

Chemoprophylaxis in Colorectal Cancer: Can Prevention be Better than Cure?

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Abstract

Colorectal cancer continues to be a leading cause of death across the world, in spite of advances in detection and treatment. The concept of chemoprevention has come into the highlight once again, after almost four decades of arguments and counter arguments. At this point, we go back into the history of chemoprophylaxis, to look at the various modalities that were once promising and their current status in the literature.

The agents used for chemoprophylaxis are many and hence we decided to classify them according to the level of evidence available. A literature search was performed with keywords including, but not exclusively "colorectal cancer", "prevention", "prophylaxis", and "diet". Studies were reviewed and only chemo-preventive agents were looked at in detail, though some dietary extracts and other factors of potential interest to a clinician have been noted. Though these agents are yet to be used in primary prevention of colorectal cancer, the evidence for some is overwhelming enough to require further investigation.

Keywords: Colorectal cancer; Prevention; Prophylaxis; Diet

Introduction

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The agents used for chemoprophylaxis are many and hence we decided to classify them according to the level of evidence available. A literature search was performed with keywords including, but not exclusively "colorectal cancer", "prevention", "prophylaxis", and "diet". Studies were reviewed and only chemo-preventive agents were looked at in detail, though some dietary extracts and other factors of potential interest to a clinician have been noted. Though these agents are yet to be used in primary prevention of colorectal cancer, the evidence for some is overwhelming enough to require further investigation (Table I).

Aspirin and NSAIDs

Perhaps the most studied agent of CRC chemoprevention, aspirin has been in the limelight for over 4 decades [2]. Aspirin has been shown to reduce the incidence of colorectal cancer, though this effect varied according to the duration of treatment, follow up and the dose. The initial evidence in support of aspirin in CRC has been extrapolated from studies looking at the cardiac and vascular effects. Hence the dose involved was higher (300 to 1200 mg). Subsequent analyses showed the positive effect of aspirin even at lower doses (75-300 mg) [3]. Primary CRC prevention was not the primary endpoint in these studies, though adenoma prevention and CRC prevention in hereditary cancers have been successfully studied and clinically used by others. A review by Rothwell et al. [3] observed an absolute risk reduction of 1.5% in colorectal cancer after a 5-year period of treatment with at least 75 mg Aspirin. The Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers (ASCOLT) study will shed some interesting light on the issue of CRC treatment with Aspirin, when complete [4].

The side effect profile of aspirin, like GI bleed, intracranial bleed, macular degeneration, asthma, urticaria, hepatic dysfunction and drug

interactions, limits its use in the wider population. The addition of PPIs or H2 blockers might alleviate some of these side effects, but this needs further evaluation at a community level. The ongoing AspECT trial (Aspirin Esmoprazole Chemoprevention Trial), which has just closed for recruitment, might answer some of these questions.

A recent meta-analysis that confirmed the positive impact of aspirin on primary CRC showed that, the effect is maximal on right-sided cancer and hardly on rectal cancer. But a reduction of adenoma causing subsequent cancer reduction would not be expected to have such effect, unless the patho-physiology of adenoma-carcinoma sequence varies on either side. The current two theories of aspirin's mechanism of action are the irreversible COX inhibition and the antiplatelet properties, both of which explains the reduction of blood borne metastasis, rather than the site specific reduction in CRC incidence.

The cost effectiveness of this approach has been studied in detail. Though the use of this chemoprophylaxis has not been found to be cost effective in general population [5], a low dose aspirin in a screening population has been found to be cost effective in a study by Hassan et al. [1]. The efficacy of this approach is accepted as cost effective in medium and high-risk population by most authors. The window of benefit in general population would be between 55 to 75 years, with less than 55 years having a low incidence of CRC and in over 75 years, the risk potentially outweighing benefits.

NSAIDs represent a chemically diverse group with multiple biological effects and aspirin in just one of them. The anticancer efficacy of each agent varies, with Sulindac and Aspirin more widely

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Table I: Summary of chemo-preventive agents.

