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Review

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Eflornithine for the Chemoprevention of Luminal Gastrointestinal Neoplasms: A Systematic Review

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Abstract

Background: Gastrointestinal (GI) tract malignancies represent a significant global health burden, being major contributors to cancer-related morbidity and mortality globally, with over 7.7 million cases reported. While aspirin is a well-studied chemopreventive agent for GI neoplasms, its use may be limited due to the underlying bleeding risk. Eflornithine (DFMO) is an inhibitor of the ornithine decarboxylase (ODC) which inhibits polyamine synthesis, and has shown promise as an alternative chemopreventive agent, particularly in animal studies and limited clinical trials.

Methods: Following PRISMA guidelines, we conducted a systematic review of studies evaluating DFMO alone or in combination for chemoprevention in premalignant GI lesions including chronic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia. The protocol was registered in Prospero (CRD42022309307). Randomized controlled trials (RCTs) and cohort studies in English or Spanish were included.

Results: Nine studies (six RCTs and three phase I-II trials) met inclusion criteria. Phase I-II trials involving Barrett's esophagus and gastric cancer did not report significant benefits. Phase III-IV trials combining DFMO with nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with reductions in adenoma recurrence, size, and polyamine levels in high-risk GI cancer populations. Side effects included ototoxicity, reversible upon discontinuation, and mild GI events, both occurring at higher doses.

Conclusion: While aspirin remains a frontline chemopreventive agent for GI neoplasms, this review shows that phase III-IV trials suggest promising outcomes in combination with NSAIDs, warranting further investigation. Notably, DFMO's low cost and favorable toxicity profile may position it as a viable alternative, emphasizing the need for additional RCTs to delineate its efficacy and safety in GI cancer prevention. Further investigation into DFMO's optimal dosage, duration, and side effect management is essential to establish it as a safe and effective chemopreventive agent.

Keywords: Chemoprophylaxis; Gastrointestinal luminal cancer; Eflornithine; DFMO

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Introduction

Gastrointestinal (GI) tract malignancies are an important cause of cancer-related morbidity and mortality worldwide. Colorectal cancers (CRCs) are reported as the second major cause of deaths related to cancer, while stomach cancer is the fourth major cause. In 2020, colorectal, esophageal, and stomach cancers had a combined prevalence of 7.7 million, causing 2.2 million deaths [1, 2]. Thus, a significant amount of research has been invested in the prevention of these malignancies.

Currently, aspirin is the best-studied medication for the prevention of GI neoplasms. In 2016, the United States Preventative Service Task Force (USPSTF) recommended low-dose aspirin for primary prevention of colon and rectal cancers (grade B recommendation), for 50- to 59-year-old patients without increased bleeding risk for at least 10 years. A grade C recommendation was made for those aged 60 - 69 [3]. This recommendation followed research suggesting that CRC risk is associated with chronic inflammation. Specifically, cyclooxygenase-2 (COX-2) activation has been theorized to play a key

role in CRC progression through its role in inhibiting apoptosis and promoting angiogenesis, tumor proliferation, and invasion. Due to its inhibitory effects on COX-2, aspirin was thought to be a candidate for chemoprevention of GI malignancies in specific populations [4-6]. Chemoprevention is the use of drugs to prevent or delay the development of malignancy. Ng et al studied 799 patients with stage 3 colon cancer who were undergoing adjuvant chemotherapy, and reported that aspirin was associated with slight improvement in recurrence-free survival with a hazard ratio (HR) of 0.51 (95% confidence interval (CI): 0.28 - 0.95) [7]. For those solely using aspirin for CRC prevention, the benefits were more often seen with long-term use. A 2010 study following participants of five randomized controlled trials (RCTs) treated with aspirin 75 - 300 mg daily found a reduction in CRC mortality at 20 years of treatment (HR: 0.65, 95% CI: 0.48 - 0.88) [8]. Other NSAIDs, particularly naproxen, sulindac, and celecoxib have also been studied; however, the exact dose needed to treat a population and long-term follow-up studies are still needed [9]. Since the USPSTF recommendation, follow-up studies and additional reporting from existing studies have emerged. In particular, the ASPREE trial, an RCT following 19,114 participants aged 65 - 70 for a median of 4.7 years, found no significant difference for all cancer rates in the aspirin administration and placebo group (HR: 1.04, 95% CI: 0.95 - 1.14). Nonetheless, the patient group that received treatment with aspirin was found to have higher rates of metastatic cancer at the time of diagnosis than the placebo group [10]. The positive impact of aspirin treatment on the risk of cancer may be found with long-term treatment. However, considering the findings of the ASPREE trial along with the known bleeding risk associated with aspirin use, it seems that starting aspirin for chemoprevention could be a highly individualized decision.

