REVIEW ARTICLE

Complex roles of the old drug aspirin in cancer chemoprevention and therapy

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Abstract
The nonsteroidal anti-inflammatory agent aspirin is widely used for preventing and treating cardiovascular and cerebrovascular diseases. In addition, epidemiologic evidences reveal that aspirin may prevent a variety of human cancers, while data on the association between aspirin and some kinds of cancer are conflicting. Preclinical studies and clinical trials also reveal the therapeutic effect of aspirin on cancer. Although cyclooxygenase is a well-known target of aspirin, recent studies uncover other targets of aspirin and its metabolites, such as AMP-activated protein kinase, cyclin-dependent kinase, heparanase, and histone. Accumulating evidence demonstrate that aspirin may act in different cell types, such as epithelial cell, tumor cell, endothelial cell, platelet, and immune cell. Therefore, aspirin acts on diverse hallmarks of cancer, such as sustained tumor growth, metastasis, angiogenesis, inflammation, and immune evasion. In this review, we focus on recent progress in the use of aspirin for cancer chemoprevention and therapy, and integratively analyze the mechanisms underlying the anticancer effects of aspirin and its metabolites. We also discuss mechanisms of aspirin resistance and describe some derivatives of aspirin, which aim to overcome the adverse effects of aspirin.

KEYWORDS
aspirin, cancer, cancer therapy, chemoprevention, cyclooxygenase

Abbreviations: AMPK, AMP-activated protein kinase; CDK, cyclin-dependent kinase; COX, cyclooxygenase; CVD, cardiovascular disease; DHBA, dihydroxybenzolic acid; ER, estrogen receptor; GPIIa, glycoprotein IIa; H2S, hydrogen sulfide; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MDSC, myeloid-derived suppressor cells; MGST1, microsomal glutathione S-transferase 1; mTORC1, mTOR complex 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; PC, phosphatidylcholine; PFA, platelet function analyzer; PGE2, prostaglandin E2; RCTs, randomized controlled trials; SNP, single-nucleotide polymorphism; TNBC, triple negative breast cancer; TXA2, thromboxane A2; VEGF, vascular endothelial growth factor
1 | INTRODUCTION

Aspirin (acetylsalicylic acid) is an old drug that is widely administered for preventing and treating cardiovascular and cerebrovascular diseases. As precursors of aspirin, medicines have been made from willow and other salicylate (2-hydroxybenzolic acid) rich plants by ancient Sumerians and Egyptians. In 1838, the Italian chemist Raffele Piria developed a method to obtain salicylic acid. Sixty years later, Felix Hoffmann and Arthur Eichengrün, two chemists at Bayer, jointly developed a good method to synthesize pure acetylsalicylic acid from salicylic acid refluxed with acetic anhydride. Finally, the wonder drug aspirin is widely applicated since 1899.

After oral administration of aspirin, it is absorbed in the gastrointestinal system and then converted into salicylic acid, followed by metabolic processing (Figure 1). During circulation, a large proportion of salicylic acid (50–80%) binds to albumin, which impairs the biological activity of salicylic acid. Instead, free salicylic acid is biologically active. Salicylic acid can be widely distributed to many tissues. Liver is the primary organ for salicylic acid metabolism. After salicylic acid is coupled with glycine, it is converted into salicylic acid. Instead, salicylic acid is metabolized into acyl glucuronide and phenolic glucuronide after it conjugates with glucuronic acid. In addition, salicylic acid can be hydroxylated into dihydroxybenzolic acid (DHBA), including gentisic acid (2,5-DHBA), pyrocatechuic acid (2,3-DHBA), and alpha-resorcylic acid (2,6-DHBA). Finally, these metabolites, together with free salicylic acid, are excreted through the kidney.

As the most commonly used drug in the world, aspirin is one of the nonsteroidal anti-inflammatory drugs (NSAIDs). Since inflammation is associated with the development and progression of many diseases including cardiovascular disease (CVD) and cancer, accumulating evidence have demonstrated that regular aspirin intake markedly reduces the incidence of CVD and cancer. It is projected that increased use of aspirin by high-risk people may improve life expectancy. The U.S. Preventive Services Task Force has advocated the administration of aspirin to prevent colorectal carcinogenesis. Here, we update recent studies on the use of aspirin for cancer prevention and therapy, and analyze the molecular mechanisms for the prevention and treatment of cancer by aspirin.

**FIGURE 1** Aspirin metabolism in humans
The relationship between aspirin and cancer was first reported in 1971. Over the last several decades, many pre-clinical studies demonstrate that aspirin has anticancer effects. As an anti-inflammatory and antithrombotic agent, aspirin can protect cardiovascular and cerebrovascular systems. Since 1988, many randomized clinical trials have been conducted to determine the effects of aspirin use on prevention of CVD. These trials have repeatedly and convincingly demonstrated that aspirin is beneficial for secondary prevention of CVD events, namely prevention of preclinical or clinical CVD progression. Although those clinical trials are not intended to address the association of aspirin use with cancer risk, subsequent analyses of those clinical trials suggest that aspirin is associated with a lower risk of human tumorigenesis, especially in inflammation-related cancer. The chemoprevention role of aspirin in various types of inflammation-related cancers, such as colorectal cancer, gastric cancer, and liver cancer, are described in following sections. Also, the association of aspirin with breast cancer is highlighted.

### 2.1 Aspirin and colorectal cancer

Patients with inflammatory bowel disease are susceptible to colitis-associated colorectal cancer. In addition, sporadic colorectal cancer is promoted by chronic inflammation. Epidemiologic studies demonstrate that aspirin is able to prevent colorectal adenoma or carcinoma. Notably, the primary analyses of several randomized controlled trials (RCTs) for aspirin to prevent colorectal carcinogenesis are discouraging after medium-term follow-up, while they do show reductions in the risk of adenoma recurrence among individuals who have a history of colorectal tumor. Nevertheless, the secondary analyses of these RCTs demonstrate that aspirin does prevent colorectal carcinogenesis. Secondary analyses of RCTs originally conducted for prevention of CVDs show that aspirin use for 5 or more years at doses of more than 75 mg/day leads to a decrease in the long-term risk of colorectal cancer by 24% compared with placebo. Although other NSAIDs also protect against colorectal cancer, a meta-analysis of randomized clinical trials demonstrates that low-dose aspirin has superior benefit to risk profile for reducing the risk of metachronous neoplasia in individuals who have suffered from colorectal neoplasia. Interestingly, a recent study suggests that aspirin and other NSAIDs use is inversely associated with the incidence of colorectal cancer in men but not in women among Japanese, Latino, African-American, and white groups. However, these results appear to be inconsistent with results in other studies, which suggest that aspirin use is able to prevent colorectal cancer in women. Therefore, it warrants more studies in diverse populations to clarify this issue.

The effects of aspirin on colorectal carcinogenesis may be modified by the status of immune response and proto-oncogenes. According to data from the Nurses’ Health Study and Health Professionals Follow-up Study in the United States, regular aspirin intake reduces the risk of tumors that have low levels of tumor-infiltrating lymphocytes. Moreover, Braf is a principle effector of Ras signaling cascade that has a critical role in colorectal carcinogenesis. Mutations in Braf are found in about 10% of colorectal cancer. A study in 127,865 individuals demonstrates that aspirin inhibits the development of colorectal cancer with wild-type Braf, whereas it does not affect Braf-mutated cancer. It is possible that Braf-mutant colon cancer cells may be resistant to aspirin. In fact, Braf mutation is one of key mechanisms underlying drug resistance in colorectal cancer. BRAF mutation also compromises the response to anti-EGFR monoclonal antibodies panitumumab and cetuximab.

