RESEARCH PAPER

Aspirin's Dual Role in Cancer: A Systematic Review of the Current Evidence

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ABSTRACT

Background:

Aspirin is widely studied for its anticancer effects, such as immune response regulation, reduced platelet activation, and cyclooxygenase (COX) inhibition. However, concerns remain about its potential to promote cancer in certain scenarios and the risk of serious bleeding events.

Aim and Objective:

This systematic review aims to analyze long-term aspirin effects on cancer incidence, progression, mortality, and associated hazards, including bleeding and potential tumor growth in the elderly.

Materials and Methods:

The association between aspirin usage, adverse events, and cancer outcomes was established by analyzing data from significant randomized controlled trials, cohort studies, and mechanistic investigations, such as the Lancet, CAPP2, ASPREE, and Women's Health Study trials.

Result: Long-term aspirin usage had a moderate protective effect against ovarian cancer and considerably decreased the incidence and death of colorectal cancer. According to mechanistic research, aspirin may stop metastases by boosting T-cell-mediated immunity and blocking platelet-derived thromboxane A_2 (TXA_2). Findings in older groups, however, is variable; some research suggested no mortality benefit and even a potential rise in late-stage cancer deaths. Significant bleeding in the brain and gastrointestinal tract continued to be significant side effects, especially in older patients.

Conclusion Aspirin has encouraging long-term chemo preventive benefits, particularly in ovarian and colorectal malignancies. However, the substantial bleeding hazards and unknown consequences in elderly persons outweigh its advantages. Before routinely prescribing aspirin usage for cancer prevention, a thorough risk-benefit analysis and customized dose regimens are necessary.

Keywords: Aspirin, cancer prevention, colorectal cancer, ovarian cancer, platelet inhibition, cancer promotion, chemoprevention.

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INTRODUCTION

A group of disorders known as cancer is defined by the body's aberrant cells growing and spreading out of control. Cancer is still one of the major causes of death globally, despite tremendous progress in both research and therapy. A common anti-inflammatory and antiplatelet drug, aspirin has drawn a lot of interest due to its dual function in preventing cancer and, in some situations, promoting it. Aspirin's actions on cyclooxygenase (COX) enzymes and regulation of

inflammatory pathways may reduce the incidence of several malignancies, including colorectal cancer, according to an increasing number of studies. The incidence and death of colorectal cancer are considerably decreased by long-term aspirin usage[1].Concerning the prevention of cancer, the mechanisms behind aspirin's anticancer effects highlight how it inhibits COX enzymes and affects platelet function and immunological response. Aspirin prevents cancer through a number of interrelated mechanisms, including both COX-dependent and COX-independent pathways, to prevent cancer. It mainly causes irreversible inhibition, which lowers the synthesis of prostaglandin E2 (PGE2) production. In the tumour microenvironment PGE2 is an essential modulator of inflammation, cell proliferation, and immunological suppression in the tumour microenvironment. This decrease in PGE2 promotes apoptosis and inhibits the development of tumour cells. Furthermore, by inhibiting thromboxane A2, aspirin's antiplatelet effect interferes with platelet-tumour cell interactions that are essential for metastasis, such as the epithelial-mesenchymal transition and the immune system's ability to recognize circulating tumour cells. Additionally, aspirin alters immunological responses by boosting natural killer cells and T-cells, reinforcing immune surveillance against newly developing malignancies. Furthermore, it interferes with the Wnt/β-catenin signalling system, notably significant in colorectal cancer, lowering oncogenic gene transcription and cancer stem cell renewal.[3]

