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REVIEW

Olive oil and health: Summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008

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Abstract Olive oil (OO) is the most representative food of the traditional Mediterranean Diet (MedDiet). Increasing evidence suggests that monounsaturated fatty acids (MUFA) as a nutrient, OO as a food, and the MedDiet as a food pattern are associated with a decreased risk of cardiovascular disease, obesity, metabolic syndrome, type 2 diabetes and hypertension. A MedDiet rich in OO and OO per se has been shown to improve cardiovascular risk factors, such as lipid profiles, blood pressure, postprandial hyperlipidemia, endothelial dysfunction, oxidative stress, and antithrombotic profiles. Some of these beneficial effects can be attributed to the OO minor components. Therefore, the definition of the MedDiet should include OO. Phenolic compounds in OO have shown antioxidant and anti-inflammatory properties, prevent lipoperoxidation, induce favorable changes of lipid profile, improve endothelial function, and disclose antithrombotic properties. Observational studies from Mediterranean cohorts have suggested that dietary MUFA may be protective against age-related cognitive decline and Alzheimer's disease. Recent studies consistently support the concept that the OO-rich MedDiet is compatible with healthier aging and increased longevity. In countries where the population adheres to the MedDiet, such as Spain, Greece and Italy, and OO is the principal source of fat, rates of cancer incidence are lower than in northern European countries. Experimental and human cellular studies have provided new evidence on the potential protective effect of OO on cancer. Furthermore, results of case-control and cohort studies suggest that MUFA intake including OO is associated with a reduction in cancer risk (mainly breast, colorectal and prostate cancers).

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Introduction

Morbidity and mortality from chronic diseases in the general population have a multifactorial origin, resulting from the interaction between genetic background and environmental factors. Among the latter, diet is probably

the most relevant. After decades of epidemiological, clinical and experimental research, it is clear that consumption of specific foods and, particularly, dietary patterns have a profound influence on health outcomes, including coronary heart disease (CHD). For both food investigators and consumers, the focus has shifted recently towards a holistic

approach that considers both health aspects and pleasure components. In this regard, the Mediterranean Diet (MedDiet) has been rediscovered as the dietary pattern that best fulfills the need for nourishment, health and pleasure. Adherence to the MedDiet is associated with longevity and a lower incidence of chronic diseases, particularly CHD [1]. Most foods consumed in the MedDiet are also present in other healthy dietary models. However, in opposition to all other healthy diets, the MedDiet has a high content of total fat as its most distinguishing feature. This is because of the customary high intake of olive oil (OO), the characteristic culinary fat of the Mediterranean area [2].

In October 2004 the First International Conference on the Healthy Effects of Virgin Olive Oil (VOO) convened in Jaén, Spain and a summary of scientific evidences was published [3]. Accumulating knowledge prompted scientific experts to assemble in November 2008 in Córdoba and Jaén, Spain for the Second International Conference on Olive Oil and Health, where new scientific evidence on the topic was presented and is summarized in this report (Table 1).

Bioactivity of minor olive oil components

The beneficial effects of OO on CHD risk in the context of the MedDiet have been attributed to its high monounsaturated fatty acid (MUFA) content. This was the basis for the health claim authorized for OO labels by the US Federal Drug Administration in November 2004. However, evidences have accumulated on the beneficial properties of minor though highly bioactive components of OO. These minor components are classified into two types, the unsaponifiable (non-polar) and the soluble (polar) fraction, which includes the phenolic compounds [4]. Phenolic compounds from VOO are bioavailable in humans in a direct relationship with the phenolic content of VOO administered [5]. In experimental

studies, both components of OO have shown a broad spectrum of bioactive properties, including anti-inflammatory, antioxidant, antiarrhythmic, and vasodilatory effects [6].