Although aspirin has promising effects on preventing colorectal cancer, combination of aspirin and other natural agent may be more effective in preventing carcinogenesis. Colitis is an established risk factor for colon carcinogenesis. Combination of aspirin and curcumin can effectively inhibit azoxymethane/dextran sulfate sodium-induced colitis-accelerated colorectal cancer. Population-based studies are necessary to evaluate the advantages of combining aspirin and curcumin or other agents in cancer prevention. So far, there are more than seven registered clinical trials to investigate the efficacy of aspirin in colorectal cancer prevention, including one trial to combine aspirin with efomithine and another trial to combine aspirin and folate (Table 1).
### TABLE 1  Registered trials of aspirin for cancer prevention (data from ClinicalTrials.gov)

| Identifier | Study title                                                                 | Cancer type              | Primary outcome measures                                                                 | Locations                                      |
|------------|------------------------------------------------------------------------------|--------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------|
| NCT02394769 | ASPirin intervention for the REDuction of colorectal cancer risk            | Colorectal cancer        | Urinary prostaglandin metabolites (PGE-M).                                                | Massachusetts General Hospital, USA            |
| NCT00468910 | Aspirin in preventing colorectal cancer in patients at increased risk of colorectal cancer | Colon cancer             | Change of a spectral biomarker for colonic carcinogenesis                                 | Northwestern University, USA                   |
| NCT00331786 | Nitric oxide-releasing acetylsalicylic acid in preventing colorectal cancer in patients at high risk of colorectal cancer | Colorectal cancer        | Effects of NO-aspirin (NCX-4016) on aberrant cryptic foci multiplicity after the second dose at 6 months | Stony Brook University Cancer Center, USA       |
| NCT02965703 | Aspirin in preventing colorectal cancer in patients with colorectal adenoma | Colorectal adenoma       | Ratio of cell proliferation to apoptosis biomarkers (Ki67 index and BAX index)           | Vanderbilt University/Ingram Cancer Center, USA |
| NCT00983580 | Acetylsalicylic acid and efflowerthine in treating patients at high risk for colorectal cancer | Colorectal cancer        | Adenoma recurrence rate for the treatment arm relative to placebo                          | University of Illinois College of Medicine; University of Chicago Comprehensive Cancer Center; Mayo Clinic, USA |
| NCT00272324 | Aspirin/folate prevention of large bowel polyps                             | Colorectal cancer        | 1. Colorectal adenomas during years 1–3 and years 4–8; 2. Advanced colorectal adenomas during years 1–3 and years 4–8; 3. Colorectal cancer | USC/Kaiser, Los Angeles, California, USAs (and 8 more) |

(Continues)
| Identifier   | Study title                                                                 | Cancer type                  | Primary outcome measures                                                                 | Locations                                      |
|--------------|------------------------------------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------|
| NCT02813824  | Effect of chemoprevention by low-dose aspirin of new or recurrent colorectal adenomas in patients with Lynch syndrome | Lynch syndrome              | Number of patients with at least one adenoma seen on chromo-endoscopy 48 months after complete withdrawal of polyps and initiation of treatment (aspirin or placebo) [Time frame: 4 years] | Hôpital Avicenne, Bobigny, France             |
| NCT02497820  | Finding the best dose of aspirin to prevent Lynch syndrome cancers            | Lynch syndrome I (colon cancer) | Overall cumulative Lynch syndrome cancer                                                   | Sourasky Medical Center Tel Aviv, Israel       |
| NCT02757365  | Efficiency study of aspirin to prevent the occurrence of prostate cancer      | Prostate cancer              | 1. PSA; 2. Digital rectal examination; 3. Ultrasound of the prostate; 4. Biopsy of the prostate; 5. fPSA | West China Hospital, China                    |
| NCT00357682  | A phase III, randomized, study of aspirin and esomeprazole chemoprevention in Barrett’s metaplasia | Esophageal cancer            | Conversion of Barrett’s esophagus to adenocarcinoma or high-grade dysplasia               | Unknown                                       |
| NCT01496521  | Chemoprevention of esophageal squamous cell carcinoma with aspirin and tea polyphenols | Esophageal cancer            | Occurrence of high-grade dysplasia and invasive esophageal cancer                          | Beijing Friendship Hospital, Capital Medical University, China |
| NCT00000479  | Women’s Health Study (WHIS): a randomized trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer | Cancer                       | 1. Number of participants with major cardiovascular events; 2. Number of participants with cancer, excluding nonmelanomaskin cancer | Unknown                                       |
| NCT01038583  | Aspirin in reducing events in the elderly                                   | Cancer                       | The primary endpoint is death from any cause or incident, dementia, or persistent physical disability | The University of Alabama at Birmingham, Birmingham, Alabama, USA (and 50 more) |
2.2 Aspirin and gastric cancer

*Helicobacter pylori* (*H. pylori*) is a major inducer of chronic atrophic gastritis, which may develop into gastric cancer.\(^{27}\) Multiple meta-analyses demonstrate that low-dose aspirin or nonaspirin NSAIDs intake is inversely associated with gastric cancer risk, especially noncardia gastric cancer.\(^ {28-31}\) Recent studies confirm that aspirin use is inversely associated with risk of gastric cancer.\(^ {32,33}\) Especially, one study demonstrates that aspirin use is inversely associated with the incidence of diffuse-type gastric cancer, but positively associated with risk of intestinal-type gastric cancer.\(^ {33}\) However, it warrants further studies to clarify whether aspirin indeed increases the incidence of intestinal-type gastric cancer. Compared to aspirin, nonaspirin NSAIDs intake reduces risk of gastric cancer to similar extent.\(^ {30}\) Since gastric mucosa damage is one of the side effects of aspirin, it needs to weigh the balance between benefit and adverse effects before or during regular aspirin use for individuals who have suffered from chronic gastritis. An aspirin derivative that does not injure gastric mucosa may be preferable for preventing gastric cancer.

2.3 Aspirin and liver cancer

Chronic hepatitis is a major risk factor for hepatocarcinogenesis. The majority of hepatocellular carcinoma (HCC) cases may be attributable to chronic infection of hepatitis B virus (HBV) and hepatitis C virus (HCV), alcoholic or nonalcoholic fatty liver diseases, and aflatoxin B1 intake, which lead to persistent hepatic injury and inflammation.\(^ {34,35}\) During HBV- or HCV-induced chronic hepatitis, the liver tissue is subjected to hepatocellular damage, regeneration, inflammation, and cirrhosis, which contribute to the development of HCC.\(^ {36}\) Aspirin appears to be a promising chemopreventive agent for HBV-related liver cancer.\(^ {37}\) A large population-based study demonstrates that aspirin prevents the development of HCC, while nonaspirin NSAIDs do not reduce HCC risk.\(^ {38}\) In addition, a recent cohort study in Korea also shows that aspirin use reduces HCC risk, especially in young individuals with viral hepatitis.\(^ {39}\) Another retrospective study demonstrates that treatment of patients with chronic hepatitis B with aspirin and/or another antiplatelet agent clopidogrel (a P2Y12 ADP receptor antagonist) reduces the risk of HCC.\(^ {40}\) Moreover, a pooled analysis of data from prospective cohort studies reveals that aspirin use inversely correlates with HCC risk, while the NSAID ibuprofen does not reduce HCC risk.\(^ {41}\) In a chronic HBV-induced HCC model, combination of aspirin and clopidogrel successfully prevents or delays hepatocarcinogenesis in mice.\(^ {36}\) However, it is unknown whether aspirin alone can significantly prevent HBV-induced HCC in that mouse model. Except for HBV- or HCV-related HCC, it warrants further study to determine whether aspirin can prevent HCC that is related to aflatoxin B1, alcoholic or nonalcoholic fatty liver disease in both animal models and humans.

2.4 Aspirin and cholangiocarcinoma

The prognosis for patients with cholangiocarcinoma is very poor.\(^ {42}\) Individuals with primary sclerosing cholangitis or exposure to asbestos are at high risk of cholangiocarcinoma.\(^ {43}\) After a radical surgical resection of cholangiocarcinoma, the recurrence rate is as high as 60%.\(^ {44}\) Thus, chemopreventive agents are needed to prevent cholangiocarcinoma in high-risk populations or prevent the relapse of cholangiocarcinoma after surgical resection. A study finds that aspirin use significantly reduces the risk of cholangiocarcinoma.\(^ {45}\) Analysis of prospective cohort studies on 1,084,133 individuals, 679 and 225 of whom developed hepatocellular carcinoma and intrahepatic cholangiocarcinoma, respectively, reveals that aspirin use reduces the risk of hepatocellular carcinoma.\(^ {42}\) In addition, aspirin use correlates with a decreased risk of intrahepatic cholangiocarcinoma in men but not women.\(^ {41}\) A case-control study from United Kingdom also indicates that aspirin may prevent the development of cholangiocarcinoma, whereas nonaspirin NSAIDs intake is not associated with risk of cholangiocarcinoma.\(^ {46}\) Aspirin can inhibit cholangiocarcinoma cell growth and induce apoptosis. Mechanistically, aspirin reduces cyclin D1, cyclin-dependent kinase (CDK) 4 and BCL2 expression, and induces the expression of tumor suppressor p53.\(^ {47}\) More prospective clinical trials are needed to validate aspirin use as a potential preventive strategy in high-risk populations and patients with resected cholangiocarcinoma.
2.5 | Aspirin and pancreatic cancer