Lynch syndrome, a genetic disorder linked to an increased risk of colorectal cancer, had comparable protective effects.[2]Aspirin significantly lowers the long-term risk of colorectal cancer in people with a hereditary susceptibility, according to the CAPP2 randomized controlled study. Aspirin may specifically trigger apoptosis in MMR-deficient cells, as those in Lynch syndrome, by aggravating DNA damage and improving immunological identification of neo antigens generated by microsatellite instability (MSI). Additionally, it triggers AMP-activated protein kinase (AMPK), which suppresses mTOR signalling and ultimately causes metabolically stressed tumour cells to undergo autophagy and apoptosis. These strategies work together to target genetically unstable cells and alter the tumour-promoting milieu, which may explain the long-term decrease in cancer incidence shown in the CAPP2 experiment. According to studies, frequent long-term use of low dose aspirin was associated with a decreased incidence of epithelial ovarian cancer, demonstrating that aspirins benefits go beyond colorectal cancer.[4] Similarly, older adults who regularly used aspirin had 18% lower risk of colorectal cancer, suggesting that body mass index and lifestyle choices may influence the protective effects.[5] Further studies emphasise initiatives to reduce aspirin's possible adverse effects, such as gastrointestinal bleeding, while enhancing its effectiveness in preventing cancer.[6] But there are also worries about aspirin's possible contribution to the development of cancer. According to recent research, aspirin has been shown to prevent cancer in middle-aged populations, but its usage in older adults especially those over 70 may be linked to an increased rate of mortality from cancer.

The ASPREE experiment brought attention to this paradoxical result, which might be caused by a number of age-related variables. First, older persons may not survive long enough to benefit from aspirin's cancer-preventive effects, which usually need sustained use often more than five years instead face acute dangers like gastrointestinal bleeding. Furthermore, deterioration in immune function, is linked to ageing and may make it more difficult for the body to eradicate early cancer cells. This might change the immunomodulatory effects of aspirin and promote the growth of tumours. Additionally, older people are more likely to have preclinical, undiscovered malignancies that might react erratically to aspirin, perhaps hastening the course of the illness. Adverse effects may also be caused by variations in tumour biology, slower drug metabolism, and interactions with other drugs that older adults often take.All of these results highlight the necessity of age-specific recommendations when using aspirin to prevent cancer, daily low-dose aspirin was linked to an unanticipated rise in cancer-related fatalities, according to research evaluating the impact of aspirin on all-cause mortality in healthy older adults.[7]This research highlights the need for a cautious, customized approach by posing issues regarding the situations in which aspirin may be more harmful than beneficial. When taken as a whole, these studies highlight the complicated but encouraging link between aspirin consumption and cancer.

When considering aspirin for long-term use in cancer prevention strategies, a balanced and individualised approach is required because of the possibility of negative consequences, including the possibility of increased cancer-related mortality in certain populations, even though evidence suggests significant benefits, especially in lowering the chance of colon cancer. This systematic review aims to evaluate and

summarise the available data regarding aspirin's dual function in promoting and preventing cancer.

MATERIALS AND METHOD:

These procedures were taken in order to perform the literature review in a systematic manner.

Creating a plan for the literature search, defining the research topic, finding and obtaining pertinent articles, extracting data, and analysing and assessing the evidence gleaned from the literature.

Thus, the research questions

1. Does long-term aspirin use reduce the incidence of cancer, especially colorectal cancer?

2. what effects does starting aspirin use after the age of 70 have aon older people?

PICO

- Population: Older patients those with v disease, and those with cancer were in
- Intervention: 75-300mg of aspirin ea for more than five years.
- Comparison: Placebo
- Outcome: Decrease in cancer amon term everyday users. It may potential negative consequences.

INCLUSION CRITERIA:

- Studies involving randomised cor trials, cohort studies and meta-analyse
- Studies assessing aspirin use in dia cancer patients and healthy individuals
- Studies reporting the incidence, me and mortality outcome.
- Studies involve articles restricted to E

EXCLUSION CRITERIA:

- Studies that don't isolate aspirin as the study of interest.
- Studies that are not solely in the English language.

INFORMATION SOURCES:

- PubMed
- Elsevier Scopus
- Science direct

SEARCH STRATEGY

A search was conducted on the above-mentioned databases. The keywords used were a combination of keywords and MeSH terms, including "cancer," "aspirin," "promotion," "prevention," "aged people," "long-term effect," "colorectal cancer," and "Lynch syndrome." MeSH terms were used along with Boolean operators.

