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TOPIC HIGHLIGHT

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Primary prevention of colorectal cancer: Myth or reality?

Marcela Crosara Teixeira, Maria Ignez Braghiroli, Jorge Sabbaga, Paulo M Hoff

Marcela Crosara Teixeira, Maria Ignez Braghiroli, Jorge Sabbaga, Paulo M Hoff, Division of Medical Oncology, Instituto do Câncer do Estado de São Paulo, Hospital Sírio Libanês, São Paulo, SP CEP 01246-000, Brazil
Author contributions: Crosara Teixeira M, Braghiroli MI and Sabbaga J performed the literature search and wrote the paper; Hoff PM reviewed the article and provided critical appraisal.
Correspondence to: Marcela Crosara Teixeira, MD, Division of Medical Oncology, Instituto do Câncer do Estado de São Paulo, Hospital Sírio Libanês, Avenida Dr. Arnaldo 251, São Paulo, SP CEP 01246-000, Brazil. marcela.teixeira@icesp.org.br
Telephone: +55-11-38932686 Fax: +55-11-30831746
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Abstract

Colorectal cancer incidence has been rising strongly in parallel with economic development. In the past few decades, much has been learned about the lifestyle, dietary and medication risk factors for this malignancy. With respect to lifestyle, compelling evidence indicates that prevention of weight gain and maintenance of a reasonable level of physical activity can positively influence in lowering the risk. Although there is controversy about the role of specific nutritional factors, consideration of dietary pattern as a whole appears useful for formulating recommendations. Though quite often recommended, the role for many supplements, including omega-3, vitamin D, folate, and vitamin B6, remains unsettled. Only calcium and vitamin D supplementation appear to add a modest benefit, particularly in those with a low daily intake. With regard to chemoprevention, medications such as aspirin and nonsteroidal anti-inflammatory drugs, and postmenopausal hormonal replacement for women might be associated with substantial reductions in colorectal cancer risk, though their utility is affected by their side effect profile. However, the role of agents such as statins, bisphosphonates and antioxidants have yet to be determined. Ultimately, primary prevention strategies focusing on modifying environmental, lifestyle risk factors, and chemopreventive drugs are options that have already been tested, and may impact on colon cancer incidence.

Key words: Primary prevention; Colorectal cancer; Physical activity; Diet; Chemoprevention

Core tip: There is an interesting potential for primary prevention of colorectal cancer focusing on modifying environmental, lifestyle risk factors, and using chemopreventive drugs. Consistent evidence supports some of these approaches, but others are controversial, although quite accepted by the general population. Since the primary prevention is an important complement to colorectal cancer screening, adding to reduce its incidence, we review the data supporting some of these widespread recommendations on physical activity, diet and drugs for colorectal cancer prevention.

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INTRODUCTION

Colorectal cancer (CRC) is a common and lethal disease. In the United States, nearly 6% of individuals will develop this malignancy during their lifetime and one-half of those will die from it. The risk of developing CRC is influenced by both environmental and genetic factors[1]. Worldwide, the CRC incidence rose in parallel with economic development, with the majority of cases occurring in industrialized countries since it has been strongly associated with a Western lifestyle. A large number of factors have been reported to be associated with a decreased risk

Table 1 Diet and colorectal cancer prevention

Role on CRC prevention	Evaluated in randomized clinical trails	Recommendation for general population	Recommendation for high risk population
Fruits and vegetables	No	Balanced diet	Balanced diet
Dietary fiber	Alberts *et al*[23], 2000 Schatzkin *et al*[24], 2000	Balanced diet	Balanced diet
Resistant starch	Mathers *et al*[26], 2012	No	No
Folate	Cole *et al*[33], 2007 Logan *et al*[34], 2008 Wu *et al*[36], 2009	Recommended daily dose	Recommended daily dose
Vitamin B6	No	No	No
Vitamin D	Wactawski-Wende *et al*[45], 2006	Recommended daily dose	Recommended daily dose
Calcium	Wactawski-Wende *et al*[45], 2006	No	Calcium supplementation Dose: 700-1250 mg/d
Dairy products	No	Balanced diet	Balanced diet
Omega-3	West *et al*[56], 2010	Balanced diet	Omega-3 supplementation (eicosapentaenoic acid) Dose: 2 g/d

CRC: Colorectal cancer.

of CRC development[2] but others such as obesity[3] high red meat consumption[4], cigarette smoking[5] and alcohol abuse[6]. Although the best strategy for reducing CRC mortality is based on early diagnosis, primary prevention strategies focusing on modifying environmental and lifestyle risk factors are options that have already been tested.