Since our first report [3], some questions have been answered and new fields have opened regarding the beneficial health effects of minor components of VOO. Recently, it was shown that the triacylglycerol concentration of triacylglycerol-rich lipoproteins (TRL) and their particle size were higher and the number of TRL particles was lower after VOO, with a high content of non-polar constituents, than after refined OO [7]. Furthermore, intake of high-oleic acid sunflower oil was associated with higher postprandial triacylglycerol increases compared with VOO or VOO enriched with non-polar components, and incubation of postprandial TRL formed after ingestion of VOO with endothelial cells was associated with a greater reduction in prostaglandin E₂ and thromboxane B₂ production [8]. The insoluble fraction of VOO has been shown to inhibit both low-density lipoprotein (LDL) receptor-related protein expression and activity [9].

By showing that phenolic compounds in VOO can reduce cardiovascular risk factor levels, the EUROLIVE study [5] provided clear evidence that VOO is more than just MUFA. In that study, OOs with different phenolic content were given, and all of them reduced serum triacylglycerols and increased high-density lipoprotein (HDL)-cholesterol and the reduced-to-oxidized glutathione ratio. However, the increased HDL-cholesterol and reduced oxidative damage to lipids was related to the phenolic content of VOO in a dose-dependent manner [5].

Oxidative DNA and RNA modifications appear to play pivotal roles in the pathogenesis of major degenerative diseases. In an EUROLIVE substudy [10], urinary 8-oxo-deoxyguanosine levels was reduced in association with the intake of VOO, regardless of the phenolic content.

In recent years, the anti-inflammatory and vasculo-protective properties of VOO polyphenols have been

Table 1 Recent studies supporting the health effects of the Mediterranean Diet rich in olive oil.

Level of evidence	Type of effect (reference)
Demonstrated by dietary intervention trials in different populations	<ol style="list-style-type: none"> 1. Beneficial effects on the lipid profile, with a decrease in LDL-cholesterol and higher HDL/total cholesterol ratio versus SFA [5,42,67,68] 2. Reduction of LDL oxidizability [17,42] 3. Improvement of glucose metabolism in normal subjects and patients with type 2 diabetes. Substitution of MUFA for SFA results in lower insulin requirement and plasma glucose concentrations, and is at least as effective as CHO [56–59] 4. Improved blood pressure control [42,69,70]. 5. Improvement of endothelial function [17,64] 6. Promotion of a less prothrombotic environment compared with SFA-rich diets, influencing different thrombogenic factors: reduction of platelet aggregation, thromboxane B₂ production, von Willebrand factor (vWf), tissue factor, tissue factor pathway inhibitor, PAI-1, Factor VII and Factor XII [18,19,62].
Suggested by a few dietary intervention trials, observational studies, or in vitro experiments	<ol style="list-style-type: none"> 1. Favorable effects on obesity [18,36–38] 2. Lower NF-κB activation when compared with other types of diet, both in fasting and postprandial state [71,72]. 3. Reduction in age-related cognitive decline and Alzheimer's disease of increased adherence [85,86].

vWf, Von Willebrand factor; LDL, low density lipoprotein; HDL, High density lipoprotein; MUFA, Monounsaturated fatty acids; SFA, saturated fatty acids; CHO, carbohydrates; PAI-1, plasminogen activator inhibitor type 1; NF-κB, nuclear factor kappaB.

extensively investigated (Table 2). Out of 4 clinical studies [11–14], three of them reported reductions in thromboxane B₂ [11–13]. The effects of phenolic compounds from VOO on cell adhesion molecules are controversial. In a 3-week study in patients with CHD [15], consumption of VOO high and low in phenolic compounds decreased inflammatory markers, but had no effects on VCAM-1 and ICAM-1 plasma concentrations. An study showed postprandial decreases in cell adhesion molecules after intake of phenol-rich VOO compared with refined OO [16]. Furthermore, improved post-ischemic hyperemia via reduced oxidative stress and increased nitric oxide metabolites was reported after the intake of phenol-rich VOO in comparison with a low-phenol VOO [17].

Concerning hemostatic factors, two studies [18, 19] showed that consumption of meals rich in VOO was associated with changes of postprandial hemostatic profile to a less thrombogenic state.