STUDY SELECTION

- An initial screening of abstracts and titles was carried out utilizing predefined inclusion and exclusion criteria.
- Full text review of the articles selected.
- Data extraction from standard database.

Figure 1: PRISMA 2020 flow diagram for newly conducted systematic reviews that solely involved database and registration searches

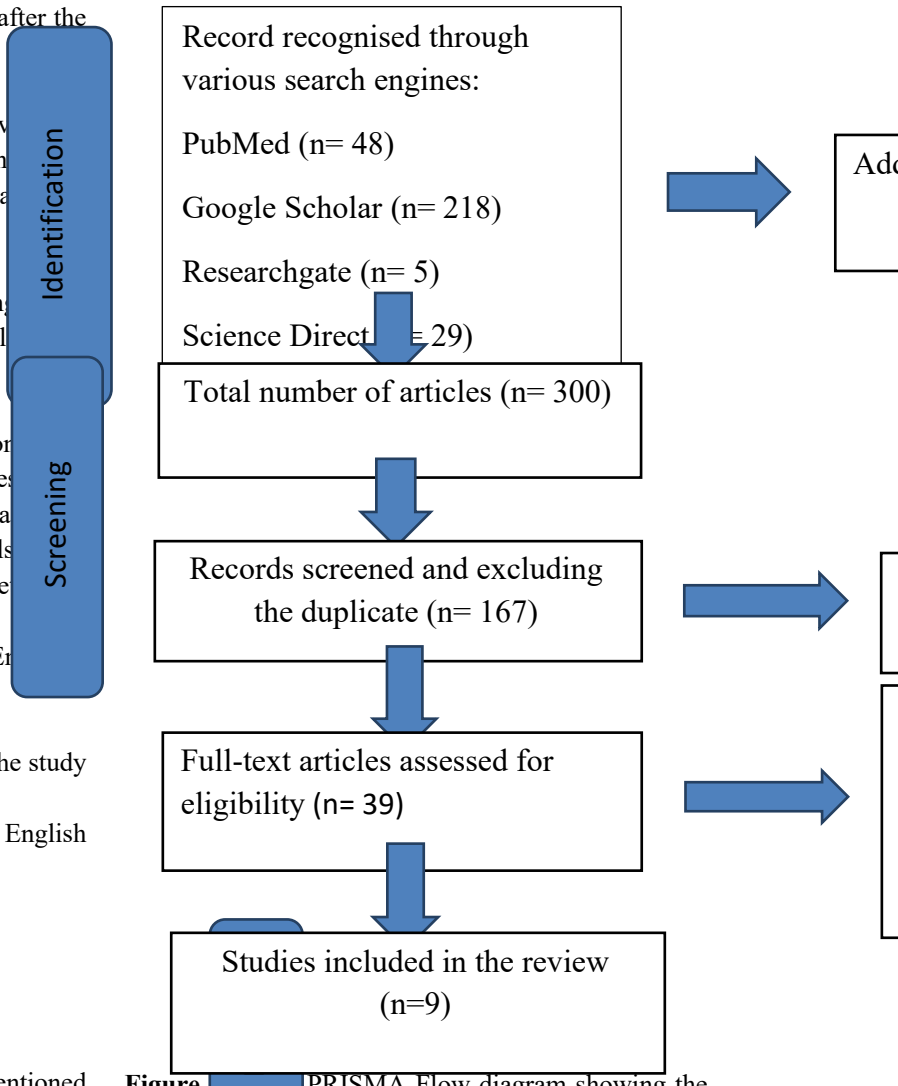

Figure PRISMA Flow diagram showing the number es identified, screened, assessed for eligibility, excluded and included in the systematic review[24]

