Colorectal cancer is the third most common cancer worldwide, especially in developed countries where an estimated 60% of all cases occur. There is evidence of a higher risk for CRC in Western society, where people tend to eat more red and processed meat than do those living along the Mediterranean coast, who have a decreased overall cancer mortality, which is correlated to their eating habits, such as Mediterranean diet. The aim of this review was to evaluate the correlation between three components of the Mediterranean diet (olive oil, red wine, and tomatoes) and incidence and progression of colorectal cancer. As such, we conducted a literature search using keywords "colorectal cancer," "dietary pattern," "Mediterranean diet," "olive oil," "protective effects," "resveratrol," and "lycopene." Olive oil polyphenols, red wine resveratrol, and tomato lycopene showed several characteristics in vitro that interfere with molecular cancer pathways. At the same time, many clinical studies have reported an association of these components with a reduction in cancer initiation and progression. More clinical studies are needed to identify the precise dose and administration of single agents or their combination to produce a coadjuvant treatment to those already applied in chemoprevention and oncologic treatment.

Introduction

Colorectal cancer (CRC) is the third most frequent cancer, especially in developed countries where an estimated 60% of all CRC cases occur [1,2]. There is evidence of a higher risk for CRC in Western society, where people tend to eat more red and processed meat than do those living along the Mediterranean coast, who have decreased overall cancer mortality, which is correlated to their eating habits, such as Mediterranean diet (MedD) [3].

In 2010, UNESCO recognized the MedD as an “intangible cultural heritage of Italy, Greece, Spain and Morocco” for multiple reasons, such as the preservation of local biodiversity and a variety of health benefits starting from a reduction of CRC risk and the percentage of deaths caused by cardiovascular accidents [4–6].

The MedD is characterized by a high consumption of fruits, vegetables, and complex carbohydrates; low consumption of fish and meat; and a daily glass of red wine. In the MedD, the main source of fat is from olive oil [7].

Prevention of CRC has important public health implications. Many studies have demonstrated that fibers and phytochemicals included in the MedD have a strong chemopreventive role in the onset of CRC [8,9].

The 2015 Italian Association of Cancer Registries included data of prevalence and incidence of CRC in Italy. It showed that the prevalence of CRC in 2015 in the northwestern section of Italy was 764 cases and in the northeastern part was 775 instead, a difference could be found analyzing data from the southern part of Italy had 437 cases of CRC in 2015. The significant differences might be due to different lifestyles and, primarily, different eating habits, as the population of southern Italy mainly follows a MedD [10].

Common mutations, chromosomal changes, and translocations have been reported to affect important pathways (WNT, MAPK/PI3 K, TGF-β, TP53), and mutations in colon cancer cells [11] (Fig. 1). We focused on clinical studies evaluating some specific components of the MedD.

The association between MedD and CRC has been examined by many clinical case-control and cohort studies through questionnaires analyzing dietary intake of nutrients. The resulting
scores and indexes showed an inverse association between the use of MedD and the risk for CRC [12–15]. Although these results in vivo, the difficult interpretation relies in the real role played by a single compound of the MedD in prevention of CRC; some measurement bias in dietary questionnaires and their scores may exist. Other studies analyzed whether any association exists between the MedD and a change in blood concentrations of vitamins A, C, and E included in most of the foods in a MedD. These studies generally have been inconclusive or reported only a possible preventive action for vitamins A and E and β-carotene [16–18].

Preclinical studies play a key role in understanding how a single MedD compound can modify molecular pathways of signaling in human colon cell lines to prevent onset of CRC. In fact, preclinical studies have always been focused on the effects that each component of the MedD could exert on this kind of cancer cell to better understand their pathways and the molecular mechanism of action affected by each dietary
compound [19]. The present review focused on olive oil (polyphenols), red grapes (resveratrol), and tomatoes (lycopene) to evaluate the correlation between them and the incidence of CRC in clinical studies to support the ideal "chemoprevention" strategy with routine consumption of the macro- and micronutrients included in the MedD.

