

Mediterranean Diet and Cancer: A Current Perspective

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Cancer is one of the most common causes of death in the world.^[1,2] In 2020, the most recent cases were breast (2.26 million cases), lung (2.21 million cases), colon and rectum (1.93 million cases), prostate (1.41 million cases), skin (non-melanoma/1.20 million cases), and stomach (1.09 million cases) cancer.^[3,4] Although cancer usually has a homogeneous distribution between the genders, the incidence among the species has changed.^[1,5,6] Cancer risk factors include genetic and environmental factors (factors such as ultraviolet, radiation, asbestos, tobacco smoke, arsenic, aflatoxin). Furthermore, the individual's high BMI (body mass index), low fruit and vegetable intake, alcohol consumption, lack of physical activity, and some carcinogenic chronic inflammations (*Helicobacter pylori*, human papillomavirus, Hepatitis B, Hepatitis C, Epstein-Barr virus) were all considered cancer risk factors.^[1,7-9] It has been observed that some cancers can be prevented with a proper diet, adequate physical activity, and ideal BMI protection.^[10] Obesity and its effects have been linked to an increased risk of cancer.^[11] When studies examining the relationship between cancer and fruit and vegetable consumption were reviewed, nearly all of them showed that it had a protective

ABSTRACT

Cancer covers a significant proportion of deaths worldwide. Genetic and environmental factors are involved in cancer pathophysiology. It generally shows a heterogeneous distribution over the genders. Nutritional approaches attract attention in the treatment of cancer, one of our age's diseases. Current cancer statistics and the most common types of cancer have been specifically reviewed in the literature. Various studies in different neoplasias are needed in the future to clarify the relationship between the Mediterranean diet (MD), which has been shown to be effective in cardiovascular diseases, and cancer. This review explained the MD could provide preventive or protective effects against various neoplasms with bioactive compounds such as fiber, flavonoid, hydroxytyrosol, and antioxidants at different stages. The relationship between the MD, which is accepted as an ideal and healthy diet, and cancer were also discussed in the review.

Keywords: Antioxidants, cancer, Mediterranean diet

effect. For many cancers, the group that consumed the least fruits and vegetables and the group that ate the most fruits and vegetables were found to have two times higher risk of cancer in the under-consuming group.^[12] In the early stages of cancer, a diet rich in antioxidants, folic acid, selenium, and vitamins has been shown to be protective. Sulforaphane, an anti-cancer chemical, is found in cruciferous vegetables such as broccoli, cauliflower, cabbage, and Brussels sprouts. The consumption of cruciferous vegetables was found to be inversely linked to the presence of isothiocyanate in urine in a study.^[13,14] High red meat consumption, particularly processed meat, has been linked to colorectal cancer (CRC).^[15] The results of studies on the health effects of alcohol consumption are sometimes contradictory. While moderate alcohol use was found to be protective at the beginning of kidney cancer, excessive consumption was found to be a risk factor for various malignancies.^[1] When these studies are included in the common link, a diet high in fiber

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and vitamins, low meat consumption, moderate milk consumption, and moderate alcohol (typically red wine) consumption, which varies by location, can be regarded as the ideal diet for cancer prevention. This diet model is the Mediterranean diet (MD). MD is seen as the best dietary model that can reflect the ideal healthy diet. The main dietary model can contribute to a long life, prevent heart disease, and stop progression.^[16-18] In summary, this review aimed to reduce the risk of cancer by analyzing studies examining the effect of MD on more current types of neoplasia.

MEDITERRANEAN DIET

The Mediterranean diet was characterized in the 1960s as a dietary model based on red and other meats with a low quantity of saturated fat and a higher amount of vegetable fats, especially seen in Greece and Southern Italy.^[19] Traditional eating habits are seen in the Mediterranean and surrounding geographical regions are united on a common basis, although they are unique to every country and culture. MD consists primarily of vegetables, fruits, grains, nuts, and legumes cooked in olive oil, with moderate amounts of fish, shellfish, and dairy products. There is also limited meat and alcohol intake (mostly red wine). In traditional practice, fruits are consumed as sweets or intermediate meals, cheeses are accompanied by salads, and red meat is consumed only on special occasions.^[20] Recommended portion quantities for these food groups come across as a dietary pyramid. Dietary pyramids have been considered a useful way to specify an average rate for the quantities of food groups. In 1993, the first MD pyramid was developed in cooperation with Oldways Foundation for Conservation and Exchange, the World Health Organization (WHO), and the Food and Agriculture Organization (FAO).^[21] The pyramid prepared by the Greek Dietary guidelines is based on a more traditional approach.^[22] The Mediterranean Diet Foundation (MDF) created a pyramid that shows a more flexible and universal MD.^[23] Figure 1 shows a sample MD pyramid based on MDF's portion and intake recommendations. Compared to these three dietary pyramids, the general structure of the basic food groups and the times in which they are located are the same or similar. In the three pyramids, the recommendations for vegetables, fruits, olive oil, bread, and cereals are nearly identical. Nuts and legumes, fish/seafood, and chicken are all recommended differently in different pyramids. The Oldway pyramid for the purchase of pulses stated each meal, while the MDF and Greek nutrition