Mediterranean Diet, olive oil and risk of chronic diseases

There is now sufficient scientific evidence supporting the notion that increasing adherence to the dietary pattern characteristic of Mediterranean countries is associated with a reduction of overall, cardiovascular and cancer mortality, and incidence of CHD, cancer, and neurodegenerative

diseases [20–26], together with a reduced prevalence of risk phenotypes [23, 27–29]. Among the many variations of the MedDiet found in different Mediterranean countries, the use of OO as main culinary fat is the common denominator. From the epidemiological standpoint it is somewhat difficult to disentangle OO from the other components of the MedDiet, mainly because most scores of adherence to the MedDiet have used the MUFA:SFA ratio instead of OO proper following the MedDiet score originally described by Trichopoulou et al [30]. Nevertheless, OO has been proposed as a key factor for the health benefits associated with the MedDiet [2,3].

Obesity, metabolic syndrome and diabetes

Mediterranean Diet and olive oil in obesity

Traditionally, nutritional advice for treating obesity has emphasized avoiding animal fat and, preferably, all kinds of dietary fat, and replacing them with carbohydrate (CHO). The debate on what is the best nutrient to replace energy sources from SFA in the diet, CHO or MUFA, has indirectly been solved by the Women's Health Initiative study [31] showing the lack of protective effect of a high-CHO diet against CHD. Nevertheless, it must be pointed out that when a high-CHO diet is recommended for health it is usually a high-fibre diet, and increased dietary fibre intake

Table 2 Human studies on the effect of olive oil phenolic compounds on inflammatory markers and cell adhesion molecules.

Subjects	Type of study	Intervention	Biomarkers	Effects	Author, year (Reference)
12 Postmenopausal women	2 Consecutive periods, no washout, ad libitum diets	VOO vs oleic acid-rich sunflower oil	TXB ₂ in PRP TXB ₂ in urine 6-keto-PGF _{1α}	Lower in VOO Similar Similar	Oubiña et al., 2001 [13]
5 patients with type 1 diabetes	Single intervention	Olive mill waste water (HT: 25 mg first day; 12.5 mg/d during 3 days)	Serum TBX ₂	Decrease at day 4	Lèger et al., 2005 [14]
Hyperlipidemic patients (12 men and 10 women)	Randomized, crossover	VOO vs refined olive oil (intervention, 40 mL/d, 7 weeks; washout period, 4 weeks with usual diet)	Serum TBX ₂	Decrease with the phenolic content of the olive oil	Visioli et al., 2005 [11]
12 Healthy men	Randomized, crossover postprandial	VOO vs refined olive oil (50 mL with potatoes)	Plasma LTB ₄ Plasma TBX ₂	Decrease with the phenolic content of the olive oil	Bogani et al., 2006 [12]
Healthy (14) and hypertriglyceridemic (14) men	Randomized, crossover, postprandial	Fat meal with VOO vs refined olive oil, after 1 week of each (50 mg/m ² body surface)	Serum ICAM-1 and VCAM-1 area under curve	Decrease with the phenolic content of the olive oil	Pacheco et al., 2007 [16]
28 Men with CHD	Randomized, crossover, controlled	VOO vs refined olive oil (intervention period, 50 mL/d, 3 weeks; washout period 2 weeks with refined olive oil ad libitum)	hsCRP, Interleukin-6 Serum ICAM-1 Serum VCAM-1	Decrease with the phenolic content of the olive oil No changes	Fitó et al., 2008 [15]

TXB₂, thromboxane B₂; 6-keto-PGF_{1α}, 6-keto-prostaglandin 1α; PRP, platelet-rich plasma; HT, hydroxytyrosol; LTB₄, leukotriene B₄; CHD, coronary heart disease; hsCRP, high sensitivity C reactive protein; VOO, virgin olive oil.

has been consistently linked with beneficial health outcomes [32–35].