Chronic pancreatitis is a well-known risk factor for pancreatic carcinogenesis.48 Recent studies suggest that specific microbes may be involved in inflammation-linked pancreatic cancer.49,50 Even if there is no overt pancreatitis, pancreatic tumorigenesis is promoted by varied grade inflammation, which may be induced by high-fat diet, obesity, and metabolic abnormalities.51 A study in 601,733 patients shows that aspirin use reduces overall cancer risk, especially colorectal and digestive system cancers.52 A case-control study in Chinese patients finds that regular aspirin use may lead to a significant decrease in the risk of pancreatic cancer.53 Although regular aspirin intake may reduce the risk of pancreatic cancer, it was found that termination of this drug may paradoxically increase the risk of pancreatic cancer.54 Moreover, a meta-analysis suggests that aspirin may be effective for inhibiting the development of pancreatic cancer.55

However, a prospective cohort study in the United States demonstrates that regular aspirin intake fails to reduce pancreatic cancer risk in general population, whereas it is effective for preventing this disease among individuals with diabetes.56 Another case-control study of the combined or confounding effects of statin and aspirin on pancreatic carcinoma risk demonstrates that both exclusive stain and aspirin users have reduced pancreatic carcinoma risk, while combination of statin and aspirin does not lead to a further decrease in the risk.57 In contrast, another case-control study reveals that NSAIDs or statins have no significant effects on pancreatic carcinoma.58,59 Surprisingly, one study shows that the risk of pancreatic cancer is even increased in women with aspirin intake for more than 20 years.60 Therefore, it is still inconclusive whether aspirin is able to prevent pancreatic carcinoma. The reason for the inconsistency among the previous studies remains unclear. Some studies suggest that combination of aspirin and other drugs may synergistically prevent pancreatic carcinoma.61,62 In addition, low-dose nitric oxide (NO) releasing aspirin (NO-aspirin), a derivative of aspirin, can inhibit pancreatic carcinogenesis in Kras (G12D/+), transgenic mice that recapitulate human pancreatic cancer progression.63 It warrants further studies to evaluate whether new derivatives of aspirin, or combination of aspirin and other agents, have superior effects on preventing pancreatic carcinoma than aspirin alone.

2.6 | Aspirin and prostate cancer

Previous studies have demonstrated that inflammation and prostatic infection can promote prostate tumorigenesis.64,65 A recent population-based retrospective cohort study in 13,453 patients with ischemic cardio- or cerebrovascular disease demonstrates that use of low-dose aspirin twice or more per week correlates with a lower risk of prostate cancer.66 The Physicians’ Health Study shows that regular aspirin intake reduces the risk of lethal prostate cancer among all participants.57 In addition, African-American men who take aspirin regularly have lower possibility of advanced stage prostate cancer and longer disease-free survival.68 Another large case-control study (35,600 patients vs. 177,992 population controls) shows that long-term, consistent low-dose aspirin (75–150 mg) use may provide modest protection against prostate cancer.69 Accumulating evidence demonstrates that aspirin use is associated with a decreased overall prostate cancer risk.70–72

A competing risk regression analysis combined prescription and over-the-counter aspirin use in the Finnish prostate cancer screening trial shows that aspirin use leads to a decrease in overall cancer mortality.73 Moreover, the REDUCE study shows that aspirin intake is markedly associated with a decrease in total and high-grade, but not with low-grade, prostate cancer risk.74 Male BRCA mutation carriers are more susceptible to prostate cancer than BRCA-unmutated men. A survey of 74 men in families with a BRCA mutation suggests that daily aspirin use may protect BRCA mutation carriers from prostate cancer.75

Surprisingly, a cohort study of participants in the Korean National Health Insurance Service-National Sample Cohort database shows that aspirin increases the risk of prostate cancer and kidney cancer.76 In addition, a population-based cohort study in Sweden reveals no effect of aspirin on the risk for any prostate cancer or high-grade prostate cancer.77 It is unclear whether the genetic variances or other factors among different populations may influence the effects of aspirin on prostate carcinogenesis. A clinical trial to test the efficacy of aspirin use for preventing prostate cancer is ongoing (Table 1).

3.0 | Future perspectives

Aspirin has been shown to have beneficial effects on preventing cancer in various population groups. Nevertheless, the effects of aspirin on different cancers vary among different populations. Future studies need to make clear the effects of aspirin on specific cancers in different populations to further confirm or correct the results of these studies.
2.7 Aspirin and breast cancer

The prevalence of breast cancer keeps increasing around the world. Although mammary carcinogenesis is not linked to specific infection agents, studies have suggested that NSAIDs may prevent breast cancer. A recent review updates new evidence from epidemiologic and clinical studies that address the effects of aspirin in mammary tumorigenesis. A meta-analysis of cohort studies including 857,831 participants confirms that aspirin reduces the risk of breast cancer in a dose-dependent manner.

Elevated mammographic density is a risk factor for the development of breast cancer. A large screening cohort study demonstrates that there is an independent association between aspirin use and lower mammographic density, especially for younger and African-American women. Notably, breast cancer is a disease with multiple subtypes defined by histological and molecular characteristics. According to a study in a cohort of female professionals in public schools, individuals who take three or more tablets of low-dose aspirin per week is less susceptible to breast cancer, especially the estrogen/progesterone receptor-positive and ErbB2-negative subtype. This study suggests that low-dose aspirin may prevent defined subtypes of breast cancer. Notably, inflammatory breast cancer is a highly aggressive subtype. It warrants further study to determine if aspirin is able to prevent inflammatory breast cancer.

A prospective cohort of women over 70 years old (14,386 women) suggests that aspirin use may prevent breast cancer in elderly women. Although an analysis of 2925 postmenopausal women diagnosed with Stage I–III breast cancer from the National Cancer Institute's Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial suggests that prediagnostic aspirin use does not lead to a decrease in breast cancer specific mortality overall, it does reduce the mortality by approximately 50% among lymph node negative breast cancer patients. However, a study in 84,602 postmenopausal women reveals that aspirin use does not correlate with the risk of postmenopausal breast cancer. Notably, a prospective study of 50,884 women who have a sister suffering from breast cancer demonstrates that there is significantly reduced risk of breast cancer for any NSAIDs among premenopausal women. Thus, it remains to be known whether aspirin use only decreases the risk of premenopausal breast cancer.

3 ASPIRIN USE FOR CANCER THERAPY

Aspirin is not only used for cancer prevention, but also administered for adjuvant cancer therapy. Over the last several decades, there are many studies to determine the effects of aspirin on tumor progression and recurrence. Indeed, preclinical studies demonstrate that aspirin is able to suppress tumor growth in animal models of various types of cancers. Furthermore, the therapeutic application of aspirin is evaluated in patients with a variety of cancers, including colorectal, breast, prostate, and endometrial cancers. Randomized clinical trials are advancing to clarify the efficacy of aspirin for adjuvant cancer therapy. The therapeutic effects of aspirin on human cancer are highlighted below.

3.1 Aspirin for colorectal cancer therapy

The majority of colorectal cancers start as adenomas. A meta-analysis demonstrates that low-dose aspirin can reduce the recurrence of colorectal adenoma, and the nonaspirin NSAID celecoxib is even more effective in reducing adenoma recurrence. An unselected population based study finds that postdiagnosis aspirin intake independently correlates with improved colorectal cancer specific survival. Another study also reveals that aspirin significantly improves survival for patients with hepato-biliary and colorectal carcinoma. Aspirin use during preoperative chemotherapy and/or radiotherapy for rectal cancer improves the pathological response, 5-year progression-free survival and overall survival. Although aspirin has no effect on local relapse, it reduces the risk of rectal cancer metastasis. Postdiagnostic aspirin or nonaspirin NSAIDs use is associated with favorable overall survival and colorectal cancer specific survival among patients with KRAS wild-type colorectal cancer. Moreover, a meta-analysis demonstrates that prediagnostic aspirin use does not improve overall survival among patients with colorectal cancer, while postdiagnostic aspirin intake is associated with favorable overall survival. These data suggest that there is no difference in the prognosis among...
colorectal cancer patients who have taken aspirin or not before the diagnosis, although aspirin can prevent colorectal carcinogenesis. Nevertheless, postdiagnostic aspirin use may improve the outcome in colorectal cancer patients. So far, there are more than ten registered clinical trials to investigate if aspirin is able to improve the outcome of colorectal cancer patients (Table 2). The major outcome measures in these clinical trials include biomarkers such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), tumor size, cancer recurrence or metastasis, and disease-free survival or overall survival. In addition, some of these clinical trials focus on specific subtypes of colorectal carcinoma, such as PIK3CA-mutated colon cancer.