It is estimated that 50% of neoplasm are preventable[7]. The fear of developing cancer leads asymptomatic people to modify lifestyle risk factors and even undergo medical interventions to prevent the onset of disease. While evidence supports some of these approaches, others are controversial, although quite accepted by the general population. In this article we review the data supporting some of these widespread recommendations of protective factors.

PHYSICAL ACTIVITY

Much of the evidence for the benefit of physical exercise comes from long-term observational studies but the mechanism underlying the apparent protective association of physical activity and colorectal cancer development is not well known. Biological mechanisms include the reduction in the intestinal transit time, decreased insulin and insulin-like growth factor levels and modulation of the immune system[8].

Several data suggest that regular physical activity, either occupational or in leisure time, appears to be associated with protection from colorectal cancer[9]. In a meta-analysis of 21 studies, there was a significant 27 percent reduced risk of proximal colon cancer when comparing the most *vs* the least active individuals (RR = 0.73; 95%CI: 0.66-0.81) and an almost identical result was found for distal colon cancer (RR = 0.74; 95%CI: 0.68-0.80)[10].

Despite the enthusiasm, the evidence from clinical trials to establish the benefit of exercise is inadequate. Successful, randomized clinical trials require good adherence in order to show a difference between groups. Also, from an ethical or practical standpoint it is not possible to prevent those assigned to the control group from engaging in exercise activities. Another bias is that after several years of follow up, the total exercise hours might be similar in both groups, thereby preventing any definitive conclusion on its value as a preventive measure. So, no intervention trials of physical activity for CRC prevention have been reported yet. It is not known if, as observed in cardiovascular diseases, the type and intensity of exercise would matter and whether weight loss alone in the absence of increased physical activity would be enough to decrease CRC risk in adults[7].

DIET

Several studies have examined various strategies utilizing specific dietary factors and their ability to modulate the development of cancers of the gastrointestinal tract[11]. The effects of fruits and vegetables, fat, red meat, fish and fiber, on colorectal carcinogenesis have been reasonably well defined. Folate, antioxidants, vitamins, calcium and omega-3 fatty acids have emerged as possible agents in chemoprevention. Table 1 summarizes the dietary factors discussed below reporting the best evidence in studies evaluating this intervention.

Fruit and vegetables

An association between diet and high intake of fruits on colorectal cancer incidence has been reported in several epidemiological studies[11,12]. An observational cohort study found that individuals who consumed less than 1.5 servings of fruit and vegetables per day had a relative risk for developing colorectal cancer of 1.65 (95%CI: 1.23-2.20, P_{trend} = 0.001) compared with individuals who consumed more than 2.5 servings[12]. On the other hand, a prospective study that combined subjects from the nurses' health study (88764 women) and the health professionals' follow-up study (47325 men) found no significant association between the consumption of fruits,

vegetables, or both on the incidence of either colon or rectal cancer[13]. In a more recent pooled analysis, this association was shown to be even less consistent[14,15]. The data that included 14 cohort studies concluded that eating more than 800 g of fruits and vegetables daily, compared to less than 200 g, decreased risk for distal (RR = 0.74; 95%CI: 0.57-0.95) but not for proximal colon cancer[14]. A later meta-analysis of 19 cohort studies concluded that there was a weak protective effect of fruit and vegetable when compared highest *vs* lowest intakes (RR = 0.92; 95%CI: 0.86-0.99) and that the protective effect appeared limited to colon cancers[16]. Most of the risk reduction was attributable to increasing intake above a threshold value of 100 g/d, with relatively little benefit associated with higher quantities. Taking into account that 100 g is the weight of a small apple, there might be little or no benefit of increasing the consumption of fruits and vegetables beyond the levels of a reasonably balanced diet.

Dietary fiber

The relationship between various types of high fiber diets and colorectal cancer risk was investigated in many epidemiological studies. Fiber derived from fruits, vegetables and grains were proposed to dilute or adsorb fecal carcinogens, modulate colonic transit time, alter bile acid metabolism, reduce colonic pH, or increase the production of short-chain fatty acids lowering the risk of colonic neoplasm[17].

