Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
and
Position Statement on Aspirin

Introduction

Aspirin is part of a group of medications called non-steroidal anti-inflammatory drugs (NSAIDs), but differs from most other NSAIDs in its mechanism of action. Though it, and others with similar structure, called the salicylates, have similar effects (reduction of fever), anti-inflammatory, and analgesic to the other NSAIDs and inhibit the same enzyme cyclooxygenase (COX), aspirin does so in an irreversible manner and, unlike others, affects more the COX-1 variant than the COX-2 variant of the enzyme (Burke, Smythe & FitzGerald, 2006).

[Picture Credit: Aspirin]

Aspirin is one of the most widely used medications in the world, with an estimated 40 000 tons of it being consumed each year. In countries where 'Aspirin' is a registered trademark owned by Bayer, the generic term is acetylsalicylic acid (ASA). It is on the World Health Organization's List of Essential Medicines, a list of the most important medications needed in a basic health system.

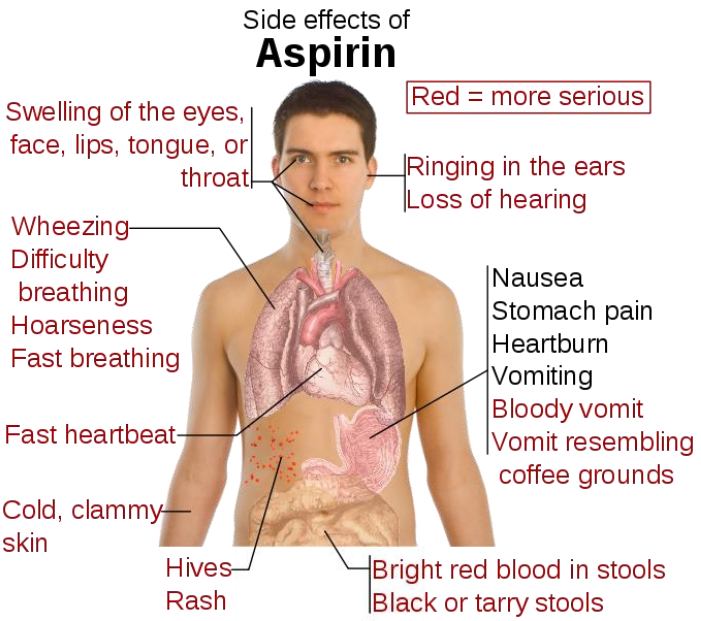
A Warning Against the Indiscriminate Use of Aspirin

Although taking an occasional aspirin or two is safe for most adults to use for headaches, body aches or fever, daily use of aspirin can have serious side effects, including internal bleeding. One should take a daily aspirin only if one's doctor advises to do so. If one has had a heart attack or stroke, a doctor will likely recommend taking a daily aspirin unless there is evidence of a serious allergy or history of bleeding. If someone has a high risk of having a first heart attack, a doctor might recommend aspirin after weighing the risks and benefits. No one should start daily aspirin therapy on their own.

One should not use aspirin if one has a bleeding disorder such as haemophilia, a recent history of stomach or intestinal bleeding, or if one is allergic to a non-steroidal anti-inflammatory drug (NSAID) such as Advil, Motrin, Aleve, Orudis, Indocin, Lodine, Voltaren, Toradol, Mobic, Relafen, Feldene, and others.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Even though aspirin is freely available, it should not be given indiscriminately to a child or teenager with a fever, flu symptoms, or chicken pox as it can cause Reye's syndrome (a rare but serious illness that can affect the brain and liver that occurs most commonly in kids recovering from a viral infection), a serious and sometimes fatal condition in children.



[Picture Credit: Aspirin Side Effects]

To make sure aspirin is safe to use, one should inform one's doctor about:

- asthma or seasonal allergies
- stomach ulcers
- liver disease
- kidney disease
- a bleeding or blood clotting disorder
- heart disease, high blood pressure, or congestive heart failure
- gout
- nasal polyps

Aspirin may be harmful to an unborn baby's heart, and may also reduce birth weight or have other dangerous effects. Women should inform their doctor if they are pregnant or plan to become pregnant while taking aspirin. Aspirin can pass into breast milk and may harm a nursing baby. Women should, therefore, not breast-feed while using this medicine.

Aspirin and Non-Communicable Diseases

Non-communicable diseases (NCDs) accounted for two of every three deaths (34,5 million) worldwide in 2010. An important way to tackle cardiovascular diseases (CVD) inclusive of stroke prevention is to encourage people to adopt healthier behaviours and diets as well as the use of life-long aspirin (daily, low dose) for secondary prevention of CVD as this is well established and included in many evidence-based guidelines (Algra, 2013). This should, however, only be done after consultation with a medical practitioner.

Aspirin and Reducing the Risk for Cancer

The following are recorded scientific findings on Aspirin and cancer:

<u>Lowering the Risk for Cancer</u>

Not everyone should start swallowing a daily aspirin. The drug comes with some very real drawbacks - most notably an increased risk for internal bleeding.

