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Review Article

Review Article on Aspirin for prevention of cancer-A potential!

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ABSTRACT

Cancer has been a worldwide threat now with millions of cases of morbidity and mortality owing to it. According to the World Health Organization (WHO), cancer accounted for 8.2 million deaths worldwide by 2012 and its prevalence is predicted to increase in the next decade. There are, however, new data that reinforce the notion that low-dose aspirin intake may also help to prevent cancer and prevent the multiplying of cancer cells. Over the last few years, many studies have combated or supported the substantiation of the relationship between aspirin and cancer that have awakened the interest of researchers in this area. Many studies with follow-up period as long as 20 years have been carried out to analyze the effect that regular use of low-dose aspirin (75-300mg) can have on cancer prevention, especially colorectal cancer and the results have been promising. With the comprehensive analysis of risks and benefits and the linking evidences showing that aspirin, at low doses, can lower the risk of developing colorectal cancer by 40%, the U.S. Preventive Services Task Force (USPSTF) in 2015 released a draft recommendation around the use of aspirin to help prevent cardiovascular disease and colorectal cancer. The guidance was later released in April 2016. By far, there have been evidences for both COX-dependent and COX-independent mechanisms in aspirin cancer prevention. Based on the data that we have from various RCT's and pharmacovigilance sources, the safety profile of aspirin looks reasonably good with the most commonly reported adverse event being Gastrointestinal bleeding. Although some clinical trials have shown that the risk may only be modest it however, cannot be ignored

Keywords: Cancer, Aspirin, prevention.

Introduction

Cancer has been a worldwide threat now with millions of cases of morbidity and mortality owing to it. According to the World Health Organization (WHO), cancer accounted for 8.2 million deaths worldwide by 2012 and its prevalence is predicted to increase in the next decade.[1]

Maintaining a healthy lifestyle and being physically active along with eating lots of fruits and vegetables have been the recommendations made when it comes to cancer prevention by the Centers for Disease Control and Prevention. There are, however, new data that reinforce the notion that low-dose aspirin intake may also help to prevent cancer and prevent the multiplying of cancer cells.[1] There are millions of adults worldwide who take aspirin to decrease their risk of heart attack or stroke. However studies done over the last two decades make a suggestion that regular use of aspirin may have additional significant advantage to the people: reducing the risk of developing some types of cancer.[2] The strongest data favoring aspirin as a preventive are for cancers of the colon and rectum, stomach, and esophagus.[3]

History

American Cancer Society epidemiologists using data from the Society's Cancer Prevention Study II conducted the first major study on aspirin and lower risk of colorectal cancer in humans and the result was published in The New England Journal of Medicine in 1991.The researchers Michael J. Thun, Mohan M Namboodiri and Clark W. Heath found decreased death rates related to colon cancer in both men and women with frequent use of low dose aspirin.[4] At that point of time the actual mechanism leading to the findings were not clear but this study did sow seeds for the many other researches carried out to find more answers

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pertaining to the potential of low dose aspirin in cancer prevention.

Over the last few years, many studies have combated or supported the substantiation of the relationship between aspirin and cancer that have awakened the interest of researchers in this area.[5]

Many studies with follow-up period as long as 20 years have been carried out to analyze the effect that regular use of low-dose aspirin (75-300mg) can have on cancer prevention, especially colorectal cancer and the results have been promising.[6,7] A study that gathered and analyzed data from randomized trials found that the benefit from low-dose aspirin on adenocarcinomas was not related to age or sex but increased with age and duration of intake of aspirin in low-dose.[8]

There are numerous examples of such studies that have been done in the past decade to study the potential of aspirin as chemo-preventive. A One year study result of a 4 year long trial study published in 2003 suggested that daily soluble aspirin was related with reduced risk of recurrent adenomas.[9] The 4 year end result of the same study, however, found that there was no difference in the percentage of patients with at least one recurrent adenoma between control and treatment group. Hence, Daily low-dose aspirin decreased adenoma recurrence drastically at 1 year but not at year 4 .[10]

Another randomized trial in the same area with study population being patients with previous colorectal cancer published result in 2003 stating that daily use of aspirin was associated with significant reduction in the incidence of colorectal adenomas in the study population although the dose used (81mg) could not be concluded as an exact for the same.[11] There are many other studies that have recorded similar findings as above emphasizing on the fact that it takes at least 5 years of consistent regular use of aspirin to gain its cancer protective benefit with maximum benefit at dose of at least 14 tablets/week.[12,13] These positive findings also lay the foundation for hopefulness concerning the development of aspirin as effective chemo-preventive therapy against colorectal cancer to the least.[14]

A meta-analysis in 2009 focusing on randomized trials on aspirin use for cancer prevention (till then), concluded at the end of its analysis that aspirin did reduce the risk of recurrence of colorectal adenomas. With the considerable size of the relative reduction in risk being 28% for advanced adenomas in their analysis and 26% in the evaluated clinical trials, the study indicated potential health benefit of aspirin use.[15]