Case-control studies have generally shown a protective association[18], meaning a decreased risk of colonic adenomas and CRC with higher intake of fiber, as also observed in three large epidemiological studies[19-21]. On the other hand, a pooled analysis of 13 prospective cohort studies involving 725628 individuals with a 20 years-follow up found that the association between dietary fiber intake and CRC risk was not significant after accounting for other dietary risk factors[22]. Results from randomized controlled studies are also discordant. Two randomized trials, fiber supplementation had no significant protective effect for the development of total colorectal adenomas[23,24] in a four-year follow up. Multiple potential explanations may account for the different results found among studies, and the amount of fiber intake may be one important factor. As was found in the wheat bran supplement trial[23], only 74% of the high-fiber group consumed more than 75% of their supplement compared to 84% of the low-fiber group. Probably, the daily long-term consumption of higher levels of fiber would be impractical in the general population and might be not feasible even in the context of a clinical trial.

Resistant starch

The starch that we eat is digested at different rates; the resistant starch found in some types of beans and intact grains goes all the way through the small intestine without being digested at all. In this way, it is more like fiber, and in some cases is classified and labeled as fiber. The fact that resistant starch is fermented into potentially beneficial short-chain fatty acids in the colon raised initial enthusiasm to its potential as a chemopreventive agent. In humans, resistant starch reduces cell proliferation in the upper part of the colonic crypts, and some epidemiological studies have supported an inverse association between resistant starch intake and colorectal neoplasia[25]. A randomized multi-center control trial conducted among European individuals with Lynch syndrome failed to show a beneficial impact of resistant starch at a dose of 30 g/d[26]. Although it has been hypothesized that higher amounts of resistant starch intake might have a protective effect, the 30 g dose tested was already more than three times higher than typical daily intake.

Vitamin B

B vitamins have a role in the 1-carbon metabolic pathway, which involves the transfer of 1-carbon groups for DNA synthesis and DNA methylation[27]. On that premise, B vitamins, especially folate and vitamin B6, have been studied to investigate if its low levels may increase cancer risk through aberrations in DNA synthesis, methylation and repair.

Folate: Among different types of B vitamins, folate has been extensively investigated in terms of its relation to cancer risk. There is evidence from epidemiologic, animal and human studies suggesting that folate status modulates the risk of developing cancers in colorectum tissues[28]. Folate depletion appears to enhance carcinogenesis and may induce *p53* mutations. The immunohistochemical assay for p53 expression in colon cancer specimens from a large prospective cohort found that low dietary folate was associated with increased risk of colorectal cancers with *p53* mutations[29].

Several studies evaluated dietary folate and folic acid (the synthetic form of folate) supplementation as a protective factor. Substantial observational data found that a folate long-term intake of $\geqslant$ 800 μg/d is associated with a lower risk of colorectal cancer (RR = 0.69, 95%CI: 0.51-0.94) compared with < 250 μg/d[30]. However, A meta-analysis of 16 studies suggested that the protective effect of folates might be limited to dietary rather than supplemental intake[31]. There is some evidence that folate's protective effect may also depend upon an individual's particular genotype for methylenetetrahydrofolate reductase, an enzyme involved in folate metabolism[32]. The role of folate as a preventive agent has become uncertain with the results of at least two randomized controlled trials. Folic acid supplementation in individuals with a history of colorectal adenoma did not reduce the risk of recurrent adenomas[33,34]. In one of the trials, folate supplementation was even associated with an increased risk of having three or more adenomas and of developing other kinds of cancers, indicating the possibility of a detrimental rather than beneficial role in adults[33]. Findings from population-based studies support this possibility since a small increase in the incidence of colon cancer was observed concurrent with the fortification of the

United States food supply with folic acid for prevention of neural tube defects[35]. Although these studies suggest that an additional supplement of folic acid is unlikely to benefit those who already have had a colonic neoplasm, the effect of folic acid supplementation among individuals with baseline folate deficiency is yet not known. Indeed, another randomized trial has shown a significant decrease in adenoma recurrence among individuals with low plasma folate concentrations at baseline (RR = 0.61; 95%CI: 0.42-0.90)[36].

Vitamin B6: It was only over the last decade that the association between vitamin B6 and risk of colorectal cancer gained attention. Prospective studies examining the association between vitamin B6 intake or blood levels of pyridoxal 5'-phosphate (PLP), the active form of vitamin B6, and the risk of colorectal cancer have shown inconsistent results[37,38]. A meta-analysis of prospective studies, demonstrated a pooled relative risk of colorectal cancer for the highest *vs* lowest intake of vitamin B6 intake and of blood levels of PLP of 0.90 (95%CI: 0.75-1.07) and 0.52 (95%CI: 0.38-0.71), respectively. After omitting one study from The Netherlands that had a narrow range of exposure to vitamin B6 (0.6- to 0.7-mg difference in median intake between the highest and lowest groups) the protective effect of highest *vs* lowest vitamin B6 intake on colorectal cancer risk was statistically significant (pooled RR = 0.80; 95%CI: 0.69-0.92)[39].