That is especially true among older adults or those who drink alcohol, have a history of ulcers, or who take anticoagulant drugs. The risk of bleeding may be too great to recommend an aspirin regimen, research suggests.

While bleeding risks are lower among people taking low-dose aspirin compared to those on full-strength versions of the drug, aspirin swallowers are still twice as likely to suffer from life-threatening bleeding compared to those not on aspirin. Low doses of aspirin or "baby aspirin" are generally 81 milligrams.

A daily low-dose aspirin (81mg) may make sense for people at high risk for certain types of cancer, but the potential side effects mean aspirin certainly is not for everyone. Only one's doctor can help one weigh the benefits against the risks.

Patients receiving cancer treatment could increase their chance of survival by up to 20% and help stop their cancer from spreading by taking a low-dose of aspirin, new research suggests.

In a systematic review of the available scientific literature a team from Cardiff University's School of Medicine found a significant reduction in mortality and cancer spread by patients who took a low-level dose of aspirin in addition to their cancer treatment (average study follow-up length over 5 years).

The researchers found that there is a growing body of evidence that taking aspirin is of significant benefit in reducing some cancers. Whilst it is known that a low-dose of aspirin has been shown to reduce the incidence of cancer, its role in the treatment of cancer remains uncertain. The team's review looked at all of the available data including five randomised trials and forty two observational studies of colorectal, breast and prostate cancers.

Hybiak, J., Broniarek, I., Kiryczyński, G., Los, L.D., Rosik, J., Machaj, F., Sławiński, H., Jankowska, K. & Urasińska, E. 2020.
"Aspirin (acetylsalicylic acid), the oldest synthetic drug, was originally used as an anti-inflammatory medication. Being an irreversible inhibitor of COX (prostaglandin-endoperoxide synthase) enzymes that produce precursors for prostaglandins and thromboxanes, it has gradually found several other applications. Sometimes these applications are unrelated to its original purpose for example its use as an anticoagulant. Applications such as these have opened opportunities for new treatments. In this case, it has been tested in patients with cardiovascular disease to reduce the risk of myocardial infarct. Its function as an anticoagulant has also been explored in the prophylaxis and treatment of pre-eclampsia, where due to its anti-inflammatory properties, aspirin intake may be used to reduce the risk of colorectal cancer. It is important to always consider both the risks and benefits of aspirin's application. This is especially important for proposed use in the prevention and treatment of neurologic ailments like Alzheimer's disease, or in the prophylaxis of myocardial infarct. In such cases, the decision if aspirin should be applied, and at what dose may be guided by specific molecular markers. In this revived paper, the pleiotropic application of aspirin is summarized."

Simon, T.G., Duberg, A.S., Aleman, S., Chung, R.T., Chan, A.T. & Ludvigsson, J.F. 2020.
Background: More information is needed about the long-term effects of low-dose aspirin (≤160 mg) on incident hepatocellular carcinoma, liver-related mortality, and gastrointestinal bleeding in persons with chronic hepatitis B or hepatitis C virus infection.

Methods: Using nationwide Swedish registries, we identified all adults who received a diagnosis of chronic hepatitis B or hepatitis C from 2005 through 2015 and who did not have a history of aspirin use (50,275 patients). Patients who were starting to take low-dose aspirin (14,205 patients) were identified by their first filled prescriptions for 90 or more consecutive doses of aspirin. We constructed a propensity score and applied inverse probability of treatment weighting to balance baseline characteristics between groups. Using Cox proportional-hazards regression modeling, we estimated the risk of hepatocellular carcinoma and liver-related mortality, accounting for competing events.
Results: With a median of 7.9 years of follow-up, the estimated cumulative incidence of hepatocellular carcinoma was 4.0% among aspirin users and 8.3% among nonusers of aspirin (difference, -4.3 percentage points; 95% confidence interval [CI], -5.0 to -3.6; adjusted hazard ratio, 0.69; 95% CI, 0.62 to 0.76). This inverse association appeared to be duration-dependent; as compared with short-term use (3 months to <1 year), the adjusted hazard ratios were 0.90 (95% CI, 0.76 to 1.06) for 1 to less than 3 years of use, 0.66 (95% CI, 0.56 to 0.78) for 3 to less than 5 years of use, and 0.57 (95% CI, 0.42 to 0.70) for 5 or more years of use. Ten-year liver-related mortality was 11.0% among aspirin users and 17.9% among nonusers (difference, -6.9 percentage points [95% CI, -8.1 to -5.7]; adjusted hazard ratio, 0.73 [95% CI, 0.67 to 0.81]). However, the 10-year risk of gastrointestinal bleeding did not differ significantly between users and nonusers of aspirin (7.8% and 6.9%, respectively; difference, 0.9 percentage points; 95% CI, -0.6 to 2.4).
Conclusions: In a nationwide study of patients with chronic viral hepatitis in Sweden, use of low-dose aspirin was associated with a significantly lower risk of hepatocellular carcinoma and lower liver-related mortality than no use of aspirin, without a significantly higher risk of gastrointestinal bleeding. (Funded by the National Institutes of Health and others.).

