. Preventive Services Task Force (USPSTF) strongly recommends screening for men and women 50 years of age or older for CRC ("A" recommendation) (3). Biannual fecal occult blood testing can reduce CRC-related death by 21%, and it has been reported that flexible sigmoidoscopy reduces death by 60% for lesions within reach of the instrument. Further, data suggest that sigmoidoscopy followed by colonoscopy when polyps are found could decrease CRC incidence by up to 80% (4). Despite evidence of the effectiveness of several screening methods, adoption of routine CRC screening by eligible individuals, using any method, continues to be low in the United States (5–8).

A CRC chemoprophylactic strategy may be used as a complement to or instead of a screening strategy. Several basic science, population-based, and experimental studies have suggested a protective effect of aspirin (ASA) and non-ASA nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2 inhibitors, on colorectal adenomas and CRC. However, 2 long-term, randomized, controlled trials, the Physicians' Health Study (9) and the Women's Health Study (10), did not show a beneficial effect of low-dose ASA on CRC incidence. Furthermore, these agents are not without harms. Clinically significant gastrointestinal hemorrhage can occur with all of these agents, although it is substantially lower with COX-2 inhibitors. More recently, interest has focused on a potentially prothrombotic effect of selective COX-2 inhibitors and nonnaproxen NSAIDs. In fact, during the conduct of our systematic review, 2 COX-2 inhibitors (rofecoxib and

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valdecoxib) were withdrawn from the U.S. market because of concerns about their cardiovascular toxicity, leaving only celecoxib remaining and uncertainty about the future of others, such as lumiracoxib and etoricoxib. These developments have resulted in uncertainty about the safety of COX-2 inhibitors and non-ASA NSAIDs when used long-term, such as in the setting of CRC prevention (11).

At the request of the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention (CDC), and the USPSTF, we conducted a systematic review to ascertain the effectiveness of non-ASA NSAIDs and COX-2 inhibitors in the chemoprevention of colorectal adenomas, CRC, and CRC-related death in average- to higher-risk individuals. We also examined the harms associated with these agents.

METHODS

Data Sources

We developed the search strategy in MEDLINE and modified it for other databases. The search was limited to English-language reports of human studies. We searched the following databases: MEDLINE (1966 to December [week 4] 2006), EMBASE (1980 to the 14th week of 2005 publication years 2003 to 2005), Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Library Issue 4, 2004. Beyond these dates, we surveyed several sources to ascertain additional potentially eligible studies. PubMed Cancer subset was searched for non-MEDLINE material.

Search terms were derived from the National Cancer Institute (NCI) Cancer topic searches for "colorectal cancer" and "adenomatous polyps." We derived a comprehensive retrieval strategy from the indexing in MEDLINE and EMBASE, investigator-nominated terms, and previous reviews (12–14).

We developed a search strategy in MEDLINE (2003 to the third week of December 2006) to detect recent systematic reviews that appeared to address the harms of non-ASA NSAIDs and COX-2 inhibitors. We implemented a weekly monitoring strategy to detect emerging information on cardiovascular harms associated with COX-2 inhibitors. We also monitored the U.S. Food and Drug Administration News Digest and Health Canada's Health Product Information mailing list for announcements related to COX-2 inhibitors and cardiovascular harms (monitoring dates, 14 January 2005 to 26 May 2005). Beyond these dates, we surveyed several sources to ascertain additional potentially eligible studies.

Study Selection

Citation records were screened to identify potentially relevant articles and retained records were assessed for relevance to identify articles meeting inclusion criteria. A third screening phase was included to discriminate between the different study designs. At each screening stage, 2 members of the review team selected articles for inclusion after an initial calibration exercise. Conflicts were resolved by consensus.

We considered randomized, controlled trials (RCTs); controlled, clinical trials; and observational studies (cohort and case–control studies) of the efficacy of non-ASA NSAIDs and COX-2 inhibitors for inclusion if they fulfilled the population and outcome criteria.

We considered studies for inclusion if participants were at average risk for CRC (that is, no known risk factors for colorectal adenoma or CRC, other than age). We also considered studies of higher-risk individuals with a personal or family history of colorectal adenoma or a family history of sporadic CRC. Included studies addressed the incidence of colorectal adenomas, CRC, or both and CRC-related death or overall death. We excluded studies of high-risk patients with familial adenomatous polyposis or hereditary nonpolyposis colon cancer syndromes (Lynch I or II) and secondary prevention studies of patients with a personal history of CRC.

We sought existing systematic reviews to address the gastrointestinal, cardiovascular, and renal harms associated with the use of non-ASA NSAIDs and COX-2 inhibitors considering the number of reviews already done on these topics.

Data Extraction and Quality Assessment

Several members of the team extracted data independently by using a Web-based system (SRS 4.0, TrialStat Corp., Ottawa, Ontario, Canada). We extracted data by using the PICOS (participant, intervention and exposure, comparator, outcome, and study design) approach.

We used predefined criteria from the USPSTF to assess the quality of included systematic reviews, clinical trials, and observational studies, which we rated as good, fair, or poor (11). This scale relies on 4, 6, 7, and 7 criteria for systematic reviews, case–control studies, cohort studies, and RCTs, respectively. A good rating was given when all criteria were met; a fair rating when at least 80% were met and the study had no fatal flaws; and a poor rating when less than 80% of the criteria were met, when there was a fatal flaw, or both.

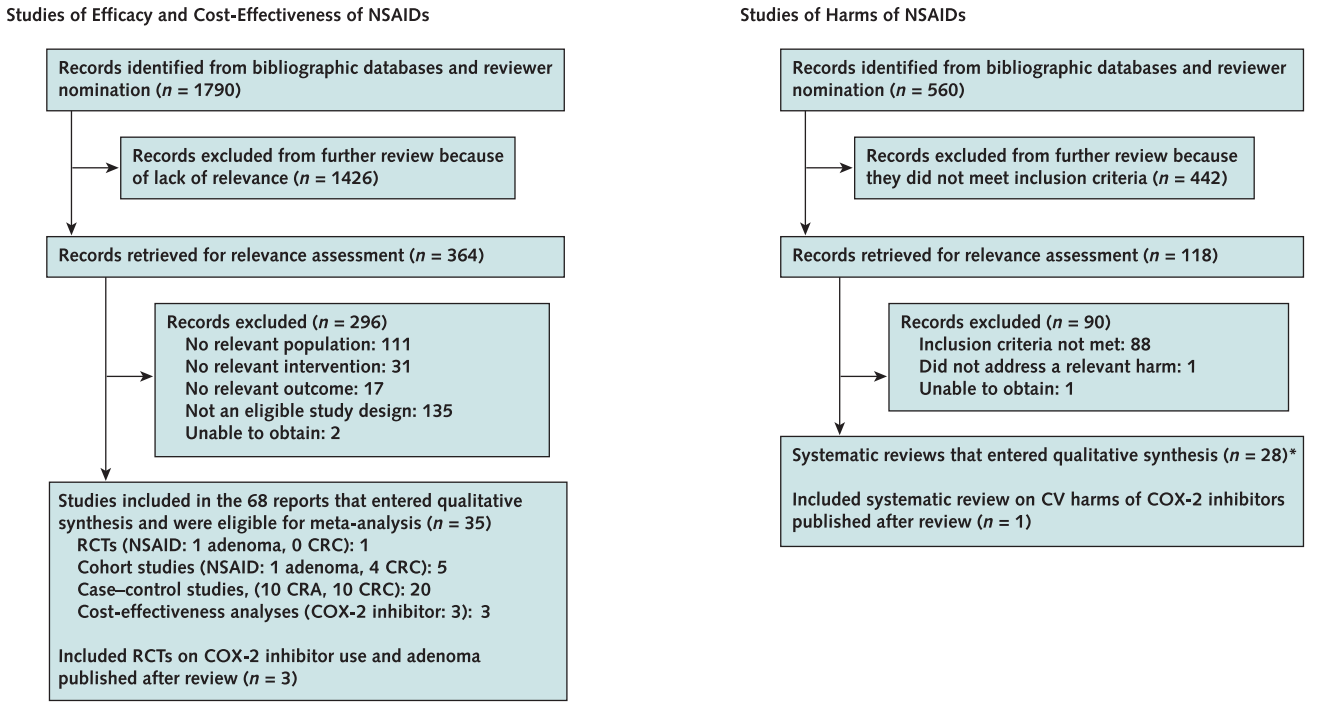
Data Synthesis and Analysis

We used an analytical framework to facilitate study grouping and subsequent data analysis in an effort to minimize clinical heterogeneity. We initially grouped studies by disorder (that is, colorectal adenoma or CRC), study design, study population, and medication exposure and subsequently subcategorized studies based on measures of dose effect, duration of exposure, and secondary outcomes (when reported). Definition of categories, such as "regular use," can be found elsewhere (11).

We summarized and presented harms data from the included systematic reviews as a qualitative synthesis.

