Pharmacology & Therapeutics 237 (2022) 108252

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Vitamin D as a chemopreventive agent in colorectal neoplasms. A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Available online 01 August 2022

Editor: S.J. Enna

Keywords:
Adenomas
Colorectal cancer
Colorectal polyps
Vitamin D

ABSTRACT

Colorectal cancer (CRC) is the third most common cancer in both sexes and the second in terms of mortality. Apart from genetic predisposition, dietary and lifestyle factors have been implicated in the development of CRC. Several studies suggested that vitamin D (Vit—D) might be a promising strategy in CRC prevention, while other studies did not confirm this finding. The aim of our study was to examine the role of Vit-D supplementation in the prevention of colorectal neoplasms (CRC and polyps). We conducted a systematic search in Pubmed, Embase and Web of Science databases for Randomized Controlled Trials (RCTs) examining the incidence of colorectal neoplasms in patients taking Vit-D supplementation compared to placebo. We synthetized results using Risk Ratio along with 95% Confidence Intervals (CIs). Nine RCTs ($N = 71,386$) were included. Non-significant correlations were observed between Vit-D supplementation and CRC incidence (RR:1.06, $p = 0.52$). Similarly, non-significant associations were observed between the use of Vit-D supplements and colorectal adenoma incidence (RR:1.00, $p = 0.91$). Advanced adenomas (OR:1.05, $p = 0.63$) and serrated polyps (RR:1.03, $p = 0.63$) were also not significantly inversely associated with Vit-D supplementation. Our study shows that Vit-D does not seem to have a role in the chemoprevention of colorectal neoplasms. However, additional well-designed studies are needed in order to draw safe conclusions. A potentially beneficial role of Vit-D supplementation in CRC primary prevention in individuals with severe vitamin D deficiency as well in the primary prevention of early-onset CRC, requires further investigation.

Contents

Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; CPGs, Clinical Practice Guidelines; CRC, Colorectal cancer; CT, Computed Tomography; NSAID, non-steroid anti-inflammatory drugs; RCTs, Randomized controlled trials; RR, Risk Ratio; SD, Standard Deviation; SSA, Sessile serrated adenoma; Vit-D, Vitamin D; WHO, World Health Organization.

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https://doi.org/10.1016/j.pharmthera.2022.108252
0163-7258/

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in both sexes and the second in terms of mortality, according to the GLOBOCAN database (https://gco.iarc.fr/). Recent cancer statistics showed that the lifetime risk of CRC is 4.2% in men and 4% in women, and one-half of affected individuals will die from CRC (Siegel, Miller, Fuchs, & Jemal, 2022).

CRC is considered an etiologically heterogeneous disease as both environmental and genetic factors play a major role in the pathogenesis (Baidoun et al., 2021). The majority of CRC (>90%) arise from colon polyps. Three different pathways are implicated in colorectal carcinogenesis. The adenoma-carcinoma sequence is considered the main pathway, with the serrated and inflammatory pathways being less common and accounting for fewer cases (Keum & Giovannucci, 2019).

Adenomatous (adenomas) and serrated polyps are the two major neoplastic lesions that act as precursors for the majority of CRCs (Dekker, Tanis, Vleugels, Kasi, & Wallace, 2019). Approximately 85–90% of CRCs develop on a background of adenomatous tissue over a period of many years, while 10–15% originate from serrated polyps (Conteduca, Sansonno, Russi, & Dammacco, 2013). Colonoscopy is considered the gold standard diagnostic modality for CRC and colorectal polyps. Population screening programs with colonoscopy aim to identify and remove pre-malignant polyps, which have been associated with a decrease in advanced CRC and overall mortality (Brenner, Stock, & Hoffmeister, 2014).

The high incidence of CRC in the general population, especially in adults older than 50 years, raised the requirement for primary prevention beyond early diagnosis with population screening programs. Several agents including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), calcium supplements, statins and vitamins, have been studied as primary CRC prevention over the last years (Thanikachalam & Khan, 2019), and some of them have been found to be protective in specific population groups, attracting the interest of several scientific groups.

