Aspirin as a Chemopreventive Agent for Cancer: a New Hope?

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ABSTRACT

Introduction: Inflammation has been shown to play a major role in the pathogenesis of cancer. Inflammatory process activates the immune system through pro-inflammatory mediators and subsequent triggers transformation into malignant cells. Some tumors or cancers has been associated with chronic infections, such as hepatitis B and C viruses (hepatocellular carcinoma), human papilloma virus (cervical cancer), Helicobacter pylori (gastric cancer and lymphoma), and prostatitis (prostate cancer). A considerable study has investigated the benefits of aspirin for the prevention and treatment of cancer or tumors. Objectives: This paper aims to describe the relationship between inflammation and cancer incidence, so that use of aspirin as an anti-inflammatory agent is a rational choice in the treatment and prevention of cancer. Conclusion: Aspirin potential for chemoprevention of various types of cancer. Considering the high risk of side effects of aspirin, aspirin is not intended as a routine therapy to prevent the occurrence of cancer.

Keywords: inflammation, cancer, aspirin

INTRODUCTION

Cancer is a genetic disorder involving the failure of apoptosis and DNA repair (Zingde, 2001). DNA damage is caused by various factors such as radiation, carcinogenic chemicals, and infection, through the mechanism of tissue damage due to inflammation. Chronic inflammation in a cell or tissue activates immune cells to produce pro-inflammatory mediators such as cytokines, chemokines, adhesion molecules and free radicals. Inflammatory mediators will intervene so that the normal cells transform into malignant cells which capable of invasion and metastasis (Deng et al., 2012).

A great body of research have been done on aspirin use, an anti-inflammatory analgesic, in the treatment of cancer. The results of the studies showed that the use of aspirin and other NSAIDs in several cancers has been shown to be beneficial (to be discussed in the following section), thus, supporting the effectiveness of aspirin for cancer therapy and chemoprevention in certain risk of population.

REFERENCES

Correlation between Cancer and Inflammation

A number of studies has shown that inflammation is directly associated with incidence of cancer. Some medical conditions have been reported to be associated with the incidence of cancer including hepatitis B and C viruses (hepatocellular carcinoma), human papilloma virus (cervical cancer), Helicobacter pylori (gastric cancer and lymphoma) (Trinchieri, 2011; Zhu et al., 2012). The inflammatory microenvironment is similar to that of tumor in which the inflammatory component is also present in the micro environment of neoplastic tissues (Zhu et al., 2012). In an inflammatory microenvironment, reactive oxygen species (ROS) and...
reactive nitrogen species (RNS) are also present, which are the physiological mechanism of immune cells to the inflammatory stimulation (Trinchieri, 2011), as well as an indicator that cells undergo oxidative stress (Moossavi & Bishehsari, 2012). Increased ROS and RNS cause genetic instability and impaired DNA repair through post-translational modification of tumor suppressor genes such as p53 and PRB, triggering transformation into malignant cells (Deng et al., 2012).

Some of the things that show the link between inflammation and cancer include:

1. Hematopoietic cells, epithelial cells, endothelial cells, fibroblasts, lymphocytes, dendritic cells, mast cells, and stromal cells entering into the tissues are the beginning of cancer progression. These various immune cells are activated by chronic infections such as Hepatitis B virus infection (HBV), Human Papilloma Virus (HPV), H. pylori, and Eipstein Barr Virus (EBV) (Deng et al., 2012), triggering inflammation by secreting pro-inflammatory factors. Inflammation also causes obstacles to the anti-tumor immune response and then be able to determine the response of tumor cells to drug therapy (Deng et al., 2012)

2. Nuclear factor kappa-B (NF-κB), transcription factors in eukaryotic cells that function in gene promoter for inflammation (Trinchieri, 2011), the immune response, and antiapoptotic mechanisms present in cancer cells (Xiong et al., 2003). A transcription factor that will stimulate the production of proinflammatory cytokines (Trinchieri, 2011), activation of oncogenes in malignant cells (Moossavi & Bishehsari, 2012) and plays an important role in tumor cell survival (Chattopadhyay et al., 2012).

