American Institute for Cancer Research 11th Annual Research Conference on Diet, Nutrition and Cancer

The Mediterranean Diets: What Is So Special about the Diet of Greece? The Scientific Evidence[1]

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ABSTRACT The term "Mediterranean diet," implying that all Mediterranean people have the same diet, is a misnomer. The countries around the Mediterranean basin have different diets, religions and cultures. Their diets differ in the amount of total fat, olive oil, type of meat and wine intake; milk vs. cheese; fruits and vegetables; and the rates of coronary heart disease and cancer, with the lower death rates and longer life expectancy occurring in Greece. Extensive studies on the traditional diet of Greece (the diet before 1960) indicate that the dietary pattern of Greeks consists of a high intake of fruits, vegetables (particularly wild plants), nuts and cereals mostly in the form of sourdough bread rather than pasta; more olive oil and olives; less milk but more cheese; more fish; less meat; and moderate amounts of wine, more so than other Mediterranean countries. Analyses of the dietary pattern of the diet of Crete shows a number of protective substances, such as selenium, glutathione, a balanced ratio of (n-6):(n-3) essential fatty acids (EFA), high amounts of fiber, antioxidants (especially resveratrol from wine and polyphenols from olive oil), vitamins E and C, some of which have been shown to be associated with lower risk of cancer, including cancer of the breast. These findings should serve as a strong incentive for the initiation of intervention trials that will test the effect of specific dietary patterns in the prevention and management of patients with cancer. J. Nutr. 131: 3065S–3073S, 2001.

KEY WORDS: • *diet of Crete* • *(n-3) fatty acids* • *wild plants* • *antioxidants* • *cancer* • *(n-6) fatty acids*

The health of the individual and the population in general is the result of interactions between genetics and a number of environmental factors. Nutrition is an environmental factor of major importance (1–4). Our genetic profile has not changed over the past 10,000 y, whereas major changes have taken place in our food supply and in energy expenditure and physical activity (5–17). Today industrialized societies are characterized by the following: *1*) an increase in energy intake and decrease in energy expenditure; *2*) an increase in saturated fat, (n-6) fatty acids and *trans* fatty acids and a decrease in (n-3) fatty acid intake; *3*) a decrease in complex carbohydrates and fiber intake; *4*) an increase in cereal grains and a decrease in fruit and vegetable intake; and *5*) a decrease in protein, antioxidant and calcium intake (5–17). Furthermore, the ratio of (n-6) to (n-3) fatty acids is 16.74:1, whereas during evolution it was 2–1:1 (**Table 1**, **Fig. 1**).

Recent investigations of the dietary patterns and health status of the countries surrounding the Mediterranean basin clearly indicate major differences among them in both dietary intake and health status. Therefore, the term "Mediterranean diet" is a misnomer. There is not just one Mediterranean diet but in fact many Mediterranean diets (18), which is not surprising because the countries along the Mediterranean basin have different religions, economic and cultural traditions and diets. Diets are influenced by religious habits, that is, Muslims do not eat pork or drink wine and other alcoholic drinks, whereas Greek Orthodox populations usually do not eat meat on Wednesdays and Fridays but drink wine, and so on. Although Greece and the Mediterranean countries are usually considered to be areas of medium-high death rates (14.0–18.0 per 1000 inhabitants), death rates on the island of Crete have been below this level continuously since before 1930 (19). No other area in the Mediterranean basin has had as low a death rate as Crete, according to data compiled by the United Nations in their demographic yearbook for 1948. It was 11.3–13.7 per 1000 inhabitants before World War II and ~10.6 in 1946–1948 (19). Cancer and heart disease caused almost three times as many deaths proportionally in the United States as in Crete (19). The diet of Crete represents the traditional diet of Greece before 1960. The Seven Countries Study was the first to establish credible data on cardiovascular disease prevalence rates in contrasting populations (United States, Finland, The Netherlands, Italy, former Yugoslavia, Japan and Greece), with differences found on the order of 5- to 10-fold in coronary heart disease (20). In 1958, the field work started in Dalmatia in the former Yugoslavia.

[1] Presented as part of the 11th Annual Research Conference on Diet, Nutrition and Cancer held in Washington, DC, July 16–17, 2001. This conference was sponsored by the American Institute for Cancer Research and was supported by the California Dried Plum Board, The Campbell Soup Company, General Mills, Lipton, Mead Johnson Nutritionals, Roche Vitamins Inc. and Vitasoy USA. Guest editors for this symposium publication were Ritva R. Butrum and Helen A. Norman, American Institute for Cancer Research, Washington, DC.

