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Mediterranean Dietary Pattern in a Randomized Trial

Prolonged Survival and Possible Reduced Cancer Rate FREE

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ABSTRACT

Background The Mediterranean dietary pattern is thought to reduce the risk of cancer in addition to being cardioprotective. However, no trial has been conducted so far to prove this belief.

Methods We compared overall survival and newly diagnosed cancer rate among 605 patients with coronary heart disease randomized in the Lyon Diet Heart Study and following either a cardioprotective Mediterranean-type diet or a control diet close to the step 1 American Heart Association prudent diet.

Results During a follow-up of 4 years, there were a total of 38 deaths (24 in controls vs 14 in the experimental group), including 25 cardiac deaths (19 vs 6) and 7 cancer deaths (4 vs 3), and 24 cancers (17 vs 7). Exclusion of early cancer diagnoses (within the first 24 months after entry into the trial) left a total of 14 cancers (12 vs 2). After adjustment for age, sex, smoking, leukocyte count, cholesterol level, and aspirin use, the reduction of risk in

experimental subjects compared with control subjects was 56% (*P*=.03) for total deaths, 61% (*P*=.05) for cancers, and 56% (*P*=.01) for the combination of deaths and cancers. The intakes of fruits, vegetables, and cereals were significantly higher in experimental subjects, providing larger amounts of fiber and vitamin C (*P*<.05). The intakes of cholesterol and saturated and polyunsaturated fats were lower and those of oleic acid and omega-3 fatty acids were higher (*P*<.001) in experimental subjects. Plasma levels of vitamins C and E (*P*<.05) and omega-3 fatty acids (*P*<.001), measured 2 months after randomization, were higher and those of omega-6 fatty acids were lower (*P*<.001) in experimental subjects.

Conclusions This randomized trial suggests that patients following a cardioprotective Mediterranean diet have a prolonged survival and may also be protected against cancer. Further studies are warranted to confirm the data and to explore the role of the different lipids and fatty acids in this protection.

MEDITERRANEAN populations are known to be protected against coronary heart disease (CHD) and certain cancers. Their dietary habits (low intake of saturated and polyunsaturated fats but high intake of oleic acid, omega-3 fatty acids, fibers, natural antioxidants, and vitamins of the B group) have been proposed to explain this protection.[1-6] So far, no trial has clearly demonstrated this hypothesis.

In the Lyon Diet Heart Study, a randomized secondary prevention trial in Lyon, France, testing the effect of an α-linolenic acid–rich Mediterranean-type diet on the rate of coronary recurrences, a major reduction of the risks was demonstrated; depending on the clinical end point (sudden death, nonfatal infarction, stroke, pulmonary embolism, or severe heart failure), the reduction of risk varied from 50% to 70%.[7,8] In the absence of major bias[9] and in view of the good compliance with the experimental diet and the lack of

between-group contamination,[7-9] the Lyon trial may offer the opportunity to examine the effect of this dietary pattern on overall survival and newly diagnosed cancer rate, although sample size and duration of follow-up were not calculated specifically for this purpose. Given the number of cancers observed in a similar middle-aged CHD population[10] and the Lyon study sample size, the expected number of cancers in this study was calculated to be approximately 40 during a follow-up of 4 years. It was thus conceivable (in accordance with epidemiological data) to detect a 50% reduction of the risk of cancers in the trial, assuming a type 1 error of 5%. In addition, the hypothesis appeared to be biologically plausible, as the experimental diet consisted of high intakes of fruits, vegetables, and cereals, providing large amounts of fiber and natural antioxidants known to be associated with a reduced risk of cancer,[11-14] and also of supplemental omega-3 fatty acids thought to retard tumor growth, at least in experimental models.[15,16]

Most of the data regarding the relationship between diet and cancer in humans have come from case-control and cohort studies, with their known methodological limitations, and randomized trials testing the effect on carcinogenesis of 1 single dietary factor were disappointing.[17-20] So far, no randomized trial has properly tested the effect of a dietary pattern (such as a Mediterranean-type diet) on cancer incidence and survival. As there are many Mediterranean countries with wide variations in eating patterns both geographically and over time, in the present study Mediterranean diet refers to a diet low in total fat and in saturated and omega-6 fatty acids, but rich in omega-3 fatty acids, oleic acid, fiber, antioxidants, vegetable proteins, and vitamins of the B group. The data suggest, for the first time in a prospective randomized trial, that this type of diet may protect against some forms of cancer. Although further research is needed to assess whether results were produced by chance alone or by other specific mechanisms, these data may open new perspectives for the prevention of cancer.