**Olive oil polyphenols**

Olive oil is a central compound in the MedD and is the main source of dietary fat. The MedD is distinguishable from other healthy dietary models for its high fat content [5,12]. Many experimental studies outline the biological and molecular mechanism by which each component of olive oil could realize multiple health benefits [20–22]. The consumption of olive oil exerts a protective effect in reducing risk for CRC many other types of cancer, including prostatic and breast [23,24]. This property has been referred to by its content of monounsaturated fats, mainly oleic acid [19]. However, olive oil is a functional and complex food that contains several minor bioactive compounds, including tocopherols, squalene, alcohols, and many polyphenols such as oleuropein, hydroxytyrosol, and tyrosol, which represent approximately 80% of olive oil's phenolic content [21,25].

Although the mechanisms involved remain uncertain, preclinical studies have attributed many chemopreventive effects to the components of olive oil mostly because they interfere with the initiation, promotion, and progression of cancerogenesis pathways [21,25–29] (Table 1).

Dietary fat has been implicated in cancer development, both positively and negatively.

Many case–control studies have been conducted to determine an epidemiologic correlation between digestive system cancers (stomach, colorectum, and pancreas) and olive oil [30]. Psaltopoulou et al. conducted a meta-analysis studying eight case–control studies and found that a high intake of olive oil could lead to a significant 30% lower probability of having digestive system cancers compared with a lower intake of olive oil [31]. Moreover, in a large case–control study in Italy that included 1953 patients with CRC (1225 colon; 728 rectum) and 4154 controls, the odds ratios (ORs) for successive tertiles, compared with the lowest, were 0.87 (95% confidence interval [CI], 0.75–1.01) and 0.83 (95% CI, 0.70–0.99; P = 0.03) in CRC. Analyzing colon and rectal cancer separately researchers have found ORs of 0.82 (95% CI, 0.68–0.98) and 0.81 (95% CI, 0.66–0.99; P = 0.04), and 0.96 (95% CI, 0.77–1.19) and 0.88 (95% CI, 0.66–1.12), respectively. In the same population, monounsaturated fat intake appeared insignificant [32]. Benito et al. obtained similar results [33]. The OR for an increment of one portion of fried foods per week was 0.89 for colon cancer, 0.97 for rectal, and 0.93 for colorectal, for the use of olive oil [34]. Meta-analysis of prospective cohort studies suggests that cancer morbidity and mortality are lower in Mediterranean countries, where olive oil represents an important amount of dietary fat [35].

Using a straightforward formula suggested by Wahrendorf [36], Trichopoulou et al. hypothesized that people of industrial countries could reduce their incidence of CRC by ~25% by switching from a Western diet (weighted relative risk [RR]) calculated by summing the products of the fraction of the population in each quintile of MedD score [6] with the RR for CRC for the quintile = 0.2 × 1 + 0.2 × 2.5 + 0.2 × 4 + 0.2 × 5.5 + 0.2 × 7 = (4.00) to a MedD (weighted RR = 0.37 × 1 + 0.2 × 2.5 + 0.2 × 4 + 0.2 × 5.5 + 0.03 × 7 = 2.98) [37].

Stoneham et al. conducted an ecologic study using international databases from 28 countries. Their aim was to calculate the relation between CRC and dietary factors. Using a multiple regression model, they concluded that 76% of the intercountry variation in CRC incidence rates could be caused by three main dietary foods: meat, fish, and olive oil. A positive association resulted for meat and fish instead of an inverse correlation found between olive oil and risk for CRC. Olive oil may exert its protective effect, influencing polyamine metabolism in cells leading to a reduction in cancerogenesis progression [38].

Recently, Steck et al. compared CRC risk, the MedD score, and the Healthy Eating Index (HEI) and defined a novel Dietary Inflammatory Index (DII). Comparing different published studies (U.S. and European patients), the authors concluded that higher MedD and HEI scores were associated with lower risk for CRC (8–54% and 20–56%, respectively) [39].

**Red grapes and resveratrol**

Resveratrol is a phenolic compound mainly found in the external skin of red grapes, as well as in other foods (e.g., berries and nuts). In the MedD, resveratrol can be found mainly in red wine. However, its concentration in red wine varies widely depending on the quality of the red grape species and the climate in which the grapes were grown [40].

Resveratrol has pleiotropic pharmacologic properties, such as the repression of platelet aggregation and eicosanoid synthesis. It promotes protection against damage from reactive oxygen species and from flogistic events, resulting in cardiovascular protective benefits and, certainly, anticancer activities [41,42].

