

The Protective Effect of the Mediterranean Diet: Focus on Cancer and Cardiovascular Risk

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Key Words

Mediterranean diet • Anti-inflammatory agent • Antioxidant • Omega-3 • Olive oil • Red wine • Cancer • Cardiovascular disease

Abstract

The lower occurrence of cancer and cardiovascular disease in the population around the Mediterranean basin has been linked to the dietary habits of the region. Indeed, this so-called Mediterranean diet is essentially different from the diets consumed in Western and Northern European countries and is rich in nuts, fruits, vegetables, legumes, whole-wheat bread, fish, and olive oil, with moderate amounts of red wine, which is mainly consumed during meals. Although a variety of cultural and religious traditions exist among the peoples of the Mediterranean area, olive oil, fish, and red wine hold a traditional and central position in the culinary routines of the region. The components of the diet contain an ample source of molecules with antioxidant and anti-inflammatory actions, among which omega-3 fatty acids, oleic acid, and phenolic compounds hold a prominent place. This review will summarize the results of important epidemiological studies that have investigated the protective effect of fish and olive oil on the risk of breast, prostate, and colorectal cancer and of wine on the risk of cardiovascular disease. The

present review also aims to elucidate the various mechanisms by which various dietary components exhibit their beneficial action. In this respect, emphasis will be placed on the properties of omega-3 fatty acids from fish, oleic acid from olive oil, and phenolic compounds from olive oil and red wine.

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Introduction

More than in other regions, the population of the area around the Mediterranean basin adheres to the so-called Mediterranean diet, which is rich in nuts, fruits, vegetables, legumes, whole-wheat bread, fish, and olive oil. Alcohol, mostly in the form of red wine, is consumed with meals in moderate amounts. These ingredients make this diet essentially different from the diets of Western and Northern European countries. Thus, the relatively lower occurrence of chronic diseases in this region, such as cancer, diabetes, obesity, and cardiovascular disease, has been linked to dietary habits. Recent data from a general study of the Greek population, with a sample size of 25,623 participants and a median follow-up of 7.9 years, has provided evidence that adherence to the traditional Greek Mediterranean diet is associated with a 12% reduc-

tion in overall cancer incidence [1]. Analyzing the impact of a particulate dietary variable on cancer development, the highest reduction in cancer incidence was observed for the ratio of monosaturated to saturated lipids, vegetables, and olive oil (respective hazard ratios of 0.91, 0.96, and 0.97).

These interesting data provide further support to the pioneering Seven Countries Study conducted by Keys et al. [2], which was an intercohort study carried out in Finland, Italy, Greece, the former Yugoslavia, the Netherlands, Japan, and the USA. This investigation found a relatively low incidence of cardiovascular disease and cancer in the Mediterranean cohorts. Although the Mediterranean area has different cultural and religious traditions, for many centuries olive oil, fish and (red) wine have held a central and appreciated culinary position. Olive oil, especially virgin olive oil, and fish are the major sources of fat which – together with the ingredients of red wine – give rise to antioxidant and anti-inflammatory actions presumably contributing to the prevention of chronic diseases.

This review will summarize the results of important epidemiological studies that have investigated the protective effect of fish and olive oil on the risk of breast, prostate, and colorectal cancer and of wine on the risk of cardiovascular disease. The scope of this paper is to provide a survey of the relevant knowledge of the effect of the Mediterranean diet on these illnesses, which are among the most prevalent disabling and fatal diseases. The present review also aims to elucidate the various mechanisms by which many dietary components exhibit their beneficial action. In this respect, emphasis will be put on the properties of omega-3 fatty acids from fish, oleic acid from olive oil, and phenolic compounds from olive oil and red wine.

Data Sources

A search of PubMed, Embase, and Web of Science was conducted using the keywords Mediterranean diet, anti-inflammatory agent, antioxidant, omega-3, olive oil, red wine, cancer, and cardiovascular disease, in relevant combinations. Literature, restricted to articles written in English, was retrieved from the full history of publications up to February 1, 2010. Full articles were retrieved by the selection of electronically obtained summaries. An effort was made to include only the more recent of multiple articles on the same subject in the list of references published over the last decennium.

