The benefit-risk consideration in long-term use of alternate-day, low dose aspirin: focus on colorectal cancer prevention

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Summary

Evidence has recently showed that aspirin may provide prophylaxis for cancer, primarily colorectal cancer, but also gastric cancer as well as breast, ovarian, prostate, and lung cancer [1]. It is reported that the benefits increase with use duration and an earlier effect was shown in trials using higher doses [2,3]. However, these meta-analyses were limited to trials of daily aspirin use. Previous analyses from the Women's Health Study (WHS) found no effect of alternate-day low dose aspirin on cancer risk, including colorectal cancer, over a mean follow up of 10 years [4].

Recently, the WHS published a follow up for cardiovascular and cancer outcomes since its active drug intervention in 2004 [5]. The extended study primarily aimed to examine long-term, a median 18-year follow-up effects of alternate-day, low-dose aspirin on cancer risk, particularly colorectal cancer, in healthy women. 39,876 women aged 45 years or older were enrolled in a median 10-year intervention of aspirin or placebo, and 33,682 women were observed in a post-trial follow up through March 2012. Participants were sent annual supplies of monthly calendar packs containing aspirin or placebo in a blinded fashion during the intervention period. At 6 and 12 months and then yearly, participants were mailed questionnaires on drug adherence, adverse effects, non-study aspirin use, clinical endpoints, and risk factors. At the end of the active intervention, participants were opted in or out for further annual follow up. The results showed that over the entire follow-up period, aspirin had no effect on overall (hazard ratio [HR] 0.97, 95%CI 0.92-1.03, P=0.31), breast (HR 0.98, 95%CI 0.90-1.07, P=0.65), or lung (HR 1.04, 95%CI 0.86-1.26, P=0.67) cancer risk. However, colorectal cancer was reduced in the aspirin group (HR 0.80, 95%CI 0.67-0.97, P=0.021), primarily proximal colon cancer (HR 0.73, 95%CI 0.55-0.95, P=0.022). The difference emerged after 10 years, with a post-trial reduction of 42% (HR 0.58, 95%CI 0.42-0.80, P<0.001). Among participants in the aspirin group, not using post-trial aspirin was associated with 33% lower rate of colorectal cancer (HR 0.67, 95%CI 0.43-1.02), while participants who continued to use aspirin had 43% lower cancer rate (HR 0.57, 95%CI 0.35-0.93); the difference not being statistically significant. There was no extended effect on cancer deaths or colorectal polyps, when the analyses were restricted to participants having endoscopy at least once during overall follow up. More gastrointestinal (GI) bleedings (HR 1.14, 95%CI 1.06-1.22, P<0.001) and peptic ulcers (HR 1.17, 95%CI 1.09-1.27, P<0.001) occurred in the aspirin group. The between-group differences for GI bleeding and peptic ulcers were restricted to the trial period, with no further post-trial carry over effect. The authors concluded that long-term use of alternate-day, low-dose aspirin may reduce the risk for colorectal cancer, but it also increases the risk for GI bleeding.

Opinion

The WHS, the elaborate observational follow up of a large randomized trial involving several thousands of healthy women finally showed the effect of alternate-day, low dose aspirin on colorectal cancer after a median follow up of 18 years. These results are compatible with other recent studies results supporting a delayed effect of daily aspirin on colorectal cancer [2,3]. In a previous meta-analysis [2], allocation to aspirin reduced the 20-year risk of colon cancer (incidence HR 0.76, 95%CI 0.60-0.96, P=0.02) by 24%, especially of proximal colon cancer (HR 0.45, 95%CI 0.28-0.74, P=0.001) while the HR for colorectal cancer in this WHS is 0.80 (HR 0.73 for proximal colon cancer).
In this trial, the long-term use of every other day low dose aspirin was chosen with the expectation of decreasing its common adverse effects of GI bleeding. A meta-analysis of 35 randomized controlled trials of aspirin using doses of 75 to 325 mg per day estimated a HR for major GI bleeding of 1.55 (95% CI, 1.27-1.90) compared with their inert control reagents [6]. A latest systematic review which focused on the possible harm of prophylactic aspirin use in primary prevention of cardiovascular diseases and cancer in randomized controlled trials showed an increased relative risk for GI bleeding by 37% (RR 1.37, 95% CI 1.15 to 1.62) in the aspirin group. The numbers of bleeding events for 10,000 persons followed for 10 years were 117-182 for GI bleedings, 46-48 for all kinds of major bleedings, and 8-10 for hemorrhagic strokes [7].

Although there have been no similar clinical trial, the low risk (HR 1.14) for GI bleeding in this study might support the advantage of the alternate-day taking method in long-term aspirin use, without compromising the reduction in the colorectal cancer risk. However, the information on GI bleeding and peptic ulcers was only self-reported during the extended follow up, and the severity of GI bleedings was not described clearly.

Moreover, it would be better if the extended post-trial effect on colorectal cancer risk was sub-analyzed according to different age groups for a more accurate risk-benefit calculation; the risk of adverse events during long-term aspirin use being higher in the elderly, especially in those with significant baseline predisposing risk factors. The US Preventive Services task force recommended against the routine use of aspirin for colorectal cancer prevention: consistent evidence from randomised and observational studies. Lancet 2007;369:1603-1613.

This study has three more limitations. Post-trial ascertainment bias could not be ruled out because some women did not undergo extended follow up and there was a possibility to enroll women who were more likely to have had endoscopic screening in the placebo group. Moreover, enrollment of women who had been more adherent to study pills (aspirin/placebo) could make the preventive effects during the post-trial follow up more evident by removing the diluted data from the less adherent subjects. Finally, the authors arbitrarily defined post-trial aspirin use as more than 3 days per month, but it is not clear what the scientific basis for the definition is.

Despite the aforementioned limitations, this study updates the current knowledge by suggesting that the use of even low doses of aspirin on alternate days could prevent colon carcinogenesis. A clear risk-benefit reconsideration in low risk populations should be determined in future studies.

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