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Aspirin and Pancreatic Ductal Adenocarcinoma: A Comprehensive Narrative Review of Chemoprevention and Clinical Outcomes

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers, with a consistently low five-year survival rate. The increase in cases and resistance to standard treatments makes it important to explore ways to prevent this disease. Aspirin, a non-steroidal anti-inflammatory drug, has gained attention for its possible cancer-fighting properties. This review summarizes current evidence on how aspirin use relates to PDAC risk and outcomes. Recent studies show mixed results. Some studies indicate a significant risk reduction, especially in diabetics, while others show no connection. Proposed biological mechanisms include COX-dependent and independent pathways. These pathways involve blocking cyclooxygenase-2, altering insulin signaling, and reducing oncogenic KRAS activity. There is also evidence that aspirin may affect how cancer spreads. Long-term use appears to be linked to lower rates of metastatic disease at diagnosis and higher rates of surgical resectability. The role of aspirin in PDAC is complicated and seems affected by dosage, length of use, and individual factors like diabetes status. Future research should prioritize personalized strategies. This includes using molecular subtyping and well-planned combination therapies to effectively utilize aspirin in managing PDAC.

Keywords: Aspirin, Cancer prevention, COX-2 inhibition, KRAS signaling, Metastasis.

Research Paper

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the toughest cancers to treat, with a five-year survival rate that has only recently increased to about 10% [1]. Worldwide, PDAC causes nearly 500,000 deaths each year, and its incidence rates are steadily increasing. Projections suggest it will become the second leading cause of cancer-related deaths in the United States by 2030 [2]. The aggressive nature of PDAC includes early spread of tumors, a dense fibrous stroma, and strong resistance to standard treatments. This highlights the urgent need for effective prevention strategies and new therapy options [3].

The causes of PDAC involve a mix of genetic, environmental, and metabolic factors. Common risk factors include smoking, obesity, chronic pancreatitis, diabetes, and genetic predisposition [4]. On a molecular level, PDAC is mainly driven by mutations in the KRAS gene (over 90%) and the loss of key tumor suppressor genes like TP53, CDKN2A, and SMAD4 [5]. The tumor microenvironment (TME) in PDAC is notably immunosuppressive and fibrotic, which adds to its resistance to treatment and helps the disease progress [6]. Early diagnosis is very challenging due to the absence of specific early symptoms and effective screening tools. Only 15-20% of patients have resectable tumors at diagnosis [7].

Aspirin (acetylsalicylic acid), a non-steroidal anti-inflammatory drug (NSAID), has been a key treatment for preventing cardiovascular diseases because of its lasting effects on platelets. Recently, studies have suggested that aspirin may also have strong anticancer effects, especially against gastrointestinal cancers [8].

This has led to increased interest in its potential role in PDAC, a cancer known to have an inflammatory component. This narrative review aims to gather current evidence on the connection between aspirin use and PDAC. It will look at the epidemiological data, explain the possible biological mechanisms, discuss clinical implications, and highlight future research and clinical practice directions.

METHODOLOGY

This narrative review was conducted through a comprehensive search of the electronic PubMed database for relevant literature published primarily within the last five years, up to [Current Month, 2023]. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and keywords, including: "Pancreatic Neoplasms/drug therapy"[Mesh], "Adenocarcinoma/drug therapy"[Mesh], "Aspirin/therapeutic use"[Mesh], "Aspirin/pharmacology"[Mesh], "Anti-Inflammatory Agents, Non-Steroidal", "chemoprevention", "cyclooxygenase 2", "insulin", "KRAS", and "diabetes mellitus". The reference lists of retrieved articles were also manually screened to identify additional relevant publications.

Inclusion criteria focused on original research studies (case-control, cohort, and randomized controlled trials), systematic reviews, meta-analyses, and high-impact review articles that specifically addressed the relationship between aspirin use and pancreatic cancer risk, pathogenesis, or treatment outcomes. Articles were excluded if they were not published in English, focused solely on other NSAIDs, or did not provide specific data on pancreatic adenocarcinoma. The data from selected studies were extracted and synthesized to provide a critical overview of the current state of evidence, highlighting consensus findings, controversies, and gaps in knowledge.

