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REVIEW

Olive oil and prevention of chronic diseases: Summary of an International conference

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Abstract Olive oil is the foremost source of fat in the Mediterranean area and, among other features, sets the Mediterranean diet apart from other dietary regimens. In January 2018, the International Olive Council convened several worldwide experts at the Robert Mondavi Institute (Davis, CA), to discuss and summarize the available data on the effects of olive oil consumption on human health. In this paper, we critically provide a synthesis of the main reported findings, which underscore how and why consuming this oil as part of a balanced diet and healthful lifestyle improves prognosis and extends life- and health-spans.

Introduction

Olive oil is the foremost source of fat in the Mediterranean area and, among other features, sets the Mediterranean diet apart from other dietary regimens. In the past >2000 years, olive oil is being mostly employed for spiritual and religious purposes and it is mentioned in the Bible and the Holy Koran, as well as in Homer's works [1].

Many ecological studies – starting from the Seven Countries one – have long being correlating a Mediterranean dietary pattern with longevity and lower incidence of coronary heart disease (CHD), cancer, and neurodegeneration. Being the Mediterranean diets multifactor in nature, it is difficult to single out the precise health contribution of any of its components. However, the case of olive oil might be different because research on this item is very much advanced and allows for some evidence-based claims.

In January 2018, the International Olive Council convened several worldwide experts at the Robert Mondavi Institute (Davis, CA), to discuss and summarize the available data on the effects of olive oil consumption on human health. In this paper, we critically provide a synthesis of the main reported findings and propose further areas of research on olive oil and human health.

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Fat intake and cardiovascular disease. Brief summary of the evidence

Starting from the Seven Countries Study at the middle of the 20th century [2], nutritional approaches for the prevention of coronary heart disease (CHD) have continually emphasized replacing saturated fat (SFA) by unsaturated fat including polyunsaturated (PUFA) and monounsaturated fat (MUFA). The Seven Countries study was based on international comparisons following an ecological design, where communities, not individuals, were the units of analysis. The Seven Countries Study identified the Mediterranean diet as a model in which olive oil, rich in MUFA, instead of butter (rich in SFA) was the culinary fat.

In those early years of research on diet and cardiovascular disease, another line of evidence was provided by small controlled feeding experiments (typically less than 50 subjects) that used serum total cholesterol as the primary outcome. Compared to the same number of calories from carbohydrate, intake of SFA increased serum total cholesterol, whereas PUFA intake reduced cholesterol levels. Based on this evidence, PUFAs from liquid oils partly replaced butter in the American diet, and this was associated with a large decrease in CHD mortality, even though several other factors such as an overall improvement in medical and surgical procedures also contribute to an uncertain extent [3]. The benefit of replacing saturated fat with PUFA has been recently challenged based on the assumption that PUFAs, namely linoleic acid from seed oils (and incorporated into margarines, baked goods, and other foods), are the precursors of pro-inflammatory prostaglandins. However, accumulated human data do not support this biochemical hypothesis and actually suggest the contrary [4].

In addition to guidelines promoting the substitution of MUFA or PUFA for SFA, another line of dietary advice, based on little evidence, emphasized reduction in total fat intake regardless of its composition. This misleading advice promoted the reduction of both saturated and unsaturated fats for chronic disease prevention including cardiovascular disease and breast cancer and, as a consequence, encouraged consumption of sugar and refined starch.

Contention about the role of SFA intake in the etiology of CHD was stirred by a 2014 meta-analysis that brought butter and SFA onto magazine covers [5]. A major limitation of this and similar contentions is that they have usually not specified the comparison macronutrient in an iso-caloric analysis. Thus, this ignores the fact that the effect of saturated fat on CHD risk may depend on the replacement source of calories. These substitutions or exchanges are of utmost importance in nutritional science, and would be routinely considered in controlled feeding studies. Because nearly half of total energy intake in most Western diets is composed of refined carbohydrates (starch and sugar), unless a specific comparison source of calories is specified, SFA is by default being compared largely with refined carbohydrates and added sugars. Therefore, the apparent "neutrality" of SFA would only mean in this context that SFA is as approximately as bad as refined carbohydrate.

In contrast to most studies of CHD risk until now, in the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS), SFA intake was iso-calorically compared with unsaturated fats or carbohydrates. In these analyses, compared with SFA, equivalent energy intake from PUFA, MUFA, or high-quality carbohydrates (from whole, unrefined, i.e. with low-glycemic index cereals) was associated with significantly lower CHD risk. Conversely, substitution of carbohydrates from refined starches or added sugars for SFA was not associated with lower CHD risk [6].

