

Review Article

Aspirin and Cancer: An Updated Minireview

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1. Independent researcher

Aspirin (acetylsalicylic acid), synthesized by Bayer chemist Felix Hoffmann in 1897, remains one of the most extensively studied repurposed drugs in oncology. It is a component of the World Health Organization's List of Essential Medicines due to its safety, efficacy, and affordability.

Decades of epidemiological data, long-term follow-up of cardiovascular prevention trials, and dedicated chemoprevention studies have established that regular aspirin use is associated with reduced incidence of colorectal cancer and, to varying degrees, several other solid tumors. Proposed mechanisms include irreversible inhibition of cyclooxygenase-1 (COX-1) in platelets, suppression of COX-2-driven prostaglandin signaling in tumor and stromal tissue, disruption of platelet–tumor cell interactions that facilitate metastatic seeding. Other less clearly known mechanisms are: modulation of the gut microbiome, and enhancement of antitumor immune surveillance, and intracellular pH reduction. By inhibiting COX-2, aspirin not only reduces inflammation but also disrupts tumor-promoting signaling pathways, including those involved in DNA repair, apoptosis, and cell cycle regulation.

In recent years, a growing interest for aspirin as primary and secondary prevention of cancer has stimulated its research in anti-cancer schemes. Landmark trials such as CAPP2 (in Lynch syndrome) and the 2025 ALASCCA trial (in PIK3CA-altered colorectal cancer) provide some of the strongest randomized evidence to date, while the ASPREE trial and its long-term extension have complicated the picture by showing that aspirin initiated in healthy adults aged 70 and older does not reduce cancer incidence and is instead associated with increased cancer-related mortality. This paper synthesizes the pharmacological rationale, the trajectory of clinical trial evidence, the evolution of preventive-care guidelines, and the persistent risk of gastrointestinal and intracranial bleeding that constrains aspirin's use as a general chemopreventive agent. The overall picture that emerges is one of a biologically plausible but context-dependent anticancer effect, most convincingly established in

younger and middle-aged adults and in molecularly defined patient subgroups, rather than a universal anticancer therapy suitable for the general population.

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1. Introduction

Cancer remains a leading cause of death worldwide, and the search for inexpensive, widely available agents that might reduce its incidence or improve outcomes after diagnosis has long included aspirin, also known as ASA or by its chemical name, acetylsalicylic acid.

Aspirin's pharmacological history begins with the willow bark extracts (Figure 1) described by Hippocrates (willow bark and other salicylate-containing plants have been used for pain relief since ancient times) and later chemically isolated as salicin in the early nineteenth century, culminating in Hoffmann's 1897 synthesis of acetylsalicylic acid for Bayer (Figure 1).



Willow tree (genus salix)

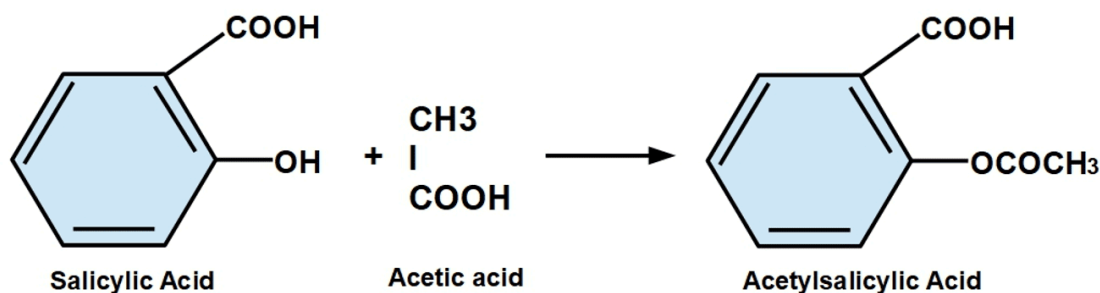
Figure 1. Varieties of willow tree. The bark of the willow tree was the original source of a precursor of salicylic acid.

1.1. Chemistry

Salicin is a drug that has been found in the bark of willow tree and has been used for more than two thousand years in different medical situations such as fever and inflammation. Salicin is metabolized in the human gut into the active compound salicylic acid.

In the second half of the nineteenth century, chemists at Bayer Laboratory started to look for a less irritating replacement of salicylic acid. In 1854, Charles Gerhardt in Bayer, treated sodium salicylate acid with acetic acid and obtained acetylsalicylic acid, for the first time. But it was Felix Hoffmann in 1897 who came up with acetylsalicylic acid in a pure and stable format. Figure 2. By the end of the century, acetylsalicylic acid renamed aspirin was available for clinical use.

Acetylsalicylic acid is a member of the class of benzoic acids that is salicylic acid in which the hydrogen that is attached to the phenolic hydroxy group has been replaced by an acetoxy group. Acetylsalicylic acid appears as odorless white crystals or crystalline powder with a slightly bitter taste. It is a non-steroidal anti-inflammatory drug with cyclooxygenase inhibitor activity.



Aspirin is absorbed in the gastrointestinal tract after oral administration, and then converted into salicylic acid which is further metabolized. During salicylic blood circulation the biological activity is impaired due to the large amount of salicylic acid (50-80%) bound to albumin

Figure 2. Acetylsalicylic acid (aspirin) was synthesized by Hoffmann in 1897 by acetylating the salicylic acid obtained from willow bark.

1.2. Aspirin beyond its anti-inflammatory properties

For most of the twentieth century, aspirin's clinical reputation rested on its analgesic, antipyretic, and anti-inflammatory properties. In the 1950s Lawrence L. Craven published a series of papers [\[1\]\[2\]\[3\]](#)

^[4] showing that aspirin reduced the risk of thrombotic events in coronary disease patients. These papers were not given the credit they deserved and went unnoticed until the 1970s.

In 1967-1968 Weiss et al. ^[5] elucidated the mechanism of action of aspirin's anti-thrombotic effects: platelet antiaggregation. This was further confirmed by Evans et al. ^[6] in the same year. These findings established antiplatelet aggregation and aspirin as cornerstones in cardiovascular disease in the 1970s.

