Does regular use of aspirin reduce the risk of colorectal cancer?

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Use of at least two standard aspirin weekly, for 10 years or more, reduces colon cancer risk in women. Subject to certain caveats, aspirin should be considered for colon cancer prophylaxis.

The recent update of the Nurses' Health Study (see opposite) provides data on the relationship between aspirin use and colorectal cancer occurrence. In this report, a lower risk of colon cancer was observed in regular aspirin users (≤2 x standard 325 mg tablets per week) than in women who did not regularly use aspirin. Dose and duration of use were important; if a woman consumed 2–5 standard aspirin per week, the RR was modestly reduced, while at higher doses (>14 tablets per week) the risk reduction after 10 years was highly significant ($P<0.001$). The aspirin protection was limited to the colon and was seen for early-stage (stage I and II) but not for later-stage (stage III and IV) colorectal cancers. Non-aspirin NSAIDs were also associated with dose-dependent cancer risk reduction in the colon, but not in the rectum. No protection was afforded by regular use of paracetamol.

The greatest potential impact on colorectal cancer incidence and mortality so far appears to have come from screening measures, with colonoscopic polypectomy preventing cancer in some individuals undergoing aggressive screening.[1] Economic models have suggested colonoscopy alone to be more cost-effective than most other cancer screening measures, and have found lower efficacy and higher costs for aspirin chemoprevention compared with endoscopic screening, mainly because of the need to treat complications of its use. If aspirin were already in use, for example for cardiovascular protection, then the addition of colonoscopy would yield a life-years saving greater than either measure alone.[2] The field of colorectal cancer chemoprevention has become very active in recent years, with much interest in NSAIDs, including aspirin.[3]

A key question is whether the benefit of long-term aspirin, high-dose aspirin, or both warrants recommendation for its use as prophylaxis against colon cancer. Randomised prospective trials utilising aspirin have demonstrated a reduction in adenoma recurrence in subjects with a previous adenoma or cancer.[4,5] Interestingly, despite the major differences in endpoints and study design, the magnitude of risk reduction in these studies is very similar to that seen in the study of Chan et al. Taken together, these studies provide a consistent body of evidence in favour of a protective effect of aspirin.

Of course a number of questions remain unanswered. Why is a protective effect not seen in the rectum? Why is there a reduction in early-stage but not later-stage colon cancers? Is at least some of the risk reduction related to bleeding from tumours induced by the anti-platelet effect of aspirin? Is the protective effect of non-aspirin NSAIDs global or are there differences in magnitude of benefit gained depending on which agent is taken? Do we sufficiently understand the biochemical pathways by which aspirin exerts its protective effect? Might further work enable more-effective, less-risky agents or combinations of agents to be developed? Notwithstanding the

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need for further study, it must be concluded that aspirin reduces risk of incident and recurrent colon neoplasia. Whether the individual clinicians are willing to prescribe aspirin prophylactically will depend on whether they believe, in the absence of a specific indication from the FDA, that such use is warranted, and on the potential cardiovascular risks and benefits for the individual. Subjects prescribed aspirin prophylaxis would have to be monitored carefully for other adverse events, especially gastrointestinal bleeding, and appropriate colorectal cancer screening examinations should still be performed. This study, although not really designed to rigorously address such matters, did not show any substantial excess in bleeds among the long-term or high-dose aspirin users.

References

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Synopsis

A Chan, E Giovannucci, JA Meyerhardt, et al. (2005) **Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer.** *JAMA 294:914–923*

Background. Regular aspirin use for 1–3 years reduces the risk of recurrent adenoma in patients with a history of colorectal adenoma or cancer, but it is unclear whether aspirin similarly reduces risk of incident colorectal cancer and whether nonsteroidal anti-inflammatory drugs (NSAIDs) have similar anticancer effects in these patients.

Objective. To prospectively examine whether long-term use of aspirin and NSAIDs might prevent the development of colorectal cancer.

Design and intervention. Women participating in the Nurses' Health Study were prospectively studied biennially for medication use from 1980 to 2000, using self-completed questionnaires, the content of which was adjusted with time to reflect changes in lifestyle, diet and medications. The questionnaire included a validated assessment of diet and patterns of use of aspirin and NSAIDs. Participants were requested to record the weekly number of pills taken and the number of years of use. Reports of cancer were confirmed by medical records and by death reports from the National Death Index, and cancer stage was classified according to the sixth edition of the American Joint Committee on Cancer's *Cancer Staging Handbook*. Individuals with a history of inflammatory bowel disease, cancer, familial polyposis syndrome or hereditary nonpolyposis colorectal cancer were excluded from analysis.

Outcome measures. Incident colorectal cancer was the primary outcome measure.

Results. During 1,592,017 person-years, there were 962 cases of colorectal cancer among the 82,911 eligible women. After controlling for other potential risk factors, the risk of colon cancer was lower in regular aspirin users (≤2 x standard 325 mg tablets per week) than in women who were not regular aspirin users (<2 standard tablets per week; multivariate relative risk [RR] 0.77; 95% CI 0.67–0.88). A reduction in risk did not occur until at least 5 years of use, and this effect strengthened after 10 years of use (multivariate RR 0.67; 95% CI 0.54–0.85; $P<0.001$). The effect of aspirin was dose-dependent, with the greatest reduction in risk achieved with cumulative doses of more than 14 standard tablets per week (multivariate RR 0.68; 95% CI 0.49–0.95; $P<0.001$). The relative risk was modestly reduced in women taking 2–5 standard aspirin tablets per week (RR 0.89; 95% CI 0.73–1.10). A protective effect of aspirin was seen for early-stage cancers (stage I and II; multivariate RR 0.67; 95% CI 0.55–0.82), but not for later-stage colorectal cancers (stage III and IV; multivariate RR 0.86; 0.71–1.05), or for rectal cancers (multivariate RR 0.94, 95% CI 0.72–1.23). Other, non-aspirin NSAIDs were also associated with a dose-dependent risk reduction for colon cancer but not for rectal cancer. Regular use of paracetamol had no protective effect.

Conclusions. Long-term, regular use of aspirin or NSAIDs was associated with a significant reduction in the risk of incident colorectal cancer in an average-risk population.

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