Although it is difficult to ascertain the cause and effect mechanism in vivo settings, resveratrol has been shown to affect a number of molecular targets based on cancer type, resveratrol formulation, stage of disease, and dose and duration of resveratrol. It is being increasingly recognized that the combinatorial approaches of resveratrol and other natural agents are likely useful in advanced stages of cancers because deregulation of multiple pathways affect cancer cell growth and oncogenic signaling [43,44].

Several preclinical and clinical studies have reported the beneficial effects of resveratrol in tumor prevention [45–48]. One of the major topics investigated was the precise amount of red wine that includes these beneficial effects. Resveratrol has been found to be safe and well tolerated at ≤5 g/d, either as a single dose or as part of a multiple daily dosing consumption [49].

However, when using resveratrol in patients with cancer, it is important to remember that these studies were done in healthy populations.

Patel et al. studied how 20 patients with CRC reacted to a daily oral administration of resveratrol such as 0.5 or 1 g for 8 d before surgery. Detecting resveratrol metabolites in CRC resection tissue, the researchers found that resveratrol decreased volume tumor by 5% [48]. These data support the hypothesis that resveratrol, as a MedD component, acts as a chemopreventive

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<th>Table 1</th>
<th>Cellular effects of olive oil on colon cancer initiation and progression</th>
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<td>• Downregulation of COX-2 [26]</td>
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<td>• Downregulation of BCL-2 [27]</td>
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<td>• ROS generation in cancer cell [28]</td>
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<td>• Downregulation of EGFR expression [29]</td>
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COX, cyclooxygenase; EGFR, epidermal growth factor receptor; ROS, reactive oxygen species
agent even if these doses are not attainable by normal consumption of wine.

Kontou et al. studied 250 Greek patients with CRC using questionnaires to assess their clinical and lifestyle characteristics and their adherence to the MedD, as evaluated through the MedD score. The researchers demonstrated that an intake <12 g/d of alcohol significantly reduced colon cancer risk in men and women. However, there was a significant resveratrol-related reduction of the risk for CRC in men compared with women. According to Kontou et al. [47], a Mediterranean-style diet is independently related to a decrease in risk for CRC in men and women.

Crockett et al. performed the retrospective North Carolina Colon Cancer study analyzing 1033 cases and 1011 controls from that state. They found that moderate alcohol intake (especially from wine) was negatively associated with distal colon and rectal cancer [50].

Previous meta-analyses of studies on alcohol intake and risk for CRC have shown that alcohol increases risk in a linear dose-related manner [51–53].

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) reported that alcohol consumption increased the risk for CRC with a summary RR of 1.06 (95% CI, 1.01–1.12) per 10 g/d of alcohol [54].

Several studies have reported that the association between alcohol intake and CRC is stronger in men than in women [52,55]. On the contrary, the Norfolk, UK cohort showed that daily consumption of one or more units of wine was inversely related to CRC risk (hazard ratio [HR] 0.61; 95% CI, 0.44–0.94), with no evidence for sex-specific relationships [56]. Moreover, the North Carolina study found that moderate intake of wine was inversely associated with CRC (OR, 0.69; 95% CI, 0.56–0.86) [50].

However, a meta-analysis showed that even moderate alcohol intake was related to increased risk for CRC (RR, 1.21; 95% CI, 1.13–1.28) [57].

Preclinical studies suggested a potential beneficial effect of resveratrol; however, clinical studies led to controversial results, perhaps related to dose and type of alcoholic beverages.

Tomatoes and lycopene

According to Smith, “tomato pills cure all your ills” [58]. In fact, tomatoes, which are central protagonists in the MedD, have several beneficial effects, especially in the prevention of cardiovascular diseases, osteoporosis, and cancer. A reduction of risk for CRC of >20% has been linked to the daily intake of fruits and vegetables, including tomatoes [59]. The extraordinary action of tomatoes has been attributed to their elevated content of carotenoids, primarily β-carotene and lycopene [60,61].