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TABLE 1

Ratios of (n-6) to (n-3) fatty acids in various populations

Population	(n-6):(n-3)	Reference
Paleolithic	0.79	8
Greece before 1960	1.00–2.00	9
Current United States	16.74	8
Current United Kingdom and northern Europe	15.00	10
Current Japan	4.00	11

From the inception of the research program, an important focus was on the diet and its possible relationship to the etiology of coronary heart disease. The 5-y follow-up found favorable all-cause death rates in Greece, Japan and Italy compared with the other areas, as well as a lower incidence rate of coronary disease (20). The Seven Countries Study was designed to investigate relationships between diet and cardiovascular disease, primarily described in terms of the fatty acid composition of the diet.

This paper describes the characteristics of the traditional diet of Greece before 1960 as exemplified by the diet of Crete and its relationship to cancer. The diet of Crete or the traditional diet of Greece resembles the Paleolithic diet in terms of fiber, antioxidants, saturated fat, monounsaturated fat and the ratio of (n-6) to (n-3) fatty acids (Table 1) (21). The Lyon Heart Study (22–25) and subsequently the study of Singh et al. (26,27) support the importance of having a diet consistent with human evolution. Western diets today deviate from the Paleolithic diet and are associated with high rates of cardiovascular disease, diabetes, obesity and cancer.

The diet of Crete and its relation to cardiovascular disease and cancer

Over the past 15 y, a number of animal experiments, epidemiologic investigations and double-blind, controlled clinical trials have confirmed the hypotriglyceridemic, anti-inflammatory and antithrombotic aspects of (n-3) fatty acids (28–35) and the essentiality of (n-3) fatty acids, particularly docosahexaenoic acid [DHA,[3] 22:6(n-3)], for the development of retina and brain of the premature infant. It therefore became important to investigate the (n-3) fatty acid composition of diets that have been shown to be associated with a decreased rate of cardiovascular disease and cancer. Such an opportunity presented itself in the diet of Crete (21).

The results of the Seven Countries Study are interesting because they show that the population of Crete had the lowest rates of cardiovascular disease and cancer, followed by the population of Japan (20). The investigators concluded that the reason for these low rates must be the high olive oil intake and the low saturated fat intake of the Mediterranean diet. The fact that Crete had a high fat diet (37% of energy from fat) and Japan had a low fat diet (11% of energy from fat) was not discussed extensively nor were any other fatty acids considered despite the fact that the people of Crete ate 30 times more fish than did the U.S. population. Furthermore, the people of Crete ate a large amount of vegetables (including wild plants), fruits, nuts and legumes, all rich sources of folate, calcium, glutathione, antioxidants, vitamins E and C and minerals. In addition, because the meat came from animals that grazed rather than being fed grain, it contained (n-3) polyunsaturated fatty acids (PUFA) as did the milk and milk products, such as cheese (**Table 2**). The population of Crete eats snails during Lent and throughout the year. Renaud (Serge Renaud, INSERM, Bordeaux, France, personal communication) has shown that the snails of Crete and Greece contain more (n-3) fatty acids and less (n-6) fatty acids than do the snails of France.

The traditional Greek diet, including the diet of Crete, includes wild plants. Wild plants are rich sources of (n-3) fatty acids and antioxidants (36–38). Purslane, a commonly eaten plant (**Table 3**), is rich in α-linolenic acid [LNA, 18:3(n-3); 400 mg/100 g] as well as in vitamin E (12 mg/100 g), vitamin C (27 mg/100 g) and glutathione (15–20 mg/100 g) (37). In Crete and Greece, purslane is eaten fresh in salads, soups and omelets or cooked with poultry; during the winter months, dried purslane is used in soups and vegetable pies and as a tea for sore throat and earache. It is highly recommended for pregnant and lactating women and for patients with diabetes.

The purslane study was just the beginning of our involvement in a series of studies that investigated the (n-3) fatty acids in the Greek diet under conditions similar to those before 1960 (36). In the Greek countryside, chickens wander on farms, eat grass, purslane, insects, worms and dried figs, all good sources of (n-3) fatty acids. **Table 4** shows the composition of the Ampelistra (Greek) egg (39,40). It has a ratio of (n-6) to (n-3) of 1.3 whereas the USDA egg has a ratio of 19.4. As a result, noodles made with milk and eggs in Greece also contain (n-3) fatty acids.

