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Drug Reposition: The Analysis of the Possibility of Using Aspirin for the Prevention of Cancers

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Abstract

Aspirin is one of the oldest medicines that humans have used to treat a wide range of diseases. A good example is its use in the prevention of various tumors. Past studies have identified 11 types of cancer can be prevented by using aspirin. Within the past few decades, researchers have identified the mechanism through which aspirin prevents the development of cancer. Specifically, researchers have found out that it has the potential to influence how cyclooxygenase-2(COX-2) is expressed in the body and its product, prostaglandin E2 (PGE2). These two compounds, COX-2 and PGE2, are essential in dictating the process of tumor cells. Past studies focusing on patients' health outcomes have also revealed that aspirin has the potential to influence the progression of cancer. However, there are limitations regarding the study and role of aspirin, such as side effects and inadequacy in research. Nonetheless, the progress of aspirin on a wide range of cancers continues to enhance patients' medical experiences and outcomes. This research reviewed several clinical trials related to aspirin and various types of cancers and analyzed the potential application of aspirin in cancer prevention. Several limitations, including the side effects of aspirin, appropriate dosage, and research constraints, have been taken into account.

Keywords

Aspirin, COX, cancer, colorectal cancer

1. Introduction

1.1 Using aspirin for cardiovascular diseases to cancers

Aspirin, known as the “drug of the century”, is the “omnipotent king” in the drug circle and the “cornerstone” for the prevention and treatment of cardiovascular and cerebrovascular diseases. In recent years, it has been considered the best anti-cancer health care product God has given to mankind. There was originally a study that looked at aspirin and cancer risk in women. Results of a 20-year study showed that, compared to those who did not take aspirin, there was a significantly lower risk of colorectal cancer and death in women who took aspirin more than twice a week. Another study has reported that daily aspirin intake can significantly reduce the likelihood of cancer metastasis. Of the 17,285 participants, 987 developed the new type of cancer after an average of 6.5 years. Daily use of aspirin (≥75mg daily) reduced the risk of distant metastasis. Since then, other studies have suggested that long-term aspirin use can partly reduce the risk of prostate, pancreatic, skin, and lung cancers. Of course, some studies have shown that aspirin has little or no effect on cancer prevention, and the mechanism of how aspirin reduces cancer is not clear. In addition, aspirin has a positive effect on lung cancer. Results show that aspirin, metformin, and statins work together to reduce the risk of lung cancer [1]. Compared with non-aspirin users, low-dose aspirin users had significantly lower rates of liver cancer and death from liver cancer, with no significant gastrointestinal bleeding.

1.2 The hallmarks of cancer

In 2012, there were about 14.1 million new cancer population and 8.2 million people died due to cancers around the world [2]. In 2020, 89500 or so new cancer population and 9270 deaths in adolescents and young adults from 15-39 ages (AYAs) occurred [2]. In recent years, researchers have identified the ten hallmarks [3] of cancer and tried to find the potential mechanism to prevent and cure cancer.

As shown in the graph, the features of cancer, ranging from evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, sustained angiogenesis to tissue invasion and metastasis, these features were all been reported to be related to COX2 and PGE2, which are considered as targets of aspirin will be affected by COX-2 and PGE2. As mentioned in the previous section, aspirin has an evident effect on the prevention of colorectal cancer, as aspirin can influence the expression of cyclooxygenase-2(COX-2) and its product prostaglandin E2 (PGE2). COX-2 and PGE2 play a key role in influencing the development of colorectal cancer.

As mentioned before, aspirin affects colorectal cancer, the main target of aspirin is COX2 and PGE2, these two targets have been identified with a role in several carcinogenic processes the hallmark cancer including metastasis, angiogenesis to tissue invasion and limitless replicative potential, was reported that closely related to COX2 OR PGE2 behaviors [3].

2. Anti-tumor study of aspirin

2.1 Brief introduces Aspirin as NSAIDS, and used for the prevention of CVD, nowadays widely used for prevention of varies cancers

Nowadays, aspirin is mainly known as a non-steroidal anti-inflammatory drug (NSAIDs). However, aspirin is the derivative of willow. The extracts of willow can treat fever, inflammation and relieve pain. In 1763, the Reverend Edward Stone described the functions of powder of willow bark in treating malarial fever in a letter to the Earl of Macclesfield. In 1826, Henri Leroux extracted “salicin” from willow bark. In 1828, Johann Buchner purified the same compound--salicin. Raffaele Piria produced salicylic acid from salicin in 1838 and Charles Frederic Gerhardt created acetylsalicylic acid in 1853. In 1897, the Garman chemist working in the Bayer company, Felix Hoffman produced aspirin for pain relief. His acetylation of salicylic acid of aspirin is also essential to prevent cardiovascular events.

