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Mediterranean Diet and Colorectal Cancer: a systematic review

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STRUCTURED ABSTRACT

Background: Colorectal cancer (CRC) 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 in Western society whose behaviours are characterised by higher consumption of red and processed meat than in people living along Mediterranean coast, who have a decreased overall cancer mortality correlated to eating habits such as Mediterranean Diet.

Aim: This review evaluate the correlation between 3 components of MedD (olive oil, red wine and tomatoes) and incidence and progression of CRC.

Methods: a literature scanning was conducted using key words "Colorectal cancer" "dietary pattern" "Mediterranean Diet" "olive oil" "protective effects" "resveratrol" "lycopene". Olive oil polyphenols, red wine resveratrol and tomatoes lycopene showed several capabilities in vitro to interfere with molecular cancer pathways, at the same time many clinical studies reported their ability to reduce cancer initiation and progression. More clinical studies are needed to identify the precise dose and way of administration of single agents or their combination to produce a coadjutant treatment to the ones already applied in chemoprevention and oncological treatment.

Key words: Mediterranean Diet; Colorectal cancer; polyphenols; resveratrol; lycopene.

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ABBREVIATIONS:

CRC = Colorectal Cancer

MedD = Mediterranean Diet

HT= hydroxytyrosol

EVOO= extra-virgin olive oil

ROS= reactive oxygen species

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INTRODUCTION

In the world 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 CRC risk in Westernized society whose behaviours are characterised by higher consumption of red and processed meat than in people living along Mediterranean coast, who have a decreased overall cancer mortality correlated to their eating habits such as Mediterranean Diet. [3]

In 2010 UNESCO recognized the Mediterranean Diet (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 colorectal cancer risk and the percentage of deaths caused by cardiovascular accidents. [4,5,6]

Mediterranean diet is characterized by an high consumption of fruits, vegetables and complex carbohydrates, followed by a low amount of fish and meat and a daily glass of red wine; in this diet the mainly source of fat is olive oil. [7]

CRC prevention has an important public health implication. Many studies have demonstrated that fibres and phytochemicals included in MD have a strong chemo preventive role in the onset of CRC. [8,9]

The Italian Cancer Register published in 2015 data of prevalence and incidence of CRC in Italy, in particular: prevalence of CRC in 2015 in North-West Italy was 764 and in North-East part was 775 instead, a difference could be found analysing data from The Southern part of Italy with their 437 cases of CRC in 2015. Maybe these great differences could be explained by different lifestyle and primarily different eating habits, where in the South there is a clearly Mediterranean diet. [10]

Common mutations, chromosomal changes and translocations have been reported to affect important pathways (WNT, MAPK/PI3K, TGF-β, TP53), and mutations in colon cancer cells. [11] (figure 1). We focused on clinical studies evaluating some specific components of the Mediterranean Diet.

The association between MedD and CRC have already been examined by many clinical studies, case-control and cohort types through questionnaires analysing dietary intakes of nutrients; the resulted scores and indexes showed and inverse association between the use of MedD and the risk of CRC. [12,13,14,15] Although these results in vivo, the difficult interpretation relies in the real role played by single compound of Mediterranean Diet in prevention of CRC, moreover some measurement bias in dietary questionnaire and their scores may exist. Therefore others studies analysed if there is any association between MedD and a changing in blood concentrations of vitamins A, C and E included in most part of MD foods, these have generally been inconclusive or reporting only a possible preventive action for vitamin A, vitamin E and β-carotene. [16,17,18]

Thus pre-clinical studies play a key role in understanding how single MedD compound modifies molecular pathways of signalling in human colon cell lines to prevent CRC onset. In fact pre-clinical studies have always been focused on the effects that each component of the MedD could exerts on this kind of cancer cells to better understand their pathways and molecular mechanism of action affected by each dietary compounds [19]. In this regard, this review is focused on: olive oil, red grapes and tomatoes.