The results of observational studies in Mediterranean countries, where people complying with the MedDiet consume significant amounts of OO, suggest that increasing adherence to such high-fat, high-MUFA dietary pattern is associated with decreasing obesity rates [36–38]. However, recent results from EPIC [39], indicate that adherence to the MedDiet inversely relates to abdominal adiposity, but not to BMI. Another prospective study from a Mediterranean country has shown that increasing OO use is not associated with weight gain [40]. Restricted energy diets that were relatively high in fat because they incorporated OO were effective alternatives to the traditional low-fat diet for initial weight loss and maintenance in feeding studies in obese persons, while showing better palatability and compliance [41]. Furthermore, the PREDIMED study showed no 3-month weight gain with these high MUFA diets [42]. A satiating effect of OO intake with ensuing food compensation might explain its lack of a fattening effect. In this regard, recent experimental evidence has been provided that mobilization of intestinally-derived oleoylethanolamide, a lipid messenger of satiety, is enabled by uptake of dietary oleic acid [43].

Mediterranean Diet and olive oil in metabolic syndrome (MetS)

Epidemiological studies suggest that Western-style dietary patterns promote MetS, while diets rich in fruits, vegetables, grains, fish and low-fat dairy products have a protective role [44, 45]. Recently, two studies in Southern European populations showed that a greater adherence to the MedDiet was associated with reduced prevalent [46] and incident [47] MetS.

Four feeding trials have assessed the effect of dietary patterns on MetS status to date [48–51]. These studies used a behavioral program to implement a relatively low-fat MedDiet [48], intensive lifestyle intervention with inclusion of a vegetable-rich diet restricted in animal fat [49], the DASH diet [50], and two MedDiets supplemented with VOO or nuts [51] in comparison with standard advice. In all studies, a decreased prevalence of MetS was shown in the intervention groups. The recent data from EPIC [39] showing lower waist girth with increasing adherence to the MedDiet also support a beneficial role on MetS. Results of a recent study in overweight, insulin-resistant patients also suggest that, by comparison with a low-fat diet, a high-VOO diet prevents the redistribution of body fat from peripheral to visceral adipose tissue without affecting total body weight [52].

Mediterranean Diet and olive oil in diabetes

Because diabetes is a frequent outcome in patients with sustained MetS, it is reasonable to assume that the MedDiet might also prevent the development of diabetes [53]. Two prospective studies from Southern European cohorts suggest a lower incidence of diabetes with increasing adherence to MedDiet in previously healthy persons [54] or survivors of a myocardial infarction [55].

Diets high in SFA consistently impair both insulin sensitivity and blood lipids, while substituting CHO or MUFA for SFA reverts these abnormalities [56]. Postprandial lipemia and glucose homeostasis are also improved after meals containing MUFA from OO compared to meals rich in SFA [57,58]. An examination of the association of dietary and membrane fatty acids with insulin secretion in the cross-sectional Pizarra study [59] showed that dietary MUFA from OO and polyunsaturated fatty acids (PUFA) contributed to the variability of β -cell function.

The question as to what was the best nutrient to replace energy sources from SFA in diabetic diet, CHO or MUFA, was hotly debated. Since the 1980s, many feeding trials have compared the effects of isoenergetic high-CHO and high-MUFA diets on insulin sensitivity in healthy subjects and on glycemic and lipid control in diabetic patients [60,61]. Garg's meta-analysis [60] favored high MUFA diets. The studies reviewed by Ros [61] were performed on an outpatient basis with natural foods and OO as the main source of MUFA; the conclusion was that both dietary approaches provided a similar degree of glycemic control. Nevertheless, high-MUFA diets generally had more favorable effects on proatherogenic alterations associated with the diabetic status, such as dyslipidemia, postprandial lipemia, small LDL, lipoprotein oxidation, inflammation, thrombosis, and endothelial dysfunction [61]. Of particular interest was the ability of an OO-rich MedDiet to improve mild systemic inflammation in subjects with MetS in the study of Esposito et al. [48] and in the PREDIMED study [42].