3. Signal transducer and activator of transcription 3 (STAT3), a factor that plays a role in maintaining tumor cell survival, proliferation and spread of tumor cells, is expressed in cancer cells. Moreover, STAT3 also maintain the cancer cells alive by inhibiting apoptosis through p53 suppression and controlling pro-angiogenic factors and metastasis (Trinchieri, 2011).

4. The inflammatory receptors in the cytoplasm activate caspase 1, and then stimulate the production of interleukin (IL) -1β and IL-18 as pro-inflammatory cytokines (Trinchieri 2011; Dinarello, 2010).

5. The cyclooxygenase-2 (COX-2) enzyme expressed in large amounts in colon disorder such as inflammatory bowel disease (IBD) and colorectal cancer, which in conditions of normal colonic epithelium the enzyme was not expressed (Moossavi & Bishehsari, 2012). In addition, it was found that prostaglandin levels were significantly higher in cancer tissue than in normal tissue (Holmes et al., 2010).

Based on these explanation, it is obvious that malignancy is directly due to the involvement of the immune system, cytokines, chemokines, and transcription factors, which together form an “orchestra” in the pathogenesis of tumor (Zhu et al., 2012). Various immune cells in the inflammatory process would stimulate the production of cytokines and chemokines which play a major role in the pathogenesis of cancer (Deng et al., 2012). The phenomenon is more common in cells having abnormal or premalignant lesions. Chronic activation of the immune system, stromal fibroblasts, mesenchymal cells and vascular backers in premalignant lesions causing premalignant lesions become larger, because of the involvement of a variety of immune cells is immunosuppressive. Therefore, this situation can be considered as wounds that do not heal, and triggers the progression of cancer (Shiao et al., 2011).
associated with chronic inflammation in a variety of solid organs (Antonoff & D'Cunha, 2011). Repairs to premalignant lesions in turn will be able to reduce the risk the development of normal cells into cancer cells.

Studies on Aspirin in Cancer Prevention

a. Aspirin and Colorectal Cancer

Colorectal cancer is the most common malignancy studied related to the use of aspirin for the prevention and treatment of cancer. Short-term use of aspirin (less than 3 years) does not significantly reduce the risk of colorectal cancer (Rothwell et al., 2012a). Low-dose aspirin (75mg/day) effectively prevention of cancer incidence after 5 years (odds ratio [OR] 0.78; 95% confidence interval [CI]=0.65 to 0.92, p=0.004). The preventive effect of the use of aspirin on cancer has been shown after one year and increase with longer use (Din et al., 2010). An observation for 20 years found a lower cancer mortality by 20% with aspirin therapy compared with no aspirin therapy (Rothwell et al., 2011).

As chemoprevention, aspirin and other NSAIDs are effective for preventing the incidence of colorectal cancer mortality in patients simultaneously Lynch syndrome (Barton, 2012), adenoma (Manzano & Perez-Segura, 2011), and familial adenomatous polyposis (Chan, 2011). Aspirin also been proven to prevent cancer in addition to colorectal cancer associated with Lynch syndrome, such as endometrial cancer, brain, small intestine, pancreas, ureter, stomach, and kidney (Barton, 2012).

b. Aspirin and Gastric Cancer

A cohort study showed that regular use of aspirin is associated with a lower risk of gastric cancer of the distal (HR 0.73; 95% CI=0.61-0.89; P trend 0.009), compared with no aspirin (HR 1.00; 95% CI= 0.81-1.24; P trend=0.99) (Eppleine, et al., 2009). Other studies showed similar results, in which aspirin lowers the risk of gastric cancer compared with no aspirin, with an OR of 0.7 (95% CI=0.6-1.0). The risk of gastric cancer decreased with increasing frequency of aspirin (Akre et al., 2001).