Thus a pattern began to unfold. The diet of Greece, including Crete, before 1960 contained (n-3) fatty acids in every meal—breakfast, lunch, dinner and snacks. Figs stuffed with walnuts are a favorite snack. Both figs and walnuts contain LNA. Contrast this snack with a chocolate chip cookie that contains *trans* fatty acids and (n-6) fatty acids from the partially hydrogenated oils used in preparation (41). Although these studies were carried out between 1984 and 1986, further analyses of blood specimens from the Seven Countries Study were published in 1993 by Sandker et al. (42), indicating that the serum cholesteryl esters of the population in Crete had threefold more LNA than did the population of Zutphen (**Table 5**). Similar data indicated that the Japanese population also had higher concentrations of (n-3) fatty acids than did the

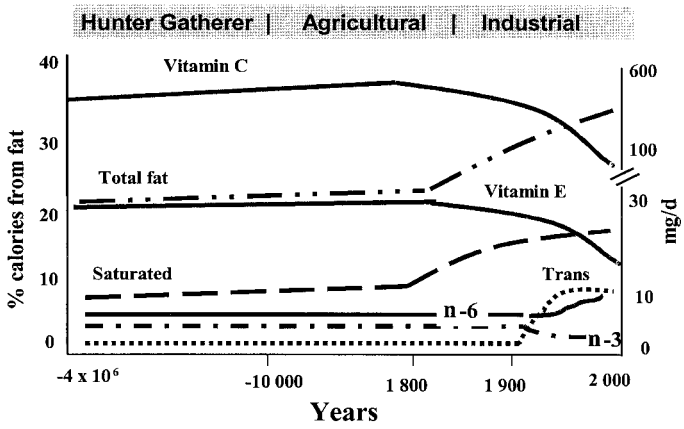

FIGURE 1 Hypothetical scheme of fat, fatty acid (n-6, n-3, *trans* and total) intake (as percentage of energy from fat) and intake of vitamins E and C (mg/d). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 y (12).

[3] Abbreviations used: AA, arachidonic acid; DHA, docosahexaenoic acid; EFA, essential fatty acids; EPA, eicosapentaenoic acid; LA, linoleic acid; LNA, α-linolenic acid; LT, leukotrienes; PUFA, polyunsaturated fatty acids.

TABLE 2

Fatty acid content of various cheese[1]

	2% Milk	Cheddar	American	Swiss	Greek myzithra	Greek feta
			g/100 g			
Total saturated fat	1.2	21.00	19.69	16.04	9.30	7.20
12:0 (lauric acid)	<1	0.54	0.48	0.57	—	—
14:0 (myristic acid)	<1	3.33	3.21	2.70	1.90	1.60
16:0 (palmitic acid)	<1	9.80	9.10	7.19	5.40	3.90
18:0 (stearic acid)	<1	4.70	3.00	2.60	2.00	1.70
Total monounsaturated fat	1	9.99	8.95	7.05	3.90	3.00
Total polyunsaturated fat	0.07	0.94	0.99	0.62	0.80	0.58
18:2(n-6) (linoleic acid, LA)	0.04	0.58	0.61	0.34	0.38	0.29
18:3(n-3) (α-linolenic acid, LNA)	0.03	0.36	0.38	0.28	0.30	0.20
			mg/100 g			
20:4(n-6) (arachidonic acid)	—	—	—	—	14	10
20:5(n-3) (eicosapentaenoic acid, EPA)	—	—	—	—	18	14
22:5 (docosapentaenoic acid)	—	—	—	—	31	23
22:6(n-3) (docosahexaenoic acid, DHA)	—	—	—	—	5.5	5.1
Total fat, *g*	2.27	31.93	29.63	23.71	14.00	10.78

[1] Milk, cheddar, American and Swiss from U.S. Department of Agriculture Handbook No. 8. Greek myzithra and Greek feta from National Institute on Alcohol Abuse and Alcoholism analyses. Source; Ref. 9.

population of Zutphen. Here then was the missing link. It was the higher concentrations of (n-3) fatty acids that added protection against cardiovascular disease, not only the olive oil, wine, fruits and vegetables of the "typical" Mediterranean diet.

The two populations with the lowest coronary heart disease in the Seven Countries Study had a higher intake of LNA. The Japanese obtained it from canola oil and soybean oil and the population of Crete obtained it from purslane, other wild plants, walnuts and figs. Additional studies showed that the population of Crete not only had higher serum cholesteryl ester levels of LNA but also lower linoleic acid [LA, 18:2(n-6)] (Table 5) (42).