Protective Mechanisms of Omega-3 Polyunsaturated Fatty Acids against Cancer Risk

Omega-6 and omega-3 polyunsaturated fatty acids (PUFAs), also named n-6 and n-3 PUFAs after the position of the final double bond from the end of the methyl group position, cannot be synthesized *de novo* by mammalian cells. Therefore, the presence of these acids is highly dependent on dietary intake, and members of the n-6 and n-3 families are often called ‘essential fatty acids’ [3]. The precursor of the n-6 family is linoleic acid (LA), and the precursor of the n-3 family is alpha-linolenic acid (ALA). LA can be obtained from eggs, poultry, vegetable oils, and whole-grain bread, and ALA from flaxseed, linseed, soy oils, walnuts, and leafy green vegetables. The metabolism of dietary LA and ALA requires the same set of delta-6 and delta-5 desaturases and elongases, although the n-3 family members are the preferred substrates. The n-6 metabolite γ -linolenic acid and the n-3 metabolites, i.e. eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and their biochemical derivatives called eicosanoids, are biologically active agents with anti-inflammatory effects; these compounds can be taken directly as dietary components to bypass the slow enzymatic processes in the n-6 and n-3 families.

Eicosanoids are hormone-like lipids with a chain length of 20 carbon atoms. An important eicosanoid member of the n-6 family, arachidonic acid (AA), the major n-6 PUFA in cell membranes, is metabolized to the 2-series of prostanoids and the 4-series of leukotrienes. These AA-derived eicosanoids have a proinflammatory action. Suppression of the biosynthesis of these proinflammatory molecules can be achieved by a higher intake of n-3 PUFAs, resulting in an increased presence in the cell membrane at the expense of the AA concentration and its metabolites. In addition, an increased level of EPA from n-3 precursors or dietary supplements gives rise to the formation of anti-inflammatory lipid mediators, including resolvins, protectins, and maresins, known to suppress the immune response [4]. Although inflammation is part of the host defense system, sustained inflammation due to environmental and biological triggers may lead to the overproduction of reactive species, causing DNA damage and modification as well as the activation of oncogenes and the inactivation of repair and tumor suppressor genes.

Apart from the above described mechanism, n-3 PUFAs can regulate transcription factors serving as endogenous ligands. For instance EPA and DHA, ligands of the peroxisome proliferator-activated receptors, can ex-

hibit antiproliferative effects in colon cancer cells [5], induce apoptosis [6], and have an anti-inflammatory action [7]. Likewise, activation of the nuclear transcription factor-kappa B (NF- κ B), which is involved in cell proliferation and adhesion processes, can be decreased by n-3 PUFAs [8]. Furthermore, n-3 PUFAs alter the basic properties of the architecture and biochemical makeup of the cell membrane, influencing the process of signal transduction and inducing apoptotic cell death in cancer cells [9]. Also, PUFAs of the n-3 series but not the n-6 series can diminish estrogen formation and consequently the estrogen-induced growth of breast cancer cells, for example [10]. An important feature of n-3 PUFAs is the modification of the inflammatory response generated by free radicals and reactive oxygen and nitrogen species within the cell. Interesting experiments by Yaqoob and Calder [11] and Kenar et al. [12] have demonstrated that n-3 fatty acid supplementation suppresses inflammation and diminishes oxidative stress.

Protective Mechanisms of Olive Oil Components against Cancer Risk

Olive oil-associated mechanisms presumably contributing to good health primarily entail anti-inflammatory and antioxidant properties [13, 14]. The phenolic compounds present in olive oil may interact with the inflammatory cascade via their antioxidant action. This interaction is primarily related to their ability to scavenge free radicals, thus preventing cellular injury [15]. In addition, a relatively high concentration of oleic acid, the main monounsaturated fatty acid (MUFA) of olive oil in the membrane phospholipids, makes the cell less susceptible to oxidation by reducing the formation of proinflammatory molecules [16]. These chemoprotective properties may translate into a number of protective mechanisms beneficial to health, including protection against viral infection and cancer development, as well as cardiovascular protection.