Zhang, X., Feng, Y., Liu, X., Ma, J., Li, Y., Wang, T. & Li, X. 2019.
PURPOSE: Aspirin, one of the most commonly used nonsteroidal anti-inflammatory drugs (NAIDS), not only shows cancerchemoprevention effects but also improves cancer therapeutic effects when combined with other therapies. Studies that focus on aspirin regulation of the hallmarks of cancer and the associated molecular mechanisms facilitate a more thorough understanding of aspirin in mediating chemoprevention and may supply additional information for the development of novel cancer therapeutic agents.
METHODS: The relevant literatures from PubMed have been reviewed in this article.
RESULTS: Current studies have revealed that aspirin regulates almost all the hallmarks of cancer. Within tumor tissue, aspirin suppresses the bioactivities of cancer cells themselves and deteriorates the tumor microenvironment that supports cancer progression. In addition to tumor tissues, blocking of platelet activation also contributes to the ability of aspirin to inhibit cancer progression. In terms of the molecular mechanism, aspirin targets oncogenes and cancer-related signaling pathways and activates certain tumor suppressors.
CONCLUSION: Beyond a chemopreventive agent, aspirin is a master regulator of the hallmarks of cancer.

<u>Aspirin can lower cancer mortality</u>
There is some evidence from randomised trials that short-term (2–3 years) aspirin use can lower cancer mortality. When compared with controls, aspirin use resulted in fewer deaths due to cancer. Aspirin also tended to reduce the incidence of female reproductive cancers and death due to colorectal cancer and lymphoma (Yelsengekar & Mahandas, 2012).

Aspirin and a decreased risk for cancer

According to Pasche, *et al*. (2014) 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.

Aspirin, lifestyle and colon cancer

Lifestyle, including aspirin use, has the effect of modulating age-associated DNA methylation changes in the colonic epithelium and thereby impacts the evolution of cancer methylomes in colon cancer (Noreen, *et al*., 2014).

In a study carried out by researchers from a number of institutions across Europe and the US, including Queen Mary University of London, it was found that people aged between 50 and 65 who take aspirin every day for 10 years could cut their risk of bowel cancer by 30% and cancers of the throat and stomach by 25%, according to the study published in the Annals of Oncology. Aspirin is an antiplatelet, which means it reduces the risk of clots forming in your blood. Platelets may also protect cancer cells in the body, and it has been suggested aspirin's effect on them may hinder this process. However, the exact mechanism is not well understood and more research is needed.

Taking aspirin every day comes with a serious health warning as it can cause serious side effects such as ulcers and bleeding from the stomach, particularly in elderly people. However, the researchers argue the benefits of taking the drug need to be balanced against the harms. Anyone thinking of taking aspirin for prevention should talk to their medical practitioner first (NHS Choices.UK; WebMD).

The earliest and strongest evidence that aspirin can prevent cancer emerged from studies showing that a daily dose of aspirin reduced the risk of colorectal cancer by 20%. Early on, it appeared that people had to take aspirin for at least five years to reduce their risk of developing cancer, but some of the newer studies suggest that 2 years may also help prevent cancer (Booker).

Burn, J., Sheth, H., Elliott, F., Reed, L., Macrae, F., Mecklin, J.P., Möslein, G., McRonald, F.E., Bertario, L., Evans, D.G., Gerdes, A.M., Ho, J.W.C., Lindblom, A., Morrison, P.J., Rashbass, J., Ramesar, R., Seppälä, T., Thomas, H.J.W., Pylvänäinen, K., Borthwick, G.M., Mathers, J.C., Bishop, D.T.; CAPP2 Investigators. 2020.

Background: Lynch syndrome is associated with an increased risk of colorectal cancer and with a broader spectrum of cancers, especially endometrial cancer. In 2011, our group reported long-term cancer outcomes (mean follow-up 55·7 months [SD 31·4]) for participants with Lynch syndrome enrolled into a randomised trial of daily aspirin versus placebo. This report completes the planned 10-year follow-up to allow a longer-term assessment of the effect of taking regular aspirin in this high-risk population.

Methods: In the double-blind, randomised CAPP2 trial, 861 patients from 43 international centres worldwide (707 [82%] from Europe, 112 [13%] from Australasia, 38 [4%] from Africa, and four [<1%] from The Americas) with Lynch syndrome were randomly assigned to receive 600 mg aspirin daily or placebo. Cancer outcomes were monitored for at least 10 years from recruitment with English, Finnish, and Welsh participants being monitored for up to 20 years. The primary endpoint was development of colorectal cancer. Analysis was by intention to treat and per protocol. The trial is registered with the ISRCTN registry, number ISRCTN59521990.

