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## COVER STORY

### The Disease-Preventive Power of the Mediterranean Diet

By Dale Kiefer

Earlier this year, news headlines extolled the health and anti-aging benefits of the Mediterranean diet, characterized by fish that provide omega-3 fatty acids, relatively copious amounts of olive oil, and antioxidant-rich fruits, vegetables, and herbs.

Epidemiological evidence has long suggested that the Mediterranean diet offers life-extending benefits. Recent studies associate this diet with lowered cardiovascular risk and increased life span.<sup>1</sup> This is especially true among Greeks and Spaniards, who adhere most closely to the “classic” Mediterranean diet that is believed to specifically reduce cancer risk and protect cardiovascular health.<sup>2-8</sup>

The traditional Mediterranean diet is closely associated with the olive-growing regions of the Mediterranean Sea. Monounsaturated fats from olive oil and omega-3 fatty acids from fish are the predominant fats in the Mediterranean diet. Saturated fat, which is far more common in the diets of North Americans, makes up a relatively small portion of the Mediterranean diet.



#### AN EPIC STUDY

Earlier this spring, scientists involved in Europe's massive EPIC-elderly study released key findings from nearly a decade of research. EPIC (European Prospective Investigation into Cancer and Nutrition) is the largest study to date to provide convincing evidence that diet directly affects life span.

More than 74,000 healthy seniors aged 60 years or older from nine European countries participated in this eight-year study of factors affecting the incidence of cancer and other chronic diseases. Biological, dietary, lifestyle, and environmental factors were examined in relation to overall health. Researchers assessed the impact on health and longevity of omega-3 essential fatty acids such as those found in fatty fish like salmon and mackerel, as well as of monounsaturated fats obtained almost exclusively from olive oil.

The researchers developed a 10-point scale to quantify degree of adherence to the modified diet, and then compared scores with mortality data. Subjects who adhered most closely to the classic Mediterranean diet while consuming the least saturated fat earned the highest scores. Higher scores were clearly associated with longer life span. As the scientists noted, “. . . adherence to a modified Mediterranean diet . . . was associated with a significantly longer life expectancy in apparently healthy elderly people . . .”<sup>9</sup>

In essence, the data from this enormously important study show that adherence to a Mediterranean-type diet can extend life. Individuals who improved their scores by just two points on the 10-point scale increased their life expectancy by 7%. As an example, a 60-year-old man who adhered to the diet could expect to live a year longer than another man of the same age who did not follow the diet. According to the researchers, “The reduction in mortality in relation to a dietary score was more striking than expected . . .”<sup>9</sup>

In a further study, the EPIC scientists found that the longevity-promoting effects of the Mediterranean diet were even more dramatic in adults with coronary heart disease. When individuals with prevalent coronary heart disease at the time of enrollment improved their adherence to the Mediterranean diet by two points on the 10-point scale, they experienced a 27% lower rate of mortality and a 31% lower rate of cardiac death.<sup>10</sup>

The great question associated with the anti-aging benefits ascribed to the Mediterranean diet is how, exactly, the diet is responsible for the impressive, observed effects on longevity. Five years earlier, researchers had estimated that up to 25% of the incidence of colorectal cancer, about 15% of the incidence of breast cancer, and roughly 10% of the incidence of prostate, pancreatic, and endometrial cancers could be prevented by replacing the typical Western diet—high in saturated fat and low in omega-3 fatty acids, phytonutrients, and antioxidants—with the Mediterranean diet.<sup>11</sup>



To gain a better understanding of how the Mediterranean diet prolongs life, we need to examine the diet's fundamental components, which include fatty acid-rich fish, antioxidants, phytonutrients, and olive oil.

## DANGERS OF POLYUNSATURATED FATS

An enormous amount of scientific data documents the health risks associated with excess consumption of polyunsaturated fatty acids. While the polyunsaturated fats known as omega-6 fatty acids are essential to optimal health, most Americans and citizens of other Western nations consume far too many omega-6 polyunsaturated fatty acids and not enough omega-3 polyunsaturated fatty acids. Although a roughly 2:1 ratio of omega-6 to omega-3 fatty acids is considered optimal, most Americans consume these fats in a lopsided ratio that approaches 10:1.<sup>12,13</sup> For optimal health and longevity, it is critical to achieve a dietary balance of these important nutrients. Given that the vast majority of people in Western countries consume excessive amounts of omega-6 fatty acids, attention should be focused on consuming adequate amounts of omega-3 fatty acids.

