Published in final edited form as:
Semin Oncol. 2014 June ; 41(3): 397–401. doi:10.1053/j.seminoncol.2014.04.012.

Prevention and treatment of cancer with aspirin: where do we stand?

Boris Pasche, M.D., Ph.D., **Minghui Wang, M.D.**, **Michael Pennison**, and **Hugo Jimenez**
Department of Cancer Biology and Comprehensive Cancer Center, Wake Forest University, Medical Center Blvd, Winston Salem, NC 27157-1082

INTRODUCTION

Aspirin is arguably the synthesized drug that has been the most commonly used in human history. Aspirin was originally developed and marketed for the treatment of inflammatory disorders at the end of the 19th century but its mechanism of action remained unknown until the second half of the 20th century. Since the latter part of the 20th century aspirin has also been used for the primary and secondary prevention of cardiovascular diseases given its anti-thrombotic properties. An association between intake of aspirin and decreased cancer risk was identified in the past decades. Whether aspirin can be used as an anticancer agent in patients with a diagnosis of cancer was unknown until recently. Recent studies suggest that aspirin might provide therapeutic benefit in the adjuvant treatment of certain forms of cancer. The main purpose of this article is to provide a critical update on this topic, which has potential implications for oncologists and their patients.

History of salicylates

The use of decoction of willow leaves for joint pain goes back to antiquity as documents from the ancient Egyptians and Hippocrates already recommended its use(Jack 1997). As early as 1763, the therapeutic effects of extracts of willow leaves were documented and in 1876 the first clinical trial of salicin was reported by a British physician who gave it to patients with acute rheumatism and observed disappearance of fever and joint pain(MacLagan 1876). A German pharmacologist isolated bitter, yellow, crystalline salicin in 1828 from willow bark and meadowsweet. A French chemist was the first to synthesize salicin in crystalline form(Leroux 1830). An Italian chemist subsequently showed that salicin was a glycoside and successfully split the compound into salicylic acid(Piria 1838). In the following years the use of salicylic acid increased because of its reported beneficial properties. In 1859, Frederic Kolbe discovered salicylic acid’s benzene ring-based structure and was able to synthesize it. By 1874 salicylic acid became widely available. While salicylic acid relieved pain and fever, its bitter taste and gastrointestinal side effects,

Phone: 336-716-7971, Fax: 336-716-0293, bpasche@wakehealth.edu

particularly vomiting, limited its long-term use. Acetylsalicylic acid, better known as aspirin, was first synthesized in pure form by Felix Hoffmann in 1897. This new drug was tested on patients the following year and commercial production of aspirin began. Clinical results as well as the results from animal experiments were published in 1899(Dreser 1899). In 1904, tablet aspirin replaced the powder form, which made it much more popular for daily use. Since then aspirin has become the most commonly used drug worldwide.

Aspirin and cancer prevention

Epidemiological evidence

Multiple retrospective studies on inflammation and cancer have been published since the late 80s suggesting a preventive role of anti-inflammatory drugs, especially aspirin(Kune, Kune et al. 1988). The effect of long-term use of aspirin on the development on colorectal cancer incidence and mortality was recently analyzed by Rothwell and collaborators(Rothwell, Wilson et al. 2010). In a combined analysis of four randomized trials designed for the primary or secondary prevention of cardiovascular events, it was found that use of aspirin at doses of at least 75 mg daily was associated with a 24% reduction of incidence and 35% reduction in mortality from colon cancer but such an association was not observed for rectal cancer. Interestingly, the association between aspirin intake and decreased colon cancer was strongest for the proximal colon. In a subsequent study the authors analyzed the association between aspirin intake and other forms of cancer(Rothwell, Fowkes et al. 2011). While no association was found between aspirin use and cancer risk for individuals using aspirin for less than five years, a significant association was found between aspirin use and risk for all cancers in long-term aspirin users, i.e. more than five years of use(Rothwell, Fowkes et al. 2011). The association between aspirin intake and risk for cancer resulted in an overall 20% decreased risk of dying from cancer. Analysis by tumor type with 20 years of follow-up showed an association between use of aspirin and reduced risk of esophageal cancer, colorectal cancer and lung cancer. In 2012, another study by the same group revealed that aspirin use was associated with reduced risk of cancer with distant metastases, HR 0.64, 95% CI, 0.48-0.84. Reduced risk was only associated with adenocarcinoma, HR 0.54, 95% CI 0.38-0.75, not for other types of solid tumors. Aspirin use was associated with reduced risk of adenocarcinoma with metastases at initial diagnosis, HR 0.69, 95% CI 0.50-0.95, and with risk of metastasis development in patients without metastases at the time of initial diagnosis, HR 0.45, 95% CI 0.28-0.72(Rothwell, Wilson et al. 2012).