The anti-cancer potential of aspirin was discovered through a combination of epidemiological observations and preclinical research. Interest in aspirin's oncological potential emerged from an unexpected source: long-term follow-up of cardiovascular prevention trials originally designed to assess myocardial infarction and stroke outcomes.

Investigators who extended observation of these cohorts using national cancer registries began to notice reduced incidence of colorectal and other cancers among participants randomized to aspirin, an effect that often took five to ten years to become apparent. This observation, combined with a large body of case-control and cohort data, established aspirin as one of the most intensively investigated chemopreventive candidates of the past three decades ^[7]. Table 1 summarizes the history of aspirin role in cancer.

Period	Discovery
1970s-1980s	Early preclinical evidence: Anti-cancer effects first identified in pre-clinical models (cell cultures and animal studies) showing aspirin inhibited cancer cell growth ^[8] .
1980s-1990s	Epidemiological observations: Population studies found people taking daily aspirin had reduced colorectal cancer risk and lower cancer mortality ^[9] .
1990s-2000s	Clinical evidence accumulates: Multiple studies observed reduced metastasis in breast, bowel (colorectal), and prostate cancer patients taking aspirin.
2000s-2010s	Lynch syndrome trial: First major clinical trial (CAPP2) tested aspirin in Lynch syndrome patients (high colorectal cancer risk).
2010s-2020s	Policy changes: Federal advisory panel (UCS) supported aspirin for colorectal cancer risk reduction; multiple countries revised guidelines to recommend aspirin for high-risk individuals.
2025	Mechanism discovered: Cambridge researchers (Nature, 2025) found aspirin prevents metastasis by inhibiting thromboxane A2 (TXA2), releasing T cells from suppression.
2025	Policy changes: Aspirin for cancer prevention is restricted to young population (under 60) due to hemorrhagic adverse events in older population.

Table 1.

The evidence base, however, is neither uniform nor static. Trials in younger and middle-aged populations have generally supported a delayed but durable reduction in colorectal cancer risk, while a major trial in adults aged 70 and older found no reduction in cancer incidence and, unexpectedly, an increase in cancer-related death. More recent biomarker-driven trials have begun to identify specific molecular subgroups, such as colorectal cancers with PI3K-pathway alterations, in which aspirin's adjuvant benefit appears particularly strong. This paper reviews the mechanistic rationale for aspirin's anticancer activity, traces the clinical trial evidence across cancer prevention and treatment settings, and considers how these findings have shaped, and continue to reshape, clinical guidance.

2. Pharmacology and Proposed Mechanisms of Action

2.1. Cyclooxygenase-dependent pathways

Aspirin's best-characterized molecular action is irreversible acetylation of the active site serine residue of cyclooxygenase enzymes (COX-1 and COX-2), which catalyze the conversion of arachidonic acid into prostaglandin precursors. At low daily doses (roughly 75-100 mg), aspirin permanently inactivates platelet COX-1, suppressing thromboxane A₂ (TXA₂)-dependent platelet activation for the lifespan of the affected platelets, an effect central to its cardiovascular benefit and increasingly implicated in its antitumor activity as well, since platelet activation contributes to tumor-associated inflammation and to the survival of circulating tumor cells in the bloodstream ^[10].

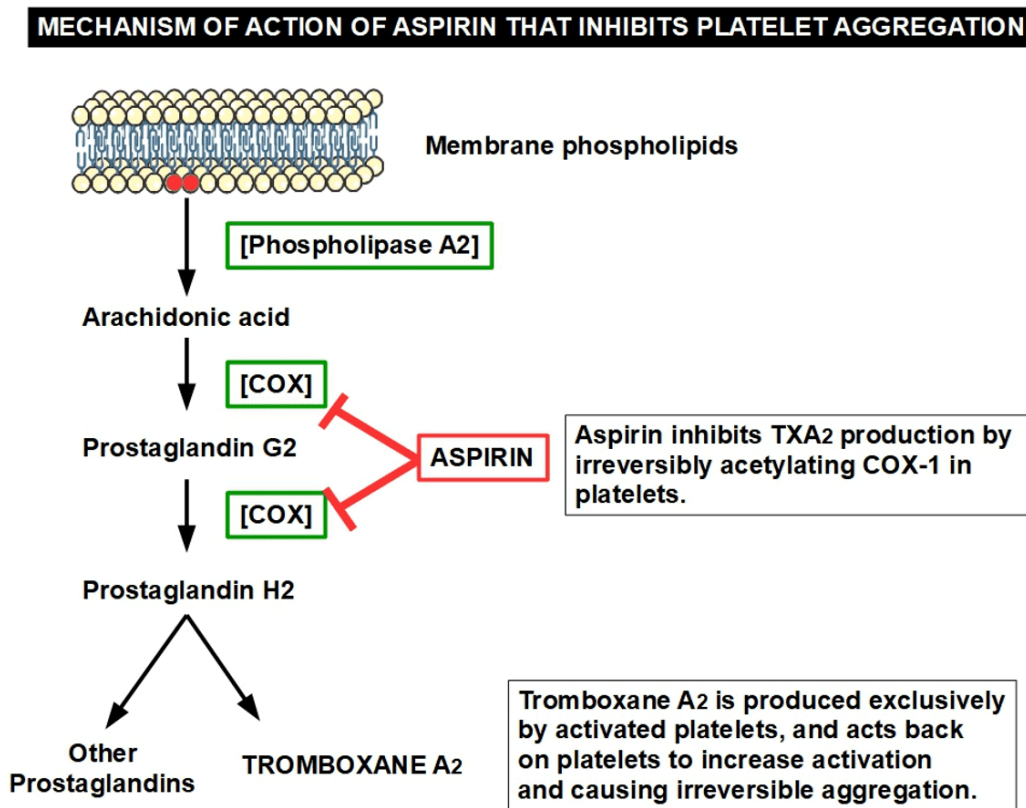


Figure 3. Aspirin inhibits platelet aggregation by blocking thromboxane A₂ synthesis through COX1 inhibition ^[11].