SUBJECTS AND METHODS

The design, methods, patients, and main results of the trial have been published.[7,8] In brief, 605 survivors (10% women) of a first acute myocardial infarction were recruited during their stay in the coronary care unit and randomized 2 months later into either a control (patients following a diet close to the step 1 prudent diet of the American Heart Association) or an experimental group. Patients in the experimental group were instructed to follow a Mediterranean-type of diet with more bread and cereals, more fresh fruit and vegetables, more legumes, more fish, fewer delicatessen foods, less meat (beef and pork to be replaced with poultry), and no butter and cream, which were to be replaced with an experimental canola oil–based margarine (Astra-Calve, Paris, France) rich in oleic and α-linolenic acids. The oils recommended for salad and food preparation were canola and olive oils exclusively.[7,8] Moderate red wine consumption was allowed at meals. Patients in the experimental group and their families were seen by the dietitian at the randomization visit, 2 months later, and then once a year. The specific techniques used to instruct these patients have been previously described,[9] and compliance with the dietary intervention was checked by a dietary survey (including a 24-hour recall and a food frequency questionnaire at each visit) and analyses of plasma fatty acids.[21] Patients in the control group were expected to follow the dietary advice given by their attending physicians (not involved in the study) and close to the step 1 diet of the American Heart Association (characterized as 30% of total energy as fats, 10% saturated, 10% monounsaturated, and 10% polyunsaturated, and cholesterol intake lower than 300 mg/d). As previously reported,[7-9] potential confounders, such as smoking, physical activity, and associated drug treatment, were closely monitored during the entire follow-up and, if necessary, included in the statistical analyses, in particular the Cox model to calculate adjusted risk ratios and confidence intervals.

Primary end points were deaths from cardiovascular causes (including sudden death as well as deaths after acute myocardial infarction, stroke, pulmonary embolism, or episodes of heart failure) and nonfatal acute myocardial infarction. Subsidiary end points included noncardiac deaths and several cardiovascular conditions, provided they required hospital admission and cardiac investigations.[8] Also, the occurrence of malignant and nonmalignant tumors was carefully monitored, since populations living in Mediterranean regions are known to have a low incidence of most neoplasms. As neither participating physicians nor patients were aware of a cancer hypothesis, there was no reason to suspect any cancer ascertainment bias. In addition, in a specific study conducted to detect any attending physician (or other) bias that could have influenced the collection of the data, no significant bias was found.[9] At each visit, investigators systematically questioned the patients regarding hospitalization, clinical investigations, or treatment that could have suggested that the patient had a tumor or that a tumor had been suspected. When a relevant tumor end point was suspected or reported by the patients at the annual visit, medical records were requested from hospitals and attending physicians. Diagnoses of malignant or nonmalignant tumors were validated only after histopathological reports were obtained.

The biochemical techniques used to measure plasma fatty acid concentrations have been reported.[21] Briefly, plasma fatty acids were analyzed by gas-liquid chromatography with the use of a capillary column. Among the *trans*–fatty acids, only *trans* 16:1(n-7) and *trans* 18:1(n-9) were clearly identified, accurately quantified, and thus reported. Concentrations of fatty acids (measured 2 months after randomization) of cancer cases in each group were compared with those of patients who did not develop cancer (no-cancer subgroups).

An initial follow-up of 5 years was foreseen for each patient. An intermediate

analysis was performed, at the request of the Scientific Committee, after a mean follow-up of 27 months, and was published.[7] After the publication of these preliminary results, we invited all the patients still alive to come to the research unit to terminate the study, giving an extended follow-up (a mean total follow-up of about 4 years) in the 2 groups. Dietary data obtained in the 2 groups at that visit were compared with those recorded after 27 months of follow-up[7,21] to examine whether a significant between-group contamination (in particular, switching of control patients to the experimental diet) occurred after the publication of the preliminary results. In fact, slight changes were observed in the diet of the control group, but the differences between groups remained highly significant (see "Results" section).