Renaud et al. (43) had been working with LNA and had shown that it decreases platelet aggregation. Everything seemed to fall into place in terms of defining the characteristics of the diet of the population of Crete. Their diet was very similar to the Paleolithic diet in composition (Table 1). The diet was low in saturated fat, balanced in the essential fatty acids [EFA; (n-6) and (n-3)], very low in *trans* fatty acids and high in vitamins E and C. This diet formed the basis of the diet used by de Lorgeril and Renaud in their now famous Lyon Heart Study (22–25). The Lyon Heart Study was a prospective randomized, single-blind secondary prevention trial that compared the effects of a modified Crete diet enriched with LNA with those of a Step I American Heart Association diet. The study showed a decrease in death rate by 70% in the experimental group and clearly showed that a modified Crete diet low in butter and meats such as deli products but high in fish and fruits and vegetables and enriched with LNA is more efficient than the American Heart Association or similar prudent diets in the secondary prevention of coronary events and total deaths (22). The same subjects were followed for 5 y. At 4 y of follow-up, de Lorgeril et al. (24) reported that the

TABLE 3

Fatty acid content of plants[1]

Fatty acid	Purslane	Spinach	Mustard	Red leaf lettuce	Buttercrunch lettuce
			mg/g wet weight		
14:0	0.16	0.03	0.02	0.03	0.01
16:0	0.81	0.16	0.13	0.10	0.07
18:0	0.20	0.01	0.02	0.01	0.02
18:1(n-9)[2]	0.43	0.04	0.01	0.01	0.03
18:2(n-6)	0.89	0.14	0.12	0.12	0.10
18:3(n-3)	4.05	0.89	0.48	0.31	0.26
20:5(n-3)	0.01	0.00	0.00	0.00	0.00
22:6(n-3)	0.00	0.00	0.001	0.002	0.001
Other	1.95	0.43	0.32	0.12	0.11
Total fatty acid content	8.50	1.70	1.101	0.702	0.60

[1] Modified from Ref. 36.
[2] Oleic acid.

TABLE 4

Fatty acid levels in chicken eggs yolks[1,2]

Fatty acid	Greek egg	Supermarket egg
	mg fatty acid/g egg yolk	
Saturated fatty acids		
Total	100.66	80.65
Monounsaturated fatty acids		
16:1(n-7)	21.70	4.67
18:1	120.50	109.97
20:1(n-9)	0.58	0.68
22:1(n-9)	—	—
24:1(n-9)	—	0.04
Total	142.78	115.36
(n-6) fatty acids		
18:2(n-6)	16.00	26.14
18:3(n-6)	—	0.25
20:2(n-6)	0.17	0.36
20:3(n-6)	0.46	0.47
20:4(n-6)	5.40	5.02
22:4(n-6)	0.70	0.37
22:5(n-6)	0.29	1.20
Total	23.02	33.81
(n-3) fatty acids		
18:3(n-3)	6.90	0.52
20:3(n-3)	0.16	0.03
20:5(n-3)	1.20	—
22:5(n-3)	2.80	0.09
22:6(n-3)	6.60	1.09
Total	17.66	1.73
Ratio of fatty acids to saturated fats	0.4	0.44
Ratio of (n-6) to (n-3)	1.3	19.4

[1] The eggs were hard-boiled, and their fatty acid composition and lipid content were assessed as described in Ref. 39.
[2] Modified from Ref. 39. 16:1(n-7), palmitoleic acid; 20:1(n-9), gondoic acid; 22:1(n-9), docosenoic acid.

reduction of risk in the experimental subjects compared with control subjects was 56% ($P = 0.03$) for total deaths and 61% ($P = 0.05$) for cancers, indicating that a modified diet of Crete was associated with lower risk for coronary heart disease and cancer.

Bioprotective nutrients and mechanisms

Although the investigators of the Seven Countries Study emphasized the low saturated fat intake and the high monounsaturated fat intake from olive oil as the major factors responsible for the biological health effects of associating the diet of Crete with the lowest rate of coronary heart disease and the longest life expectancy, there is good evidence that foods rich in (n-3) fatty acids and antioxidants could account for the decreased death rate of the people of Crete and lower rates of coronary heart disease and cancer (22–25). Wine, fruits, vegetables (particularly wild plants) and olive oil provide high amounts of resveratrol, glutathione, vitamin C, vitamin E, lycopene, β-carotene, polyphenols and other antioxidants (44–48). The importance of a Cretan-type diet, rich in LNA from vegetables and fruits and eicosapentaenoic acid [EPA, 20:5(n-3)] and DHA from fish, was demonstrated in the Diet and Reinfarction Trial (or DART) (49), the Lyon Heart Study (22–25), the study by Singh et al. (26,27) and the most recent Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial (50).

Olive oil is high in the monounsaturated fatty acid oleic acid [18:1, (n-9)] and low in saturated and (n-6) fatty acids; it does not compete with the desaturation and elongation of LNA nor with the incorporation of (n-3) fatty acids into the red cell membrane phospholipids, providing an additional benefit to the functions of (n-3) fatty acids (5). Furthermore, the (n-6) to (n-3) ratio in the Greek diet is between 2:1 and 1:1, which is very close to the dietary ratio of the Paleolithic diet (Table 1). The beneficial effects of such a ratio and their importance in normal growth and development (51–53) and in the prevention and management of cardiovascular disease, hypertension, diabetes, arthritis and possibly cancer have been reviewed extensively (5,28–35,54–57).