We combined results numerically only if clinically and statistically appropriate. We chose relative risk as the effect measure. In case-control studies, a direct estimate of the

Figure. **Study flow diagram.**



Studies not shown but included were acetylsalicylic acid (*ASA*) studies or studies that considered more than 1 intervention, outcome, or both. The Nurses' Health Study (*NHS*) represents an initial publication (46) and a follow-up publication (34) for colorectal cancer (*CRC*) and a separate publication for colorectal adenoma (*CRA*) (47). Three cyclooxygenase (*COX*)-2 inhibitor polyp studies and a systematic review were added after we submitted our report to the U.S. Preventive Services Task Force and the Agency for Health Research and Quality. *11 of these considered harms of ASA. CV = cardiovascular; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial.

relative risk is not possible. However, when event rates are low, as was the case in our review, the odds ratio provides a close approximation of the relative risk. In what follows, we simply refer to the relative risk. We assessed heterogeneity by using the I^2 statistic. We combined studies when I^2 was 50% or less (15). We directly abstracted point estimates of the adjusted relative risks and their 95% CIs from the reports of primary studies. One source of heterogeneity may be study-to-study variation in the method of selecting confounders for which to adjust and the final set of confounders chosen. In **Appendix Tables 1** and **2** (available at www.annals.org), we summarize these characteristics for each study. Further, a detailed discussion of the methodological considerations is presented in the USPSTF report (11). We computed standard errors by dividing the CI width by 2×1.96. We conducted quantitative synthesis by using inverse variance weighting and a random-effects model (17).

Role of the Funding Sources

The evidence synthesis on which this article was based was funded by the CDC, the Agency for Health Research and Quality, and the USPSTF. Its design, conduct, and reporting was based on specific directives from these agencies.

RESULTS

Study Selection

Our literature search yielded 1790 potentially relevant bibliographic records that addressed the use of ASA, COX-2 inhibitors, and other non-ASA NSAIDs (11). For non-ASA NSAIDS, we retrieved 364 articles for relevance assessment, and 29 studies met final inclusion criteria. One study of rofecoxib (18) and 2 studies of celecoxib (19, 20) were published after completion of the task force report (11) and we include them herein.

A CRC-related death in 1 cohort study (21) was reported. The chemoprophylaxis of CRC was addressed in 10 case–control studies (22–31) and 3 cohort studies (32–34). The chemoprophylaxis of colorectal adenoma was addressed in 10 case–control studies (31, 35–43), 1 cohort study (44), and 4 RCTs (18–20, 45). The **Figure** (46, 47) describes the flow of reports through our review, and **Appendix Tables 3, 4,** and **5** (available at www.annals.org) describe the included studies. A table of duplicate and companion articles is available in the AHRQ report (11).

Study Quality and Methodological Considerations

The understanding of the important sources of heterogeneity among the included observational studies is key to interpreting the results of this review and the ASA review

(11), also in this issue of *Annals of Internal Medicine*. This was discussed in detail elsewhere (11), and we present it here in brief. We produced an a priori, hierarchical framework that identified key characteristics that were expected to be common to all the included studies. We used this framework to facilitate study grouping and subsequent data analysis. We anticipated certain key characteristics, such as the dose across studies, to show important heterogeneity. Measuring the dose effect depended on the intervention dose, the frequency and duration of use, and whether the use was current and ongoing or had occurred at some time in the past. For example, some studies defined specific dose levels, whereas in other studies, researchers reported dose effect in terms of frequency of use, such as number of pills per week or prescription refills in a given time period, thereby combining the effects of dose and duration. One way to handle this inconsistency across studies was to define regular use and specific duration intervals in the developed framework (11) to group studies with similar dose effects. Other sources of inconsistency also existed, such as the methods and timing of ascertainment of exposure (for example, questionnaires, patient records, and databases) and outcome (for example, colonoscopy, patient records, and databases). Lastly, the type of NSAIDs used varied among studies between non-ASA NSAIDs alone, ASA included among NSAIDs (herein referred to as "any NSAIDs"), and COX-2 inhibitors alone. We analyzed the data separately for each of these 3 types of exposures. In some situations, individual study differences precluded statistical pooling.

The quality of the included studies was good for 3 of the 4 RCTs, good to fair for the 5 cohort studies, and fair for most of the case–control studies (5 good, 11 fair, and 4 poor).

Colorectal Cancer Mortality

A single cohort study of fair quality assessed the effect of ibuprofen on CRC mortality (21). The study used an administrative database to identify 113 538 participants who filled at least 1 ibuprofen prescription over a 6-year period. A statistically significant increase in all-cause mortality was observed with ibuprofen, but no effect on death due to bowel or rectal cancer was observed (**Table 1**).

Colorectal Cancer Incidence

Table 1 summarizes the effects of regular use of non-ASA NSAIDs on CRC incidence. The available data are limited to observational studies.

Cohort Studies

Three cohort studies assessed the effect of non-ASA NSAIDs on CRC incidence (32–34). The Nurses' Health Study (34) was a large, good-quality, 20-year prospective follow-up of average-risk U.S. women (34). It showed a statistically significant dose-dependent protective effect of non-ASA NSAIDs on CRC. The magnitude of the relative risk reduction was up to 30% in colon cancer, whereas no benefit was observed for rectal cancer alone. When specific dose subgroups were analyzed, patients receiving less than 6 tablets per week or those receiving non-ASA NSAIDs irregularly did not seem to show a reduction in CRC incidence. Two other large administrative database studies of fair quality showed a statistically significant protective effect of regular non-ASA NSAIDs on the incidence of CRC (32, 33).

Case-Control Studies

The regular use of non-ASA NSAIDs and of any NSAIDs was associated with statistically significant reductions in CRC frequency in the pooled analyses (relative risk, 0.70 for non-ASA NSAIDs [22, 23, 25, 49] vs. 0.57 for any NSAIDs [26–29, 31]). Two other case–control studies (1 large prescription database study of good quality [30] and 1 study of fair quality [24]) demonstrated statistically significant reductions in CRC frequency, but their method of quantifying regular NSAID use prevented statistical pooling with the other studies.

Dose and Duration of Use

In cohort studies (33, 34) and case–control studies (22, 30, 31), higher dose levels of any NSAIDs were generally associated with statistically significant relative risk reductions in CRC frequency, whereas lower dose levels were not (**Tables 2** and **3**). Two studies of fair quality (25, 28) demonstrated inconsistent dose effects, which may be due to underpowered subgroup analyses.

Similarly, longer durations of non-ASA NSAID use (that is, beyond 2 to 5 years) generally resulted in statistically significant reductions in risk for CRC, whereas lower durations of use did not (22, 25, 26, 30). The largest and best-quality study in the group demonstrated a statistically significant reduction in risk for CRC with non-ASA NSAID use of at least 11 years but not for shorter durations (30). Small studies of poor quality did not demonstrate a consistent duration effect (27, 31).

Colorectal Adenoma

Randomized, Controlled Trials

In patients with a history of colorectal adenomas, 3 recent, good-quality RCTs on COX-2 inhibitor (celecoxib [19, 20] and rofecoxib [18]) demonstrated statistically significant reductions in the incidence of all adenomas and advanced adenomas over a 3-year follow-up (pooled relative risk, 0.72 [95% CI, 0.68 to 0.77] vs. 0.56 [CI, 0.42 to 0.75], respectively) (**Table 1**). A nonsignificant trend was observed toward a greater relative risk reduction in advanced versus all adenomas for celecoxib (19). However, patients with advanced adenoma seemed to derive less benefit from rofecoxib than those without advanced adenomas (18). Patients also seemed to have a reduced benefit with rofecoxib over time. Further, in a small subgroup of ran-

Table 1. **Chemopreventive Efficacy of Regular Use of Nonsteroidal Anti-inflammatory Drugs (NSAID)***