Analyses were done on the intention-to-treat principle. For a patient who has survived an acute myocardial infarction, the most important thing is to improve life expectancy and quality of life. Results of the present study are therefore expressed as end points that combine death with cancer and recurrent infarction. The latter was included because the Mediterranean diet is thought to influence not only the occurrence of deaths and cancer but also, more surely, that of new myocardial infarction. This is actually a major point to be considered when a patient has to decide whether to adopt that diet. The Cox proportional hazards model was used to estimate the risk ratios for the following end points: cancer, total or cardiac death, combined total death and nonfatal cancer, and combined total death, nonfatal cancer, and nonfatal myocardial infarction. Adjustments were made for sex, age at baseline, smoking, total cholesterol level, blood pressure, leukocyte count, and aspirin use. These potential confounders were included because they were significant predictors in univariate analysis or because they are commonly used (age, sex, smoking) in studies analyzing cancer or cardiovascular morbidity and mortality. For each risk ratio, the 95% confidence intervals and 2-sided *P* value were calculated.

RESULTS

Patient accrual and follow-up have been reported.[7,8] During a mean follow-up of 44.9 months in the control group (n=303) and 46.7 months in the experimental group (n=302), there were a total of 38 deaths (24 in the control group and 14 in the experimental group), which included 25 cardiac deaths (19 in the control group and 6 in the experimental group). In addition, 22 patients (15 in the control group and 7 in the experimental group) developed a malignant disorder (cancer or leukemia), and 2 control patients developed either a cardiac myxoma or a pheochromocytoma. Also, 33 nonfatal acute myocardial infarctions occurred (25 in the control group and 8 in the experimental group).

Clinical characteristics of the control and experimental groups have been published, showing that at baseline the 2 groups were homogeneous.[7,8] The main baseline characteristics of cancer cases and those of the patients who were still in the study at the last visit and did not develop any cancer in the 2 groups during the follow-up are indicated in Table 1. Data for the 2 no-cancer subgroups were essentially similar to those of the 2 whole groups recorded at baseline.[7,8] Patients who developed cancer in the 2 groups included a high percentage of smokers, and patients who developed cancer in the experimental group only had low levels of high-density lipoprotein cholesterol and high levels of triglycerides. Main descriptive characteristics of the patients who developed cancer are shown in Table 2; in the control and experimental groups, respectively, there were 4 cancers and 1 cancer of the digestive tract, 4 cancers and 1 cancer of the urinary tract, 3 and 0 cancers of the throat, and 2 and 4 cases of lung cancer. After exclusion of cases diagnosed during the first 24 months after entry into the study, there were 12 cancers in the control group vs 2 in patients in the experimental group. Given the number of person-years (1383 and 1467 in the control and experimental groups, respectively), cancer rates per 100 patients per year were 1.61 and 0.72 in

the control and experimental groups, respectively. Adjusted risk ratios and 95% confidence intervals are shown in Table 3 and survival curves in Figure 1 and Figure 2.

Table 1. Baseline Characteristics of Patients Who Did and Did Not Develop Cancer*

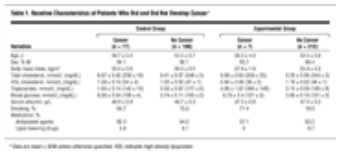

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Table 2. Characteristics of Patients Who Developed Cancer in the 2 Groups*

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	Control Group (n = 17)	Experimental Group (n = 7)
Age at diagnosis, y	63.5 ± 1.9	59.7 ± 3.5
Time between randomization and diagnosis, mo	35.8 ± 3.8	20.9 ± 4.6
Cases diagnosed after 24 mo, No.	12	2
Fatal cases, No.	4	3
Time to death after diagnosis, mo	16.0 ± 7.0	9.0 ± 3.5
Cancer site, No.		
Lung	2	4
Digestive tract	4	1
Urinary tract	4	1
Throat	3	0
Others	4	1

*Data are mean ± SEM unless otherwise noted.

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Table 3. Number of Events and Risk Ratios*

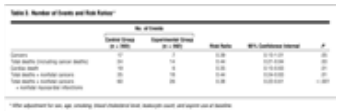

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Figure 1.

Cumulative survival without nonfatal cancer among patients in the experimental and control groups.