Aspirin is used for many reasons these days: to prevent cardiovascular diseases, to reduce pain and fever, to reduce some joints diseases, even to prevent cancer. Researchers found that eating low-dose aspirin can prevent and cure heart attacks and other cardiovascular diseases. One to three grams one day is helpful to relieve pain. Acetylation of the platelet cyclooxygenase of aspirin can prevent the formation of platelet-dependent. That can help reduce the risk for ischemic vascular events and cardiovascular diseases. Aspirin as a kind of NSAIDS has antipyretic, anti-inflammatory, and analgesic properties because aspirin can suppress the synthesis of prostaglandin also through inhibiting the cyclooxygenase [4].

Aspirin is the potential to reduce the incidence of some cancers, especially colorectal cancer (CRC). In 1968, there was the first indication of using aspirin in cancer therapy. During the research, there was a 50% reduction in metastases of mice which was associated with platelet reduction.

Up to now, an increasing number of studies have already shown that aspirin can play a key role in reducing cancer prevalence and mortality of colorectal cancer, breast cancer, esophageal cancer, gastric cancer, and endometrial. Until April 12 in 2016, explicitly proposed that aspirin can be used for the prophylaxis of colorectal cancer. Its anti-cancer effects were first recognized by American public health organizations and were officially included in official guidelines. There are mainly two large randomized trials of aspirin effects on preventing cancer that got to similar conclusions: aspirin can reduce the risk of colorectal cancer in women, especially proximal rectal cancer. After 18 years of follow-up, the risk of colorectal cancer was about 20 percent lower in the aspirin group than in the control group.

Researchers gradually found that aspirin has anti-tumor effects not only in colorectal cancer, but also in other cancer diseases such as stomach, breast, ovarian, liver, prostate and lung cancers. So far, the Meta-analysis of aspirin’s anti-tumor effects and randomized trials has proved that aspirin can lower the overall risk of cancer from an evidence-based perspective, indicating that it has anti-tumor effects in many malignancies.

2.2 An experiment about aspirin on the risk of Hepatocellular carcinoma (HCC) by Hwang

Hwang *et al*. conducted a cohort study including a total of 460755 participants at an average of 49-58 years in a viral hepatitis endemic area. There are 395973 subjects in this control group and 1954 subjects suffering from HCC. The aim of Hwang's study is to investigate and analyze the relationship between aspirin and HCC, and to explore whether aspirin can reduce the risk of hepatocellular carcinoma (HCC).

Patients with hepatocellular carcinoma (HCC) took part in different conditions such as taking or not taking, taking the dose, and their proportion in the total experimental population. In addition, Cox proportional hazards regression model is used to calculate the disease risk under different doses of aspirin [5].

The most important results in this paper are as follows (Table 1):

Table 1. Incidence and HRs of HCC associated with aspirin use

			Incidence rate of HCC			Risk* of HCC			P trend
	No. of subjects	No. of HCC	per 10^5 person-years	95% CI		Adjusted HR	95% CI		
Non-user (<30 DDDs)	395,973	1,954	76.18	72.87	79.63	1			0.02
User (≥30 DDDs)	64,782	382	95.41	86.3	105.47	0.87	0.77	0.98	
30–365 DDDs	31,188	200	103.68	90.26	119.09	0.98	0.84	1.15	
365–730 DDDs	13,781	75	88.09	70.25	110.46	0.79	0.62	1.00	
>730 DDDs	19,813	107	87.46	72.36	105.7	0.75	0.60	0.91	

Data from Hwang *et al*. (2018)

It is explained that the risk of taking the aspirin group is n times that of the non-taking group. Hwang also found that the effects of aspirin were enhanced (HR = 0.65), when combined with other nonsteroidal anti-inflammatory drugs (NSAID). According to the results of incidence and hrs of HCC associated with aspirin use, the incidence rate of HCC for < 30, ≥ 30, 30 – 365, 365 – 730 and > 730 Daily Defined Doses [DDDs] were 76.18, 95.41, 103.68, 88.09 and 87.46 respectively, and P trend was 0.02, indicating that there was a dose-dependent correlation between DDDs and incidence rate of HCC; the most important indicator was hrs, the experimental group taking dose ≥ 30 DDDs. The risk of HCC was 0.87 times as that of the non-user group (95ci [0.77,0.98]); the risk of HCC of experimental group taking 30 – 365 DDDs was 0.98 times as that of the non-user group (95ci [0.84,1.15]); the risk of HCC of the experimental group taking 365 – 730 DDDs was 0.79 times as that of the non-user group (95ci [0.62,1.00]); the risk of HCC of the experimental group taking more than 730 was 0.75 times as that of the non-user group (95ci [0.60,0.91]). According to the results, the use of aspirin can reduce the risk of HCC in a dose-dependent manner. In general, the risk of HCC will decrease with the increase of dose [6].