Lycopene is synthesized by plants and confers the color red not only to tomatoes but also to red oranges and apricots. After the consumption of tomatoes, the concentration of lycopene in plasma depends on several biological mechanisms. In fact, lycopene is modified during the digestive process, thus decreasing its bioavailability. To facilitate lycopene absorption, it is better to introduce tomatoes in combination with lipids, such as occurs in sauces or juices [62].

In a randomized crossover trial, a low-carotenoid diet based on daily consumption of 330 mL tomato and carrot juice was compared. At the end of the study, fecal water showed an elevated dose-related cytotoxicity and the ability to suppress cancer cell proliferation on colon adenocarcinoma cells HT29 in both group of treatment. These results suggested that 2-wk interventions with carotenoid- and lycopene-rich juices could lead to changes in luminal biomarkers relevant to colon carcinogenesis [63].

Wallisch et al. suggested that a high level of serum insulin-like growth factor (IGF) in patients with colon cancer is a marker of augmented risk for the disease. The researchers showed that plasma concentration of IGF-I was significantly reduced by 25% with supplementation of tomato lycopene extract [64].

The majority of case–control studies examined the association of CRC for carotenoids and vitamins using dietary intake estimated from questionnaires. Most of these studies reported an inverse association between dietary vitamin C and risk for CRC [65]. However, pooled analyses of prospective studies showed no association between dietary intakes of carotenoids and any of the vitamins A, C, or E and CRC risk [66,67].

The EPIC (European Prospective Investigation into Cancer and Nutrition) case–control study assessed the association of prediagnostic plasma concentrations and dietary intakes of carotenoids and vitamins A, C, and E with the risk for CRC [68].

They found that plasma retinol was inversely associated with (proximal) colon cancer and intakes of dietary β-carotene and vitamins E and C were inversely associated with (distal) colon cancer. The authors suggested that fruit and vegetable consumption confers a protective effect on carcinogenesis based on components with antioxidative properties [69]. However, clear evidence for this is still lacking.

Previously observed associations for fruit and vegetable consumption and related fiber were found to be stronger for colon than for rectal cancer [70,71].

A recent meta-analysis of studies evaluated the association between lycopene consumption and the risk for CRC. The RR for the highest versus lowest categories did not indicate a significant association between lycopene consumption and the risk for CRC (RR, 0.94; 95% CI, 0.80–1.10). However, a significant inverse association was observed between lycopene consumption and the site of cancer in the colon (RR, 0.88; 95% CI, 0.81–0.96) [72].

Further research is needed in this area to provide conclusive evidence.

Conclusions

A MedD lifestyle includes particular types of food and drink, which exert a nutritional synergy when consumed together [6]. The traditional MedD is centered on the consumption of fruits, vegetables, and fish, as well as a low consumption of red meat. Several preclinical and clinical studies have focused on how the MedD dietary pattern could affect cancer initiation and progression. Olive oil polyphenols, red wine resveratrol, and tomato lycopene are secondary antioxidants produced by plants. They showed several capabilities in vitro to interfere with molecular cancer pathways. At the same time, many clinical studies have reported how olive oil, red wine, and tomatoes to reduce cancer initiation and progression.

However, due to the complex interaction between active compound in foods and bioavailability of antioxidants in humans after ingestion of food, it is very difficult to identify the quantity of specific nutrients that could prevent carcinogenesis. Moreover, cancer results from the combined effects of many different factors such as smoking, lack of physical activity, and genetics.

More clinical studies are needed to identify the precise dose and path of administration to produce a coadjuvant treatment to those currently applied in oncology. Therefore, the supplementation of brightly colored vegetables and fruit or nuts and
almonds, as in the MedD, is particularly recommended for patients with cancer [6,7].

A very recent evaluation of the burden of cancer in European counties found that prior cigarette smoking was the risk factor responsible for the greatest cancer burden; however, adiposity also plays an important role. A history of smoking could explain 24% (95% CI, 22.2–26.0%) of the total cancer burden followed by physical inactivity (4.9%; 95% CI, 0.8–8.1%) and adiposity (1.8%; 95% CI, 0.2–2.8%) [73].

In the present review, we focused on different components of the MedD that could be useful in preventing CRC. More population studies are needed to confirm this data, however, due to the proven preventive effects of the MedD on various other diseases, clinicians can safely suggest this lifestyle approach to their patients.

References