Cardiovascular risk factors

Our first report [3] highlighted the cardiovascular benefits of VOO intake in the context of the MedDiet. Since then, further evidences on the cardiovascular benefits of a MedDiet rich in VOO have been published (Table 3). An increase in HDL-to-cholesterol ratio, additional evidence of the antihypertensive effect of VOO [42], and improved postprandial thrombotic profiles, both in healthy and hypercholesterolemic subjects, have been reported [62,63]. During the postprandial state, diets rich in SFA impair vascular reactivity, while consumption of VOO preserves endothelial function [64].

Recent studies have reinforced the proposed mechanisms by which VOO can exert its beneficial effects on cardiovascular risk [65,66], including: (1) improvement of lipid profile, through a decrease in total and LDL-cholesterol and an increase of the HDL-to-cholesterol ratio [42,67,68]; (2) reduction of LDL susceptibility to oxidation and amelioration of oxidative vascular damage [17,42]; (3) improved endothelial function [17,64]; (4) improved blood pressure control [69,70]; and (5) favorable modifications of hemostasis [18,19,62].

Most of the above effects are likely interconnected by a common upper regulation, such as nuclear factor κ B (NF- κ B). It has been shown that after a meal rich in SFA, but not if the meal contains VOO, NF- κ B is transiently activated preceding the postprandial increase in markers of inflammation, oxidation, and thrombosis [71]. Furthermore, NF- κ B in mononuclear cells is less activated after

Table 3 Overview of recent clinical studies showing effects of dietary interventions with olive oil on cardiovascular risk factors.

Subjects	Type of study	Intervention	Biomarkers	Effects	Author, year (Reference)
8 healthy men	Randomized, crossover, postprandial	VOO meal vs butter and walnut meals	NF-Kb	Less activated	Bellido et al. 2004 [71]
169 men and women	Randomized	MedDiet enriched in VOO vs Low fat diet	LDL-C, Triglycerides	Decrease	Vincent-Baudry et al. 2005 [67]
5 men and 16 women, hypercholesterolemic	Randomized, crossover, postprandial	Olive oil with high (400 ppm) vs low (80 ppm) phenolic content	Reactive ischemic hyperemia Nitrates/nitrites Liperoxides 8-epi-prostaglandin-F2 α	Increase Increase Decrease Decrease	Ruano et al. 2005 [17]
200 healthy men	Randomized, crossover	Olive oil with high (366 mg/kg) vs medium (164 mg/kg) or low (2.7 mg/kg) phenolic content	HDL-C/TC ratio Oxidized LDL	Increase Decrease	Covas et al. 2006 [5]
772 persons at high CVD risk	Randomized	2 Mediterranean diets (enriched with VOO or mixed nuts) vs a low fat diet	HDL-C/TC ratio Systolic blood pressure	Increase Decrease	Estruch et al. 2006 [42]
21 healthy subjects	Randomized	High-fat, high olive oil diet vs high carbohydrate diet	HDL-C/TC ratio	Increase	Ahuja et al. 2006 [68]
14 healthy men	Randomized, crossover, postprandial	VOO vs refined olive oil	Fibrinogen t-PA PAI-1	Decrease Decrease Decrease	Pacheco et al. 2006 [18]
16 healthy men	Randomized, crossover	High-fat SFA-rich diet vs Mediterranean high olive oil diet vs high carbohydrate diet enriched in α -linolenic acid	NF-kB VCAM-1	Decrease Decrease	Perez-Martinez et al. 2007 [72]
20 healthy men	Randomized, crossover, Postprandial	VOO meal vs butter and walnut meals	Reactive ischemic hyperemia Nitrates/nitrites	Increase Increase	Fuentes et al. 2008 [64]
20 healthy men	Randomized, crossover, postprandial	VOO and walnut meals vs butter meal	FVIIc PAI-1	Decrease Decrease	Delgado-Lista et al. 2008 [62]

CVD, cardiovascular; FVIIc, factor VII coagulant activity; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NF- κ B, Nuclear transcription factor KB; PAI-1, plasminogen activator inhibitor-1; VOO, virgin olive oil; TC, total cholesterol; tPA, tissue-type plasminogen activator.

consumption of a VOO-rich MedDiet compared with a Western diet [72].