Alongside the established role of aspirin in the primary prevention of cardiovascular disease, recent studies have shown that aspirin and NSAIDs might also be beneficial in the primary prevention of CRC (Dubé et al., 2007; Rostom et al., 2007). The use of aspirin and NSAIDs have been associated with a reduction in the risk of CRC and colonic adenomas by 20–40%, depending on the dose and duration of treatment. Despite these encouraging preliminary results, current clinical practice guidelines (CPGs) do not recommend globally the use of aspirin and NSAIDs in the primary prevention of CRC, probably because of concerns regarding the adverse effects related to their use that do not outweigh the anticipated benefit. Physicians' recommendations are individualized depending on the patient's bleeding risk and anticipated life (Bibbins-Domingo, 2016; Shaukat et al., 2021).

In 2008 the World Health Organization (WHO) International Agency for Research on Cancer conducted a meta-analysis of observational studies examining the association between vitamin D (Vit—D) status and the risk of cancer (IARC, 2008). The analysis showed that low serum 25(OH)Vit-D concentrations might be associated with increased risk of colorectal adenomas and CRC. A more recent international pooling project of 17 cohorts (McCullough et al., 2019) concluded that higher 25(OH)Vit-D concentrations are associated with significantly decreased risk of CRC in women, whereas in men the results did not reach statistical significance. Supplementation with Vit-D could be a promising strategy because of its numerous roles in maintaining and regulating normal cellular functions (Heaney, 2008). This hypothesis is further strengthened by in vitro data which show that Vit-D can stimulate apoptosis and inhibit cell proliferation (Fleet et al., 2012). Calcitriol regulates several cellular and metabolic pathways and Vit-D receptor polymorphisms may affect the risk of several cancers including CRC (Gnagnarella et al., 2020).

The encouraging preliminary results of the role of Vit-D for CRC chemoprevention were further tested in randomized controlled trials (RCTs). The results of several RCTs were variable and often conflicting. We conducted a systematic review and meta-analysis of all available evidence to assess the role of Vit-D supplementation in the prevention of colorectal neoplasms.

1.1. Study design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021) (**Supplementary File 1**). The protocol of this study has been submitted to the OSF platform https://osf.io/jwd4c/

1.2. Data sources

A systematic search of the literature was performed in MEDLINE via PubMed, Embase and Web of Science databases up to June, 1st, 2022 using the following search terms: colon adenomas, rectal adenomas, colorectal adenomas, CRA, colon polyps, rectal polyps, serrated adenomas, serrated polyps, colon cancer, rectal cancer, colorectal cancer, colon neoplasms, rectal neoplasms, colorectal neoplasms, Vitamin D, 25(OH) Vitamin D, 25-hydroxyvitamin D, calcitriol, calcifediol, which were modified accordingly for each database. Prospero database was also screened to identify possible upcoming or ongoing studies with the same topic. A detailed search strategy can be found in **Supplementary File 2.**

1.3. Eligibility criteria and outcomes

Eligible studies were RCTs which examined the role of Vit-D supplementation in comparison to placebo in CRC prevention and with follow-up of at least 3 years. All formulas of Vit-D supplementation were acceptable. Target population for our study was adult patients (≥18 years old) with no history of CRC. Studies including subjects with CRC history, pregnant women and other severe comorbidities were excluded. Observational studies and/or non-randomized controlled trials were also excluded.

The primary outcome of our study was the incidence of colon/rectal/colorectal cancer and adenomas, which were diagnosed by either colonoscopy or other screening methods. Secondary outcome was the incidence of advanced colon/rectal/colorectal adenomas and serrated polyps. Studies only in the English language were included in our systematic review.

1.4. Studies selection and data extraction

Records retrieved from our systematic search of the literature were exported into a reference manager software (Endnote X9, Clarivate) and were screened for eligibility by two reviewers (GE and DB) independently. Any disagreement was solved by the involvement of a third reviewer (GK). References were also manually screened to identify relevant to the topic studies.

Data extraction of eligible studies was performed independently by two authors (GE) and (DB) into a previously agreed Microsoft excel form. Any discrepancies were solved by consensus. Data extracted from each study were first author's last name, year of publication, NCT number, county of origin, number of participants, sex and mean age of patients, type of intervention, mean daily dose of Vit—D, mean daily dose of calcium, duration of intervention, follow-up diagnostic method used, findings from a baseline colonoscopy if available, and the number of subjects that developed colon/rectal/colorectal adenomas (advanced or not), cancer, sessile serrated adenomas (SSA) and serrated polyps.