This review aimed to evaluate the correlation between 3 main protagonists of MedD (olive oil, red wine and tomatoes) and the incidence of CRC in clinical studies to support the ideal "chemoprevention" strategy by the routinely consumption of macro and micronutrients included in MedD.

WHAT DOES THIS PAPER ADD TO LITERATURE

Clinical and pre-clinical studies have always been always adding more data to support the hypothesis that the MedD could protect from colorectal cancer. In this background, our paper would aim to add to literature an organised review of clinical and pre-clinical studies about the chemopreventive role of 3 major components of MedD: olive oil with its polyphenols, red wine with its resveratrol, and tomatoes with their lycopenes.

OLIVE OIL POLYPHENOLS

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

Although the mechanisms involved remain uncertain, thanks to preclinical studies it has been attributed to olive oil's components many chemopreventive effects mostly because they interfere with the initiation, promotion and progression of cancerogenesis pathways. [21,25, 26] (Tab 1).

Dietary fat has been implicated to cancer development, either positively or negatively.

Many case control studies were conducted to find out an epidemiological correlation between digestive system cancers (stomach, colorectum and pancreas) and olive oil. Psaltopoulou et al made 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 than a lower intake of olive oil. [31] Moreover, in Italy a large case-control study including 1953 patients with colorectal carcinoma (1225 colon and 728 rectum) and 4154 controls, the ORs for successive tertiles, compared with the lowest one, were 0.87 (95%CI 0.75 to 1.01) and 0.83 (95%CI 0.70 to 0.99) ($p = 0.03$) in colorectal carcinoma. Analyzing colon and rectal carcinoma separately Authors found a ORs of 0.82 (95%CI 0.68 to 0.98) and 0.81 (95%CI, 0.66 to 0.99) ($p=0.04$), and 0.96 (95%CI 0.77 to 1.19) and 0.88 (95% CI 0.66 to 1.12) respectively. In the same population

monounsaturated fat intakes appeared uninfluential [32]. Similar results were obtained by Benito et al. [33]. The OR for an increment of one portion of fried foods per week was 0.89 for colon cancer, 0.97 for rectum and 0.93 for colorectum, for the use of olive oil [34]. Meta-analysis of prospective cohort studies suggest that cancer morbidity and mortality are lower in Mediterranean countries, where olive oil represents an important quote of dietary fat [35].

Trichopoulou and Co-Authors by using a straightforward formula suggested by Wahrendorf [36] hypotesize that people of industrial countries could reduce their incidence of colorectal cancer by ~25% by switching from a Western diet (weighted relative risk calculated by summing the products of the fraction of the population in each quintile of Mediterranean diet score with the relative risk of colorectal cancer for the quintile = 0.2*1 + 0.2*2.5 + 0.2*4.0 + 0.2*5.5 + 0.2*7 = 4.00) to a Mediterranean diet (weighted relative risk = 0.37*1 + 0.2*2.5 + 0.2*4.0 + 0.2*5.5 + 0.03*7 = 2.98) [37].

Stoneham and his coworkers conducted an ecological study using international databases from 28 countries. Their aim was to calculate the relation between CRC and dietary factors. Using a multiple regression 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 CRC risk. Olive oil may exert its protective effect influencing polyamine metabolism in cells leading to a reduction in cancerogenesis progression. [38]

Recently, Steck and Co-Workers associated colon rectal cancer risk, Med D Score and the Healthy Eating Index (HEI) furthermore; and define a novel Dietary Inflammatory Index (DII). Comparing different published studies (US and European patients), the authors concluded that higher MedD score were associated with lower colorectal cancer risk (8-54%), as well as higher HEI scores were associated with lower colorectal cancer risk (20-56%). [39].