3.2 | Aspirin for liver cancer therapy

Preclinical studies demonstrate that aspirin can inhibit HCC in vitro and in vivo. In a metastatic rat HCC model, treatment with aspirin suppresses lung metastasis of HCC, while another NSAID indomethacin does not inhibit metastasis of HCC. Combination of aspirin and the multikinase inhibitor sorafenib more significantly inhibits HCC than each agent alone in mice model. Moreover, aspirin can overcome sorafenib resistance in HCC by inhibiting the glycolytic enzyme PFKFB3. Together, these studies demonstrate that combination of aspirin and sorafenib is a promising regimen for treating HCC. It warrants further study to test the efficacy of aspirin in combination with sorafenib in clinical setting. In addition, a retrospective study shows that aspirin may improve the anticancer effect of transarterial chemoembolization for patients with unresectable HCC. For patients with HBV-related HCC, aspirin use is associated with improved prognosis after liver resection. Therefore, more prospective clinical trials are necessary to validate the effect of aspirin alone or combination with other standard procedures on HCC treatment.

3.3 | Aspirin for prostate cancer therapy

Previous studies have revealed mixed results on the association between postdiagnostic aspirin intake and the prognosis of prostate cancer patients. In the Health Professionals Follow-up Study, there were 3,986 patients who were diagnosed with prostate cancer between 1990 and 2005. Analysis of data from these cases demonstrates that postdiagnostic aspirin use does not correlate with prostate cancer mortality. In addition, a study of 11,779 nonmetastatic prostate cancer patients in the U.K. National Cancer Data Repository, Clinical Practice Research Datalink, and associated databases demonstrates that postdiagnostic aspirin intake does not correlate with an improved prognosis. Another analysis of nonmetastatic prostate cancer patients in the Cancer Prevention Study-II Nutrition Cohort shows that postdiagnostic daily aspirin use does not correlate with prostate cancer specific mortality. However, the same study demonstrates that postdiagnostic daily aspirin intake correlates with decreased prostate cancer specific mortality among patients with advanced-stage prostate cancers. Moreover, a study based on NIH-AARP Diet and Health Study and PLCO Cancer Screening Trial suggests that aspirin use correlates with longer overall survival, while aspirin is not associated with prostate cancer specific survival. Four clinical trials are ongoing to evaluate the efficacy of aspirin in treating prostate cancer (Table 2).

3.4 | Aspirin for breast cancer therapy

The effects of postdiagnostic aspirin use on breast cancer are still conflicting. Triple negative breast cancer (TNBC) remains to be a subtype of breast cancer with limited therapeutic targets and poor prognosis. A retrospective analysis of 222 Stage II/III TNBC patients in the University of Texas Southwestern Medical Center TNBC registry shows that aspirin intake increases disease-free survival rate and reduces the risk of cancer metastases in Stage II/III TNBC patients. In contrast, analysis of a breast cancer cohort from the U.K. Clinical Practice Research Datalink demonstrates little evidence of a correlation between postdiagnostic prescriptions for aspirin and breast cancer specific mortality. However, it should be noted that these studies are lack of information on medication compliance or over-the-counter use of aspirin, which may affect the findings. It is also possible that postdiagnostic aspirin use may have beneficial effects on selective subtypes of breast cancer patients.
### TABLE 2  Registered clinical trials of aspirin for cancer therapy (data from ClinicalTrials.gov)

| Identifier   | Study title                                                                 | Cancer type          | Primary outcome measures                                                                                                                                                                                                 | Locations                                                                 |
|--------------|------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| NCT00578721  | Trial of aspirin and arginine restriction in colorectal cancer                | Colorectal cancer    | To demonstrate a > 50% decrease in rectal tissue putrescine levels from baseline in study subjects, as a measure of polyamine reduction in the target tissue of colorectal cancer patients [Time frame: 3 years] | Chao Family Comprehensive Cancer Center, USA                               |
| NCT02607072  | Aspirin for prevention of postsurgical recurrence and metastasis in Asian colorectal cancer patients: a multicenter randomized trial | Colorectal cancer    | 3-year disease-free survival [Time frame: 3 years]                                                                                                                                                                       | The Fourth Affiliated Hospital of Anhui Medical University, China         |
| NCT02467582  | Adjuvant aspirin treatment for colon cancer patients                          | Colon cancer         | Disease-free survival [Time frame: up to 6 years after first patient in]                                                                                                                                                  | Hôpital Universitaire Brugmann Brussels, Belgium (and 54 more)            |
| NCT00565708  | Aspirin for Dukes C and high risk Dukes B colorectal cancers                  | Colorectal cancer    | Disease-free survival [Time frame: 5 years]                                                                                                                                                                              | Bankstown-Lidcombe Hospital Bankstown Cancer Centre, Australia (and 66 more) |
| NCT02301286  | A trial of aspirin on recurrence and survival in colon cancer patients        | Colon cancer         | 5 year overall survival [Time frame: 5 years]                                                                                                                                                                             | Ziekenhuisgroep Twente Almelo, Netherlands (and 34 more)                 |
| NCT02647099  | Adjuvant low dose aspirin in colorectal cancer                               | Colorectal cancer    | Time to recurrence [Time frame: 3 years]                                                                                                                                                                                  | Karolinska University Hospital, Sweden                                   |
| NCT02945033  | Study on aspirin versus placebo in resected colon cancer with PI3K mutation stage III or II high risk | Colorectal cancer    | Number of patient with local or distant recurrence or second colorectal cancer or death from any cause, whichever occurred first [Time frame: 3 years]                                                                 | Rouen University Hospital, France                                        |
| NCT03047837  | A randomized, 2×2 factorial design biomarker prevention trial of low-dose aspirin and metformin in stage I–III colorectal cancer patients | Colon cancer         | NFx B (Time frame: 1 year)                                                                                                                                                                                               | Medical Oncology Ente Ospedaliero Ospedali Galliera, Italy               |

