

## Review

# The impact of Mediterranean diet on colorectal cancer recurrence following chemotherapy treatment: A systematic review

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## Background

Previous research suggests that the Mediterranean diet (a diet high in fruits and vegetables, lean protein, legumes, whole grains, and olive oils) provides protective effects against colorectal cancer. However, there has been little research to determine how the Mediterranean diet could help prevent the recurrence of colorectal cancer following chemotherapy treatment.

## Objective

This systematic review assesses the impact of the Mediterranean diet on the rate of recurrence following colorectal cancer treatment.

## Methods

A systematic search on PubMed, UNE Library, and EMBASE was conducted to find all research studies assessing the Mediterranean diet and its effects on colorectal cancer and post-treatment effects. Article titles and abstracts were screened for relevance in addition to full article screening for eligibility and were quality rated based on ANDEAL criteria.

## Results

Sixteen studies met the eligibility criteria and, as a result, were included. One study assessed lifestyle factors; three studies assessed the components of the Mediterranean diet and their effects on colorectal cancer; one study assessed the dietary inflammatory index and its impact on colorectal cancer; five studies assessed adherence to the Mediterranean diet; four studies assessed diet following cancer treatments; and two studies assessed long-term nutritional intervention on cancer recurrence. The results revealed that the Mediterranean diet has a positive impact on reducing the risk of colorectal cancer, with potential health benefits following treatment for colorectal cancer. Limitations in analyzing results include being a time-locked study, inability to access all articles on the topic, use of English-only articles, and limitation of search terms utilized.

## Conclusions

While previous research reveals evidence that the Mediterranean diet reduces the risk of colorectal cancer, there is compelling data to suggest that adherence to the Mediterranean diet, as a normal diet pattern following treatment for colorectal cancer, could reduce the rate of recurrence. Future research is needed to examine the effects of the Mediterranean diet following colorectal cancer treatment.

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## INTRODUCTION

Colon cancer is the third (3) leading cause of cancer-related deaths in the United States in men, the fourth (4) leading cause in women, and the second (2) leading cause when men and women are combined, expected to cause roughly 53,010 deaths in 2024 (American Cancer Society 2024). There is expected to be about 106,590 new cases of colon cancer (54,210 in men and 52,380 in women) as well as about 46,220 new cases of rectal cancer (27,330 in men and 18,890 in women) in 2024 (American Cancer Society 2024). There are various factors that can increase the risk of colon cancer such as lifestyle and nutrition, along with genetic influences. While there are many studies that investigate diet and the prevention of colon cancer, little research has been done on the impact of the Mediterranean diet (MedDiet) following treatment of colon cancer (Winkels et al. 2014). This study analyzes lifestyle factors, Mediterranean diet and first-time colorectal cancer diagnosis, contributions from the dietary inflammatory index, adherence to the MedDiet, post diagnosis and the MedDiet, and long-term follow-up post diagnosis. The purpose of this systematic review is to assess the impact of the Mediterranean diet following colorectal cancer treatments on the rate of recurrence.

Colon cancer, like many other cancers, causes a large amount of inflammation; and while inflammation of the tissue in the colon does not directly initiate colorectal tumors, it does follow tumor development (Terzić et al. 2010). Innate immune system, adaptive immune cells, intestinal epithelial cells, and other stromal cells all play a role in cancer-associated inflammation (Long et al. 2017). Intestinal microflora plays a major role in homeostatic immune and metabolic functions by metabolizing non-absorbed carbohydrates, dead epithelial cells, and mucus, while also producing metabolites that affect epithelial cell function, energy balance, and immune response (Terzić et al. 2010; Irrazábal et al. 2014). The intestinal barrier becomes compromised when intestinal tissue is associated with colorectal cancer. When the intestinal microbiota is seriously disrupted by any means, there is a dramatic increase in the risk of developing colorectal cancer (Terzić et al. 2010; Irrazábal et al. 2014).

The Mediterranean diet incorporates many foods and food patterns (higher intake of fruits and vegetables, whole grains, and legumes with decrease of salt and saturated fats) with anti-inflammatory properties which may help reduce the risk of colorectal cancer returning following chemotherapy treatment. Here we review some of these in detail.