RED GRAPES AND RESVERATROL

Resveratrol is a phenolic compound mainly represented in the external skin of red grapes but also in other vegetables (for example berries and nuts). In MedD, resveratrol can be found mainly in red wine. However its concentration in red wine varies widely depending upon which quality of red grapes species and the climate. [40]

Resveratrol has pleiotropic pharmacological properties such as the repression of platelet aggregation, and eicosanoid synthesis. It promote the protection from ROS damage and from flogistic events resulting in cardiovascular protective benefits and, certainly, anti-cancer activities. [41,42]

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

Several preclinical and clinical studies have reported the beneficial effects of resveratrol in tumour prevention. [45,46,47,48] One of the major interesting topics investigated was the precise amount of red wine that has these beneficial effects. Resveratrol has been found to be safe and well-tolerated at up to 5 g/day, either as a single dose or as part of a multiple-day dosing comsumption [49].

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

Patel et al. studied how twenty CRC patients reacted to a daily oral administration of resveratrol such as 0.5 g or 1.0 g for 8 days prior to surgery. Detecting resveratrol-metabolites in CRC resection tissue, they found that resveratrol decreased volume tumour by 5%. [48] These data

support the hypothesis that resveratrol, as a MedD component, plays a role as a chemopreventive agent even if these doses are not attainable by normal consumption of wine.

Kontou, Psaltopoulou and their colleagues studied 250 Greek CRC patients using questionnaires assessing their clinical and lifestyle characteristic and their adherence to Mediterranean diet evaluated through MedDietScore. They demonstrated that an intake less than 12g of alcohol per day significantly reduces coloncancer risk in men and women. However there was a significant reduction resveratrol-related of CRC risk odds more in men than in women. According to Psaltopoulou and Kontou Mediterranean-style diet is independently related to a decrease of CRC risk both in men and women. [47]

Crockett et al performed a retrospective study analysing 1033 cases and 1011 controls from North Carolina and 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 of colorectal cancer (CRC) have shown that alcohol increases risk in a linear dose-related manner. [51,52,53]

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

Several studies have reported that the association between alcohol intake and CRC is stronger in men than in women. [52,55] On contrary the Norfolk UK cohort showed that daily consumption of 1 or more units of wine was inversely related to CRC risk (HR 0.61; 95% CI, 0.44 to 0.94), with no evidence for sex- specific relationships [56]. Moreover the North Carolina Colon Cancer study found that moderate intake of wine was inversely associated with CRC (OR 0.69; 95% CI, 0.56 to 0.86). [50]

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

Preclinical studies suggested a potential beneficial effects of resveratrol however clinical studies lead to controversial results. The reason is possibly related to dose and types of alcoholic beverages.

TOMATOES AND LYCOPENE

According to Smith "tomato pills cure all your ills" [58]: in fact tomatoes, central protagonists in MD, have several beneficial effects especially in the prevention of cardiovascular diseases, osteoporosis and cancer. A reduction of CRC risk more than 20% has been linked to the daily intake of vegetables, including tomatoes. [59] This extraordinary action of tomatoes has been attributed to their elevated content of carotenoids, first of all b-carotene and lycopene. [60,61]

Lycopene is synthesized by plants and confers red colours not only to tomatoes but also to red oranges and apricots. After the consumption of tomatoes, lycopene plasma concentration is dependent upon several biological mechanisms; in fact lycopene is modified during the digestive process decreasing its bioavailability. To facilitate lycopene absorption is better to introduce tomatoes in combination with lipids like it happens in sauces or juices. [62]

In a randomised cross-over trial a daily low-carotenoid diet based on daily 330 ml tomato or carrot juice was compared. At the end of the study faecal water showed an elevate dose-related cytotoxicity and the ability to suppress cancer cell proliferation on colon adenocarcinoma cells HT29. These results suggested that 2 week interventions with carotenoid-rich and lycopene-rich juices could led to changes in luminal biomarkers relevant to colon carcinogenesis. [63]

Walfisch et al suggested that high level serum of insulin-like growth factor in colon cancer patients is a marker of augmented risk of colon cancer. They showed that plasma concentration of IGF factor-I reduced significantly by 25% using tomato lycopene extract supplementation. [64]