This paper is investigating the utility of eflornithine or difluoromethylornithine (DFMO) as a possible medication for the chemoprevention of GI luminal malignancies. DFMO is currently marketed for its uses in facial hair reduction and West-African trypanosomiasis. The mechanism of action is irreversible inhibition of ornithine decarboxylase (ODC), which is a rate-limiting factor involved in the synthesis of polyamines. All mammalian cells depend on ODC to produce polyamine necessary for the synthesis of DNA, RNA, and proteins. It is one of the enzymes transcriptionally activated by the MYC oncogene to convert ornithine to putrescine, which then provides the propylamine group to spermidine synthetase (SRM). The polyamine group is subsequently transferred from SRM to the eukaryotic translocation initiation factor 5A2 (9eIF5A2), which has been shown to have oncogenic potential [11]. In gastric mucosa, DFMO treatment in gerbils that had been infected with *H. pylori* was associated with decreased gastric epithelial dysplasia and gastric carcinogenesis. These effects were thought to be attributed to the inhibition of polyamine synthesis and oxidation [12]. In a study of 10 participants with Barrett's esophagus, mucosal biopsies of patients treated with DFMO for 3, 6, and 12 months showed a reduction in mucosal polyamines [13]. Moreover, DFMO treatment was associated with a down-regulation of transcription factors associated with cell proliferation. In rodent models, DFMO given at small doses was shown to inhibit intestinal and colon carcinogenesis [14-17].

A systematic review was done with the goal of studying the efficacy and safety of DFMO as a single agent or in combination for luminal GI neoplasm prevention.

Materials and Methods

This protocol is developed following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols [16]. The protocol for this systematic review was registered in Prospero with CRD42022309307.

Inclusion criteria

We included any study design evaluating DFMO alone or in combination use as chemoprevention for premalignant lesions, and RCTs and cohort studies published in English or Spanish. We excluded observational studies and non-RCTs.

Types of participants

Participants were all adults (male and female), over 18 years old, with a premalignant GI lesion that was treated with DFMO as a chemopreventive agent. The primary outcome was the progression of premalignant lesions. The secondary outcome was to assess the toxicity and tolerability of DFMO.

Search strategy

A comprehensive search strategy was developed and run in six databases: Medline (Ovid), Embase (Elsevier), Cochrane Library, Web of Science Core Collection, Scopus, and the US National Institutes of Health (NIH) Clinical Trials Registry platform. The search consisted of a combination of keywords and subject headings used in the title and the abstract as keywords. Search terms focused on GI tumor, cancer or neoplasm, and DFMO-related terms and synonyms. Limits were added to the searches to retrieve only humans and English-language studies. The search was executed in each database from inception to March 28, 2023. The final Medline strategy is provided (Supplementary Material 1, gr.elmerpub.com). The results from all databases used were aggregated in Endnote and deduplicated using the Covidence tool [18] for further screening. All searches in this study were developed and executed by a medical librarian (MR).

Results

Baseline characteristics

We identified 1,790 publications. After removing duplicates and screening phases, we selected articles for full-text screening. Finally, nine studies were included in the meta-analysis (Fig. 1). Six studies were RCTs and three were phase I-II trials.