Study, Year (Reference)	Participants, *n*	Quality Score	Population	Dose and Duration	Relative Risk (95% CI)
Effects on mortality					
Cohort study ($n = 1$)					
North Jutland Population Database; Lipworth et al., 2004 (21)	113 538	Fair	Average-risk men and women	Ibuprofen for ≥5y	All-cause: 1.11 (1.05–1.16)† Bowel cancer: 0.93 (0.6–1.3)† Rectal cancer: 1.46 (0.9–2.3)†
Effects on the incidence of CRC					
Cohort studies ($n = 3$)					
Nurses' Health Study; Chan et al., 2005 (34)	82 911	Good	Average-risk women	≥2 tablets of non-ASA NSAIDs per wk for 20 y	CRC overall: 0.79 (0.64–0.97) Colon cancer: 0.71 (0.56–0.91) Rectal cancer: 1.04 (0.72–1.52)
North Jutland Population Database; Sørensen et al., 2003 (32)	183 693	Fair	Average-risk men and women	≥10 prescriptions for non-ASA NSAIDs over 9 y	Colon cancer: 0.7 (0.6–0.9)‡ Rectal cancer: 0.6 (0.4–0.9)‡
Tennessee Medicaid Program; Smalley et al., 1999 (33)	104 217	Fair	Elderly men and women	Regular use of non-ASA NSAIDs for ≥1 y	0.61 (0.48–0.77)
Case–control studies ($n = 8$)					
García-Rodríguez and Huerta-Alvarez, 2001 (22)	12 002	Good	Average-risk men and women	Regular use of non-ASA NSAIDs for ≥1 y	0.7 (0.63–0.78)
Slattery et al., 2004 (26)	4403	Fair	Average-risk men and women	Regular use of non-ASA NSAIDs for ≥1 y	0.7 (0.6–0.8)
Kune et al., 1988 (23)	1442	Fair	Average-risk men and women	Regular use of non-ASA NSAIDs for ≥1 y	0.77 (0.6–1.01)
Reeves et al., 1996 (25)	477	Fair	Average-risk women	Regular use of non-ASA NSAIDs for ≥1 y	0.43 (0.2–0.89)
Summary for the regular use of non-ASA NSAIDs					0.7 (0.63–0.78)
Coogan et al., 2000 (29)	11 754 (in 4 separate studies)	Fair	Average-risk men and women	Regular use of any NSAID for ≥1 y	0.4 (0.2–0.9); 0.5 (0.4–0.7); 0.5 (0.3–0.9); and 0.7 (0.6–0.9)
Slattery et al., 2004 (26)	2157	Fair	Average-risk men and women	Regular use of any NSAID for ≥1 y	0.8 (0.6–1.1)
Shaheen et al., 2003 (28)	1308	Fair	Average-risk men and women	Regular use of any NSAID for ≥1 y	0.54 (0.39–0.75)
Peleg et al., 1996 (31)	505	Poor	Average-risk men and women	Regular use of any NSAID for ≥1 y	0.34 (0.12–0.94)
Muscat et al., 1994 (27)	1011	Poor	Average-risk men and women	Regular use of any NSAID for ≥1 y	Men: 0.64 (0.42–0.97); women: 0.32 (0.18–0.57)
Summary for the regular use of any NSAID					0.57 (0.47–0.68)
Effects on the incidence of colorectal adenomas					
RCTs ($n = 3$)					
PreSAP; Arber et al., 2006 (20)	933 vs. 628	Good	Higher risk (previous adenoma)	Celecoxib, 400 mg/d, for 3 y	Any adenoma: 0.64 (0.56–0.75) Advanced adenoma: 0.49 (0.33–0.73)
APC; Bertagnolli et al., 2006 (19)	685 vs. 671 vs. 679	Good	Higher risk (previous adenoma)	Celecoxib, 400 mg/d, for 3 y Celecoxib, 800 mg/d, for 3 y	Any adenoma: 0.67 (0.59–0.77) Advanced adenoma: 0.45 (0.33–0.63) Any adenoma: 0.43 (0.31–0.61) Advanced adenoma: 0.34 (0.24–0.50)
APPROVe; Baron et al., 2006 (18)	1158 vs. 1218	Good	Higher risk (previous adenoma)	Rofecoxib, 25 mg/d, for 3 y	Any adenoma: 0.76 (0.69–0.83) Advanced adenoma: 0.70 (0.58–0.86)
Summary for celecoxib, 400 mg/d, or rofecoxib, 25 mg/d					Any adenoma: 0.72 (0.68–0.77) Advanced adenoma: 0.56 (0.42–0.75)

Table 1—**Continued**

Study, Year (Reference)	Participants, *n*	Quality Score	Population	Dose and Duration	Relative Risk (95% CI)
Cohort study (n = 1)					
Polyp Prevention Study; Tangrea et al., 2003 (44)	1905	Good	Higher risk (previous adenoma)	Any NSAID use for 4 y	0.64 (0.48–0.85)
Case–control studies (n = 8)					
García-Rodríguez and Huerta-Alvarez, 2000 (38)	11 864	Good	Average-risk men and women	Regular use non-ASA NSAIDs for ≥1 y	0.7 (0.3–1.5)
Bigler et al., 2001 (35)	1502	Fair	Average-risk men and women	Regular use non-ASA NSAIDs for ≥1 y	0.4 (0.2–0.7)
Logan et al., 1993 (36)	300	Fair	Average-risk men and women	Regular use non-ASA NSAIDs for ≥1 y	0.56 (0.3–1.2)
Boyapati et al., 2003 (37)	405	Poor	Average-risk men and women	Regular use non-ASA NSAIDs for ≥1 y	0.4 (0.2–0.7)
Summary for the regular use of non-ASA NSAIDs					0.55 (0.4–0.76)
Martin et al., 2002 (43)	719	Good	Average-risk men and women	Regular use any NSAIDs for ≥1 y	0.5 (0.3–0.8)
Martínez et al., 1995 (41)	637	Good	Average-risk men and women	Regular use any NSAIDs for ≥1 y	0.46 (0.29–0.75)
Lieberman et al., 2003 (42)	1770	Fair	Average-risk men and women	Regular use any NSAIDs for ≥1 y	0.67 (0.5–0.89)
Logan et al., 1993 (36)	300	Fair	Average-risk men and women	Regular use any NSAIDs for ≥1 y	0.33 (0.1–1.4)
Peleg et al., 1996 (31)	525	Poor	Average-risk men and women	Regular use any NSAIDs for ≥1 y	0.56 (0.2–1.52)
Summary for the regular use of any NSAID					0.57 (0.46–0.71)

* Any NSAIDs include non-ASA NSAIDs and ASA. APC = Adenoma Prevention with Celecoxib; APPROVe = Adenomatous Polyp Prevention on Vioxx; ASA = acetylsalicylic acid; CRC = colorectal cancer; PreSAP = Prevention of Colorectal Sporadic Adenomatous Polyps; RCT = randomized, controlled trial.
† Data are standardized mortality ratios (95% CI).
‡ Data are standardized incidence ratios (95% CI).

domly assigned patients who agreed to undergo colonoscopy in year 4 post-study completion, patients in the rofecoxib group had a higher risk for adenomas than those in the placebo group, suggesting a possible rebound effect (18).

Another small RCT (45) of fair quality found that 4 months of sulindac, 30 mg/d (non-ASA NSAID), did not cause a statistically significant regression of colorectal adenomas (<1.0 cm), which were initially identified by using flexible sigmoidoscopy.

Cohort Studies

In a single cohort study of good quality (44), regular use of any NSAID significantly reduced the incidence of colorectal adenomas in patients with a history of colorectal adenoma (relative risk, 0.64 [CI, 0.48 to 0.85).

Case–Control Studies

The regular use of non-ASA NSAIDs (36, 38, 50, 51) and any NSAID (31, 36, 41–43) in average-risk individuals was associated with statistically significant reductions in frequency of colorectal adenoma (relative risk, 0.54 [CI, 0.4 to 0.74] vs. 0.57 [CI, 0.46 to 0.71], respectively).

Dose and Duration of Use

A nonstatistically significant trend for greater reduction in adenoma incidence was observed with celecoxib, 800 mg/d, compared with celecoxib, 400 mg/d, in 1 RCT (19). In 3 case–control studies (31, 37, 42), higher NSAID doses were associated with statistically significant reductions in frequency of colorectal adenoma, whereas lower doses were not (**Table 2**).

The use of any NSAID had less consistent duration effects on adenoma prevention than on CRC prevention. Two studies (36, 39) demonstrated statistically significant reductions in adenoma frequency with the use of any NSAID for at least 5 years, whereas another study (42) demonstrated a nonsignificant trend toward greater adenoma reduction with more than 19 years of use of any NSAID compared with fewer than 10 years of use of any NSAID. The remaining studies (31, 38, 41) demonstrated

Table 2. **Dose–Response Effects of Nonsteroidal Anti-inflammatory Drugs (*NSAIDs*) on the Incidence of Colorectal Cancer (*CRC*) and Adenomas***