Researchs from 3 case-control study of gastric cancer had a RR of 0.67 (95% CI=0.56-0.80), from 4 study cohort of 0.93 (95% CI=0.82-1.05), and to the whole study of 0.84 (95% CI=0.76-0.93) (Bosetti et al., 2009). Continuous use of aspirin also determine the final outcome. A regular aspirin use (OR 0.57 (95% CI=0.44-0.74)) reduces the risk of gastric cancer, is greater than the irregular (OR 0.84 (95% CI=0.66-1.07)).

c. Aspirin and Lung Cancer

Consuming aspirin regularly after resection of lung cancer can improve survival rate by 5% (p=0.05) (Fontaine et al., 2010). Routine use of aspirin in patients with lung cancer had RR of 0.70 (95% CI=0.56-0.88) of two case-control studies, 0.96 (95% CI=0.91-1.02) of 6 study cohort, and 0.94 (95% CI=0.89-1.00) for the entire study (Bosetti et al., 2009). A meta analysis study found that the value of RR on six case-control studies of 0.63 (95% CI=0.47-0.86), in the eight study cohort of 0.78 (95% CI=0.62-0.98), whereas for the overall study of 0.79 (95% CI=0.66-0.95). For lung cancer, the type of small-cell has a better prognosis (RR 0.48; 95% CI=0.30-0.75) compared with the type of non-small cell (RR 0.66; 95% CI=0.56-0.79) (Khuder et al., 2005).

d. Aspirin and Breast Cancer

Breast cancer with positive estrogen receptor (ER +), can be treated with anti estrogen. However, when the estrogen receptor is negative (ER-), the use of anti estrogen is not effective, so that conventional therapies such as chemotherapy and radiotherapy were still an option. In vivo study by Chattopadhyay, et al. (2012) demonstrated that the use of aspirin in ER-breast cancer is effective in controlling the growth of cancer cells characterized by the reduction of cancer size whereas in vitro studies found that it inhibited tumor cell proliferation (due to inhibited cell cycle), increased apoptosis, decreased expression of NF-kB, decreased thioredoxin reductase activity, and increased concentration of ROS in tumor cells. Holmes, et al. (2010) found that administration of aspirin for one year after the diagnosis of breast cancer can reduce the risk of metastasis, cancer mortality, and death due to other causes. The benefits of aspirin therapy is not dependent on the stage of the cancer, menopausal status, body mass index, and estrogen receptor status (ER+ or ER-).

e. Aspirin and Other Cancer

In cases of esophageal cancer, the RR of two case-control studies was shown to be 0.41 (95% CI=0.29 to 0.57), from 4 study cohort of 0.83 (95% CI; 0.70-0.98), and for the total study was 0.72 (95% CI=0.62-0.84) (Bosetti et al., 2009). A regular aspirin therapy is more effective and cost-effective compared with no aspirin at 0.19 quality-adjusted life years (QALY). The combination of aspirin therapy and surveillance using...
an endoscope generated a 0.27 QALY compared with no aspirin therapy, and save US $13,400 with the cost effectiveness ratio of 49 600 US $/QALY. This therapy model is highly dependent on the age and the delay in starting aspirin therapy (Hur et al., 2004).

Researches on pancreatic cancer showed the value RR in two case-control studies were 1.00 (95% CI=0.72-1.39) and from 5 cohort studies accounted for 0.96 (95% CI=0.92-1.01). The limited number of research on pancreatic cancer caused no conclusive evidence for the relationship between the use of aspirin and the incidence of pancreatic cancer (Bosetti et al., 2009).

Aspirin's administration to Hodgkin lymphoma has been shown to reduce the risk of incidence of Hodgkin's lymphoma with OR 0.60 (95% CI=0.42-0.85), whereas the use of NSAIDs non aspirin couldn't reduce the risk of this cancer, with an OR 0.07 (95% CI=0.73-1.30) (Chang et al., 2004). For non-Hodgkin lymphoma, pooled RR of four case-control studies of 0.98 (95% CI=0.85-1.14), from 2 cohort studies was at 1.08 (95% CI=0.78-1.51), while for the overall study the value of RR was 1.00 (95% CI=0.88-1.14) (Bosetti et al., 2009).

The different results were obtained for malignancy of the prostate and kidney. Relative risk of prostate cancer, the value of pooled RR of five case-control studies was 1.02 (95% CI=0.90-1.16), from 10 cohort studies were 0.97 (95% CI=0.94-1.01) and from total study 0.98 (95% CI=0.95-1.01) respectively. The finding shows that the regular administration of aspirin did not lower the risk of prostate cancer. For malignancy of kidneys, the value of pooled RR of five case-control studies were 1.21 (95% CI=1.07-1.36), from 3 cohort studies were 0.45 (95% CI=0.87-2.40), and from the whole studies were 1.22 (95% CI=1.08-1.37) respectively. These findings showed that the use of aspirin can increase the risk of kidney cancer. This result might have been due to the use of combined phenacetin and aspirin (Bosetti et al., 2009).