guidelines were included in the pyramids 3-4 times a week. The MDF recommends daily nuts, while other pyramids recommend fewer portions. Throughout history, a unique diet has been formed as a result of the complexity and years of interaction between natural food sources and people in the Mediterranean geography. It has received fresh meaning and usefulness in the medical world throughout the previous century.^[24] Ancel Keys studied how hunger affected human physiology at the end of World War II, researching nutritional methods that could improve health after starvation.^[25] First, Ancel Keys and his colleagues evaluated MD as a diet that is poor in saturated fats and has a protective effect on the cardiovascular system with low cholesterol levels in the blood. It was later described as a nutrient-dense diet that can prevent a variety of illnesses.^[26,27] A randomized controlled heart study evaluated the effects of a modern, French version of MD in patients with acute myocardial infarction. To make the most of the functions of MD, which is rich in omega-3 alpha-linolenic acid but poor in omega-6 linoleic acid, colza oil, and olive oil have been used together. It not only decreased the number of acute coronary attacks in half, but it also reduced the number of new cancer cases and overall mortality. The Mediterranean diet's health benefits are now widely recognized in medicine as the "Mediterranean diet".^[28-30]



Figure 1. Mediterranean Diet Pyramid (This diagram was created by comparing various MD pyramids)^[31,32]

MEDITERRANEAN DIET BIOACTIVE COMPONENTS

Olive oil, the symbol of MD, is considered an important bioactive food with high nutritional value.^[31] In the Mediterranean region, pasta, rice, vegetables, other vegetable foods, and other starchy

foods that are at the heart of meals are cooked with olive oil, and their nutritional values are increased. Extra virgin olive oil (EVOO) has been shown to have a protective role in the primary step of cardiovascular diseases and is effective in some cancers.^[32-34] To avoid oxidative stress damage, the European Food Safety Authority (EFSA) found that daily intake of derivatives such as 5 mg of hydroxytyrosol, oleuropein complex, and tyrosol in olive oil is required in a balanced diet.^[35,36] Antioxidants from vegetable products, vegetables, fruits, legumes, extra virgin olive oil and wine, fiber and phytosterols, monounsaturated fatty acids found in olive oil, omega-3 fatty acids from seafood and nuts, and probiotics derived from fermented foods such as cheese and yogurt are all considered sources of MD's beneficial effect.^[37,38] Multiple mechanisms of these components cause physiological and metabolic changes. These modifications were linked to a reduced risk of chronic disease and a longer lifespan.^[39] MD contains antioxidants such as plant-derived vitamin C, vitamin E, β -carotene, glutathione, lycopene, and polyphenols, all of which aid in the reduction of oxidative damage. Flavonoids with antioxidant properties found in red wine, olive oil, coffee, tea, nuts, fruits, vegetables, herbs, and spices are important polyphenols.^[40] Polyphenols play a role in intracellular signal transmission, which allows them to influence gene expression. Polyphenols decrease enzymes such as xanthine oxidase, nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), and angiotensin-converting enzyme 2 (ACE2) to promote cardiovascular repair.^[41,42] MD is also inversely related to colon cancer and modulates plasma cholesterol by having foods high in dietary fiber.^[43-45] Fibrous foods promote weight loss by increasing satiety.^[46] MD also recommends purchasing seafood and shellfish, which are essential in the second stage of the pyramid, ensuring enough omega-6/omega-3 fatty acid intake. As a result, less inflammation than in other western diets helps to lower the risk of chronic diseases including diabetes and atherosclerosis.^[47-49]