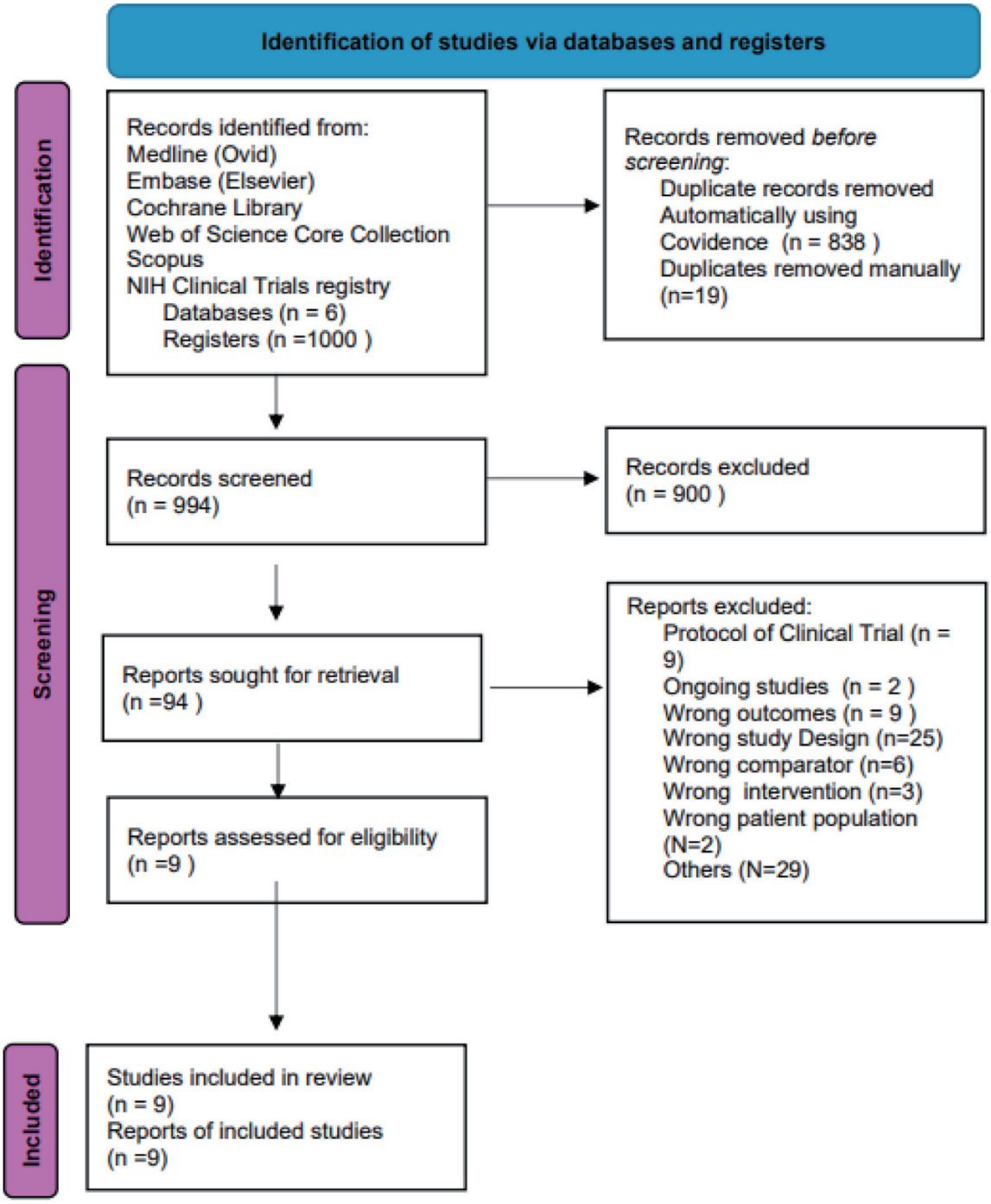

Figure 1. Eflornithine study selection flow diagram (PRISMA 2009).

Outcomes

Phase I-II trials

A review of randomized studies on Barrett's esophagus or low-grade dysplasia involving 10 subjects showed no significant benefits during endoscopic monitoring, nor any efficacy in reducing the tissue content of polyamines, and one patient experienced subclinical ototoxicity [13]. A phase I-II study of chemotherapy plus DFMO compared to chemotherapy alone with seven gastric cancer subjects showed no benefits, and the major side effect was reversible ototoxicity after stopping treatment with DFMO [19]. High-dose intravenous DFMO in a phase II trial for CRC was not associated with any response in 14 subjects that received a monthly schedule of 3 weeks of

treatment and 1 week without treatment [20].

Phase III-IV trials

The publications ranged from 2008 to 2020. Patients were followed up from 6 to 36 months, and the intervention arm was DFMO and sulindac or aspirin or celecoxib. The primary outcome was disease progression, adenoma number, or adenoma size. There were four RCTs using DFMO combined with NSAIDs for colon and rectal cancer chemoprevention demonstrating a reduction in reported adenomas (Table 1) [21-26]. Additionally, ototoxicity was reported as the most common side effect of therapy in five studies, which was more common at high doses and was reversible upon discontinuation. Anemia was reported as an adverse effect in three studies, and minor GI side effects were reported in all studies. There were several undergoing studies evaluating chemoprevention with DFMO for CRC and gastric cancer.

