Review: Evidence from observational studies, but not randomized trials, suggests that long-term aspirin prevents colorectal cancer

Dubé C, Rostom A, Lewin G, et al. **The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force.** Ann Intern Med. 2007;146:365-75.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Gastroenterology ★★★★★★☆ Oncology ★★★★★☆☆

QUESTION

Is aspirin effective and safe for primary prevention of colorectal cancer?

METHODS

Data sources: MEDLINE (to December 2006), preMEDLINE (to April 2005), EMBASE/Excerpta Medica (to April 2005), the Cochrane Library (Issue 4, 2004), and the PubMed Cancer subset.

Study selection and assessment: English-language studies that evaluated the efficacy of aspirin for primary prevention of colorectal cancer in persons at "average" risk and systematic reviews that assessed the harms of long-term aspirin use. Studies of familial colon cancer were excluded. 4 randomized controlled trials (RCTs) (n = 63 340), 9 cohort studies (n = 1 303 573), 13 case–control studies (n = 1 148 086), and 12 reviews met the selection criteria.

Outcomes: Colorectal cancer mortality, colorectal cancer, colorectal adenoma, hemorrhagic stroke, and gastrointestinal bleeding.

MAIN RESULTS

Evidence from cohort and case–control studies, but not RCTs, indicated that long-term aspirin use prevented colorectal cancer mortality, colorectal cancer, and colorectal adenomas (Table). Aspirin was effective for secondary prevention of colorectal adenomas (Table). The benefits of aspirin were greater with higher doses and longer duration of treatment. Aspirin increased risks for hemorrhagic stroke and gastrointestinal bleeding (Table), especially at higher doses.

CONCLUSIONS

Evidence from observational studies suggests that aspirin prevents colorectal adenomas, colorectal cancer, and death from colorectal cancer, but these findings were not confirmed by 2 randomized trials. Aspirin is associated with increased risks for hemorrhagic stroke and gastrointestinal bleeding.

Sources of funding: Centers for Disease Control and Prevention for the Agency for Healthcare Research and Quality and the U.S. Preventive Services Task Force.

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Aspirin for prevention of colorectal cancer in persons at average risk*

Outcomes	Study design	Number of studies (n)	Summary RRR/RRI (95% CI)†
Colorectal cancer mortality	RCT	1 (39 876)	Not significant
	Cohort	1 (1 083 531)	RRR: 28% to 42%‡
Colorectal cancer	RCT	2 (61 947)	RRI: 2% (–16 to 25)
	Cohort	5 (203 294)	RRR: 22% (3 to 37)
	Case–control	7 (23 797)	RRR: 10% to 68%‡
Colorectal adenoma	RCT	1 (22 071)	RRR: 14% (–10 to 32)
	Cohort	2 (137 346)	RRR: 28% (15 to 39)
	Case–control	5 (1 126 059)	RRR: 13% (2 to 23)
Colorectal adenoma (secondary prevention)	RCT	2 (1393)	RRR: 18% (5 to 30)
	Cohort	2 (2769)	RRR: 18% to 48%‡
	Case–control	2 (934)	RRR: 9% to 91%‡
Hemorrhagic stroke	RCT	1 SR	RRI: 84% (24 to 174)
Gastrointestinal bleeding	RCT, cohort, case–control	7 SRs	RRI: 60% to 210%‡

*RCT = randomized controlled trial; COX = cyclooxygenase; SR = systematic review; other abbreviations defined in Glossary.

†RRR, RRI, and CI calculated from relative risk and CI in article using a random-effects model.

‡Range of RRRs or RRIs in individual studies or subgroups; no summary relative risk provided because of heterogeneity among studies.

COMMENTARY

The comprehensive review by Dubé and colleagues highlights notable discrepancies between RCTs and observational studies regarding aspirin's efficacy as a chemopreventive agent. Although the observational studies showed preventive effects for first adenoma incidence, colorectal cancer incidence, and colorectal cancer mortality among regular aspirin users, the 2 RCTs measuring these endpoints were negative.

We usually regard RCTs as the gold standard, trumping the findings of observational studies because the latter are subject to bias through confounding factors. Although a good-quality observational study can adjust for such known confounders as smoking status, body mass index, and physical activity, unknown factors may affect both exposure and risk for outcome (1). Despite our usual reliance on RCTs to provide definitive answers to clinical questions, in this instance the weight of evidence from multiple observational studies points to a true chemopreventive effect. While the RCTs were well-designed, each answered only a narrow question and did not negate the findings of the many observational studies that showed consistent, biologically plausible results.

The Physicians Health Study, the first RCT evaluating aspirin as a chemopreventive agent, found no reduction in colorectal cancer incidence among persons randomized to aspirin, but the dose was relatively low (325 mg every other day), and follow-up was only 5 years (2). Because the progression to adenoma and carcinoma typically proceeds over the course of a decade, one might see a divergence between aspirin and placebo in studies with longer follow-up. The Women's Health Study (3) provided exposure and follow-up of 10 years but used an even lower dose of aspirin (100 mg every other day). Thus, the negative findings of these RCTs may have been a result of inadequate dose or duration.

The trials of aspirin for adenoma prevention provide additional evidence that insufficient exposure and length of follow-up are important factors to consider in the RCTs with negative results. Although the 2 RCTs cited above found no reduction in the incidence of a first colorectal adenoma, a subsequent RCT of participants with a previous adenoma found an absolute risk reduction of 9% in patients who took aspirin, 81 mg, for at least 1 year (4). Because this trial recruited patients who were already predisposed to polyp formation, it was sufficiently powered. In addition, it involved a mandatory follow-up colonoscopy (not included in the earlier RCTs).