Because Greeks have a cultural dislike for animal fats, the saturated fat intake of the Greek diet is lower than that for other Mediterranean and Western diets (19). The Greek diet, then, is characterized by being moderate in fat (~35%), low in saturated fat (7–8%), high in monounsaturated fat and balanced in the (n-6) and (n-3) EFA. The content of antioxidants, phytoestrogens and other phytochemicals is much higher than in other diets of the people around the Mediterranean basin because Greeks continue to eat wild greens that are rich sources of LNA, vitamin C, vitamin E and glutathione (36–38). The beneficial effects of the various compounds found in the vegetables and fruits eaten by Greeks have been shown to have hypoglycemic, hypocholesterolemic and antitumor properties in animal experiments (44). Even today, the mortality from breast cancer is lower in Greece than in the United States, Japan and Europe (58). Finally, the Lyon Heart Study based on the modified diet of Crete described by de Lorgeril et al. (22–25) clearly showed cardioprotective and anticancer effects in a French population, indicating that such a diet is not only palatable but can be adapted to other populations. Furthermore, one could consider that the traditional diet of Greece even in its present form is the diet that is closer than the diets of other developed countries to the diet on which humans evolved (Fig. 1) (18).

EFA and cancer

Although the purpose of the Lyon trial was to study the effect of a modified Cretan diet on cardiovascular disease, it also indicated a protective effect against clinical manifestation of cancer (24).

TABLE 5

Mean fatty acid composition of cholesteryl esters in serum of 92 elderly men from Crete and 97 elderly men from Zutphen[1,2]

	% methylesters	
Fatty acid	Crete	Zutphen
16:0	11.1 ± 1.0	11.9 ± 1.3
16:1	3.2 ± 1.1	2.9 ± 1.6
18:0	0.7 ± 0.3	1.1 ± 0.5
18:1	31.0 ± 2.7	21.4 ± 3.9
18:2(n-6)	41.9 ± 3.7	53.1 ± 6.5
18:3(n-3)	0.9 ± 0.5	0.3 ± 0.4
20:4(n-6)	6.5 ± 1.6	4.5 ± 1.5
Others	4.6 ± 3.3	4.7 ± 3.7
Ratio 18:2/18:1	1.37 ± 0.20	2.60 ± 0.75

[1] Results are expressed as mean % (by weight) methylesters ± SD.
[2] Modified from Ref. 42.

There are two families of EFA, the (n-6) and (n-3) families. The principal EFA in the U.S. diet is LA, an (n-6) fatty acid. One of the main functions of EFA in the body is as a precursor for eicosanoids, which are mediators of inflammation and cellular growth. EFA are converted to prostaglandins by cyclooxygenases and to leukotrienes (LT) by lipoxygenases. Arachidonic acid [(AA); 20:4(n-6)] and EPA, an (n-3) fatty acid, compete for cyclooxygenases and lipoxygenases, resulting in the production of eicosanoids with opposing effects. In general, AA-derived eicosanoids, such as the 2-series prostanoids and 4-series LT, have proinflammatory effects, whereas EPA-derived eicosanoids, such as the 3-series prostanoids and 5-series LT, have anti-inflammatory effects. There is competition and opposition of EFA in the body; thus research has been conducted to determine the importance of the (n-6) to (n-3) ratio rather than the absolute level of either class of PUFA in cancer prevention (5,59).

Animal studies and cell lines. In animal studies (rats) LA increases the size and number of tumors, whereas fish oil [containing the (n-3) fatty acids EPA and DHA] decreases both (60,61). Studies in rats suggest that inhibitors of prostaglandin synthesis, such as indomethacin and flurbiprofen, can inhibit mammary carcinogenesis. The prostaglandin-inhibitory effect of fish oils has been tested in animal tumor systems by many investigators, and the studies provide evidence that at optimal levels, (n-3) fatty acids may be useful as inhibitory agents in some colon, lung, mammary, pancreatic and prostatic tumors in experimental animals, whereas LA supports tumor growth (62). Studies in cell lines and animals appear to support the epidemiologic evidence concerning the protective role of a ratio of (n-6) to (n-3) of $< 2:1$ against the development of mammary cancer and to provide evidence that (n-3) fatty acids could have the potential to be used as an adjuvant therapy to prevent recurrence and metastases of mammary cancer (59).

Epidemiologic studies. The effects of (n-6) and (n-3) fatty acids on the growth and progression of tumors are different. Epidemiologic studies in humans during the past two decades have demonstrated that the consumption of fish oil protects against the development of cancers, especially mammary cancer (63). Klein et al. (64) showed that low LNA levels in mammary adipose tissue were inversely correlated with increased mammary cancer risk in women. In patients with prostate cancer, fish intake was inversely related to cancer (65).