The majority of case–control studies examined the association with CRC for carotenoids and vitamins using dietary intakes estimated from questionnaires. Most of these studies reported an inverse association between dietary vitamin C and CRC risk. [65] However, pooled analyses of

prospective studies showed no association between dietary intakes of carotenoids or between any of the vitamins A, C or E and CRC risk. [66,67]

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

They found that plasma retinol was inversely associated with (proximal) colon cancer and dietary intakes of dietary b-carotene and dietary vitamins E and C were inversely associated with (distal) colon cancer. Authors suggested a protective effect from fruit and vegetable consumption 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 of colorectal cancer. The relative risk for highest versus lowest category indicated no significant association between lycopene consumption and the risk of colorectal cancer [RR = 0.94, 95% 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 will be needed in this area to provide conclusive evidence

CONCLUSIONS

MedD Lifestyle included a particular type of food and drink, which exerts a nutritional synergy when assumed in combination [6]. The traditional MedD is centred on the mainly assumption of fruits, vegetables and fish and low red meat intake. Several pre-clinical and clinical studies have focused on how a MedD dietary pattern could affect cancer initiation and progression. Olive oil polyphenols, red wine resveratrol and tomatoes lycopene are secondary anti-oxidants produced by

plants and they showed several capabilities in vitro to interfere with molecular cancer pathways, at the same time many clinical studies reported olive oil, red wine and tomatoes ability to reduce cancer initiation and progression.

However due to the complex interaction between food and due to the bioavailability of antioxidants in man it is very difficult to define dose and dose-related effects. Moreover cancer results from the combine effects of many different factors such as: smoking habits, physical activity, genetic.

More clinical studies are needed to identify the precise dose and way of administration to produce a coadjutant treatment to the ones already applied nowadays in oncology. Therefore the supplementation of vegetables and fruit with bright colours or nuts and almonds as in MedD is particularly recommended in cancer patients [6,73].

A very recent evaluation of burden of cancer in European Counties found that former cigarette smoking combined was the risk factor responsible for the greatest cancer burden, but also adiposity play an important role. Ever smoking could explain 24.0% (95% CI = 22.2% to 26.0%) of total cancer burden followed by physical inactivity (4.9%, 95% CI = 0.8% to 8.1%) and adiposity (1.8%, 95% CI = 0.2% to 2.8%). [74]

In this review we focused on different components of MedD that could be useful in preventing CRC. More population studies are needed to confirm this data, however due to the good prevention of MedD in other different disease clinician can safely suggest this lifestyle approach to patients.