One gut component that is suggested to promote the integrity of the intestinal mucosa is short-chain fatty acids (SCFAs). SCFAs are created through the fermentation of non-digestible dietary starches. The most common SCFAs are acetate, propionate, and butyrate (Cox et al. 2015). Butyrate is a common energy source for healthy colonic epithelial cells (Irrazábal et al. 2014). In colon cancer cells, butyrate inhibits proliferation and suppresses the growth of cancer cells (Gonçalves and Martel 2013). Butyrate has been found to be one of the most important mediators of epithelial function and regulation. One study demonstrated that people with the highest colonic content of butyrate

have the lowest risk (1:100,000) of colon cancer (Cox et al. 2015). In a follow-up study where low colonic SCFAs and high bile acids in high colon cancer risk populations were assessed, the fecal SCFAs were decreased in the population with a higher risk of colon cancer. This supports the idea that SCFA production is lower in this high-risk population, which includes those following chemotherapy treatments for colorectal cancer (O'Keefe et al. 2009).

Gut microbiota play a role in maintaining the gastrointestinal (GI) barrier and intestinal homeostasis. When intestinal homeostasis is disrupted, inflammation results (Terzić et al. 2010; Irrazábal et al. 2014; Ou et al. 2012). Recent data have implied that gut microbiota composition is associated with metabolic disorders and inflammatory bowel disorders (Ríos-Covián et al. 2016). The gut microbiota is greatly impacted based on macro- and micronutrient intake (Ríos-Covián et al. 2016). With a diet high in protein or fat with adequate dietary fiber, SCFAs can be increased, levels of beneficial microbes can be restored, and the levels of toxic metabolites can be decreased (Koh et al. 2016).

The dietary fiber referred to here is an indigestible plant fiber that passes through the GI tract, binds to potential nutrients and other substances in the gut, and helps with absorption and metabolism (Ou et al. 2012; Ríos-Covián et al. 2016). Dietary fiber has been shown to counteract the earliest stages of colonic carcinogenesis. Similarly, resistant starches, which are a slowly digested fiber, have a protective effect to the DNA as they prevent mutations that may lead to colorectal cancer (Zeng et al. 2014). This protective effect comes from dietary fiber's ability to resist digestion in the small intestine and enter the colon; here it is fermented to create SCFAs that improve the overall health of the gut due to their ability to induce apoptosis in cancer cells (Zeng et al. 2014). Increased intake of dietary fiber and resistant starches suggest the gut microbiota is one of the leading defense systems against colorectal cancer development and that the gut microbiota can be positively impacted, overall decreasing risk of colorectal cancer recurrence following treatment.

Certain dietary patterns have been associated with inflammation within the body and the dietary inflammatory index (DII) assesses diet for anti- and pro-inflammatory factors in addition to assessing health outcomes. The DII is associated with C-reactive proteins and interleukin-6 (IL-6) cytokines (Wirth et al. 2015). IL-6 induces the synthesis of C-reactive proteins, which leads to increased inflammation, thus causing a higher DII score, which has been associated with an increased risk of colorectal cancer (Waldner et al. 2012; Zamora-Ros et al. 2015). The western diet (high in potatoes, red and processed meat, poultry, and cake) pattern is known to have a high DII score, while the Mediterranean diet has a lower DII score (Wirth et al. 2015). The Mediterranean diet is high in fruits and vegetables, which lowers the DII score, in part due to its increased dietary fiber and reduced energy intake (Whalen et al. 2014).

The primary components of the Mediterranean diet include fruits, vegetables, fish, whole grains, and olive oil as the primary fat source; whereas alcohol, red wine, and

dairy products are included in moderation (Schwingshackl et al. 2016). Fruits and vegetables have a high content of flavonoids, which have antioxidant, anti-inflammatory, anti-mutagenic, and anti-proliferative properties (George et al. 2017). Apigenin, a flavonoid common in plant-based foods, has been shown to have anti-mutagenic and anti-promotion properties through inhibition of ornithine decarboxylase activity, which plays a major role in tumor growth (Nicolas et al. 2011). Some types of fish are high in omega-3 fatty acids, which are believed to suppress carcinogenesis and can be a protective factor against tumor initiation and progression (Volpato and Hull 2018). Omega-3 fatty acids have also been shown to integrate into the plasma membrane of cancer cells to inhibit signal transduction and promote apoptosis, and thus, a substantially increased intake of omega-3's have been shown to reduce the risk of colorectal cancer by 50% (Volpato and Hull 2018; Kantor et al. 2014). Through increased fruit and vegetable consumption along with a higher fish intake, flavonoids, and an increase in omega-3 fatty acids, this dietary pattern may help prevent tumor growth and progression following colorectal cancer treatment.