Chemo-preventive Agent	Possible Mechanism of Action	References	Evidence type	Author conclusions
Aspirin and NSAIDs	Irreversible COX inhibition and antiplatelet properties	[1-6]	Meta-analysis RCTs	Perhaps the most studied agent with encouraging results , more notable in right-sided tumours Cost effective in medium and high risk patient groups Optimum dose and side effect profile in the general population are issues being investigated Other NSAIDs don't necessarily have the same effect
Oestrogen	ER β receptors in the colon reduce the production of carcinogenic secondary bile acids, limit DNA damage and microsatellite instability	[7-10]	Retrospective studies Animal Studies	No evidence to support its use May have some therapeutic role in the future
Metformin	Reducing insulin resistance Activation of adenosine monophosphate activated protein kinase (AMPK) which suppresses cellular protein synthesis	[11]	Meta-analysis Retrospective studies	Promising result not only in colorectal but in other cancers Needs further specifically-designed clinical trials
Calcium	The calcium sensing receptor (CaSR) which is present in colonic cells is thought to play a role in CRC	[12-21]	Meta-analysis RCTs	Well-studied with conflicting reports in the literature Some effect in adenoma prevention Effects possibly affected by magnesium vitamin D or fibre intake Needs further studies to decide optimum dose and combination
Vitamin D		[24-26]	Meta-analysis	No chemo-preventive role
Magnesium	Involved in a number of biological reactions which regulate DNA proliferation, synthesis and apoptotic pathways.	[16-18,27,28]	Meta-analysis Case control studies	Good evidence of preventive role in adenomas and CRC, more in colon than rectal New focus on polymorphism of proteins involving Magnesium transport
Dietary Fibre	Bacterial fermentation of carbohydrates to yield biologically active short-chain fatty acids	[29-32]	Meta-analysis Observational Studies	Conflicting evidence, probably has some role as a preventive agent
Folate	Important for the synthesis of purines and thymidylate which is essential for DNA synthesis and repair.	[34-45]	Meta analysis RCTs Epidemiological studies	Conflicting reports in the literature May have a preventive role but could also promote growth of precancerous lesions

used in clinical studies, while agents like Rofecoxib show minimal effect. This makes the mechanism of cancer prevention of NSAIDs more controversial and causes the theory of COX inhibition to be questioned again. Other COX independent targets are being studied and a possibility of a highly specific new class of chemo-preventative agent looks promising [6].

Estrogen

Almost 80 years since Lacassagne's demonstrated the role of oestrogen in cancer, it's once again in the limelight [7]. Fraumeni et al. noted an increased incidence of CRC in nuns, apart from breast cancer [8]. But further studies did not deliver convincing evidence, suggesting a possible dose and source dependent effect; with long term endogenous oestrogen increasing the risk and short term concentrated exogenous oestrogen exposure being protective. Oestrogen receptors (ER) are subdivided into ER α , expressed more in breast endometrium and hypothalamus, and ER β expressed more in intestinal mucosa, prostate, lung and heart. Review by Foster concluded that normal colon is afforded some protection by oestrogen action most likely through the predominant ER β in colon. His review of evidence suggested that ER β reduces the production of carcinogenic secondary bile acids, limits DNA damage and microsatellite instability. Overall, though the prophylactic role of oestrogen in CRC is promising in animal studies,

it's therapeutic role in CRC, like in other hormone dependent cancers like breast and endocrine cancer, looks more promising [9,10].

Metformin

Metformin is a widely used drug for treatment of type-2 diabetes mellitus by reducing the circulating levels of glucose and insulin and thus improving the insulin resistance associated hyperinsulinemia and hyperglycemia. Cancer incidence was noted to be higher in diabetic patients and Insulin resistance is a risk factor for cancer. Hence, this mechanism of metformin's action is attributed to its anti-cancer role, apart from other possible mechanisms like activation of adenosine monophosphate activated protein kinase (AMPK) which suppresses cellular protein synthesis. A recent meta-analysis by Zhang et al. showed a 78% risk reduction in liver cancer incidence, 46% in pancreatic cancer and a 23% reduction in CRC incidence in patients on metformin. Another study by Currie et al., on a cohort of diabetic patients showed that patients on metformin had the lowest risk of cancer [11]. The effect on metformin in this role has to be further assessed in a clinical trial setting.

Diet and supplements

Various vitamins and micronutrients like Vitamin B6, Vitamin D, calcium, magnesium, iron, zinc and selenium, dietary folate, Butyrate, fiber, fat and protein have been implicated to have a protective effect in CRC.

