Review

Cancer and Mediterranean Dietary Traditions

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Abstract

The incidence of cancer overall in Mediterranean countries is lower than in Scandinavian countries, the United Kingdom, and the United States. This is mostly accounted for by the lower incidence among Mediterranean countries of cancer of the large bowel, breast, endometrium, and prostate. These forms of cancer have been linked to dietary factors, particularly low consumption of vegetables and fruit, and to a certain extent, high consumption of meat. The traditional Mediterranean diet is characterized by high consumption of foods of plant origin, relatively low consumption of red meat, and high consumption of olive oil, which in several studies has been reported to be more beneficial against cancer than other forms of added lipids. By taking into account the established or presumed nutritional causation of major forms of cancer and the composition of the traditional Mediterranean diet, estimates can be derived concerning the fraction of cancer occurrence in highly developed Western countries that could be attributed to their diets in comparison with the healthy traditional Mediterranean diet. Although estimates can only be crude, it can be calculated that up to 25% of the incidence of colorectal cancer, ~15% of the incidence of breast cancer, and ~10% of the incidence of prostate, pancreas, and endometrial cancer could be prevented if the populations of highly developed Western countries could shift to the traditional healthy Mediterranean diet.

Introduction

The purpose of this review is to examine whether Mediterranean populations are characterized by a distinct pattern of cancer occurrence and to what extent this pattern can be explained on the basis of the traditional Mediterranean diet. The review has six parts. In the first part, the nature of Mediterranean diet will be considered, and an operational definition will be given. In the second part, cancer incidence in Mediterranean countries will be presented and compared with cancer incidence in Scandinavian countries, the United Kingdom, and the United States. No attempt will be made to provide comprehensive data or detailed information; such data are available in easily accessible databases and books (1–3). In the third part, the evidence concerning analytical studies undertaken in Mediterranean countries and focusing on diet and cancer will be summarized. There is no reason to expect that a study focusing on an important component of the Mediterranean diet in relation to cancer will be more valid if it were undertaken in a Mediterranean rather than a non-Mediterranean country. There are two reasons, however, to incorporate only information from Mediterranean studies in this review: (*a*) some components of this diet, notably olive oil, are rarely consumed outside this area; and (*b*) other components of the Mediterranean diet, like vegetables, fruits, and legumes, are consumed in substantially higher quantities by substantial fractions of the population in the Mediterranean region than in northern Europe or North America. Thus, higher genuine variation is generated in the countries of the former region, so that, other things been equal, studies evaluating these factors are inherently more powerful when undertaken in Mediterranean areas.

In the fourth section, the differences in availability of particular food groups, between Mediterranean countries on the one hand and Scandinavian countries, United Kingdom and the United States on the other, will be identified, using data from the FAO[2] of the United Nations food balance sheets and cross-checked with data from household budget surveys (4–6). In the fifth section, relative risk estimates will be assigned to associations of particular cancer sites with specified intake increments of certain food groups that are thought to be linked to the corresponding cancer sites (7). Lastly, in the sixth section, an attempt will be made to estimate the fraction of the incidence of some cancer types in northern European and North American countries that could be avoided by adherence to the principles of the Mediterranean diet, taking into account, in a crude way, misclassification issues.

A note of caution is required. For many Mediterranean countries, particularly North African ones, existing data are limited or of questionable accuracy, and this hinders their utilization.

The Mediterranean Diet

The Mediterranean basin has been for millennia a crossroads of people and civilizations, and this is reflected in the culture, the scenery, the flora, and the food resources. Some plants, like the olive tree, wheat, and the grapevine, have apparently been in this area even during mythological times. Oranges and lemons, however, as well as tomatoes, eggplants, corn, rice, beans, and potatoes, were imported at different time periods. All of these, however, have found their way into the Mediterranean diet, which is the most recognized expression of a balanced ecosystem supported by the benevolent climate of this region (8, 9).

Different countries and regions in the Mediterranean basin have their own dietary traditions, but in all of them olive oil occupies a central position. From a health point of view, olive oil is important, not only because it has in itself beneficial properties (10, 11), but also because it facilitates the consump-

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[2] The abbreviation used is: FAO, Food and Agriculture Organization.