In colorectal cancer prevention, whole grains are essential for increased dietary fiber intake as fiber reduces the transit time of stool, ultimately reducing the impact of potential carcinogenic substances on the colonic epithelium (George et al. 2017). In a study assessing fiber intake and risk of colorectal cancer, there was an inverse association between risk of colorectal cancer and total fiber intake (Kantor et al. 2014). From this study, fiber is believed to dilute fecal carcinogens, shorten fecal transit time, and reduce contact of carcinogens in the colon epithelium (Kantor et al. 2014).

Olive oil contains a high amount of polyphenols, which can reduce oxidative damage to cellular DNA, reducing the risk of colorectal cancer developing (Borzi et al. 2018). The antioxidant activity of olive oil in colorectal cancer blocks tumor formation, inhibits proliferation and invasion, induces apoptosis, and regulates the inflammatory response (Crespo et al. 2018). Polyphenols have been shown to prevent TNF- $\alpha$  induced inflammatory effects in cellular senescence (Crespo et al. 2018). This is a process that limits the proliferation of premalignant cells, which has the potential to reduce the risk of colorectal cancer recurrence following treatment (Crespo et al. 2018).

Recent studies have examined the Mediterranean diet as a potential option to reduce the risk of colorectal cancer (Ríos-Covián et al. 2016; Cheng et al. 2018; Fung et al. 2014). In a meta-analysis of 11 cohort studies that examine the correlation between the Mediterranean diet and risk of colorectal cancer, there was a 13% reduction in overall cancer mortality (Ríos-Covián et al. 2016). In a study examining evolutionary-concordant and Mediterranean diet patterns, there is evidence to suggest that diet patterns are inversely associated with colorectal cancer risk, but do not improve risk in those with poor lifestyle patterns including smoking, physical inactivity, and obesity (Cheng et al. 2018). In another study that assessed post-diagnosis diet quality and colorectal cancer survival in women, individuals who consumed a higher intake of fruits and vegetables and less red and/or processed meat had a longer overall survival rate (Fung et al. 2014).

While studies have assessed nutrition interventions to prevent colorectal cancer and post-treatment guidelines, there is little research on a diet status post colorectal cancer treatment. However, there are studies that have linked inflammation and various diets to increased risks of colorectal cancer recurrence (Cheng et al. 2018; Fung et al. 2014). These studies provide promising results for improved outcomes in colorectal cancer patients by utilizing specific dietary patterns and optimizing nutrition post-treatment to help prevent recurrence of colorectal cancer. This systematic review will investigate the impact of adherence to the Mediterranean diet and colorectal cancer recurrence following treatment for colorectal cancer.

## METHODS

A systematic search and review of literature based on the PRISMA model was conducted (Moher et al. 2015).