Calcium

Calcium is involved in a number of metabolic reactions and disease such as diabetes and pancreatitis. Studies using colonic cell lines have shown high levels of calcium to inhibit proliferation and low levels promote it [12]. The calcium sensing receptor (CaSR) which is present in colonic cells is thought to play a role in CRC. Loss of CaSR may be an early step in tumourigenesis; as CRC's which are poorly differentiated and have a poorer prognosis are associated with less expression of CaSR. These cancers are less likely to respond to chemotherapy [13].

Calcium was once investigated as promising prophylactic agent and the Calcium Polyp Prevention study Group (CPPSG) in 1999 showed that calcium supplements could reduce the incidence of colorectal adenomas [14]. However, further studies on CRC development did not reflect this positive finding [15]. More recently, Dai et al. reported a conditional positive effect of calcium only when the calcium:magnesium intake ratio is low [16]. Magnesium has already been positively implicated in CRC prevention with a recent meta-analysis showing a 12% reduction in CRC risk with every 100 mg/day increase in magnesium intake [17,18]. Calcium and magnesium have the potential to antagonize each other's physiological effect and this could have potentially influenced the inconsistencies in calcium-alone studies. The importance of calcium:magnesium intake ratio has been further confirmed by the a subgroup analysis of the CPPSG data [19].

A meta-analysis of double blinded RCTs included 10 trials. Trial data analysis concluded no evidence of protective effect from calcium intake without vitamin D supplementation on risk of CRC or on total cancer [20].

Investigators from Women's Health Initiative (WHI) presented data from the clinical trial.

36,282 postmenopausal women in the U.S were included between the ages 50-79 years. They were given 1000 mg of elemental calcium carbonate plus 400 IU of vitamin D3 daily or placebo, with average intervention period of 7 years. They concluded that there was no evidence that supplementation reduced the incidence of CRC among post-menopausal women ($P=0.51$) [15]. Of note in the clinical trial, sigmoidoscopy or colonoscopy for participants were left to the discretion of their personal physician, resulting in 15% having no bowel assessment. In addition, the same cohort was also randomized to oestrogen and progesterone in a study. This may have confounded the results of the study.

In a chemoprevention study, a pilot of 194 CRC patients were randomized to calcium dose of 1800mg daily or placebo, over a period of 5 years. Patients were followed up with colonoscopy at 1, 3, and 5 years. The treatment arm showed 53% lower recurrence of an adenoma than in those taking placebo ($P=0.01$). Toxicity of calcium was also analyzed rates were similar between the two groups only one patient experienced hypercalcemia of >3.4 mmol/L [21]. Although the study was small, results and study design are promising enough to be trialed with a larger number of patients. The dosages used in this study were higher than previous studies examined.

In a European case-control study, researchers reported that for every 100 mg/day of calcium in the diet, the risk of CRC reduced by 5% (OR 0.95, 95% CI 0.92-0.99). A 37% risk reduction in CRC was associated when dietary calcium intake was 1000 mg/day. Results showed that increase in dietary fibre attenuated the effects of calcium on CRC, though when stratified by site this was not proven for rectal cancer [22].

A model of cost analysis of calcium as a chemopreventive agent found calcium supplementation combined with aspirin and colonoscopy screening as cost effective, preventing deaths. Daily intake of Aspirin and Calcium (carbonate form) was modelled at 81 mg for ten years and 1,200 mg at 25 years, respectively [23].

Vitamin D

Data from observational studies showed no evidence of a protective effect of vitamin D. A Cochrane review of vitamin D supplementation on cancer risk found no evidence for Vitamin D use and risk reduction in any cancer. In particular five RCTs with 45,598 participants were included in the analysis for CRC, analysis showed no evidence that vitamin D reduces the risk of CRC (RR 1.11) [24].

Wong et al. studied the relationship between Plasma 25-hydroxyvitamin D (25(OH)D) concentration and the incidence of prostate, lung and colorectal cancers in older men. They concluded that lower levels of vitamin D may reduce prostate cancer risk. By contrast, levels of vitamin D did not predict incidence of colorectal or lung cancers [25].