Table 1 Approximate age-adjusted (to the world population) incidence rates for selected cancer sites per 100,000 person-years, ~1990

	Stomach		Large bowel		Pancreas		Breast	Endometrium	Prostate
	Males	Females	Males	Females	Males	Females	Females		
Mediterranean	19	8	18	14	6	4	43	10	17
Scandinavian	14	7	22	18	8	6	64	13	48[a]
United Kingdom	16	6	31	22	8	6	70	10	30[a]
United States	8	3	37	26	8	6	90	18	100[a]

[a] The large variation reflects different rates of application of screening for prostate-specific antigen.

tion of large quantities of vegetables and legumes in the form of raw salads and cooked foods. Without the presumption of a scientific definition, the Mediterranean diet could be considered as the dietary pattern found in the olive oil-growing areas of the Mediterranean region in the late 1950s and early 1960 s, before the invasion of the fast food culture in the area. Beyond olives and olive oil, the Mediterranean diet is also characterized by the consumption of wheat, grapes, and their derivative products. Total lipid intake may be high, ~40% of total energy intake as in Greece, or moderate, ~30% of total energy intake as in Italy, but in all instances the ratio of monounsaturated:saturated dietary lipids is much higher than in other places of the world, notably northern Europe and North America. In Italy, pasta is consumed in high quantities, whereas in Spain and Portugal (an "adopted" Mediterranean country), fish consumption is particularly high. This review has a small bias toward the Greek variant of the Mediterranean diet for three unimportant reasons: Greeks have been in the area longer than other Mediterranean peoples, the early studies that pointed to the beneficial effects of the Mediterranean diet were largely based in Greece, and we are more familiar with the Greek data which, however, convey messages similar to those suggested by data from other Mediterranean countries (9).

Overall, the traditional Mediterranean diet may be thought of as having eight components: 1, high monounsaturated:saturated fat ratio; 2, moderate ethanol consumption; 3, high consumption of legumes; 4, high consumption of cereals (particularly bread); 5, high consumption of fruits; 6, high consumption of vegetables; 7, low consumption of meat and meat products; and 8, moderate consumption of milk and dairy products. A diet that has all of the characteristics of the Mediterranean should, thus, take a score of 8, whereas a diet with none of these characteristics should take a score of 0. High and low values in each of the eight components can be quantified in more detail and expressed as fractions of a unit (12, 13). A linear score is necessary for the operationalization of Mediterranean diet and its evaluation as an integral entity in epidemiological investigations (see below).

In the Mediterranean diet, meals are usually accompanied by large quantities of whole grain bread. Legumes and vegetables are consumed in large amounts in cooked dishes, soups, and salads prepared with olive oil. Intake of milk is moderate, but consumption of cheese and, to a lesser extent, yogurt is high; feta cheese is regularly added to most salads and vegetable stews. Meat, being expensive, used to be rarely consumed, whereas fish consumption was a function of proximity to the sea. Wine is consumed in moderation and almost always during meals. The high content in the diet of vegetables, fresh fruits, and cereals and the liberal use of olive oil guarantees a high intake of vitamin C, tocopherols, β-carotene, various important minerals, and several possibly beneficial nonnutrient substances, such as polyphenols and anthocyanines (14).

Cancer Incidence in the Mediterranean and Other Economically Developed Countries

Cancer incidence data are very reliable in the Scandinavian countries and reasonably reliable in the United Kingdom and the United States. In contrast, cancer registration in the Mediterranean countries is not always satisfactory. We have considered using mortality statistics, as was done by Doll and Peto (15) for the United States some 20 years ago. Efficiency of therapeutic care, however, is likely to be different in the various countries, so that mortality rates would reflect variability not only in incidence but also in fatality rates. Incidence data, on the other hand, can also reflect intensity of screening as is evident in the highly variable incidence rates of prostate cancer in the United Kingdom and the United States, notwithstanding the similarity of mortality rates in these countries.

