

R E V I E W

Polyphenols, Olive oil and Colonrectal cancer: the effect of Mediterranean Diet in the prevention.

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Abstract. In recent years, scientific research has shown that the incidence of various diseases, including some cancers, is relatively low in the Mediterranean Countries compared to that of other European countries or North America. This supports the hypothesis that the Mediterranean diet, rich in bioactive food components, including methyl group donors, polyphenols, and fatty acids has efficacy in terms of prevention. Few studies evaluated the efficacy of Med Diet on colon cancer however they all support the beneficial effects of this Diet in preventing cancer. (www.actabiomedica.it)

Key words: cancer, Mediterranean Diet, polyphenols, olive oil

Introduction

Colorectal cancer (CRC) is the second leading cause of death in industrialized countries and, specifically, the third leading cause of death in women (1).

In recent years, several studies have shown that the incidence of colon cancer, is low in the Mediterranean basin compared to that of other European countries or North America. The Mediterranean diet (MedD), rich in bioactive food components, including methyl group donors, polyphenols, fatty acids, isothiocyanates and allyl compounds seems to play a central role in prevention of colon cancer (1,2).

The Mediterranean diet has several positive health effects: it has anti-inflammatory effects, which makes it useful in various chronic gastro-intestinal diseases and it acts on endothelial dysfunction leading to a prevention of non-communicable diseases (3,4).

MedD is characterized by high intake of cereals, vegetables, fruits, legumes, low intake of meat and meat products, a moderate intake of fish and seafood

and a modest consumption of alcohol, accompanied by a regular intake of olive oil mainly extra virgin olive oil (EVOO) (4). A typical Italian meal includes a portion of extra virgin olive oil as a fat component, a glass of red wine and the intake of a cup of espresso coffee. It can be hypothesized that consumed at the same time, they can interact synergistically, strengthening the bio-availability of their phenolic compounds (2,4,5,6).

Consumption of olives or olive oil is considered important for preserving a healthy life. The largest producers of olive oil in the world are Spain, Italy, Greece, Portugal and Turkey, all Countries bordering the Mediterranean basin.

The main source of unsaturated fat in MedD is olive oil that has high concentration of polyphenols. The consumption of olive oil contributes to a significant reduction in the risk of cancer of the colon and rectum in Mediterranean populations (1).

Polyphenols have been linked to the maintenance of intestinal epithelium homeostasis that contribute to protection from carcinogenesis (5,7) Biological

activity of single phenols, especially hydroxytyrosol, tyrosol and their derivatives oleuropein, oleacein and oleocanthal were widely investigated on different types of cancer cells: colorectal, prostate, hepatocellular, pancreatic, and lung cancer (8,9,10). Anticancer properties were attributed to antioxidant activity of phenolic compound present in olive oil (11). (**Figure 1**)

Most national dietary guidelines promote the intake of fruits and vegetables, etc., in large quantities and advise people to limit their intake of processed foods. These are the foundations of the Mediterranean diet in which the main sources of polyphenols are berries, grapes, olive oil, cocoa, nuts, peanuts and other fruits and vegetables, which contain up to 200-300 mg of polyphenols per 100 g of weight (2).

The recent COVID-19 pandemic has profoundly changed eating habits in industrialized countries due to the quarantine imposed by governments which has led to an increase in smart working, distance learning and a reduction in physical activities (12,13,14,15).

Della Valle and coworkers showed that adherence to the MD during lockdown might have increased in some settings, while the determinants of such a trend are to be further explored. They underline the need to research further the impacts and long-term consequences of COVID-19 containment measures on dietary and lifestyle habits. (12). The analysis of food sales in Italy showed an increase in the consumption of flour, sweets and a reduction in the intake of fruit and vegetables (16).

Our search strategy was designed to inform this Narrative Review relating to effects of polyphenols on colon cancer. We searched MEDLINE, Scopus and Web of Science. In brief, we used a combination of terms relating to polyphenols (eg, “polyphenols” and “olive oil”) and colon cancer (eg, “colon cancer” and “colon rectal cancer”). For studies to be included in this Review, they had to report on primary research, be published in peer-reviewed journals, be written in English. We included papers describing the effects of any polyphenols on colon cancer in the last 20 years.