Protective Mechanisms of Red Wine against Cardiovascular Disease Risk

Red wine contains a variety of phenolic compounds which exert anti-inflammatory, antioxidant, and anti-atherogenic actions [17]. Although the consumption of drinks containing alcohol (ethanol) has been linked to a lower total mortality [18], the bulk of experimental stud-

ies demonstrate the 'beyond-alcohol effect' of red wine consumption. Among the phenolic compounds in red wine, resveratrol (3,4,5-trihydroxystilbene) takes a prominent place. This antioxidant is a phytochemical predominantly present in red wine that originates from the skin and seeds of grapes. In contrast, white wine contains a lower concentration of this molecule as its production process uses fermentation after the removal of the grape seeds and skin. Resveratrol serves as an antifungal and antibacterial agent to protect the grape against its environment. This compound has been most extensively studied in relation to its cardiovascular health benefits attributed to beneficial actions on LDL oxidation, thrombogenicity, ischemia, and vascular tone [19]. Its antioxidant activity has been attributed to the inhibition of TNF- α -activated NF- κ B signaling, which leads to a reduced biosynthesis of proinflammatory prostaglandins and a reduced activity of cyclooxygenase-2 [20]. Other substances of interest in red wine include procyanidins and proanthocyanidins. Corder et al. [21] have shown that these compounds improve vasodilatory activity by reducing the production of the vasoconstrictor, i.e. endothelin. However, red wine is a complex fluid in which more than 500 compounds have been found, only a few of which have been explored [22].

Epidemiological Studies on Omega-3 Fatty Acids and Cancer Risk

Effects on the Risk of Breast Cancer

A systematic review published between 1966 and 2005 by MacLean et al. [23] in 2006 identified 8 studies from 6 different cohorts that evaluated the effects of omega-3 fatty acids on breast cancer risk. The authors concluded that this risk was not clearly related to the consumption of EPA and DHA. The studies that were included in their review estimated fatty acid intake on the basis of questionnaires. More recently, various epidemiological studies have drawn a different picture. The ones that relate the levels of EPA and DHA in erythrocyte membranes demonstrate a significant inverse association between breast cancer risk and EPA concentration, but not DHA concentration ($p < 0.0006$) [24, 25]. This important information is based on the new concept of fatty acid assessment and casts doubt on the results of previously published studies on the same subject, although the questionnaire-based study by Kim et al. [26] published in 2009 also found a significant reduction in breast cancer risk. Based on a 103-item food questionnaire, these researchers applied a

multivariate logistic regression model and found a reduced risk in both premenopausal ($p < 0.001$) and postmenopausal women ($p = 0.005$). These beneficial results were obtained in those who had a high consumption of fish. Postmenopausal women consuming more than 0.1 g of EPA and 0.2 g of DHA from fish per day, respectively, showed a 62 and 68% decrease in breast cancer risk compared to the reference group, which consumed less than 0.01 g of EPA and 0.04 g of DHA per day.

Effects on the Risk of Prostate Cancer

A large prospective cohort study by Leitzmann et al. [27] published in 2004, comprising 47,866 US health professionals with a follow-up of 14 years, found that men with a high consumption of fish had a lower prostate cancer risk. This finding is in contrast with the results obtained in an 18-year follow-up study in 40,230 US male health professionals by Virtanen et al. [28] published in 2008. With the inclusion of 4,690 cancer cases, the latter study had enough power to detect any change in risk in relation to fish intake. The authors mention that a small health benefit might be counterbalanced by cancer-promoting fish contaminants such as dioxins and polychlorinated biphenyls [29]. Both the study by Leitzmann et al. [27] and that by Virtanen et al. [28] were carried out using dietary questionnaires on subjects that were health care professionals and who would be more likely than any other group to provide reliable data on dietary intake. Another recent questionnaire-based case-control study investigated the dietary habits of 386 cancer patients and concluded that a fish diet was associated with a 2-fold reduction in prostate cancer risk ($p = 0.017$), whereas meat diets appeared to be associated with a 3-fold increased risk of prostate cancer ($p = 0.027$) [30].

As mentioned above, results based on membrane fatty acid assessment might provide new insight into this matter, but such studies are practically impossible to carry out on a large group of subjects. A study by Ritch et al. [31] of 24 cases of prostate cancer in Jamaica supports the association between dietary fatty acids and prostate cancer risk. In particular, these investigators found that n-6 PUFAs stimulate prostate cancer progression while n-3 PUFAs inhibit it.