African Americans have a higher colorectal cancer risk than Caucasians and most recent studies of aspirin have been conducted in Caucasians. However, one study assessed the use of NSAIDs and risk of colon cancer in a population-based, case control study of African Americans and Caucasians (Sansbury, Millikan, 2005). The inverse associations between regular NSAID use and colon cancer were similar for African Americans and Caucasians. They were also similar for aspirin non-aspiring NSAIDs.

Recent studies have also assessed the association between aspirin use and risk for some other tumor types:

Prostate cancer—a meta-analysis of 24 case control studies, which had been performed until 2013, was recently published (Huang, Yan et al. 2014).Regular use of aspirin was associated with decreased overall and advanced prostate cancer risk (pooled RR 0.86, 95 % CI 0.81– 0.92; pooled RR 0.83, 95 % CI 0.75–0.91, respectively). In analyses restricted to studies with long-time regular aspirin use, i.e. four years of more, the association between aspirin intake and decreased prostate cancer risk became stronger (pooled RR 0.82, 95 % CI 0.72–0.93; pooled RR 0.70, 95 % CI 0.55–0.90, respectively). A separate study revealed that aspirin use is associated with improved outcome in patients with high risk prostate cancer receiving radiation therapy(Jacobs, Chun et al. 2014).

Esophageal cancer—In a meta-analysis of nine observational studies of patients with Barrett's esophagus, a condition associated with increased risk for esophageal cancer, aspirin use was associated with reduced risk of esophageal adenocarcinoma or high grade dysplasia (RR=0.63, 95% CI=0.43–0.94)(Zhang, Zhang et al. 2014).

Melanoma—There is no clear evidence of an association between aspirin intake and risk for melanoma, either in the general population or in high risk individuals as the results from various studies are not consistent (Goodman and Grossman 2014).

Breast cancer—A consensus panel concluded in 2011 that aspirin and other NSAIDs only have minimal effects, if any, in the prevention of breast cancer(Cuzick, DeCensi et al. 2011).

Functional evidence

In 1971, John Vane discovered that aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) inhibit the activity of cyclooxygenase which was initially named COX but has since then been renamed PTGS for prostaglandin-endoperoxide synthase and cyclooxygenase. The PTGS gene encodes two isoforms of the enzyme, a constitutive isoform named PTGS1 and an inducible isoform named PTGS2. PTGS2 is known to be over-expressed at sites of inflammation and overexpression is triggered by a wide spectrum of growth factors and pro-inflammatory cytokines(Blom, Klein-Nulend et al. 2000). Chronic inflammation is a known risk for cancer, especially colorectal cancer as patients who suffer from inflammatory bowel diseases such as ulcerative colitis and Crohn's disease have a significantly increased lifelong risk of developing colorectal cancer(Adams and Bornemann 2013). Elevated PTGS2 expression is found in approximately 50% of colorectal adenomas and 85% of colorectal adenocarcinomas(Eberhart, Coffey et al. 1994, Gupta and DuBois 2001, Marnett and Dubois 2002). Importantly, elevated PTGS2 is associated with the worst survival among patients with colorectal cancer(Ogino, Kirkner et al. 2008). In 1983, Waddell and Loughry reported the case of a patient whose rectal polyps disappeared while taking two commonly used NSAIDs (indomethacin and sulindac) for pain relief (Blomhoff 1997). As aspirin and other NSAIDs are potent inhibitor of PTGS2, it has been hypothesized that their predominant antitumor effect might be through downregulation of PTGS2 (Vane and Botting 1998). Upregulated PTGS2 is also found in skin, lung, breast, prostate, bladder, pancreatic and head/neck carcinomas as well (Gupta and DuBois 2001).