NCT00002527  | Aspirin in treating patients with colorectal cancer that has been surgically removed | Colorectal cancer    | 1. Reduction in tumor size [Time frame: up to 4 years]  
2. Reduction in number of tumors [Time frame: up to 4 years]  
3. Disease-free survival [Time frame: up to 4 years] | CCOP—Scottsdale Oncology Program, USA (and 41 more) |
| Identifier   | Study title                                                                 | Cancer type                        | Primary outcome measures                                                                 | Locations                                                                 |
|-------------|-----------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| NCT03326791 | Aspirin in colorectal cancer liver metastases                               | Colorectal cancer                  | Disease-free survival after three years treatment [Time frame: 3 years]                  | Aarhus University Hospital, Denmark (and 13 more)                        |
| NCT02659384 | Anti-programmed cell death-1 ligand 1 (aPDL-1) antibody atezolizumab, bevacizumab, and acetylsalicylic acid in recurrent platinum-resistant ovarian cancer | Recurrent platinum-resistant ovarian cancer | Progression free survival (PFS) at 6 months assessed by Response Evaluation Criteria in Solid Tumors (RECIST) [Time frame: 6 months] | Centre Hospitalier Universitaire Vaudois, Switzerland                    |
| NCT03378297 | IMPACT: a nonrandomized WOO study of novel therapeutic agents in women triaged to primary surgery for EOC | Ovarian cancer                     | Changes in the expression of biomarkers [Time frame: 3 months]                           | Helse Bergen HF, Haukeland University Hospital; Oslo University Hospital; Helse Stavanger HF, Stavanger University Hospital, Norway |
| NCT01612247 | Low-dose chemotherapy with aspirin in patients with breast cancer after neoadjuvant chemotherapy | Breast cancer                      | Toxicity and safety [Time frame: 18 months]                                             | Dartmouth Hitchcock Medical Center, Maimonides Cancer Center; University of Vermont, USA |
| NCT02927249 | Aspirin in preventing recurrence of cancer in patients with node positive HER2 negative stage II–III breast cancer after chemotherapy, surgery, and/or radiation therapy | Node-positive HER2-negative breast cancer | Invasive disease free survival [Time frame: time from randomization to first occurrence of any one of the following: distant recurrence, locoregional recurrence, ipsilateral or contralateral breast cancer, second primary (nonbreast) invasive cancer or death, or any cause, assessed up to 5 years] | Anchorage Associates in Radiation Medicine, USA (and 1052 more) |
| NCT01431053 | Study of aspirin and exemestane as adjuvant treatment in breast cancer       | Breast neoplasms                   | Quality of life [Time frame: 4 years]                                                   | Cancer Institute and Hospital, Chinese Academy of Medical Sciences, China |
| NCT00727948 | The effect of aspirin on angiogenesis proteins in women on tamoxifen therapy | Breast cancer                      | Changes in pro-angiogenic and anti-angiogenic protein levels [Time frame: 75 days]       | University of Vermont, USA                                               |
| Identifier  | Study title                                                                 | Cancer type                       | Primary outcome measures                                                                 | Locations                                                                 |
|------------|------------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| NCT03103152 | A study to examine the effectiveness of aspirin and/or vitamin D3 to prevent prostate cancer progression | Prostate cancer                    | Rate of patient recruitment to a randomized chemoprevention study in men enrolled on an Active Surveillance program for prostate cancer. Number accrued per month [Time frame: 18 months] | University Hospital of Wales, UK (and 5 more)                              |
| NCT00316927 | Dexamethasone, aspirin, and diethylstilbestrol in treating patients with locally advanced or metastatic prostate cancer | Prostate cancer                    | Prostate-specific antigen (PSA) response                                                | Bristol Haematology and Oncology Centre, UK (and 14 more)                 |
| NCT02420652 | Metformin hydrochloride and aspirin in treating patients with hormone-dependent prostate cancer that has progressed after surgery or radiation therapy | Recurrent prostate cancer          | Change in stable PSA rates after 6 months of metformin hydrochloride and aspirin or placebo therapy in patients who have received 4 months of open label treatment [Time frame: baseline to up to 6 months] | Rutgers Cancer Institute of New Jersey, USA                                 |
| NCT01428869 | The effect of combination statin, acetylsalicylic acid and dutasteride use on prostate cancer—a subanalysis of the REDUCE trial | Prostate cancer                    | Diagnosis of prostate cancer [Time frame: 4 years]                                     | University Health Network, Canada                                          |
| NCT01936233 | Clinical study of antiviral and aspirin treatment in liver cancer after radical surgery | Liver cancer                       | Recurrence-free survival [Time frame: 36 months]                                       | Liver Cancer Institute, Shanghai, China                                    |
| NCT02748304 | Sorafenib combined with aspirin to prevent the recurrence in high-risk patients with hepatocellular carcinoma | Liver cancer                       | Overall survival [Time frame: 5 years]                                                  | Huashan Hospital, Shanghai, China                                         |
| NCT03290820 | aspirin improve survival of N2-3 nasopharyngeal carcinoma patients            | Nasopharyngeal carcinoma           | Distant metastasis free survival [Time frame: 5 years after diagnosis]                  | Sun Yat-sen University Cancer Center, China                                |
| NCT03170115 | Induction chemotherapy plus chemoradiotherapy with or without aspirin in high risk rectal cancer | Rectal cancer                      | Tumor downstaging after induction chemotherapy followed by chemoradiotherapy with or without aspirin [Time frame: 8–10 weeks after chemoradiotherapy] | INCA—Instituto Nacional de Cáncer Rio de Janeiro, Brazil                   |
| Identifier | Study title | Cancer type | Primary outcome measures | Locations |
|------------|-------------|-------------|--------------------------|-----------|
| NCT01707823 | Low-dose acetylsalicylic acid in treating patients with stage I–III non-small cell lung cancer | Non-small cell lung cancer | Change in PGE2 biosynthesis from baseline and at 14 days after discontinuation of a 7-day course of 325 mg ASA per day [Time frame: 14 days] | Vanderbilt-Ingram Cancer Center, USA |
| NCT02326779 | Low-dose aspirin therapy for esophageal cancer | Esophageal cancer | 1. Disease-free survival [Time frame: 5 years]  
2. Overall survival [Time frame: 5 years] | Unknown |
| NCT03245489 | Pembrolizumab in combination with antiplatelet therapy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck | Head and neck cancer | Effect of pembro + antiplatelet on major cellular parameters [Time frame: 12 weeks] | Medical University of South Carolina, USA |
| NCT01968798 | ASPREE cancer endpoints study | Cancer | To examine the effect of daily low-dose aspirin (100 mg) compared to placebo, on specific DNA biomarkers and selected specific incident and recurrent cancer and metastases [Time frame: every 6 months] | The University of Alabama at Birmingham, USA (and 39 more) |
| NCT02804815 | Add-aspirin: a trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumors | Non-metastatic cancer | 1. Overall survival [Time frame: 10 years follow-up]  
2. Invasive disease free survival [Time frame: 6 years follow-up]  
3. Disease-free survival [Time frame: 6 years follow-up]  
4. Overall survival [Time frame: 5 years follow-up]  
5. Biochemical recurrence free survival [Time frame: 5 years follow-up] | William Harvey Hospital, UK (and 66 more) |
Experimental data show that aspirin combined with the estrogen receptor (ER) antagonist tamoxifen can downregulate cyclin D1 and block breast cancer cell cycle in G0/G1 phase. In addition, aspirin can potentiate the downregulation of c-myc in tamoxifen-resistant breast cancer cells, thus restoring tamoxifen sensitivity in ER(+) breast cancer cells. It warrants further studies to investigate whether combination of aspirin and tamoxifen may improve the prognosis of ER(+) breast cancer patients. There are four registered clinical trials to determine the efficacy of aspirin in treating human breast cancer (Table 2).

3.5 | Aspirin for endometrial cancer therapy

The effect of aspirin use on endometrial cancer remains controversial. Endometrial cancers have long been divided into estrogen-dependent type I and the less common clinically aggressive estrogen-independent type II. Matsuo et al. reported that low-dose aspirin use improved 5-year disease-free survival rate and disease-specific overall survival rate for endometrial cancer patients. Notably, young patients with low-grade endometrial cancer are more likely to benefit from aspirin use, especially when combined with postoperative radiotherapy. However, a prospective U.K. cohort study of 3058 endometrial cancer patients suggests that postdiagnostic use of low-dose aspirin poorly correlates with the survival rate. Another study demonstrates that nonsteroid anti-inflammatory agent even increases endometrial carcinoma specific mortality by 66% among patients with type I endometrial carcinoma, while it does not correlate with recurrence or endometrial carcinoma specific mortality among patients with type II tumors.

In addition to the above-described types of cancer, a prospective study of 313 patients with small-cell lung cancer reveals that regular aspirin use for more than 2 years has no effect on survival and cancer metastasis, which may be due to relatively low expression of cyclooxygenase (COX) 2 in small-cell lung cancer. Another study suggests that postdiagnostic use of low-dose aspirin does not reduce lung cancer specific mortality. Moreover, analysis of two large cohorts in the United Kingdom reveals that low-dose aspirin use does not improve survival of esophageal or gastric cancer patients.

So far, it may be hard to recommend aspirin to treat cancer according to observational studies. It is necessary to conduct randomized clinical trials to test the efficacy of aspirin use for treating cancer. Such trials are underway around the world (Table 2). The Add-Aspirin trial is a randomized clinical trial to investigate whether regular aspirin intake is able to prevent tumor recurrence after standard therapy and improve survival rate in participants with four non-metastatic common solid tumors. The primary outcome of this trial is 5-year and biochemical disease recurrence-free survival. As registered in ClinicalTrials.gov, there are more than six ongoing clinical trials to test the efficacy of adjuvant aspirin treatment in preventing postsurgical recurrence and metastasis, or improving survival in high-risk colorectal cancer patients (Table 2). More than three clinical trials are conducted to investigate the effects of aspirin treatment on breast cancer (Table 2). In the era of precision medicine, it has been recognized that not all patients may benefit from a given drug. Future clinical trials on aspirin and cancer therapy may pay emphasis on identifying which types of cancer patients, if any, may benefit from aspirin use.

Aspirin not only reduces cell proliferation or viability, but also synergistically sensitizes cancer cells to other anticancer agents. In clinical setting, it may be more promising to combine aspirin and other treatments. A recent study demonstrates that aspirin significantly increases the cytotoxicity of sorafenib, especially in Ras-mutant cancer. Another preclinical study shows that combination of aspirin and apatinib, a selective VEGFR2 inhibitor, suppresses gastric tumorigenesis. Moreover, aspirin synergistically sensitizes osteosarcoma cells to cisplatin and radiotherapy. Combination of photo-thermal therapy and aspirin has promising anticancer effects. Randomized clinical trials are necessary to evaluate the efficiency of combined cancer therapy including aspirin, molecular targeted therapy, chemotherapy, and radiotherapy. A randomized clinical trial (ClinicalTrials.gov Identifier: NCT02748304) to test the effect of sorafenib and aspirin on preventing cancer recurrence in high-risk HCC patients is ongoing (Table 2). Notably, aspirin may relieve the adverse effects of some chemotherapeutic agents. It has been reported that aspirin can minimize gentamicin-induced ototoxicity, while it does not protect from cisplatin-related ototoxicity.
Malignant tumors are of typical hallmarks, such as sustained tumor cell proliferation, invasion, metastasis, evasion of immune surveillance, drug resistance, evasion of cell death, aberrant metabolism, tumor angiogenesis, and uncontrolled inflammation. These biological behaviors drive carcinogenesis and tumor progression, and often lead to cancer recurrence or evolution after therapy. In fact, aspirin and its metabolites can target multiple oncogenes or tumor suppressor genes, thereby impacting diverse signaling pathways in different cell types that collaboratively drive tumorigenesis. The mechanisms underlying the anticancer effects of aspirin are described below.