COX-2, in contrast, is typically expressed at low levels in normal tissue but is markedly up-regulated in many epithelial tumors, including colorectal, gastric, esophageal, and breast cancers. COX-2-derived prostaglandin E₂ (PGE₂) promotes tumor cell proliferation, resistance to apoptosis, angiogenesis, epithelial–mesenchymal transition, and suppression of antitumor immunity. By reducing PGE₂ synthesis, aspirin is thought to counteract several of these tumor-promoting processes, a rationale that also underlies the chemopreventive interest in more selective COX-2 inhibitors, although those agents carry their own cardiovascular liabilities.

2.2. COX-independent and platelet-mediated pathways

A substantial body of mechanistic work indicates that aspirin's anticancer activity extends beyond cyclooxygenase inhibition. Proposed COX-independent mechanisms include:

- activation of AMP-activated protein kinase (AMPK) ^[12];
- inhibition of nuclear factor kappa B (NF- κ B) signaling ^{[13][14]};
- inhibition of mTORC1 signaling ^[15];
- modulation of Wnt/ β -catenin signaling but the effect is context-dependent and best supported in colorectal cancer and some stem/progenitor cell systems ^{[16][17]}.
- acetylation of non-COX proteins ^{[18][19]} involved in DNA repair ^{[20][21]} and cell metabolism (The final effects on DNA repair and metabolism are not clear); aspirin interacts with metabolic enzymes, but the direction and clinical importance depend on the dose, the enzyme, and the drug combination ^[22];
- effects on intestinal microbial composition that may influence local inflammation and carcinogenesis in the colon.
- inhibition of the IL-6/JAK/STAT3 pathway in colon ^[23]
- aspirin has increased the efficacy of some chemotherapeutic agents, suggesting its utility as an adjunct therapy in cancer treatment. The mechanisms in these cases are largely unknown or context and drug-dependent ^[24].

In 1968 Gasic et al. ^[25] showed that decreasing the number of platelets decreased the number of experimental metastasis. Four years later, Gasic et al. showed for the first time that aspirin could achieve the same results ^[26] without reducing the number of platelets. Many authors confirmed that reducing the number of platelets or their activity could reduce the number of metastasis under experimental conditions ^{[27][28][29]}. However, this was not an entirely new concept. In 1968, Ryan et al. described that

warfarin markedly reduced spontaneous lung metastases in mice [\[30\]](#), and Clifton et al. found that inhibiting fibrinolysis in mice increased pulmonary metastasis while heparin diminished them [\[31\]](#). Can platelet anti-aggregation and anticoagulation be considered equivalents in metastatic reduction? The answer is no.

Platelet anti-aggregation and anticoagulation both can reduce metastasis-related processes, but they act on different parts of the thrombo-inflammatory cascade and should not be treated as interchangeable. Antiplatelet therapy mainly blocks platelet activation and aggregation, which matters because platelets coat circulating tumor cells and help them survive shear stress, evade immunity, and seed distant sites. Anticoagulation mainly suppresses coagulation cascade activity and fibrin formation, which can also support metastatic niche formation and tumor cell lodging in the vasculature. Both strategies can reduce metastatic spread in experimental systems, but the evidence suggests they do so through overlapping yet non-identical mechanisms. In other words, they are better viewed as adjacent anti-metastatic interventions rather than equivalent ones [\[32\]](#).

Platelet biology has emerged as a particularly active area of mechanistic research. Circulating tumor cells can recruit and activate platelets, which form protective aggregates that shield malignant cells from immune surveillance and shear stress while facilitating their adhesion to and invasion of distant tissue, a process central to hematogenous metastasis [\[33\]\[34\]\[35\]](#). Figure 4. By suppressing TXA2-dependent platelet activation, low-dose aspirin is hypothesized to impair this platelet-tumor cell cooperation, providing a mechanistic explanation for findings, discussed below, that aspirin use is associated with reduced risk of cancer presenting with distant metastasis. Systematic reviews of this evidence note that while the antimetastatic association is consistent across preclinical and clinical studies, the relative contribution of platelet inhibition, direct TXA2 signaling effects, and epithelial-mesenchymal transition modulation has not yet been fully disentangled.

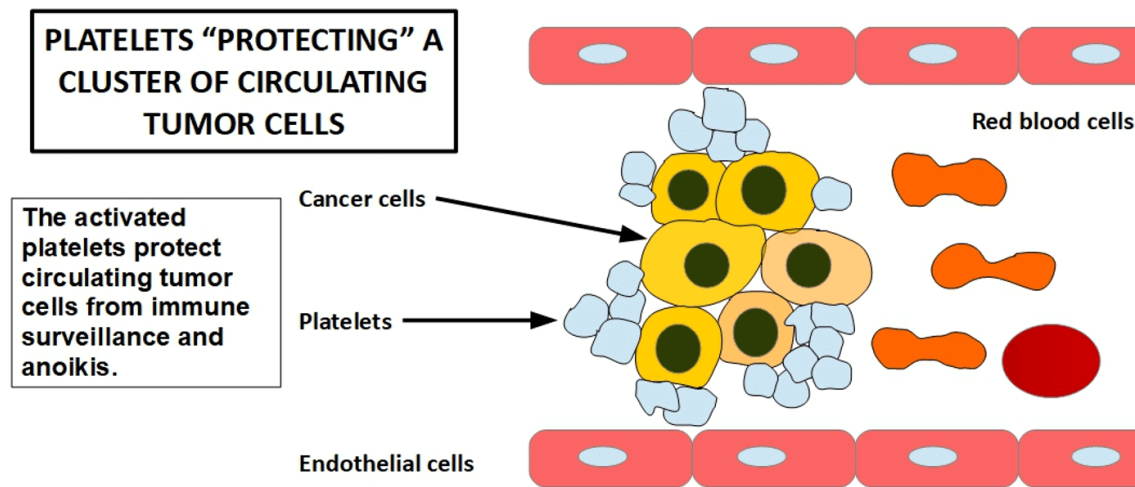


Figure 4. Activated platelets can protect circulating cancer cells from shear stress, immune attack and anoikis, thus facilitating their survival in circulation. This “facilitation” can increase metastatic potential.