Vitamin D

The majority of Vitamin D in our body is synthesized by UVB irradiation of the skin, but this vitamin can be found in dietary sources also. Its active form, 1, 25 dihydroxy vitamin D (25OHD), is responsible for the established role of vitamin D in calcium homeostasis via activation of the vitamin D receptor (VDR)[40]. Upon activation by vitamin D the VDR binds to response elements on DNA and transactivates several genes that control cell proliferation, differentiation and apoptosis as well modulation of the immune response, perhaps influencing CRC development[41]. Observational studies suggested an association between poor vitamin D status and the risk of almost all cancers[42], with colon cancer been identified as the most related one.

A meta-analysis of nine case-control studies showed that each 4 ng/mL increase in pre-diagnosis of 25OHD serum level was associated with a 6% decrease in colorectal cancer risk[43]. For interventional trials, the results of vitamin D supplementation are, once again, discordant. A meta-analysis showed a 50% lower incidence of colorectal cancer in individuals with higher serum levels of 25OHD ($\geq$ 33 ng/mL) compared with levels < 12 ng/mL[44]. The largest randomized trial included was the Women's Health Initiative, with 36282 postmenopausal women receiving daily supplementation of 400 IU vitamin D plus 1000 mg of calcium or placebo. Initially, this trial found an inverse association between baseline levels of 25OHD and colorectal cancer risk, but over a follow-up period of 7 years the association was no longer significant[45].

Calcium and dairy products

A protective effect of dietary calcium on the risk of colorectal cancer has been proposed assuming that Calcium can bind to toxic secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon[46]. An alternative explanation for the protective association is the effect of calcium in decreasing cell proliferation, stimulating differentiation, and inducing apoptosis in the colonic mucosa[47].

An analysis of two large prospective trials examining the association between calcium intake and colon cancer risk, found an inverse association between higher total calcium intake (> 1250 mg/d *vs* $\leqslant$ 500 mg/d) and distal colon cancer[48]. The analysis also suggests a minimal incremental benefit for additional calcium intake beyond the dose of 700 mg/d. Similarly, a pooled analysis of 10 prospective cohort studies showed 22% reduction in risk of colorectal cancer, comparing individuals in the highest to the lowest quartile of calcium intake[49].

The findings from observational studies have been evaluated in at least 3 randomized trials. A meta-analysis of these 3 trials comprising 1485 subjects with previously removed adenomas concluded that the risk of recurrence of colorectal adenomas was significantly lower in patients randomized to calcium supplementation[50]. Despite these benefits in adenoma prevention trials, whether calcium supplementation reduces the risk of colorectal cancer is unproven. The only large controlled trial to evaluate this issue found no significant difference in the rate of invasive colorectal cancer with calcium and vitamin D supplementation[45]. Questions have been raised as to whether the doses of calcium and vitamin that were used in the trial were sufficient to prevent colon cancer.

Some dairy products have been hypothesized to protect against colorectal neoplasia because of their high calcium content. A meta-analysis of 19 cohort studies showed a protective effect of diet with higher milk and total dairy product against colon cancer risk but not rectal cancer (RR = 0.83; 95%CI: 0.78-0.88)[51].

Omega-3

Based on the premise that populations with a high intake of fish have low incidence and mortality from CRC cancer, some studies have evaluated the role of omega-3 as a protective factor[52]. While some observational studies suggested an inverse association between diet with higher rates of fish consumption and colorectal cancer[53], others did not find a consistent relation[54]. A meta-analysis of 33 observational studies found an overall colorectal cancer risk reduction of 12% with fish consumption. The significant inverse association was more pronounced for rectal cancer (summary OR = 0.79; 95%CI: 0.65-0.97)[55].