### LITERATURE SEARCH

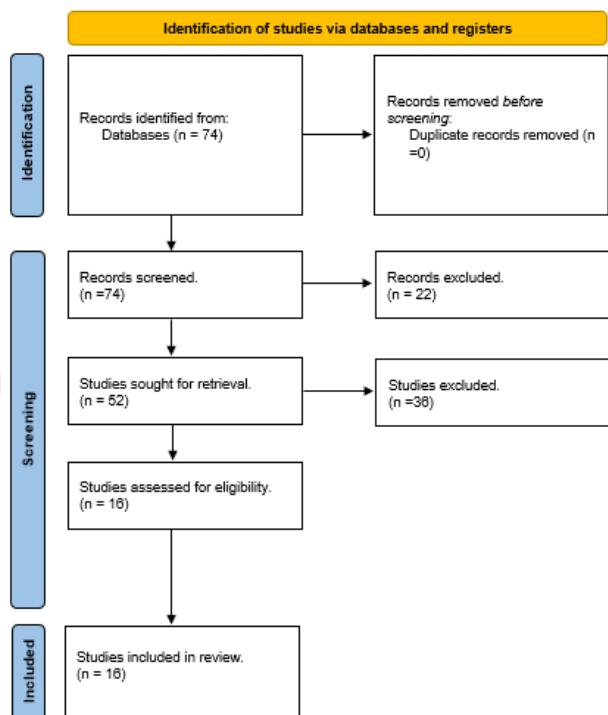
Three databases (PubMed, UNE Library, and EMBASE) were searched from January 2010 to June 2020 to identify relevant publications. Search terms included "Chemotherapy", "Colorectal Cancer", "Colorectal cancer treatment" along with "Mediterranean Diet", "MeDi", "Adults", and "Clinical Trials". The search was further limited to research trials including cohort studies, randomly controlled trials, and case-control studies, all of which had to be human studies. The main focus of this review is to analyze the impact of diet on adults following chemotherapy treatment for colorectal cancer. A combination of these terms was used to search articles that met the inclusion and exclusion criteria for this review.

### INCLUSION/EXCLUSION

For inclusion, research-based articles had to be published in English between the years 2010 and 2020. The study had to include adults over the age of 18 who had undergone chemotherapy treatment for colorectal cancer. Studies had to be clinical trials, cohort studies, and/or observational studies. Studies were excluded if published before 2010, trials that include participants under the age of 18, and reports that were not available in English. Meta-analysis and systematic reviews were also excluded.

### STUDY SELECTION

Studies were reviewed and those that met the inclusion criteria were included. Through database searches, 74 articles were identified and screened. 22 articles were excluded based on publication date. The remaining 52 articles were assessed for eligibility. 36 were excluded due to animal-based trials, prospective studies, systematic reviews, and addressing additional cancers. The remaining 15 articles were included in this systematic review. From the 15 studies, the primary data extracted were outcomes, confidence intervals, and P-values to compare statistical results. The statistical analysis of each study was analyzed and compared through qualitative synthesis. All articles were assessed for quality/bias. The AND EAL quality rating was used to determine that 8 of the articles were strong and 7 of the articles had a medium strength with a neutral rating (Academy of Nutrition and Dietetics 2016)



**Figure 1.** PRISMA diagram for search results

## RESULTS

Sixteen articles were analyzed to assess the impact of the Mediterranean diet following chemotherapy treatment in colorectal cancer patients.

### LIFESTYLE FACTORS

Individuals with certain lifestyle factors, such as tobacco use, alcohol intake, low physical activity, and a diet high in saturated fats, have an increased risk of developing colorectal cancer. A case-control study (n=1,014) found that patients who are diabetic ( $p<0.001$ ), are smokers ( $p<0.001$ ), are obese ( $p<0.05$ ), have familial history of colorectal cancer ( $p<0.001$ ), lower physical activity rates ( $p<0.001$ ), and consume greater quantities of alcohol ( $p=0.016$ ) have a greater risk of developing colorectal cancer than controls (Grosso et al. 2014). In addition, the dietary patterns that closely aligned with the Mediterranean diet guidance were associated with mediating the adverse effects of the unhealthy conditions when adherence was medium ( $p=0.004$ ) to high ( $p=0.020$ ) (Grosso et al. 2014). Despite the risk of developing colorectal cancer being higher in diabetic and obese patients, adhering to the Mediterranean diet revealed a positive association with protective qualities in this population (Grosso et al. 2014).

### MEDITERRANEAN DIET AND COLORECTAL CANCER

In a case-control study conducted in Saudi Arabia, consumption of dairy products, legumes, leafy vegetables, olive oil, black tea, and coffee were assessed weekly in 137 colorectal cancer patients (Azzeh et al. 2017). Logistic regression was used to determine protective diet associations with the Mediterranean diet, which were seen with 3-5 servings each of legumes (CI=0.08-0.96,  $p=0.025$ ), of leafy vegetables (CI=0.05-0.67,  $p=0.01$ ), and of olive oil (CI=0.1-0.61,  $p=0.003$ ) (Azzeh et al. 2017).

