Association Between the Mediterranean Diet and Cancer Risk: A Review of Observational Studies

Lisa Verberne
Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain and Wageningen University, Division of Human Nutrition, Wageningen, Netherlands

Anna Bach-Faig
Mediterranean Diet Foundation, Barcelona, Spain

Genevieve Buckland
Unit of Nutrition, Environment, and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain

Lluís Serra-Majem
Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain and Mediterranean Diet Foundation, Barcelona, Spain

INTRODUCTION

Cancer is currently one of the most important public health issues; each year approximately 11 million new cases of cancer and almost 7 million cancer deaths are recorded globally, and projections expect this to double by 2030 (1). Despite the heavy global cancer burden, few cancers are due to an inherited high susceptibility, and environmental factors (that are largely modifiable) play a major role in the cancer etiology. As a consequence, a large proportion of cancers are in principle preventable.

Historically, the incidence of overall cancer was lower in Mediterranean countries compared to northern European countries, the United Kingdom, and the United States (2). This difference has been linked to the Mediterranean food pattern consumed in the Mediterranean countries. Although there are variations in the components of the traditional Mediterranean diet (MD) between and within countries, the diet is generally characterized by abundant plant foods (fruit, vegetables, cereals, potatoes, beans, nuts, and seeds); fresh fruit as the typical daily dessert; olive oil as the principal source of fat; dairy products (principally cheese and yogurt); fish, poultry, and eggs consumed in low to moderate amounts; red meat consumed in low amounts; and wine consumed in low to moderate amounts, normally with meals. As a result, this dietary pattern is low in saturated fat (less than or equal to 7–8% of energy), with total fat ranging from <25% to >35% of energy throughout the Mediterranean region (3).

The classic reductionist approach of studying individual foods or nutrients has been limited by the fact that food...
components are not consumed in isolation, and their health effects are often synergistic (4). As a result, it has been difficult to isolate their individual health benefits. Therefore, in the past two decades, scientists have started focusing on measuring multiple dietary exposures simultaneously, such as the health benefits of the MD as a prudent dietary pattern. (4). Component and cluster analysis (5) and many a priori MD indexes (6) have been used to study the relationship between the MD pattern and health parameters such as mortality or chronic disease risk relationships. Most of the studies have used a priori indexes or scores that are conceptually similar to define and evaluate the adherence to the MD pattern among the study populations.

There has been a decrease in the adherence to the MD in Mediterranean countries in the past half century (7) as well as an increase in sedentary lifestyles among other lifestyle factor changes. It is not clear how these changing dietary and lifestyle patterns could influence cancer risk of these areas.

In addition, it is difficult to study the health effects of the MD, since it is not only a dietary pattern but also represents a way of life and a cultural model. It is also difficult to separate out the specific effect of a single component of the MD in relation to a disease. There is increasing epidemiological evidence of the health benefits of the MD, which have been summarized in several literature reviews (8–12). Although the MD is historically most famous for its cardio-protective effect, there is increasing research on its relationship with cancer. This article will systematically review observational studies that assess the adherence to a MD as a single exposure in relation to risk of cancer.

No isolated study or study type can provide evidence that any factor is a cause of, or is protective against, any disease (1). Thus, as the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) state, the causation of diseases can be more accurately deduced if they are based on a variety of epidemiological studies. In order to objectively evaluate diet–cancer risk relationships, systematic reviews such as this are needed, and they should be used to provide evidence-based dietary guidelines that support public health recommendations and policies.