Anti Cancer Mechanism of Aspirin

Aspirin acts as an anti-cancer by inhibiting proliferation and inducing apoptosis. Antitumor mechanism occurs through the barriers of the cell cycle (phase G0/G1) and a shift in the balance between Bax/Bcl-2 (Lai et al., 2008). Aspirin activates caspase-8, 9 and 3, as well as break down and translocate Bid, thereby inducing conformational changes, Bax translocation and release of cytochrome. Caspase-8/ Bid and Bax activation is a major role in cancer cell apoptosis induced by aspirin (Gu et al., 2005).

Factors Influencing the Success of Aspirin Therapy

NSAIDs regular administration prior to colorectal cancer diagnosis is associated with improved survival of colorectal cancer, especially in long-term use (Coghill et al., 2011). Given the provision of long-term aspirin treatment can prevent cancer it can be concluded that aspirin has two role for primary prevention. First role in preventing cardiovascular attacks as an anti-platelet aggregation, and second role is to prevent the onset of cancer. The thing to note is, how to identify the right population, to obtain the maximum benefit with minimum side effects (Antonoff & D' Cunha, 2011).

A meta-analysis showed an inverse association between moderate use of NSAIDs (including aspirin) and colorectal cancer incidence in both men and women, but different types of cancers other than colorectal cancer (males: HR 0.84, 95% CI=0.72-0.97; female: HR 1.18, 95% CI=0.97-1.44; P<0.01) in (Brasky et al., 2012). This suggests that gender may affect the cancer prevention using a long-term aspirin use.

Other factors that influence the success of aspirin therapy were histology or type of cancer. Satisfactory results have been shown in aspirin therapy in adenocarcinoma cancer. Some research results showed a less satisfactory results of aspirin therapy including non-adenocarcinoma cancers (Antonoff & D'Cunha, 2011). For lung cancer, the higher the success achieved on the type of small-cell lung cancer compared with non-small cell (Khuder et al., 2005). In addition, the success of cancer chemoprevention is also greater on a variety of cells with high expression of COX-2 compared to COX-2 expressing little or no expression at all (Chan et al., 2007).
DISCUSSIONS

Collectively, the available data showed that the use of aspirin in cancer therapy may provide a new hope. Anticancer mechanism aspirin is based on the ability of aspirin to inhibit cancer cell proliferation, induces apoptosis, inhibits cell cycle progression, signaling suppress NF-kB and its antiplatelet nature. The mechanism of action enables rational therapy with aspirin to prevent the incidence of various types of cancer. The success of cancer therapy with aspirin is influenced by various factors, such as the start of therapy, gender, and cancer histology. Although it looks promising, it is worth noting that aspirin therapy has the potential to cause side effects that can be fatal. Therefore, most doctors still see the cancer risk reduction as an added benefit for patients requiring aspirin for the treatment of disease (e.g. arthritis), not as a routine therapy aimed at preventing the occurrence of cancer.

Research on the benefits of using aspirin on a wide variety of organ cancer shows a conflicting result both in the final outcome of therapy and the dose and duration of use. In addition, many studies have not been able to demonstrate the type of patients who get cancer risk reduction benefits exceeding the risk of bleeding complications. Inconsistent results of research on aspirin and other non steroidal anti-inflammatory, indicates the need for further research before aspirin can be recommended as a cancer chemopreventive agent. However, to avoid a risk factor for cancer is much more beneficial for lowering the risk of cancer, along with the early detection of cancer for those who have risk factors. This has proven to be the best prevention, as well as to decrease the number of deaths due to cancer.

CONCLUSIONS

Aspirin gives hope as chemopreventive agent and cancer therapy. Factors that may affect the outcome of cancer therapy with aspirin including the start of therapy, gender, and cancer histology. It is worth noting that the regular and long-term aspirin administration can have serious side effects, thus aspirin use has not been recommended for cancer prevention. The benefits of aspirin as a chemoprevention is considered as an additional benefit for patients requiring aspirin for the treatment of inflammatory diseases.

REFERENCES:


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