2.3. *NF- κ B, cancer, and aspirin*

NF- κ B is a pro-inflammatory and pro-tumoral transcription factor that is constitutively over-expressed or over-active in many tumors [36]. This is particularly evident in advanced tumors.

In 1994, Kopp and Gosh [37] described for the first time the anti-inflammatory mechanism of salicylates and aspirin. They found that aspirin inhibited the activation of NF- κ B.

Thakkar et al. [38] treated different pancreatic cancer cells with a combination of aspirin, curcumin and sulphoraphane all at low concentrations and found a 70% decrease in cell viability and induced 51% of apoptosis. NF- κ B DNA binding was reduced by 45% and 75% according to different malignant cells tested. Aspirin's inhibitory effects on the NF- κ B pathway are summarized in table 2.

Aspirin inhibits NF- κ B through a mix of upstream blockade of inflammatory signaling, stabilization of I- κ B repression, and, at higher or context-dependent concentrations, direct interference with signaling enzymes and transcriptional outputs. In resting cells, NF- κ B is held in the cytosol by I- κ B proteins. Proinflammatory stimuli such as TNF- α and IL-1 normally activate an I- κ B kinase-dependent cascade that phosphorylates I- κ B, targets it for degradation, and releases NF- κ B to enter the nucleus and drive transcription of survival, adhesion, cytokine, and invasion genes. Aspirin interrupts this sequence, so NF- κ B remains functionally restrained and its target genes are not fully induced.

Step	Normal NF- κ B Activation	Aspirin's Inhibition
1. Stimulus	TNF α or IL-1 binds receptor	Same stimulus
2. I κ B phosphorylation	I κ B α undergoes phosphorylation	Aspirin BLOCKS phosphorylation of I κ B α and I κ B β [39]
3. I κ B degradation	Phosphorylated I κ B degraded by proteasome	Aspirin PREVENTS I κ B degradation [18]
4. NF- κ B release	I κ B degradation releases NF- κ B	NF- κ B remains bound to intact I κ B
5. Nuclear translocation	Free NF- κ B enters nucleus	NF- κ B retained in cytosol
6. Gene transcription	NF- κ B activates inflammatory genes	NF- κ B-dependent transcription inhibited
7. NF- κ B expression		Aspirin suppresses NF- κ B1 expression (p50 subunit) [40]

Table 2. Aspirin effects on the NF- κ B pathway

In summary, aspirin inhibits both I κ B α and I κ B β phosphorylation/degradation in a dose-dependent manner

2.4. Immunomodulation and the PI3K pathway

Additional proposed mechanisms include immunomodulatory effects that may enhance natural killer cell and T-cell-mediated tumor surveillance, alongside reduction of chronic low-grade inflammation that is itself a recognized driver of carcinogenesis. Of particular translational significance is the interaction between aspirin and the phosphoinositide 3-kinase (PI3K) signaling pathway. Mutations in PIK3CA, which encodes the catalytic subunit of PI3K, are among the most frequent genetic alterations in colorectal cancer and cause constitutive activation of the PI3K–AKT–mTOR axis, a pathway central to tumor growth, survival, and resistance to apoptosis. Retrospective analyses first reported in 2012 suggested that patients with PIK3CA-mutated colorectal tumors who used aspirin after diagnosis had

improved survival relative to non-users, a finding that motivated the prospective, biomarker-driven trials described in Section 4 ^[41]. Aspirin seems to have a dual mechanism of action:

1. inhibiting macrophage-driven inflammation
2. while simultaneously actively encouraging phagocytic capacity and anti-inflammatory signaling.

These effects are also context dependent differing between acute and chronic inflammatory conditions ^[42].

2.5. Cytosolic acidification

Aspirin can decrease intracellular pH. Aspirin lowers intracellular pH primarily through intracellular trapping of the weak acid under acidic extracellular conditions (such as found in tumors), combined with inhibition of pH-regulating ion transporters ^[43]. Aspirin (acetylsalicylic acid, $pK_a \approx 3.5$) diffuses across the membrane as the neutral protonated form. Inside the cell ($pH \sim 7.2$), it dissociates into $\text{salicylate}^- + \text{H}^+$. The charged salicylate^- cannot easily exit, accumulating intracellularly and releasing H^+ ions that lower pH.

Under acidic extracellular conditions, aspirin increases apical membrane permeability to acid, promoting H^+ back-diffusion from the extracellular space into cells ^[44]. However, this happens at very low levels of extracellular pH (under 4.5) such as seen in the gastric mucosa. Although tumors have a low extracellular pH (around 6.5–6.8) we do not know if this mechanism also works at this level of acidity.

Aspirin inhibits the Na^+ -dependent anion antiport that normally normalizes pH_i after acidification. This reduces bicarbonate import (a base), leaving the cell more acidic ^[45].

The effect is condition-dependent: intracellular pH lowering occurs significantly only when extracellular pH is acidic (e.g. gastric mucosa), where intracellular trapping of aspirin is observed. In neutral extracellular conditions, aspirin may not significantly alter intracellular pH.

2.6. Aspirin inhibits angiogenesis

Aspirin inhibits angiogenesis through multiple mechanisms, both COX-dependent and COX-independent, making it an important contributor to its anti-cancer effects.

Therapeutic aspirin concentration (0.5 mM) cause COX-independent striking reduction in endothelial tubule formation in 3D collagen angiogenesis assays. Salicylate has a similar effect. On the other hand, selective COX inhibitors lack this effect. High aspirin concentrations (beyond therapeutic level) cause

endothelial cell apoptosis ^[46]. Aspirin down-regulates VEGF-A, and VEGF-C expressions in a dose dependent manner ^{[47][48]}.

Heparanase has been found as an important mediator in angiogenesis and tumor progression ^{[49][50][51]}. Importantly, aspirin can target heparanase reducing angiogenesis and metastasis in the experimental setting ^[52].