METHODS

The literature review focused on observational studies that have investigated the association between adherence to a MD and cancer. A systematic search was conducted in PubMed and
<table>
<thead>
<tr>
<th>Author/Year of Publication</th>
<th>Country/Study Population</th>
<th>Sex</th>
<th>Age at Entry</th>
<th>Follow-up</th>
<th>Cases/Total</th>
<th>MD Definition (components)</th>
<th>Outcome</th>
<th>Results</th>
<th>Adjustments</th>
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<tbody>
<tr>
<td>Knoops et al. 2004 (13)</td>
<td>Belgium, Denmark, France, Greece, Hungary, Italy, the Netherlands, Portugal, Spain, Switzerland, Finland; HALE project</td>
<td>M/F</td>
<td>70–90 yr</td>
<td>10 yr</td>
<td>233/2,152</td>
<td>8 items MDS (c): 1. MUFA/SFA. 2. Legumes, nuts, and seeds. 3. Grains. 4. Fruit. 5. Vegetables and potatoes. 8. Fish. (−): 6. Meat. 7. Dairy.</td>
<td>Overall cancer mortality</td>
<td>-HR of adhering to a MD (≥4 points): 0.90 (95% CI = 0.70–1.17)</td>
<td>OH, PA, smoking, age, sex, years of education, BMI, study, region, center, occupation, waist circumference, marital status, and energy intake.</td>
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<tr>
<td>Fung et al. 2006 (14)</td>
<td>United States; Nurses Health Study</td>
<td>F</td>
<td>30–55 yr</td>
<td>18 yr</td>
<td>3,580/71,058</td>
<td>9-item MDS (c): 1. Vegetable (without potatoes). 2. Legumes. 3. Fruit. 4. Nuts. 5. Whole grain cereals. 6. MUFA/SFA. 7. Fish. (−): 8. Red and processed meat (−m). 9. OH.</td>
<td>Breast cancer risk (postmenopausal)</td>
<td>ER+: RR of Q5 vs. Q1: 1.05 (95% CI = 0.91–1.18), P for trend = 0.23 –ER−: RR.</td>
<td>Age, BMI, PA, age at menopause, hormone therapy, smoking, energy intake, family history, weight change since age 18 yr, supplement use, history of benign breast disease.</td>
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<td>Lagiou et al. 2006 (15)</td>
<td>Sweden; Uppsala Health Care Region</td>
<td>F</td>
<td>30–49 yr</td>
<td>12 yr</td>
<td>280/42,237</td>
<td>9-items MDS (c): 1. Vegetables. 2. Legumes. 3. Fruits and nuts. 4. Cereals. 5. Fish and seafood. 6. MUFA/SFA. 7. Fish. 8. Dairy (−m). 9. OH.</td>
<td>Overall cancer mortality; main cancers: breast and lung</td>
<td>-HR of high vs. low MDS: 0.80 (95% CI = 0.57–1.13), P = 0.20 For a 2 point increase in score: Subjects &lt;40 yr: T3 vs. T1 1.07 (95% CI = 0.79–1.43) –Subjects ≥40 yr: T3 vs. T1 0.84 (95% CI = 0.71–1.01)</td>
<td>Age at enrolment, height, BMI, smoking, PA, education, energy intake, potato intake, egg intake, polyunsaturated lipid intake, sweet and sugar intake, nonalcoholic beverage intake</td>
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<td>Benetou et al. 2008 (17)</td>
<td>Greece; EPIC study</td>
<td>M/F</td>
<td>20–86 yr</td>
<td>7.9 yr</td>
<td>851/25,623</td>
<td>9-items MDS (c): 1. Vegetables. 2. Legumes. 3. Fruits and nuts. 4. Cereals. 5. Fish. (−): 6. MUFA/SFA. (−): 7. Meat. 8. Dairy. (−m): 9. OH.</td>
<td>Overall cancer incidence (nonmelanoma skin cancer excluded). Main cancers: –Men: Lung and prostate –Women: Breast and large bowel</td>
<td>-HR of high vs. low MDS: Total: 0.78 (95% CI = 0.64–0.94) –Men: 0.83 (95% CI = 0.63–1.09) –Women: 0.73 (95% CI = 0.56–0.96)</td>
<td>Age, years of education, smoking, BMI, height, PA, supplement use, total energy intake, consumption of eggs, confectionary, and nonalcoholic beverages</td>
</tr>
<tr>
<td>Study</td>
<td>Country/Region</td>
<td>Gender</td>
<td>Age Range</td>
<td>Duration</td>
<td>Cases/Total</td>
<td>Mediterranean Diet Score</td>
<td>Dietary Components</td>
<td>Disease</td>
<td>RR/Q1 vs Q5 (95% CI)</td>
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| Reedy et al. 2008     | United States; NIH AARP Diet and Health Study       | M/F    | 50–71 yr  | 5 yr     | 3,110/492,382 | 9-items MDS<sup>b</sup>; (+); 1. Whole grains. 2. Vegetables. 3. Fruit. 4. Fish. 5. Legumes. 6. Nuts. (-); 7. MUFA/SFA. 8. Red meat and processed (+m); 9. OH. | Colorectal cancer                      | -Men: 0.72 (0.63–0.83)  
Women: 0.89 (0.72–1.11) |            |            | Age, ethnicity, education, BMI, smoking, PA, menopausal hormone therapy, and energy intake |
| Buckand et al. 2009   | Europe (United Kingdom, France, Denmark, Sweden, Germany, Italy, Spain, The Netherlands, Norway, Greece) | M/F    | 35–70 yr  | 8.9 yr   | 449/485,044  | 9-item MDS<sup>d</sup>; (+); 1. Fruit, nuts, and seeds. 2. Vegetables (without potatoes). 3. Legumes. 4. Fish and seafood (fresh or frozen, excluding fish products and preserved fish). 5. Cereals. 6. Olive oil. (-); 7. Meat. 8. Dairy. (+m); 9. OH. | Gastric adenocarcinoma Subsites: Cardia, noncardia Subtypes: Intestinal and diffuse | -HR of high vs. low MDS: 0.67 (0.47–0.94),  
P = 0.020. No evidence of heterogeneity between subsites or subtypes. |            |            | Age, center (strata), sex, BMI, education level, smoking, energy intake |