Findings: Between January, 1999, and March, 2005, 937 eligible patients with Lynch syndrome, mean age 45 years, commenced treatment, of whom 861 agreed to be randomly assigned to the aspirin

group or placebo; 427 (50%) participants received aspirin and 434 (50%) placebo. Participants were followed for a mean of 10 years approximating 8500 person-years. 40 (9%) of 427 participants who received aspirin developed colorectal cancer compared with 58 (13%) of 434 who received placebo. Intention-to-treat Cox proportional hazards analysis revealed a significantly reduced hazard ratio (HR) of 0·65 (95% CI 0·43-0·97; p=0·035) for aspirin versus placebo. Negative binomial regression to account for multiple primary events gave an incidence rate ratio of 0·58 (0·39-0·87; p=0·0085). Per-protocol analyses restricted to 509 who achieved 2 years' intervention gave an HR of 0·56 (0·34-0·91; p=0·019) and an incidence rate ratio of 0·50 (0·31-0·82; p=0·0057). Non-colorectal Lynch syndrome cancers were reported in 36 participants who received aspirin and 36 participants who received placebo. Intention-to-treat and per-protocol analyses showed no effect. For all Lynch syndrome cancers combined, the intention-to-treat analysis did not reach significance but per-protocol analysis showed significantly reduced overall risk for the aspirin group (HR=0·63, 0·43-0·92; p=0·018). Adverse events during the intervention phase between aspirin and placebo groups were similar, and no significant difference in compliance between intervention groups was observed for participants with complete intervention phase data; details reported previously.
Interpretation: The case for prevention of colorectal cancer with aspirin in Lynch syndrome is supported by our results.
Funding: Cancer Research UK, European Union, MRC, NIHR, Bayer Pharma AG, Barbour Foundation.

Grancher, A., Michel, P., Di Fiore, F. & Sefrioui, D. 2018.
"Colorectal cancer is a worldwide public health problem. Aspirin has been identified as a protective factor against the apparition of colorectal cancer. There are several mechanisms about the actions by aspirin on colorectal tumorogenesis. These are not perfectly known nowadays. On one hand, there are direct mechanisms on colorectal mucosa, on the other hand there are indirect mechanisms through platelet functions. Aspirin also plays a role by its anti-inflammatory action and the stimulation of antitumor immunity. Several studies show that long-term treatment with low-doses of aspirin decreases the incidence of adenomas and colorectal cancers. In the United States, aspirin is currently recommended for primary prevention of the risk of colorectal cancer in all patients aged 50 to 59, with a 10-year risk of cardiovascular event greater than 10 %. However, primary prevention with aspirin should not be a substitute for screening in colorectal cancer. Furthermore, aspirinseems to be beneficial when used in post-diagnosis of colorectal cancer. It could actually decrease the risk of metastasis in case of a localized colorectal cancer, and increase the survival in particular, concerning PIK3CA mutated tumors. The association of aspirin with neoadjuvant treatment of colorectal cancer by radiochimiotherapy seems to have beneficial effects. French prospective randomized study is currently being conducted to investigate postoperative aspirin in colorectal cancers with a PIK3CA mutation."

<u>Aspirin as a promising agent for cancer prevention and treatment</u>
High-quality evidence suggests that aspirin is a promising agent for cancer prevention and treatment. Direct inhibition of cyclooxygenase-2 (COX-2) pathway is generally thought to be the main mechanism by which aspirin inhibits cancer development. However, either pharmacological properties of aspirin or recent results of epidemiologic studies do not support that mechanism. To address this inconsistency, we hypothesize that antiplatelet effect of aspirin via inhibition of COX-1 may be one of potential mechanisms to inhibit carcinogenesis. Aberrant platelet activation will lead to promote hostility of tumour microenvironment by releasing an abundant array of angiogenesis regulators. Given the outstanding ability of antiplatelet, aspirin may restore balance of pro- and anti-angiogenic factors released from platelet to "normalise" tumour vasculature and shape tumour microenvironment to some extent, which will not only diminish tumour aggressiveness and

progression, but also enhance the sensitivity to therapeutic treatment. Thus, targeting the platelet activation leading to alter tumour microenvironment may provide a novel way to tumour therapy (Su, *et al*., 2014).

Anti-cancer effects of Aspirin

According to Alfonso, *et al*., (2104) Salicylates from plant sources have been used for centuries by different cultures to treat a variety of ailments such as inflammation, fever and pain. A chemical derivative of salicylic acid, aspirin, was synthesised and mass produced by the end of the 19th century and is one of the most widely used drugs in the world. Its cardio-protective properties are well established; however, recent evidence shows that it can also act as a chemo-preventive agent. Its antithrombotic and anti-inflammatory actions occur through the inhibition of cyclooxygenases. The precise mechanisms leading to its anticancer effects are not clearly established, although multiple mechanisms affecting enzyme activity, transcription factors, cellular signalling and mitochondrial functions have been proposed. This review presents a brief account of the major COX-dependent and independent pathways described in connection with aspirin's anticancer effects. Aspirin's unique ability to acetylate biomolecules besides COX has not been thoroughly investigated nor have all the targets of its primary metabolite, salicylic acid been identified. Recent reports on the ability of aspirin to acetylate multiple cellular proteins warrant a comprehensive study to investigate the role of this posttranslational modification in its anticancer effects. In this review, we also raise the intriguing possibility that aspirin may interact and acetylate cellular molecules such as RNA, and metabolites such as CoA, leading to a change in their function.