Study, Year (Reference)	Participants, *n*	Quality Score	NSAID Dosage	Relative Risk (95% CI)	*P* value for dosage (trend)
Incidence of CRC					
Cohort studies					
Nurses' Health Study; Chan et al., 2005 (34)	82 911	Good	0.5–1.5 tablets/wk 2–5 tablets/wk 6–14 tablets/wk *P* value for dosage (trend)	1.00 (0.82–1.21) 0.91 (0.69–1.19) 0.69 (0.51–0.95)	<0.001
Tennessee Medicaid Program; Smalley et al., 1999 (33)	104 217	Fair	Low average dosage over 5 y Medium average dosage over 5 y High average dosage over 5 y	0.53 (0.26–1.08) 0.59 (0.45–0.77) 0.77 (0.41–1.45)	
Case–control studies					
Collet et al., 1999 (30)	19 217	Good	Highest dosage over >10 y Lowest dosage over >10 y	Colon cancer: 0.57 (0.36–0.89); rectal cancer: 0.26 (0.11–0.61) Colon cancer 1.01 (0.88–1.15); rectal cancer: 0.80 (0.66–0.98)	Colon cancer: 0.01; Rectal cancer: <0.001
García-Rodríguez and Huerta-Alvarez, 2001 (22)	12 002	Good	Low–medium daily dosage High daily dosage	0.7 (0.5–1.1) 0.4 (0.3–0.7)	
Shaheen et al., 2003 (28)	1308	Fair	Low average dosage Medium average dosage High average dosage	0.54 (0.39–0.75) 0.80 (0.59–1.01) 0.49 (0.34–0.71)	
Reeves et al., 1996 (25)	477	Fair	<7 doses/wk 7–14 doses/wk >14 doses/wk	0.5 (0.2–1.2) 0.6 (0.2–1.2) 0.7 (0.3–1.5)	
Peleg et al., 1996 (31)	505	Poor	Low cumulative dosage Moderate cumulative dosage High cumulative dosage	0.58 (0.26–1.32) 0.19 (0.09–0.52) 0.22 (0.09-0.56)	
Incidence of colorectal adenomas					
RCT					
APC; Bertagnolli et al., 2006 (19)	685 vs. 671 vs. 679	Good	Celecoxib, 400 mg/d, for 3 y Celecoxib, 800 mg/d, for 3 y	Any adenoma: 0.67 (0.59–0.77); advanced adenoma: 0.45 (0.33–0.63) Any adenoma: 0.43 (0.31–0.61); advanced adenoma: 0.34 (0.24–0.50)	
Case–control studies					
García-Rodríguez and Huerta-Alvarez, 2000 (38)	11 864	Good	Low–medium daily dosage High daily dosage	0.7 (0.4–1.3) 0.6 (0.4–0.9)	
Lieberman et al., 2003 (42)	1770	Fair	<Daily ≥Daily	0.71 (0.49–1.01) 0.65 (0.48–0.89)	
Peleg et al., 1996 (31)	525	Poor	Low cumulative dosage Moderate cumulative dosage High cumulative dosage	0.59 (0.23–1.48) 0.56 (0.20–1.52) 0.31 (0.11–0.84)	

* NSAIDs may include non–acetylsalicylic acid NSAIDs, acetylsalicylic acid plus non–acetylsalicylic acid NSAIDs, or cyclooxygenase-2 inhibitors. APC = Adenoma Prevention with Celecoxib; RCT = randomized, controlled trial.

inconsistent results mostly because of underpowered subgroup analyses (**Table 3**).

Harms Due to Non-ASA NSAIDs and COX-2 Inhibitors

All-Cause Mortality

Three reviews (52–54) reported no statistically significant differences in all-cause mortality between different NSAIDs or between NSAIDs and placebo. Compared with placebo, neither less selective COX-2 inhibitors (etodolac, meloxicam, nabumetone, or nimesulide) used in 51 RCTs (relative risk, 0.68 [CI, 0.3 to 1.6]) nor selective COX-2 inhibitors (celecoxib and rofecoxib) used in 17 RCTs (relative risk, 1.02 [0.6 to 1.9]) were associated with a difference in mortality (52). No deaths were reported in 3 RCTs comparing celecoxib with placebo or other NSAIDs (53), and mortality rates were similar between rofecoxib (0.5%) and naproxen (0.4%) in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (54) and between rofecoxib (0.93%) and placebo (0.92%) in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial (18). However, 1

Table 3. **Effects of Duration of Regular Nonsteroidal Anti-inflammatory Drug (*NSAID*) Use on the Incidence of Colorectal Cancer (*CRC*) and Adenomas***

Study, Year (Reference)	Participants, *n*	Quality Score	Duration of Regular NSAID Use, *y*	Relative Risk (95% CI)
Incidence of CRC in case–control studies				
Collet et al., 1999 (30)	19 217	Good	2–5 (at highest dosage)	Colon cancer: 0.97 (0.76–1.24); rectal cancer: 1.29 (0.94–1.78)
			6–10 (at highest dosage)	Colon cancer: 0.94 (0.71–1.24); rectal cancer: 0.77 (0.5–1.18)
			11–15 (at highest dosage)	Colon cancer: 0.57 (0.36–0.89); rectal cancer: 0.26 (0.11–0.61)
García-Rodríguez and Huerta-Alvarez, 2001 (22)	12 002	Good	1	0.6 (0.3–1.2)
			1–2	0.4 (0.2–0.7)
			>2	0.6 (0.4–0.8)
Slattery et al., 2004 (26)	4403	Fair	1–5	0.7 (0.6–1.0)
			>5	0.6 (0.5–0.9)
Reeves et al., 1996 (25)	477	Fair	<2	0.7 (0.4–1.3)
			2–5	0.3 (0.2–0.7)
			>5	1.1 (0.6–2.0)
Muscat et al., 1994 (27)	1011	Poor	1–4	0.77 (0.34–1.75)
			5–9	0.93 (0.45–1.97)
			>9	0.47 (0.21–0.94)
Peleg et al., 1996 (31)	505	Poor	1	0.34 (0.12–0.94)
			2	0.09 (0.02–0.35)
			4	0.14 (0.02–0.90)
			≥5	0.12 (0.04–0.39)
Incidence of colorectal adenomas in case–control studies				
García-Rodríguez and Huerta-Alvarez, 2000 (38)	11 864	Good	1	0.9 (0.5–1.6)
			2–3	0.4 (0.2–0.8)
			>3	0.7 (0.5–1.1)
Martínez et al., 1995 (41)	637	Good	<5	0.39 (0.21–0.71)
			5–40	0.6 (0.32–1.14)
Lieberman et al., 2003 (42)	1770	Fair	<10	0.71 (0.52–0.96)
			10–19	0.63 (0.41–0.99)
			>19	0.49 (0.3–0.8)
Breuer-Katschinski et al., 2000 (39)	542	Fair	≤5	0.65 (0.31–1.34)
			≥5	0.21 (0.04–0.99)
Logan et al., 1993 (36)	300	Fair	≤5	0.74 (0.2–2.3)
			≥5	0.21 (0.1–0.8)
Peleg et al., 1996 (31)	525	Poor	1	0.59 (0.22–0.63)
			2	0.24 (0.07–0.83)
			3	0.26 (0.07–1.0)
			4	0.24 (0.06–0.95)
			≥5	0.25 (0.08–0.79)

* NSAIDs may include non–acetylsalicylic acid NSAIDs or acetylsalicylic acid plus non–acetylsalicylic acid NSAIDs.

administrative database study of fair quality (21) and a systematic review using a biologic progression model (55) found a small, statistically significant increase in all-cause mortality with non-ASA NSAIDs.

Cardiovascular Harms

Eight systematic reviews (53, 54, 56–61) addressed the magnitude of cardiovascular harms associated with the use of COX-2 inhibitors. They reported on RCT data, thereby providing high-level evidence, and 1 review (59) also included observational studies. Two of the reviews (56, 59) extracted cardiovascular harms of non-ASA NSAIDs. Cardiovascular events reported across the systematic reviews included death due to such events, serious cardiovascular events (overall), acute myocardial infarction (MI), acute stroke, arterial hypertension, congestive heart failure, edema, and thrombotic events (**Table 4**).

Four reviews found no significant differences in death due to cardiovascular events with the use of a COX-2 inhibitor compared with placebo, nonnaproxen NSAIDs, or naproxen (53, 54, 56, 59).

Three reviews (56, 58, 59) reporting overall serious cardiovascular events consistently demonstrated an excess risk for these events with the use of COX-2 inhibitors compared with use of placebo or naproxen. The risk for cardiovascular events was greatest in patients at high risk for such events (patients for whom aspirin is indicated) (58). The risk associated with the use of nonnaproxen non-ASA NSAIDs (mostly high-dose diclofenac and ibuprofen) seemed similar to that shown with the use of COX-2 inhibitors.