<sup>a</sup>Abbreviations are as follows: MD, Mediterranean Diet; M, male; F, female; MDS, Mediterranean Diet Score created by Trichopoulou et al. (<sup>b</sup>) and variations of it (<sup>c</sup>d and <sup>e</sup>); MUFA/SFA, ratio of monounsaturated to saturated fat; Meat, meat and meat products; Dairy, milk and dairy products; (+), positive components; (-), negative components; (+m), components positive in moderation; HR, hazard ratio; OH, alcohol consumption; PA, physical activity; CI, confidence interval; BMI, body mass index; P, P for trend; ER+, estrogen receptor positive, ER–, estrogen receptor negative; RR, relative risk; Q: quartile; T, tertile; AARP, American Association of Retired Persons; EPIC, European Prospective Investigation into Cancer.
<table>
<thead>
<tr>
<th>Author/Year of Publication</th>
<th>Country</th>
<th>Sex</th>
<th>Age</th>
<th>Cases/Controls</th>
<th>MD Definition (components)</th>
<th>Cancer Outcome</th>
<th>Results</th>
<th>Adjustments</th>
</tr>
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<tbody>
<tr>
<td>Bosetti et al. 2003 (20)</td>
<td>Italy</td>
<td>1. M/F; 2. M/F; 3. M/F</td>
<td>1. &lt;78 yr (median age: 57 yr); 2. &lt;77 yr (median age: 60 yr); 3. &lt;79 yr (median age: 61 yr)</td>
<td>1. 598/1,491; 2. 304/743; 3. 460/1,088</td>
<td>8-item MDS&lt;sup&gt;b&lt;/sup&gt;: (+): 1. MUFA/SFA, 2. Cereals, 3. Legumes, 4. Fruits, 5. Vegetables, 6. Fish, 7. Meat, 8. Dairy, (+m): 8. OH.</td>
<td>1. Oral/pharyngeal cancer; 2. Esophageal cancer; 3. Laryngeal cancer</td>
<td>- With 1 point increase MDS: 1. OR = 0.77 (95% CI = 0.71–0.83), 2. OR = 0.72 (95% CI = 0.65–0.81), 3. OR = 0.71 (95% CI = 0.65–0.78), P &lt; 0.001.</td>
<td>Age, sex, study center, education, smoking, BMI, total energy intake</td>
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<tr>
<td>Dalvi et al. 2007 (21)</td>
<td>United States F</td>
<td>35–79 yr</td>
<td>488/461</td>
<td>9-item MDS&lt;sup&gt;b&lt;/sup&gt;: (+): 1. MUFA/SFA, 2. Grains, 3. Legumes, 4. Fruits, 5. Vegetables, 6. Fish, 7. Meat, 8. Dairy, 9. OH</td>
<td>Endometrial cancer</td>
<td>OR for a modified scoring method based on the 3 indexes, for the Q5 vs. Q1: 0.92 (95% CI = 0.59–1.4)</td>
<td>Age, race/ethnicity, use of oral contraceptives, parity, energy intake, PA, use of hormone therapy, BMI</td>
<td></td>
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<tr>
<td>Wu et al. 2009 (22)</td>
<td>United States, Asian Americans F</td>
<td>25–74 yr</td>
<td>1,248/1,148</td>
<td>10-item MDS&lt;sup&gt;c&lt;/sup&gt;: (+): 1. Vegetables, 2. Legumes, 3. Fruit/nuts, 4. Cereals, 5. Fish and seafood, 6. MUFA/SFA, 7. Meat, 8. Dairy, 9. Carbohydrates, 10. OH</td>
<td>Incident breast cancer</td>
<td>RR of scoring ≥8 vs. 0–3: 0.65 (95% CI = 0.44–0.95), P = 0.009, RR = 0.7 (0.48–1.04), P trend = 0.033 after fully adjustment</td>