Recent experiments in rats fed VOO, triolein and oleic acid showed a similar blood pressure-lowering effect for the three interventions, while feeding the oleic acid analogues stearic acid and elaidic acid had no such effect [73]. While these observations concur with the hypothesis that the benefit of OO was mainly related to its MUFA content [74], there are also evidences for a beneficial role of minor components. Triterpenoid compounds of VOO have shown anti-inflammatory effects through promotion of prostacyclin synthesis in human vascular smooth muscle cells [75]. Squalene has also shown promising properties as an anti-inflammatory molecule in animal models of accelerated atherosclerosis [76]. Notably, oleocanthal, a VOO phenolic component, showed a strong anti-inflammatory activity mediated by inhibition of cyclooxygenase-1 and -2 [77]. Together with the emerging evidences on the beneficial effects of VOO rich in phenolic compounds (12, 15–23), these data strongly suggest that the cardiovascular benefit of VOO is attributable to the combined properties of all its constituents, namely MUFA and minor polar and non-polar compounds.

Oxidation, aging and cognitive decline

The increase in average human lifespan is a public health problem due to the rising numbers of persons reaching advanced age and the frequency of age-related diseases, such as CHD, stroke, Alzheimer's and Parkinson's disease.

Oxidation

Most age-related diseases have been associated with low-grade inflammation triggered and sustained by oxidative stress. The relationship between increased oxidation and age-related diseases has been inferred from observational studies in which an increased antioxidant content of diets was associated with lower chronic disease rates [78]. In this regard, traditionally the beneficial effect of dietary OO on oxidation was exclusively attributed to its high oleic acid content, which is enriched in lipoproteins and cellular membranes, thereby protecting them from oxidative damage [79]. However, VOO contains minor components with antioxidant properties that permitted to uncover their added antioxidant effect in clinical studies that compared OOs with different phenolic content [5,12,70]. Limited evidence from animal studies suggest that MUFA-rich membranes are more resistant to oxidative processes, protecting the aged cell [80,81]. Mitochondrial structure, integrity and DNA stability to oxidation were also enhanced when rats consumed a VOO-rich diet [81].

Aging and life expectancy

Prospective studies have shown that adherence to a typical MedDiet is associated with lower mortality and increased longevity [82,83]. In the meta-analysis of 12 prospective studies by Sofi et al. [20], a two-point increase in a score of MedDiet adherence was associated with improved health status, as shown by a significant reduction in mortality (9%),

cardiovascular diseases (9%), cancer (6%), and the incidence of Parkinson's and Alzheimer's disease (13%). This benefit was also apparent in non-Mediterranean populations [20].

Cognitive impairment, MUFA and olive oil

An important health-promoting property of the MedDiet is its possible benefit on the cognitive status of the elderly. Recent studies have focused on the identification of individual components or foods in the MedDiet that may reduce the progression to dementia at a preclinical or early stage of disease [84]. Cognitive impairment of vascular or neurodegenerative origin often share the same cardiovascular risk factors. Because dietary habits clearly influence the risk of vascular diseases, an effect on cognitive impairment can be expected. Indeed, recent studies have suggested that dietary fatty acids play a role in cognitive decline associated with aging or dementia [85]. An analysis of 704 participants in the population-based ILSA study [86] showed that high MUFA and PUFA intake was associated with better cognitive performance in a 8.5-year follow-up. This protective effect of unsaturated fatty acids was ascribed to their influence in both maintaining the structural integrity of neuronal membranes and enhancing fluidity of synaptosomal membranes, thereby regulating neuronal transmission. Results of a substudy of 278 elderly participants in ILSA focusing on incident mild cognitive impairment (MCI) [22,87], suggested that dietary fatty acids were not associated with MCI and only PUFA showed a non-significant protective trend. Conversely, a recent report of 732 older participants in the EPIC-Greece cohort [88] found that MUFA intake was associated directly albeit nonsignificantly with better cognitive performance, while PUFA intake showed an inverse association.