Table 1: Characteristics of Interventions in the Study

S.no	author	year	Sample Size	Patients Characteristics	duration	Patient allocation
1.	Charlotte Skriver et al.	2023	1909531	Cancer free individuals aged 40 – 70 years.	20 years	Group 1 – low dose aspirin (75 – 150mg) Group 2 – high dose aspirin (500mg)
2.	Chris R. Cardwell et al.,	2014	4794	Primary colorectal cancer patients.	10 years	Group 1 -Colon cancer: Group 1a – No. of prescription, low dose. Group 1b – no. of days, low dose. Group 2 – rectal cancer: Group 2a – No. of prescription, low dose Group 2b – No. of days, low dose.
3.	Joseph J.Y. Sung et al.	2019	13528	Colorectal cancer patients	10 years	Group 1 - patients using aspirin before CRC diagnosis and continued or discontinued aspirin after surgery Group 2 - patients, who never used aspirin prior to CRC diagnosis, continued or stopped taking aspirin after surgery.
4.	Kenji Yokoyama et al.	2018	14688	Patients aged 60 – 85 years with hypertension, dyslipidaemia, and diabetes mellitus.	5 years	Group 1 – patients who take enteric coated aspirin. Group 2 – patients who do take aspirin.
5.	Guo et al.,	2021	94540	Patients aged 70 years or more.	Pooled analysis	Group 1 – 65249 white women (97.1%) Group 2 – 24915 white men (96%)
6	Rothwell, P. M., et al.	2010	5085	Men aged 45 – 69 years who are at high risk of vascular events.	20 years	Group 1 - 2540 patients under aspirin. Group 2 –

						2545 placebo individuals.
7.	Burn, J., et al.	2011	937	People with lynch syndrome.	10 years	Group 1 – 427 people under Aspirin (600mg) Group 2 – 434 people Aspirin placebo. Group 3 – 76 people under starch resistant
8.	L. Baandrup et al.,	2014	62809	Patient aged 30 – 84years with first diagnosis of ovarian cancer.	5 years	Group 1 – 4103 females with ovarian cancer. Group 2 – 58706 control.
9.	McNeil, J. J., et al	2018	19114	People aged 70years or older with no cardiovascular disease, dementia, or disability.	4.7 years	Group 1 – 9525 under 100mg of enteric coated aspirin Group 2 – 9589 placebo.

Table 1 shows the key characteristics of case–control, cohort, and observational studies evaluating the association between aspirin use and cancer outcomes**,** including study design, population characteristics, exposure duration and dosage, and outcome measures**,** providing an overview of the epidemiological evidence supporting aspirin's anticancer effects.

TABLE 2:

S.N0	AUTHOR	YEAR	EFFECT MEASURE	RESULT
1.	Charlotte Skriver et al.	2023	Estimates the associations between aspirin use (low dose or high dose)and both overall and site-specific cancer incidence.	Long-term use of low-dose aspirin was linkedto **lower risk of CRC**. It indicates that aspirin plays a role in site-specific cancer prevention (especially colorectal), but **not as a broad chemo preventive agent.**
2.	Chris R. Cardwell et al.,	2014	The relationship between post-diagnosis Low-Dose Aspirin and survival in Colorectal Cancer Patients.	Low-dose aspirin usage after diagnosis of colorectal cancer **did not increase survival time**
3.	Joseph J.Y. Sung et al.	2019	The effect of low-dose aspirin use in colorectal cancer patients after surgery.	Low-dose aspirin after surgery **lowers the CRC-related mortality and all-cause mortality,** irrespective of aspirin use before surgery.
4.	Kenji Yokoyama et al.	2018	Assesses the relationship between daily aspirin use and cancer-related outcomes in the elderly Japanese population	Low-dose aspirin use was linked to a noticeably **increasedincidence** of newly diagnosed cancer, and aspirin did not prevent cancer incidence or death. It also suggests that aspirin may lead to earlier detection of cancer through bleeding-related investigations.

