View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Portal Jurnal Universitas Islam Sultan Agung (UNISSULA)

Sains Medika Journal of Medicine and Health
• pISSN: 2085-1545
• eISSN: 2339-093X
http://jurnal.unissula.ac.id/index.php/sainsmedika

REVIEW ARTICLE

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

Isnatin Miladiyah
Pharmacology Department Medical Faculty of Islamic Indonesian University (FK UII) Yogyakarta
Corresponden : Kaliurang Street Km 14,5 Sleman 55584 Yogyakarta
Office : (0274) 898444 psw 2096; Fax (0274) 898444 psw 2007
Mobile : 081 328 470 270

ABSTRAK

Pendahuluan: Saat ini diketahui bahwa inflamasi berperan besar dalam patogenesis kanker. Proses inflamasi mengaktifkan sistem imun melalui mediator pro inflamasi dan selanjutnya memicu transformasi sel menjadi ganas. Beberapa tumor atau kanker dikaitkan dengan infeksi kronis, seperti virus hepatitis B dan C (karsinoma hepatoseluler), *human papilloma virus* (kanker serviks), *Helicobacter pylori* (kanker lambung dan limfoma), dan prostatitis (kanker prostat). Banyak penelitian yang telah mengkaji manfaat aspirin untuk pencegahan dan terapi kanker atau tumor. **Tujuan:** Tulisan ini bertujuan untuk memaparkan keterkaitan antara inflamasi dengan kejadian kanker, sehingga penggunaan aspirin sebagai agen antiinflamasi merupakan pilihan yang rasional dalam terapi dan pencegahan kanker. Aspirin potensial untuk kemoprevensi berbagai jenis kanker. Mengingat efek samping aspirin cukup besar, maka pemberian aspirin tidak dimaksudkan sebagai terapi rutin untuk mencegah kejadian kanker.

Kata kunci: inflamasi, kanker, aspirin

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 have 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.

LITERATURE REVIEW

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), and 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

Copyright @ 2015 Authors. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (http://creativecommons.org/licenses/by-nc-sa/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original author and source are properly cited.

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).

Anti Inflammation Agent, Aspirin, in Cancer Chemoprevention

Aspirin is the prototype of non-steroidal anti-inflammatory (NSAID). Unlike other NSAIDs reversibly inhibiting enzymes, aspirin inhibits COX enzymes irreversibly. This is because aspirin causes acetylation of a serine residue at the terminal carbon group of the COX enzyme. Thus, to produce a new prostanoid synthesis requires other COX enzyme (Vane and Botting, 2003). This process is important due to its association with the effect of aspirin, in which the duration of the effect is highly dependent on the rate of turn over COX enzymes (Roy, 2007).

An improved understanding that chronic inflammation triggers cancer incidence encourages researches aiming at determining the efficacy of the use of many anti-inflammatory drugs to prevent the incidence of cancer. The concept of cancer chemoprevention using aspirin showed that the use of long-term aspirin at the of at least 75 mg/day can prevent the incidence of cancer and decrease the number of mortality (Rothwell et al., 2010; Rothwell et al., 2011; Rothwell et al., 2012a), as well as reduce the possibility of metastasis if given right after cancer diagnosis is established (Rothwell et al., 2012b). Reduction in the number of mortality from cancer has been assumed to be due to repairs premalignant lesions, which are

• pISSN: 2085-1545
• eISSN: 2339-093X
http://jurnal.unissula.ac.id/index.php/sainsmedika

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) (Epplein, 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). Continuos 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)). Irregular use of aspirin had the same result without aspirin therapy (Wang et al., 2003).

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-κB, 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).

Anticancer mechanism of aspirin is also based on its function as an anti-platelet agent. The advance in science shows that platelets produce pro coagulant that facilitates coagulation of cancer cells, which can be recruited into the tumor cells, thus protecting the cancer from immune response and facilitate the growth and spread of cancer. This might explain the mechanism of aspirin as an anticancer (Bambace & Holmes, 2009).