Marine  $\omega$ -3 polyunsaturated fatty acids (PUFA) are

found primarily in dark, fatty fish such as salmon, mackerel, and sardines (Van Blarigan et al. 2018). In a study assessing the diet of 1011 colon cancer patients during and following chemotherapy treatments, marine  $\omega$ -3 PUFA consumption was assessed to determine its relationship with disease-free survival (Van Blarigan et al. 2018). In order to obtain these data, dietary assessment was conducted prior to chemotherapy and 6 months following chemotherapy (Van Blarigan et al. 2018). Through cox proportional hazards regression, researchers found a higher intake of marine  $\omega$ -3 PUFA ( $\geq 0.15\text{g/d}$ ) was associated with a 70% lower risk of mortality following colorectal cancer treatment (95% CI, 0.14-0.64,  $p<0.001$ ) compared to those who made little or no change in its consumption (Van Blarigan et al. 2018). In contrast, in the previously mentioned case-control study, there was no significant difference ( $p>0.05$ ) seen between colorectal cancer patients and the control group regarding seafood consumption, with attention given primarily higher-content fish such as tuna, mackerel and sardines (Azzeh et al. 2017).

In another case-control study (n=500), a standardized questionnaire was used to examine lifestyle, dietary characteristics, and nutritional behaviors in 250 newly-diagnosed colorectal cancer patients and 250 controls matched on age and sex (Kontou et al. 2013). Adherence to the Mediterranean diet was evaluated by the MedDietScore and multiple logistic regression analysis was used to examine the number of meals per day in association with colorectal cancer risk, which revealed a higher number of meals consumed lowered the risk of colorectal cancer in the control group ( $p<0.001$ ) (Kontou et al. 2013). Mediterranean diet adherence was associated with 13% lower odds of developing colorectal cancer, while coffee consumption (95% CI, 0.22-4.53), added table salt (95% CI, 1.05-2.49), and non-stick cookware (95%CI, 1.03-2.40) were associated with increased odds of developing colorectal cancer due to higher risk of metabolic syndrome, cardiovascular disease and hypertension (Kontou et al. 2013).

### DIETARY INFLAMMATORY INDEX

Through a food-frequency questionnaire, the association between the inflammatory potential of diet and survival following colorectal cancer were assessed (Ratjen et al. 2019). 1,404 patients, who had histologically confirmed colorectal cancer, researchers created an energy-adjusted dietary inflammatory index score and assessed Mediterranean diet adherence through the MedDietScore (Ratjen et al. 2019). Through a cox proportional hazards regression model, a 1.36 higher risk of all-cause mortality was seen with a more pro-inflammatory diet (95% CI: 0.88-2.09) (Ratjen et al. 2019). Each increase of DII score, or those with a lower intake of fruits and vegetables along with poorer adherence to the Mediterranean diet, also revealed an 8% higher risk of mortality (95% CI: 0.97-1.20) (Ratjen et al. 2019). While no significant association was seen between dietary inflammatory index score and all-cause mortality in overall sample ( $P=0.46$ ), significance was seen between a more pro-inflammatory diet and individuals with a history of metastasis ( $P=0.01$ ) (Ratjen et al. 2019).

### ADHERENCE TO MEDITERRANEAN DIET

In a cohort study following 35,372 United Kingdom women for a median length of 17.4 years, a 10-component score for

adherence to the Mediterranean diet was created to assess adherence levels (Jones et al. 2017). A cox proportional hazard regression was used to determine that a 2-point increment in this Mediterranean diet score resulted in a hazard ratio (95% CI) of 0.69 and a 62% linear reduced risk (hazard ratio 0.38, 95% CI: 0.20 to 0.74,  $p < 0.001$ ) in women with the highest Mediterranean diet score (Jones et al. 2017). Additionally, in a case-control study, 2301 people who had no prior history of colorectal neoplasms completed a questionnaire on diet. Using a multivariable-adjusted odds ratio comparison, individuals who had the highest adherence to the Paleolithic and Mediterranean diets were more likely to be adenoma free compared to the controls ( $p = 0.02$  and  $p = 0.05$ , respectively) (Whalen et al. 2014). With a 1-2% decrease in adenoma frequency for each 1-point increase in Paleolithic and Mediterranean diet score, the results indicate a significant impact on Mediterranean diet and colorectal adenomas (Whalen et al. 2014).

