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Deciphering the Rosetta Stone of Aspirin Chemoprevention

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Introduction

You can walk into any pharmacy, grocery or convenience store and buy aspirin without a prescription. Aspirin is very commonly used and easily available drug with a potential role in preventing the colorectal cancer, lung and head and neck cancers.

Aspirin is speculated to prevent cancer by many mechanisms: 1) increasing the rate of apoptosis in cancer cells, 2) inhibition of cyclooxygenase enzyme- COX-2. This inhibition may influence epidermal growth factor receptor expression (EGFR) and decreasing production of prostaglandin E2 and leading to increased degradation of CTNNB [1].

Systematic reviews show the following facts about aspirin

Regular use of aspirin reduced the incidence of colonic adenomas in randomized controlled trials (relative risk [RR] 0.82, 95% CI 0.7-0.95), in case-control studies (RR 0.87, 95% CI 0.77-0.98), and in cohort studies (RR 0.72, 95% CI 0.61-0.85). Similar estimates were made in a later meta-analysis of four placebo-controlled trials of aspirin [1,2].

Studies of aspirin use among patients with established colorectal cancer have also observed a survival benefit, particularly among those with COX-2 positive or PIK3CA mutant tumors [3-7].

In a meta-analysis of 51 randomized trials that compared aspirin with placebo. It found that aspirin use was associated with a decrease in death from all cancers starting three years after the initiation of aspirin (OR 0.85, 95% CI 0.76-0.96), including a decrease in deaths due to colorectal cancer [3-6]. A reduction in the number of patients with distant metastases at the time of diagnosis was also noted in a meta-analysis of 195 observational studies (OR 0.69, 95% CI 0.57-0.83) [7-10].

Mortality due to cancer was examined in a meta-analysis of 51 randomized trials that compared aspirin with placebo [9]. It found that aspirin use was associated with a decrease in death from all cancers starting three years after the initiation of aspirin (OR 0.85, 95% CI 0.76-0.96), including a decrease in deaths due to colorectal cancer (OR 0.58, 95% CI 0.38-0.89). The meta-analysis of observational studies also showed a decrease in 20-year mortality due to colorectal cancer (OR 0.58, 95% CI 0.44-0.78).

Head and squamous cell cancer could be the other target for the preventive effects of aspirin as its pathogenesis involves key regulation by COX-2 pathway. The causal relation and the role can easily be established by a cohort study of individuals using tobacco as in a country like India.

Thus, aspirin is useful for primary prevention of colorectal cancer and has a role in secondary prevention by reducing the risk of developing metastatic colorectal cancer or dying from colorectal cancer. It also has a survival benefit, particularly among those with COX-2 positive or PIK3CA mutant tumors.

Secondary analyses of cardiovascular trials showed that daily low-dose aspirin use may also reduce the incidence of all cancers combined, although uncertainty remains about the magnitude of the potential benefit.

There are many important questions, not answered yet to consider it as a standard of care prevention strategy.

They are: 1) how much dosage, 2) how long duration, 3) at what cost and risk and 4) whom the benefits worth the risks and the cost?

1) Some evidence indicates that the dosage required to produce a benefit is a moderate doses (that is used for the prevention of cardiovascular disease) and even alternate day low dose aspirin are sufficient. However, uncertainty regarding the optimal dose and the increased incidence of adverse effects associated with higher doses, use of such high doses cannot be routinely recommended.

2) At least 10 years of regular aspirin use may be necessary to achieve substantial reductions in risk of colorectal cancer.

So, it will take a very long time to find the robust evidence to recommend it.

4) High-risk population may be defined as individuals with established colorectal cancer that have undergone a resection for curative intent and individuals and patients with hereditary nonpolyposis colorectal cancer syndrome.

This mode of prevention is further challenged by effective and available alternatives or complementary approaches like screening through colonoscopy or sigmoidoscopy. But still it may be recommended in the 3rd world countries where screening through scopies is not possible but aspirin prevention is very much possible.

Aspirin is a wonderful drug preventing cardiovascular, stroke and cancer risk. But, the question of the dosage, duration and the potential beneficiary population always remains.

The future to the chemoprevention may be defined or decided by the better designing of new trials or results of ongoing primary prevention trials (ASCEND, ACCEPT-D, ARRIVE and ASPREE).

Development of novel biomarkers to more-precisely predict the target population and define the potential optimal dose and dosing regimen for long-term aspirin treatment may enlighten us about an effective and inexpensive strategy of cancer prevention.

Studies to develop novel biomarkers to more-precisely define the potential optimal dose and dosing regimen for long-term aspirin treatment.

Daily aspirin use has been convincingly shown to reduce the risk of colorectal cancer but in average-risk populations this benefit alone does not outweigh harm from aspirin-induced bleeding and systematic side effects.

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