2.3 Long-term use of low-dose aspirin for cancer prevention: A 10-year population cohort study in Hong Kong

Studies have shown that aspirin can prevent cancer, but such studies are only based on Western subjects, and there is no sufficient proof in Asian subjects. Therefore, the purpose of this study is to verify whether aspirin plays a consistent role in cancer prevention in Asian populations, and this report also focuses on various types of cancer. The value of aspirin in cancer prevention was discussed more concretely. Therefore, the characteristics of this paper mainly focus on whether aspirin still plays a role in the prevention of cancer in the Asian population, and what kind of cancers aspirin will play a preventive role. Tsoi *et al*. selected 204170 patients who took Aspirin from 2000 to 2004 as observation objects. Meanwhile, 408339 non-Aspirin users with matched age and gender were selected as the control group, and all patients were followed up to 2013.

The important results of this paper are as follows:

Firstly, the results in the above table are relatively clear, showing the incidence of various cancers in people taking aspirin and not taking aspirin. According to the results in Table 2 Cancer incident between aspirin and non-aspirin groups, the patients with esophagus, liver, pancreas, stomach and colorectum cancers in the aspirin group are 0.59, 0.49, 0.54, 0.42, and 0.71 times as those in the non-aspirin group, and there is a significant difference in the incidence of esophagus, liver, pancreas, stomach and colorectum cancer between those who take aspirin and those who do not take aspirin.

In non-GI cancers, lung and leukemia cancer in the aspirin group are 0.65 and 0.67 times as that in the non-aspirin group, and there is a significant difference in the incidence of lung and leukemia cancer between the aspirin group and the non-aspirin group [7].

Table 2. Cancer Incidence between aspirin and non-aspirin groups

Cancer	Cancer incidence		Relative risk (95% CI)	p-value
	Aspirin group (n = 204,170)	Non-aspirin group (n = 408,339)		
		GI cancers		
Oesophagus	557 (0.3%)	2,077 (0.5%)	0.59 (0.52–0.67)	<0.001
Liver	1,984 (1.0%)	7,386 (1.8%)	0.49 (0.45–0.53)	<0.001
Pancreas	684 (0.3%)	2,075 (0.5%)	0.54 (0.47–0.62)	<0.001
Stomach	1,385 (0.7%)	4,442 (1.1%)	0.42 (0.38–0.46)	<0.001
Colorectum	5,118 (2.5%)	13,336 (3.3%)	0.71 (0.67–0.75)	<0.001
		Non-GI cancers		
Lung	6,142 (3.0%)	18,766 (4.6%)	0.65 (0.62–0.68)	<0.001
Leukemia	484 (0.2%)	1,277 (0.3%)	0.67 (0.57–0.79)	<0.001
All cancers	26,929 (13.2%)	70,755 (17.3%)	0.75 (0.73–0.77)	<0.001

Data from Tsoi *et al*. (2019)

Furthermore, based on the results of various cancer risks in people taking aspirin and people not taking aspirin, the risk of all types of cancers in the group taking aspirin is 0.75 times in comparison with the group not taking aspirin, and there is a significant difference in the incidence of cancer between people taking aspirin and people not taking aspirin. In general, taking aspirin can indeed reduce the risk of cancer, which also shows that this result is also applicable to the Asian population. Likewise, taking aspirin is targeted to reduce the risk of cancer. Taking aspirin is extremely effective for GI cancers, but for some cancers such as multiple myeloma, taking aspirin may not affect its incidence.

2.4 A meta-analysis of low-dose aspirin in cancer adjuvant therapy from 2015 to 2017

The main purpose of this meta-analysis for Elwood *et al.* [8] is to sort out the research on the role of aspirin in improving the cancer survival rate and reducing cancer metastasis and diffusion. More specifically, this study focuses on whether to take aspirin and cancer mortality.