Interventional trials addressing this issue have not been reported yet. The best evidence comes from randomized trial that found a significant reduction in the

Table 2 Drugs and colorectal cancer prevention

Role on CRC prevention	Evaluated in randomized clinical trails	Recommendation for general population	Recommendation for high risk population
Aspirin	Logan *et al*[34], 2008 Baron *et al*[61], 2003 Sandler *et al*[62], 2003 Benamouzig *et al*[63], 2011 Rothwell *et al*[65], 2010	No	Aspirin supplementation Dose: 80-1200 mg/d
NSAIDs	Arber *et al*[69], 2006 Baron *et al*[70], 2006 Bertagnolli *et al*[71], 2006	No	No, due to toxicity profile
Antioxidants	Lippman *et al*[76], 2009 Greenberg *et al*[77], 1994	No	No
Statins	Pedersen *et al*[80], 1996 Sacks *et al*[81], 1996 Emberson *et al*[82], 2012	No	No
Bisphosphonates	No	No	No
Postmenopausal hormonal therapy	Chlebowski *et al*[93], 2004	No	No, due to toxicity profile

CRC: Colorectal cancer; NSAIDs: Nonsteroidal antiinflammatory drugs.

incidence of adenomas with omega-3 supplementation in individuals with familial adenomatous polyposis[56].

DRUGS

In order to lower the risk of CRC some medications have been investigated as potential protective agents. Table 2 summarizes the drugs discussed below reporting the best evidence in studies evaluating this intervention.

Aspirin and *nonsteroidal antiinflammatory drugs*

The first evidence of a chemopreventive role of aspirin in colorectal cancer development came from a large case-control study published in 1988 exploring potential relation between numerous medications and colorectal cancer[57]. The authors were surprised with an inverse association between aspirin use and risk of colorectal cancer. Subsequently, substantial observational and intervention trials investigating aspirin and others nonsteroidal antiinflammatory drugs (NSAIDs) demonstrated a risk reduction of colonic adenomas and colorectal cancer in the range of 20% to 40%[58-60].

Evaluating the chemopreventive use of aspirin, most interventional placebo controlled trials included individuals with a history of colorectal adenomas or cancer[34,61-63], and a meta-analysis of these trials found an absolute risk reduction of 6.7% (95%CI: 3.2%-10.2%) on incidence of adenomas for aspirin users[64]. Although the analysis was not updated with the four-years follow-up and the results from one of the clinical trials showed no difference in adenoma recurrence rate, more and more data are coming out bringing robust evidence supporting the protective effects of aspirin.

Late reports of the British randomized controlled trials of aspirin primarily addressing cardiovascular endpoints reported reductions of up to 50% in colorectal and other cancer incidences and death, after a period of at least five years[65].

Data regarding the optimal dose and duration of aspirin intake for colorectal neoplasia prevention is still not well established. Trials evaluated daily doses varying from 80 to 325 mg[34,61-63], 600 mg/d on studies with Lynch syndrome population[66], and two large randomized trials even used higher doses of 1200 mg/d[65]. Lower and higher doses of aspirin appear to be beneficial and the effect was more pronounced for longer durations of use, although the minimum dose and duration of aspirin to achieve the protective effect is still uncertain.

For non-aspirin NSAID, several observational data supporting their role in colorectal cancer prevention have been reported[59,67,68] but few interventional trial data are available. Evaluating the COX-2 selective inhibitors celecoxib and rofecoxib, three randomized trials showed lower adenoma recurrence among patients with a prior history of adenoma who took these medications[69-71]. Patients randomized to celecoxib (200-400 mg/d) experienced a significant risk reduction for adenoma with a 45% lower risk for higher and 33% lower risk for lower doses[71]. A similar benefit was noted in a trial using rofecoxib, but this drug is no longer commercially available because of its association with cardiovascular events, as was observed with celecoxib, and bleeding from peptic ulcers[70].

The NSAID sulindac has been evaluated in a prospective trial that randomized 375 individuals with a history of adenomas to either combination of sulindac and ornithine decarboxylase inhibitor difluoromethylornithine (DFMO) or placebo[72]. The combination therapy showed a significantly lower recurrence rate of overall adenomas and a lower risk for advanced adenomas (0.7% *vs* 8.5%; RR = 0.085; 95%CI: 0.011-0.65), or multiple adenomas (1% *vs* 13.2%; RR = 0.055; 95%CI: 0.0074-0.41). Despite the encouraging results, concerns about potential harmful adverse effects such as hearing loss and cardiovascular toxicity decreased the enthusiasm for prescribing this combination.

Antioxidants

Several antioxidants, such as b-carotene, vitamin A, vitamin C, vitamin E and selenium are supposed to have a cancer preventive role since they fight free-radicals that may cause oxidative DNA damage and ultimately cancer development[73].