2.7. Aspirin and the Wnt/ β -catenin pathway

Aspirin can inhibit canonical Wnt/ β -catenin signaling, in a context-dependent manner. In colorectal cancer cell lines, aspirin dose-dependently reduced TCF-driven reporter activity (TCF = T cell factor), lowered Wnt target gene expression, and increased β -catenin phosphorylation; the study linked this effect to PP2A (Protein Phosphatase 2A) inhibition. A later review summarized multiple experimental and clinical studies connecting aspirin with canonical Wnt signaling in colorectal cancer.

Aspirin has also been reported to promote oligodendroglial differentiation by inhibiting Wnt/ β -catenin signaling ^[53], again with increased β -catenin phosphorylation. In mesenchymal stem cells, aspirin was associated with downregulation of Wnt/ β -catenin signaling and reduced cyclin D1 expression ^[54].

One proposed mechanism is that aspirin inhibits PP2A activity, which then alters β -catenin phosphorylation and downstream transcriptional output. Another reported mechanism in a later study is suppression of prostaglandin signaling leading to reduced Wnt production ^{[55][56]}.

2.8. Aspirin and the mutated PI3K

Aspirin appears to be more beneficial in cancers with PI3K pathway mutations, especially PIK3CA-mutant colorectal cancer, than in wild-type tumors. The relationship is usually described as a biomarker effect: PI3K mutation may predict greater aspirin sensitivity or survival benefit ^[57].

In colorectal cancer, observational and translational studies reported improved survival in patients whose tumors carried PIK3CA mutations and who used aspirin after diagnosis. A later review summarized that the mechanistic link is still not fully settled, but the effect may involve both COX-dependent and COX-independent pathways.

In breast cancer, preclinical work suggested aspirin suppresses growth in **PI3K-mutant** cells, supporting the idea that altered PI3K signaling can confer aspirin responsiveness. More recent CRC work also

suggests benefit in tumors with broader PI3K pathway alterations, not only classic PIK3CA hotspot mutations [58].

One proposed mechanism is that aspirin reduces PI3K pathway output indirectly through COX-2/prostaglandin signaling, which can feed into PI3K/AKT/mTOR activity. However, the exact mechanism is not fully resolved, and the literature still treats this as an active research area.

3. Clinical Evidence for Cancer Prevention

3.1. Epidemiological and observational data

A large and fairly consistent body of observational evidence, comprising case-control studies, cohort studies, and pooled meta-analyses encompassing well over a hundred individual studies, associates regular aspirin use with reduced incidence of several cancer types, most consistently colorectal, gastric, and esophageal cancer, with somewhat less consistent but still favorable associations reported for breast, ovarian, endometrial, prostate, and pancreatic cancer [59][60][61][62]. A comprehensive meta-analysis of observational studies found reduced risk across this broad range of tumor types, with a stronger protective association among long-term users (five years or more) and among North American cohorts. For pancreatic cancer specifically, meta-analyses of observational data have reported roughly a 20 to 25 percent reduction in incidence among aspirin users [63][64], though without a corresponding reduction in pancreatic cancer mortality, underscoring that incidence and mortality benefits do not always track together and that observational associations remain susceptible to confounding and reverse causation. Reduced risk of pancreatic cancer was seen in most categories of aspirin use, for both low-dose aspirin and regular-dose aspirin. Interestingly, termination of aspirin use within 2 years of interview was associated with increased risk of pancreatic cancer [65].

3.2. Randomized evidence from cardiovascular prevention trials

The most influential randomized data on aspirin and cancer prevention emerged indirectly, from long-term follow-up of trials originally designed to evaluate cardiovascular outcomes. Analyses of British cardiovascular trials that randomized participants to aspirin doses ranging from 300 to 1200 mg daily found that aspirin produced a significant, duration-dependent reduction in colorectal cancer incidence, with the largest effect (a roughly 75 percent relative reduction) observed ten to fourteen years after randomization among those who had received scheduled treatment for five years or more [66][67][68]. A

subsequent twenty-year follow-up of five randomized trials confirmed that aspirin reduced both colorectal cancer incidence and mortality, with the protective effect emerging only after a latency of approximately ten years, a delay that mirrors the multistep, decade-spanning process of colorectal carcinogenesis from adenoma to invasive cancer ^[69]. Complementary analyses of the same trial cohorts reported that daily aspirin reduced deaths from several cancers in aggregate, including colorectal and pancreatic cancer, with most of the benefit again concentrated in those who had taken aspirin for five years or longer.

A particularly notable analysis examined the effect of aspirin on the metastatic pattern of incident cancers diagnosed during these trials and found that participants randomized to aspirin were less likely to present with cancer that had already spread to distant sites at diagnosis, an effect consistent with the platelet-mediated antimetastatic mechanisms described in Section 2.2. ^[70] Not all randomized evidence has been concordant, however: the Women's Health Study, which tested alternate-day low-dose aspirin in women over ten years, found no reduction in colorectal cancer during the trial period itself, though a protective association emerged in extended follow-up during the second decade after randomization, again illustrating the long latency characteristic of aspirin's chemopreventive effect ^[71].

A 2019 updated meta-analysis combining randomized and observational data estimated that five years of regular aspirin use is associated with approximately a 20 percent reduction in colorectal cancer risk, rising to approximately 30 percent with ten years of use, with the magnitude of benefit appearing to plateau at longer durations and to vary by dose, with low-dose aspirin (75-100 mg) producing a more modest reduction than higher doses, although estimates at higher doses are based on fewer studies and should be interpreted cautiously ^{[72][73]}.

3.3. Dedicated chemoprevention trials: CAPP2 and Lynch syndrome

The most direct prospective evidence for aspirin's chemopreventive effect comes from the CAPP2 trial, a double-blind, placebo-controlled study conducted across forty-two international centers in carriers of Lynch syndrome, an inherited condition caused by germline mutations in DNA mismatch repair genes that confers substantially elevated lifetime risk of colorectal and other cancers. CAPP2 randomized trial enrolled 861 Lynch syndrome carriers, with a mean age in the early forties, receiving 600 mg aspirin daily or placebo for a planned duration of approximately two years ^{[74][75]}. Participants were randomly assigned to aspirin or placebo, resistant starch or placebo, for up to about 4 years, with extended follow-

up after treatment ended. The aspirin report used intention-to-treat and per-protocol analyses and showed that benefit was more evident among those who completed at least 2 years of aspirin.