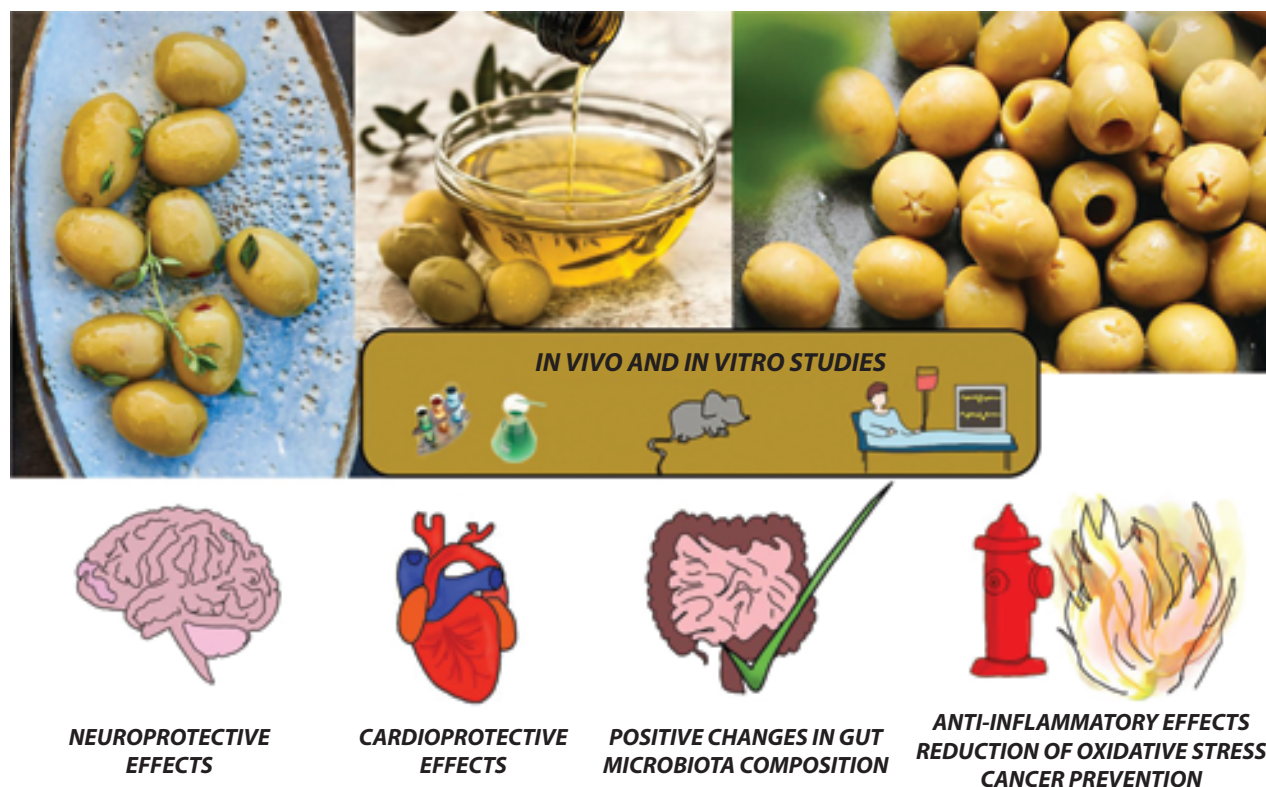


Figure 1. Effects of olive oil on human health.

The aim of this narrative mini-review is to describe the state of the art of the relationship between the polyphenols and the onset of CRC. We specifically analyzed the olive oil effects.

In-vitro and in-vivo studies

Hydroxytyrosol (HT), is one of the main phenolic components of olive oil, has several biological properties, including a remarkable antioxidant and anti-inflammatory power.

The European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies indicated HT as a polyphenol able to protect low density lipoproteins (LDL) against oxidative modifications, and recommended a daily consumption of at least 5 mg of HT and its derivatives (i.e., oleuropein complex and tyrosol) in Olive oil (17). So far, the properties of the phenolic extract of olive oil and extra-virgin olive oil (EVOO) on colon cancer have been poorly studied, however it contain a variety of antioxidants and antitumoral substances.

Di Francesco et al. have described an epigenetic regulation mechanism, such as DNA methylation; in particular they described how there is a regulation of the CNR1 gene expressed in human colon cancer cells (CACO-2). There appears to be a reduction in CNY1 promoter methylation; the CNR1 gene promoter is higher in CACO-2 cells. They also investigated the effects of evo0 administration in rats; in rats that received a 10-day administration, they observed an increase in *cnr1* gene expression; they also observed a decrease in methylation in the colon sample, similar to what was observed in vitro (18).

Pamploni et al. have shown how polyphenols could have an action at different levels in the path of cancerogenesis, inducing an anti-proliferative effect on colon cancer cells, through interaction with estrogen receptors; in particular they have seen how the estrogen receptor beta sub-unit is over-expressed in healthy colon cells. A reduction in its expression was seen in CRC cells. The authors have noted that polyphenols, having a chemical structure similar to that of estrogens, can act as inhibitors of the proliferation of tumor cells (19).

Still Hashim et al. reported some interesting results on the down-regulation of integrin alpha and beta sub-units; in particular, they noted a reduction in the expression of the alpha2 subunit, which appears to be overexpressed in the CRC. They administered 25 mg for kg during 2, 8 and 10 weeks to Severe Combined Immuno Deficiency (SCID) balb-c model mouse. The result was a reduction in the production of fibronectin, with a decrease not only in the size of the tumor but also in distant metastases. This study therefore suggests a role of inhibition on distant metastases (20).