In a meta-analysis of prospective cohort studies including 2330 CRC patients, Maalimi et al. reported a strong association between mortality of CRC and levels of serum 25(OH)D, whereby higher levels were associated with a significant reduction in overall and disease specific mortality [26].

Magnesium

Magnesium is involved in a number of biological reactions which regulate physiological processes including DNA proliferation, synthesis and apoptotic pathways. Though the exact pathways have not been elucidated, it has shown to be involved in colon carcinogenesis [27]. A meta-analysis by Wark et al., which included three case control studies, found a 13% risk reduction in development of colorectal adenomas, when the daily intake was 100 mg/day. A case control study by the same researchers found that magnesium intake was associated with reduction in colorectal adenomas. When data was stratified by BMI and age; overweight individuals and subjects aged ≥ 55 had fewer incidences of adenomas with a higher magnesium intake [17].

This association between a higher magnesium intake and a slightly reduced risk of CRC, in particularly colon cancer, was highlighted in another meta-analysis by Chen et al. [18].

A recent meta-analysis which included seven of the eight studies used by Chen et al. [18], excluding a nested case-control study identified by authors to contribute significantly to heterogeneity in their analysis, found a higher risk reduction, of 19% highest vs lowest consumption of magnesium. Dose response analysis found a risk reduction of 18% per 100 mg/day, however there was evidence of significant heterogeneity among studies ($P=0.01$; $I^2=62.5\%$). When data was stratified by site of cancer, risk ratios were 0.76 and 0.82 for colon and rectal cancer without heterogeneity, but only statistically significant for risk of colon cancer ($P<0.001$) [28].

There is a new focus on polymorphism in genes which encode proteins for transporters of magnesium. Polymorphism in Transient Receptor Potential Melastatin (TRPM7), a newly found gene essential to magnesium absorption and homeostasis, has been shown to have a 60% risk of development of colorectal adenomas if there is an associated consumption of diets with a high calcium: magnesium intake ($P<0.01$) [16]. These findings provide one possible explanation for inconsistencies in previous studies of the association of magnesium intake with risk of CRC.

Fibre

Observational studies report that higher intake of dietary fibre (a heterogeneous mix including non-starch polysaccharides and resistant starches) is associated with reduced risk of colorectal cancer, but no randomised trials with prevention of colorectal cancer as a primary endpoint have been done.

A meta-analysis of 21 prospective studies showed a significant, dose-dependent protective effect of dietary fibre intake against colorectal

cancer [29]. Dietary fibre is a food-based measure that attempts to estimate the heterogeneous mix of carbohydrates that escape digestion in the small bowel and flow to the large bowel where they exert a wide range of physiological effects due, in part, to the bacterial fermentation of these carbohydrates to yield biologically active short-chain fatty acids [30]. An inverse association exists between starch intake and risk of colorectal cancer [31], which could be due to resistant starch (i.e., the dietary starch and starch degradation products that escape digestion in the small intestine of healthy individuals) [32].

In the Colorectal cancer Adenoma/carcinoma Prevention Programme (CAPP2) study, 463 individuals with Lynch syndrome were randomly assigned in a two-by-two factorial design to receive 600 mg aspirin or aspirin placebo or 30 g resistant starch or starch placebo, for up to 4 years.

There was no evidence that dietary supplementation with resistant starch affected risk of colorectal cancer in carriers of hereditary colorectal cancer.

Folate

Habitual Consumption of natural folates has been shown by studies to reduce cancer development. Folic acid is found abundantly in fruits and green leafy vegetables. Data from epidemiologic studies reports 40-60% reduction in the risk of sporadic colorectal neoplasms in individuals with high dietary folate intake [33-35]. This risk reduction is also reported in ulcerative colitis [36], a condition known to be associated with increased risk toward colorectal cancer [37].

Conversely, there is also an association between excessive folate intake and an increase in colon, prostate and breast cancer presumably by promoting the growth of precancerous lesions; this seems to be related to the dose and duration [38-40].

The exact mechanism of action of folate in CRC is not fully understood [34]. Folate is known to be important for the synthesis of purines and thymidylate [41], which is essential for DNA synthesis and repair.