The trial's initial 2008 report, based on a relatively short mean follow-up of around 29 months, found no significant reduction in colorectal neoplasia. However, as follow-up extended, a markedly different picture emerged. A 2011 analysis with a mean follow-up of nearly five years found a significant reduction in colorectal cancer incidence among those who completed at least two years of aspirin treatment. A subsequent ten-year follow-up, with registry-based data extending to twenty years for many participants, confirmed a substantially lower incidence of colorectal cancer among those originally randomized to aspirin, along with reduced incidence of other Lynch syndrome-associated cancers including endometrial, ovarian, and gastric cancer. Investigators calculated that only twenty-four Lynch syndrome carriers would need to be treated with aspirin to prevent one colorectal cancer over this extended horizon. Notably, this protective effect persisted for many years after the intervention itself had ended, a so-called legacy effect that has informed subsequent thinking about optimal timing of aspirin chemoprevention. On the basis of this evidence, aspirin is now recommended as standard chemoprevention in many clinical guidelines for individuals with confirmed Lynch syndrome.

CAPP2 is important because it provided some of the strongest randomized evidence that aspirin can prevent colorectal cancer in a genetically high-risk population. It also helped establish the idea that aspirin's protective effect may have a latency of years, which is relevant to chemoprevention more broadly [76].

3.4. Evidence in other cancer types

Beyond colorectal cancer, the strength of evidence varies considerably by tumor type. Observational cohorts and pooled analyses suggest reduced biochemical recurrence and disease-specific mortality among prostate cancer patients using aspirin after definitive treatment, with the largest relative benefit observed in those at the highest baseline risk of recurrence. Breast cancer evidence is similarly drawn primarily from observational cohorts, including large prospective studies of nurses diagnosed with early-stage disease, which have reported improved survival among aspirin users, though randomized confirmation in unselected breast cancer populations remains limited. Gastric and esophageal cancers, particularly squamous cell and adenocarcinoma subtypes, show some of the most consistent risk reductions in observational meta-analyses, plausibly reflecting the role of chronic mucosal inflammation in their pathogenesis.

Table 3 summarizes the possible cancer risk reduction in other tumors beyond colorectal cancer.

Tumor type	Evidence summary	Reference
Gastric cancer	Observational/meta-analytic evidence suggests reduced risk.	[66]
Esophageal cancer	Reduced risk reported, especially for squamous-cell and adenocarcinoma subtypes.	[66]
Hepatobiliary cancers	Some evidence of reduced risk in meta-analysis.	[66]
Pancreatic cancer	Some evidence of reduced risk in meta-analysis.	[66]
Breast cancer	Several cohort/meta-analytic studies suggest reduced risk.	[77]
Prostate cancer	Several cohort/meta-analytic studies suggest reduced risk.	[71]
Lung cancer	Some cohort/meta-analytic evidence suggests reduced risk. However, evidence is poor and contradictory.	Modest risk reduction [78] [79] . Increased risk [71] . Reduction of risk in women [80]
Ovarian cancer	Observational evidence and cohort studies, suggest a possible reduction in risk.	[81] [82] [83] [84] [85] [86] [87] [88]
Head and neck cancer	Mixed but some meta-analytic evidence suggests reduced risk.	[66]
Brain tumors / meningioma	Long-term cohort data suggest lower risk.	[89]
Melanoma	Long-term cohort data suggest lower risk.	[83] [90] [91] [92]
Thyroid cancer	Long-term cohort data suggest lower risk. The findings are controversial.	Risk reduction [83] [93] No risk reduction [94]
Non-Hodgkin and Hodgkin lymphoma	Long-term cohort data suggest lower risk.	[83] [95] [96]

Tumor type	Evidence summary	Reference
Leukemia	Long-term cohort data suggest lower risk. However, findings are controversial.	[83][92][98]

Table 3.

The meta-analysis of 88 cohort studies by Wang et al ^[71] showed that:

“regular aspirin use reduced the risk of colorectal cancer (CRC) (RR=0.85, 95%CI: 0.78-0.92), gastric cancer (RR=0.67, 95%CI: 0.52-0.87), breast cancer (RR=0.93, 95%CI: 0.87-0.99) and prostate cancer (RR=0.92, 95%CI: 0.86-0.98), but showed no association with lung cancer risk. Additionally, meta-analyses of RCTs showed that aspirin use had a protective effect on CRC risk (OR=0.74, 95%CI: 0.56-0.97). When combining evidence from meta-analyses of cohorts and RCTs, consistent evidence was found for the protective effect of aspirin use on CRC risk. Subgroup analysis showed that high frequency aspirin use was associated with increased lung cancer risk (RR=1.05, 95%CI: 1.01-1.09). Dose-response analysis revealed that high-dose aspirin use may increase prostate cancer risk”.

Table 3 suggests that there is strong supportive evidence for low-dose chronic aspirin intake as a moderate risk reduction (approximately 10%) for ovarian cancer even in population at high risk.

4. Aspirin as Adjuvant Treatment After Cancer Diagnosis

4.1. Observational evidence

A separate and clinically important question is whether aspirin initiated after a cancer diagnosis improves outcomes, independent of any preventive effect on initial cancer development. Observational cohort data, drawn from large prospective studies following thousands of cancer survivors, have generally suggested improved disease-free and overall survival among post-diagnosis aspirin users across colorectal, breast, and prostate cancer, with some of the most striking associations reported in colorectal cancer patients whose tumors carry PIK3CA mutations. These observational findings, while subject to the same confounding concerns that affect prevention studies, motivated a series of prospective randomized trials.

4.2. The ALASCCA trial: a biomarker-driven success

The most significant recent advance in this area is the ALASCCA trial ^{[99][100]}, a randomized, double-blind, placebo-controlled study conducted across thirty-three hospitals in Sweden, Denmark, Finland, and Norway, with results published in the New England Journal of Medicine in September 2025. The trial screened 3,508 patients with stage I–III rectal cancer or stage II–III colon cancer for somatic alterations in the PI3K signaling pathway; 1,103 patients (37 percent) had a qualifying alteration. Patients with PIK3CA hotspot mutations in exon 9 or 20 were assigned to "Group A," while those with other moderate- or high-impact alterations in PIK3CA, PIK3R1, or PTEN were assigned to "Group B." A total of 626 patients were randomized within three months of curative surgery to receive either 160 mg aspirin daily or matched placebo for three years.