5.	Guo et al.,	2021	Investigates the risk of CRC among older adults who initiated aspirin use before and after the age of 40yrs.	The study demonstrates a **20% reduction** in CRC incidence among older adults regularly using aspirin – but only if aspirin use is initiated before age 70 years. Starting aspirin at or after 70 years did not confer a significant benefit.
6.	Rothwell, P. M., et al.	2010	Assesses the long-term effect of aspirin on CRC incidence and mortality using 4 randomized controlled trials.	Daily aspirin use is associated with a **significant reduction** in both CRC incidence and mortality, particularly in the proximal colon (55% risk reduction) when used over a prolonged period.
7.	Burn, J., et al.	2011	Evaluates the effect of aspirin on risk and recurrence of lynch syndrome-related cancers and CRC using hazard ratios (HRs) and Incidence Rate Ratios (IRRs).	Daily aspirin at 600 mg for 2 years **significantly reduced** long-term Lynch-associated cancer and colorectal incidence in genetically predisposed individuals. The protective effect was strongest among those who adhered to the full course of treatment and became more apparent with extended follow-up.
8.	L. Baandrup et al.,	2014	Assesses the link between the risk of epithelial ovarian cancer and low dose aspirin use.	Use of low-dose aspirin was **not significantly associated** with a reduced risk of ovarian cancer.
9.	McNeil, J. J., et al	2018	ASPREE (Aspirin in Reducing Events in the Elderly) analysed the effect of aspirin on elderly individuals for a median of 4.7 years.	There was no discernible difference between the aspirin and placebo groups; nevertheless, aspirin was linked to a significantly higher risk of serious bleeding and **increased all-cause mortality**, especially deaths from cancer.

Table 2 presents the key findings from the studies included in the review, highlighting how aspirin use was associated with reduced cancer incidence, slowed tumor progression, improved survival outcomes, and decreased cancer-related mortality**.** The table also summarizes dose- and duration-dependent effects**,** variations across cancer types, and evidence from observational and cohort studies indicating modulation of inflammatory and oncogenic pathways**,** with generally acceptable safety profiles**.**

TABLE 3: RISK OF BIAS ASSESSMENT

S. No	Author (Year)	Selection Bias	Confounding	Exposure Assessment (Aspirin Use)	Outcome Assessment (Cancer)	Blinding	Attrition / Follow-up	Selective Reporting
1	**Charlotte Skriver et al. (2023)**							
2	**Chris R. Cardwell et al. (2014)**							
3	**Joseph J.Y. Sung et al. (2019)**							

S. No	Author (Year)	Selection Bias	Confounding	Exposure Assessment (Aspirin Use)	Outcome Assessment (Cancer)	Blinding	Attrition / Follow-up	Selective Reporting
4	Kenji Yokoyama et al. (2018)							
5	Guo et al. (2021)							
6	Rothwell et al. (2010)							
7	Burn et al. (2011)							
8	Baandrup et al. (2014)							
9	McNeil et al. (2018) ASPREE							

Low Risk Some Concerns High Risk

Table 3 shows the bias analysis of all included studies.it is categorized as High risk, Some concerns and Low risk.[25,26]

DISCUSSION:

A popular anti-inflammatory and antiplatelet medication, aspirin has been thoroughly investigated for its possible impact on cancer prognosis and prevention, especially in colorectal cancer (CRC) and other cancers. Numerous studies have demonstrated that aspirin has complex and multifaceted effects on the development of cancer as well as the outcomes after diagnosis. The effectiveness of aspirin is influenced by many interconnected elements, including dosage, duration of usage, age at initiation, kind of cancer, genetic predisposition of the patient, tumor biology, and even immune modulatory pathways. Results among senior citizens have been inconsistent, particularly those without a history of cancer or cardiovascular disease. Contrary to previous evidence suggesting aspirin's protective effect.

ASPREE trial McNeil et al., 2018[6] found no survival benefit among healthy adults over 70 and even reported increased cancer-related mortality. These findings suggest that age-related biological changes (such as immune decline, altered drug metabolism, and increased frailty) may lessen or even undo the advantages of aspirin.

According to Guo et al.,[11] taking aspirin did not lower the risk of colorectal cancer in older adults. This could be due to preventing the benefit as it takes a long time to show results or less successful when initiated later in life. In contrast, Yokoyama et al.[10] Japanese cohort research found no discernible rise in cancer mortality among senior aspirin users, stressing the significance of population-specific and physiologically relevant risk assessment and the potential effect of genetic, dietary, and pharmacologic (for example,COX enzyme expression, baseline inflammation, concurrent medication usage) variations on outcomes.