4.1 Multiple targets of aspirin and its metabolites

Chronic inflammation increases the risk of developing CVDs, cerebrovascular disease, and cancer. As an anti-inflammatory agent, regular aspirin use may relieve inflammation thereby avoiding repeated damage to normal tissues and preventing stroke, heart attacks, and tumorigenesis. COX catalyzes the production of prostaglandins such as prostaglandin E2 (PGE2), prostaglandin D2, and thromboxane A2 (TXA2), which trigger pain, inflammation, fever, or blood clotting. Activation of COX1 in platelets leads to the production of TXA2 and platelet activation.\(^{121}\) COX is a direct target of aspirin. Aspirin inhibits COX1 and COX2 in platelets and epithelial cells, respectively, thereby blocking the production of prostaglandins.\(^{121}\) Although salicylic acid is a key mediator of aspirin’s anticancer effects, aspirin also donates acetyl group to target proteins, leading to target proteins acetylation. Aspirin acetylates COX1 and COX2 at S529 and S516, respectively, inhibits arachidonic acid binding, and prevents arachidonic acid transfer to TXA2.\(^{122,123}\) Inhibition of COX and platelets activation may underlie, in part, the anticancer effects of aspirin. Activated platelets not only trigger the expression of COX2 in epithelial cells, which has diverse effects on cell proliferation and survival, but also help cancer cells spread.\(^{124}\) Moreover, activated platelets are able to suppress T-cell immunity against cancer. Mechanistically, LRRC32 in platelets membrane can convert latent TGF-\(\beta\) into active TGF-\(\beta\), which inhibits T-cell immunity.\(^{125}\) Therefore, aspirin can inhibit platelets activation thereby relieving inflammation, immune escape, epithelial cells growth, and cancer metastasis.

Wnt/\(\beta\)-catenin signaling is tightly involved in tumorigenesis. COX-mediated synthesis of PGE2 stimulates \(\beta\)-catenin signaling through the G protein coupled receptor EP2.\(^{126}\) Mechanistically, activation of EP2 leads to Akt activation and GSK3\(\beta\) inactivation, which relieves the inhibitory phosphorylation of \(\beta\)-catenin.\(^{127}\) As a COX inhibitor, aspirin can inhibit the synthesis of PGE2, thereby relieving \(\beta\)-catenin signaling.\(^{127}\) In addition, aspirin can induce the inhibitory phosphorylation of protein phosphatase 2A, a positive regulator of \(\beta\)-catenin.\(^{128}\) Consistent with this regulation, aspirin increases the stability of phosphorylated \(\beta\)-catenin and suppresses \(\beta\)-catenin signaling.\(^{129}\)

Another target of aspirin is AMP-activated protein kinase (AMPK). Salicylic acid can directly bind to AMPK and activate it.\(^{130}\) However, aspirin may also indirectly activate AMPK.\(^{131}\) Our previous study reveals that the multikinase inhibitor sorafenib can inhibit the induction of AMPK phosphorylation by aspirin.\(^{95}\) Notably, AMPK may be a context-dependent tumor suppressor or oncogene.\(^{132}\) On one hand, AMPK may inhibit mTORC1 (mTOR complex 1), which regulates many cellular processes including autophagy, nucleotides, and protein synthesis.\(^{133}\) Inhibition of mTORC1 and promotion of autophagy may contribute to the tumor-suppressive effects of AMPK agonists. On the other hand, AMPK may reprogram energy metabolism and help cells tolerate energy stress. Although AMPK reportedly inhibits BRAF-overexpressed melanoma cells, some studies demonstrate that AMPK activation has protumor effects in these cells.\(^{134-136}\) In fact, we have found that AMPK is able to promote mTORC2 activation and MCL-1 expression thereby antagonizing the anticancer effects of aspirin in hepatoma HepG2 and colon carcinoma SW480 cells.\(^{95}\) Inhibition of AMPK sensitizes HepG2 and SW480 cells to aspirin.\(^{95}\) In addition, inflammation is one of cancer hallmarks. By activating AMPK, salicylate can enhance the inhibitory phosphorylation of JAK1 and inhibit STAT phosphorylation thereby antagonizing inflammatory signaling.\(^{137}\) Thus, aspirin may inhibit inflammation through targeting both COX and AMPK.

The list of aspirin targets keeps increasing. Aspirin reportedly acetylates P53 and histone,\(^{138}\) and induces FoxD3 promoter demethylation and FoxD3 expression thereby inducing IncRNA OLA1P2, which inhibits the nuclear import
of phosphorylated STAT3. Moreover, aspirin inhibits NF-kB signaling thereby relieving acquired drug resistance in breast cancer. Treatment of KRAS-expressing nonsmall cell lung carcinoma cells with aspirin results in decreased expression of E-cadherin repressor Slug, a regulator of epithelial–mesenchymal transition and cell migration. A recent study demonstrates that aspirin inhibits cancer metastasis and angiogenesis via targeting heparanase. In addition, aspirin reportedly inhibits tumor growth and stemness in colorectal cancer by downregulating Nanog. Therefore, aspirin and its metabolites may inhibit multisteps in tumor progression, such as tumor initiation and metastasis.

Aspirin and its metabolites also regulate CDKs. Aspirin reportedly acetylates CDK1, while it remains unclear how CDK1 acetylation would affect its activity and whether aspirin directly regulates CDK1 activity. Moreover, salicylic acid directly binds to CDK2 and downregulates its expression and activity. Notably, the metabolites of salicylic acid may also have anticancer effects. Hydroxylation of salicylic acid generates 2,3-dihydroxybenzoic acid (2,3-DHBA) and 2,5-dihydroxybenzoic acid (2,5-DHBA), as well as derivatives 2,4-dihydroxybenzoic acid (2,4-DHBA) and 2,6-dihydroxybenzoic acid (2,6-DHBA), which inhibit CDK1 activity. In addition, the activity of CDK6 can be inhibited by 2,3-DHBA and 2,6-DHBA, while 2,4,6-trihydroxybenzoic acid is a broad-spectrum CDK inhibitor that inhibits CDK1/2/4/6. Given that CDK has critical roles in tumorigenesis, it warrants further studies to determine if inhibition of CDK significantly contributes to the anticancer effects of aspirin.

### 4.2 The effects of aspirin on multiple types of cells

Except for acting on multiple molecular targets, aspirin also elicits effects on diverse cell types, including platelets, epithelial cells, cancer cells, stromal cells, immune cells, and endothelial cells. Thus, aspirin not only affects the parenchyma in normal tissues or tumor, but also impacts the stroma or tumor microenvironment. Although aspirin inhibits COX1 in platelets, it inhibits COX2 in epithelial cells and tumor cells. COX2 not only promotes cancer cell survival, but also enhances cancer metastasis. Furthermore, COX2/PGE2 can upregulate the pluripotency transcription factor SOX2 and promote cancer stem-like cells expansion.

Evasion of immune surveillance underlies accelerated carcinogenesis and tumor progression. Previous studies demonstrate that COX activity is linked to immune suppression (Figure 2). COX-catalyzed production of PGE2 induces expansion of myeloid-derived suppressor cells (MDSC), which inhibit antitumor immunity by decreasing anti-tumor immunity.
antitumor effector cells, and increasing regulatory T cell (Treg) and regulatory dendritic cell responses in the tumor microenvironment.\textsuperscript{156} Thus, inhibition of COX may alleviate MDSC expansion. In addition, inhibition of COX by aspirin may increase the secretion of CXCL9 and CXCL10, which is able to recruit natural killer cells and cytotoxic T lymphocytes, and inhibit the expression of T lymphocyte co-inhibitory molecules CTLA4, PD-1, and its ligand PD-L1.\textsuperscript{157–159} Moreover, COX2 inhibition blocks M1 macrophage polarization thereby reducing its conversion into M2 macrophage that inhibits immune response.\textsuperscript{157,159} Thus, COX may accelerate tumor progression through evasion of immune surveillance. Inhibition of COX by aspirin can be synergistic with anti-PD-L1 blockade in eradicating tumors.\textsuperscript{152} The association of aspirin use with colorectal cancer survival is stronger in patients with PD-L1-low tumor than PD-L1-high tumor.\textsuperscript{160} A clinical trial (NCT02659384) in Switzerland to test the efficacy of anti-PD-L1 antibody atezolizumab, bevacizumab, and aspirin in recurrent platinum-resistant ovarian cancer is ongoing (Table 2).