Several authors have also described the antioxidant role of polyphenols in olive oil, thus reducing the formation of free radicals and consequently the inhibition of oxidative damage at the DNA level. This effect has also been described by Salvini et al. in post-menopausal women, achieving a 30% reduction of oxidative damage in peripheral blood lymphocytes (21).

In addition positive effects has been reported in young men suffering from coronary artery disease and in pre-menopausal women (2,4,7,21,22).

Human studies

It is believed that the health benefits of the Mediterranean diet are also caused by the high content of polyphenols (PP) (23). Therefore, dietary PPs are increasingly being studied as nutraceuticals against metabolic diseases (24). PPs also exert their health benefits through the modulation of hypothalamic inflammation and oxidative stress, which can enhance the functionality of several neural hormones that act within the brain, although more research is needed given the difficulty in determining these effects in humans (24). The study of the potential beneficial effects of polyphenols in humans is conditioned by the bioavailability of the phenolic compounds within the human organism and the same metabolism of polyphenols was described by De la torre in 2008 (23). However, little information is available from clinical studies (24).

Currently the EPIC, prospective cohort study, is the largest study investigating the correlation between polyphenol intake and colorectal cancer risk. The study involved 521,324 adults extrapolating data from the IARC board (25). In this study the highest polyphenol

Table 1. Main OO-oil effects on cell line of Colon rectal cancer described in literature

Author	Cell Line	Molecular action	Cell effects
Yumi-Hashim et al. (20)	HT115	Down regulation of alfa- 2 sub-unit of integrin	Decrease spread tumor and number of metastasis in vitro and murine model
Di Francesco et al. (18)	CACO-2	Down regulation of promoter on CNR-1 that is over expressed in CRC	Reduced proliferation of caco-2 cells in vitro and ex-vivo model
Corona et al. (35)	CACO-2	Inibition of extracellular signal-regulated kinase (ERK)1/2 phosphorylation and a downstream reduction of cyclin D1 expression	Reduced proliferation of caco-2 cell in vitro
Pampaloni et al. (19)	HCT-8	Interaction with estrogen dependent signals	Reduced cell proliferation in vitro
Notarnicola et al. (36)	SW620	FAS inhibition	Reduced cell proliferation and gain of apoptosis in vitro
Khanal et al. (37)	HT29	Down regulation of COX-2	Reduced cell proliferation and apoptosis

intake was given by the coffee. An association between polyphenol intake and the reduction of colon cancer in humans has been observed in the EPIC, in addition they found a positive association with the onset of rectal cancer in women, as well as with mortality.

Also in the Fukuoka study, an association between the intake of coffee and tea polyphenols and the decreased risk of CRC has been described (26).

There are no data to support this observation regarding the polyphenols from olive oil; however Sieri et al described the EPIC-Italy experience describing how the food model oil and salads has a role in reducing the onset of colorectal tumors (27).

A recent randomized crossover study conducted on 12 healthy volunteers showed that the interaction between EVOO and red wine increases the absorption of phenolic compounds such as tyrosol (TYR), and hydroxytyrosol (HT) present in EVOO and with antioxidant properties and anti-inflammatory (28). Phenolic compounds generally have poor bioavailability but in this study it is evident that a mixture of a fatty and a hydro-alcoholic matrix can influence the increase in the bioavailability of EVOO (29,30).

Phenolic compounds have different effects in women compared to men (30,31) In beverages and

food, phenolic compounds are stored as a glycone or as glycosidic conjugates. In the organism, they are widely metabolized. Some CYPs are differently expressed in women and men: CYP2B6, CYP2A6, and CYP3A have higher activity in women than in men, on contrary, CYP2D6, CYP2E1, and CYP1A2 have slightly higher activity in men than in women. The effects of quercetin, gallic acid and caffeic acid on CYP1A, CYP2A, CYP2E1 and CYP3A are related to sex leading to potential differences in the use of antioxidants in the prevention of colorectal cancer (32,33).

Interestingly, green tea and coffee have been also indicated as good sources of polyphenols and some recent studies suggest a clinical indication in prevention of colon cancer (32,33,34).

Conclusions

These studies describes that the modulation of gene expression by EVOO or its phenolic compounds through multiple mechanisms, both in vitro and in vivo, can provide a new therapeutic way for the treatment and/or prevention of colon cancer. Daily intake of polyphenols in olive oil, which is one of the most

important component of the Mediterranean diet, should be recommended for young adults and women, in particular post-menopausal women.

Generally, where possible, an effective strategy to reduce one's risk of developing non-communicable diseases is to control the activities of inflammatory mediators via modifiable risk factors such as diet, exercise, and healthy lifestyle choices.

Further studies, especially clinical trials, are recommended to investigate the action of polyphenols on humans.

List of abbreviations: CRC: Colorectal cancer; MedD: Mediterranean Diet; EVOO: Extra-virgin olive oil; HT: Hydroxytyrosol; PPs: high polyphenol

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