<td>Age, specific ethnicity, education, birthplace, years of residence in the United States, PA, marital status, parity, age at menarche, type of menopause, age at menopause, BMI and energy intake</td>
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<tr>
<td>Murtaugh et al. 2008 (23)</td>
<td>United States; The Four Corners Breast Cancer F</td>
<td>25–79 yr</td>
<td>Hispanic: 757/867; non-Hispanic: 1,524/1,598</td>
<td>Via factor analysis: MD pattern included high factor loadings for liquor consumption, poultry, seafood, vegetables, salad greens, and high-fat salad dressings.</td>
<td>Breast cancer</td>
<td>OR of Q4 vs. Q1 = 0.76 (95% CI = 0.63–0.92), P trend &lt; 0.01</td>
<td>Age, medical center, education, ethnicity, menopausal status, family history, smoking, total activity, energy intake, dietary fiber, dietary calcium, height, parity, BMI, Hormone exposure Center, age, energy intake, ethnic origin, education, BMI, PA, smoking, aspirin use, furosemide use, calcium supplement use, and hormone replacement therapy</td>
<td></td>
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<tr>
<td>Dixon et al. 2007 (24)</td>
<td>United States; The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial M/F</td>
<td>55–74 yr</td>
<td>3,592/3,397</td>
<td>8-item MDS&lt;sup&gt;b&lt;/sup&gt;: (+): 1. Vegetables, 2. Legumes, 3. Fruit and nut, 4. Cereals, 5. Fish, 6. MUFA/SFA, 7. Meat, 8. Dairy, (+m): 8. OH.</td>
<td>Distal colorectal adenoma</td>
<td>–OR of high MD adherence (≥6 points) vs. low (&lt;2 points): –Men: 0.79 (95% CI = 0.68–0.92), P trend &lt; 0.001; –Women: 0.99 (95% CI = 0.81–1.23), P trend = 0.302</td>
<td>Center, age, energy intake, ethnic origin, education, BMI, PA, smoking, aspirin use, furosemide use, calcium supplement use, and hormone replacement therapy</td>
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<sup>a</sup>Abbreviations are as follows: MD, Mediterranean diet; M, male; F, female; MDS, Mediterranean Diet Score created by Trichopoulou et al. (<sup>b</sup>) and variations of it (<sup>c</sup>); (+), positive components; MUFA/SFA, ratio of monounsaturated to saturated fat; (−), negative components; Meat, meat and meat products; Dairy, milk and dairy products; (+m), components positive in moderation; OH, alcohol consumption; OR, odds ratio; CI, confidence interval; BMI, body mass index; Q, quartile; PA, physical activity; RR, relative risk.
ious modifications were made. In the studies of Fung et al. (14), the adherence to the MD applying the Trichopoulou et al. (25) criteria (13–24). The studies were classified as cohort (13–19) or case-control (20–24) studies. The methodology and the results of the studies have been detailed in Tables 1 and 2: characteristics of study sample (country of origin, age, gender, and size of the sample), length of follow-up (in cohorts), definition of the MD (components), and confounding variables.

