

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Mediterranean Diet in Hypercoagulable States and Cancer



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H&O What are the characteristics of the Mediterranean diet?

MM The traditional Mediterranean diet refers to the dietary pattern that was typical until the mid-1960s of people living in the areas of the Mediterranean basin where olive trees grow, such as Greece, Southern Italy, and Spain. It is characterized by the use of olive oil as the main culinary fat; high consumption of vegetables, fruits, nuts, legumes, and unprocessed cereals; moderate consumption of poultry, eggs, and dairy products—which include yogurt and cheese but not whole milk, butter, or cream—and low consumption of sweet desserts, red meat, and processed meat. It is traditional to consume a moderate amount of alcohol during meals, especially wine.

The total intake of lipids can be moderate or high. The traditional Italian diet has a moderate lipid content—approximately 30% of calories come from fat. In Greece, calories from fat may account for more than 40% of total energy intake. In all instances, the ratio of monounsaturated to saturated lipids is high because of the use of olive oil, which is rich in monounsaturated fat. As for fish consumption, this used to correlate with distance from the sea but tends to be moderate overall.

H&O What is the mechanism by which the Mediterranean diet might mitigate the predisposition to develop hypercoagulability tendencies?

MM The Mediterranean diet has been shown to be very effective at decreasing blood pressure, lipid profiles, and markers of inflammation. These markers of inflammation include C-reactive protein (CRP), proinflammatory

cytokines such as interleukin 6 (IL-6), and adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1). Low-grade, chronic inflammation is a key contributor to atherosclerosis, and therefore to coronary heart disease and stroke.

H&O How effective is the Mediterranean diet at reducing the risk for developing cardiovascular disease?

MM Numerous cohort studies have supported a link between the Mediterranean diet and a reduction in cardiovascular disease risk. According to a meta-analysis of cohort studies that Dr Francesco Sofi and colleagues published in *Public Health Nutrition* in 2014, each 2-point increase in a score assessing adherence to the Mediterranean diet was associated with a significantly reduced risk of cardiovascular disease (relative risk [RR], 0.90; 95% CI, 0.87-0.92).

One of the few randomized controlled trials to examine the use of the Mediterranean diet is PRE-DIMED (Prevención Con Dieta Mediterránea). In this primary prevention trial, more than 7000 men and women at elevated risk for cardiovascular disease were randomly assigned to one of 3 diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts, and a control diet in which participants received advice on eating a low-fat diet. After a median of 4.8 years, the rate of cardiovascular events—myocardial infarction, stroke, or death from cardiovascular disease—was significantly lower with the Mediterranean/olive oil diet (hazard ratio [HR], 0.70; 95% CI, 0.53-0.91) and the Mediterranean/nut diet (HR, 0.70; CI, 0.53-0.94) than with the control diet, as reported in *Progress in Cardiovascular Diseases* in 2015.

H&O Is there evidence that the Mediterranean diet can affect the development of venous thromboembolic disease?

MM We do not have good evidence at this time for an association between the Mediterranean diet and venous thrombosis.

H&O What studies have looked at the use of the Mediterranean diet for secondary prevention of cardiovascular disease?

MM The landmark trial for secondary prevention of cardiovascular disease is the Lyon Diet Heart Study by Dr Michel de Lorgeril and colleagues, which was published in 1994. This was the first randomized trial to show that a dietary intervention could offer strong cardiovascular protection. A total of 605 patients who had experienced a prior myocardial infarction were randomly assigned to either a Mediterranean-type diet or a “prudent” diet that was consistent with the American Heart Association

People who adhered most closely to a Mediterranean diet were at significantly reduced risk of developing or dying of all types of cancer.

Step 1 diet. The Mediterranean-type diet included a special margarine that was rich in linolenic acid; participants were asked to use this in place of butter and cream; to eat more fish, fruits, and vegetables; and to eat less red meat. After an average of 27 months, the rate of coronary events was 73% lower in the Mediterranean-type diet group than in the prudent diet group, and overall mortality was 70% lower.

H&O What is the mechanism by which the Mediterranean diet might affect cancer?

MM Olive oil appears to play an important role. Olive oil is rich in oleic acid, which has an antiproliferative effect; it cuts down on the growth of malignant cells by affecting the expression of human oncogenes. Another component of olive oil is the hydrocarbon squalene, which has been

reported to exert a beneficial effect on intracellular oxidative stress and DNA oxidative damage in mammary epithelial cells. When DNA is oxidized, it is more likely to cause cancer. Extra-virgin olive oil also contains polyphenols, which may play a role in breast cancer prevention. For example, the polyphenol oleocanthal has been shown to inhibit tumor growth and proliferation, tumor migration, and invasiveness of breast cancer cells in in vitro and in vivo breast cancer models. The polyphenol oleuropein has been shown to increase apoptosis of cultured breast cancer cells.

H&O What studies have looked at the Mediterranean diet as a way to reduce the risk for cancer?

MM The largest study is the EPIC (European Prospective Investigation Into Cancer and Nutrition) trial, a cohort study of nearly half a million people. In a 2011 analysis of this study, Dr Elisabeth Couto and colleagues concluded that following a Mediterranean diet could avoid 4.7% of cancers among men and 2.4% of cancers among women.

The first randomized trial to find an effect of the Mediterranean diet on breast cancer incidence is the PRE-DIMED study. In a 2015 analysis, Dr Estefanía Toledo and colleagues found that the rate of breast cancer was significantly lower with the Mediterranean/olive oil diet (HR, 0.32; 95% CI, 0.13-0.79) than with the control diet after a median of 4.8 years.

The meta-analysis of cohort studies from Dr Francesco Sofi and colleagues found that each 2-point increase in the adherence score to the Mediterranean diet was associated with a significantly reduced risk of developing or dying of cancer (RR, 0.96; 95% CI, 0.95-0.97). This finding was consistent with the results from EPIC.

Another meta-analysis, which Dr Lukas Schwingshackl and Dr Georg Hoffmann published in the *International Journal of Cancer* in 2014, included 21 cohort studies and 12 case-control studies. This study found that people who adhered most closely to a Mediterranean diet were at significantly reduced risk of developing or dying of all types of cancer (RR, 0.90; 95% CI, 0.86-0.95; $P < .0001$), colorectal cancer (RR, 0.86; 95% CI, 0.80-0.93; $P < .0001$), prostate cancer (RR, 0.96; 95% CI, 0.92-0.99; $P = .03$), and esophageal/pharyngeal cancer (RR, 0.44; 95% CI, 0.26-0.77; $P = .003$).

H&O Have studies looked at whether the Mediterranean diet can reduce the risk for cancer recurrence?

MM An ongoing randomized controlled trial called DIANA (Diet and Androgens)-5 by Dr Anna Villarini

and colleagues is looking at whether a diet based on Mediterranean and macrobiotic principles can reduce recurrences of breast cancer in women with early-stage invasive disease, but we do not have any data at this time.

Suggested Readings

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