Aspirin also releases hydrogen sulfide (H2S), which will suppress NF-κB signaling in breast cancer cell line MDA-MB-231 ER-. Consequently, it inhibits cancer cell cycle in phase Go/G1, causes decreased activity of thioredoxin reductase, an increased in ROS, induction of apoptosis, and decreased activity of NF-κB. Also tumor size reduced in vivo (Chattopadhyay et al., 2012). The effect of aspirin on the binding of NF-κB on DNA, was significantly correlated with the effect of aspirin on cell growth (Williams et al., 2012).

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-κB 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 chemoprevention 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:

Akre K, Ekstrom AM, Signorello LB, Hanson LE, Nyren O. Aspirin and risk for gastric cancer: a population-based case-control study in Sweden. *British J Cancer* 2001; 84: 965–968.

Antonoff MB, D'Cunha J. Killing Two Birds With One Salicylate: Aspirin's Dual Roles in Preventative Health. *Semin Thoracic Surg* 2011; 23:96-98.

Bambace NM, Holmes CE. The platelet contribution to cancer progression. *J Thromb Haemostasis* 2011; 9: 237-249.

Barton MK. Daily Aspirin Reduces Colorectal Cancer Incidence in Patients With Lynch Syndrome. cA: *A Cancer J for Clinicians* 2012; 62: 143-144. doi:10.3322/caac.21136.

Bosetti C, Gallus S, La Vecchia C. Aspirin and Cancer Risk: A Summary Review to 2007. In : Hans-Jörg Senn et al.. (Eds.), *Cancer Prevention II. Recent Results in Cancer Research 181*, DOI: 10.1007/978-3-540-69297-3. Springer-Verlag Berlin Heidelberg, 2009.

Brasky TM, Potter JD, Kristal AR, Patterson RE, Peters U, Asgari MM, Thornquist MD, White E. Non-steroidal Anti-inflammatory Drugs and Cancer Incidence by Sex in the Vitamins And Lifestyle (VITAL) Cohort. *Cancer Causes Control* 2012; 23: 431-444. doi:10.1007/s10552-011-9891-8.

Chan AT. Aspirin and familial adenomatous polyposis: coming full circle. *Cancer Prev Res* 2011; 4: 623-7.

Chang ET, Zheng T, Weir EG, Borowitz M, Mann RB, Spiegelman D, Mueller NE. Aspirin and the Risk of Hodgkin's Lymphoma in a Population-Based Case. *J Natl Cancer Inst* 2004; 96: 305–15.

Chattopadhyay M, Kodela R, Nath N, Barsegian A, Boring D, Kashfi K. Hydrogen sulfide-releasing aspirin suppresses NF-kB signaling in estrogen receptor negative breast cancer cells in vitro and in vivo. *Bichem Pharmacol* 2012; 83: 723-732.

Coghill AE, Adams SV, Newcomb PA, Campbell PT, Poole EM, Potter JD, Burnett-Hartman AN, Ulrich CM. Prediagnostic Non-steroidal anti-inflammatory drug use and survival after diagnosis of colorectal cancer. Gut 2011; 60: 491–498. doi:10.1136/*gut*.2010.221143.

Deng S, Hu B, Shen KP, Xu L. Inflammation, macrophage in cancer progression, dan Chinese herbal medicine. *J Basic and Clin Pharm* 2012; 3: 269-272.

Din FVN, Theodoratou E, Barnetson RA, Campbell H, Farrington SM, Cetnarsky R, Dunlop MG, Stark L, Tenesa A, Porteus ME. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. *Gut* (2010). doi:10.1136/gut.2009.203000.

Dinarello CA. Anti-inflammatory agents: Present and future. *Cell* 2010; 140: 935-950.

Epplein M, Nomura AMY, Wilkens LR, Henderson BE, Kolonel LN. Nonsteroidal Antiinflammatory Drugs and Risk of Gastric Adenocarcinoma, The Multiethnic Cohort Study. *Am J Epid* 2009; 170. doi: 10.1093/aje/kwp162.

Fontaine E, McShane J, Page R, Shackcloth M, Mediratta N, Carr M, Soorae A, Poullis M. Aspirin and non-small cell lung cancer resections: effect on long-term survival. *Eur J Cardio-thoracic Surg* 2010; 38: 21-26.