The simple message of reducing all sources of fat has been misleading. The key message should have been instead to select the healthier sources of fat (e.g., tree nuts, avocado, olive oil, other unsaturated plant oils and fatty fish) to replace unhealthy fat sources (red and processed meats or dairy). In support of this "modulate/fine-tune" rather than "reduce" total fat advice, in the NHS and HPFS [7–9] the hazard ratios of total mortality comparing highest with lowest quintiles of specific dietary fats were 1.08 (95% CI, 1.03–1.14) for SFA, 0.81 (95% CI, 0.78–0.84) for PUFA and 0.89 (95% CI, 0.84–0.94) for monounsaturated fatty acid (MUFA). The specific contribution of olive oil to the total MUFA intake is, to date, relatively unexplored. Moreover, major sources of MUFA in the US historically included beef and other meats, not mainly olive oil although this pattern is changing [9]). However, it should be noted that, in terms of CHD risk, olive oil does reduce the ratio of total to HDL cholesterol [10] whether compared with saturated fat or carbohydrate, thus lowering one of the manifold risk factors for CHD. Of note, data from Crete (a region that historically has enjoyed high longevity) show that calorie intake from fat approximates 40% of total calories, about half of which has been from olive oil [11]. In recent ecological analyses from the Seven Countries Study the 50-year all-cause mortality rates was correlated inversely ($r = -0.51$ to -0.64) with the ratios MUFA/SFA, (MUFA + PUFA)/(SFA + Trans fatty acids), and with the ratio hard fats/vegetable oils [12].

The take-home message is that available evidence does not support a benefit from reducing the percentage of energy from total fat in the diet, and that recommendations focused on decreasing total fat are misleading. More important, is the type of dietary fat, which should emphasize unsaturated fats from natural plant sources.

Cardioprotection: mechanistic studies

As mentioned, most of the evidence correlating olive oil intake with lower incidence of some diseases comes from epidemiological observations. However, there is now abundant literature that provides mechanistic insights into the healthful properties of olive oil and its components. Back in 1993, pure hydroxytyrosol was isolated from extra-virgin olive oil and in vitro experiments began to

investigate its antioxidant properties. Of note, such experiments were performed in what is now an outdated model, i.e. copper-oxidized low-density lipoproteins (LDL) [13]. Even though the EUROLIVE study [14] confirmed these data in humans, the true contribution of oxidized LDL to atherosclerosis and CHD is still unclear; yet many researchers used this method as a proxy for in vivo lipid peroxidation and the European Food Safety Authority granted hydroxytyrosol a [sometimes debated] health claim based on this activity [15]. In these first experiments both oleuropein (commercially available) and hydroxytyrosol inhibited copper sulfate- and peroxidase-induced LDL oxidation [13], stimulating further research on the free radical scavenging potential of olive oil phenolics [16]. It must be underscored that in these papers (and many other ones dealing with polyphenols) researchers used and still use simplified in vitro systems that are now proven to be of dubious in vivo relevance.

A very important yet often overlooked issue of (poly) phenol research concerns bioavailability of these molecules. Very often, health claims are exclusively based on in vitro or rodent studies. However, accumulated data clearly show that – very frequently – (poly)phenols' bioavailability is quite low and in vivo, i.e. circulating concentrations are often inadequate to exert relevant biological effects. One notable example is that of resveratrol, where a considerable amount of money has been invested before (and even after) this molecule was proven to have negligible bioavailability and, in turn, no relevant human actions [17]. In 2000, the first human evidence of olive oil (poly)phenols' absorption was published [18]. Since then, many studies clarified absorption and metabolism of, e.g. hydroxytyrosol when given as component of olive oil [19] or as supplement [20]. Interestingly, the urinary concentration of hydroxytyrosol's metabolites is predictive of cardiovascular disease [21].

Over the years, many human studies have been performed in various settings and the near totality of them indicate that olive oil (poly)phenols can modulate a variety of surrogate markers of cardiovascular disease [22]. From a molecular, mechanistic viewpoint, research on the healthful potential of olive oil (poly)phenols, especially hydroxytyrosol, is very much advanced and comprises nutrigenomic [23] and proteomic [24] studies. Even though the effects of hydroxytyrosol on cholesterol concentrations are modest (see above), many other risk factors of CHD are positively modulated by such molecules and – when added – might at least in part explain the cardioprotective properties attributed to extra virgin olive oil [22]. Indeed, the most credible underlying mechanism is anti-inflammatory in nature [22]. As an example, hydroxytyrosol given per os lessens the cutaneous manifestations of psoriasis [25]. In addition to anti-inflammation, the PREDIMED trial (see below) demonstrated that a Mediterranean diet rich in olive oil was able to improve the functionality of HDL particles [26], which might be more important than the mere HDL concentrations [27].