Aspirin and oesophageal cancer

Aspirin is the most widely used among all nonsteroidal anti-inflammatory drugs (NSAIDs), which is cheap and acceptable to patients. Several observational results provide the further investigation of prevention and therapy of aspirin or similar drugs in oesophageal cancer. Data from case control studies, cohort studies and randomized controlled trials (RCTs) also give some support of a beneficial role of aspirin on oesophageal squamous cell carcinoma (ESCC). Experimental data suggest that aspirin may prevent carcinogenesis of ESCC by favourably affecting proliferation, apoptosis, or other as yet unidentified growth-regulating processes. But the mechanism by which aspirin influence on oesophageal squamous cell carcinoma needs further investigation (Li, Cheng & Zhang, 2014).

Song, Y., Zhong, X., Gao, P., Zhou, C., Shi, J., Wu, Z., Guo, Z.& Wang, Z. 2020..

Background: Aspirin is one of the most commonly prescribed drugs worldwide and has been reported to possess anti-cancer properties in addition to antipyretic and analgesic effects. This umbrella review summarizes systematic reviews and meta-analyses that investigate the association between aspirin and cancer risk, aiming to help clinical and public health decision-makers interpret the results of these studies when re-positioning aspirin.

Methods: An umbrella review of systematic reviews and meta-analyses.

Results: The associations that reached statistical significance (17 in total) indicated potential preventive effects of aspirin on certain cancers or precancerous lesions. We found that no association was supported by strong evidence. Only one association (aspirin and overall cancer risk) was supported by highly suggestive evidence. The evidence supporting the association between aspirin and the risk of breast cancer, non-cardia gastric cancer, or prostate cancer was considered to be highly suggestive. The remaining 23 associations were supported by weak (13) or not suggestive evidence (10).

Conclusions: The association between aspirin and a reduced risk of esophageal squamous cell carcinoma is supported by strong evidence, researchers and policy makers should pay more attention to the potential merit of repositioning aspirin to prevent esophageal squamous cell carcinoma.

Aspirin and ovarian cancer

Taking aspirin daily may cut a woman's risk of ovarian cancer by 20%, according to a study published February 6, 2014 in the *Journal of the National Cancer Institute*. This new research adds to the large number of studies conducted in recent years showing aspirin may help prevent certain types of cancers.

Aspirin and Pancreatic Cancer

Regular use of aspirin by people living in Shanghai, China, was associated with decreased risk for developing pancreatic cancer, according to data published in *Cancer Epidemiology, Biomarkers & Prevention*, a journal of the American Association for Cancer Research. Data from this new study and meta-analysis of data from 18 other studies suggest that over the past two decades, as the general population's use of aspirin has increased, the effect of aspirin in decreasing pancreatic cancer risk has become more pronounced.

Aspirin and Prostate Cancer

Aspirin use may positively affect lethal Prostate Cancer.

Downer, M.K., Allard, C.B., Preston, M.A., Wilson, K.M., Kenfield, S.A., Chan, J.M., Mucci, L.A., Giovannucci, E. & Stampfer, M.J. 2019.

BACKGROUND: Aspirin use probably protects against some malignancies but its effects on lethal prostate cancer (PC) are unclear.

OBJECTIVE: To investigate the association between regular aspirin use and lethal PC.

DESIGN, SETTING, AND PARTICIPANTS: Participants were aged 40-75 yr at baseline in 1986 and have been followed with biennial questionnaires. The risk analysis includes 49 409 men. The survival analysis includes 5 980 PC patients without metastatic disease at diagnosis.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: We used Cox proportional hazards regression to examine the association between current, past, or never regular aspirin use (≥2 d/wk) in relation to lethal (metastatic or fatal) PC. We also examined years of use among current users and years since stopping among past users. In the risk analysis, aspirin was updated throughout follow-up. In the survival analysis, aspirin use after diagnosis was assessed.

RESULTS AND LIMITATIONS: Some 29% of participants used aspirin regularly at baseline, which increased to 60% by 2010. In the risk analysis, 804 men were diagnosed with lethal PC. Current regular aspirin was associated with a lower risk of lethal prostate cancer (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.66-0.96) compared to never users. In the survival analysis, 451 of the men diagnosed with nonmetastatic PC later developed lethal disease. Current postdiagnostic aspirin was associated with a lower risk of lethal PC (HR 0.80, 95% CI 0.64-1.00) and overall mortality (HR 0.79, 95% CI 0.69-0.90). When restricted to highly screened men, the risk analysis associations were stronger and survival analysis associations remained statistically significant. Reverse causation and residual confounding remain concerns, as demonstrated by the attenuated results in sensitivity analyses.