The quality of the studies was measured with the modified Newcastle-Ottawa scale (mNOS), ranging from 5 to 9 points. Loss of points in most studies corresponded to low health research inclusivity (HRI) population representativeness, non-reported characteristics of salient patients, and limited follow-up.

Discussion

This systematic review thoroughly analyzes recent studies involving adults with either familial adenomatous polyposis (FAP) or prior history of colorectal adenomas to highlight the possible chemoprophylactic role of either DFMO as a single agent or its combination with NSAIDs for the prevention of luminal GI neoplasms.

Two of the studies considered FAP, as the presence of multiple adenomas and accumulation of mutations occurring in the GI tract serve as a good model syndrome for CRC chemoprevention [16]. These studies included subjects with FAP and pathogenic variants of APC independently of colectomy status (including pre-colectomy and post-colectomy with preserved colon segments subgroups) [21, 27].

Yang et al in their study reported the use of DFMO as a chemoprevention therapy for CRC. They found that DFMO combination significantly reduces the incidence of adenomas in patients with recurrent CRC. However, there was no difference in control of disease progression in FAP with DFMO combination therapy [28].

Multiple prior research suggests that many cancers produce COX-2 to induce angiogenesis and inhibit apoptosis in early stages [29-31]. While inhibition of COX-2 aids in decreasing the inflammatory process, such as in esophageal cancer and Barret's esophagus patients [32], polyamines have also been shown to be essential for cancer cells survival [33]. Recently, a study done on Barrett's esophagus showed that polyamine expression was higher in intestinal metaplasia compared to normal gastric and squamous mucosa [34]. This finding suggests a correlation between elevated polyamine levels and tumorigenesis and cancer cell proliferation. Conversely, the inhibition of polyamine synthesis has been associated with a decrease in cancerous cell growth [35-37].

Prior and ongoing research is being conducted to study the role of chemoprophylaxis in preventing and controlling luminal GI neoplasms. Some chemoprophylactic benefits include decreasing GI cancer incidence, mortality, and latency period. These benefits subsequently lead to a decrease in GI cancer burden and cost to the patient plus healthcare system. NSAIDs and aspirin are widely investigated as possible agents for chemoprevention, especially in GI cancers, but until recently, the use of DFMO by itself or concomitantly with NSAIDs has not been thoroughly researched.

Aspirin ingestion is associated with reduced stomach, colorectal, and esophageal carcinomas as reported in multiple studies [38-40]. For example, a study showed that aspirin use is associated with lower risk of colon cancer, taking into account the dose and duration of exposure [41, 42]. Thus, it has been thought that aspirin could be playing a role in both cancer prevention and progression via its COX-2 inhibitory role [43]. Furthermore, another study supporting this theory of inhibiting chemically induced carcinogenesis highlighted a decrease in incidence and multiplicity of colonic tumors with NSAIDs use, regardless of NSAIDs agent type or treatment timing [44].

Multiple studies have been performed on the anti-tumor effect that DFMO has on pancreatic, skin, breast, prostate, blood, and ovarian cancers, due to its action on apoptotic signaling [45, 46]. However, few studies are being conducted on its chemoprophylactic effect, either as a single agent or its combination with other agents, mostly NSAIDs. DFMO works by irreversibly inhibiting polyamine metabolism, specifically the overexpressed enzyme ODC, which is the rate-limiting enzyme for polyamines synthesis that is present in patients with FAP [47, 48]. Taking this into account, DFMO could have a role in polyp prevention in this population [8, 9].

Different trials have been carried out on the minimal effective dosing and potential toxicities of DFMO. In the analyzed studies, the minimal dose of DFMO ranged from 500 to 750 mg daily [17, 21-24, 27]. The average minimal dosing needed to achieve potential effective chemoprevention in any particular organ has been estimated at 0.5 g/m^2/day, which causes the reduction in polyamine levels [17, 23]. Interestingly, in some studies, it was found that DFMO causes a decrease in colorectal mucosal ratios of polyamines with doses as low as 0.1 g/m^2 daily for 4 weeks [17, 49].

All of the studies in Table 1 evaluated the efficacy of DFMO for the prevention of colonic polyposis and neoplasms in an effort to reduce CRC incidence and improve outcomes.