Effects on the Risk of Colorectal Cancer

A most interesting study by Norat et al. [32] reported on the incidence of colorectal cancer in relation to fish intake. This study prospectively followed 478,040 cancer-free men and women from 10 European countries between 1992 and 1998 with a mean follow-up of 4.8

years. During this questionnaire-based study 1,329 participants were diagnosed with colorectal cancer. The study showed that the disease and the consumption of red and processed meat are positively related ($p = 0.001$), whereas the association with fish intake appeared to be inverse ($p = 0.003$). Another large study, the ongoing Physicians Health Study which started in 1982, comprised 22,071 healthy male physicians. During a follow-up period of 22 years, 500 men had a confirmed diagnosis of colorectal cancer. Fish intake, and more specifically n-3 fatty acid intake, was inversely related to both colon and rectal cancer risk ($p = 0.01$) [33]. These large studies were questionnaire-based and, to the best of our knowledge, only 1 human study relating the fatty acid composition in the erythrocyte membrane to colorectal cancer has been published; that study, by Kuriki et al. [34], showed a decreased risk of colorectal cancer in relation to the ratio between saturated and n-3 fatty acids ($p < 0.005$).

Epidemiological Studies on Olive Oil and Cancer Risk

Effects on the Risk of Breast Cancer

A recent case-control study in 1,703 breast cancer patients and 2,045 controls performed in the San Francisco Bay Area showed that cooking with olive oil, which is rich in oleic acid, reduced the risk of breast cancer compared with hydrogenated fats (OR 1.58; 95% CI 1.20–2.10) or with vegetable/corn oil, which is rich in linoleic acid (OR 1.30; 95% CI 1.06–1.58) [35]. The so-called Potsdam (Germany) study was a prospective investigation of the effect of high-fat food choices on the incidence of breast cancer [36]. This study followed 15,351 female subjects over an average period of 6.0 years. The investigation concluded that the total dietary fat rather than specific fatty acids is associated with a 2-fold increased risk of breast cancer (hazard ratio 2.00; 95% CI 1.30–3.09), comparing extreme tertiles of the pattern score. The French component of the European Prospective Investigation into Cancer and Nutrition (EPIC) documented the MUFA intake in 19,934 women, 363 of whom developed breast cancer during an average follow-up of 7 years [37]. The intake of *cis*-MUFA (a group to which oleic acid belongs) appeared to be unrelated, whereas an increased risk was associated with increasing levels of *trans*-MUFA, the odds ratio being 1.75 (95% CI 1.08–2.83), when comparing the highest quintile with the lowest. Interestingly, the large prospective EPIC study com-

prising 319,826 women identified 7,119 women who developed breast cancer over a mean period of 8.8 years of follow-up. No significant association with total fat, MUFA, or PUFA could be determined, although a weak positive association between saturated fat intake and breast cancer risk in postmenopausal women who never used hormone therapy was found [38].

Concerning the phenolic constituents of olive oil, a high concentration of these antioxidants is associated with a protective effect on oxidative damage as reviewed by Fitó et al. [39]. A multicenter, double-blind, randomized, crossover controlled intervention trial in Southern, Central, and Northern European countries showed a reduction in DNA oxidation of 13% ($p = 0.008$) for all types of olive oil consumed, although no association was found with the level of phenolics. How far these results translate into a reduced risk of breast cancer or any other cancer is uncertain and warrants further study [40].

Effects on the Risk of Prostate Cancer

The aforementioned EPIC study also investigated whether dietary fat might be a contributing factor in the etiology of prostate cancer. This objective was assessed in a multicenter study in 142,520 men. After a median follow-up of 8.7 years, prostate cancer was diagnosed in 2,727 men. Analysis of the data obtained by country-specific validated food questionnaires did not reveal an association between any type of dietary fat, including olive oil, and prostate cancer risk [41]. This outcome confirms the results of a previously published large prospective study in which no association between these 2 entities could be demonstrated [42].

Effects on the Risk of Colorectal Cancer

A large 7-year case-control study by Theodoratou et al. [43] on oleic acid and other fat consumption included 1,455 cases and 1,455 matched controls. The results showed no clear association between oleic acid intake and colorectal cancer risk as opposed to the inverse relationship found for omega-3 fatty acid intake. A differently designed study [44] of an ecological nature examined the national levels of dietary factors, with particular reference to olive oil. The researchers found that 76% of the intercountry variation in colorectal cancer was explained by 3 significant dietary factors in combination: meat, fish, and olive oil. Olive oil was negatively associated with cancer incidence, which was emphasized by Cicerale et al. [45] in an excellent review on olives, olive oil, and disease prevention.