Omega-3 polyunsaturated fatty acids have been shown to have anti-cancer, anti-inflammatory, and antihypertensive effects, and to reduce the risk of stroke, heart arrhythmias, dementia, and heart attack when consumed in balance with omega-6 fatty acids.<sup>14-21</sup>

Omega-3 fatty acids influence health and well-being through a variety of mechanisms. These include modulation of cell membranes' physical and chemical properties, and regulation of the metabolism of immune system components that are involved in inflammation.

Evidence also suggests omega-3 polyunsaturated fatty acids regulate body functions through the modulation of specific genes.<sup>17,22</sup>

The omega-3 fatty acids EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) are found in abundance in fatty fish and some marine mammals, as well as in the algae (seaweed) upon which they feed. A third polyunsaturated fatty acid, alpha-linolenic acid, can be converted into DHA and EPA. While alpha-linolenic acid is available from sources such as canola oil, flaxseed oil, and walnuts, its conversion to DHA is slow and inefficient.<sup>23,24</sup> Scientists believe that direct consumption of DHA and EPA is the best way to obtain adequate omega-3 polyunsaturated fatty acids.<sup>16,25-32</sup>

The importance of DHA and EPA cannot be overstated. For example, adequate intake of omega-3 fatty acids during early childhood is thought to play a role in preventing attention deficit hyperactivity disorder (ADHD) and in improving learning and academic performance.<sup>30</sup> In older adults, consuming omega-3 fats such as DHA and EPA may reverse signs of brain aging and protect against development of Alzheimer's disease and other causes of age-associated dementia and decline.<sup>18,27-29,33-36</sup>

## POWER OF OLIVE POLYPHENOLS

For millennia, olives have provided a staple source of high-energy food and critical nutrients for the many civilizations that have thrived in the Mediterranean area.

Researchers in Barcelona and other southern European cities lead the world in investigating the remarkable health benefits of olives.<sup>37-41</sup> While the monounsaturated fats in olive oil are clearly a crucial component of the Mediterranean diet, a lesser known but no less important component is the rich mixture of antioxidant polyphenols in olives.<sup>5</sup> Once discarded as a by-product of the olive oil-extraction process, olive polyphenols concentrated in the watery juice of the olive fruit have an impressive array of beneficial properties.<sup>37,41-62</sup>

For example, laboratory studies of cells grown in culture have shown that the primary olive oil polyphenol—hydroxytyrosol—scavenges the dangerous free radical hydrogen peroxide, which is a by-product of normal cellular respiration.<sup>42</sup> As Life Extension members are well aware, the damage caused by free radicals includes DNA damage that can lead to premature aging, cancer, and other degenerative conditions.<sup>63-65</sup>

In addition to in-vitro experiments, tests with hydroxytyrosol-rich polyphenols in vivo have also yielded impressive results. For

example, scientists in the Netherlands fed animals either polyphenol-rich extra-virgin olive oil or extra-virgin olive oil with the polyphenol components removed. Levels of the antioxidant vitamin E were significantly increased in the animals that received the polyphenols, indicating that olive oil polyphenols improved antioxidant defense systems.<sup>59</sup> Removal of hydroxytyrosol-rich polyphenols from the diet also rendered LDL (low-density lipoprotein) more susceptible to oxidation. As Life Extension members are aware, LDL oxidation is thought to play an important role in the development of atherosclerosis and cardiovascular disease.

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#### OLIVE POLYPHENOLS AND CHOLESTEROL

Wondering whether hydroxytyrosol's LDL-protective effect could be reproduced in humans, researchers in Spain solicited healthy volunteers to participate in a randomized, double-blind, controlled crossover study. Subjects consumed three different extra-virgin olive oils with incrementally greater levels of polyphenols. At the end of each study period, blood plasma levels of LDL were examined for degree of oxidation. Levels of beneficial HDL (high-density lipoprotein) were also assayed. As the polyphenol content of the olive oil increased, LDL oxidation decreased. Polyphenol-rich olive oil also raised HDL levels. Both effects are associated with an improved cardiovascular risk profile.<sup>37</sup> Other researchers have observed similar results demonstrating the ability of olive oil polyphenols to prevent damaging oxidative processes.<sup>52-54,58</sup>