Data are more favourable in younger and middle-aged populations: the CAPP2 trial and research by Rothwell et al. (2010)[1] showed that long-term aspirin use, particularly when started earlier in life, significantly lowers the colorectal cancer incidence and mortality rate. After a latency of roughly five to ten years, the effect becomes noticeable, supporting and the notion that early commencement and consistent use are essential. In particular, the CAPP2 experiment found that the incidence of colorectal cancer has significantly decreased among Lynch syndrome(MMR-deficient, microsatellite-instable) carriers who received high-dose aspirin(600 mg/day for at least two years), indicating that genetically predisposed individuals may benefit from enhanced defence as a result of aspirins pro apoptotic, anti-platelet and anti-inflammatory qualities.

According to a 10 year follow up sung et al.,[9] postoperative CRC patients had a decreased mortality rate, which may indicate that aspirin is more advantageous in case of early disease or with less residual burden. Nevertheless, observational research

by Guo et al.,[11] and cardwell et al.,[8] did not conclusively show improved survival in CRC survivors using aspirin post-diagnosis, suggesting that aspirin's benefit may be limited by tumour biology, stage, and residual disease load. These findings suggest that aspirin's role after cancer diagnosis is still variable, going beyond incidence prevention.

Beyond colorectal cancer, Chen and Holmes et al.,[13] analysis of breast cancer revealed that several observational studies associated consistent aspirin usage with better survival; however, randomized trial data are still absent, and the mechanisms (platelets, COX-2, inflammation, and hormone/PI3K pathways) are still unknown. The gap between observational and interventional evidence in this context was highlighted more recently when a major randomized, placebo-controlled study of aspirin (300 mg/day) in survivors of early breast cancer revealed no advantage for recurrence or survival. The mechanisms underlying aspirin's anticancer properties are becoming more elucidated.

According to Lichtenberger and Vijayan et al.,[12] platelet COX-1 is the main anticancer target of low-dose aspirin, which inhibits platelet-driven activities such as angiogenesis, tumour cell-platelet interactions, and epithelial–mesenchymal transition [EMT]. In response, a study by Yang, Yamashita-Kanemaru et al., states that aspirin inhibits platelet-derived thromboxane A_2 (TXA_2) to prevent metastasis. This frees T cells from repression through ARHGEF1-dependent signalling, which improves antitumor immunity.

Guo et al., (2021)[15] discovered that aspirin is an adjuvant sensitizer to chemotherapy in epithelial ovarian cancer (EOC) by inhibiting tumour development and improving sensitivity of cisplatin both in vitro and in vivo, most likely through p53 acetylation and downstream gene activation. Dosage, duration, and compliance are also highlighted by larger preventive trials: Although aspirin has potential, design and dosage issues are still complicated, according to Jacobs & Thun et al.,[16]

Cook et al.'s[17] long-term observation revealed that while some risk reductions (particularly for CRC) were seen in healthy women, the magnitude was modest, and risks (such as bleeding) needed to be considered. According to a 20-year Danish cohort Skriver et al.,[7] regular, long-term aspirin users had lower risks of gastrointestinal and other cancers. However, the effect was closely associated with continuous high-compliance, regular long-term usage, and dose mattered.

Noor JJ et al. (2025) showed that gingerol suppresses cancer-promoting signaling while enhancing tumor-suppressor activity. Similarly, aspirin modulates key inflammatory and proliferative pathways, including COX-2 and NF-κB**,** promoting apoptosis and cell-cycle control. Despite differing in origin, both agents converge on common molecular mechanisms that inhibit tumor progression.

The anticancer effects of aspirin appear to be **dose-dependent**, yet the optimal dose for cancer prevention or adjuvant therapy remains uncertain. Most epidemiological and mechanistic evidence supports the efficacy of **low-dose aspirin (75–100 mg/day)**, particularly for colorectal cancer prevention. At this dosage, aspirin achieves **irreversible inhibition of platelet COX-1**, reducing thromboxane A_2 (TXA_2)–mediated platelet activation without substantial systemic COX-2 suppression. This platelet-focused mechanism is now considered central to aspirin's anticancer action.