Six reviews (54, 56, 58–61) reported on the risk for acute MI in patients taking COX-2 inhibitors or non-ASA

Table 4. **Cardiovascular Harms of Non–Acetylsalicylic Acid (*ASA*) Nonsteroidal Anti-inflammatory Drugs (*NSAIDs*) and Cyclooxygenase (*COX*)-2 Inhibitors***

Outcome	Naproxen	Non-Naproxen, Non-ASA NSAIDs	COX-2 Inhibitors
All-cause mortality	NA	No difference [52–54] to increased [21, 55] (all non-ASA NSAIDs): SMR, 1.11 (1.05–1.16) [21] and 3.4 (1.3–8.7) [55]	No difference [52]: 1.02 (0.6–1.9) vs. placebo
Cardiovascular mortality	No difference [56]: 1.47 (0.90–2.40) for COX-2 inhibitors vs. naproxen	No difference [56] (similar to COX-2): 0.67 (0.43–1.06) for COX-2 inhibitors vs. non-naproxen NSAIDs	No difference [53, 54, 56, 59]: 1.49 (0.97–2.29) vs. placebo [56] and 0.79 (0.29–2.19) [59]
Serious cardiovascular events	Neutral or reduced [56]: 0.92 (0.67–1.26) vs. placebo or 1.57 (1.21–2.03) for COX-2 inhibitors vs. naproxen	Increased [56]: 1.51 (0.96–2.37) for ibuprofen vs. placebo; 1.63 (1.12–2.37) for diclofenac vs. placebo; similar to COX-2, 0.88 (0.69–1.12) for COX-2 inhibitors vs. nonnaproxen NSAIDs	Increased [56, 58, 59]: 1.42 (1.13–1.78) vs. placebo [56]; 1.55 (0.05–2.29) [59]; 1.89 (1.03–3.45) [58]; 4.89 (1.41–16.88) for high-risk patients [58]; 1.57 (1.21–2.03) for COX-2 inhibitors vs. naproxen [56]
Myocardial infarction	Neutral or reduced [56, 59]: 0.86 (0.75–0.99) (heterogeneity) [59] or 2.04 (1.41 to 2.96) for COX-2 inhibitors vs. naproxen [56]	Increased (similar to COX-2 inhibitors) [56, 59]: 1.20 (0.85–1.68) for COX-2 inhibitors vs. nonnaproxen NSAIDs [56] and 1.55 (0.55–4.36) for rofecoxib vs. nonnaproxen NSAIDs [59]	Increased [54, 56, 58, 61]: 1.86 (1.33–2.59) for COX-2 inhibitors vs. placebo [56]; 2.04 (1.41–2.96) for COX-2 inhibitors vs. naproxen [56]; 2.93 (1.36–6.33) for rofecoxib vs. naproxen [59]; 5.0 (1.5–13.2) for rofecoxib vs. naproxen [54]; 2.83 (1.24–6.43) for high-dose rofecoxib [59]; 2.17 (1.03–4.59) for rofecoxib ≥6 mo [59]
Stroke	No difference [56, 61]: 0.08 (0.00–1.36) vs. rofecoxib [61] and 1.10 (0.73–1.65) for COX-2 inhibitors vs. naproxen [56]	No difference [56, 59]: 0.62 (0.41–0.95) for COX-2 inhibitors vs. NSAIDs [56] and 1.02 (0.54–1.93) for rofecoxib vs. NSAIDs [59]	No difference [54, 56, 58, 59, 61]: 1.02 (0.71–1.47) for COX-2 vs. placebo [56]; 1.10 (0.73–1.65) for COX-2 vs. naproxen [56]; 1.02 (0.54–1.93) for rofecoxib vs. NSAIDs [59]; 1.12(0.43–2.91) for rofecoxib vs. NSAIDs [54]; 1.43 (0.99–2.07) for rofecoxib vs. celecoxib [58]

* Data reported are relative risks (95% CIs), unless otherwise noted. Numbers in brackets are references. NA = not applicable; SMR = standardized mortality ratio.

NSAIDs. The results consistently demonstrated statistically significant increases in the relative risk for MI with the use of COX-2 inhibitors compared with placebo or naproxen. High-dose, nonnaproxen, non-ASA NSAIDs (mostly diclofenac and ibuprofen) seemed to have a similar risk for MI as that of COX-2 inhibitors (56). One of the identified reviews (59) showed a statistically significant protective effect of naproxen on MI; however, that analysis demonstrated significant heterogeneity.

Five reviews reported on acute stroke (54, 56, 58, 59, 61). The results consistently showed no statistically significant increased risk for stroke with COX-2 inhibitors compared with placebo, nonnaproxen NSAIDs, or naproxen. One high-quality review (56) demonstrated a statistically significant lower risk for acute stroke with COX-2 inhibitors than nonnaproxen NSAIDs in an analysis primarily driven by the effect of high-dose diclofenac.

The risks for hypertension and renal toxicity may also be elevated with COX-2 inhibitors and are reported elsewhere (62).

Gastrointestinal Harms

The included systematic reviews of the gastrointestinal harms of NSAIDs summarized data from RCTs (12, 50, 55, 63, 64), cohort studies (55, 65, 66), and case–control studies (55, 63, 65). Two of the systematic reviews of RCTs (12, 52) focused primarily on prevention of NSAID-induced upper gastrointestinal toxicity through the use of prophylactic agents or the use of COX-2 inhibitors. One of these (12) reported the rate of gastrointestinal complications in patients taking NSAIDs. Twelve systematic reviews assessed COX-2 inhibitors with data on celecoxib (12, 52, 53, 66–69), rofecoxib (12, 50, 54, 57, 61), valdecoxib (60, 70, 71), and meloxicam (12, 50, 72). Rostom and colleagues (12) updated their COX-2 inhibitor review to include data for lumiracoxib, valdecoxib, and etoricoxib. The updated review is currently in press, and the pooled estimates remain similar to those presented here.

All of the included studies reported an increased risk for peptic ulceration and gastrointestinal hemorrhage with non-ASA NSAID use. The risk for complicated peptic ulcers (perforation, obstruction, or bleeding) in those receiving NSAIDs compared with those who were not was elevated in pooled analyses for RCTs (odds ratio, 5.36 [CI, 1.79 to 16.1]), cohort studies (relative risk, 2.7 [CI, 2.1 to 3.5]), and case–control studies (odds ratio, 3.0 [CI, 2.5 to 3.7]) (63). The best RCT evidence of the risk for perforation, obstruction, or bleeding with NSAIDs was derived from the original Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) study (12, 13, 73) and corroborated with recent data from the NSAID groups of the COX-2 inhibitor trials (12, 74–76). A risk for perforation, obstruction, and bleeding of approximately 1.5% to 2% per year was observed in average-risk individuals taking standard non-ASA NSAIDs. The risk for perforation, obstruction, or bleeding can reach 10% or more in higher-risk individuals, including those who have had previous peptic ulcers; who are older; and who have comorbid conditions, such as cardiovascular disease (12, 13, 70, 74).

We estimated the absolute risk difference of perforation, obstruction, or bleeding for patients taking NSAIDs compared with those not taking NSAIDs to be 0.48% for the included RCTs and 0.22% for the included cohort studies.

The risk for upper gastrointestinal toxicity due to non-ASA NSAID use can be reduced through the use of a concomitant gastroprotective agent. Misoprostol was associated with a statistically significant 40% relative risk reduction in clinical ulcer complications due to combined NSAID use (12, 13, 73). Histamine-2–receptor antagonists (H2RAs) and proton-pump inhibitors have only been evaluated in endoscopic ulcer studies (12, 13). Double-dose H2RAs (equivalent to ranitidine, 300 mg twice daily) and standard dose proton-pump inhibitors were associated with statistically significant reductions in the risk for NSAID-induced duodenal and gastric ulcers. Standard-dose H2RAs were not effective at reducing the risk for NSAID-induced gastric ulcers (12, 13).

The use of a COX-2 inhibitor compared with a non-ASA NSAID (ibuprofen, diclofenac, or naproxen) results in statistically significant relative risk reductions for the following: the incidence of endoscopically detected gastroduodenal ulcers by approximately 75% (12, 52–54, 61, 66, 67); clinically significant ulcer complication (perforation, obstruction, or bleeding and symptomatic ulcers) by 40% to 60% (12, 52–54, 57, 60, 67, 70, 72); and gastrointestinal symptoms, such as dyspepsia (12, 52, 61, 67, 71). The effects were similar when non-ASA NSAIDs were pooled and when each was compared separately with COX-2 inhibitors (12).

In several systematic reviews, no statistically significant difference in gastrointestinal bleeding or ulceration was reported when COX-2 inhibitors were compared with placebo (12, 53, 54, 60, 67, 70). However, 1 review (66) showed that patients receiving celecoxib, 200 mg/d, were not at an increased risk for endoscopic ulcers compared with those receiving placebo but patients receiving celecoxib, 400 mg/d, were at increased risk (relative risk, 2.35; CI, 1.02 to 5.38) (66). Compared with placebo, rofecoxib was associated with a statistically significant increased risk for total adverse events (relative risk, 1.32 [CI, 1.11 to 1.56]) and total gastrointestinal events accrued at 6 weeks (relative risk, 3.39 [CI, 1.47 to 7.84]) (61). The APPROVe study found that the risk for symptomatic ulcer, bleeding, perforation or obstruction was higher with rofecoxib than with placebo over a 3-year follow-up period (relative risk, 4.9 [CI, 1.98 to 14.5]).