The trial met its primary endpoint. In Group A, the three-year cumulative incidence of recurrence was 7.7 percent in the aspirin arm versus 14.1 percent in the placebo arm (hazard ratio 0.49, 95% confidence interval 0.24–0.98), corresponding to a 51 percent relative reduction in recurrence risk; three-year disease-free survival improved from 81.4 percent to 88.5 percent. In Group B, the effect was, if anything, more pronounced: recurrence fell from 16.8 percent to 7.7 percent (hazard ratio 0.42, 95% confidence interval 0.21–0.83), a 58 percent relative reduction, with disease-free survival improving from 78.7 percent to 89.1 percent. The benefit was observed regardless of whether patients had received neoadjuvant therapy, adjuvant chemotherapy, or both. On the strength of these results, the National Comprehensive Cancer Network updated its colon cancer guidelines (version 4.2025) to recommend PIK3CA pathway testing for patients with stage II–III disease, with low-dose aspirin (100–162 mg daily for three years) now a recommended component of adjuvant management for those found to carry a qualifying mutation.

ALASCCA is notable not only for its clinical findings but for its design: it represents one of the first biomarker-driven randomized trials of adjuvant aspirin in oncology, explicitly testing the hypothesis, derived from earlier retrospective genomic analyses, that PI3K-pathway status predicts response to aspirin. This stands in contrast to an earlier trial, ASCOLT ^[101], which tested adjuvant aspirin in an unselected (non-biomarker-defined) colorectal cancer population and, when published in early 2025, did not meet its primary endpoint. Taken together, the contrast between ALASCCA's positive, biomarker-selected result and ASCOLT's negative, unselected result suggests that aspirin's adjuvant benefit in colorectal cancer may be concentrated in molecularly defined subgroups rather than uniformly distributed across all patients, reinforcing a broader shift toward precision-oncology approaches to chemoprevention and adjuvant therapy.

4.3. The Add-Aspirin program and ongoing trials

Beyond colorectal cancer, the multi-tumor Add-Aspirin trial program ^[102] has evaluated adjuvant aspirin across several early-stage solid tumors, including breast, gastroesophageal, and prostate cancer, following curative-intent treatment. As with ASCOLT, results across these broader, less molecularly selected populations have been more equivocal than the targeted ALASCCA findings, and mature outcome data for several tumor cohorts within this program remain pending or have not shown the magnitude of benefit seen in PI3K-altered colorectal cancer. The overall trajectory of adjuvant trial evidence, then, points toward a future in which aspirin's role in cancer treatment is likely to be defined by molecular patient selection rather than broad, unselected application.

5. The Age Paradox: Reassessment in Older Adults

A striking and clinically consequential departure from the broader pattern of aspirin's anticancer benefit emerged from the ASPIrin in Reducing Events in the Elderly (ASPREE) trial ^{[103][104][105]}, a randomized, double-blind, placebo-controlled study of daily low-dose aspirin (100 mg) versus placebo in 19,114 community-dwelling Australian and American adults aged 70 or older (65 or older for U.S. racial and ethnic minority participants) who were free of cardiovascular disease, dementia, or significant physical disability at enrollment. Initial results, published in 2018, showed that aspirin did not extend disability-free survival and was instead associated with higher all-cause mortality than placebo, a finding attributed primarily to excess cancer-related death.

A detailed follow-up analysis of cancer outcomes within the trial found that aspirin had no effect on overall cancer incidence but was associated with an increased risk of cancer presenting at an advanced stage and with higher cancer-related mortality, suggesting that in older adults aspirin may influence later stages of tumor progression rather than initial carcinogenesis, a pattern essentially opposite to the delayed protective effect seen in younger cohorts. Long-term post-trial follow-up, published in JAMA Oncology in early 2026 and encompassing a median of 8.6 years of observation, confirmed that low-dose aspirin was not associated with reduced cancer incidence in this older population, while cancer mortality risk remained significantly elevated (hazard ratio 1.15, 95% confidence interval 1.03-1.29) among those originally randomized to aspirin. Reassuringly, this elevated risk did not appear to persist as a lasting "legacy" effect once participants stopped taking trial medication; among participants who completed the

trial without developing cancer, cancer mortality risk in the subsequent observation period was no longer significantly different between groups ^[106].

Researchers involved in ASPREE have proposed that this divergence from younger cohorts may reflect age-related immune senescence and chronic low-grade inflammation ("inflammaging") that could blunt or even reverse aspirin's antitumor immunomodulatory effects in older adults, though the precise biological explanation remains an active area of investigation. The clinical implication is significant: aspirin's apparent oncological benefit cannot be assumed to generalize uniformly across age groups, and initiating aspirin specifically for cancer prevention in healthy adults aged 70 and older is not supported by current evidence and may be actively harmful.

6. Risks and Harms

Any assessment of aspirin's role in cancer prevention or treatment must be weighed against its well-documented bleeding risks. Systematic reviews conducted for the U.S. Preventive Services Task Force found that very-low-dose aspirin (100 mg daily or less) used for primary prevention increases the risk of major gastrointestinal bleeding by approximately 58 percent and the risk of hemorrhagic stroke by approximately 27 percent relative to placebo. Within the ASPREE cohort specifically, aspirin was associated with a particularly pronounced increase in upper gastrointestinal bleeding (hazard ratio 1.87) and a meaningful increase in intracranial bleeding (hazard ratio 1.50), although, reassuringly, no significant increase in fatal gastrointestinal bleeding was observed in this older population, consistent with broader meta-analyses suggesting that while aspirin increases the frequency of bleeding events, it does not appear to substantially increase fatal bleeding risk in primary prevention settings. Age, male sex, smoking, hypertension, elevated body mass index, and diabetes have all been identified as independent risk factors that compound aspirin's intrinsic bleeding risk, meaning that the harm side of the risk–benefit equation is itself highly individual-specific.