Finally, it is worth noting that isolated olive phenols such as hydroxytyrosol have been investigated for their toxicity, in light of their use as supplements/functional foods [28,29]. Data point to the safety profile of these molecules, which have been granted GRAS and Novel Food status. As a cautionary note, hydroxytyrosol as pure molecule has been investigated in only two human pilot trials, which provided unclear data [30,31]. Further research is, therefore, necessary to clarify the human effects of olive oil and its minor components, along with basic science investigations that will elucidate their molecular activities (Fig. 1).

Chemoprevention

Early epidemiological publications reported an inverse association between adherence to the Mediterranean diet and incidence of breast cancer, more specifically, on postmenopausal breast cancer prevention [32,33] (Fig. 1). Of note, the inverse association between Mediterranean diet and incidence of breast cancer is more robust for ER- tumors and becomes stronger when alcohol consumption (a known risk factor for breast cancer) is excluded from the analyses [33]. It is worth noting that some epidemiological studies usually compute monounsaturated fatty acids (MUFAs) and do not distinguish between olive oil use and other sources of MUFAs, when addressing the association between the adherence to the traditional Mediterranean diet and breast cancer incidence. One notable exception is the EPIC study, which specifically included olive oil consumption as one item for assessing the adherence to the traditional Mediterranean diet and the incidence of breast cancer [34]. Also, a recent paper by Zong et al. reported largely different associations with CHD risk of MUFAs from plant origin those from animal foods, suggesting that plant-based foods are the preferable sources of MUFAs for CHD prevention [35]. These data (to be confirmed in intervention settings) might be applicable to the cancer arena.

Finally, we would like to underscore that the near totality of data in support of chemopreventive activities of olive oil consumption come from observational epidemiological studies. One important exception is the PREDIMED trial that we discuss in detail later on. Briefly, as a secondary analysis, we assessed the effect of a dietary intervention fostering the adherence to the traditional Mediterranean diet on the incidence of postmenopausal breast cancer among 4152 women aged 60–80 years of age [36]. Those women allocated to the Mediterranean diet intervention who received 1 l/week of extra-virgin olive oil experienced a 62% significant reduction (HR: 0.38, 95% CI: 0.16–0.87) in the risk of breast cancer compared to women in the control group (advise to follow a low-fat diet) (Fig. 1). Since the reduction in the group of women allocated to a Mediterranean diet who received 30 g/d of mixed nuts – instead of the free provision of extra-virgin olive oil – was not that strong (HR 0.62, 95% CI 0.29–1.36), consumption of extra-virgin olive oil seemed to be instrumental for the observed risk reduction. In fact, it was observed that women with an extra-virgin olive oil consumption of at least 15% of their