Despite the encouraging results from observational studies[74,75], intervention trials did not find a strong relationship between antioxidants intake and colorectal neoplasia incidence. A randomized placebo-controlled trial designed to examine antioxidant supplements such as oral selenium (200 μg/d) and vitamin E (400 IU/d), did not find any pre-specified cancer risk reduction, including colorectal cancer[76]. In another trial including individuals with prior adenoma, no association with risk of recurrent adenoma was demonstrated by vitamin C, vitamin E, and b-carotene supplements[77].

A meta-analysis of eight placebo-controlled trials with a total of 17620 participants found no convincing evidence that antioxidant supplements including b-carotene and vitamins A, C, and E, had a significant beneficial effect on primary or secondary prevention of colorectal adenomas[78], and its use cannot be recommended for this purpose.

Statins

Observational studies have raised the possibility that the use of statins may decrease overall risk of cancer including colorectal cancer[79]. Two large clinical trials evaluating the benefit of simvastatin[80] and pravastatin[81] for coronary artery disease showed a reduction in the incidence of colon cancer, as a secondary endpoint.

A recent meta-analysis of 27 randomized trials involving 174149 patients found no effect of statins on the incidence or mortality from, any type of cancer in a median follow-up of 4.9 years (RR = 0.98; 95%CI: 0.92-1.05)[82]. But so far, none of the trials were specifically designed to investigate its role in colorectal cancer prevention.

Bisphosphonates

In preclinical studies, bisphosphonates were shown to inhibit angiogenesis, invasion and adhesion of tumor cells, and overall tumor progression[83] and a reduced proliferation and induction of apoptosis of colon cancer cells has also been demonstrated[84]. On the clinical scenario of bisphosphonate, two large case-control trials suggested that long-term bisphosphonate use was associated with a reduced risk of colorectal cancer[85,86].

Recently, a meta-analysis with one cohort and three case-control studies including a total of 94405 individuals exposed to bisphosphonates and 283181 unexposed to bisphosphonates, 16998 colorectal cancer cases and 108197 controls, suggested a reduced risk of colorectal cancer with any exposure to oral bisphosphonates (OR = 0.71; 95%CI: 0.78-0.97)[87]. The analysis, however, did not include a null cohort study of 86277 women enrolled onto the nurses' health study with 801 documented cases colorectal cancer[88].

Postmenopausal hormonal therapy

Observing that the ratio of women to men with colorectal cancer is lower for premenopausal women than for postmenopausal women[89], researchers investigated whether postmenopausal hormonal therapy could reduce risk of colorectal cancer.

Observational data suggest an protective effect between postmenopausal hormone use and risk of colorectal cancer (multivariate RR = 0.65; 95%CI: 0.50-0.83)[90], and two meta-analyses including epidemiological studies confirmed this findings[91,92].

The protective effect was also seen in the Women's Health Initiative (WHI) randomized, placebo-controlled trial conducted among nearly 17000 post-menopausal women. Combined estrogen plus progestin hormone therapy but not estrogen alone was associated with a reduction in colorectal cancer risk[93]. Although, longer term follow up of this study suggest the possibility that estrogen plus progestin therapy may decrease cancer incidence but not mortality since CRCs diagnosed in ones receiving combined therapy were more advanced at diagnosis and were associated with a non-significant higher mortality rate[94].

CONCLUSION

We reviewed here data with reasonable potential to support primary prevention of colorectal cancer through incorporation of physical activity on daily routine, but regarding dietary factors and medications, the available data do not allow us to make definitive life changing recommendations.

Aspirin and other NSAID have consistently been shown to be protective factors, but due to the concern about potential toxicities, their routinely use is not recommended in general. So, we should attempt to prescribe pharmacological prevention to specific high risk groups, for which the benefits associated with their use may outweigh the risks. Although the preventive benefit seen with postmenopausal hormone therapy seems consistent, the balance between pros en cons do not support a recommendation for its use as a means of preventing colorectal cancer only , specially taking into account the increased risk of developing breast cancer and cardiovascular diseases[95].

Increasing consumption of fruits and vegetables or fiber do not have a strong anti-cancer benefit, and neither do supplementation of folate, vitamin D, calcium or vitamin B6. Also there is no convincing evidence of chemopreventive use of statins, antioxidants or oral bisphosphonates that would allow their recommendation for CRC lowering risk.

Thus, primary prevention is an important complement to colorectal cancer screening and prevention, adding to reduce its incidence. Being said that, further research is still needed to better define the protective agents that are worthwhile recommending lifestyle modifications.

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