DISCUSSION

1. The Epidemiological Evidence and the Role of Aspirin in PDAC Risk Reduction

The epidemiological research on the link between aspirin use and the risk of pancreatic ductal adenocarcinoma (PDAC) is fascinating but complex and sometimes contradictory. Several large studies have tried to clarify this relationship, but the results are mixed. Factors like dose, duration, and patient characteristics may influence aspirin's effect. A substantial amount of evidence supports its potential preventive role [9]. For instance, a significant nested case-control study using the UK Biobank, which included 9,951 subjects, showed a notable risk reduction in regular aspirin users, reporting an adjusted odds ratio (OR) of 0.80. This protective effect was particularly strong among individuals with diabetes, who are at a higher risk for PDAC. However, other well-designed studies did not replicate these findings. A large prospective case-control study from Iran, with 996 participants, found no link between regular low-dose aspirin use and a lower PDAC risk (OR: 1.01) [10]. This difference highlights challenges in research methods, such as recall bias in case-control studies, variations in patient health profiles, and differences in how studies define "regular" aspirin use. The timing of aspirin use may also be essential. Some evidence suggests that more recent use may reduce risk more than past use and that using it for a longer duration (at least 5 years) may be necessary to see significant benefits [11]. While meta-analyses generally lean toward a modest protective effect, the inconsistencies among primary studies call for further exploration of the biological mechanisms behind these varied results to identify which groups may benefit the most.

2. The Role of Insulin and Hyperinsulinemia in PDAC Pathogenesis

To understand how aspirin might affect the development and progression of PDAC, it is vital to consider the main pathways of pancreatic cancer development that it could influence. The development of PDAC is a multi-step process, often starting with pancreatic intraepithelial neoplasias (PanINs) that gradually acquire cancer-causing mutations, including a common initiating mutation in the KRAS gene. A key target for aspirin is the cyclooxygenase (COX) enzyme pathway, especially the inducible COX-2 isoform [5]. COX-2 is overexpressed in many PDAC cases and their precursor lesions. This enzyme converts arachidonic acid to prostaglandins, such as prostaglandin E2 (PGE2), which promotes tumor growth, new blood vessel formation, immune evasion, and invasion [12]. Aspirin permanently modifies COX-2 to stop this harmful inflammatory process. Yet, aspirin's effects go beyond inhibiting COX. It is increasingly recognized that mechanisms not related to COX may also play significant roles, especially since doses lower than those needed for full COX-2 inhibition still show anti-cancer effects [4]. These alternate mechanisms include blocking NF-κB signaling, a critical regulator of inflammation and cell survival, and triggering programmed cell death. Furthermore, aspirin may alter the tumor environment by affecting how platelets interact with tumor cells [13]. Platelets can shield circulating tumor cells from the immune system and aid in the spread of cancer. Aspirin's strong effect on platelets could disrupt this process, potentially explaining data that connects aspirin use with a lower rate of metastatic disease at diagnosis. This multi-targeted action makes aspirin uniquely positioned to tackle several cancer hallmarks relevant to PDAC's biology [6].

The connection between diabetes, insulin signaling, and PDAC is two-way and complex, highlighting a critical way aspirin may have an impact. Long-term type 2 diabetes is a known risk factor for PDAC, and new diabetes can indicate the disease early [14]. Hyperinsulinemia, a sign of insulin resistance in