A meta-analysis of folic acid supplementation for the prevention of recurrence of colorectal adenomas included 5 RCTs. It found the use of folate supplementation had no protective effects on the recurrence of colorectal adenomas, $P=0.49$ [42]. Another meta-analysis included 3 RCTs; it found similar evidence that there was no protective effect from folate on development of colon adenomas. However, it reported participants who received folate for over 3 years, the risk of an adenomatous lesion was increased [43]. This effect may result from timing of folate administration. Folate administration prior to the existence of early tumours may prevent development, whereas folate supplementation once early lesions are established may promote carcinogenesis [44].

A confounding factor in these studies is that those with higher intakes of folate tend to be health conscious, non-smoker; exercise more, take supplements and NSAIDs and have lower BMI [45].

Vitamin B6

Vitamin B6, a water-soluble vitamin, is essential for amino acid, glucose and lipid metabolism; a co-enzyme in reactions including DNA, RNA Synthesis and methylation [46]. The active form of this vitamin is pyridoxal 5-phosphate (PLP), the serum levels of which can be measured. Studies have either measured vitamin B6 intake from FFQ (Food Frequency questionnaires) or measured serum PLP levels.

A meta-analysis by Larsson et al. included nine studies on vitamin B6 intake and four studies on blood PLP levels. Results from studies on vitamin B6 intake were inconsistent, and there was significant heterogeneity. When one study was removed as it contributed

significantly to study heterogeneity, the results illustrated a 20% reduction in risk of CRC; 0.80 (95% CI, 0.69-0.92). Furthermore measurement of PLP in the four nested case controls showed for every 100-pmol/mL increase in blood PLP levels risk of CRC decreased by 49% [47]. The relationship between, vitamin B6 intake and blood PLP may not be correlated as bioavailability may differ from source [48] and its effects on CRC may be independent.

A large cohort study which followed up participants for 28 years showed there was no significant evidence that Vitamin B6 had any effect on development of colorectal cancer. Researchers also investigated whether time modified the risk of CRC, similar to the effects of folate; no association was found [48,49]. However, a smaller study with participants from Japanese, Caucasian, and Native Hawaiian descent (241 were recruited with CRC) showed that vitamin B6 may be protective against the development of colorectal adenomas; hence against the early stages of colorectal carcinogenesis. Though this study used flexible sigmoidoscopy to diagnose adenomas, the results were independent of other risk factors ($P_{\text{trend}}=0.002$). Interestingly, the study also measured plasma folate and vitamin B12, after adjusting for risk factors and plasma vitamin B6, there was no statistically significant association with adenoma risk ($P_{\text{trend}}=0.35$) [50].

Research has also focused on pre-diagnostic plasma PLP levels as a marker of overall mortality in CRC. 472 CRC patients were included from 3 cohorts (Nurses' Health Study, cohorts, Health Professionals Follow-up Study and Physicians Health Study) of which 169 CRC deaths were identified. Plasma PLP levels were grouped in quartiles <45 to ≥ 110 $\mu\text{mol/ml}$. It found that pre-diagnostic plasma PLP levels had no overall effect on CRC survival. When levels were stratified by stage of disease there was an association but that was not statistically significant [51].

Furthermore an observational study has further reported no significant association between vitamin B6 intake and CRC risk [52].

It is difficult to extract if Vitamin B6 affects CRC out of the independent effect of vitamin B6 from other nutrients such as vitamin D, folate and calcium given that their intakes are positively correlated with a risk reduction in CRC. There are no RCT's of effect of Vitamin B6 on CRC risk, although there is evidence that plasma PLP is related to reduced risk of CRC.

Boswellic acid

Boswellic acid is a mixture of pentacyclic triterpenes including beta-boswellic acid, 3-acetyl beta-boswellic acid, 11-keto-beta-boswellic acid and acetyl-11-keto-beta-boswellic acid (AKBA), all derived from the resin of *Boswellia* plants. Acetyl-boswellic acids exhibit anti-inflammatory behavior by inhibiting leukotriene synthesis and therefore has been studied in asthma, Inflammatory bowel disease, rheumatoid arthritis and osteoarthritis, with some beneficial effects [53].

In mice models, APC mice were exposed to AKBA, with a 48.9% ($P<0.001$) reduction adenomas, this may have an inhibitory effect tumorigenesis and further malignant progression [54]. The same research group demonstrated a 41.6% reduction of *in vitro* human colon adenocarcinomas with AKBA supplementation. Aspirin at 300 mg/kg was used as a comparison; it illustrated a similar reduction in tumours but this dosage of aspirin was toxic to the mice [55].

