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Aspirin for the Primary Prophylaxis of Colorectal Cancer

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Context: Increasing epidemic of colorectal cancer worldwide and the expenses of the current screening and treatment of this potentially fatal condition have raised the interest of in finding a primary prophylactic measure. Aspirin has been administrated for more than 40 years to achieve this.
Evidence Acquisitions: In this manuscript, we reviewed the best available evidence on the prophylatic use of aspirin for colorectal cancer prevention.
Results: The analysis and large cohort studies revealed that although using ASA would probably decrease the risk of colon cancer, this would not occur before 5-8 years after treatment. ASA usage would increase the risk of major gastrointestinal bleeding.
Conclusions: Aspirin has been proposed as a chemopreventive agent in colorectal cancer (CRC) for many years, but there are still debates on the proper candidates, treatment time and cost benefit analysis of this potentially harmful drug. This brief review would try to answer these questions using the currently available evidence.

Keywords: Aspirin; Colorectal Cancer; Primary Prevention

1. Context

The rising trend in the incidence of worldwide colorectal cancer (CRC) and its impact on global burden of diseases, makes preventive measures for this potentially fatal disease (1). Although the success of screening for early detection of CRC and reducing mortality was encouraged, there are still cases, which cannot be diagnosed with screening in a timely manner, and the idea of prevention rather than early detection seems more plausible both in individual and community prospects. ASA is one of the proposed preventive measures for CRC. The drug is well known for its anti-inflammatory and antiplatelet effects and there are controversial reports on its preventive effects on different cancers.

2. Evidence Acquisitions

2.1. Benefits of Aspirin in CRC Primary Prevention

Several studies with different designs have shown the beneficial effects of aspirin to reduce the incidence of colorectal adenoma and CRC and its mortality (2-4). Even in high-risk patients such as patients with Lynch syndrome, aspirin reduced the risk of CRC by near 40% [Intention-to-treat analysis of time to first colorectal cancer HR of 0.63 (95% CI 0.35-1.13, P = 0.12)] (5). But, there are also null reports about the effects of aspirin on the incidence of new cases of colorectal cancers. Two large studies entitled physicians' health study and women's health study did not show any effect of aspirin in reducing the CRC incidence (6, 7). The short follow up and the alternate-day dosing of aspirin have been claimed as the causes of these null effects (8). There seems to be delay in onset of aspirin action as a chemopreventive agent and the beneficial effects may only reveal after 10 to 20 years of follow up (9). Similarly, there are inconsistent reports on the efficacy of 5-aminosalicylic acid (5-ASA) a derivative of aspirin in chemoprevention of CRC in inflammatory bowel disease (IBD) (10, 11). The short follow up and different dosages as well as nonhomogeneity of patients with IBD as a group of diseases may have contributed to this inconsistency in findings (12, 13). Overall, the bulk of evidence is toward the beneficial effect of aspirin in primary prevention of CRC. The effect is more on proximal colon cancers with up to 70% decrease in incidence of these types of cancers (HR 0.35, 0.20 – 0.63; P < 0.0001) (14). The incidence of rectal cancer is also decreased but to a lesser degree (HR 0.58, 0.36 – 0.92, P = 0.02) (14).

Implication for health policy/practice/research/medical education:
There is insufficient data to recommend aspirin for primary prophylaxis of colorectal cancer in general population. Aspirin for this purpose could be used in high-risk groups including those with a strong family history of colon cancer, especially in members of families with Lynch syndrome.

2.2. Dose and Duration of Chemoprevention With Aspirin

In a recent meta-analysis focusing on the dose and duration of aspirin therapy , it was concluded that low dose (between 75 to 325 mg per day) , long term (more than 5 years) and regular use of aspirin (two to seven times per week) reduced the risk of CRC (15). In another meta-analysis the preventive effect was reported only with doses of 75 mg per day, and there was no increased beneficial effect by increasing the dose (14). Yet, others have reported that only doses of more than 300 mg per day reduced the incidence of CRC (3). Based on the study of the patients with Lynch syndrome, the recommended dose in these high-risk patients was higher at 650 mg daily indefinitely (5, 16). In summary, it seems that the least effective dose is 70 mg per day at least two times per week. In those with higher risk, higher doses could be used.

2.3. Aspirin Mechanism of Action in Cancer Prevention

The cardiovascular benefit of aspirin is mostly attributed to permanent acetylation of platelet-activated prostaglandin-endoperoxide synthetase-1 or COX-1 which occurs even with low doses (< 75 mg/day) (17). The mechanism of antineoplastic effect of aspirin is less clear. It probably involves both COX-dependent and independent mechanisms (18). Aspirin should be used in high dose to block COX2. In contrary, preventive effect of aspirin for cancers is seen with low dose, which is effective on blocking the COX1 and not the COX2 pathways. It has been postulated that inactivation of platelets may block the release of mediators that could induce COX-2 expression in adjacent tissues (18, 19). In addition to these effects, other molecular pathways may also be involved. For instance, inhibition of PAK1 (p21-activated kinase-1), a novel pathway in carcinogenesis of colonic polyps was proposed (20). Modulation of nuclear factor kappa B (NFκB) and polyamine catabolism are also considered as possible mechanisms of antitumor activity (18, 21).