In Burke et al's study, it was found that the use of DFMO resulted in 40% of patients having FAP progression compared to progression of disease in 32% and 38% DFMO-sulindac and sulindac groups, respectively [21]. Another interesting finding was that the average time to progression was the longest in the DFMO-sulindac combined group of 32.3 months, compared to sulindac-only and DFMO-only groups, which had progression rates of 23.6 and 21.8 months, respectively [21]. There was an increase in time to progression, but not to a level of statistical significance. DMFO has also been shown to delay or prevent the need for lower gastrointestinal tract surgery in patients with FAP as described by Balaguer et al [24].

Table 1. General Characteristics of the Included Studies

Study	Year	Risk of bias	Population	Design and follow-up	Study Arms (N)	Endpoint(s)	Conclusion
Burke [21]	2020	"Low" SB "Low" PB "Low" AB	Adults aged 18 years or older who had clinical FAP and pathogenic variants of APC.	Randomly assigned in a 1:1:1 ratio, up to 24 months. To prevent CRC	DFMO 750 mg and sulindac 150 mg (N = 56) vs. DFMO 750 mg + placebo (N = 57) vs. sulindac 150 mg + placebo (N = 58).	Assessed in a time-to-event analysis, was disease progression.	HR for disease progression of 0.30 (95% CI, 0.30 - 1.32) DFMO + sulindac vs. sulindac and 0.20 (95% CI, 0.03 - 1.32) DFMO + sulindac vs. DFMO.
Lynch [22]	2016	"Low" SB "Low" PB "Low" AB	Adults aged 18 - 65 years who had clinical diagnosis of familial adenomatosis.	Randomized phase II trial To prevent CRC 6 months.	DFMO 0.5 g/m^2/day rounded down to the nearest 250 mg dose + CXB 400 mg/day (N = 57) vs. CXB + placebo (N = 55).	Percentage change in adenoma count per field. Adenoma burden determined by adenoma diameter and video review of colorectum.	DFMO plus CXB yielded moderate synergy and video-based improvement. No significant difference in adenoma count.
Meyskens [23]	2008	"Low" SB "Low" PB "Low" AB	Adults aged 40 - 80 years with a history of ≥ 1 resected adenoma of at least 3 mm within 5 years before study entry.	Randomized, double-blinded placebo-controlled trial to test the reduction in the recurrences of colorectal adenomas. To prevent CRC Up to 3 years.	DFMO 500 mg + sulindac 150 mg/day (N = 191) vs. DFMO placebo + sulindac placebo (N = 184).	Adenoma burden and the total size and number of adenomas in the colon and rectum.	DFMO, when combined with sulindac, reduces risk of recurrent adenomas in patients with non-familial adenomas by about 70%.
Balaguer [24]	2022	"Low" SB "Low" PB "Low" AB	Adults with FAP.	Randomized, double-blinded placebo-controlled trial to evaluate the impact of DFMO-sulindac combination versus monotherapy in delaying time to disease progression in the lower GI tract of patients with FAP.	DFMO (750 mg) once daily (N = 51) vs. sulindac (150 mg) once daily (N = 53) vs. DFMO (750 mg) + sulindac (150 mg) once daily (N = 54) for up to 48 months.	Time to first disease progression in the lower GI tract.	DFMO-sulindac combination therapy was superior to either drug alone in delaying or preventing the need for lower GI tract surgery in patients with FAP.
Sinicrope [25]	2019	"Low" SB "Low" PB "Low" AB	Adults aged 46 to 83 years who had current or prior advanced colorectal adenomas.	Randomized, double-blinded, and placebo-controlled trial; taken continuously for 1 year. To prevent CRC	DFMO 500 mg/day + aspirin 325 mg/day (N = 43) vs. DFMO placebo + aspirin placebo (N = 44).	Compare adenoma number in at 1-year follow-up.	Compared to placebo, in a high-risk patient population, DFMO in addition to aspirin did not reduce adenoma recurrence in the colon or rectum at 1 year, but it did show lower risk of aberrant cryptic foci in the rectum.
Morgan [26]	2024	"Low" SB "Low" PB "Low" AB	Patients with GPMC from rural Honduras and Puerto Rico, aged 30 - 60 years, with high prevalence of *H. pylori* infection.	Randomized controlled trial; follow-up duration of 24 months.	DFMO vs. placebo.	Tolerability, safety, changes in Correa histopathology score, and DNA damage (%pH2AX positive cells).	DFMO treatment was safe and well tolerated in GPMC patients in Latin America. DFMO reduced long-term DNA damage in patients after completing treatment.