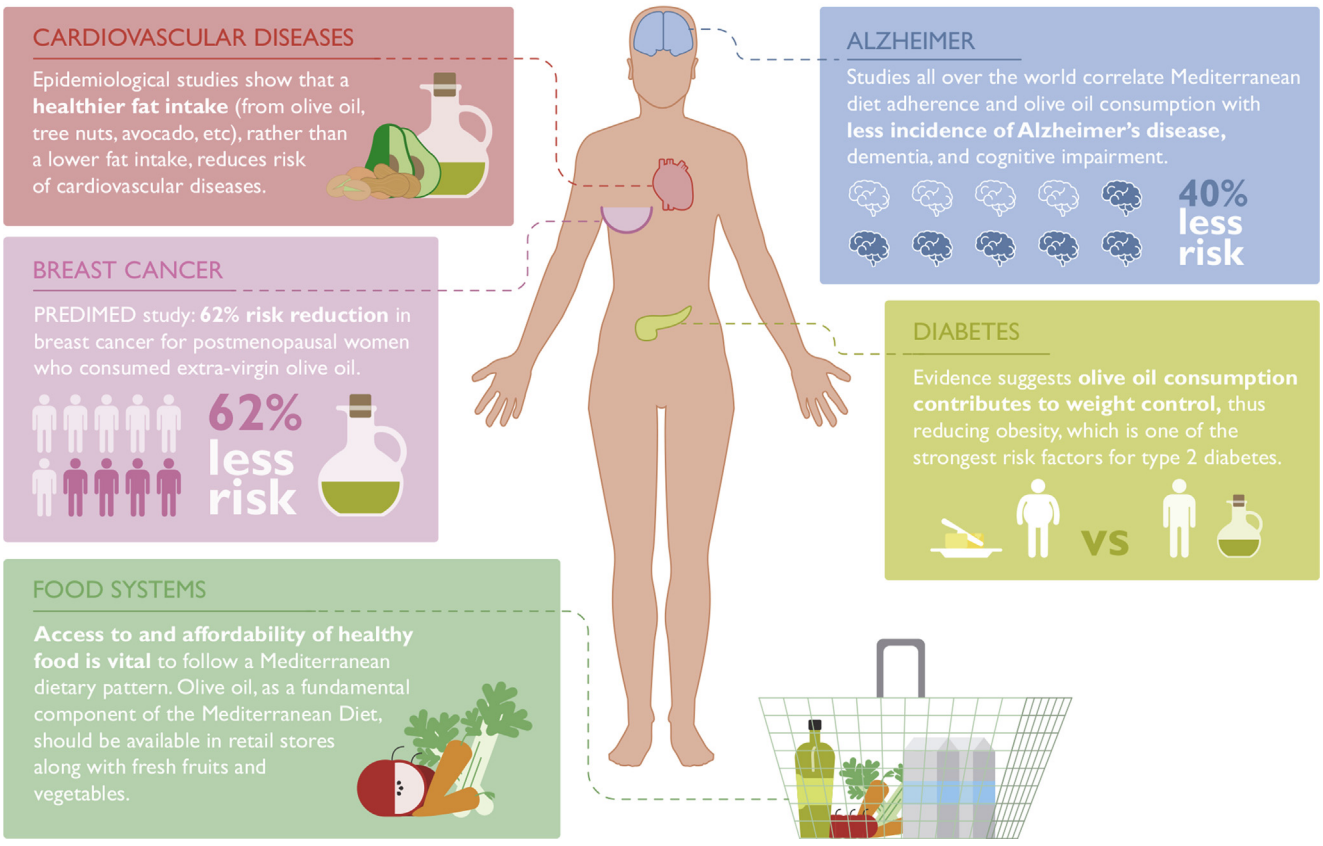

Figure 1 The manifold health properties of olive oil.

total energy intake showed a significant reduction in their breast cancer risk, compared to women with an extra-virgin olive oil consumption lesser than 5% of their total caloric intake (Fig. 1).

Also, potential beneficial effects of the Mediterranean diet on colorectal [37–39] or prostate cancers [37] have been described in large epidemiological studies, even though fewer such studies are available and the effects are stronger for breast cancer prevention.

In terms of mechanisms of action, several in vitro studies suggest that much of the potential beneficial effects of olive oil can be attributed to its minor components, which are abundant in extra-virgin olive oils. Chemopreventive actions are multiple and include inhibition of cell proliferation and tumor progression as well as increased rates of apoptosis [40]. Also, lower generation of noxious substances (most of which oxidized in nature) is conceivable in the gastrointestinal tract, where olive oil (poly)phenols and vitamin E are present in higher concentrations than the blood stream and might dampen digestion-induced lipoperoxidation [41,42].

Neuropsychiatric disorders

"Cognitive disorders" are a group of syndromes that could be classified as dementia [43], mild cognitive impairment (MCI) [44], and age-related cognitive decline [45], and which are caused by several neurodegenerative pathologies, including Alzheimer's disease (AD), the most common cause of dementia [46]. The amyloid hypothesis has dominated research on the etiology, prevention, and treatment of AD, but amyloid based strategies for treatment have failed thus far [47], and there is no known prevention or cure. However, the FINGER study [48] provided proof of principle that multimodal approaches that include dietary interventions can prevent the development of cognitive decline that leads to dementia. Observational studies show that higher adherence to the Mediterranean diet pattern, characterized by a high consumption of olive oil, fruit, vegetables, whole grain, fish, low-fat dairy and (poly)phenols, and low consumption of animal foods [49], has been associated with a decreased risk of MCI [50] and dementia [50]. These associations

seem to be mediated by lower cerebrovascular disease and lower neurodegeneration [51]. The individual contribution of olive oil vs. the aggregate contribution of the Mediterranean diet pattern on lower risk of cognitive impairment is unclear. For example, studies of the Mediterranean diet in New York City, in which olive oil consumption was relatively low, but unsaturated fatty acids other than monounsaturated fatty acids (as in olive oil), were taken into account, reported an association of higher adherence of the Mediterranean diet with lower dementia risk. Studies of the Mediterranean diet across the world, including countries in the Mediterranean basin, where olive oil is the most important unsaturated fatty acid, have observed an association with lower risk of cognitive impairment [52]. A study in mice who were given extra virgin olive oil and compared with a control diet showed that the mice given olive oil had less Alzheimer's disease neuropathology in their brains [53].