1.5. Quality assessment

The evaluation of the quality of included studies was performed using the Cochrane Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019). Assessment of each study was conducted independently by two reviewers (GE and DB) and any disagreement was resolved with the help of a third reviewer (GK). According to the RoB 2 assessment tool, bias for each study derived from five separate domains: bias in the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Studies were classified as *"low risk of bias"*, *"some concerns"* or *"high risk of bias"*. The risk of bias was estimated for each outcome and overall, for each study.

1.6. Statistical analysis

Number of events and total number of subjects were extracted for each group (Vit-D and placebo group). Mantel-Haenszel random-effects model was used as effect size and Risk Ratio (RR) as a summary statistic model of the included studies. Heterogeneity was estimated using the Cochrane Q test ($p < 0.1$: existence of heterogeneity) and I^2 statistic. I^2 values >50% indicated substantial heterogeneity within the eligible studies. Publication bias was assessed with funnel plots. All statistical analyses were performed using the Review Manager software (version 5.4) (Review Manager Web (RevMan Web), 2020).

2. Findings

2.1. Search results

The literature search yielded a total of 6839 records and after duplicate removal, 4493 records were screened on title-abstract level leading to the exclusion of 4469 records. Full-text screening was performed for 24 studies. Finally, nine studies fulfilled the inclusion criteria and were included in the analysis. The flow chart for the study selection process is outlined in Fig. 1.

2.2. Characteristics of included studies

All included studies were published as full text articles (Baron et al., 2015; Chatterjee et al., 2021; Crockett et al., 2019; J. Lappe et al., 2017; J. M. Lappe, Travers-Gustafson, Davies, Recker, & Heaney, 2007; Manson et al., 2019; Pommergaard, Burcharth, Rosenberg, & Raskov, 2016; Song et al., 2021; Wactawski-Wende et al., 2006). The total number of participants was 71.386. Mean follow-up time was 3–7 years. Mean daily dose of Vit-D was 400–4000 IU. In three studies participants were only women (J. Lappe et al., 2017; J. M. Lappe et al., 2007; Wactawski-Wende et al., 2006). The mean age of the participants ranged from 57.8 (±6.6) to 67.1 (±7.1) years and the mean body mass index (BMI) of the participants ranged from 28.1 (±5.7) to 32.1 (±4.4) kg/m^2. All quantitative variables were presented as mean and standard deviation (SD). Characteristics of the included studies are summarized in Table 1.