Gu Q, Wang JD, Xia HHX, Lin MCM, He H, Zou B, Tu SP, Yang Y, Liu XG, Lam SK, Wong WM, Chan AOO, Yuen MF, Kung HF, Wong BCY. Activation of the caspase-8/Bid and Bax pathways in aspirin-induced apoptosis in gastric cancer. *Carcinogenesis* 2005; 26: 541-- 546. doi:10.1093/carcin/bgh345.

Holmes MD, Chen WY, Lisa L, Hertzmark E, Spiegelman D, Hankinson SE. Aspirin Intake and Survival After Breast Cancer. *J Clin Oncol* 2010; 28: 1467-1472.

Hur C, Nishioka NS, Gazelle S. Cost-Effectiveness of Aspirin Chemoprevention for Barrett's Esophagus. *J Natl Cancer Inst* 2004; 96: 316-25.

Khuder SA, Herial NA, Mutgi AB, Federman DJ. Nonsteroidal Antiinflammatory Drug Use and Lung Cancer, A Metaanalysis. *CHEST* 2005; 127:748-754.

Lai MY, Huang JA, Liang ZH, Jiang HX, Tang GD. Mechanisms underlying aspirin-mediated growth inhibition and apoptosis induction of cyclooxygenase-2 negative colon cancer cell line SW480. *World J Gastroenterol* 2008; 14: 4227-4233.

Manzano A, Perez-Segura P. Chemoprevention in sporadic colorectal cancer: the role of Salycilates, NSAIDs, and Coxibs. *J Cancer Sci Ther* 2011; S3. http://dx.doi.org/10.4172/1948-5956.S3-005.

Moossavi S, Bishehsari F. Inflammation in sporadic colorectal cancer. *Arch Iran Med* 2012; 15: 166-170.

Rothwell PM, Jacqueline FP, Fowkes FGR, Zanchetti A, Roncaglioni MC, Tognoni G, et al.. Short-term eff ects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Published on line at www.thelancet.com. 2012a. doi:10.1016/S0140-6736(11)61720-0.

Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010; 376: 1741-50.

Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 2012b: doi:10.1016/S0140-6736(12)60209-8.

Rothwell RM, Fowkes FGR, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011; 377: 31-41. doi:10.1016/S0140-6736(10)62110-1.

Roy V. Pharmacology Autacoids: Nonsteroidal Antiinflammatory Drugs, Antipyretics, Analgesics: Drugs used in Gout. 2007. www.nsdl.niscair.res.in/bitstream/123456789/744/1/revised+autacoids+nonsteroidal+antiinflammatory+drugs.pdf. Cited on 19.10.2012.

Shiao SL, Ganesan P, Rugo HS, Coussens LM. Immune microenvironments in solid tumors: new targets for therapy. *Genes Dev.* 2011; 25: 2559-2572.

Trinchieri G. Innate inflammation and cancer: is it time for cancer prevention? *F1000 Medicine Reports* 2011; 3. doi: 10.3410/M3-11. http://f1000.com/reports/m/3/11.

Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res* 2003; 110: 255-58.

Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BCY. Non-steroidal Anti-inflammatory Drug Use and The Risk of Gastric Cancer: A Systematic Review and Meta Analysis. *J Natl Cancer Inst* 2003; 95: 1784 –91.

Williams J, Ji P, Ouyang N, Liu X, Rigas B. NO-donating aspirin inhibits the activation of NF-kB in human cancer cell lines and Min mice. *Carcinogenesis* 2008; 29: 390–397. doi:10.1093/carcin/bgm275.

Xiong S, She H, Takeuchi H, Han B, Engelhardt JF, Barton CH, et al. Signalling role of intracellular iron in NFκB activation. *J Biol Chem* 2003; 278: 17646-17654.

Zhu Z, Shen Z, Xu C. Inflammatory pathways as promising targets to increase chemotherapy response in bladder cancer. *Mediators of Inflammation.* 2012. doi:10.1155/2012/528690.

Zingde SM. Cancer Genes. Current Sciences 2001; 81:508-514.