In a variation of this study, Spanish researchers tested the effects of feeding three olive oils with incrementally greater levels of polyphenols to a group of healthy male volunteers. Subjects in this randomized, double-blind study consumed standardized doses of polyphenol-rich olive oil. After a washout period, subjects were blindly switched to another polyphenol-rich olive oil formulation. The researchers assessed plasma LDL oxidation and the activity of glutathione peroxidase and other markers of antioxidant status. Oxidized LDL decreased, glutathione antioxidant activity increased, and HDL levels increased in the participants. These effects were proportionally greater as olive polyphenol content increased. All of these changes reflect improvements in surrogate markers of cardiovascular health.<sup>39</sup>

Another study conducted by researchers at the same Barcelona medical research facility showed similar results. Markers of oxidative stress, implicated in the development of cardiovascular disease,<sup>41</sup> were assessed after ingestion of a single dose of polyphenol-rich extra-virgin olive oil. LDL's resistance to oxidation improved after consumption of the polyphenol-rich olive oil,<sup>40</sup> while glutathione-related enzyme activities also improved.<sup>40</sup> Other studies have reported similar results.<sup>38</sup>

#### SESAME LIGNANS: PHYTONUTRIENT POWER

Like polyphenols from olives, sesame seeds are rich in compounds with powerful antioxidant properties. Sesame seeds contain lignans, a class of chemicals known as phytonutrients that are responsible for a range of health benefits.



For example, lignans have the ability to modulate immunity and may prevent various types of cancer.<sup>66-73</sup> When Scandinavian researchers fed the sesame lignan sesamin to laboratory animals, they documented an increase in bioavailable levels of the important antioxidant gamma tocopherol, a potent and biologically active form of vitamin E.<sup>74</sup> Japanese researchers have shown that when sesamin is added to the diets of animals bred for their susceptibility to hypertension and stroke, various markers of cardiovascular damage are significantly improved, especially among salt-sensitive hypertensive animals.<sup>75</sup>

In a similar experiment, scientists fed vitamin E, sesamin, or both to animals prone to hypertension and stroke. A control group received normal feed. As they aged, the control animals developed high blood pressure and elevated levels of an oxidative stress marker, and exhibited an increased tendency to develop clots that could precipitate stroke. By contrast, the animals fed sesamin, vitamin E, or a combination of the two nutrients were significantly protected from these deadly conditions.<sup>76</sup>

#### REDUCING INFLAMMATION

More recent work on the mechanisms underlying these effects indicates that sesamin reduces levels of inflammatory prostaglandins and leukotrienes, immune system components that are associated with pathological inflammatory conditions.<sup>77</sup> Many scientists now believe that low-grade inflammation is an underlying condition that contributes to a broad range of degenerative diseases such as atherosclerosis, heart disease, arthritis, cancer, Alzheimer's disease, and Parkinson's disease.<sup>78-84</sup> Omega-3 fatty acids are also known to reduce inflammation,<sup>14,85</sup> and recent research indicates that they may increase levels of anti-inflammatory compounds in the bloodstream.<sup>21,86-87</sup>

Sesame seed components, including sesamin and sesamol, may also reduce the effects of reactive oxygen species, a class of highly reactive, damaging free radicals that are generated in response to injuries such as those caused by stroke. In an experiment designed to simulate stroke damage, Chinese scientists deprived nerve cells of oxygen in the laboratory. In cells treated with sesamin and sesamol, cell death was reduced significantly compared to untreated cells. The scientists concluded that the sesame seed lignans may have suppressed the generation of reactive oxygen species and inhibited the release of mitogen-activated protein kinases,<sup>88</sup> a family of immune system proteins responsible for inducing programmed cell death, or apoptosis.<sup>89</sup> Recently, Taiwanese researchers reported findings that appear to confirm this ability of sesame lignans to intervene in apoptosis by modulating immune system signaling events.<sup>90</sup>

### **LOWERING BLOOD PRESSURE**

Sesame seed lignans may also reduce blood pressure. In an effort to document sesame's antihypertensive effects, Japanese researchers worked with animals bred to serve as a model of human hypertension. One group of animals was fed a normal diet supplemented with sesamin, while the other group received only the normal diet. After five weeks, aortic superoxide, an indicator of cardiovascular stress, was measured in both groups. Sesamin-fed animals had lower superoxide levels and lower blood pressure; conversely, animals fed a normal diet developed hypertension and elevated levels of superoxide. The scientists concluded that sesamin may inhibit production of aortic superoxide, and that sesamin's antioxidant activity may contribute to its ability to reduce blood pressure.<sup>91,92</sup>