RESULTS

Study Characteristics

A total of 12 studies were identified that met all the search criteria (13–24). The studies were classified as cohort (13–19) or case-control (20–24) studies. The methodology and the results of the studies are summarized in Table 1 and Table 2. All studies were published between 2003 and 2009. Most of the studies were carried out in non-Mediterranean populations despite the fact that the main exposure of interest was the Mediterranean-like dietary pattern. In fact, most of the studies (7 studies) were from the United States. Two studies were conducted in Mediterranean countries—in Greece and in Italy (17,20). The study by Bosetti et al. (20) conducted in Italy included 3 different case-control studies. Three studies were carried out in Sweden (15) or in several European countries including Mediterranean countries (13,19). In total, 5 studies were conducted in females only and 7 in men and women of which 2 studies showed the results for men and women separately.

Definition of the MD

Almost all cohort studies included in this review assessed the adherence to the MD applying the Trichopoulou et al. (25) Mediterranean diet score (MDS), although in some studies, various modifications were made. In the studies of Fung et al. (14), Buckland et al. (19), and Mitrou et al. (16), potatoes were excluded from vegetable intake. Knoops et al. (13) combined the group of legumes and nuts to one group, and Buckland et al. (19) used tetriles as cut-offs instead of medians and olive oil instead of the dietary lipid ratio.

The case-control studies have used different methods to assess the adherence to the MD. Bosetti et al. (20), Dalvi et al. (21), Dixon et al. (24), and Wu et al. (22) used the key components of the definition of Trichopoulou et al. (25), although with some modifications. For instance, Bosetti et al. (20) only used 8 items, excluding fish. Dalvi et al. (21) added some components such as olive oil, eggs, sweets, and poultry, and Wu et al. (22) incorporated a low consumption of carbohydrates as a detrimental component.

Generally, most of these dietary indexes are based on assigning a score according to the daily intake of the components. The medians of the sample, specific for sex, were used as cut-off points in most of the studies (25). For beneficial components presumed to fit the traditional MD (vegetables, legumes, fruits and nuts, cereal, fish, etc.), subjects whose consumption was below the median were assigned a value of “0,” and subjects whose consumption was at or above the median were assigned a value of “1.” The scoring was inverted for components presumed to be detrimental and not fit the MD pattern (meat and meat products and dairy products). For ethanol, a value of “1” was commonly assigned to moderate consumption. In general, healthy intervals were defined as 10 and 50 g/day for men and 10 and 25 g/day for women. Finally, in general, for lipid intake, a value of “1” was assigned to individuals with a monounsaturated to saturated lipids ratio at or above the median.

Main Outcomes

Out of the cohort studies, 4 studies assessed overall cancer (13,15–17), and 3 studies looked specifically at breast (14), gastric (19), and colorectal (18) cancers. In the Nurses’ Health study, no significant association of the MD and postmenopausal breast cancer risk was found (18). However, when the analyses were separated into estrogen receptor positive and negative tumors, there appeared to be a 7% reduction in breast cancer risk (P = 0.02) for an increase of 10% in the MD score in the receptor negative tumor group. In the European Prospective Investigation into Cancer (EPIC) study, a high compared to a low MD score was associated with a 33% reduction [95% confidence interval (CI) of 6–53%] in gastric adenocarcinoma (19). In a cohort study set in the United States (18), a 28% reduced risk of colorectal cancer was observed in men who consumed a more Mediterranean-like dietary pattern.

Two out of the four cohort studies that looked at overall cancer found a significant inverse association with the MD (16,17). A 2-point increase in the MDS resulted in a significant reduction in overall cancer incidence by 12% in the Greek EPIC cohort (17) and by 6% in men in the National Institute of Health study in the United States (16). In an earlier study in the Greek EPIC cohort, a 2-point increase in the MD score was associated with
a 24% reduction in overall cancer mortality, with a 95% CI of 2–41%. The 2 other cohort studies that assessed overall cancer mortality did not find significant results, but some borderline or partial evidence (within subgroups) was observed (13,15). For instance, among women less than 40 yr old at enrollment, there was no association of the MD with cancer mortality, mainly focusing on breast and lung cancer (15). However, among women 40 to 49 yr old at enrolment who were followed up for approximately 12 yr, a 2-point increase in the MD score was associated with reduced mortality from cancer of 16% (95% CI = −1 to 29%) (15). In the European HALE study (13), the MD did not significantly reduce overall cancer mortality. However, the effect of the MD together with a healthy lifestyle [(moderate alcohol consumption, nonsmoking, and being physically active)] was inversely related to cancer mortality even at ages 70 to 90 yr (HR \( = 0.31 \) (95% CI = 0.19–0.50)).