In a cohort study of general adult populations in Europe, 480,308 participants completed a food-frequency questionnaire and were followed to determine cancer incidence and mortality (Bamia et al. 2013). A cox proportional hazard model was used to determine a statistically significant reduction in colorectal cancer risk through increased fish intake (HR:0.90,  $p = 0.03$ ). In contrast to other similar studies, there was found to be only an 11% reduction in colorectal cancer risk with Mediterranean diet adherence (Bamia et al. 2013).

In a case-control study ( $n = 500$ ) used to evaluate the impact of the Mediterranean diet on metabolic syndrome and colorectal cancer, a food-frequency questionnaire was used to assess dietary patterns of 250 patients who had been diagnosed with colorectal cancer and 250 participants without any signs or symptoms of colorectal cancer (Kontou et al. 2012). Metabolic syndrome was 44% higher in cases compared to the control and was significantly linked to colorectal cancer ( $p = 0.04$ ) (Kontou et al. 2012). A 1-unit increase in Mediterranean diet score was associated with 12% lower odds of having colorectal cancer ( $p < 0.001$ ), which had also been confirmed in other studies (Bamia et al. 2013; Kontou et al. 2012; Fliss-Isakov et al. 2018). Adherence to the Mediterranean diet is inversely associated with advanced colorectal cancer polyps ( $p < 0.001$ ), but not with non-advanced adenomas ( $p = 0.279$ ) (Fliss-Isakov et al. 2018). Additionally, there was a negative association between the number of Mediterranean diet components and cases as well as odds of advanced polyps (Fliss-Isakov et al. 2018).

#### POSTDIAGNOSIS MEDITERRANEAN DIET

In a cohort study following women who were diagnosed with stage I-III colorectal cancer, the diet was assessed using a food frequency questionnaire at least 6 months after diagnosis (Fung et al. 2014). The alternate healthy eating index (AHEI-2010), which is similar to the Mediterranean diet (i.e., high in vegetables, fruit, whole grains, long-chain omega-3 fatty acids, and low in red/processed meat, sodium, and trans-fats), revealed a 30% lower mortality rate (HR=0.71) for a higher AHEI score (95% CI: 0.52-0.98,  $p = 0.01$ ) (Fung et al. 2014). Additionally, a food-frequency questionnaire was used to assess 1404 colorectal cancer patients who had been diagnosed between 2002 and 2005. The Cox proportional hazard regression model determined

that for every one point increase in Mediterranean diet score, the hazard of mortality had declined by 11% (HR: 0.89, 95% CI,  $p = 0.004$ ) (Ratjen et al. 2017).

A pilot study conducted in 2016 assessed the nutritional adequacy and diet quality in a group of colorectal cancer patients following surgery (Alegria-Lertxundi et al. 2016). 142 randomly selected colorectal cancer patients, ages 50-69, who had a surgical resection completed a food frequency questionnaire that utilized the Healthy Eating Index for Spanish Diet (HEISD) and the MedDietScore (MDS) to assess diet quality (Alegria-Lertxundi et al. 2016). The results revealed 94% had inadequate carbohydrate intake, 48% exceeded protein intake, and 67% exceeded fat intake, while subjects who were overweight/obese had a higher inadequate intake of folic acid (OR=4.99,  $p = 0.015$ ), vitamin A (OR=4.95,  $p = 0.016$ ), and zinc (OR=7.05,  $p = 0.008$ ) (Alegria-Lertxundi et al. 2016). The results of this study showed a mean percentage of adherence to the Mediterranean Diet was 66%, but 85.1% had “no healthy diet” according to HEISD (Alegria-Lertxundi et al. 2016). Limitations of this study show a small sample size, lack of control of confounding variables such as comorbidities and lack of physical activity. Overall, this study shed light on non-compliance with dietary changes following CRC surgery may be linked to lack of education on proper nutrition, thus, certain food components of the Mediterranean diet were lacking, resulting in the risk for colorectal cancer recurrence to remain high in this population.