The putative role of PTGS2 overexpression in cancer development was confirmed in animal models. Using a transgenic mice model (with murine mammary tumor virus promoter/enhancer controlling Ptgs2 expression), Liu et al. demonstrated that Ptgs2 overexpression is sufficient to induce cellular transformation (Liu, Chang et al. 2001).Furthermore, genetic studies conducted by Oshima et al. revealed that the number and size of polyps was reduced in the *Ptgs2*$^{-/-}$ mice compared with *Ptgs2* wild-type mice. Treatment of the *Apc* $^{\Delta 716}$/*Ptgs2* wild-type mice with a Ptgs2 inhibitor or the NSAID sulindac also reduced polyp numbers (Oshima M 1996, Blomme, Zhou et al. 1999).

Cellular studies have found that high doses of NSAIDs can modulate the growth of cultured cells independently and their ability to bind and inhibit PTGS1 or PTGS2 (Zhang X 1999, Blomqvist and Torkzad 2003). Transformed fibroblast cell lines derived from either wild-type, *Ptgs1*$^{-/-}$, *Ptgs2*$^{-/-}$ or *Ptgs1*$^{-/-}$/*Ptgs2*$^{-/-}$ mice all show comparable sensitivity to NSAID-induced cell death (Zhang X 1999). The effects of NSAIDs on PTGS may involve some additional targets such as the NFKB signaling pathway (Blondel, Talbot et al. 1990, Kopp E 1994). Other potential anticancer mechanisms of aspirin have been investigated. An experiment using fibrosarcoma cells as a metastatic model showed that aspirin treatment resulted in a significant reduction in lung metastases (Gasic, Gasic et al. 1972). It was suggested that aspirin first affects platelets, then leads to a subsequent interaction between platelets and PTGS2 (Smith, Elwood et al. 2014). Despite the existence of several putative mechanisms of actions for the anticancer effects of aspirin, its exact mechanism of action remains unknown.

Adjuvant treatment of colorectal cancer with aspirin

Among the 142,000 patients diagnosed with colorectal cancer in the United States in 2013, it is estimated that in 72% of cases the tumor arises from the colon and in 28% of cases from the rectum(Siegel, Naishadham et al. 2013). Colorectal cancer is predominantly a disease affecting older individuals as 90% of new cases and 94% of deaths occur in individuals aged 50 and older. In the 1980s 5-fluorouracil-based adjuvant chemotherapy became the standard of care for resectable stage III colorectal cancer and reduced mortality by 33%(Moertel, Fleming et al. 1990). Over the past two decades several additional lines of therapy have been assessed in this setting in combination with 5-fluorouracil-based chemotherapy but only one agent, oxaliplatin, was shown to further reduce mortality by 4% compared to 5-fluorouracilbased chemotherapy(Saltz, Niedzwiecki et al. 2007, André, Boni et al. 2009, Allegra, Yothers et al. 2011, Alberts, Sargent et al. 2012). Hence, little progress has been made in the adjuvant treatment of stage III colorectal cancer and novel therapeutic options are sorely needed(Pasche 2012).

Epidemiological evidence

In the past few years there has been emerging evidence from retrospective studies that the use of aspirin after a diagnosis of colorectal cancer may be associated with decreased risk for disease recurrence. The first report suggesting that aspirin intake may lower the risk of disease recurrence in patients with stage III colorectal cancer was published in 2009(Chan, Ogino et al. 2009). In that study 1279 patients enrolled in the Nurses' Health Study and the Health Professionals Follow-up Study, prior to a diagnosis of colorectal cancer stage I, II or

III, were followed up for an average of 11.8 years. During the follow-up period 480 patients died, 222 from colorectal cancer. Aspirin use was assessed prior to enrollment in the studies and every other year thereafter. Forty percent of all participants did not regularly use aspirin before and after diagnosis, 29% regularly used aspirin before and after diagnosis, 15% regularly used aspirin before diagnosis but discontinued use after diagnosis, and 14% did not regularly use aspirin before diagnosis but, started use after diagnosis. Regular use of aspirin after diagnosis of colorectal cancer was associated with a 21% reduced risk of death and 29% reduced risk of colorectal cancer-specific mortality(Chan, Ogino et al. 2009).