The cancer outcomes of the case-control studies were breast, endometrial, oral/pharyngeal, esophageal, colorectal, and laryngeal cancer. The 3 case-control studies from Italy (20) found strong significant inverse associations between the MD and 3 upper aero-digestive tract cancers. A 1-point increase in the MDS was associated with a reduced risk of oropharyngeal, esophageal, and laryngeal cancer by 23% (95% CI = 17–29%), 28% (95% CI = 19–35%), and 29% (95% CI = 22–35%), respectively.

For colorectal cancer, a case-control study (24) found that following the current U.S. dietary recommendations or a Mediterranean dietary pattern was associated with a 21% reduced risk in men.

The 2 case-control studies on breast cancer found a reduced risk of breast cancer with increasing adherence to a MD (22,23). A 24% lower incidence of breast cancer was observed among American Hispanic and non-Hispanic women in the highest quartile of MD consumption analyzed via factor analysis (23). Similarly, a 35% lower risk of breast cancer was observed among Asian American women with highest MD scores (more than 8 points) compared to the lowest (0–3 scores) (22).

One out of the 5 case-control studies found no evidence of an association between the MD pattern and endometrial cancer risk among the American adult female population at their level of consumption of the MD (21). These results were the same regardless of the MD definition or score used to assess the adherence to the MD (25,26).

**DISCUSSION**

Although research on the beneficial role of MD on health began in the early 1970s in the classic Seven Countries Study by Keys et al. (27), epidemiological studies have only started investigating the protective role of the MD on cancer relatively recently, with most research conducted within the last 5 yr. This current review summarizes the observational studies to date that have investigated the role of the Mediterranean dietary pattern on cancer incidence and mortality. We found that out of the 12 studies reviewed (7 cohort and 5 case-control), 10 studies (6 cohort and 4 case-control) provided some evidence that the MD was associated with a reduced risk of cancer incidence or mortality. Collectively, the evidence from these observational studies suggests that the MD is a cancer-preventive dietary pattern.

If the strength of evidence for this relationship is assessed according to criteria set out in the WCRF/AICR 2007 report (1), it appears most of criteria for a “probable” relationship are met; 1) the evidence comes from at least two independent cohort studies. In fact, the results from 6 cohort studies have been summarized in a meta-analysis by Sofi et al. (12), providing a pooled relative risk of 0.94 (95% CI of 0.92–0.96) for risk of occurrence of or mortality from cancer for each 2-point increase in the MD score (25). Four case-control studies also provided some evidence of an association; 2) although there was no substantial unexplained heterogeneity within or between study types or different populations (i.e., European vs. United States and Mediterranean vs. non-Mediterranean), the associations varied somewhat depending on the populations’ characteristics, status, and cancer-sites; 3) there is evidence from good quality studies that can exclude the possibility that the observed results are due to random or systematic error. For instance, there are several large prospective cohort studies with a long follow-up time (around 10 yr) studying incident and mortality end points, depending on the study. In addition, 2 of the EPIC studies calibrated the dietary measurements using data from 24-h recalls, and 4) presence of plausible biological gradient—many of the studies reported a dose-response relationship, with a greater reduction in risk of cancer as adherence to the MD increased from low to high. However, there is a lack of evidence from randomized control trials in humans, the main source of evidence to be able to establish a causal relationship. The number of years an individual needs to be able to obtain such a beneficial effect is also unknown, and only 1 intervention study, the Lyon Heart randomized control trial (28), has investigated the effect of the Mediterranean-like diet (rich in oleic and alpha-linolenic acid) and cancer incidence. The results are only suggestive because of the relatively few numbers of cases (\( n = 24 \)) that occurred during the 4-yr follow-up. However, the MD group had significantly lower risk of cancer, RR 0.39 (0.15, 1.01), compared to the control group (following a Step-1 AHA prudent diet).