2.4. Other Health Benefits of Aspirin

Aspirin was initially introduced for primary prevention of cardiovascular diseases (22). This was subjected to several large trials including physicians' health study, women's health study, the Primary Prevention Project, the Aspirin for Asymptomatic Atherosclerosis Trial, and the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial to mention some of the most famous studies (23-26). Although the result of each trial may have differed in some aspects, but a recent meta-analysis on nine major trials revealed that aspirin at low dose decreased the risk of all cardiovascular problems, especially nonfatal myocardial infarction and aspirin users had a small but statistically significant decrease in all causes mortality (27). The odds ratio for the latter was 0.934 with 95% confidence interval (0.874, 0.999) and p-value for treatment favoring aspirin (P = 0.045) (28). There was no effect on mortality from cardiovascular diseases and overall coronary artery diseases in this large sample (27). Similar findings were reported by other groups (29). In some cases mortality reduction related to reduced death following cancer. (relative risk for cancer mortality 0.77 (95% CI, 0.63-0.95, I(2) = 0%)) (30).

There are some reports on preventive effect of regular use of low dose aspirin on dementia (31). It may also improve the survival rate and decrease the progression of dementia (32). These studies were criticized for their methodology in gathering data and high dropout rates (33). There are also reports of null effect of aspirin on dementia especially in middle aged population (34).

Reduced risk of gastric cancer was with long term (more than 4 years) and low dose (1 to 4.5 times /week) use of aspirin (15). Aspirin also reduced the risk of esophageal adenocarcinoma [OR of 0.671 (95% CI 0.526-0.856, P = 0.001) among all aspirin users] (35). Aspirin is associated with reduced risk of breast cancer (odds ratio [OR] = 0.86, 95% confidence interval [CI] = 0.81, 0.92) (36). A reduced incidence of melanoma in postmenopausal women was also proposed in analyzing the data from women's health study (hazard ratio, 0.79; 95% confidence interval, 0.63-0.98) (37). Another meta-analysis revealed the reduced risk of endometrial cancer with aspirin only in obese women (BMI $\geq$ 30 kg/m^2) (risk ratio = 0.72) (0.58-0.90) (38).

3. Results

It can be concluded that daily aspirin use would reduce deaths due to several common cancers including colorectal and other solid tumors (all cancers' death, hazard ratio (HR) 0.66, CI: 0.50-0.87) (9). The benefit was confined to lung adenocarcinoma and esophageal cancers (9, 39). This beneficial effect is usually seen after 5 years of treatment and may last even after discontinuation of treatment. The effect is more delayed in colorectal, gastric and prostatic cancers (9).

3.1. The Challenge of Risk Benefit Analysis of Low Dose Aspirin

When we give a drug to a healthy person to prevent a disease we must ensure about its safety. Aspirin is not harmless. It may induce severe gastrointestinal bleeding both in upper and lower GI tracts (40, 41). In most reports, those receiving aspirin were at increased risk of cerebral hemorrhage (22). It can be concluded that the risk of major bleeding is increased with aspirin (RR 1.54, 95% 1.30-1.82) (22). There are reports indicating that increased dose of aspirin to more than 200 mg per day would increase the risk of gastrointestinal bleeding by 30% (42), while decreasing the frequency to alternate day would

decrease the risk. The risk of gastrointestinal bleeding is almost twice in men compared to women and increases with age (43). History of dyspepsia especially previously confirmed acid peptic disease also increases the risk of gastrointestinal bleeding with low dose aspirin up to three times (44). Combined use of other nonsteroidal antiinflammatory drugs quadruples the risk (45). The risk of gastrointestinal bleeding is highest in the first three years of starting aspirin therapy and reduces to baseline after 5 years of treatment (46). Because of these complications, the use of aspirin in healthy individuals cannot be recommended without clearly showing that the benefits outweight the hazards. It is estimated that for every 1000 individuals who received aspirin over a 5-year period, 2.9 major cardiovascular events are prevented but there would be 2.8 major bleeds (47). Even for prevention of cardiovascular disease it could be only recommended when the risk of major cardiac diseases is more than 5 / 1000 in the coming 5 years (48).

Although colorectal cancer is becoming the most common gastrointestinal cancer in many parts of the world including at least parts of Iran (49), the beneficial effect of possible reduction of 40% in cancer incidence is still much lower than its hazardous side effects as the risk of cancer is not so high in general population. For this reason, currently aspirin prophylaxis cannot be recommended for average risk population for cancer prevention (45, 50). Enteric coated and buffered aspirin do not eliminate the risk of gastrointestinal bleeding (33). To prevent avoidable harms, the risk of individuals' gastrointestinal bleeding should be assessed before starting aspirin therapy (44).

4. Conclusions

At present, there is insufficient data to recommend aspirin for primary prevention of colorectal cancer. For instance the United States preventive services task force do not recommend aspirin for primary prevention of colorectal cancer in average risk adults (50). Aspirin for this purpose could be used in high-risk groups including those with a strong family history of colon cancer, especially in members of families with Lynch syndrome. In this group, higher doses of aspirin might be more effective; though, there would be possibility of the increased risk of bleeding. There is a misconception of considering aspirin prophylaxis as a substitute for screening colonoscopy (48). This should be clearly discussed with patients when a decision is made to start aspirin therapy.

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