Research from other scientific studies has demonstrated that AKBA may increase apoptotic proteins in tumour cells, modulate b-catenin (an adherin-associated protein), for cell adhesion and signalling pathways in carcinogenesis, suppress inflammatory markers and circulating VEGF for angiogenesis [54-56].

AKBA has not exhibited any toxicity in mouse models; there is good scientific evidence for the use of AKBA as a chemo preventative agent.

More studies on human models are needed to see if similar results can be extracted.

Urodeoxycholic acid

Ulcerative colitis (UC) is known to increase the risk of CRC. Primary sclerosing cholangitis (PSC) is a condition characterized by progressive inflammation and fibrosis of the intra and extrahepatic bile ducts and 70% of cases are associated with ulcerative colitis. Patients with PSC and UC are at an increased risk of CRC compared to those with UC alone [57].

Ursodeoxycholic acid (UDCA) is a synthetic bile acid that is the 7- β epimer of chenodeoxycholic acid (CDCA). UDCA is used in the treatment of PSC and although there is some evidence of improvement of liver biochemistry, the effect on outcomes is not clear [58-61].

Experimental data suggest the use of UDCA in AOM mice models reduced the risk of colonic cancers when UDCA was supplemented in the diet.

In an RCT in patients with known colonic adenoma, UDCA was given to one group at 8-10mg/kg and they were followed up for 3 years. Compared to the placebo group there was no significant difference in the overall rate of adenoma recurrence, there was a significant UDCA-related reduction in recurrence of adenomas with high-grade dysplasia adjusted odds ratio (OR): 0.61, (95% CI: 0.39-0.96; $P=0.03$) [62].

Mechanism of UDCA actions are not completely understood, UDCA may prevent colonic neoplastic transformation by counteracting the tumor-promoting effects of secondary bile acids such as DCA. A trial which included 56 patients using high dose UDCA (28-30 mg/kg/day), found an increase in the risk of colorectal cancer $P=0.02$ [63].

A meta-analysis evaluating the use of UDCA in IBD found that there was no overall protective effect compared to controls. However there was very little uniformity between studies as the dosages of UDCA given to participants varied or was not calculated accurately leading to heterogeneity [64].

The numbers of participants in studies are small, lack of consistency between trials means that there is no strong evidence for the use of UDCA as a chemo preventative agent for CRC especially in patients with PSC.

Green tea

The exposure of green tea has been studied mainly in case-control studies which have found an inverse correlation to the amount of green tea drank and the incidence of CRC. However, this runs the risk of recall bias.

One meta-analysis included six studies; of which only four included sufficient data when analyzing the green tea consumption and the risk of colon or rectal cancer. Though anti-oxidant properties have been reported of green tea, there is very little evidence to support green tea consumption as a chemopreventive agent [65].

Carnitine

Carnitine (3-hydroxy-4-N-trimethylaminobutyric acid) is an essential cofactor in the metabolism of lipids and essential to the production of cellular energy. It is a potent anti-free radical agent and inhibitor of lipid peroxidation [66]. Its ability to protect tissues against oxidative damage is well established [67]. Although results of mice studies have been promising [68], data from human studies is lacking.

Conclusion

This review suggests that aspirin may be effective in the prevention of CRC. If the adenomas are used as a surrogate endpoint of colorectal cancer, aspirin use as a chemopreventive agent is very convincing. However, the optimal dose of aspirin as a chemopreventive agent has

not yet been established. Aspirin is associated with adverse effects, and so the risk-benefit ratio would need to be carefully considered for each population before these agents could be recommended for chemoprevention.

Of the other agents considered in the review only calcium has been shown to be having a value as a chemopreventive agent although its effect is only on reducing incidence of adenoma rather than on prevention of colorectal cancer.

Further research is required to ascertain the longer-term risk-benefit balance for potentially effective chemopreventive agents. Large studies with follow up over decades to assess CRC incidence as an outcome would be valuable, apart from testing different combinations of the agents discussed above.

Conflict of Interest

Authors have no conflict of interest to disclose.

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