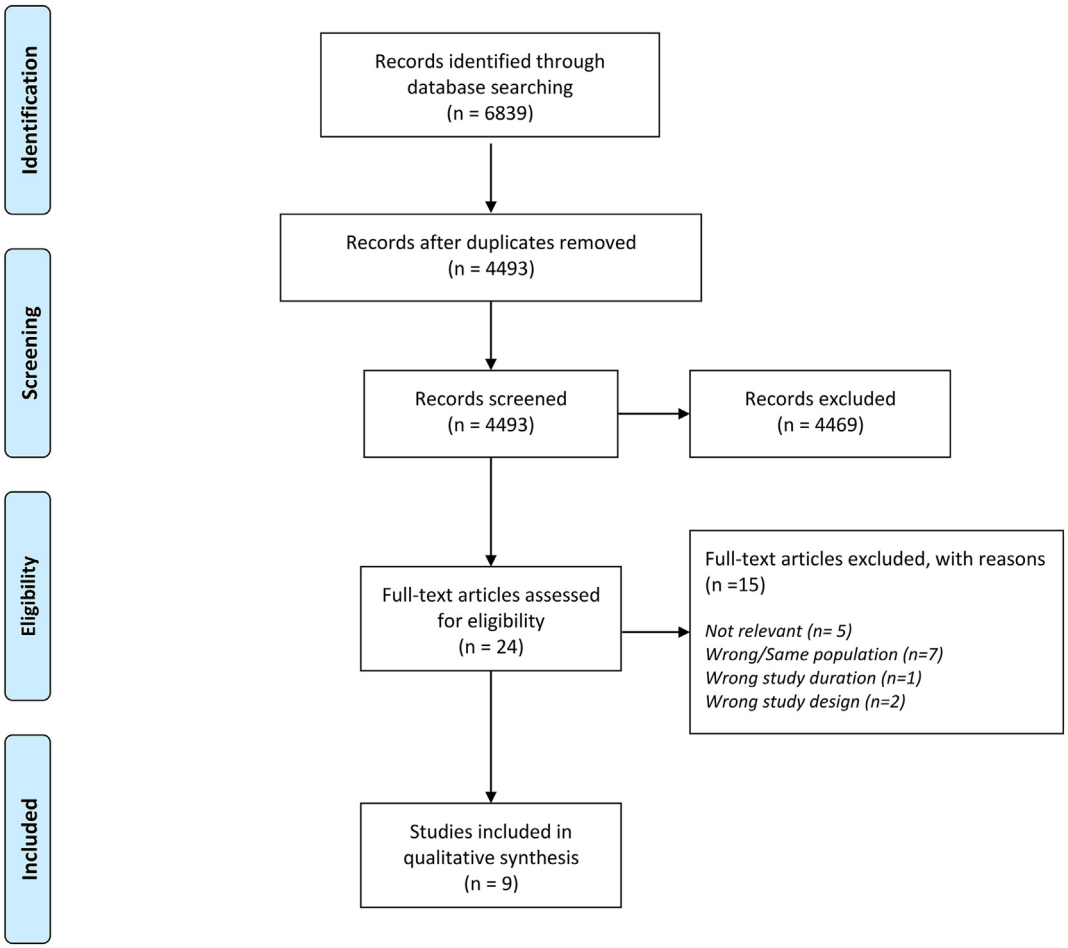

Fig. 1. Flow chart and reasons of exclusion of studies.

Table 1
Baseline characteristics of the studies included in the meta-analysis.

First author, Year, Country	Intervention	Vitamin D mean daily dose	Calcium mean daily dose	Duration of intervention	Patients randomized (Male %)	Average Age ± SD (years)	Average BMI ± SD	Diagnostic method
Baron et al., 2015, USA- Crockett et al., 2019, USA	Vit D + Ca	1000 IU	1200 mg	3–5 years	710 (49.8%)	58.0 ± 6.8	28.7 ± 5.2	Colonoscopy
	Placebo	Placebo	Placebo		415 (85.2%)	58.2 ± 7.0	29.0 ± 4.9	
	Vit D + Placebo	1000 IU	Placebo		420 (85.2%)	58.3 ± 7.0	29.1 ± 4.6	
	Ca + Placebo	Placebo	1200 mg		714 (49.8%)	57.8 ± 6.6	29.2 ± 5.5	
Chatterjee et al., 2021, USA	Vit D3	4000 IU	-	2.9 years	1194 (55.5%)	59.6 ± 9.8	32.0 ± 4.5	1.Questionnaires related to cancer screening
	Placebo	Placebo			1191 (55.4%)	60.4 ± 10.0	32.1 ± 4.4	2. Colonoscopy
Lappe et al., 2017, USA	Vit D3 + Ca	2000 IU	1500 mg	4 years	1156 (0%)	65.2 ± 6.9	29.9 ± 6.6	Medical Record
	Placebo	Placebo	Placebo		1147 (0%)	65.2 ± 7.1	30.2 ± 6.5	
Lappe et al., 2007, USA	Vit D + Ca	1100 IU	1400 mg	4 years	1179 (0%)	66.7 ± 7.3	29.0 ± 5.7	Medical Record
	Ca	Placebo	1400 mg					
	Placebo	Placebo	Placebo					
Pommergaard et al., 2016, Denmark	Calcitriol + ASA + Ca	0.5 μg	1250 mg	3 years	209 (56%)			Colonoscopy
	Placebo	Placebo	Placebo		218 (60%)			
Song et al., 2021, USA -Manson, 2019, USA	Vit D3 + N3	2000 IU	–	5.3 years	12,927 (49%)	67.1 ± 7.1	28.1 ± 5.7	Colonoscopy or Sigmoidoscopy
	Placebo	Placebo			12,944 (49%)	67.1 ± 7.1	28. 1 ± 5.8	
Wactawski-Wende et al., 2006, USA	Vit D + Ca	400 IU	1000 mg	7.0 ± 1.4	18,176 (0%)	59		Medical Record
	Placebo	Placebo	Placebo		18,106 (0%)	60		

USA: United States of America, Vit D: vitamin D, Ca: Calcium, ASA: acetylsalicylic acid, N3: n3 fatty acids, IU: International Units, mg: milligram, SD: standard deviation, BMI: body mass index.