Studies that have investigated the effect of the MD on overall cancer mortality have found some evidence that greater adherence to a MD was associated with a reduced risk of cancer, ranging from 14% to 27% depending on the increment in MD measured (16,17). Several studies have assessed specific cancer sites separately, which is of interest, as different cancer sites may be etiologically heterogeneous. Although the magnitude of the effect is related to the increment in the MD measured and the study type, a high adherence to the MD was associated with reduced risk of breast cancer, ranging from 21–55% (22,23) and a reduced risk of colorectal cancer ranging from 21–28% was observed only in men (18,24). The range of risk reduction against
the results difficult to interpret, especially as most studies have
only adjusted for many confounding variables, some residual
confounding in observation studies is almost inevitable by fac-
tors not measured in the study or by variables that are adjusted
for but were measured with error (27). For example, the effect of
dietary supplements could be an important confounder in some
populations (21), and some of the studies did not control for

An adjustment for energy intake is also necessary for the eval-
uation of food and nutrient health effects (30). Although this may
be less imperative for overall patterns analysis, this issue seems
more important in case-control studies in which misreporting
is common, especially among cases. Some attempts have been
made to reduce some of the inherent error in the dietary assess-
ment methods, such as adjusting individual components of the
index by total energy intake (16,19). Third, using MD indexes in
American and Nordic populations (13–16,21–23) might not ade-
quately represent conformity with the traditional MD, as it may
only reflect adherence to some of the MD components that are
also characteristic of a general “prudent” dietary pattern. Some
studies that were concerned that the median intake of the dietary
components might be lower in their study populations compared
to Mediterranean populations made some adjustments—using
alternate cut-off points or the highest intakes (16,19). Moreover,
small sample sizes (21) may limit the precision to be able iden-
tify cancer risk factors, and even large samples are normally
only able to estimate approximately 20–30% risk variability.

On the other hand, many of the studies reviewed have impor-
tant positive qualities that support the observed results. First is
the use of conceptually similar ways to define the dietary pattern,
as many of them include similar components and use an intuitive
and simple score based on the MD score by Trichopoulou et al.
(29), making it easy for comparisons and giving robustness to the
findings. Second, many of the studies had large sample sizes and
reasonably long follow-up of the cohorts, which allows an ade-
quate period and for cancer cases to accumulate. Third, a single
cohort enables the effects of diet and lifestyle to be assessed for
multiple types of cancer and other diseases. In addition, several
cohort studies have calibrated the dietary data using more accu-
rate data from a 24-h recall in a subsample, in order to reduce
dietary measurement error. Validated, interviewer-administered
dietary questionnaires are also frequently used (17). Moreover,
comparable results were observed using dietary indexes and factor analysis to examine the relationship of dietary pattern and cancer (22).

There is substantial evidence that diet plays an important role in the etiology of cancer. Extensive evidence exists on the relationship between key components of the MD and cancer risk (29,31–33). For instance, key findings are that an increased intake of vegetable and fruit, whole-grain foods, olive oil vs. other added fats, fish, and diets rich in n-3 PUFA are related to a reduced cancer risk (20,32,33). Meanwhile non-Mediterranean aspects such as high consumption of red and processed meat and alcohol (all types) have been associated with an increased risk of several types of cancer (1). However, in relation to cancer risk, the dietary pattern analysis approach as reviewed in this article is now gaining ground over the single nutrient or food approach (5).

The evidence of the cancer protective effect of the MD pattern is generally stronger than the evidence from individual foods, food groups, or nutrients and cancer risk (1). Some possible explanations of this could be that interactions and synergisms exist between the components; individual components could also have health effects that are undetectable alone but when integrated with other foods or nutrients in a dietary index, the health benefits become more pronounced (25). Dietary indexes can overcome the issues of collinearity or confounding between components in the score; and, finally, dietary pattern indexes evaluate only the extremes of cumulative exposure, limiting the background noise of individual components (34). Thus, all these issues justify the use of dietary pattern studies to assess cancer risk reduction (17).