Table 1 shows approximate age-adjusted (to the world population) incidence rates for selected cancer sites per 100,000 person-years, ~1990, in the Mediterranean and Scandinavian regions, as well as for the United Kingdom and the United States. The Mediterranean data may overestimate actual rates, because regional registries exist in the more developed regions that are usually characterized by higher cancer rates. On the other hand, data from the Scandinavian region do not include Denmark, because of cancer site classification incompatibilities. We did not include in this table cancers for which a nonnutritional factor of overriding etiological importance has been identified.

Nutritional Etiology of Cancer

The nutritional etiology of various forms of cancer has been evaluated in a report by the Harvard Center for Cancer Prevention, which was summarized by Willett and Trichopoulos (16) and, more recently, in an extensive and detailed report by the World Cancer Research Fund and the American Institute for Cancer Prevention (7). In Table 2, we have tried to integrate the collective evidence concerning diet in relation to cancer, taking into account these two reviews and other published information.

We have also reviewed, in some detail, over 100 case-control studies, undertaken in Mediterranean countries, that have evaluated the association of major food groups, added lipids, and alcohol with various forms of cancer. Relevant results from major cohort studies have not yet been reported. The objective was to assess whether the evidence derived from studies conducted in Mediterranean populations is compatible with the existing overall evidence (7, 16–18). In Table 3, we summarize the evidence linking each of the components of the Mediterranean diet with cancer sites considered to be nutrition related. In the cells of the table, we indicate the type of the association most frequently reported in the Mediterranean case-control studies out of the total number of such studies that have

Table 2 Risk implications for major forms of cancer by consumption of major food groups, macronutrient intake, exposure to selected nonnutrients, and nutrition-related indicators[a]

	Oral cavity	Nasopharynx	Esophagus	Stomach	Large bowel	Liver	Pancreas	Larynx	Lung	Breast	Endometrium	Cervix uteri	Prostate	Urinary bladder	Kidney
Major food groups															
Vegetables	**Reduce**		**Reduce**	**Reduce**	**Reduce**	Reduce	Reduce	**Reduce**	**Reduce**	Reduce	Reduce	Reduce	Reduce	**Reduce**	Reduce
Fruits	**Reduce**		**Reduce**	**Reduce**	Reduce		Reduce	**Reduce**	Reduce	Reduce	Reduce	Reduce		Reduce	
Red meat					**Increase**		Increase								
Macronutrients															
Protein (animal)					Increase										
Fiber					Reduce		Reduce								
Saturated fat					Increase				Increase		Increase		Increase		Increase
Monounsaturated										Reduce					
Nonnutrients															
Alcohol	**Increase**		**Increase**		Increase	**Increase**		**Increase**		Increase					
Salt		Increase		**Increase**											
Nutritional covariates															
Height					Increase					**Increase**					
Obesity					Increase					Dual	**Increase**				Increase
Physical activity					**Reduce**					Reduce			Reduce		
Hot drinks			Increase												

[a] Sources: Willett and Trichopoulos (16) and World Cancer Research Fund and American Institute for Cancer Prevention (7). Bold type indicates that data are convincing.

specifically examined the corresponding association. Thus, a moderately inverse association between vegetable intake and breast cancer was found in 8 of the 10 studies that have explicitly investigated this issue.

The patterns evident in Tables 2 and 3 are largely compatible. This is not unexpected, because a considerable amount of information concerning diet in relation to cancer has come from studies undertaken in Mediterranean countries (7, 16).

Importance of Selected Food Groups in Mediterranean and Non-Mediterranean Countries

In Table 4, availability of the food entities that correspond to the eight components of the Mediterranean diet is shown for the countries under consideration. These data are compiled and provided by the FAO of the United Nations, and their reliability has been challenged (19), mainly because they refer to availability rather than consumption. It is also true that the alcohol data are not directly interpretable, because ethanol content is much lower in beer and wine than in spirits, and yet the data refer to the quantity of alcoholic beverages, irrespectively of the specific type. The data are given for the early 1960 s and the early 1990 s. For cancer occurrence in 1990, food availability in the 1960s is more relevant than food availability in the 1990s, because the latency of most cancers is expressed in decades, even when the etiological factors under consideration are growth enhancers, rather than cancer initiators. Data from household budget surveys represent an independent resource information on food availability and have also been used for international comparisons (5, 6). Nevertheless, the FAO data (food balance sheets) are better known and more widely used.