Table 3. Aspirin treatment in colorectal and gastrointestinal cancers in 2015-2017

COLORECTAL and GASTROINTESTINAL CANCER		
Study	Outcome	HR/RR (95% CI)
Bains *et al*.	Cause specific mortality	HR 0.85 (0.79, 0.92)
	All-cause mortality	HR 0.95 (0.90, 1.01)
Frows *et al*.	Cause specific mortality	HR 0.44 (0.33, 0.58)
	All-cause mortality	HR 0.52 (0.44, 0.63)
Giamperie *et al*.	Progression free survival	HR 0.48 (0.30, 0.79)
	All-cause mortality	HR 0.43 (0.26, 0.72)
Shimoike *et al*.	Cause specific mortality	HR 1.38 (0.84, 2.26)
	All-cause mortality	HR 0.61 (0.28, 1.33)
Restivo *et al*.	Prog free survival	HR 0.20 (0.07, 0.60)
	Overrall survival	HR 0.21 (0.05, 0.89)
Ventura *et al*.	Cause specific mortality	HR 0.71 (0.52, 0.97)
	All-cause mortality	HR 1.18 (1.12, 1.23)

COLORECTAL and GASTROINTESTINAL CANCER (Continued Table 3)		
Study	Outcome	HR/RR (95% CI)
Gray *et al*.	Cause specific mortality	HR 0.69 (0.47, 0.98)
	All-cause mortality	HR 0.76 (0.57, 1.03)
Hua *et al*.	Cause specific mortality	HR 0.44 (0.25, 0.71)
	All-cause mortality	HR 0.75 (0.59, 0.95)
Vietonmaki *et al*.	Cause specific mortality	HR 1.28 (0.40, 4.12)
Murphy *et al*.	Cause specific mortality	RR 0.72 (0.34.1.53)
	All-cause mortality	RR 2.36 (1.44,.87)
Ratnsinghe *et al*.	M cause specific mortality	RR 0.68 (0.37,1.26)
	F cause specific mortality	RR 1.61 (0.91, 2.85)
Hippisley-Cox *et al*.	Cause specific mortality	HR 0.81 (0.73, 0.90)
	All-cause mortality	HR 0.85 (0.78, 0.93)
Hamada *et al*.	Cause specific mortality	HR 0.65 (0.40, 1.07)
Colorectal cancer deaths: Pooled HR for eleven studies: 0.68 (0.57, 0.81), heterogeneity p<0.0005, Egger's test for bias p = 0.09 All cause deaths: Pooled HR for nine studies: 0.76 (0.63–0.91) heterogeneity p<0.0005, Egger's test p = 0.04		

According to the comprehensive results of the selected studies, the mortality of colorectal cancer in the aspirin group was 0.68 (95% CI: 0.57, 0.81) times that in the non-aspirin group, indicating that taking aspirin can significantly reduce the mortality of colorectal cancer.

Table 4. Aspirin treatment in breast and prostate cancers in 2015-2017

PROSTATE CANCER		
BREAST CANCER		
McMenamin *et al*.	Cause specific mortality	HR 0.92 (0.75, 1.14)
	All-cause mortality	HR 1.21 (1.04, 1.40)
Shiao *et al*.	Cause specific mortality	HR 0.41 (0.20, 0.83)
	All-cause mortality	HR 0.67 (0.35, 1.27)
Ratnasinghe *et al*.	Cause specific mortality	RR 0.82 (0.49, 1.36)
MsCarthy *et al*.	Breast cancer recurrence	RR 0.65 (0.46, 0.91)
Breast cancer deaths: Pooled HR for three studies: 0.70 (0.47–1.03) heterogeneity p = 0.04, Egger's test P<0.16 All cause deaths: Pooled HR for two studies 0.98 (0.56–1.71) heterogeneity p = 0.08, Egger's test not possible		
PROSTATE CANCER		
Osborrn *et al*.	Cause specific mortality	HR0.20(0.04,1.13)
Veitonmaki *et al*.	Cause specific mortality	HR0.62(0.30,1.32)
Zhou *et al*.	Cause specific mortality	HR0.83(0.72,0.95)
	All-cause mortality	HR0.75(0.66,0.86)
Cardwell *et al*.	Cause specific mortality	OR1.02(0.78,1.34)
	All-cause mortality	OR1.22(1.02,1.45)
Ratnasing *et al*.	Cause specific mortality	RR1.11(0.60,2.05)
Downer *et al*.	Cause specific mortality	HR0.68(0.52,0.90)
	All-cause mortality	HR0.72(0.61,0.84)

3. Conclusion

Based on the above studies, it can be found that taking aspirin can significantly reduce the mortality of colorectal, gastrointestinal, breast, and prostate cancers. That is, supported by a large number of relevant research results, there are sufficient reasons to believe that aspirin can effectively improve the survival rate of cancer patients.

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