### **PREVENTING LIPID PEROXIDATION**

Sesame lignans also reduce the peroxidation of lipids. Lipid peroxidation produces harmful free radicals that can have damaging, disease-promoting effects in the body, and may precede the development of atherosclerosis. Preventing peroxidation may make lipids less likely to adhere to the lining of blood vessels, an important goal of preventive medicine.<sup>93</sup> Researchers in Japan determined that, when fed to laboratory animals, the sesame seed lignans sesamin and sesamol decrease lipid peroxidation and raise levels of alpha tocopherol, a form of vitamin E. Other researchers have confirmed this effect.<sup>94-96</sup>

Indian scientists found a similar effect when animals were fed sesame oil and sesamin. Despite induced oxidative stress, the animals fed sesame oil and sesamin retained high levels of tocopherols, or vitamin E antioxidants. The researchers suggested that sesame lignans may regenerate oxidized tocopherols, essentially sparing them in the body.<sup>96</sup>

### **CONTROLLING INFLAMMATION SYNERGISTICALLY**

Synergy refers to effects produced by two or more agents that are greater than the sum of their respective individual effects. As an example, consider the benefits of adding omega-3 fatty acids to standard chemotherapy for cancer treatment. Studies have shown that omega-3 polyunsaturated fatty acids may be cancer preventive, but that they also synergize with some anti-cancer drugs to enhance tumor-killing activity.<sup>15</sup>

Recently, scientists in Brazil reported a synergistic effect on rheumatoid arthritis of DHA- and EPA-rich fish oil combined with polyphenol-rich olive oil.<sup>16</sup> Forty-three middle-aged patients undergoing rheumatoid arthritis treatment were randomly assigned to one of three groups. In addition to standard treatment for their pain, stiffness, and inflammation, patients in group one received a placebo oil. Patients in group two received DHA- and EPA-rich omega-3 fatty acids from fish oil, while patients in group three were given a combination of fish oil and polyphenol-rich olive oil. Disease status was assessed before the beginning of the study and at three and six months. At the study's end, fish oil was found to significantly relieve various indicators of disease progression. Duration of morning stiffness decreased, joint pain intensity was reduced, handgrip strength increased, and fatigue was lessened.

Most impressive, however, were the effects observed in the group that received both fish oil and olive oil. These patients exhibited an "accentuated improvement" when DHA- and EPA-rich fish oil supplements were used in combination with polyphenol-rich olive oil.<sup>16</sup> While fish oil improved various parameters of inflammation, only fish oil and olive oil together provided additional improvements in duration of morning stiffness, the ability to turn faucets on and off, and patients' subjective assessments of satisfaction with their daily living activities.

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#### SUMMARY

The Mediterranean diet has well-substantiated health- and longevity-promoting effects.

Critical components of this diet that may account for the impressive benefits described in scientific studies include potent antioxidants from phytonutrients, the critical omega-3 fatty acids DHA and EPA, and health-enhancing polyphenols derived from olive fruit.



While the remarkable health benefits associated with antioxidant-rich phytonutrients and the omega-3 fatty acids DHA and EPA are well established, emerging research supporting the benefits of olive polyphenols is equally impressive. Particularly striking is the study just described, in which a combination of EPA/DHA and hydroxytyrosol-rich olive polyphenols produced synergistic benefits in controlling inflammation in rheumatoid arthritis patients.

Hydroxytyrosol, a potent antioxidant, is the major polyphenol present in olive extract. This and other olive polyphenols are most concentrated in water-soluble olive fruit extract, not in the oil itself. Concentrated, standardized extracts of olive fruit enable health-conscious people to consume high concentrations of these powerful nutrients without ingesting servings of extra-virgin olive oil

containing inadvisably large amounts of dietary fat and calories.

Extensive research strongly supports phytonutrients, omega-3 polyunsaturated fatty acids, and olive polyphenols as critical nutrients that likely account for many of the remarkable anti-aging and health benefits of the Mediterranean diet.

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