It is obvious from the data that, in an ecological context, the dietary pattern in the Mediterranean countries in the 1960 s was close to the pattern recommended currently. With the exception of stomach cancer, there is a general concordance between the availability rankings of the crucial food groups (Table 4) and the incidence rankings of the forms of cancer under consideration (Table 1). The high incidence of stomach cancer in the Mediterranean countries has been attributed to the high salt intake of the Mediterranean peoples and the generally early infection by *Helicobacter pylori*. The data in the lower panel of Table 4 reflect the gradual loss of the advantage of the Mediterranean countries for several common forms of cancer as dietary habits become less traditional.

Quantification of the Association of Specific Forms of Cancer with Particular Food Groups

It is theoretically possible to calculate how much a one-unit increment in the Mediterranean diet score can affect the incidence of any particular cancer or indeed any particular disease with known or presumed nutritional etiology (12, 13, 20). This process, however, has only been applied with respect to total mortality, for which a one-unit increase in the Mediterranean diet score has been found to be associated with an about 17% reduction in overall mortality among elderly (13, 20–22). Moreover, if the diet score were calculated in representative samples of two different populations, it would be possible to estimate what fraction of the difference in the incidence of a particular cancer or other disease could be explained by the difference in the degree of their adherence to the traditional Mediterranean diet (or, indeed, any diet that has been operationalized so as to be expressed in terms of a linear score). Such a shift, however, from analytical epidemiological studies to comparisons between populations requires correction of the

Table 3 Associations of the eight component characteristics of the Mediterranean diet with selected cancer sites, as ascertained in case-control studies undertaken in Mediterranean populations[a]

	Stomach	Large bowel	Pancreas	Breast	Endometrium	Prostate
Fruits	Strongly inverse 12/14	Weakly inverse 4/6	Weakly inverse 3/4	Weakly inverse 3/4	Weakly inverse 3/4	NE[b]
Vegetables	Strongly inverse 14/16	Moderately inverse 8/11	Weakly inverse 2/3	Weakly inverse 8/10	Weakly inverse 4/5	Weakly inverse 3/5
Legumes	NE	Weakly inverse 2/3	NE	Weakly inverse 1/2	NE	NE
Cereals	NE	NE	NE	Weakly inverse 2/4	Weakly inverse 2/4	NE
Meat	Weakly positive 5/9	Moderately positive 9/13	Weakly positive 3/4	Weakly positive 4/7	NE	NE
Dairy products	NE	Weakly positive 2/3	NE	NE	NE	Weakly positive 3/5
Monounsaturated:saturated lipid ratio	NE	Weakly inverse 3/6	NE	Weakly inverse 7/11	Weakly inverse 2/2	Weakly inverse 4/6
Alcohol	Weakly positive 10/13	NE	NE	Moderately positive 8/11	NE	NE

[a] In each cell, the direction and strength of the association is indicated, together with the number of studies that pointed to that direction out of the total that have adequately examined the particular association. Cancers for which a nonnutritional factor of overriding etiological importance has been identified, have not been included in the table (oral cavity, larynx, lung, and urinary bladder excluded because of the effects of smoking; hepatocellular carcinoma and cervix uteri excluded because of the effects of viral etiology; ovarian cancer excluded because of the effects of oral contraceptives and reproductive factors).
[b] NE, no evident association.