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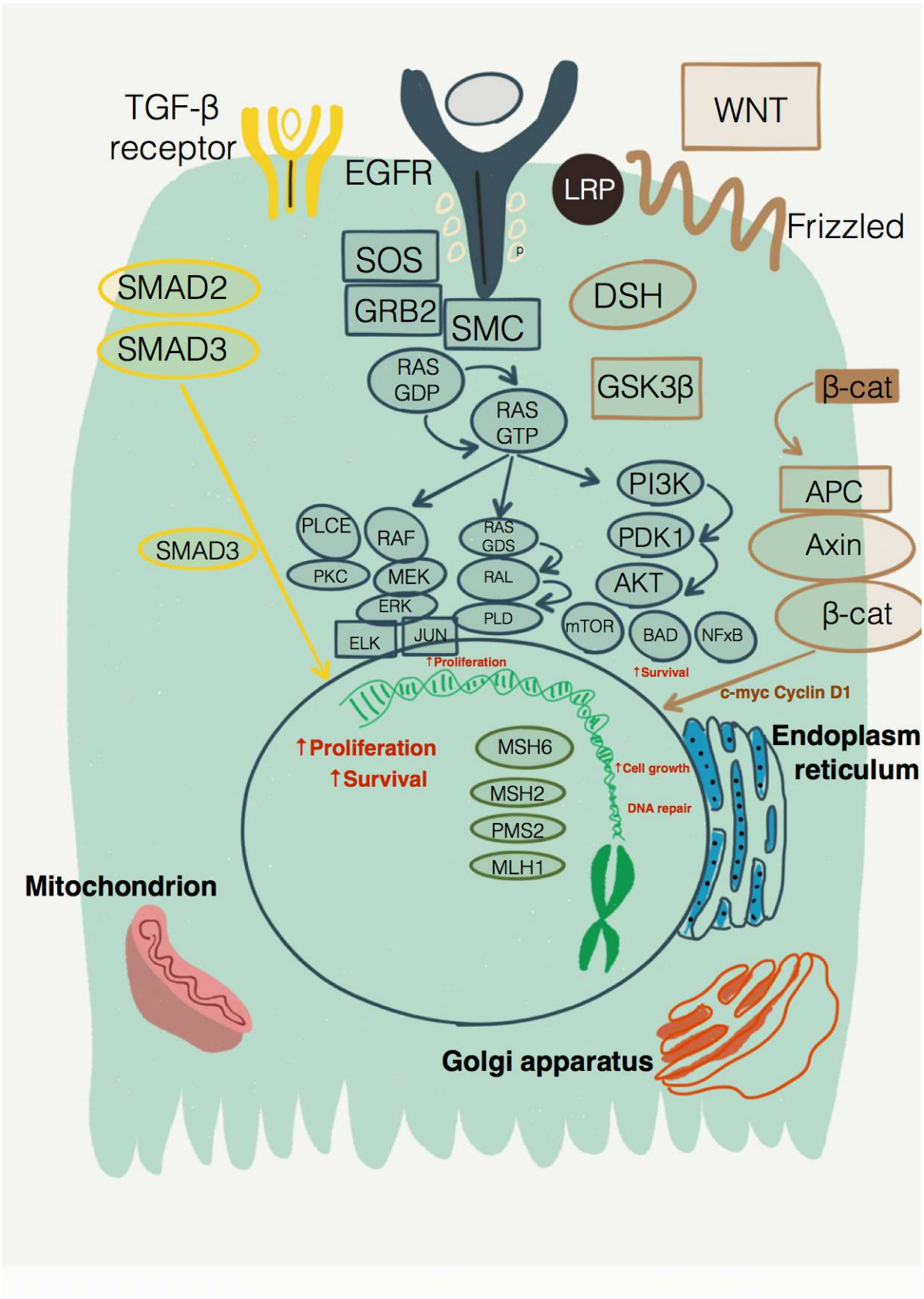
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Tab 1

Cellular effects of olive oil on colon cancer initiation and progression

- Downregulation of COX – 2 (26)
- Downregulation of BCL – 2 (27)
- ROS generation in cancer cell (28)
- Downregulation of EGFR expression (29)

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TGF-β
receptor
EGFR
WNT
LRP
Frizzled
SOS
GRB2
SMC
DSH
SMAD2
SMAD3
RAS
GDP
RAS
GTP
GSK3β
β-cat
APC
Axin
β-cat
PI3K
PDK1
AKT
SMAD3
PLCE
RAF
PKC
MEK
ERK
ELK
JUN
RAS
GDS
RAL
PLD
mTOR
BAD
NFxB
↑Proliferation
↑Survival
c-myc Cyclin D1
↑Proliferation
↑Survival
MSH6
MSH2
PMS2
MLH1
↑Cell growth
DNA repair
Endoplasm
reticulum
Mitochondrion
Golgi apparatus

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Highlights

- Colorectal cancer (CRC) is the third most common cancer worldwide and it has been correlated to eating habits such as Mediterranean Diet
- Mediterranean diet is characterized by an high consumption of fruits, vegetables and complex carbohydrates, followed by a low amount of fish and meat and a daily glass of red wine; in this diet the mainly source of fat is olive oil
- We focused on 3 components of MedD: olive oil, red wine and tomatoes.
- Preclinical studies suggest that these components have chemopreventive effects.
- More population studies are needed to confirm the efficacy of single component of MedD, however clinician can safely suggest this lifestyle approach to patients.

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