In 2012 a study from the Netherlands provided confirmatory results. In that study, 4481 patients who had been diagnosed with colorectal cancer between 1998 and 2007 were selected from the Eindhoven Cancer Registry, a population-based cancer registry(Bastiaannet, Sampieri et al. 2012). In total 26% of the patient never used aspirin or NSAIDs, 47% used aspirin or NSAIDs before and after diagnosis of colorectal cancer, and 27% only use aspirin or NSAIDs after diagnosis of colorectal cancer. Compared with nonusers, aspirin users had improved survival, adjusted rate ratio (RR) 0.77, 95% CI 0.63-0.95. A survival benefit was only observed for patients with colon cancer, RR 0.65, 95% CI 0.50-0.84, not for patients with rectal cancer, RR 1.10, 95% CI 0.79-1.54. Importantly, use of NSAIDs, other than aspirin, was associated with decreased survival, RR 1.93, 95% CI 1.70-2.20.

A British cohort of 13,994 patients, with a diagnosis of colorectal cancer, was assessed to determine whether aspirin or NSAID exposure in the year immediately following diagnosis was associated with all-cause mortality(Walker, Grainge et al. 2012). The overall mortality was slightly lower in patients taking aspirin. The hazard ratio (HR) was 0.91; 95% CI, 0.82-1.00. Interestingly, this effect was only observed in patients taking aspirin before diagnosis of colorectal cancer, HR = 0.86, 95% CI 0.76-0.98. For NSAID use, no significant effect was observed(Walker, Grainge et al. 2012).

Investigators from the Netherlands performed a subgroup analysis of a previously published cohorts and retrospective study. The survival of 536 individuals aged 70 and older diagnosed with colorectal cancer was studied in relation to the use of aspirin after diagnosis(Reimers, Bastiaannet et al. 2012). The rationale for this subset analysis is the fact that almost half of all patients with a diagnosis of colorectal cancer are aged 70 and older. Additionally, given the poor tolerance of elderly patients to adjuvant chemotherapy, which is the standard of care for patients diagnosed with stage III disease, aspirin is an attractive option. One in 5 patients included in the study started aspirin after being diagnosed with colon cancer, the remainder of the patients did not use aspirin. The overall survival of patients taking aspirin was higher than that of patients not taking aspirin, RR 0.51, 95% CI 0.38-0.70.

Functional evidence

Several studies have assessed potential biomarkers of colorectal cancer response to aspirin in the adjuvant setting. PTGS2 overexpression was assessed by immunostaining in a subset of 459 patients enrolled in the Chan et al. 2009 study who were regular users of aspirin after diagnosis of colorectal cancer(Chan, Ogino et al. 2009). Aspirin use among patients whose

tumor overexpressed PTGS2 was associated with decreased colorectal cancer-specific mortality while no association was found among patients with low or decreased PTGS2 expression.

Two additional potential biomarkers of response have been investigated over the past few years including mutations with the phosphatidylinositol-4,5-biphosphonate 3-kinase (*PIK3CA*) gene(Liao, Morikawa et al. 2012, Domingo, Church et al. 2013, Reimers, Bastiaannet et al. 2014) and HLA class I antigen(Reimers, Bastiaannet et al. 2014). The results obtained thus far are not consistent and these three potential biomarkers will need to be further validated.

Conclusions and future directions

Retrospective analyses of randomized studies designed to assess the effect of aspirin on cardiovascular events strongly suggest that intake of aspirin is associated with decreased incidence of cancer. While a randomized controlled study showed that the intake of 600 mg aspirin per day for a mean of 25 months substantially reduces the incidence of colorectal cancer in patients with hereditary colorectal cancer (Lynch syndrome)(Burn, Gerdes et al. 2011), such data is not yet available with respect to the use of aspirin in healthy individuals without an increased risk of colorectal cancer. Diverging opinions have been voiced with respect to current recommendations for aspirin use with respect to the prevention and treatment of cancer. Some advocate the potential benefit of aspirin is high enough compared to its risks, predominantly bleeding risks such as hemorrhagic stroke and gastrointestinal bleeding, that current data warrants its use in patients with stage III colorectal cancer(Neugut 2014). In contrast, most authorities advocate caution with respect to the use aspirin in the primary prevention of cancer(Potter 2012) given the fact that another meta-analysis that did not show any decreased cancer risk associated with aspirin(Seshasai, Wijesuriya et al. 2012) and because of the elevated risk for gastrointestinal bleeding and hemorrhagic stroke observed in virtually all studies(McQuaid and Laine 2006, Sostres and Lanas 2011, Rothwell, Wilson et al. 2012, Seshasai, Wijesuriya et al. 2012). While waiting for the results of randomized studies of aspirin in patients with a diagnosis of stage III colon cancer, a discussion with patients about the risks and benefits of aspirin appears to be in order. For patients who were taking aspirin prior to a diagnosis of stage III colorectal cancer, current evidence provides strong support for continuation of aspirin unless new or foreseeable bleeding risks are present. For patients who did not use aspirin prior to diagnosis of stage III colorectal cancer, low dose aspirin (75 to 81 mg per day) should be considered taking into account its potential benefits with respect to colorectal cancer recurrence and its potential bleeding risks. Identification and validation of a robust biomarker of response to aspirin may soon resolve this dilemma.