The beneficial effect of the MD on cancer risk may be mediated through several biological mechanisms such as chronic inflammation and oxidative stress. A MD-like pattern is related to a high antioxidant capacity and low oxidized LDL-cholesterol due to its richness in dietary antioxidants such as vitamin C, vitamin E, carotenoids, phenols, and flavonoids (35). Fiber may potentially offset the carcinogenic effects of N-nitroso compounds (NOC) (exogenous exposure comes from a diet such as red meat, tobacco, and other environmental sources) by acting as a nitrite scavengers (36); and the omega-6/3 fatty acids ratio may also play a role, as its constituents potentially prevent cancer initiation and progression (37,38). Additionally, a high intake of total meat, red meat, and processed meat (uncommon in traditional MDs) is associated with an increased risk of some cancers, especially colorectal and gastric cancer (1), which can be explained by several possible mechanisms including the potential carcinogenic effects of nitrite and nitrosamines, salt, and heterocyclic amines and polycyclic aromatic hydrocarbons (36). Higher adherence to the MD has been linked to decreased inflammation and coagulation processes through lower levels of C-reactive proteins, interkeukin-6, homocysteine, fibrinogen (39), and several other biomarkers of inflammation and endothelial dysfunction (14,40). Several micronutrients and food components (including folate, flavonoids, and carotenoids) showed inverse relations with cancer risk, but the main component(s) responsible for the favorable effect of a diet rich in vegetables and fruit remain undefined (41). Tomato has been shown to be beneficial in cancer prevention, particularly for prostatic cancer, and lycopene emerges as the most relevant functional component; a substantial part of the lycopene effects can be explained by its antioxidant action but also by downregulation mechanisms of the inflammatory response (42,43). Olive oil is an integral ingredient of the MD, and accumulating evidence suggests that it may have a potential role in lowering the risk of several types of cancers. The mechanisms by which the cancer-preventing effects of olive oil can be performed, however, are not completely known. However, a novel hypothesis is that oleic acid, the monounsaturated fatty acids in olive oil, is able to specifically regulate cancer-related oncogenes (44). Recent findings concerning the bioavailability of certain important minor components of olive oil, including efficient antioxidant polyphenols, the triterpene hydrocarbon squalene, and beta-sitosterol, considered as putative nutritional biomarkers, have been described in relation to the incidence of cancer (45). In addition, a MD pattern was shown to cover the average nutrient requirements much better than the Western diet (46), and this may also contribute to the overall cancer preventive effects.

Increasing our understanding of the biological mechanisms involved in cancer processes will also help to develop preventive strategies.

Patterns of production and consumption of food products, physical activity, and lifestyles in general have changed greatly throughout the past decades. These are mainly consequences of globalization, industrialization, and urbanization that have taken place, first in Europe and North America, and increasingly in most developing countries. These transformations are reflected in changes in cancer incidences and mortality, and projections estimate that by 2013, 70% of cancer deaths will occur in middle- and low-income countries (1). However, as with other diseases, the risk of cancer is modified by social, cultural, economic, and other environmental factors.

As obesity is linked to several cancers (1), the increasing obesity epidemic will add to the rising cancer trend. Therefore, the effect of the MD (11) on body weight may have an additional favorable response to cancer risk reduction (1).

The fact that the MD is associated with reduced risk of cancer does not preclude that other dietary patterns may also be protective. Actually, traditional diets in general have been associated with a lower risk of cancer (23,47). The WFCR/AICR Panel agreed that recommendations on specific foods such as the increase of fruits and vegetables and the decrease of red and processed meat actually coincide with recommendations toward a plant-based diet such as the MD or East Asian dietary pattern. The healthy effects of the traditional pattern may also be related to behavioral or cultural aspects, although some common components of the traditional diets (e.g., high consumption of legumes and vegetables, etc.) are also likely to be involved in their benefits. In contrast, substantial evidence agrees that the
Western dietary pattern is associated with an increased risk of several types of cancers (14,23). Therefore, the MD has a favorable effect on reducing cancer risk, which is relevant to the public health sector given the tendency of modern societies to shift toward a more Westernized and globalized dietary pattern (7).

Although the reviewed cohort and case-control studies had certain district study characteristics, such as being set in different populations and analyzing different cancer outcomes, the existing evidence suggests a protective role of the Mediterranean dietary pattern toward cancer in general. Specific results for several outcomes, such as different cancer sites, deserve additional research. The purpose of this review was to give a general overview of the situation so as to be able to provide possible guidelines for cancer prevention.

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