In addition, inhibition of angiogenesis underlies the anticancer effects of aspirin. Targeting angiogenesis may prevent tumor growth and progression.\textsuperscript{161} In fact, angiogenesis is a common target of many cancer chemopreventive agents including aspirin and curcumin.\textsuperscript{162} Mechanistically, aspirin inhibits the production of 11-hydroxyeicosatetraenoic acid and 15 (S)-hydroxyeicosatetraenoic acid from platelets, which can induce endothelial cell migration and the formation of tubular structure.\textsuperscript{163} In addition, the proangiogenic heparanase is a novel target of aspirin.\textsuperscript{143} Furthermore, the salicylic acid metabolite 2,5-DHBA (gentisic acid) has been identified as an inhibitor of fibroblast growth factors, which are key stimuli of angiogenesis.\textsuperscript{164} Although aspirin use decreases thrombin receptor mediated release of vascular endothelial growth factor (VEGF), another key stimulator of angiogenesis, from platelets,\textsuperscript{165} a study demonstrates that platelets may promote angiogenesis in VEGF-independent manner;\textsuperscript{166} Thus, aspirin may not only inhibit tumor cells, but also interrupt the essential blood supply.

5 BIOMARKERS FOR THE ANTICANCER EFFECTS OF ASPIRIN

Observational clinical studies indicate that some cancer patients may benefit from aspirin use, while the others may not. Recent studies have reported that colorectal cancer with mutations in the oncogene PIK3CA may be more responsive to daily aspirin regimen.\textsuperscript{167} The induction of colorectal cancer cell cycle arrest is exacerbated by PIK3CA mutations.\textsuperscript{168} Mutation in PIK3CA also sensitizes breast cancer cells to aspirin.\textsuperscript{169} It would be interesting to investigate whether other genetic cues may affect the responsiveness of tumor cells to aspirin. Although mutations in both PIK3CA and KRAS render breast epithelial cells more sensitive to aspirin than PIK3CA mutation alone, mutations in KRAS alone do not affect the sensitivity of breast epithelial cells to aspirin.\textsuperscript{91} Another recent study on colorectal cancer suggests that postdiagnostic aspirin use correlates with improved survival in patients with tumors carrying wild-type BRAF or KRAS, but not in patients with KRAS-mutated tumors.\textsuperscript{170} The reason for the inconsistency between these studies is unclear. It is possible that the effects of PIK3CA mutation on the sensitivity of cancer cells to aspirin may be affected by other co-existing mutations in diverse oncogenes or tumor suppressor genes.

The status of immune checkpoints may also affect the sensitivity of tumors to aspirin. COX-dependent immune suppression can be relieved by aspirin.\textsuperscript{153} The levels of PD-L1 in tumors negatively associate with the sensitivity to aspirin.\textsuperscript{160} It remains to know if other immune checkpoints affect the response of tumor to aspirin. Combination of aspirin and immune checkpoints blocker may be promising regimen for treating cancer.

Tumorigenesis is regulated by multiple genes and environmental cues, including complicated gene–gene interaction and gene–environment interaction. Single-nucleotide polymorphism (SNP) is a risk factor for a variety of cancers. SNP rs6983267 is localized on chromosome 8q24. The bona-fide oncogene MYC resides 335 kb downstream from rs6983267.\textsuperscript{171} Previous studies demonstrated that individuals carrying the T allele of rs6983267 are less likely to suffer from colorectal cancer than those who carry the G allele of rs6983267.\textsuperscript{172–174} Mechanistically, the T allele of rs6983267 reduces the recruitment of transcription factor complex β-catenin/TCF7L2 to MYC promoter, thereby inhibiting MYC expression.\textsuperscript{175–180} On the contrary, β-catenin/TCF7L2 constitutively binds to MYC promoter among individuals carrying the G allele of rs6983267, leading to MYC overexpression and tumorigenesis.\textsuperscript{175–178} Furthermore,
FIGURE 3  The interaction among SNP, aspirin use, and colorectal tumorigenesis
Note: aspirin and its metabolites salicylic acid, DHBA derivatives can inhibit COX1/2, heparanase, CDK, bFGF, etc., and promote AMPK activation, thereby inhibiting carcinogenesis, tumor angiogenesis, and tumor progression. SNPs such as rs6983267, rs2965667, and rs16973225 may affect the susceptibility to cancer and modify the anticancer effects of aspirin.
6 | ASPIRIN RESISTANCE

Although aspirin can effectively prevent cardiovascular and cerebrovascular disease, many patients still suffer from thromboembolic events despite of aspirin therapy, which may be due to aspirin resistance.\(^{183}\) Notably, drug resistance may be a serious problem in cancer prevention, especially for long-term administration of cancer-preventive agents. Although drug resistance during cancer therapy may be monitored by the clinical response of tumors to a given regimen, it may be hard to determine whether a chemopreventive agent is acting as expected before developing tumors. Therefore, it would be important to identify biomarkers that can determine whether aspirin works. Some biomarkers, such as prostaglandin metabolites, cell proliferation or apoptosis biomarkers, have been used to measure the outcome in clinical trials for aspirin (Table 1).

The antiplatelet effect contributes to the protection of cardiovascular and cerebrovascular systems by aspirin. The same is true for aspirin in cancer prevention. Lessons from aspirin resistance in preventing or treating CVDs may be exploited in the fight against cancer. Since platelets are major target of aspirin, it is conceived that a platelet function test may help to monitor the effects of aspirin or guiding aspirin dosing.\(^{184}\) VerifyNow is a device that measures the agglutination response of platelets to fibrinogen and arachidonic acid.\(^{185}\) Platelet function analyzer (PFA-100) is another choice to measure the platelet aggregation induced by high blood flow and platelet activator.\(^{186}\) PFA-100 is considered as one of ideal methods to detect platelet function. Notably, the responses to aspirin use may vary among individuals. The pharmacokinetics and/or pharmacodynamics may be different among individuals. Aspirin may effectively inhibit the activities of platelet COX1, but aspirin dose less than 100 mg/day is an independent predictor of aspirin resistance.\(^{187}\) Polymorphism of COX1 (-842A > G) is significantly correlated with aspirin resistance.\(^{188}\) In addition, platelet glycoprotein IIa (GPIIa) gene polymorphism (-33L > P) or GPIIa overexpression is linked to aspirin resistance.\(^{189}\) It remains to know whether these genetic factors, as well as polymorphisms of COX2 and TXA2 synthase, may compromise the anticancer effects of aspirin.

Moreover, platelet turnover may be increased by inflammation, leading to an increase in nonaspirin-inhibited platelets during the 24-hr dosing interval.\(^{190}\) Metabolic disorder also affects the responsiveness to aspirin. Aspirin intake prevents atherothrombotic events to a lesser extent among patients with diabetes mellitus than healthy individuals.\(^{191}\) It remains to know whether patients with diabetes can benefit from aspirin use for prevention of cancer. In addition, hyperhomocysteine may reduce the responsiveness of platelets to aspirin.\(^{192}\)

The mechanisms by which therapeutic resistance arises in cancer are multifactorial and more complicated than that in normal tissue. Drug efflux is one of the common mechanisms underlying chemoresistance. P-glycoprotein and multidrug resistance associated proteins are common drug transporters that are frequently overexpressed in human tumors. Upregulation of P-glycoprotein and multidrug resistance associated proteins leads to decreased drug concentration inside cancer cells, thus limiting the efficacy of drugs.\(^{193}\) In addition, alterations to cell death pathways, deregulation of gene expression pathways, epigenetic alterations, epithelial–mesenchymal transition, and cancer stem cells repopulation contribute to failure in cancer therapy.\(^{131,194,195}\) Aspirin inhibits cancer cell proliferation and induces programmed cell death or autophagy.\(^{196}\) Beclin-1 is a critical effector in autophagy. Aspirin can induce Beclin-1 acetylation, which impairs the autophagic flow and the anticancer effect of aspirin in colorectal cancer cells.\(^{197}\) Moreover, the adaptive upregulation of antiapoptotic MCL1 suppresses aspirin-induced apoptosis.\(^{95}\) Determining the causes of preventive or therapeutic failure is one of the key factors for rationalization and personalization of aspirin use as well as for further stratification of the management with regard to cancer chemoprevention and therapy.