References

Adams SM, Bornemann PH. Ulcerative colitis. Am Fam Physician. 2013; 87(10):699–705. [PubMed: 23939448]

Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, Smyrk TC, Sinicrope FA, Chan E, Gill S, Kahlenberg MS, Shields AF, Quesenberry JT, Webb TA, Farr GH Jr, Pockaj BA, Grothey A, Goldberg RM. Effect of oxaliplatin, fluorouracil, and leucovorin with or without

cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012; 307(13):1383–1393. [PubMed: 22474202]

Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, Atkins JN, Seay TE, Fehrenbacher L, Goldberg RM, O'Reilly S, Chu L, Azar CA, Lopa S, Wolmark N. Phase III Trial Assessing Bevacizumab in Stages II and III Carcinoma of the Colon: Results of NSABP Protocol C-08. journal of clinical oncology. 2011; 29(1):11–16. [PubMed: 20940184]

André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A. Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. journal of clinical oncology. 2009; 27(19):3109–3116. [PubMed: 19451431]

Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJM, van Herk-Sukel MPP, Lemmens V, van den Broek CBM, Coebergh JW, Herings RMC, van de Velde CJH, Fodde R, Liefers GJ. Use of Aspirin postdiagnosis improves survival for colon cancer patients. Br J Cancer. 2012; 106(9):1564–1570. [PubMed: 22454078]

Blom EJ, Klein-Nulend J, Klein CPAT, Kurashina K, van Waas MAJ, Burger EH. Transforming growth factor-beta 1 incorporated during setting in calcium phosphate cement stimulates bone cell differentiation in vitro. Journal of Biomedical Materials Research. 2000; 50(1):67–74. [PubMed: 10644965]

Blomhoff R. Retinoids may increase fibrotic potential of tgf-beta - crosstalk between two multifunctional effectors. Hepatology. 1997; 26(4):1067–1068. [PubMed: 9328335]

Blomme EAG, Zhou H, Kartsogiannis V, Capen CC, Rosol TJ. Spatial and temporal expression of parathyroid hormone-related protein during wound healing. Journal of Investigative Dermatology. 1999; 112(5):788–795. [PubMed: 10233773]

Blomqvist L, Torkzad MR. Whole-Body Imaging With MRI or PET/CT: The Future for Single-Modality Imaging in Oncology? JAMA: The Journal of the American Medical Association. 2003; 290(24):3248–3249. [PubMed: 14693879]

Blondel B, Talbot N, Merlo GR, Wychowski C, Yokozaki H, Valverius EM, Salomon DS, Bassin RH. Efficient induction of focus formation in a subclone of nih3t3 cells by c-myc and its inhibition by serum and by growth factors. Oncogene. 1990; 5:857–865. [PubMed: 2193293]

Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard ML, Dunlop MG, Ho JWC, Hodgson SV, Lindblom A, Lubinski J, Morrison PJ, Murday V, Ramesar R, Side L, Scott RJ, Thomas HJW, Vasen HF, Barker G, Crawford G, Elliott F, Movahedi M, Pylvanainen K, Wijnen JT, Fodde R, Lynch HT, Mathers JC, Bishop DT. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. The Lancet. 2011; 378(9809):2081–2087.