The effect of the Mediterranean diet and olive oil on brain outcomes does not seem to be specific only to cognition and cerebrovascular disease (e.g. strokes). Several studies, individually and in aggregate (as a meta-analysis), have shown that higher adherence to a Mediterranean diet is associated with lower risk of depression [52]. The individual role of olive oil in a potential benefit of depression risk is unclear. At least one observational study suggests that higher intake of olive oil is related to a lower risk of depression.

In summary, the fact that the Mediterranean diet and olive oil appear to benefit multiple cerebral disorders suggest a general protective effect on the brain (Fig. 1). More studies are needed to understand the mechanisms potentially involved in these inverse associations and whether the Mediterranean diet and olive oil in particular render the brain more resilient to the effects of aging.

Type 2 diabetes

Worldwide, type 2 diabetes is among the most prevalent chronic diseases and contributes significantly to the burden of cardiovascular disease and mortality [54]. Diet and lifestyle modifications can prevent or delay onset of type 2 diabetes [54]. Indeed, a strong risk factor for the development of type 2 diabetes is overweight and obesity, whose incidence is becoming rampant worldwide. Preventive strategies must, therefore, include appropriate caloric intake and increased physical activity. However, in addition to mere calorie control, mounting evidence is indicating that diet composition, i.e. profile also plays important roles [55].

There is substantial evidence that dietary patterns high in olive oil improve cardiometabolic risk factors and reduce type 2 diabetes risk, potentially due to its monounsaturated fatty acid content and high amounts of polyphenols (Fig. 1). In the PREDIMED intervention study (see below), those assigned to a Mediterranean diet supplemented with extra virgin olive oil had a significantly reduced risk of type 2 diabetes compared with a control diet [56]. This effect is conceivably due (at least in part) to the more effective weight control afforded by a Mediterranean diet, as reviewed by Mancini et al. [57]. The specific contribution of olive oil to weight control (which might appear counterintuitive) was first suggested by data from the SUN study [58] and confirmed in the PREDIMED [59] (see below).

Outside of the Mediterranean basin, in a study of US women, total olive oil consumption, as well as substituting olive oil for other types of fats, was inversely associated with type 2 diabetes risk after adjustment for other dietary and lifestyle factors. While further research is needed, olive oil consumption as part of a healthy dietary pattern may be able to reduce type 2 diabetes risk. Yet, before solid conclusions can be drawn, it must be noted that current lifestyle interventions are of dubious utility in cardiovascular prevention [60], possibly due to the fact that weight loss and subsequent long-term weight maintenance are difficult to implement in real-life settings. Examples include low-fat diets [61,62] and low carbohydrate diets, which often result in higher saturated fat intake. To shift focus from food quantity to diet quality and ascertain whether an energy-restricted Mediterranean dietary regimen (which includes ab libitum olive oil consumption) might prevent cardiovascular events via weight reduction, the PREDIMED^{plus} is being undertaken and will help devising public health strategies for type 2 diabetes and associated cardiovascular prevention.

The experimental proof: the PREDIMED study

As mentioned, most of the evidence linking olive oil consumption to increased life- and health-span is epidemiological in nature. The PREDIMED (Prevention with the Mediterranean Diet) randomized trial started in Navarra (Spain) in June 2003. Later, other 10 Spanish centers also signed on to recruit participants until June 2009. Finally, the trial included 7447 participants undergoing a dietary intervention with repeated contacts every 3 months during an average of five years. PREDIMED was the largest randomized trial ever conducted in Europe. The PREDIMED trial was stopped ahead of planned duration (based on data obtained up to December 2010) because of early evidence of a strong benefit on a composite primary cardiovascular end-point (myocardial infarction, stroke or cardiovascular death). The results showed that, in comparison with the control (low-fat) diet, a Mediterranean diet supplemented with extra-virgin olive oil and nuts and relatively high in fats used in primary prevention produced a 30% reduction in events after 5 years of intervention [63,64]. PREDIMED is now recognized worldwide as a landmark study that marked a turning point in the prevention of chronic diseases. The effective reduction in serious cardiovascular events when the Mediterranean diet (supplemented with free provision of either extra virgin olive oil or mixed tree nuts) was used in a randomized trial provides the best-possible scientific evidence for preventing the main cause of death in the world, i.e. cardiovascular disease [65]. It is important to point out that the PREDIMED trial did not include an energy-

restricted diet, a weight-loss objective, or any promotion of physical activity.