Table 4 Mean per capita availability (in g per day) of selected food groups and ratio of monounsaturated:saturated in added[a] lipids (M/S) in the Mediterranean and Scandinavian countries, the United Kingdom, and the United States in the early 1960s and early 1990s[b]

	Fruits	Vegetables	Legumes	Cereals	Meat	Dairy products	M/S	Alcoholic beverages
1960s								
Mediterranean	261	318	17	411	100	352	1.88	271
Scandinavian	149	92	4	288	121	827	0.16	86
United Kingdom	154	163	8	299	201	628	0.01	252
United States	253	240	10	247	260	734	0.01	188
1990s								
Mediterranean	362	471	14	360	237	588	1.29	287
Scandinavian	270	163	3	270	166	865	0.27	206
United Kingdom	212	226	15	261	207	639	0.59	340
United States	406	318	9	312	327	685	0.17	312

[a] These do not contain lipids integral to foods.
[b] Source: WHO (4).

relative risk estimates for the unavoidable nondifferential misclassification in the reporting of dietary intakes in case-control or cohort studies (23).

Correction for nondifferential dietary misclassification of the relative risk for a particular cancer per increment of intake of a specific nutritional variable is essential in every attempt to explain the difference in the incidence of this cancer between two populations with known mean intakes of the respective nutritional variable. When the misclassification generates values associated with the real values with a correlation coefficient of +0.6 (which is usual in good studies), a relative risk of 2, should be corrected to 3.2 and a relative risk of 2.5 should be corrected to 4.6 (23). As indicated, this approach is not only theoretically feasible but also very easy to implement, unless powerful confounding among dietary variables is present. The data required, however, are not routinely published in sufficient detail in the scientific literature.

In nutritional epidemiology, when subjects are divided into quintiles, a weak empirical association corresponds to a relative risk between the extreme quintiles of ~1.5 (or 0.67), a moderate empirical association to a relative risk of ~2 (or 0.5) and a strong empirical association to a relative risk of ~2.5 (or 0.4). These figures could be substituted for the descriptive statements in the body of Table 3, if desirable.

Could Diet Explain the Low Incidence of Certain Forms of Cancer in the Mediterranean Region?

Available data do not allow answering this question directly and quantitatively, and only estimates are possible. The easiest way to generate these estimates is by using a straightforward formula suggested by Wahrendorf (24). Suppose that between the extreme quintiles of the Mediterranean diet score the relative risk for colorectal cancer is ~7, an estimate compatible with empirical information (24, 25). This means that between people consuming low quantities of vegetables and fruits and high quantities of red meat and similar foods, and those who consume high quantities of vegetables and fruits and low quantities of red meat and similar foods, the relative risk is ~7. Suppose further that only 3% of the populations in Mediterranean regions have the very unfavorable combination of consuming very few foods of plant origin and a substantial amount of red meat, as compared with 20% of populations in Western countries, whereas 37% of Mediterranean populations and 20%

of Western populations have the very favorable combination of consuming a substantial amount of foods of plant origin and very little red meat. The remaining 60% in both populations would be equally distributed in the in-between categories. The data in Table 4 are compatible with this pattern (4). Finally, assume that risk for colorectal cancer increases linearly as Mediterranean diet score worsens. This means that people of major developed countries could reduce their incidence of colorectal cancer by ~25% by switching from a Western diet (weighted relative risk calculated by summing the products of the fraction of the population in each quintile of Mediterranean diet score with the relative risk of colorectal cancer for the quintile = 0.2*1 + 0.2*2.5 + 0.2*4.0 + 0.2*5.5 + 0.2*7 = 4.00) to a Mediterranean diet (weighted relative risk = 0.37*1 + 0.2*2.5 + 0.2*4.0 + 0.2*5.5 + 0.03*7 = 2.98).

Similarly, on the basis of the data in Tables 1, 3, and 4, one could conclude that adherence to the principles of the Mediterranean diet by the people of major developed countries could reduce their higher incidence of breast cancer by ~15% (seven dietary risk factors, but all of them weak; the only exception is alcohol, which is, however, also common in the Mediterranean diet), could reduced their higher incidence of prostate cancer by <10% (three dietary risk factors, all of them weak), and could reduced their relatively low incidence of cancers of the pancreas and the endometrium by <10% (three or four dietary risk factors, all of them weak).

In conclusion, the Mediterranean diet could reduce the overall incidence of cancer in northern Europe and North America by up to 10%. It should be noted, however, that the most recognizable effects of the Mediterranean diet concern cardiovascular diseases (10), a topic that is beyond the scope of this review.

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