Mechanisms. Recent data demonstrated the effectiveness of n-3 EFA in regulating growth, progression, metastasis and postexcision recurrence of mammary tumors in murine models. Furthermore, there is evidence that EFA influence [(n-6) stimulate whereas (n-3) suppress the pathway] the epidermal growth factor receptor/mitogen-activated protein kinase pathway, targeting many of the same components as drugs under development (59).

The data suggest that the most important aspect of EFA in the prevention of mammary cancer is the ratio of (n-6) to (n-3) fatty acids rather than the absolute concentration of either (59). Research data indicate that a ratio of 1:1 or 2:1 protects most against the development and growth of mammary cancer. Western diets have a ratio of 10–20:1, or 16.74 (17). Clearly, these data suggest that further research into the usefulness of dietary manipulation of EFA for the prevention or adjuvant treatment of mammary cancer, as well as continued research into the mechanisms of EFA in mammary tumor development, is warranted. Cyclooxygenase-2 is overexpressed in cancer of the colon (66). Recently, DeCaterina and Habib (R. DeCaterina, G. d'Annunzio University, Chieti, and CNR Institute of Clinical Physiology, Pisa, Italy, & A. Habib, Hopital Lariboisière, Paris, unpublished observations, 2001) showed that DHA down-regulates the expression of cyclooxygenase-2 and induces apoptosis (67–72).

Dietary supplementation with (n-3) fatty acids in clinical trials. Dietary supplementation with (n-3) fatty acids has been tested in several clinical trials. In pancreatic cancer, a malignancy associated with a persistent inflammatory response and increased energy expenditure, 3 mo of dietary supplementation with a median of 12 g/d fish oil (EPA 18% and DHA 12%) led to a significant median weight gain of 0.3 kg/mo, accompanied by a temporary but significant reduction in acute-phase protein production and by stabilization of resting energy expenditure (73). Gogos et al. (74) randomly assigned 60 patients with generalized solid tumors to dietary supplementation with either fish oil or placebo daily until death. The (n-3) fatty acids had an impressive immunomodulating effect, as reflected by the ratio of T-helper cells to T-suppressor cells in the subgroup of malnourished patients. There were no significant differences in cytokine production among the various groups. In addition, (n-3) fatty acids prolonged the survival of all patients (74). These stimulating results warrant further clinical trials to establish the exact benefits and limitations of (n-3) fatty acid supplementation in cancer patients.

Selenium. A randomized clinical trial in the United States showed that selenium supplementation (200 μg/d) decreased the incidence of prostate, lung and colorectal cancer over a mean follow-up of 4.5 y (75). An inverse association was reported between advanced prostate cancer and toenail selenium concentrations, a surrogate of long-term selenium intake (76). The Greek diet, rich in marine products, provides adequate amounts of selenium. Octopus, the Greek national appetizer, contains 90 μg selenium/100 g. In both the Lyon study and the U.S. selenium trials, the benefits in terms of cancer became apparent within 3–4 y. In animal models, selenium has been shown to interfere with carcinogenesis through several possible mechanisms (77).

Resveratrol. Resveratrol (3,4′,5-trihydroxystilbene) is a naturally occurring polyphenolic phytoalexin found in wine and medicinal plants of the *Polygonum* species (Polygonaceae). Resveratrol inhibits lipogenesis from palmitate in the liver and adipose tissue (78), inhibits the formation of lipoxygenase products (LTB_4 and LTC_4) and inhibits AA platelet aggregation (79–81). Resveratrol and its derivatives have been further shown to strongly inhibit the degranulation of polymorphonuclear leukocytes (81), and resveratrol inhibits tumor growth and causes apoptosis as a cancer chemopreventive agent (82–89). The antitumor and antimetastatic activities of resveratrol may be due to the inhibition of DNA synthesis in metastatic Lewis lung carcinoma cells, neovascularization in-

TABLE 6

Potential health effects of dietary glutathione in humans[1]

Glutathione may protect cells from carcinogenic processes through a number of mechanisms:

1. By functioning as an antioxidant (91, 95)
2. By binding with mutagenic chemical compounds (96, 97)
3. By directly or indirectly acting to maintain functional levels of other antioxidants such as vitamins E and C and β-carotene (97–99)
4. Through its involvement in DNA synthesis and repair (100, 101)
5. By enhancing the immune response (102, 103)

[1] Adapted from Jones et al. (92).