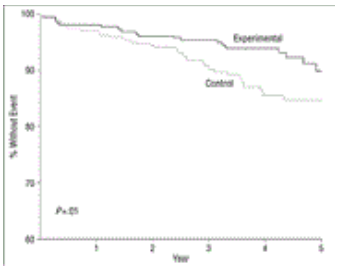

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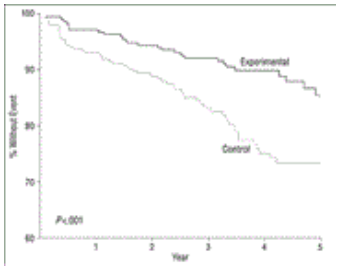
Figure 2.

Cumulative survival without nonfatal cancer and nonfatal recurrent acute myocardial infarction among patients in the experimental and control groups.



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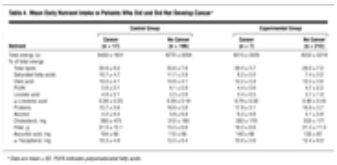
During the entire follow-up, possible sources of bias, such as tobacco use, exercise, weight, associated drug treatment, and psychosocial factors, were monitored or specifically investigated (in particular the use of lipid-lowering drugs). As previously reported, no major bias was detected.[9] In fact, the major differences between the 2 groups concerned nutrient intakes, as shown in Table 4, where data regarding patients who developed cancer in both groups are separated from those of the patients who did not subsequently develop cancer. In fact, patients who developed cancer in both groups were not distinguishable from the respective no-cancer subgroups. Results for the patients in the experimental and control groups without cancer did not bring new information (statistics not shown) compared with data of the whole groups, which have already been published.[7,21] The main statistically significant ($P<.001$) differences concerned intake of cholesterol, saturated and polyunsaturated (including linoleic acid) fat, oleic acid, and α-linolenic acid. Data also indicate that patients who developed cancer in the

experimental group actually followed the "Mediterranean advice" and consumed the experimental canola oil margarine rich in α-linolenic acid.

Table 4. Mean Daily Nutrient Intake in Patients Who Did and Did Not Develop Cancer*



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Fatty acid composition of plasma lipids in the 2 groups, evaluated 2 months after randomization, is shown in Table 5. Data for patients without cancer in both groups were similar to those previously published for the whole groups[7,21]: levels of omega-6 fatty acids were lower (*P*<.001) and those of oleic acid and omega-3 fatty acids (in particular, α-linolenic acid) were higher (*P*=.005) in the experimental group. Similar trends were observed when the cancer subgroups were compared. In cancer cases in the experimental group, α-linolenic acid (18:3 omega-3) level was high, confirming the consumption of the experimental margarine. In contrast, eicosapentanoic acid (20:5 omega-3), which is mainly derived from 18:3 omega-3 in these patients, was unexpectedly low in patients with cancer in the experimental group (*P*<.05). The only common feature of the 2 cancer subgroups was a tendency toward lower levels of the main *trans*– fatty acids with borderline nonsignificant (*P*=.06 and .07, respectively) differences when compared with their respective no-cancer subgroups (Table 5). Finally, when patients who developed cancer were pooled in a single group, comparisons with the no-cancer subgroups indicated significant differences for the sums of trans and omega-3 fatty acids (Table 6).

Table 5. Plasma Fatty Acid Composition After 2-Month Follow-up in Patients Who Did and Did Not Develop Cancer*

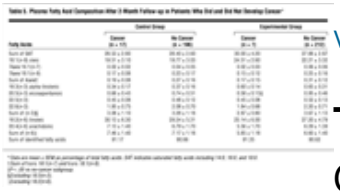

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Table 6. Significant Fatty Acid Data in Pooled Cancer Cases*

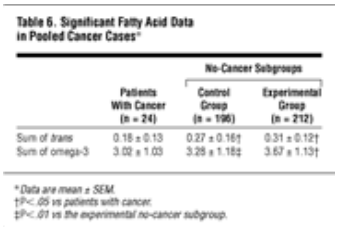

Table 6. Significant Fatty Acid Data in Pooled Cancer Cases*

	Patients With Cancer (n = 24)	No-Cancer Subgroups: Control Group (n = 196)	No-Cancer Subgroups: Experimental Group (n = 212)
Sum of *trans*	0.18 ± 0.13	0.27 ± 0.16†	0.31 ± 0.12†
Sum of omega-3	3.02 ± 1.03	3.28 ± 1.18‡	3.67 ± 1.13†

*Data are mean ± SEM.
†P<.05 vs patients with cancer.
‡P<.01 vs the experimental no-cancer subgroup.