In the review by Rostom and colleagues, the RCT evidence for chemopreventive effects of nonaspirin NSAIDs was limited to recent trials of COX-2 inhibitors because other agents have been evaluated only in observational studies. The RCT data for COX-2 inhibitors and the observational data for other NSAIDs are consistent and convincing for reductions in recurrent adenomas (with COX-2 inhibitors and other nonaspirin NSAIDs) and colorectal cancer (with nonselective,

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Review: NSAIDs and COX-2 inhibitors may prevent colorectal cancer but increase gastrointestinal and cardiovascular harm

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Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Gastroenterology ★★★★★★☆ Oncology ★★★★☆☆☆

QUESTION

Are nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors effective and safe for primary prevention of colorectal cancer?

METHODS

Data sources: MEDLINE (to December 2006), preMEDLINE (to April 2005), EMBASE/Excerpta Medica (to April 2005), the Cochrane Library (Issue 4, 2004), the PubMed Cancer subset, U.S. Food and Drug Administration News Digest, and Health Canada's Health Product Information mailing list.

Study selection and assessment: English-language studies that evaluated the efficacy of NSAIDs or COX-2 inhibitors for primary prevention of colorectal cancer in persons at "average" risk and systematic reviews that assessed the harms of these agents. Studies of familial colon cancer were excluded. 4 randomized controlled trials (RCTs) (n = 6056), 5 cohort studies (n = 486 264), 19 case–control studies (n = 69 788), and 23 reviews met the selection criteria.

Outcomes: Colorectal cancer mortality, colorectal cancer, colorectal adenoma, cardiovascular events, and gastrointestinal harm.

MAIN RESULTS

Evidence from cohort and case–control studies showed that long-term NSAID use prevented colorectal cancer and colorectal adenoma (Table). COX-2 inhibitors were effective for secondary prevention of colorectal adenomas (Table). The benefits of NSAIDs were greater with higher doses and longer duration of treatment in some, but not all, studies. Nonnaproxen nonaspirin NSAIDs and COX-2 inhibitors increased risk for serious cardiovascular events (Table). Nonaspirin NSAIDs increased risk for peptic ulcers and gastrointestinal bleeding, but COX-2 inhibitors did not (Table).

CONCLUSIONS

Evidence from observational studies suggests that nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors prevent colorectal adenomas and colorectal cancer. COX-2 inhibitors prevent recurrence of colorectal adenomas. Both NSAIDs and COX-2 inhibitors increase risk for cardiovascular harm.

Sources of funding: Centers for Disease Control and Prevention for the Agency for Healthcare Research and Quality and the U.S. Preventive Services Task Force.

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Nonsteroidal antiinflammatory drugs (NSAIDs) for prevention of colorectal cancer in persons at average risk*

Outcomes	Study design	Type of NSAID	Number of studies (*n*)	Summary RRR/RRI (95% CI)†
Colorectal cancer mortality	Cohort	Ibuprofen	1 (113 538)	RRR: 7% (–30 to 40) (bowel) RRI: 46% (–10 to 130) (rectal)
Colorectal cancer	Cohort	Nonaspirin	3 (370 821)	RRR: 21% to 40%‡
	Case–control	Nonaspirin	4 (18 324)	RRR: 30% (22 to 37)
		Any	5 (16 735)	RRR: 43% (32 to 53)
Colorectal adenoma	Case–control	Nonaspirin	4 (14 071)	RRR: 45% (24 to 60)
		Any	5 (3951)	RRR: 43% (29 to 54)
Colorectal adenoma (secondary prevention)	RCT	COX-2 inhibitor	3 (5972)	RRR: 28% (23 to 32)
	Cohort	Any	1 (1905)	RRR: 36% (15 to 52)
Serious cardiovascular events	RCT	Ibuprofen	1 SR	RRI: 51% (–4 to 137)
	RCT	Diclofenac	1 SR	RRI: 63% (12 to 137)
	RCT	COX-2 inhibitor	2 SRs	RRI: 42% (13 to 78), 89% (3 to 245)
Gastrointestinal harm	RCT, cohort, case–control	Nonaspirin	1 SR	RRI: 170% to 436%‡
	RCT	COX-2 inhibitor	6 SRs	Not different from placebo

*RCT = randomized controlled trial; COX = cyclooxygenase; SR = systematic review; other abbreviations defined in Glossary.
†RRR, RRI, and CI calculated from relative risks and CI in article using a random-effects model.
‡Range of RRRs or RRIs in individual studies; no summary relative risk provided because of heterogeneity among studies.

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nonaspirin NSAIDs). Buttressing the observational data is the further risk reduction observed with increased treatment dose and duration. Although these findings may be subject to bias because of confounding by indication, sufficient biological plausibility exists to suggest a real, if modest, chemopreventive effect.

For a drug to be a useful chemopreventive agent, it must have substantial efficacy with low toxicity because it would be used over the long term in healthy individuals. The authors of the 2 reviews pointed out that significant long-term risks are associated with each agent. The gastrointestinal toxicity associated with all agents (albeit at a lower rate among the COX-2 inhibitors) and the cardiovascular morbidity associated with COX-2 inhibitors and many nonaspirin NSAIDs preclude their use for the primary indication of chemoprevention.

More important, the chemopreventive potential of these drugs is marginalized by the currently recommended and proven strategy of screening for colorectal cancer. Because screening with colonoscopy or other methods decreases risk for colon cancer by 30% to 70%, the additional benefits from a chemopreventive agent do not outweigh the potential toxic effects.

Individuals prescribed aspirin or other NSAIDs for other conditions (e.g., cardiovascular protection or arthritis) may also derive a modest chemopreventive effect; however, this does not preclude the need for screening. The toxicities associated with these drugs do not justify their primary use for chemoprevention in persons at average risk for colon cancer.

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