TABLE 7

Glutathione content of purslane and spinach leaves[1,2,3]

	GSH	GSSX	GSH/ GSSX
Chamber-grown purslane	14.81 ± 0.78 (0.48)	2.20 ± 0.15 (0.031)	6.73
Wild purslane	11.90 ± 0.63 (0.39)	1.42 ± 0.12 (0.023)	8.38
Spinach	9.65 ± 0.62 (0.31)	2.39 ± 0.20 (0.039)	4.03

[1] Data represent mean values (mg/100 g fresh weight) from four analyses each with three replicates per plant species/type. Figures in parentheses are values expressed as μmol/g fresh weight to allow comparison with data previously reported in the literature.
[2] GSH, glutathione; GSSX, glutathione-linked disulfides.
[3] Adapted from Simopoulos et al. (37).

duced by these cells and tube formation (angiogenesis) of human umbilical vein endothelial cells by resveratrol (90).

Glutathione. The protective role of glutathione as an antioxidant and detoxifying agent has been demonstrated in various clinical studies. It is a ubiquitous compound that is synthesized rapidly in the liver, kidney and other tissues, including the gastrointestinal tract. In animal cells, glutathione acts as a substrate for glutathione peroxidase, which reduces lipid peroxides that are formed from PUFA in the diet, and as a substrate for glutathione *S*-transferase, which conjugates electrophilic compounds. Recent studies showed that glutathione obtained from the diet is directly absorbed by the gastrointestinal tract and thus dietary glutathione can readily increase the antioxidant status in humans (91). Dietary glutathione, in addition to that supplied by the bile, may be used by the small intestine to decrease the absorption of peroxides. These results indicate that in intact animals, lumenal glutathione is available for use by the intestinal epithelium to metabolize peroxides and other reactive species and to prevent their transport to other tissues.

Dietary glutathione occurs in highest amounts in fresh meats and in moderate amounts in some fruits and vegetables; it is absent or found only in small amounts in grains and dairy products (92). Only fresh asparagus (28.3 mg/100 g) and fresh avocado (27.7 mg/100 g) were higher than purslane in glutathione content in a study by the National Cancer Institute that determined the glutathione content of 98 food items that contribute 90% or more of energy, dietary fiber and 18 major nutrients to the U.S. diet (92–94).

The potential health effects of dietary intake of glutathione in humans are shown in **Table 6** (90,95–103). In a recent study by Flagg et al. (104), plasma glutathione concentrations varied widely in humans and were influenced by sex and age (increased with age in men but decreased with age and were lower in women who used estrogen-containing contraceptives).

Glutathione is now known to be widely distributed in plant cells and is the major free thiol in many higher plants (105–108). Considerable variations in levels of glutathione have been reported by different studies recording thiol levels in a variety of plant species. This may be due in part to the use of different analytical techniques and because glutathione levels vary both diurnally (109,110) and with developmental and environmental factors (111–113). Taking into account these considerations, the levels of glutathione found in purslane, 14.81 ± 0.78 mg/100 g fresh weight, were in the range of those reported for other plant species but significantly higher than the level of 9.65 ± 0.62 mg/100 g fresh weight for spinach (**Table 7**) (38). Glutathione was present in significantly greater amounts in chamber-grown purslane relative to wild plants, which may reflect a difference in the developmental stage of the plants analyzed or in the environmental conditions experienced.

In summary, many of the components of the diet of Crete—fiber, natural antioxidants from wild plants, fruit, wine, olive oil, a low ratio of (n-6) to (n-3) ratio (consistent with the Paleolithic diet)—have been shown, when studied separately, to potentially prevent cancer initiation or metastasis, prevent angiogenesis and induce apoptosis.