Chan AT, Ogino S, Fuchs CS. Aspirin Use and Survival After Diagnosis of Colorectal Cancer. JAMA: The Journal of the American Medical Association. 2009; 302(6):649–658. [PubMed: 19671906]

Cuzick J, DeCensi A, Arun B, Brown PH, Castiglione M, Dunn B, Forbes JF, Glaus A, Howell A, von Minckwitz G, Vogel V, Zwierzina H. Preventive therapy for breast cancer: a consensus statement. Lancet Oncol. 2011; 12(5):496–503. [PubMed: 21441069]

Domingo E, Church DN, Sieber O, Ramamoorthy R, Yanagisawa Y, Johnstone E, Davidson B, Kerr DJ, Tomlinson IPM, Midgley R. Evaluation of PIK3CA Mutation As a Predictor of Benefit From Nonsteroidal Anti-Inflammatory Drug Therapy in Colorectal Cancer. Journal of Clinical Oncology. 2013

Dreser H. Pharmacologisches über Aspirin (acetylsalicylsäure). Pflüger Archiv für die gesammte Physiologie des Menschen und der Tiere. 1899; 76

Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology. 1994; 107(4):1183–1188. [PubMed: 7926468]

Gasic G, Gasic T, Murphy S. Anti-Metastatic Effect of Aspirin. The Lancet. 1972; 300(7783):932–933.

Goodman J, Grossman D. Aspirin and other NSAIDs as chemoprevention agents in melanoma. Cancer Prevention Research. 2014

Gupta RA, DuBois RN. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nat Rev Cancer. 2001; 1(1):11–21. [PubMed: 11900248]

Huang, T-b; Yan, Y.; Guo, Z-f; Zhang, X-l; Liu, H.; Geng, J.; Yao, X-d; Zheng, J-h. Aspirin use and the risk of prostate cancer: a meta-analysis of 24 epidemiologic studies. International Urology and Nephrology. 2014:1–14. [PubMed: 23673775]

Jack DB. One hundred years of aspirin. Lancet. 1997; 350(9075):437–439. [PubMed: 9259670]

Jacobs CD, Chun SG, Yan J, Xie XJ, Pistenmaa DA, Hannan R, Lotan Y, Roehrborn CG, Choe KS, Kim DN. Aspirin improves outcome in high risk prostate cancer patients treated with radiation therapy. Cancer Biol Ther. 2014; 15(6)

Kopp EGS. Inhibition of NF kappa B by sodium salicylate and aspirin.pdf. Science. 1994; 265(517):4.

Kune GA, Kune S, Watson LF. Colorectal Cancer Risk, Chronic Illnesses, Operations, and Medications: Case Control Results from the Melbourne Colorectal Cancer Study. Cancer Research. 1988; 48(15):4399–4404. [PubMed: 3390835]

Leroux H. Découverte de la salicine. Journal de Chimie Médicale. 1830; 6:341.

Liao X, Morikawa T, Lochhead P, Imamura Y, Kuchiba A, Yamauchi M, Nosho K, Qian ZR, Nishihara R, Meyerhardt JA, Fuchs CS, Ogino S. Prognostic Role of PIK3CA Mutation in Colorectal Cancer: Cohort Study and Literature Review. Clinical Cancer Research. 2012; 18(8): 2257–2268. [PubMed: 22357840]

Liu CH, Chang SH, Narko K, Trifan OC, Wu MT, Smith E, Haudenschild C, Lane TF, Hla T. Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. J Biol Chem. 2001; 276(21):18563–18569. [PubMed: 11278747]

MacLagan TJ. The treatment of rheumatism by salicin and salicylic acid. The Lancet. 1876; I:342.

Marnett LJ, Dubois RN. COX-2: a target for colon cancer prevention. Annu.Rev.Pharmacol.Toxicol. 2002; 42:55–80. [PubMed: 11807164]

McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med. 2006; 119(8):624–638. [PubMed: 16887404]

Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, Ungerleider JS, Emerson WA, Tormey DC, Glick JH, Veeder MH, Mailliard JA. Levamisole and Fluorouracil for Adjuvant Therapy of Resected Colon Carcinoma. New England Journal of Medicine. 1990; 322(6):352–358. [PubMed: 2300087]

Neugut AI. Aspirin as adjuvant therapy for stage iii colon cancer: Standard of care? JAMA Internal Medicine. 2014