AB: attrition bias; CRC: colorectal cancer; CXB: celecoxib; DFMO: eflornithine; FAP: familial adenomatous polyposis; GI: gastrointestinal; GPMC: gastric premalignant condition; PB: publication bias; SB: selection bias.

In the clinical trial by Sinicrope et al, the placebo arm showed similar rate of recurrence to the study arm including DFMO and sulindac (41.1% rate after treatment for 2 - 39 months) [25]. DFMO and aspirin combination had an association with significant reduction of rectal aberrant crypt foci count in comparison to patients that were in the placebo arm ($P = 0.036$) [25].

The trial by Lynch et al revealed that the celecoxib and placebo group showed a 1% mean reduction in comparison to the DFMO and celecoxib group reporting a 13% reduction of polyps measuring a minimum of 2 mm [22].

In the trial by Meyskens et al, the research examined the effects of combining low doses of DFMO and sulindac to reduce the recurrence of colorectal adenomas identified through standard colonoscopy. Among the placebo group, 53 patients (41.1%) developed at least one adenoma, compared to only 17 patients (12.3%) in the treatment group ($P < 0.001$). Additionally, 11 patients in the placebo group had advanced adenomas, whereas only one case of advanced adenoma was observed in the DFMO plus sulindac group ($P < 0.001$) [23].

In the trial by Morgan et al, upon evaluation of DNA damage, patients receiving eflornithine demonstrated a slight increase in %pH2AX at 6 and 18 months; however, a significant reduction in this marker was noted by the end of the study period (EoS), particularly in the analysis of adjacent time points ($P = 0.012$). These findings support the safety and tolerability of eflornithine in individuals with gastric premalignant conditions in Latin America and suggest a potential role in mitigating long-term DNA damage following treatment completion [26].

Another study found that combining low doses of piroxicam and DFMO was more effective in reducing the incidence and multiplicity of colon adenocarcinomas compared to using either compound alone, even at higher doses [50].

Based on these prior studies, inhibiting ODC by DFMO may be used as a future agent for FAP suppression and progression into cancer. It is worth mentioning that troglitazone, an indirect inhibitor of ODC, induced apoptosis in an esophageal adenocarcinoma cell line but had no effect in an esophageal squamous cell carcinoma cell line [51]. Thus, the type of ODC inhibitor may have different effects on cancer chemoprophylaxis.

Although there are many studies on chemoprophylaxis agents, those about DFMO are still scarce. This systematic review represents the first comprehensive study on DFMO chemoprophylaxis use in GI neoplasms. Considering this, a variety of studies should be conducted on its effectiveness as a single agent or in combination with other chemopreventive agents. Furthermore, the benefit versus harm in treatment with these agents must be considered, along with its cost and long-term treatment associated side effects. For instance, some clinical trials using DFMO as a chemoprophylaxis resulted in a treatment-limiting toxicity, but lower effective doses did not result in ototoxicity [15, 52]. However, other side effects have not been reported or studied yet. Therefore, extensive studies should be made on DFMO before its use in chemoprophylaxis.

Beyond its role in chemoprophylaxis, DFMO could be considered as a post-cancer maintenance therapy to potentially prevent or delay the emergence of new driver mutations including TTN mutations, TP53, MUC16, and LRP1B or the progression of malignant residual disease.

Conclusions

DFMO could play a role in chemoprevention of luminal GI cancers as an affordable and nontoxic option, particularly when combined with NSAIDs. However, additional RCTs are needed, especially to evaluate its effectiveness as a standalone agent.

Supplementary Material

Suppl 1. Medline search strategy.

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None to declare.

Conflict of Interest

There is no conflict of interest to declare by all authors.

Author Contributions

Conception and design: Ambar Godoy, Daniel A. Guifarro, and Daniela Montalvan-Sanchez. Administrative support: Fortunato S. Principe-Meneses, Adrian Riva-Moscoso, Leandro Sierra, Gloria Erazo, Carlos Avila, Mirian Ramirez-Rojas, and Roberto Giron. Provision, collection, and assembly of data: Leandro Sierra, Gloria Erazo, Carlos Avila, and Mirian Ramirez-Rojas. Literature review, manuscript draft, and revision of key components: all authors. Final approval of manuscript and agreement to be accountable for all aspects of the work: all authors.

Data Availability

The data validating the findings of this study can be obtained from the corresponding author upon reasonable request.

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