The Celecoxib Long-Term Arthritis Safety Study (CLASS) (74), Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) (lumiracoxib) (76), and the valdecoxib trial (70) assessed the use of a COX-2 inhibitor in a subgroup of patients receiving ASA. In patients taking ASA the frequency of clinically important ulcer complications was not different in those who received COX-2 inhibitors or non-ASA NSAIDs. The combination of ASA and celecoxib resulted in a 4-fold increase in ulcer complications over celecoxib alone (12, 74), and the combination of valdecoxib and ASA resulted in a 9-fold increase in ulcer complications over valdecoxib alone (70). Although the data for these estimates were derived from post hoc subgroup analyses and may be subject to important bias, one needs to keep them in mind when considering a strategy for combining a COX-2 inhibitor with ASA for cardioprotection.

DISCUSSION

Colorectal cancer is an important burden on the U.S. population. The use of NSAID chemoprophylaxis, alone or in combination with a recommended screening program, is 1 strategy to reduce the incidence of colorectal adenomas, CRC, and CRC-related death.

The results of our systematic review suggest that the use of non-ASA NSAIDs for CRC chemoprevention is effective at reducing the incidence of colorectal adenomas and CRC. Cyclooxygenase-2 inhibitors seem to be effective at reducing the incidence of colorectal adenoma in patients with previous adenomatous polyps. Higher doses and longer durations of use of non-ASA NSAIDs seem to be associated with greater protection from CRC and adenomas. We found the magnitude of the relative risk reduction for CRC incidence to be approximately 30% to 40% in the pooled analyses.

We found no observational data on the effect of COX-2 inhibitors on CRC incidence or CRC-related death, although a single cohort study showed no effect of the non-ASA NSAID ibuprofen on CRC death but demonstrated a small statistically significant increase in all-cause mortality (21). Further, no RCT data exist on CRC incidence with the long-term use of COX-2 inhibitors or non-ASA NSAIDs that are similar to data from the ASA-based Physicians' and Women's Health studies (9, 10).

The use of non-ASA NSAIDs and COX-2 inhibitors are each associated with important harms. Non-ASA NSAIDs are associated with an increased risk for ulcers and clinically important ulcer complications, such as hemorrhage, perforation, or pyloric obstruction. Cyclooxygenase-2 inhibitors are associated with fewer gastrointestinal symptoms, endoscopic ulcers, and clinically important ulcer complications than non-ASA NSAIDs. However, data from the APPROVe study (18) demonstrated that over a 3-year period, COX-2 inhibitors were associated with a statistically significant increased risk for clinical ulcer complications compared with placebo (18). Although these data are in keeping with improved gastrointestinal safety of COX-2 inhibitors over non-ASA NSAIDs, the gastrointestinal safety of COX-2 inhibitors is not equivalent to that seen with placebo, as has been suggested in the past. On the other hand, COX-2 inhibitors are associated with an increased risk for adverse cardiovascular outcomes (56).

During the conduct of our systematic review, rofecoxib was withdrawn from the market because of the re-

sults of the polyp prevention APPROVe study (78), which demonstrated an excess risk for cardiovascular events (16 per 1000 events) with the use of rofecoxib, confirming the suspicions reported by the VIGOR investigators (76). Subsequently, celecoxib was also found to have an excess risk for cardiovascular events (13 to 21 per 1000 events) in another polyp prevention study (Adenoma Prevention with Celecoxib [APC]) (79). Valdecoxib was also withdrawn because of excess risk for cardiovascular events in 2 short-term cardiac surgery pain studies (Coronary Artery Bypass Graft [CABG] 1 and 2) and because of a rare dermatologic toxicity (80, 81).

A systematic review of the cardiovascular harms of rofecoxib and non-ASA NSAIDs (59) suggested a small cardiovascular protective effect of naproxen, although the included studies were heterogeneous. Naproxen's relatively long half-life of 14 hours makes a twice-daily dosing schedule theoretically capable of consistently blocking COX-1 and potentially providing some degree of cardioprotection. Clinical trial data of the quality comparable to data available for the COX-2 inhibitors is not available for non-ASA NSAIDs. However, a recent meta-analysis (56) using an extensive set of RCT data derived from published and unpublished studies suggests that, as a group, COX-2 inhibitors are associated with an increased risk for adverse cardiovascular outcomes (predominantly MI) when compared with placebo or naproxen but not when compared with nonnaproxen, non-ASA NSAIDs. These data, and evidence from some population-based studies (82–84), suggest that the increased risk for cardiovascular harms with COX-2 inhibitors is shared by nonnaproxen, non-ASA NSAIDs (higher doses of ibuprofen and diclofenac) (56).

Although it is tempting to consider adding ASA to a COX-2 inhibitor for cardioprotection, there seems to be an attenuation of the gastrointestinal safety of COX-2 inhibitors with this strategy. However, it should be noted that these observations were derived from post hoc subgroup analyses.

Non-ASA NSAIDs and COX-2 inhibitors are used for longer durations for a variety of arthritic and inflammatory conditions (12). Although their use for these conditions is more easily justified, it is much more difficult to make a case for their use for the chemoprevention of adenomas and CRC in average-risk individuals or even in individuals with a history of polyps. In light of the cardiovascular and gastrointestinal toxicity of these agents when used in a multiyear setting, the demonstration of the chemopreventive efficacy may be a "pyrrhic victory" as stated by Lynch (85) in his editorial on the APPROVe trial. Furthermore, considering the newly identified risks for cardiovascular events associated with these agents, the cost-effectiveness of a chemopreventive strategy for CRC needs to be fully evaluated, particularly because a screening strategy alone appears to be effective (4). In a simplified risk–benefit analysis, assuming that CRC incidence can be reduced by 50% with COX-2 inhibitor use, Psaty and Potter (86) suggested that significantly more cardiovascular events would occur than cases of CRC prevented. However, the balance of benefits and risks in high-risk patients, such as those with familial adenomatous polyposis and nonpolyposis syndromes and those with a history of CRC, may be quite different from that detailed here for average- to higher-risk individuals. A role for COX-2 inhibitors continues to be evaluated in the setting of these high-risk patients (85).

Although ASA seems to be an attractive candidate for CRC chemoprophylaxis, the apparent need for doses higher than that used for cardiovascular protection represents a crucial drawback (48). Likewise, the improved gastrointestinal safety profile of COX-2 inhibitors over non-ASA NSAIDs made COX-2 inhibitors an attractive candidate until their cardiovascular toxicity came to light. Nonnaproxen, non-ASA NSAIDs seem to be the least attractive option because they are associated with both gastrointestinal and cardiovascular toxicity.

In conclusion, non-ASA NSAIDs seem to be effective at reducing the incidence of colorectal adenomas and CRC in observational studies. Good-quality RCT data suggest that COX-2 inhibitors are effective at reducing the incidence of colorectal adenomas in patients with previous adenomas. However, positive data on the reduction of death is lacking for both non-ASA NSAIDs and COX-2 inhibitors.

No quantitative data exist on the risk for gastrointestinal or cardiovascular harms associated with daily, multiyear use of non-ASA NSAIDs. Available data on COX-2 inhibitors suggest that absolute risk increases of over 1% for cardiovascular events and for clinically important gastrointestinal complications can be anticipated after only 2 to 3 years of use, and higher risks may accrue over longer periods. Furthermore, the cost-effectiveness of chemoprevention needs to be considered carefully and compared with other strategies, such as colorectal cancer screening alone. Therefore, the balance of benefits and risks does not appear to favor chemoprevention with non-ASA NSAIDs or COX-2 inhibitors in average-risk individuals or in those with a history of colorectal adenomas.

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Appendix Table 1. **Confounders Addressed in Adjusted Relative Risks among the Included Case–Control Studies: Use of Nonaspirin Nonsteroidal Anti-inflammatory Drugs and the Risk for Adenomas***

Study, Year (Reference)	Source of Abstracted Data	Methods for Selecting Confounders	Confounders	Individual Study Estimate RR (95% CI)	Index of Heterogeneity and Pooled Estimate; RR (95% CI)
Recent use (e.g., current use)					I^2 = 0; 0.78 (0.66–0.92)
García-Rodríguez and Huerta-Alvarez, 2000 (38)	Table 4 (p. 379)	Stepwise model–based selection†	Age, sex, constipation	0.80 (0.70–1.00)	
Hauret et al., 2004 (51)	Table 2 (p. 987)	A priori and stepwise model–based selection†	Age, sex, family history of CRC, pack-years of smoking, BMI, waist–hip ratio, height, physical activity levels, total energy intake, dietary intake of calcium and sucrose	0.62 (0.36–1.07)	
Regular use					I^2 = 0; 0.56 (0.40–0.76)
Morimoto et al., 2002 (50)	Table 3 (p. 1016)	Backwards stepwise model–based selection†	Age, sex, BMI, HRT, pack-years of smoking, alcohol consumption	0.40 (0.20–0.70)	
Hauret et al., 2004 (51)	Table 2 (p. 987)	A priori and stepwise model–based selection†	Age, sex, family history of CRC, pack-years of smoking, BMI, waist–hip ratio, height, physical activity levels, total energy intake, dietary intake of calcium and sucrose	0.62 (0.36–1.07)	
García-Rodríguez and Huerta-Alvarez, 2000 (38)	Table 6 (p. 380) for ibuprofen	Stepwise model–based selection†	Age, sex, constipation	0.70 (0.30–1.50)	
Logan et al., 1993 (36)	Table 2 (p. 286)	A priori and stepwise model–based selection†	Age- and sex-matched cases and controls (adjusted for social class)	0.56 (0.30–1.20)	
Regular use					I^2 = 0; 0.54 (0.40–0.74)
Morimoto et al., 2002 (50)	Table 3 (p. 1016)	Backwards stepwise model–based selection†	Age, sex, BMI, HRT, pack-years of smoking, alcohol consumption	0.40 (0.20–0.70)	
Hauret et al., 2004 (51)	Table 2 (p. 987)	A priori and stepwise model–based selection†	Age, sex, family history of CRC, pack-years of smoking, BMI, waist–hip ratio, height, physical activity levels, total energy intake, dietary intake of calcium and sucrose	0.62 (0.36–1.07)	
García-Rodríguez and Huerta-Alvarez, 2000 (38)	Table 6 (p. 380) for diclofenac	Stepwise model–based selection†	Age, sex, constipation	0.60 (0.30–1.00)	
Logan et al., 1993 (36)	Table 2 (p. 286)	A priori and stepwise model–based selection†	Age- and sex-matched cases and controls (adjusted for social class)	0.56 (0.30–1.20)	