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COMMENT

Although it was not specifically designed to study overall survival and cancer rate (the participating physicians and patients were not aware of any cancer hypothesis), this trial suggests that a Mediterranean diet rich in α-linolenic acid may favorably influence clinical manifestations of cancer, in addition to its recognized effects on CHD.[7- 9] Fewer cancers of the urinary and digestive tracts and of the throat were diagnosed in the experimental group than in the control group, and 2 tumors sometimes associated with a malignant potential or with a familial cancer syndrome[22,23] were also diagnosed in the control group. When cases diagnosed within the first 24 months after entry into the trial were excluded, the difference between groups (12 vs 2, control group vs experimental group) was still more suggestive. The addition of a potential anticancer effect and an anti-infarct effect (Figure 2) as well as the excellent long-term compliance with the experimental diet (suggesting that the patients and their families adopted this diet easily) should lead the way to further research efforts in this area. On the other hand, follow-up after the diagnosis of cancer was short and, despite the difference in the number of cancers, cancer mortality in the 2 groups was similar. Nevertheless, despite the small sample size, all-cause mortality was significantly lower in the experimental group than the control group, which is probably the most important result of

the study.

To evaluate the plausibility of the results regarding cancer rate, it is important to examine how they integrate into our present clinical and epidemiological knowledge and whether there is a biological rationale to explain them. In fact, we think that these results are not surprising for at least 2 reasons. First, the Mediterranean diet includes several nutrients (eg, fiber, natural antioxidants, and a low omega-6/omega-3 fatty acid ratio) that have been shown, when taken separately, to potentially prevent cancer initiation or spread.[11-16] Second, mortality statistics from the World Health Organization,[6] as well as previous epidemiological studies,[2] have clearly documented the low incidence of most neoplasms and the long survival of people in the Mediterranean regions, despite a high prevalence of smoking.[6] As results of migrant studies (from Mediterranean regions to the United States or Australia, for instance) did not favor a hereditary (genetic) protection, it is probably the Mediterranean way of living, in particular dietary habits, that may be protective.

This study is the first controlled dietary trial to show that such protection may be achieved in a non-Mediterranean population through a well-designed dietary intervention. Also, as the diagnosis of cancer was confirmed histologically in all cases and the 2 groups similarly followed up (with an equivalent low loss to follow-up),[7-9] it is difficult to impute the difference between groups to a better ability to detect cancer in the control than the experimental group. However, although the study has the strength of a prospective randomized trial with complete follow-up, which minimizes confounding and bias,[9] this does not completely compensate for the relatively small sample size. On the other hand, when the number of newly diagnosed cancers in the control group of this study was compared with the number of new cancers in larger and clinically comparable populations, similar data were found. For instance, in the Care and Recurrent Event study, a drug trial

in which patients with CHD were recruited who were similar to those in the present trial,[10] there were 333 newly diagnosed cancers among the 4159 patients of the placebo group (14% were women; mean age, 59 years) during a mean follow-up of 5 years. Accordingly, the expected number of new cancers among the 303 control patients of the Lyon study (10% were women; mean age, 53.5 years) during a mean follow-up of 4 years was 19. As 17 new cases were actually diagnosed in our control group, the possibility is unlikely that cancer rate in this group was overestimated and gave a spuriously reduced rate in the experimental group.

Another question is the plausibility that the Mediterranean dietary pattern can be protective against these various tumor types. Whatever the tumor type (tissue type, type of genetic mutation), most tumors take a common final pathway to grow, spread, and metastasize. This process requires a suitable local (angiogenic and inflammatory factors, for instance) and systemic (eg, immunological factors) environment. We know that this environment can be influenced by dietary changes with modifications in cell membrane fatty acid composition and cell function, as clearly shown in animal models.[15] It is likely that certain angiogenic and inflammatory factors (prostaglandin and leukotrienes, for instance) involved in the final common pathway of most cancers can be modified by the fatty acid profile that characterizes the Mediterranean diet.