Higher doses (≥300 mg/day) have **not consistently demonstrated superior anticancer benefits** in randomized trials. For example, the large randomized trial in early breast cancer survivors using **300 mg/day aspirin** failed to show improvements in recurrence or survival, suggesting that escalating dosage does not necessarily translate into greater oncologic benefit. Moreover, prolonged high-dose aspirin use increases the risk of **gastrointestinal bleeding, hemorrhagic stroke, and renal toxicity**, which may offset any potential anticancer advantage.

Importantly, there is **no convincing evidence that aspirin directly induces cancer at any dose**. However, concerns arise with **chronic high-dose use** due to mucosal injury, altered immune responses, and increased bleeding risk, which may complicate cancer outcomes indirectly particularly in older adults or patients with comorbidities. Thus, while aspirin does not appear carcinogenic, inappropriate dosing may increase morbidity and limit its net benefit.

Age plays a crucial role in determining both efficacy and risk. In **younger and middle-aged adults (approximately 40–65 years)**, long-term low-dose aspirin use is associated with a favorable benefit–risk balance for colorectal cancer prevention, especially after 5–10 years of continuous use. In contrast, in **older adults (>70 years)**, evidence suggests that the protective effects of aspirin are attenuated, while adverse events particularly major bleeding become more prominent. Some studies have even reported increased cancer-related mortality when aspirin is initiated de novo in advanced age, possibly due to age-

related immune dysregulation, altered tumour host interactions, or delayed diagnosis secondary to bleeding-related complications.

Furthermore, age-related differences in platelet function, gut permeability, drug metabolism, and comorbidity burden may modify aspirin's biological effects. These findings reinforce the notion that **aspirin should not be universally recommended across all age groups** for cancer prevention or survivorship, and that timing of initiation may be as important as dose.

Aspirin's relationship with cancer prevention and prognosis is complicated and context-dependent. While early and consistent use, particularly in younger people or genetically predisposed populations, appears protective (especially for colorectal cancer), the benefits for older adults are unclear and may be counteracted by age-related changes. Results seem to be influenced by variations in tumour biology, immunological state, nutrition, population genetics, and even platelet-immune interactions. Age, hereditary risk, co-morbidities, bleeding risk, tumour stage and biology, and cultural/regional variance must all be taken into consideration when making recommendations on the use of aspirin in oncology or chemoprevention. Finally, even though aspirin has a lot of potential as a therapeutic and chemo preventive adjunct, its usage needs to be carefully considered in terms of risk and benefit, and specific studies are required to determine which patients benefit the most.

CONCLUSION:

In conclusion, aspirin's anticancer effects are **complex, context-dependent, and influenced by dose, duration, genetic susceptibility, and patient age**. Evidence consistently suggests that **early initiation and long-term use of low-dose aspirin (75–100 mg/day)** confers the greatest chemo preventive benefit, particularly for **colorectal cancer**, and especially in individuals with **Lynch syndrome or microsatellite instability**. These benefits are biologically supported by aspirin's **antiplatelet, anti-inflammatory, immune-modulatory, and anti-metastatic actions**, notably through inhibition of the **platelet COX–TXA_2 axis**, suppression of epithelial–mesenchymal transition, and restoration of T-cell–mediated antitumor immunity.

While aspirin shows promise as an **adjunctive therapy** in selected malignancies such as postoperative colorectal cancer and cisplatin-treated epithelial ovarian cancer higher doses (≥300 mg/day) have not demonstrated consistent oncologic benefit and are associated with increased bleeding risk. Importantly, findings from trials in older adults indicate that aspirin initiation in advanced age may offer **no survival advantage and potential harm**, emphasizing the necessity of **age- and risk-stratified use**.

Overall, aspirin should not be viewed as a universal anticancer agent. Its use in cancer prevention or adjuvant therapy requires **careful individualization**, balancing potential benefits against bleeding risk, comorbidities, and concomitant medications. Future research should prioritize **biomarker-guided patient selection, optimized low-dose regimens, and targeted randomized trials** to safely integrate aspirin's anticancer potential into precision oncology.

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