* BMI = body mass index; CRC = colorectal cancer; HRT = hormone replacement therapy; RR = relative risk.
† Multiple logistic regression model.

Appendix Table 2. **Confounders Addressed in Adjusted Relative Risks among the Included Case–Control Studies: Duration of Nonaspirin Nonsteroidal Anti-inflammatory Drug (*NSAID*) Use and the Risk for Adenomas***

Study, Year (Reference)	Source of Abstracted Data	Methods for Selecting Confounders	Confounders	Individual Study Estimate RR (95% CI)	Index of Heterogeneity and Pooled Estimate; RR (95% CI)
Nonaspirin NSAID use for <5 y					I^2 = 0; 0.43 (0.26–0.70)
Peleg et al., 1996 (31)	Table 4 (p. 1322)	A priori†	Age, sex, cumulative years of nonaspirin NSAID use	0.26 (0.07–1.00)	
Logan et al., 1993 (36)	Table 3 (p. 287)	A priori and stepwise model–based selection†	Age- and sex-matched cases and controls (adjusted for social class)	0.80 (0.30–2.50)	
Martínez et al., 1995 (41)	Table 3 (p. 705)	A priori and stepwise model–based selection†	Age, sex, race, cigarette smoking, family history of CRC, BMI, dietary fiber and alcohol consumption	0.39 (0.21–0.71)	
Nonaspirin NSAID use for ≥5 y					I^2 = 0; 0.56 (0.39–0.77)
Peleg et al., 1996 (31)	Table 4 (p. 1322)	A priori†	Age, sex, cumulative years of non-aspirin NSAID use	0.25 (0.08–0.79)	
Logan et al., 1993 (36)	Table 3 (p. 287)	A priori and stepwise model–based selection†	Age- and sex-matched cases and controls (adjusted for social class)	0.33 (0.10–1.40)	
Martínez et al., 1995 (41)	Table 3 (p. 705)	A priori and stepwise model–based selection†	Age, sex, race, cigarette smoking, family history of CRC, BMI, dietary fiber and alcohol consumption	0.60 (0.32–1.14)	
Lieberman et al., 2003 (42)	Table 1 (p. 2960)	A priori†	Age	0.63 (0.41–0.99)	
Regular use of nonaspirin NSAID					I^2 = 0; 0.57 (0.46–0.71)
Martin et al., 2002 (43)	Table 2 (p. 1773)	A priori and stepwise model–based selection†	Age, sex, race, BMI	0.50 (0.30–0.80)	
Martínez et al., 1995 (41)	Table 2 (p. 705)	A priori and stepwise model–based selection†	Age, sex, race, cigarette smoking, family history of CRC, BMI, dietary fiber and alcohol consumption	0.46 (0.29–0.75)	
Lieberman et al., 2003 (42)	Table 1 (p. 2960)	A priori†	Age	0.67 (0.50–0.89)	
Logan et al., 1993 (36)	Table 3 (p. 287)	A priori and stepwise model–based selection†	Age- and sex-matched cases and controls (adjusted for social class)	0.33 (0.10–1.40)	
Peleg et al., 1996 (31)	Table 2 (p. 1322)	A priori†	Age, sex, cumulative years of nonaspirin NSAIDs use	0.56 (0.20–1.52)	

* BMI = body mass index; CRC = colorectal cancer; RR = relative risk.
† Multiple logistic regression model.

Appendix Table 3. **Nonsteroidal Anti-inflammatory Drug (*NSAID*) Chemoprevention of Colonic Adenomas: Included Randomized, Controlled Trials***

Study, Year (Reference)	Location	Treatment/ Placebo, *n/n*	Duration	Population	Control Group	Exposure (Ascertainment)	Outcomes Assessed	Quality Score
Chemoprevention of colonic adenomas (3 RCTs)								
Arber et al., 2006 (20)	Multinational	933/628	3 y	Inclusion criteria: age >30 y; colonoscopy within 3 mo of enrollment showing 1 adenoma ≥6 mm or 2 to 10 adenomas of any size; documented clean colon postpolypectomy; 80% drug adherence during run-in period Exclusion criteria: nonstudy COX-2 inhibitor or NSAID use; ASA, >162.5 mg/d or 325 mg every 2 days; FAP; HNPCC; IBD; invasive cancer; colonic resection; renal, hepatic, or bleeding disorder; study or related drug hypersensitivity	Placebo	Celecoxib, 400 mg/d	Primary end point: ≥1 adenoma at year 1, 3, or both Secondary end points: adenoma ≥1.0 cm (villous or tubulovillous histology); high-grade dysplasia; intramucosal carcinoma or invasive cancer; cardiovascular outcomes and adverse events	Good
Bertagnolli et al., 2006 (19)	Multinational	1356/679	3 y	Inclusion criteria: full colonoscopy and polypectomy within 6 mo; ≥1 confirmed adenoma; history of adenoma ≥5 mm or multiple adenoma Exclusion criteria: nonstudy COX-2 inhibitor or NSAID use; ASA > "low dose"; FAP; HNPCC; IBD; invasive cancer; colonic resection; renal, hepatic, or bleeding disorder; study or related drug hypersensitivity; PUD	Placebo	Celecoxib, 200 mg BID Celecoxib, 400 mg BID	Primary end point: adenoma at colonoscopy Secondary end points: adenoma ≥1.0 cm (villous or tubulovillous histology); high-grade dysplasia; intramucosal carcinoma or invasive cancer; number of adenomas; size of largest adenoma; adenoma burden (the sum of the diameter of all adenomas; cardiovascular outcomes and adverse events	Good
Baron et al., 2006 (18)	Multinational	1293/1277	3 y	Inclusion criteria: age >40 y; colonoscopy within 12 wk; biopsy-proven adenoma; no polyps remaining Exclusion criteria: FAP or HNPCC; polyps at age <35 y; bowel resection; IBD; cancer; hypertension, MI, heart failure, stroke, TIA, or coronary revascularization within 2 years; need for long-term NSAID or ASA therapy; ASA rule relaxed to allow up to 20% using ASA ≤100 mg	Placebo	Rofecoxib, 25 mg/d	Primary end point: ≥1 adenoma at year 1 or 3 on colonoscopy Secondary end points: number of adenomas; advanced adenoma (tubulovillous or villous histology, adenoma >1 cm, high-grade dysplasia, invasive cancer); death; cardiovascular and gastrointestinal events	Good
Regression of colonic adenomas (1 RCT)								
Ladenheim et al., 1995 (45)	United States	44/40	4 mo	Inclusion criteria: adults age >50 y; with routine screening flexible sigmoidoscopy; polyps ≤1 cm Exclusion criteria: history of gastrointestinal bleeding, CRF, PUD, underlying malignant condition, long-term OTC or prescription NSAID use (except ASA); decompensated pulmonary or cardiac disease; polyps >1 cm	Placebo	Sulindac, 150 mg orally BID for 4 mo (n = 22)	Primary end point: percentage of patients for whom all polyps either disappeared or regressed	Fair

* ASA = acetylsalicylic acid; BID = twice daily; COX-2 = cyclooxygenase-2; CRF = chronic renal failure; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; IBD = inflammatory bowel disease; MI = myocardial infarction; OTC = over the counter; PUD = peptic ulcer disease; RCT = randomized, controlled trial; TIA = transient ischemic attack.