Finally, among many possibilities, at least 2 biological hypotheses could be put forward to explain the present data. First, the Mediterranean diet is also characterized by large amounts of fresh vegetables and fruits providing high amounts of various natural antioxidants, which may prevent carcinogenesis.[11,24,25] Large epidemiological studies have actually shown that people who consume more beta-carotene and carotenoids have a lower risk of various cancers.[12] However, clinical trials using nonnatural antioxidant supplements were disappointing.[17-20] In the Lyon study, patients in the

experimental group consumed more vitamin C, more fiber,[7,21] and probably more trace elements and flavonoids than control patients did. The experimental group, however, consumed less polyunsaturated fats and less vitamin E, the major lipid-soluble antioxidant vitamin.[7,21] The paradoxical consequence of that in terms of plasma levels was that plasma levels of both vitamins C and E were higher in experimental patients,[7] suggesting that adoption of Mediterranean dietary habits also results in better antioxidant defenses and lower catabolism of vitamin E. This is not surprising, because the nature of the substrate for lipid peroxidation, mainly the polyunsaturated fatty acids, and not only the antioxidants, is a dominant influence in determining the rate of lipid peroxidation.[26] The importance of the fatty acid composition of lipids, in both plasma and cell membranes, in determining their susceptibility to oxidation was impressively demonstrated by recent studies comparing lipids enriched in either linoleic acid or oleic acid in animal models as well as in humans[27,28]: lipids enriched in oleic acid were remarkably resistant to oxidation. Mediterranean patients thus had fatty acid profiles in their diet and plasma extremely favorable for protecting circulating and tissue lipids against oxidation, as oleic acid level was increased, whereas linoleic acid level was decreased.[7,21] Future trials with the purpose of reinforcing antioxidant defenses to protect against cancer should take this important point into consideration.

Second, in the Lyon study, the supplementation in omega-3 fatty acid (from plant origin) resulted in higher concentrations of long-chain omega-3 fatty acids,[7,21] which are known to interfere with eicosanoid metabolism and inflammation as well as leukocyte and platelet function.[29,30] Although the link between cancer and inflammation is by no means simple,[31] it is possible that the anticancer effect shown in the Lyon trial partly resulted from the local anti-inflammatory effect of omega-3 fatty acids. This actually agrees with findings from animal models showing that diets high in omega-3 fatty acids result in diminished tumor development and a longer tumor latency

period.[15,16] In contrast, diets rich in omega-6 fatty acids (these fatty acids were significantly reduced in both the diet and plasma of the experimental patients in the present study) enhance tumor development.[15,16] Also, dietary omega-3 fatty acids have been shown in vivo in humans to down-regulate gene expression of potent carcinogenic growth factors.[32]

It is noteworthy that the 7 patients in the experimental group who developed 1 form of cancer during the trial had rather low levels of omega-3 fatty acids, even lower than those measured in the control group (Table 5), particularly of eicosapentanoic acid, the omega-3 fatty acid that competes with arachidonic acid in the cyclo-oxygenase pathway. Blockade of the cyclo-oxygenase pathway has indeed been proposed as prophylaxis against colorectal cancer.[33] As these low omega-3 fatty acid levels could not be explained by the lack of compliance with the tested diet, it is possible that these patients had specific alterations of omega-3 fatty acid metabolism that rendered them resistant to their protective influence or to that of the Mediterranean diet itself.

Although these data do not conclusively prove a protective anticancer effect of the Mediterranean diet, they should serve as an additional strong incentive to the initiation of a new kind of intervention trial testing the effect of a specific dietary pattern rather than that of single nutrients. Furthermore, it is noteworthy that both adherence to and compliance with the experimental diet were excellent in that trial,[21] suggesting that, in contrast with the classic low-fat diet to prevent CHD, adoption of such a diet should not be so difficult to obtain in high-risk patients, permitting the testing of anticancer hypotheses in the long term. Further basic studies are also needed to examine how the local lipid environment of cancer cells may influence tumor growth, as certain fatty acids or, more precisely, certain fatty acid profiles seem to be able to retard clinical manifestations of certain cancers. Unfortunately, a long time may pass before a dietary trial actually provides a clear demonstration of the anticancer effect of the Mediterranean dietary pattern. However, in light of

conjoint information given by current epidemiological data about Mediterranean populations and the present trial, in our opinion, high-risk persons should be urged to adopt the Mediterranean dietary pattern. No deleterious side effects are likely, and in view of the frequency and severity of most cancers and the cardioprotective effect of this diet, there is no convincing argument against such a prudent attitude.

ARTICLE INFORMATION

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