CONCLUSIONS: Regular aspirin use was associated with a lower risk of lethal PC. Postdiagnostic use was associated with better survival after diagnosis.

PATIENT SUMMARY: We found that it may be advisable for prostate cancer patients to take aspirin to improve their survival for both prostate cancer mortality and other mortality outcomes.

Aspirin and Familial or Genetic Breast Cancer Risk

The use of aspirin has been associated with reduced breast cancer risk.

Kehm, R.D., Hopper, J.L., John, E.M., Phillips, K.A., MacInnis, R.J., Dite, G.S., Milne, R.L., Liao, Y., Zeinomar, N., Knight, J.A., Southey, M.C., Vahdat, L., Kornhauser, N., Cigler, T., Chung, W.K., Giles, G.G., McLachlan, S.A., Friedlander, M.L., Weideman, P.C., Glendon, G., Nesci, S. & kConFab Investigators, Andrulis, I.L., Buys, S.S., Daly, M.B. & Terry, M.B. 2019.

BACKGROUND: The use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced breast cancer risk, but it is not known if this association extends to women at familial or genetic risk. We examined the association between regular NSAID use and breast cancer risk using a large cohort of women selected for breast cancer family history, including 1054 BRCA1 or BRCA2 mutation carriers.

METHODS: We analyzed a prospective cohort (N = 5606) and a larger combined, retrospective and prospective, cohort (N = 8233) of women who were aged 18 to 79 years, enrolled before June 30, 2011, with follow-up questionnaire data on medication history. The prospective cohort was further restricted to women without breast cancer when medication history was asked by questionnaire. Women were recruited from seven study centers in the United States, Canada, and Australia. Associations were estimated using multivariable Cox proportional hazards regression models adjusted for demographics, lifestyle factors, family history, and other medication use. Women were classified as regular or non-regular users of aspirin, COX-2 inhibitors, ibuprofen and other NSAIDs, and acetaminophen (control) based on self-report at follow-up of ever using the medication for at least twice a week for ≥1 month prior to breast cancer diagnosis. The main outcome was incident invasive breast cancer, based on self- or relative-report (81% confirmed pathologically).

RESULTS: From fully adjusted analyses, regular aspirin use was associated with a 39% and 37% reduced risk of breast cancer in the prospective (HR = 0.61; 95% CI = 0.33-1.14) and combined cohorts (HR = 0.63; 95% CI = 0.57-0.71), respectively. Regular use of COX-2 inhibitors was associated with a 61% and 71% reduced risk of breast cancer (prospective HR = 0.39; 95% CI = 0.15-0.97; combined HR = 0.29; 95% CI = 0.23-0.38). Other NSAIDs and acetaminophen were not associated with breast cancer risk in either cohort. Associations were not modified by familial risk, and consistent patterns were found by BRCA1 and BRCA2 carrier status, estrogen receptor status, and attained age.

CONCLUSION: Regular use of aspirin and COX-2 inhibitors might reduce breast cancer risk for women at familial or genetic risk.

The Daily Aspirin Dose Matters

A standard dose of aspirin (one pill) is typically 325 mgs, and a low-dose or 'baby' aspirin is 81mg. Although called baby aspirin, children under 12 should not take aspirin due to the risk of Reye's Syndrome. In a study that compared daily use of very low dose aspirin (30mg) to a daily dose of 283mg for preventing vascular events, researchers found no significant difference in cancer deaths between the two groups. In six studies of daily low-dose aspirin use (75 to 100 mg) for preventing vascular events, aspirin reduced the risk for cancer by almost 25% after at least 3 years of aspirin therapy.

Daily aspirin use appeared to be particularly beneficial in reducing the risk for certain cancers of the female reproductive organs. For instance, there were significantly fewer cases of uterine cancer among the women taking aspirin every day than among the women who did not take aspirin (zero cases among women taking aspirin as compared to 9 cases in the non-aspirin group).

[Picture Credit: Aspirin]

At doses as low as 75mg, daily aspirin not only lowered the risk of heart attack and stroke, but it appears to have prevented many types of cancer, including colon cancer and uterine cancer, as well as slowed the spread of cancer to distant organs. The usual dose that is prescribed is 81mg daily. Higher aspirin doses, which increase the risk of ulcer and internal bleeding, did not appear to work any better.

While these studies are exciting and reveal aspirin to be more of a wonder drug than we ever imagined, it is important to remember that aspirin therapy is NOT for everyone. Aspirin belongs to a group of medications known as 'blood thinners'. These drugs prevent the body from making potentially harmful clots that can block blood vessels and cause heart attacks and strokes. Patients already taking blood thinners who take aspirin may be at an increased risk for internal bleeding, ranging from mild to life-threatening. Those with severe liver and kidney disease are warned against using aspirin given the potentially toxic effects on these organs. In addition, asthma patients may be particularly sensitive to aspirin and can, as a result, experience asthma-related complications (Booker).