Epidemiological Studies on Red Wine and Cardiovascular Risk

In 1979, St Leger et al. [46] reported that an inverse relationship existed between coronary heart disease (CHD) mortality and wine consumption in France. Subsequently, in 1992, Renaud and De Lorgeril [47] reported that the consumption of alcohol in France (20–30 mg/day) was associated with a reduction in the risk of CHD of at least 40%. This is an interesting finding as the French diet is well-known for its high content of saturated fat, which is known to be associated with CHD. Recent WHOSIS data still show that France has the lowest percentage of death due to cardiovascular disease of all European countries (<http://www.ehnheart.org>).

Studies on Alcohol

An excellent paper by Di Castelnuovo et al. [48] reported a meta-analysis of 34 prospective studies up to December 2005. On the basis of a total of 1,015,835 men and women and 94,533 deaths, they found that the lowest mortality occurred at 6 g of alcohol per day (RR 0.8; 95% CI 0.80–0.83). Lower mortality was observed at up to 4 drinks per day for men and up to 2 drinks per day for women compared to abstinence. One of the studies included in this meta-analysis was conducted by Gaziano et al. [49], who investigated the cause of death of 89,299 male subjects recruited from the Physicians' Health Study over a period of 5.46 years. During that period, 3.6% of the subjects died; 45.1% of them succumbed due to cardiovascular disease (CVD). The investigation showed that a risk reduction in CVD mortality amounting to 32–47% occurred even at 'more than 2 drinks a day' although the maximum benefit was reached at 1 drink per day. This result is in accordance with a prospective study by Klatsky et al. [50] in a population of 128,934 adults over a period of 7 years. They revealed a relative risk of CHD of 0.7 (95% CI 0.6–0.9), independent of the baseline risk for moderate alcohol drinkers (up to 2 drinks a day) compared to lifelong nondrinkers. The greatest reduction was observed in drinkers over 50 years of age. In contrast, individuals under 50 years of age consuming 6 or more drinks a day showed a relative risk of death from all causes of 1.9 (95% CI 1.2–2.9) compared to lifelong nondrinkers. This increased risk was more evident in women than men. Apart from these studies, other cohort studies have consistently shown that moderate alcohol use is associated with a lower risk of CHD and CVD compared to heavy drinking or abstinence. Among the most recent articles are those by Snow et al.

[51], Bazzano et al. [52], Saremi and Arora [53], and Foerster et al. [54].

Studies on Wine

Recent large epidemiological studies on cardiovascular health include those by Grønbaek et al. [55] (13,064 men and 11,459 women; follow-up about 10 years), Renaud et al. [56] (36,583 men; follow-up 13–21 years), and Klatsky et al. [57] (56,926 men and 72,008 women; follow-up 20 years or known death). From these studies, a conservative estimate on the reduced risk of cardiovascular mortality for moderate drinkers of red wine (1–3 glasses a day) amounts to 0.7 compared to nondrinkers.

An intriguing question is whether red wine has qualities beyond the ‘alcohol effect’. Studies on flow-mediated arterial dilatation found a greater effect after drinking dealcoholized red wine than after drinking regular red wine [58, 59]. Moreover, in a double-blind crossover study in 20 healthy volunteers, it appeared that endothelial dysfunction induced by cigarette smoking could be counterbalanced by the simultaneous consumption of dealcoholized red wine or regular red wine [60]. Indeed, a recent study showed that both red wine and dealcoholized red wine decrease plasma endothelin-1 levels, although the researchers could not determine a significant effect on coronary epicardial diameters or flow rate [61]. These human studies underscore the benefit of red wine beyond the known effect of alcohol. The polyphenols found in red wine, particularly resveratrol, are supposedly active on cardiovascular endpoints [62].