2.3. Risk of bias assessment

Results of the quality assessment using the RoB-2 tool for both primary and secondary outcomes can be found in **Supplementary File 3.** Five studies were classified as studies with *"some concerns"* due to inaccuracies in their randomization process and in the measurement of the outcome (diagnosis of the diseases). The four remaining studies were classified as *"low risk of bias"*.

2.4. Primary outcome analysis

2.4.1. Colon/rectal/colorectal adenomas

Four studies examined the risk of development of colorectal adenomas after Vit-D supplementation in comparison to placebo (Baron et al., 2015; Chatterjee et al., 2021; Pommergaard et al., 2016; Song et al., 2021). In all studies adenomas were detected by colonoscopy. No difference was observed between the two groups in the risk of colon/rectal/colorectal adenomas (RR = 1.00, 95%CI 0.92–1.08, $p = 0.91$). There was low heterogeneity among studies ($I^2 = 1\%$). The results are outlined in **Supplementary File 4**.

2.4.2. Colon/rectal/colorectal cancer

Six studies examined the incidence of CRC after Vit-D supplementation (Baron et al., 2015; Chatterjee et al., 2021; J. Lappe et al., 2017; J. M. Lappe et al., 2007; Manson et al., 2019; Wactawski-Wende et al., 2006). No difference was observed between Vit-D and placebo groups with regards to the risk of colon/rectal/colorectal cancer development (RR = 1.06, 95%CI 0.88–1.28, $p = 0.52$). There was low heterogeneity among studies ($I^2 = 0\%$). The results are outlined in **Supplementary File 5**.

2.5. Secondary outcomes analysis

The incidence of advanced colon/rectal/colorectal adenomas was examined in three studies (Baron et al., 2015; Pommergaard et al., 2016; Song et al., 2021). The risk was similar in the Vit-D and placebo groups, with low heterogeneity among studies (RR = 1.05, 95%CI 0.87–1.26, $p = 0.63$, $I^2 = 0\%$). The risk of serrated polyps which was examined in only two studies (Crockett et al., 2019; Song et al., 2021) did not differ between the Vit-D and placebo groups with low heterogeneity among the studies (RR = 1.03, 95% CI 0.92–1.16, p = 0.63, $I^2 = 0\%$). The detailed results can be found in **Supplementary File 6 and 7.**

3. Discussion

This systematic review and meta-analysis investigated the role of Vit-D supplementation in the primary prevention of colorectal adenomas and CRC. Our analysis included nine studies with a total of 71,386 participants and low heterogeneity. The results of our analysis do not support an association between Vit-D supplementation and lower risk of colorectal adenomas or cancer.

The average lifetime risk of CRC is about 4% (Siegel et al., 2022). In genetically predisposed individuals this risk is substantially higher. In this context, early diagnosis of colorectal adenomas/cancer with screening colonoscopy according to guidelines is paramount (Shaukat et al., 2021). Unfortunately, the acceptance of and adherence to screening programs is not universal, likely due to the nature and invasiveness of the procedure. Therefore, the question of safe and effective primary prevention is relevant. Aspirin and NSAIDs might have a beneficial role in chemoprevention as some studies have demonstrated that their use is associated with lower risk of CRC and colorectal adenomas, (Dubé et al., 2007; Rostom et al., 2007), but their wider use has been limited by safety concerns.