Not all over-the-counter pain relievers contain aspirin. If a health care provider prescribes daily aspirin to lower the risk of a heart attack and clot-related stroke, or to assist in lowering the risk for cancer, read the labels carefully to make sure it is the right product. Some drugs combine aspirin with other pain relievers or other ingredients and should not be used for long-term aspirin therapy (US Food and Drug Administration).

CANSA's Position on Aspirin

Even though Aspirin (salicylic acid) is cheap and freely available, CANSA believes that:

- Aspirin is, indeed, a 'wonder' drug, however, it should be used with caution
- Although taking an occasional aspirin or two would be safe for most adults to use to treat headaches, body aches or fever, daily use of aspirin can have serious side effects, including internal bleeding and allergic reaction especially in individuals who are inclined to allergies or suffer from asthma
- Aspirin should always be used within a safe dosage range
- The proposed safe dosage range of aspirin, for lowering the risk of certain cancers in patients who have consulted with their medical practitioner, is 81mg per day
- The safe dosage range for adults (in cases of fever and/or pain) is 325mg to 650mg orally or rectally every 4 hours as needed, but intake should not exceed 4g per 24 hours
- It should not be indiscriminately given to children and teenagers because of the risk of Reyes syndrome, allergies and possible internal bleeding

- Even though there may be scientific evidence that aspirin is advantageous against some non-communicable diseases like cardiovascular incidents and even in lowering the risk of some cancers, it should NOT be used on a continuous (long-term) basis without prior consultation with a medical practitioner

Medical Disclaimer

This Fact Sheet and Position Statement is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet and Position Statement. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet and Position Statement.

Whilst CANSA has taken every precaution in compiling this Fact Sheet and Position Statement, neither it, nor any contributor(s) to this Fact Sheet and Position Statement can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet and Position Statement.

Sources and References Consulted or Utilised

Alfonso, L., Ai, G., Spitale, R.C. & Bhat, G.J. 2014. Molecular targets of aspirin and cancer prevention. *Br J Cancer*. 2014 Jul 1;111(1):61-7. doi: 10.1038/bjc.2014.271. Epub 2014 May 29.

Algra, A.M. 2013. Towards a global brief on aspirin. *The Lancet*, 381: 1344-45. http://www.nijbakker-morra.nl/documenten/2013%20Algra%20-%20Lancet2013_global_brief_on_aspirin.pdf

American Cancer Society
http://www.cancer.org/research/acsresearchupdates/cancerprevention/aspirin-and-cancer-prevention-what-the-research-really-shows

Aspirin
http://www.aspirin81.ca/en/product/aspirin-81-daily-low-dose/index.php
https://www.telegraph.co.uk/science/2018/09/16/daily-aspirin-healthy-pensioners-may-do-harm-good-major-new/

Aspirin Side Effects
http://22.com.my/rain/aspirin-side-effects/

Booker, N.W. Aspirin: Could it reduce your risk for cancer? http://center4research.org/child-teen-health/1-general-health-and-mental-health/aspirin-could-it-reduce-your-risk-for-cancer/

Burke, A., Smyth, E. & FitzGerald, G. A. 2006. 26: Analgesic antipyretic and anti-inflammatory agents. *Goodman and Gilman's the pharmacological basis of therapeutics* (11th ed.). New York: McGraw-Hill. pp. 671–716.

Burn, J., Sheth, H., Elliott, F., Reed, L., Macrae, F., Mecklin, J.P., Möslein, G., McRonald, F.E., Bertario, L., Evans, D.G., Gerdes, A.M., Ho, J.W.C., Lindblom, A., Morrison, P.J., Rashbass, J., Ramesar, R., Seppälä, T., Thomas, H.J.W., Pylvänäinen, K., Borthwick, G.M., Mathers, J.C., Bishop, D.T.; CAPP2 Investigators. 2020. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Randomized Controlled Trial. *Lancet*. 2020 Jun 13;395(10240):1855-1863.

Downer, M.K., Allard, C.B., Preston, M.A., Wilson, K.M., Kenfield, S.A., Chan, J.M., Mucci, L.A., Giovannucci, E. & Stampfer, M.J. 2019. Aspirin use and lethat prostate cancer in the Health Professionals Follow-up Study. *Eur Urol Oncol*. 2019 Mar;2(2):126-134. doi: 10.1016/j.euo.2018.07.002. Epub 2018 Jul 31.

Drugs.com
http://www.drugs.com/aspirin.html

Elwood, P.C., Morgan, G., Pickering, J.E., Galante, J., Weightman, A.L., Morris, D., Kelson, M. & Dolwani, S. 2016. Aspirin in the Treatment of Cancer: Reductions in Metastatic Spread and in Mortality: A Systematic Review and Meta-Analyses of Published Studies. *PLOS ONE*, 2016; 11 (4): e0152402 DOI: 10.1371/journal.pone.0152402

Felix Hoffman
http://en.wikipedia.org/wiki/Felix_Hoffmann

Grancher, A., Michel, P., Di Fiore, F. & Sefrioui, D. 2018. Aspirin and colorectal cancer. *Bull Cancer*. 2018 Feb;105(2):171-180. doi: 10.1016/j.bulcan.2017.09.013. Epub 2017 Nov 15.