Ogino S, Kirkner GJ, Nosho K, Irahara N, Kure S, Shima K, Hazra A, Chan AT, Dehari R, Giovannucci EL, Fuchs CS. Cyclooxygenase-2 expression is an independent predictor of poor prognosis in colon cancer. Clin Cancer Res. 2008; 14(24):8221–8227. [PubMed: 19088039]

Oshima M, D J, Kargman SL, Oshima H, Hancock B, Kwong E, Trzaskos JM, Evans JF, Taketo MM. Suppression of Intestinal Polyposis in Apc Knockout Mice by Inhibition of Cyclooxygenase 2.pdf. Cell. 1996; 87(5):7.

Pasche B. Aspirin — From Prevention to Targeted Therapy. New England Journal of Medicine. 2012; 367(17):1650–1651. [PubMed: 23094728]

Piria R. Sur la composition de la salicine et quelques-unes de ses réactions. Comptes Rendus de l'Académie des Sciences, Paris. 1838; 6:338.

Potter JD. Aspirin and cancer prevention and treatment: are we there yet? Cancer Epidemiol Biomarkers Prev. 2012; 21(9):1439–1440. [PubMed: 22956729]

Reimers MS, Bastiaannet E, Langley RE, et al. EXpression of hla class i antigen, aspirin use, and survival after a diagnosis of colon cancer. JAMA Internal Medicine. 2014

Reimers MS, Bastiaannet E, van Herk-Sukel MP, Lemmens VE, van den Broek CB, van de Velde CJ, de Craen AJ, Liefers GJ. Aspirin Use After Diagnosis Improves Survival in Older Adults with Colon Cancer: A Retrospective Cohort Study. J Am Geriatr Soc. 2012

Rothwell PM, Fowkes FG, 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(9759):31–41. [PubMed: 21144578]

Rothwell PM, Wilson C-E, Elwin M, 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. The Lancet. 2010; 376(9754):1741–1750.

Rothwell PM, Wilson M, Price JF, Belch JFF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. The Lancet. 2012; 379(9826):1591–1601.

Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, Fields ALA, Mayer RJ. Irinotecan Fluorouracil Plus Leucovorin Is Not Superior to Fluorouracil Plus Leucovorin Alone As Adjuvant Treatment for Stage III Colon Cancer: Results of CALGB 89803. journal of clinical oncology. 2007; 25(23):3456–3461. [PubMed: 17687149]

Seshasai S, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: Meta-analysis of randomized controlled trials. Archives of Internal Medicine. 2012; 172(3):209–216. [PubMed: 22231610]

Siegel R, Naishadham D, Jemal A. Cancer statistics 2013. CA: A Cancer Journal for Clinicians. 2013; 63(1):11–30. [PubMed: 23335087]

Smith T, Elwood P, Keating C, Rothwell P, Detering E, Freedman A, Langley R, Logan R, Phillips C, Censi AD. The Aspirin Foundation Scientific Conference: the history, the present state and the future of aspirin prophylaxis. Ecancermedicalscience. 2014; 8:388. [PubMed: 24678343]

Sostres C, Lanas A. Gastrointestinal effects of aspirin. Nat Rev Gastroenterol Hepatol. 2011; 8(7): 385–394. [PubMed: 21647198]

Vane JR, Botting RM. Anti-inflammatory drugs and their mechanism of action. [Review] [113 refs. Inflammation Research. 1998; 47(Suppl-87)

Walker AJ, Grainge MJ, Card TR. Aspirin and other non-steroidal anti-inflammatory drug use and colorectal cancer survival: a cohort study. Br J Cancer. 2012; 107(9):1602–1607. [PubMed: 23011483]

Zhang S, Zhang XQ, Ding XW, Yang RK, Huang SL, Kastelein F, Bruno M, Yu XJ, Zhou D, Zou XP. Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with Barrett/'s esophagus: a meta-analysis. Br J Cancer. 2014

Zhang XMS, Langenbach R, Young DA. Malignant Transformation and Antineoplastic Actions of Nonsteroidal Antiinflammatory Drugs NSAIDs on Cyclooxygenase-null Embryo Fibroblasts.pdf. J Exp Med. 1999; 190(4):9. [PubMed: 10429666]