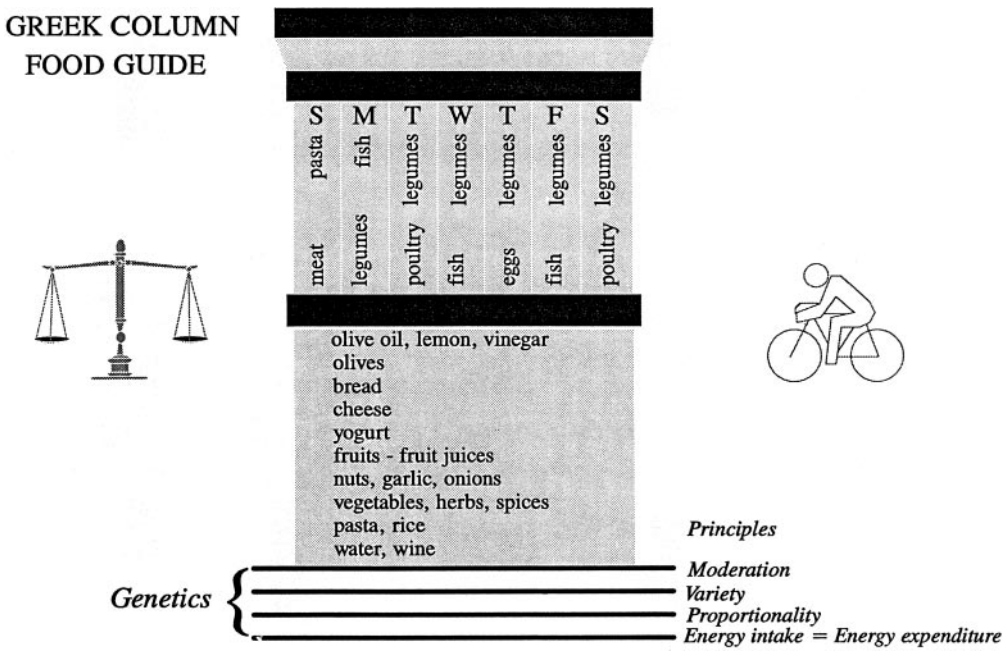

FIGURE 2 The Greek column food guide. The guide is based on genetic individuality; the principals of moderation, variety, proportionality, and equality of energy intake with energy expenditure (114).

Implementation of the diet of Crete

The Lyon Heart Study clearly showed that the diet of Crete can be adhered to over a period of 5 y (22). **Figure 2** is the Greek Column Food Guide based on the diet of Crete (114). The visualization of this food guide in the form of a Greek column includes the concepts of genetic variation and nutrition and a balanced energy intake and energy expenditure; it is based on foods, not food groups. Although it excludes certain foods made with hydrogenated oils, it does not restrict the intake of naturally occurring foods. It also takes into consideration moderation, variety and proportionality. Dietary guidelines shown in **Table 8** provide further information on how to implement the diet of Crete (21).

In conclusion, studies on the Paleolithic diet suggest that (n-3) fatty acids were present in practically all foods that humans ate and in equal amounts with (n-6) fatty acids. The depletion of the (n-3) fatty acids in Western diets is the result of agribusiness, modern agriculture and aquaculture. The high ratio of (n-6) to (n-3) fatty acids (16.74:1 instead of 1:1) is the result of excessive production of vegetable oils and the indiscriminate recommendation to substitute saturated fat and butter with oils high in (n-6) fatty acids to lower serum cholesterol levels without taking into consideration their adverse effect on overall human metabolism.

The results of the Seven Countries Studies and the Lyon Heart Study based on a modified diet of Crete indicate that a Paleolithic-type diet such as the traditional Greek diet balanced in (n-6) and (n-3) fatty acids and rich in vitamins C and E (fruits and vegetables) is associated with decreased rates of heart disease and cancer more so than any other diet or drug intervention.

What appears to be so special about the Greek diet relative to the other Mediterranean diets is the content of bioprotective nutrients, specifically the following: *1*) a more balanced intake of EFA from vegetable, animal and marine sources; a ratio of (n-6) to (n-3) fatty acids of ~2:1 instead of the 15:1 in Western and Northern Europe and 16.74:1 in the United States; and *2*) a diet rich in antioxidants, i.e., high amounts of vitamin C, vitamin E, β-carotene, glutathione, resveratrol, selenium, phytoestrogens, folate, and other phytochemicals from green leafy vegetables; phenolic compounds from wine and olive oil; high intakes of tomatoes, onions, garlic and herbs, especially oregano, mint, rosemary, parsley and dill, which contain lycopene, allyl thiosulfinates, salicylates, carotenoids, indoles, monoterpenes, polyphenols, flavonoids and other phytochemicals used in cooking vegetables, meat and fish.

Such a dietary pattern has been shown to be beneficial to health because it is associated with a reduced risk of cardiovascular disease and cancer. The time has come for the initiation of intervention trials that will test the effect of specific dietary patterns in the prevention and management of patients with cancer.

TABLE 8

The seven dietary guidelines of The Omega Diet[1]

1. Eat foods rich in (n-3) fatty acids such as fatty fish (salmon, tuna, trout, herring, mackerel), walnuts, canola oil, flaxseeds and green leafy vegetables. Or, if you prefer, take (n-3) supplements.
2. Use monounsaturated oils such as olive oil and canola oil as your primary fat.
3. Eat seven or more servings of fruits and vegetables every day.
4. Eat more vegetable protein, including peas, beans and nuts.
5. Avoid saturated fat by choosing lean meat over fatty meat (if you eat meat) and low fat over full fat milk products.
6. Avoid oils that are high in (n-6) fatty acids, including corn, safflower, sunflower, soybean, and cottonseed oils.
7. Reduce your intake of *trans* fatty acids by cutting back on margarine; vegetable shortening; commercial pastries; deep-fat fried food; and most prepared snacks, mixes and convenience food.

[1] From Simopoulos and Robinson (21).

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