In 2011, a trial was conducted where patients with Lynch syndrome (a hereditary predisposition to colorectal and other cancers) were randomized into taking either aspirin or placebo. The result showed that participants taking low-dose aspirin for more than two years showed less chances of developing cancer.[16]Another analysis of incident cancers during randomized controlled trials for aspirin study concluded that aspirin reduced risk of adenocarcinoma with metastasis at early diagnosis and risk of metastasis on subsequent follow-up in patients with no initial metastasis, largely in patients with colorectal cancer and in patients who remained on trial treatment up to or after diagnosis. This supported the fact that aspirin might help in prevention of some cancers and also provided with evidence to support the principle for pharmacological intervention especially for prevention of distant metastasis.[17]

Out of the many more studies, one that stood out was the comparative study of the use and nonuse of Aspirin amongst almost 77,000 participants extending between fifty-one randomized trials.[5,18] There were lesser cases of cancer in subjects who had taken daily low-dose Aspirin for three years or more, and a decrease of 31% in cancer deaths after more than five years on aspirin. The reduction was not just in cancers of the gastrointestinal tract, but also in breast, prostate, and lung cancer.[18]

Recent Developments

With the comprehensive analysis of risks and benefits and the linking evidences showing that aspirin, at low doses, can lower the risk of developing colorectal cancer by 40%, the U.S. Preventive Services Task Force (USPSTF) in 2015 released a draft recommendation around the use of aspirin to help prevent cardiovascular disease and colorectal cancer.[19] The guidance was later released in April 2016.[20]

The researchers who have been working in this area emphasized on the importance of the guideline and praised the panel's action.[20]

There have been many news reports in top most newspapers around the world publicizing the cancer-preventive role of aspirin ever since and even before. Furthermore, there are other studies,

which support the findings. A recent report from the Women's Health Study (WHS) concluded that giving 100 mg of aspirin to healthy women in alternate day basis reduced the risk of colorectal cancer in them during the follow up years. The same, however, could not be established for reduction in risk of breast or lung cancer or decrease in deaths due to the same cancer over the period of study.[21]

The proposed antineoplastic Mechanism of Action of Aspirin

By far, there have been evidences for both COX-dependent and COX-independent mechanisms in aspirin cancer prevention.

For the COX-dependent pathway, the primary effect is studied to come from inhibition of prostaglandins, especially Prostaglandin E2 (PGE2) which is involved in cell proliferation, migration, angiogenesis and fights apoptosis in cells.

The COX- independent pathway is believed to involve mechanisms like direct modulation of oncogene-induced expression of transcription factors like nuclear factor kappa or increase apoptosis of tumor cells through by interaction with tumor promotors and suppressors.[22]

If we dig deeper, then a more recent study suggests that the cancer protective effects of aspirin have more to do with its action on platelets rather than on tumor cells.The researchers have found that the level of an oncoprotein called c-MYC that regulate around 15% of the genes in human body is actually increased by platelets.The c-MYC regulator controls the life-and-death cycle of cells, the synthesis of proteins, and the cells' metabolism. Hence, when aspirin inhibits platelet activity, the oncoprotein levels fall and this is aspirin's major chemo protective action.[1]

Risk benefit assessment

Based on the data that we have from various RCT's and pharmacovigilance sources, the safety profile of aspirin looks reasonably good with the most commonly reported adverse event being Gastrointestinal bleeding.[23,24] Given the fact that the GI toxicity associated with long term aspirin use cannot be under looked. The US Task Force in 2007, had recommended against the use of aspirin for Colorectal cancer prevention in population with average risk.[25] Such assessment, however, had to be reviewed due to the increasing number of evidences coming from various RCTs showing the beneficial effect that aspirin had on prevention of different types of cancer that could lead to saving lives of a large number of people.[9] Hence, the US Preventive Task Force guidelines recommends use of low dose aspirin on population who are expected to get more benefit with least risk,i.e., population aged 50-59 years of age with life expectancy of at least 10 years. The guidelines are such because aspirin takes at least 5-10 years to show its potential cancer preventive benefit and people with shorter life expectancy might, hence, not see the benefits. Moreover, the potential candidate should also be healthy and not at increased risk of bleeding due to any other comorbid conditions or else.[26]

Conclusion

The potential use of aspirin as cancer protective agent is definitely likely to be a topic of discussion and debate for a very long time now. Although we have evidences from Clinical trials and observational studies supporting this role, the data are more weighed towards prevention of colorectal cancer and the result for other types of cancer like lung cancer, breast cancer have been rather mixed. Moreover, after the guidelines released by the US Preventive Task Forces with recommendation forroutine aspirin use for colorectal cancer prevention (with conditions applied), the horizon of possibilities have definitely broadened and it is now for researchers to go deeper into it. This is to say that all the guiding bodies and researchers are now at their toes,alert on the chief consideration that routine aspirin use (even at 75-325 mg dose) can bring upon people: gastrointestinal bleeding. Although some clinical trials have shown that the risk may only be modest, [2] it, however, cannot be ignored.Moreover the exact dose of aspirin to be used is still the subject of debate and study. Hence, considering the risk that the patient might be expose to with wrong routine dosing for decade or so, it is essential that we find answers to all the budding questions. The only best way to do so would be to either wait for the results from the several ongoing clinical trials in the same field or to take up the challenge and responsibility of conducting further more studies to find the answer to what shall be a very daunting question for quite some time to come: Aspirin as cancer preventive- safe potential or arisk?

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