Hybiak, J., Broniarek, I., Kiryczyński, G., Los, L.D., Rosik, J., Machaj, F., Sławiński, H., Jankowska, K. & Urasińska, E. 2020. Aspirin and its pleiotropic application. *Eur J Pharmacol*. 2020 Jan 5;866:172762.

Kehm, R.D., Hopper, J.L., John, E.M., Phillips, K.A., MacInnis, R.J., Dite, G.S., Milne, R.L., Liao, Y., Zeinomar, N., Knight, J.A., Southey, M.C., Vahdat, L., Kornhauser, N., Cigler, T., Chung, W.K., Giles, G.G., McLachlan, S.A., Friedlander, M.L., Weideman, P.C., Glendon, G., Nesci, S. & kConFab Investigators, Andrulis, I.L., Buys, S.S., Daly, M.B. & Terry, M.B. 2019. Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or genetic risk: a cohort study. *Breast Cancer Res*. 2019 Apr 18;21(1):52. doi: 10.1186/s13058-019-1135-y.

Langley, R.E. & Rothwell, P.M. 2014. Aspirin in gastrointestinal oncology: new data on an old friend. *Curr Opin Oncol.* 2014 Jul;26(4):441-7. doi: 10.1097/CCO.0000000000000098.

Li, P., Cheng, R. & Zhang, S. 2014. Aspirin and esophageal squamous cell carcinoma: bedside to bench. *Chin Med J (Engl).* 2014;127(7):1365-9.

Mayo Clinic
http://www.mayoclinic.org/diseases-conditions/heart-disease/in-depth/daily-aspirin-therapy/art-20046797

MD Anderson Cancer Center
http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-topics/prevention-and-screening/health/aspirinandcancer.html

Noreen, F., Röösli, M., Gaj, P., Pietrzak, J., Weis, S., Urfer, P., Regula, J., Schär, P. & Truninger, K. 2014. Modulation of age- and cancer-associated DNA methylation change in the healthy colon by aspirin and lifestyle. *Natl Cancer Inst*. Jun 28:106(7). pii: dju161. doi: 10.1093/jnci/dju161. Print 2014 Jul.

NHS Choices.UK
http://www.nhs.uk/news/2014/08august/pages/daily-aspirin-reduces-cancer-risk-study-finds.aspx

Pasche, B., Wang, M., Pennison, M. & Jimenez, H. 2014. Prevention and treatment of cancer with aspirin: where do we stand? *Semin Oncol*. Jun: 41(3):397-401. Doi: 10.1053/j.seminoncol.2014.04.012. Epub 2014 April 24.

Science Daily
https://www.sciencedaily.com/releases/2016/04/160420151401.htm
https://www.sciencedaily.com/releases/2016/12/161220141325.htm

Simon, T.G., Duberg, A.S., Aleman, S., Chung, R.T., Chan, A.T. & Ludvigsson, J.F. 2020. Association of aspirin with hepatocellular carcinoma and liver-related mortality. *N Engl J Med*. 2020 Mar 12;382(11):1018-1028.

Song, Y., Zhong, X., Gao, P., Zhou, C., Shi, J., Wu, Z., Guo, Z.& Wang, Z. 2020. Aspirin and its potential preventive role in cancer: an umbrella review. *Front Endocrinol (Lausanne).* 2020 Jan 23;11:3.

Su, B.B., Chen, J.H., Shi, H., Chen, Q.Q. & Wan, J. 2014. Aspirin may modify tumor microenvironment via antiplatelet effect. *Med Hypotheses*. Aug:83(2):148-50. doi: 10.1016/j.mehy.2014.05.007. Epub 2014 May 20.

US Food and Drug Administration
http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/SafeDailyUseofAspirin/ucm291434.htm

WebMD
http://www.webmd.com/cancer/news/20140806/daily-aspirin-may-help-prevent-cancer-study-shows

Wikipedia
http://en.wikipedia.org/wiki/Aspirin

World Health Organization
http://www.who.int/medicines/services/essmedicines_def/en/

Yelsengekar, A. & Mohandas, K.M. 2012. Can daily aspirin help to reduce the incidence and mortality due to cancer?
http://www.nmji.in/archives/Volume-25/Issue-5/Selected-Summaries-II.pdf

Zhang, X., Feng, Y., Liu, X., Ma, J., Li, Y., Wang, T. & Li, X. 2019. Beyond a chemopreventive reagent, aspirin is a master regulator of the hallmarks of cancer. *J Cancer Res Clin Oncol*. 2019 Apr 29. doi: 10.1007/s00432-019-02902-6. [Epub ahead of print]