type 2 diabetes, is believed to drive pancreatic cancer development. Insulin and its growth factor, IGF-1, attach to their specific receptors on pancreatic ductal cells, activating the PI3K-AKT-mTOR and RAS-RAF-MAPK pathways [15]. These pathways boost cell growth, prevent cell death, and promote tumor development. Aspirin has been shown to improve insulin sensitivity and lower fasting glucose and insulin levels in type 2 diabetes patients. This metabolic effect is likely dose-dependent, with higher doses (around 7 g/day) having more noticeable effects. However, such doses are not practical for long-term use due to toxicity [7]. The insulin-sensitizing effect of aspirin is thought to be partially due to inhibiting the IκB kinase beta (IKKβ)/NF-κB pathway, a critical link between inflammation and insulin resistance. By reducing hyperinsulinemia, aspirin may eliminate a strong growth signal from the environment surrounding pre-cancerous or cancerous pancreatic cells, thus slowing down tumor initiation and progression [16]. This mechanism offers a solid biological reason for the enhanced protective impact of aspirin seen in diabetic populations in various studies, suggesting that the metabolic context is crucial for fully understanding aspirin's effectiveness [9].

3. Aspirin and KRAS: Targeting the Untargetable

Oncogenic KRAS drives the development of PDAC, making it a highly sought-after treatment target. However, directly targeting it has been extremely challenging, earning the label of "undruggable." Recent breakthroughs with allele-specific KRAS-G12C inhibitors are promising, but this mutation is rare in PDAC; G12D and G12V mutations are more frequent [17]. Interestingly, growing preclinical evidence suggests that aspirin can modulate KRAS-driven signaling both directly and indirectly. Acetylsalicylic acid has been shown to slow the growth of KRAS-mutant cancer cells both in lab studies and in living organisms [18]. One proposed way this occurs is through aspirin acetylating other proteins that are important for RAS signaling. For instance, aspirin's acetylation of RAS itself can hinder its ability to localize to the membrane and function properly, potentially reducing its cancer-promoting signal [19]. Additionally, by inhibiting COX-2 and lowering PGE2 production, aspirin can also influence KRAS activity in an indirect way. PGE2 is known to activate EGFR and strengthen downstream KRAS signaling, which creates a positive feedback loop that aspirin might disrupt [20]. This ability to target a key weakness in PDAC—its dependence on KRAS—through various indirect mechanisms makes aspirin unique and valuable. It suggests that even if aspirin doesn't completely stop KRAS signaling, its versatile effects may disrupt the cancer process enough to delay tumor growth or work well with other treatments. This offers solid reasons for considering aspirin not just as a preventive agent but also as a supplement in treatment combinations, potentially to overcome resistance or improve the effectiveness of standard chemotherapy.

Future Recommendations

While the current evidence on aspirin and PDAC is encouraging, it is not enough to recommend widespread use for PDAC prevention in the general public. Future efforts should focus on precision prevention. Large-scale, prospective randomized controlled trials (RCTs) are needed to clearly establish causality and assess the benefit-risk ratio. These trials should aim to identify predictive biomarkers—such as COX-2 overexpression, KRAS mutation subtype, or diabetic status—to choose patient groups most likely to benefit. Further basic research is also critical to clarify the exact molecular mechanisms, especially the COX-independent pathways and how aspirin interacts with mutant KRAS. It is also important to look into the effectiveness of different doses of aspirin (low vs. standard) and various formulations. Finally, research should explore aspirin's potential role as a supplement to systemic therapy in treated PDAC, checking whether it can enhance chemotherapy response, reduce metastasis, and improve survival outcomes in treatment situations.

CONCLUSION

The connection between aspirin use and pancreatic ductal adenocarcinoma is complex, covering prevention, metabolic changes, and direct anti-tumor effects. While epidemiological data can be inconsistent, there is strong biological reasoning for a protective effect, supported by aspirin's ability to target inflammation, high insulin levels, and essential oncogenic pathways like KRAS. The benefits of aspirin seem to be most significant in specific high-risk groups, such as those with diabetes. However, the risk of gastrointestinal bleeding is an important concern. Therefore, a universal approach is not recommended. The future use of aspirin in PDAC management hinges on personalized medicine, necessitating thorough clinical trials to clearly define its role and identify the patients who would benefit the most from this common, yet potentially powerful, medication.

Ethical Statement:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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