Through a self-reported questionnaire (FFQ), 192 colorectal cancer patient’s diets were assessed prior to surgery to determine 4 dietary patterns: western diet (high in potatoes, red and processed meat, poultry, and cake), fruit and vegetable diet (high intake of vegetables, fruits, vegetable oils, and soy products), bread and butter (high intake of bread, butter, and margarine), and high carb (pasta, grain, nonalcoholic beverages, and sauces) (Gigic et al. 2018). Patients who adhered to a western diet had less improvement in health/Quality of Life (QoL) status ( $p = 0.04$ ) whereas the fruit and vegetable diet showed improvement in diarrhea (OR: 2.52,  $p = 0.01$ ) (Gigic et al. 2018). Within the 12 months post-surgery, those who followed the “fruit and vegetable diet” classified themselves as improved quality of life compared to those who followed the “western diet” (Gigic et al. 2018).

A cohort study including 1098 participants with stage I-III colorectal cancer compared differently levels of healthy lifestyle and BMI based on self-reported smoking status, physical activity level, adherence to a Mediterranean diet pattern and BMI (Barot et al. 2024). These were divided into four categories ranging from least to most healthy based on the reported data. The results concluded a significant decrease in the risk of CRC recurrence in patients adhering to a healthy lifestyle pre-diagnosis. In 992 colon cancer stage III cases, a post-diagnosis healthy lifestyle was associated with significant improvement in overall survival (Barot et al. 2024). One notable weakness of this study is reporting conflicting results on lifestyle changes, which could have led to some misclassification bias. Overall, the implication of this study supports the evidence for future examination of the Mediterranean diet and post-diagnosis cancer survival.

#### LONG-TERM FOLLOW-UP

A randomized controlled trial to examine the long-term

effects of nutritional therapy on colorectal cancer patients was conducted in 2012 (Ravasco et al. 2012). A nutritional assessment was performed on 101 patients who had been diagnosed with colorectal cancer and were divided into three groups: group 1 received individualized nutritional counseling and education sessions using regular food, group 2 received 2 cans per day of high-protein dietary supplements and consumed regular diet, and group 3 consumed usual diet of their regular foods (Ravasco et al. 2012). A Kaplan-Meier analysis revealed that group 1 had a median disease-specific survival of 7.3 years, group 2 had a disease-specific survival of 6.5y, and group 3 had a median survival of 4.9y (Ravasco et al. 2012). Group 1 maintained an adequate nutritional status, while groups 2 and 3 had higher nutritional deterioration at 3-month follow-up ( $p < 0.002$ ) (Barot et al. 2024). Overall, QoL was better in group 1 than groups 2 and 3, which is indicative of improved diet quality and it was found that with the nutrition counseling received, the group 1 participants maintained an adequate nutrition status in 91% of the group through consuming whole foods (Ravasco et al. 2012). While the Mediterranean diet was not directly utilized in this study, the group 1 patients had a better nutrition status associated with higher quality protein and energy intakes along with adequate micronutrient intake from whole foods (Ravasco et al. 2012).

## DISCUSSION

In reviewing the current literature, there is evidence that the Mediterranean diet could reduce the risk of colorectal cancer recurrence following treatment for colorectal cancer (Fung et al. 2014; Barot et al. 2024). Regarding the components of the Mediterranean diet, the increased fruit and vegetable consumption, along with the use of olive oil as the main fat source and fish as the primary protein, has been shown to have beneficial effects in prevention of and decreased recurrence of colorectal cancer (Winkles et al. 2014; Barot et al. 2024). Higher adherence to the Mediterranean diet has an inverse effect with colorectal cancer occurrence, which is evident of the beneficial effects of the diet (Whalen et al. 2014; Jones et al. 2017; Bamia et al. 2013).

The research on the Mediterranean diet to help prevent colorectal cancer is extensive, but limited research has been done on how it can prevent colorectal cancer recurrence following treatment. Four main post-treatment studies focused on diet following treatment for colorectal cancer (Fung et al. 2014; Ratjen et al. 2017; Alegria-Lertxundi et al. 2016; Gigic et al. 2018). Now, there is satisfactory evidence that reveals diets which are higher in whole grains, fruits and vegetables, long-chain omega-3 fatty acids, while low in red/processed meat, sodium, and trans-fat, had a lower mortality rate than the western diet (Fung et al. 2014; Alegria-Lertxundi et al. 2016). The evidence suggests that the Mediterranean diet would help lower the risk of colorectal cancer recurrence following chemotherapy treatment.