Vit-D has emerged as an alternative candidate for CRC chemoprevention in view of data from observational studies showing an association with reduced CRC risk (IARC, 2008; McCullough et al., 2019). These preliminary data combined with the excellent safety profile, have highlighted Vit-D as an attractive chemoprevention strategy for the general population. Potential mechanisms that may justify the inverse relationship between Vit-D intake and CRC incidence include inhibition of proliferation, angiogenesis, invasiveness, and migration of CRC cells, as well as regulation of enteric immune cells (Ferrer-Mayorga, Larriba, Crespo, & Muñoz, 2019). Moreover, 1,25-(OH) Vit-D3 and other Vit-D receptor agonists regulate the biological behavior of some types of stromal cells to such a degree that prevents the occurrence of metastases (Ferrer-Mayorga et al., 2019).

A recent observational study with a long time of follow-up which focused on women younger than 50 years old, showed that a higher total intake of Vit-D was related to an overall reduced risk of CRC and CRC precursors. This effect was more profound when the source of Vit-D was of dietary origin, particularly from dairy intake in comparison to

Vit-D intake from supplements (Kim et al., 2021). The association of Vit-D intake and CRC has been examined in two meta-analyses (Huang et al., 2020; Xu et al., 2021). These meta-analyses concluded that Vit-D has a favorable impact not only on the incidence of colorectal neoplasms, but also on the incidence of malignant progression and overall long-term survival of patients with CRC. However, these meta-analyses included data from heterogeneous cohort and case-control studies, and they concluded that further research with RCTs is needed to draw safe conclusions. Contrary to those findings, high-quality RCTs failed to demonstrate a protective role of Vit-D (Baron et al., 2015; Chatterjee et al., 2021; Crockett et al., 2019; J. Lappe et al., 2017; J. M. Lappe et al., 2007; Manson et al., 2019; Pommergaard et al., 2016; Song et al., 2021; Wactawski-Wende et al., 2006). The results of our meta-analysis are in accordance with these findings and consolidate the lack of protective role for Vit-D in CRC prevention.

To our knowledge, this is the first meta-analysis to incorporate exclusively RCTs (which provide the highest quality of evidence) which examine the role of Vit-D supplementation in the prevention of colorectal neoplasms. Our study included the most recent clinical data derived from RCTs, with a large total number of participants and long follow-up (3–5 years). In our study, literature search was conducted not only in major electronic databases but also in the 'grey' literature in order to obtain and analyze all available data. Moreover, quality analysis was performed with the most recent Cochrane ROB tool 2.0 (15), and none of the studies was deemed high-risk for bias. A very low heterogeneity was observed between the studies included (0–1%).

A possible explanation for the negative results of our analysis is that Vit-D supplementation might be beneficial only in a subset of patients with specific gene patterns. A study that analyzed gene expression patterns in blood and rectal mucosa samples, showed that higher Vit-D levels correlate with rectal mucosa gene expression patterns consistent with anti-tumor effects. However, this observation was limited to cases with blood expression changes in HIPK2 and PPP1CC (Vaughan-Shaw et al., 2021).

Our study has some limitations. A repeat colonoscopy was not required as per protocol in some studies, and the outcome was assessed based on either colonoscopy or other CRC screening methods (sigmoidoscopy, computed tomography (CT)). The primary outcome in these studies was incidence of CRC, which can be assessed with cross-sectional imaging, whereas incidence of CRC precursors (colonic adenomas or serrated polyps) that require colonoscopic assessment were not included in the outcome. Another point that should be kept in mind is that one of the trials (Baron et al., 2015) included individuals with a history of completely removed colorectal polyps at baseline colonoscopy and not individuals with an average risk of CRC. Moreover, there was insufficient data to perform subgroup analysis for early (< 50 years of age) and the older-onset (≥50) CRC. Finally, one potential limitation is that participants included in the analysis were not Vit-D deficient, where Vit-D supplementation seems to be more effective (Brenner, Jansen, Saum, Holleczek, & Schöttker, 2017).

In summary, the results of our analysis combining high-quality data do not support a protective role for Vit-D against CRC and CRC precursors. There is a possibility that Vit-D might have a role in primary prophylaxis in certain groups, such as younger women or individuals with severe Vit-D deficiency. To address this possibility, further studies are needed with repeat colonoscopy being the modality of choice for assessing outcomes. Primary chemoprevention for the third most common cancer remains an unmet need, and further large-scale research is needed in that direction.

Conflict of interest and sources of funding

The authors declare that there are no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pharmthera.2022.108252.

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