7 | ADVERSE EFFECTS OF ASPIRIN

Since long-term use is necessary for chemopreventive agents, it is very important to weigh the balance between the benefits and adverse effects. Some less serious side effects of aspirin include nausea, vomiting, stomach pain, and heartburn. A serious concern about long-term use of aspirin is gastrointestinal injury. Even low dose of aspirin can induce varied degrees of gastroduodenal mucosal injury such as erosion, ulcer, and hemorrhage.\(^{198}\) Although most of clinical
research on aspirin-induced damage focus on upper gastrointestinal tract, a recent study demonstrates that chronic aspirin intake may lead to damages in lower gastrointestinal tract. The risk factors for aspirin-induced gastrointestinal damage include a history of peptic ulcer, concomitant use of other COX2 inhibitors or antiplatelet agents, and *H. pylori* infection. Recent study demonstrates that, in a real-world setting, the risk of major bleeding on aspirin is higher in patients aged 75 years or older. Co-administration of proton pump inhibitors is a choice to reduce gastrointestinal risk. The risk of major bleeding may be reduced by 70–90% by proton pump inhibitors. Interestingly, SNPs in COX-1 (A842G and C50T), members of cytochrome P450 gene family (CYP4F11, CYP2C9, CYP2D6), and endothelial nitric oxide synthase correlate with elevated risk of gastrointestinal hemorrhage in aspirin users.

Another adverse effect of aspirin is to exacerbate respiratory disease, including asthma and chronic rhinosinusitis with nasosinusual polypsis. Mechanistically, the development of aspirin-exacerbated respiratory disease involves aberrated eicosanoid metabolisms and activated eosinophils, mast cells, and platelets. In addition, polymorphisms in ILVBL gene, dipeptidyl peptidase 10 (rs17048175), and TNF (rs1800629) are risk factors for aspirin-exacerbated respiratory disease. Furthermore, epigenetic factors such as DNA methylation may be involved in the development of aspirin-exacerbated respiratory disease. Leukotriene modulators, such as the leukotriene receptor inhibitor montelukast and the 5-lipoxygenase inhibitor zileuton, are widely used in treating aspirin-exacerbated respiratory disease. Aspirin desensitization has shown therapeutic effectiveness in treating aspirin-exacerbated respiratory disease. Given that IgE, IL5, and PGD2 have pathogenic roles in aspirin-exacerbated respiratory disease, specific antibodies against IgE (omalizumab) and IL5 (mepolizumab), as well as the antagonists of CRTH2, a PGD2 receptor, are promising therapeutics to relieve this adverse effect.

**8 | NOVEL DERIVATIVES OF ASPIRIN**

Researchers have been developing novel derivatives of aspirin to improve the water solubility and the anticancer effects, and to minimize the adverse effects of aspirin. The development of novel derivatives of aspirin is an attractive field. Phospho-aspirin is a derivative of aspirin modified at its -COOH group, which contributes to the gastrointestinal toxicity of aspirin. Compared to aspirin, phospho-aspirin inhibits tumorigenesis to a greater extent.
and has better safety than aspirin in animal models of breast, colon, and pancreatic cancers. To improve potency and minimize toxicity, aspirin ester prodrugs, such as fumarate-based aspirin prodrug, have been developed. One of the fumarate-based aspirin prodrugs, GTCpFE, effectively inhibits both NF-κB and COX thereby attenuating breast cancer stem cells.

NO-releasing aspirin is another ester derivative of aspirin. NO is an endogenous gasotransmitter that is involved in various physiological processes including protection of gastrointestinal integrity and cardiovascular system. NO-aspirin is synthesized by covalent linking aspirin to a spacer that, in turn, is associated with a NO-releasing moiety. Upon releasing from the aspirin prodrug, NO is able to prevent gastric mucosa damage by increasing mucous secretion, mucosal hemodynamics, and reducing aggregation of neutrophils to gastric mucosa. In addition, the released NO has antiplatelet action. Moreover, NO can directly modify sulfhydryl residues of proteins through S-nitrosylation. NO-aspirin is able to S-nitrosylate NF-κB p65 and reduce NF-κB protein levels. Also, NO-aspirin S-nitrosylates p53 and β-catenin. Although NO itself may induce COX2 expression, aspirin can inhibit COX2 activity thereby neutralizing the unwanted effect of NO. Therefore, it is anticipated that NO-releasing aspirin may have better anticancer activity and less gastrointestinal toxicity than its parental compound aspirin. Indeed, NO-aspirin prevents nearly 90% of ductal adenocarcinomas in animal tumor models. So far, many NO-releasing aspirin have been developed.

Except for NO, hydrogen sulfide (H₂S) is another gasotransmitter. NO and H₂S share many similar functions, such as protection against myocardial ischemia injury, cytoprotection against oxidative stress, and inhibition of inflammation. Accordingly, H₂S-releasing derivatives of aspirin have been developed. H₂S-aspirin is typically synthesized by linking aspirin to a dithiolethione or a thiobenzamide moiety. Similar to NO-aspirin, H₂S-aspirin has anticancer effects and protective effects against aspirin-induced gastric injury in preclinical models. In addition, NOSH-aspirin, a hybrid of aspirin that bears both NO- and H₂S-releasing moieties is extremely effective in inhibiting cancer cell growth. NOSH-aspirin is less toxic and better than aspirin as a cancer chemopreventive agent in animal model.

Glucose-aspirin is synthesized by conjugating aspirin to glucose. Notably, glucose-aspirin is sevenfold more water soluble and about eight- to ninefold more active in inhibiting cancer cell growth than aspirin. It warrants further studies to evaluate its anticancer activity in vivo and the mechanisms underlying its effects. Moreover, bio-organometallic chemistry is one of the active fields in medicinal chemistry to investigate the biological effects and therapeutic applications of organometallic compounds. For example, the Co₂(CO)₆–alkyne complex is an organometallic compound that can be utilized to modify established drugs. Alkyne derivatives of aspirin (Co–aspirin) have significantly modified effects on COX2, MMP7, vascularization, and angiogenesis, thereby achieving superior anticancer effects to aspirin.

Aspirin–PC (phosphatidylcholine) is another derivative in which aspirin is formulated with PC-enriched soy lecithin. PC-associated aspirin has stronger inhibitory activity on the growth of ovarian cancer cells than the parent drug aspirin, in vitro and in vivo. In addition, resveratrol-based aspirin derivatives release resveratrol to relieve the adverse effects of aspirin, and to boost its anticancer activities. Notably, the aspirin-like molecule o-(acetoxyphenyl)hept-2-ynyl sulfide inhibits COX2 much more potently and selectively than aspirin. In addition to the above-described derivatives of aspirin, an alternative strategy is to incorporate aspirin into nanoparticles. It warrants further studies to test the efficacy of these novel aspirin derivatives in clinical setting.

9 | CONCLUDING REMARKS

Based on current knowledge, aspirin is a promising chemopreventive agent, especially for gastrointestinal cancer. More randomized clinical studies are required to validate the benefits of aspirin use, especially low-dose aspirin, in preventing a variety of human cancers, such as breast cancer, prostate cancer, liver cancer, and pancreatic cancer. In addition, it warrants more studies to determine if aspirin can prevent or treat Epstein-Barr virus-related nasopharyngeal cancer and Burkitt lymphoma, and Human papillomavirus-related cervical cancer.
During the administration of aspirin, the individual response to this agent may be monitored by platelet testing and/or other biomarkers. The genetic biomarkers, if any, to predict who may be most likely to benefit from aspirin use for cancer prevention would be wonderful. Individuals at high risk for developing cancer may get greater benefit from regular aspirin use than general population. In addition, postdiagnostic aspirin use may improve the survival of patients with colorectal carcinoma. The status of mutations in oncogenes such as PIK3CA and KRAS, and the levels of expression or activity of aspirin targets such as COX, CDK, and heparanase may help identify cancer patients who may benefit from aspirin use. It remains to know whether mutations in other genes affect the outcome of patients who take aspirin. Combination of aspirin and other therapies, such as sorafenib, radiotherapy, chemotherapy, and photo-thermal therapy, may be promising regimen. Randomized clinical trials are necessary to validate aspirin-included regimens. Cautions should be made for aspirin use in elder individuals, especially those individuals with high risk of gastrointestinal bleeding, co-administration of proton pump inhibitors is recommended. It warrants further studies to determine whether genetic testing can help identify individuals who may suffer from the adverse effects of aspirin. Novel derivatives of aspirin hold promise in enhancing the tumor suppressive effects while overcoming the adverse effects of aspirin.

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