In long-term follow-up, nutritional intervention (increasing fruit and vegetable intake and inclusion of dietary olive oil) was shown to have a positive effect on survival rate and disease outcomes (Barot et al. 2024). While the Mediterranean diet was not specifically used in this study, evidence of nutritional intervention in line with it,

increased fruits and vegetables, shows promise in decreasing cancer recurrence. The DII has been used to assess inflammation caused by various nutrients, and as the Mediterranean diet is low on the index, it has been linked to a lower risk of death following a cancer diagnosis (Wirth et al. 2015; Waldner et al. 2012; Zamora-Ros et al. 2015; Whalen et al. 2014). This evidence also indicates that the Mediterranean diet may reduce the risk of recurrence of colorectal cancer following treatment (Wirth et al. 2015; Waldner et al. 2012; Zamora-Ros et al. 2015; Whalen et al. 2014).

## LIMITATIONS

The first limitation of this review is that many of the studies which were assessed only used one food-frequency questionnaire throughout the entire trial (Fung et al. 2014; Ratjen et al. 2019; Alegria-Lertxundi et al. 2016). This could result in an error in diet reporting, as diet may change over the course of the study. In addition, these were self-administered questionnaires, which could result in a certain degree of error and bias. While many of the studies adjusted for confounding variables, many had a wide age range that was assessed, which could have affected some of the data. In addition, dietary scores were calculated differently between the studies, which could lead to variation in diet scores and reporting methods. Additionally, there was only one reviewer assessing the evidence, which could result in reporting bias and a higher chance of missed errors.

Other issues include a lack of access to all papers on the topic. We made use of a limited set of data bases while there may be other databases that contain other papers that could change the conclusions of this paper. Another major limitation was only using those papers which were published in English or for which there was an English translation. While it is unlikely that there was a paper or set of papers that would change the conclusion of this particular study, there is perhaps a small risk. Finally, the largest of all the major limitations of this particular study is the systematic review process and the limitation of the search terms that were utilized. In choosing only those specific search terms, there may have again been other papers that could have added valuable pieces of information to this particular study that simply could not be included secondary to the fact that this is a systematic literature review which has a fairly rigid set of rules which limit the way in which the authorial team was able to select papers for inclusion within the paper. These limitations and others have been described in other recent systematic literature reviews (Varkey et al. 2023).

## CONCLUSION

By analyzing articles discussing the impact of lifestyle factors, MedDiet with first time colorectal cancer diagnosis, dietary inflammatory index, adherence to the MedDiet, post diagnosis MedDiet, and long-term follow-up following diagnosis, this systematic review revealed the inverse affects the Mediterranean diet has on colorectal cancer, indicating that this diet could reduce the risk of recurrence in colorectal cancer patients following treatment. While the health-protective effects of the Mediterranean diet are not necessarily new knowledge, the information reviewed reveals the positive effects of a healthy diet following colorectal cancer treatment. Future research is needed to

examine adherence to the Mediterranean diet following colorectal cancer treatment and the rate of recurrence to better understand the effects of the Mediterranean diet used for colorectal cancer prevention and recurrence reduction.

first, second, and final draft. **Emily C. Courtois:** Primary draft, critical revisions of the first, second, and final draft. **Thomas C. Varkey:** Primary draft editing, limitation section, critical revisions of the first, second, and final draft.

#### AUTHOR CONTRIBUTIONS

**Caitlyn A. Sention:** Conceptualization, initial data collection, primary draft, critical revisions of the first, second, tertiary, and final draft. **Kyle A. Sention:** Primary draft, critical revisions on the first, second, tertiary, and final draft. **Zachary I. Merhavy:** Primary draft, critical revisions of the first, second, tertiary, and final draft. **Ana F. S. Guimarães:** Primary draft, critical revisions of the first, second, and final draft. **Afaf Aijaz:** Primary draft, critical revisions of the first, second, and final draft. **Cheney E. Merhavy:** Primary draft, critical revisions of the

#### CONFLICT OF INTEREST

No conflict of interest was declared by the authors

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