Another question is whether white wine could exert effects similar to those of red wine. The large prospective studies by Klatsky et al. [57] and Mukamal et al. [63] did not detect any influence of the type of wine as far as cardiovascular risk is concerned despite the ‘bonus’ effect of red wine, in which polyphenols are more abundant [64]. This is in agreement with the results of experimental investigations suggesting that white wine can provide cardioprotection similar to that afforded by red wine if it is rich in tyrosol and hydroxytyrosol [65]. It should be realized that the effect of wine consumption is difficult to evaluate epidemiologically. If food/drink questionnaires are used, it must be recognized that a certain degree of underreporting with regard to alcohol use in general undoubtedly plays a part in the analysis. Rather than using self-reported questionnaires, nutritional biomarkers would help to evaluate wine consumption. Zamora-Ros et al. [66] validated urinary resveratrol metabolites by liquid chromatography-mass spectrometry and concluded that they may be useful as biomarkers of wine intake in

human investigations and epidemiological studies. From a pathophysiological point of view, the formation of atherosclerotic plaques in humans takes decades, starting in early childhood. There is no way to study a cohort in which the starting point is around that age.

Discussion

Despite the dietary differences in the countries and regions of the Mediterranean basin, fish, olive oil, and red wine occupy a central position in daily meals. Apart from the beneficial health effects of these components, they also facilitate the consumption of vegetables and legumes. This dietary pattern has been associated with a reduced risk of fatal and nonfatal cardiovascular disease [67, 68] and cancer [69]. In this context, it is worthwhile to mention the PREDIMED prospective study involving 19 groups from 7 regions in Spain. This study, begun in 2003 and presumably ending in 2011, monitors 7,232 people with cardiovascular risk receiving dietary and behavioral advice [70].

A recent meta-analysis by Sofi et al. [71] demonstrated that the Mediterranean diet is associated with a significant improvement in health status marked by a remarkable reduction in mortality due to CVD (9%), incidence of and mortality from cancer (6%), overall mortality (9%), and incidence of Parkinson’s and Alzheimer’s diseases (13%) [71]. These numbers are relevant for public health. It is interesting to note that in the above mentioned meta-analysis, 6 of the 8 cohort studies focused on Greek populations. A recent study by Trichopoulou et al. [72] on the Greek segment of EPIC, involving 23,349 men and women recruited throughout the country from the general population not previously diagnosed with cancer, provides evidence that after a follow-up of 8.5 years (range 10 days to 14.2 years) a higher adherence to the Mediterranean diet was associated with a statistically significant reduction in total mortality (adjusted mortality 0.86; 95% CI 0.80–0.93). The contribution of the various components has been summarized as follows: moderate alcohol consumption (23%), a low consumption of meat and meat products (16.6%), high vegetable consumption (16.2%), high fruit and nut consumption (11.2%), a high ratio of monounsaturated to saturated lipids (10.6%), and high legume consumption (9.7%). The components relating to dairy products, cereals, and, surprisingly, fish and seafood were largely inconsequential and contributed little to predicting mortality. In this respect, Simopoulos [73] previously emphasized that the

Cretan diet with its 'high intake of fruits and fruit juice, vegetables, herbs and spices, nuts (notably walnuts), garlic, onions, cereals (whole-wheat and sourdough rather than pasta), olive oil and olives, less milk, more goat cheese, less meat, more fish, yogurt, water and moderate amounts of red wine with meals' differs considerably from the diet that has been positively associated with cancer in Europe [74].

With regard to the relationship between wine and cardiovascular health, wine drinkers appear to have a healthier lifestyle than those who consume beer, spirits, or mixed drinks [75]. Wine drinkers are less likely to smoke and are more likely to have a lower body mass index and adhere to the Mediterranean diet [76]. The latter contributes to a relatively higher dietary level of omega-3 fatty acids. In addition to their anticancer effects, these PUFAs contribute to a beneficial cardiac health effect via a reduced synthesis and secretion of very-low-density lipo-

protein particles, increased triglyceride removal from these and chylomicron particles, and the upregulation of enzymes such as lipoprotein lipase [77].

Conclusion

The ideal study on the effect of the Mediterranean diet on health would be a long-term, prospective, double-blind, randomized study of sufficient power. In the absence of such a study, there is still well-documented evidence of the beneficial effects of the diet consistent with an increased understanding of the mechanisms by which components of this diet act in an integrated manner within a matrix of molecules to mitigate risk factors. Recognition of its benefits may well lead to the Mediterranean diet becoming an indispensable part of a healthy lifestyle [78, 79].

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