Regarding OO intake, it must be underlined that specific associations with cognitive decline or dementia have not been formally examined. Both the Greek EPIC study [88] and a prospective population study of 8085 elders from Southern France [89] reported nonsignificant trends for OO intake and better cognitive performance and reduced incidence of dementia, respectively. A recent report [90] suggests that adherence to MedDiet delays cognitive decline, but OO was not considered as such among the foods used to build the score of adherence. On the other hand, reports from US population cohorts suggesting that adherence to the MedDiet protects from Alzheimer's disease [91,92] are not relevant here because the US version of the MedDiet lacks OO.

Prevention and progression of cancer

Approximately 80% of human cancers (especially breast, ovary, prostate, colorectal and upper digestive and respiratory tract cancers) have been associated with unhealthy lifestyles. Epidemiological studies have provided evidence that in countries where populations follow the traditional MedDiet and OO is the main source of fat, such as Spain, Greece and Italy, cancer incidence is lower than in Northern Europe, North America and Australia [93–95]. Although analytical studies have provided some

Table 4 Studies supporting the effects of the Mediterranean Diet rich in olive oil on cancer risk.

Level of evidence	Type of effect (reference)
Shown in observational epidemiology	Reduced incidence of some cancers [93–95].
Demonstrated in analytical epidemiological studies	Modest or no association of MUFA with a decrease in breast cancer risk, while risk increases with diets rich in SFA [96].
Demonstrated by experimental in vivo studies	<ol style="list-style-type: none"> 1. Delayed breast cancer progression [98]. 2. Low histopathological degree of malignancy [99].
Suggested by experimental in vivo and human in vitro studies	<ol style="list-style-type: none"> 1. Modulation of the expression of genes involved in cell proliferation and differentiation, such as suppression of HER2/neu expression in HER2-positive breast cancer [98, 102, 103]. 2. Changes in specific signal transduction pathways in tumor cells, such as those dependent on eicosanoids and p21Ras [98, 101]. 3. Protective effect against oxidative stress [100]. 4. Antiinflammatory and immunomodulatory effects [104].

MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

inconsistent results, in general most case-control and cohort studies have shown that oleic acid and OO is associated with a reduction in the risk of cancer (mainly breast, colorectal and prostate cancer), at variance from diets rich in total fat and in linoleic acid or SFA, which have been related to an increased cancer risk [96]. In a meta-analysis of observational studies up to July 2003 [97], MUFA was not significantly associated with the risk of breast cancer. Nevertheless, studies in human cell lines and experimental models suggest a potential protective effect of VOO on cancer. Thus, there is experimental evidence concerning the favorable influence of OO on the initiation, promotion and progression of carcinogenesis, with tumors being of a lower degree of clinical and histopathological malignancy [98,99]. Such protective action on cancer may be mediated through several mechanisms, among them, changes in tumor cells related to the composition and structure of cell membranes, changes in eicosanoid biosynthesis or intracellular signaling pathways, modulation of gene expression, reduced cellular oxidative stress and DNA damage, and modulation of the immune system and hormonal balance in hormone-dependent cancers, such as breast and prostate cancers [98,100–104].

Together with MUFA and minor bioactive components, VOO consumption ensures an appropriate intake of essential PUFA, with a low ratio of n-6 to n-3 PUFA. Both features are considered important to lower the risk of breast cancer and probably other types of cancer [105]. Table 4 summarizes scientific evidences on MUFA and/or OO intake and cancer.

The beneficial effect of VOO on cancer might be due to a synergy of all its components triggering a broad range of cell responses that may play a role in cancer prevention or, if the disease already exists, result in reduced biological aggressiveness. As an environmental factor, the putative anti-cancer effects of VOO will depend on the underlying genetic background. Thus, the effects will be different in a normal cell or a cancer cell, where they will be modulated by specific genetic and/or epigenetic cellular alterations. The potential benefit of moderate intakes of VOO on cancer should be placed in the broader context of the MedDiet and a healthy lifestyle. The protective effect of

VOO on cancer might be more important if consumption begins before puberty in the first decades of life and continues throughout life thereafter.

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