This bleeding risk is mechanistically linked to the same COX-1 inhibition that underlies aspirin's antiplatelet and putative anticancer effects, meaning the benefits and harms of aspirin cannot be fully separated pharmacologically; any strategy to expand aspirin's oncological use must therefore proceed alongside careful patient selection and, where appropriate, gastroprotective co-therapy is implemented ^{[107][108]}.

7. Evolution of Clinical Guidance

The shifting balance of evidence is reflected directly in the evolution of U.S. Preventive Services Task Force (USPSTF) recommendations. In 2016, the USPSTF recommended initiating low-dose aspirin for the primary prevention of both cardiovascular disease and colorectal cancer in adults aged 50 to 59 with at least a 10 percent ten-year cardiovascular risk, no elevated bleeding risk, a life expectancy of at least ten years, and willingness to continue aspirin for at least a decade, while recommending individualized decision-making for those aged 60 to 69 ^[109].

By 2022, following the publication of several large primary-prevention trials, including ASPREE in elderly adults, ARRIVE in adults at moderate cardiovascular risk, and ASCEND in adults with diabetes, all of which found that bleeding harms offset or exceeded modest cardiovascular benefits in contemporary, well-treated populations ^[110], the USPSTF substantially narrowed its guidance. Colorectal cancer prevention was removed entirely as an indication for aspirin, the Task Force concluding that the evidence was insufficient to support aspirin's use for this purpose, even as the agency continued to recommend individualized cardiovascular risk-based decision-making in select younger adults and explicitly advised against initiating aspirin in adults 60 and older due to increasing bleeding risk with age ^[111]. This represents a notable reversal of the cancer-prevention rationale that had partly motivated the 2016 guidance, and it underscores how trial evidence in older populations, where bleeding risk is highest and the protective latency of aspirin may not have time to manifest, can outweigh the cumulative evidence from younger cohorts when general population-wide recommendations are formulated.

Clinical practice has, in parallel, moved toward more targeted recommendations: aspirin chemoprevention is recommended in established Lynch syndrome management guidelines on the strength of CAPP2, and, following ALASCCA, the National Comprehensive Cancer Network now recommends PIK3CA pathway testing and adjuvant aspirin specifically for molecularly defined subgroups of resected colorectal cancer ^[112].

8. Limitations of the Current Evidence Base and Future Directions

Several limitations temper confident interpretation of the aspirin-cancer literature. Much of the supportive evidence for cancers beyond colorectal cancer remains observational, and such studies are vulnerable to confounding by indication, healthy-user bias, and reverse causation, since individuals who take aspirin regularly may differ systematically from non-users in ways that independently affect cancer

risk. Even within randomized trials, cancer outcomes were frequently secondary or exploratory endpoints rather than the primary purpose of the study, limiting statistical power and standardization of cancer ascertainment. The long latency of aspirin's apparent chemopreventive effect, often a decade or more, makes trials difficult and expensive to conduct and complicates interpretation of shorter-duration studies that may underestimate true benefit. For example Burn et al. [\[113\]](#) found no aspirin preventive effects on the incidence of colorectal adenoma or carcinoma among carriers of the Lynch syndrome after four years of follow up. Optimal dose and duration remain unresolved, with some evidence suggesting a dose-response relationship favoring higher doses while higher doses also carry greater bleeding risk, and questions remain regarding whether enteric coating, dosing frequency, or co-administration with gastroprotective agents might improve the benefit-to-harm ratio.

The emergence of biomarker-driven trials such as ALASCCA represents a promising direction, suggesting that future research and clinical application may increasingly focus on identifying the specific molecular, demographic, and risk-factor profiles in which aspirin's benefit clearly outweighs its harm, rather than pursuing broad, unselected population-wide chemoprevention. Ongoing and planned trials are expected to further test aspirin in additional molecularly defined subgroups and to refine understanding of the mechanistic basis for the divergent age-related effects observed in ASPREE [\[114\]\[115\]\[116\]\[117\]](#).

9. What we do not know

There are many unknowns in the aspirin-cancer relationship. The following issues are incompletely known or understood:

- mechanistic relationship between mutated PI3KCA and aspirin effects;
- mechanistic relationship between the Wnt/ β -catenin signaling and aspirin;
- why aspirin can increase cancer risk in older population (evidence from ASPREE and follow-up analyses suggests low-dose aspirin may be associated with higher cancer mortality and more advanced cancer diagnoses, rather than protection. The NCI summarized this as low-dose aspirin potentially increasing the risk of being diagnosed with advanced cancer and of dying from cancer in older people);
- why aspirin can moderately decrease ovarian cancer risk even in populations with increased risk.

10. Conclusion

The relationship between aspirin and cancer is biologically plausible, mechanistically multifaceted, and supported by a substantial body of observational and randomized evidence, particularly for colorectal cancer, where decades of trial follow-up and the landmark CAPP2 study in Lynch syndrome provide some of the most convincing chemoprevention data available for any repurposed drug. The 2025 ALASCCA trial extends this evidence into the adjuvant treatment setting, demonstrating that aspirin can meaningfully reduce recurrence in a genetically defined subgroup of resected colorectal cancer patients. At the same time, the evidence base is far from uniform: aspirin's benefit appears concentrated in younger and middle-aged populations and in molecularly selected patients, while the ASPREE trial and its long-term follow-up indicate that initiating aspirin in healthy older adults confers no cancer-prevention benefit and may increase cancer-related mortality. Combined with a well-established and dose-related risk of gastrointestinal and intracranial bleeding, this evolving picture has driven a marked contraction in general population-level guidance, exemplified by the USPSTF's 2022 removal of colorectal cancer prevention as an indication for aspirin. The most defensible clinical position emerging from this evidence is one of individualized, increasingly biomarker-informed decision-making, in which aspirin is neither dismissed as ineffective nor adopted as a universal anticancer agent, but rather deployed selectively in the populations and molecular contexts where its benefits have been most rigorously demonstrated to exceed its risks.

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