It has been postulated that the link between adherence to the traditional Mediterranean diet and the risk of cardiovascular disease can be mediated by several mechanisms, including reductions in inflammation, higher levels of adiponectin, lower coagulability, improved endothelial function, lower oxidative stress, a lower concentration of atherogenic lipoproteins, lower levels of oxidized LDL particles, and a lower uptake of oxidized LDL by macrophages. Moreover, the two foods with which the diets of the participants in the PREDIMED intervention groups were supplemented (extra virgin olive oil and nuts) also have beneficial biological properties. As discussed above, extra virgin olive oil has a healthy fatty acid profile and contains numerous bioactive phenolic compounds with anti-inflammatory properties, promote the metabolism of cholesterol, improve oxidative stress markers, have an anti-aggregant effects [66], and promote mitochondrial function by stimulating mitochondrial biogenesis [67]. All of these mechanisms explain the antiatherogenic effect of a Mediterranean diet that is rich in extra virgin olive oil. In fact, in the PREDIMED trial a strong protective effect against peripheral artery disease was observed [68].

The PREDIMED team, after receiving additional funding from the NIH, has also developed studies of metabolomics profiling to obtain deeper insight into the mechanistic explanations of the trial findings on hard clinical events [69–72].

Implementing nutritional guidelines: a public health perspective

An often-overlooked yet important limitation in nutritional research and in the development of guidelines is the study of individual dietary patterns as determined by food systems, food environment and the availability and affordability of healthy foods.

Food systems refer to the elements and activities related to the production, processing, distribution, preparation and consumption of food, and its related health, socio-economic, and environmental outcomes [73]. The local food environment is defined as the physical and socio-cultural context in which consumers engage with the food system to acquire, prepare and consume food. The key elements of the food environment are: physical and economic food access; food promotion and advertising; and food quality and safety [74]. Thereby, food environments shape people's diets, and their diet-related health outcomes [75]. Different urban characteristics relate to heart disease and its risk factors including dietary patterns, hypertension, diabetes and obesity [76]. In this respect, cities offer great opportunities to improve food environments and residents' dietary patterns. It is noteworthy that 66% of the world population will live in cities by 2050. From a research perspective, Mediterranean cities present unique characteristics in terms of diversity of small food stores and public markets, whose accessibility is paramount if we want to effectively stir dietary and lifestyle habits toward healthier profiles [77,78] (Fig. 1).

Within the Heart Healthy Hoods (HHH) project (https://hhhproject.eu, funded by the European Research Council), researchers are studying the association between the Mediterranean food environment, adherence to the Mediterranean diet, and related chronic diseases [78,79]. An important gap in the current literature is the study of healthy food affordability, in terms of Mediterranean diet costs, and its influence on diet quality.

Conclusions

In addition to being used as food, olives and olive oil are of major cultural importance in the Mediterranean area. Hundreds of cultivars exist and produce assorted kinds of olive oils, the predominant source of visible fat in the Mediterranean diets. Relatively recent research – mostly stimulated by the observation that the Mediterranean diet is associated with longevity and wellbeing – is being unveiling the multiple beneficial effects that olive oil, namely the extra virgin one and its peculiar components have on human health. Low-(poly)phenol olive oils might also provide health benefits because they help lowering the proportion of saturated fat in the diet. Indirect effects of olive oil consumption, e.g. increased consumption of raw vegetables also play major roles on health, as do the social environment and the culinary civilization in which olive oil is consumed. As outlined in this paper, accrued evidence is strongly suggestive of cardioprotective activities of olive oil and data on chemoprevention of cancer and neuroprotection are accumulating (Fig. 1). This might (and should) foster dissemination of the olive oil culture in non-producing countries and – in turn – increase worldwide demand for this product.

Future research and appropriate trials will further elucidate the role of olive oil on human health and will provide further scientific evidence to the notion that consuming this oil as part of a balanced diet and healthful lifestyle improves prognosis and extends life- and healthspans.

Conflicts of interest

The authors declare no conflict of interest associated with this paper and were not compensated to participate in the workshop.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.numecd.2018.04.004.

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