Appendix Table 4. **Nonsteroidal Anti-inflammatory Drug (*NSAID*) Chemoprevention of Colonic Adenomas and Colorectal Cancer (*CRC*): Included Cohort Studies***

Study, Year (Reference)	Location	Participants, *n*	Duration, *y*	Population	Cohort Name	Exposure (Ascertainment)	Quality Score
Chemoprevention of colonic adenomas (1 study)							
Tangrea et al., 2003 (44)	United States	1905	4	Inclusion criteria: Enrollees of the Polyp Prevention Trial (1991) age ≥35 y with ≥1 histologically confirmed colorectal adenoma Exclusion criteria: History of CRC, surgical resection of adenomas, IBD, or FAP	Polyp Prevention Study	Any NSAIDs (questionnaire)	Good
Chemoprevention of CRC mortality (1 study)							
Lipworth et al., 2004 (21)	Denmark	113 538	7	Inclusion criteria: Patients with ≥1 ibuprofen prescription between 1989 and 1995 Exclusion criteria: NR	North Jutland Population Database	Ibuprofen (prescription database)	Fair
Chemoprevention of CRC (3 studies)							
Chan et al., 2005 (34)	United States	82 911	20	Inclusion criteria: Female registered nurses age 30–55 y Exclusion criteria: Baseline cancer; did not complete questionnaire	Nurses' Health Study	Non-ASA NSAIDs (mailed questionnaire)	Good
Sørensen et al., 2003 (32)	Denmark, United States, and Sweden	183 693	9	Inclusion criteria: Patients with prescribed non-aspirin NSAIDs Exclusion criteria: Occurrence of cancer excluding nonmelanoma skin cancer before the date of first recorded prescription; end of follow-up: cancer diagnosis, death, emigration, or reaching study end date (1 December 1997)	North Jutland Population Database	Non-ASA NSAIDs (prescription database)	Fair
Smalley et al., 1999 (33)	United States	104 217	13	Inclusion criteria: Enrollees of the Tennessee Medicaid program, age ≥65 y, with 5 y medical history available Exclusion criteria: Incident CRC, death, loss of eligibility, or the end of the study (December 1992)	Tennessee Medicaid Program	Non-ASA NSAIDs (prescription database)	Fair

* Any NSAIDs include non-ASA NSAIDs and ASA. ASA = acetylsalicylic acid; FAP = familial adenomatous polyposis; IBD = inflammatory bowel disease; NR = not reported.

Appendix Table 5. **Nonsteroidal Anti-inflammatory Drug (*NSAID*) Chemoprevention of Colonic Adenomas and Colorectal Cancer (*CRC*): Included Case–Control Studies***

Study, Year (Reference)	Location	Cases/Controls, *n/n*	Duration	Cases	Controls	Exposure (Ascertainment)	Quality Score
Chemoprevention of colonic adenomas (10 studies)							
García-Rodríguez and Huerta-Alvarez, 2000 (38)	Spain	1864/10 000	5 y, 8 mo	Biopsy-proven adenoma on medical records database	Randomly selected age- and sex-matched persons from database; absence of adenoma	Non-ASA NSAIDs (prescription database)	Good
Martínez et al., 1995 (41)	United States	157/480	About 19 mo	First pathologic diagnosis of colorectal adenoma and/or hyperplastic polyps	Colonoscopy-negative patients	Any NSAIDs (questionnaire)	Good
Martin et al., 2002 (43)	United States	226/493	2 y	First colonoscopic diagnosis of colorectal adenoma	Colonoscopy-negative patients	Any NSAIDs (questionnaire)	Good
Lieberman et al., 2003 (42)	United States	329/1441	3 y	Villous adenoma; high-grade dysplasia, including carcinoma in situ and intramucosal cancer; invasive cancer	Colonoscopy-negative patients	Any NSAIDs (questionnaire)	Fair
Bigler et al., 2001 (35)	United States	474/563	3y	First colonoscopic diagnosis of colorectal adenoma	Colonoscopy-negative patients	Non-ASA NSAIDs (questionnaire)	Fair
Logan et al., 1993 (36)	United Kingdom	147/153	7 y	Patients with positive FOBT result and first colonoscopic diagnosis of colorectal adenoma	Negative control patients: age- and sex-matched patients with negative FOBT results; positive control patients: age- and sex-matched patients with positive FOBT results and no polyp or mass on sigmoidoscopy and barium enema	Non-ASA NSAIDs (questionnaire)	Fair
Breuer-Katschinski et al., 2000 (39)	Germany	182/360	3.5 y	First pathologic diagnosis of colorectal adenoma	Hospital control patients: age- and sex-matched patients with negative colonoscopy; nonhospital (community) control patients: age- and sex-matched inhabitants of Essen, Germany	Any NSAIDs, non-ASA NSAIDs (questionnaire)	Fair
Sandler et al., 1998 (40)	United States	142/169	3 y	First colonoscopic diagnosis of colorectal adenoma	Colonoscopy-negative patients	Any NSAIDs, non-ASA NSAIDs (questionnaire)	Fair
Boyapati et al., 2003 (37)	United States	177/228	1 y	First colonoscopic diagnosis of colorectal adenoma	Colonoscopy-negative patients	Non-ASA NSAIDs (questionnaire)	Poor
Peleg et al., 1996 (31)	United States	113/226	2.5 y	First colonoscopic diagnosis of colorectal adenoma	Hospital patient without cancer, born in 1948, with regular follow-ups at GMH for the same duration as the case at the same time	Any NSAIDs (prescription database)	Poor
Chemoprevention of CRC (10 studies)							
Collet et al., 1999 (30)	Canada	Colon Cancer Study, 3844/15 373; Rectal Cancer Study, 1971/7882	NR	Saskatchewan Prescription Drug Plan member patients with histologically proven CRC	Age- and sex-matched Saskatchewan Prescription Drug Plan members age >35 y; without CRC and other cancer except nonmelanoma and carcinoma in situ of cervix	Any NSAIDs (prescription database)	Good
García-Rodríguez and Huerta-Alvarez, 2001 (22)	Spain	2002/10 000	3 y	Participants age 40–79 y with an incident diagnosis of biopsy-proven CRC	Randomly selected age- and sex-matched participants age 40–79 y without CRC at the index date of case	Non-ASA NSAIDs (prescription database)	Good

Appendix Table 5—**Continued**

Study, Year (Reference)	Location	Cases/Controls, *n/n*	Duration	Cases	Controls	Exposure (Ascertainment)	Quality Score
Coogan et al., 2000 (29)	United States	1526/10 228	13 y	Primary CRC diagnosis <6 mo (tumor registry of hospitals, state cancer registry)	Cancer control: diagnosis of lung or other respiratory malignant melanoma, prostate, bladder, kidney, ovary, uterus, and other cancer diagnosis <6 mo; noncancer control: patients admitted for trauma or acute infection with no history of cancer	Any NSAIDs (questionnaire by nurse interviewers)	Fair
Slattery et al., 2004 (26)	United States	952/1205	5 y, 2 mo	English-language speakers; mentally competent to complete the interview; age 30–79 y; first primary tumor in the rectosigmoid junction or rectum; May 1997–May 2001	Matched by sex and by 5-y age groups, patients age >65 y who were randomly selected from Health Care Financing Administration lists, patients age <65 y who were selected from driver's license lists	Non-ASA NSAIDs (questionnaire)	Fair
Kune et al., 1988 (23)	Australia	715/727	1 y	New diagnosis of CRC between April 1980 and April 1981	Age- and sex-matched participants	Non-ASA NSAIDs (questionnaire)	Fair
Shaheen et al., 2003 (28)	United States	475/833	4 y	Patients age 40–79 y with first-time diagnosis of colon cancer	Race-, age-, and sex-matched from general population	Any NSAIDs (questionnaire)	Fair
Juarranz et al., 2002 (24)	Spain	196/228	NR	Participants with laboratory-confirmed colon cancer between January 1995 and December 1996 who resided in Madrid	Age- and sex-matched participants without neoplasm or severe digestive disease at enrollment	Non-ASA NSAIDs (questionnaire)	Fair
Reeves et al., 1996 (25)	United States	184/293	1 y	Women age 40–74 y; local residents with new diagnosis of invasive cancer of the colon or rectum; listed telephone number	Patients with listed telephone number and either a current Wisconsin driver's license (age <65 y) or a Medicare card (age >65 y)	Any NSAIDs, non-ASA NSAIDs (questionnaire)	Fair
Muscat et al., 1994 (27)	United States	511/500	3 y	Patients with histologically confirmed CRC	Patients matched by sex, race, hospital, age (±5 y), and mo of interview; conditions unrelated to NSAID use	Any NSAIDs (questionnaire)	Poor
Peleg et al., 1996 (31)	United States	93/186	5.5 y	Incident CRC	Hospital patient without cancer, born in 1948, with regular hospital follow-ups for the same duration as the case at the same time	Any NSAIDs (prescription database)	Poor

* Any NSAIDs include non-ASA NSAIDs and ASA. ASA = acetylsalicylic acid; CRC = colorectal cancer; FOBT = fecal occult blood test; GMH = germinal matrix hemorrhage; NR = not reported.