THE RELATIONSHIP BETWEEN MEDITERRANEAN DIET AND CANCER

As a result of the studies, various types of bioactive nutrients that play a role in the development of tumors and also act as preservatives have been defined. Polyphenols, selenium, retinoids, and isothiocyanates are examples of these compounds.^[50-52] These bioactive compounds are capable of participating in liver detoxification steps, DNA repair, cell growth, death and differentiation, various modulations such

as oxidative stress and inflammation.^[53] However, in recent years, epigenetics has been used to advise the use of foods such as soy, cruciferous, green vegetables, and fruits, which have been shown to protect against cancer and aging.^[54-56] Nutrition rich in proven bioactive components; can alter the epigenome, which constitutes a diet that can benefit therapeutic purposes for health and preventive purposes.^[57,58] In this perspective, MD's anti-cancer properties as an epigenetic effective diet are based on nutrients like fruits, vegetables, nuts, legumes, seafood, and especially olive oil, which it contains in abundance. Antioxidants and anti-inflammatory properties found in these nutrients contained in MD have had a positive effect on cancer. This diet is high in nutrients that can slow cancer cell proliferation and preserve the cell membrane from spreading.^[59] MD was associated with a low risk of death due to all causes.^[60,61] The study found that following a Mediterranean-style diet was linked to a 10% reduction in overall cancer mortality risk. This dietary pattern is especially effective in colorectal (14%), prostate (4%), and gastrointestinal tract (56%) cancers.^[62-64] MD has been proven to directly affect the mammalian target of rapamycin (mTOR) and aging, as well as insulin-like growth factor-1 (IGF-1) because it contains a modest quantity of animal-derived protein and has a low glycemic index (GI). In particular, reducing animal protein intake can significantly reduce serum IGF-1 levels and suppress mTOR activity with downregulation of the signal that leads to transcription of long-life genes.^[65] Low-grade chronic inflammation caused by obesity; increases the risk of cancer. It also promotes the formation of cancer by triggering genetic mutation or epigenetic activation.^[60] Various studies have shown that traditional Mediterranean nutrition reduces the risk of the onset of various types of cancer.^[66-68] A large cohort study found that following MD regularly was linked to a decreased risk of cancer. Regular adherence can prevent 4.7% of malignancies in males and 2.4% of cancers in women.^[69] A study measured by the Italian Mediterranean diet index has shown that MD protects against colorectal cancer in general, but not cancer that develops in the proximal colon. The results did not differ by gender.^[70] Although MD-appropriate nutrition was associated with a decrease in disease risk in a case-control study, no association with breast cancer was reported.^[71,72] In contrast to this study, another case-control study found that MD was associated with a lower risk of breast cancer.^[73] According to a study, the typical MD is linked to a lower risk of cancer of the

upper gastrointestinal tract.^[74] Scientists agree on the function of MD in longevity and many diseases based on several studies. As a result, MD has been a diet that has been shown to have a good impact on health both directly and through the bioactive components, it includes.

BREAST CANCER

Breast cancer is more common among women.^[75] According to the expected age of standardized 2020 cancer incidence, women have a 47.8% incidence rate.^[1] Breast cancer is a metastatic disease that can spread to other organs.^[76] In breast cancer patients, the high-fat content of Western-style nutrition was linked to death and a poor prognosis.^[77] Increased levels of estrogen-related hormones caused by alcohol use can disrupt estrogen receptor pathways. According to meta-analysis research, drinking 35-44 grams of alcohol per day increases the risk of breast cancer by 32%.^[78,79] Even though some studies have found a negative correlation between MD and breast cancer, others have found is no link.^[80-83] As a result of the MD adaptation and breast cancer risk study in post-menopausal women, the opposite relationship was observed between breast cancer and MD adherence.^[84] In breast cancer patients, dietary intake of hydroxytyrosol, a major part of MD and an antioxidant found in olive oil, was found to significantly reduce molecules implicated in breast cancer such as cell proliferation, apoptosis, and metastasis.^[85] Estrogens can be controlled and a protective impact against free radicals can be accomplished by elevating the level of sex hormones thanks to fiber, antioxidants, flavonoids, carotenoids, and olive oil consumed with adherence to MD. As a result, MD may be a protective factor in the prevention of breast cancer.^[65,81,86,87]

COLORECTAL CANCER

In 2018, the incidence of colorectal cancer (CRC) is second worldwide and third among the causes of mortality. Overall, the CRC is expected to grow further in the next decade around the world. It is estimated that more than 2.2 million cases will be diagnosed in 2030.^[88] Due to CRC is a slow-progressing illness, it allows for intervention with preventative measures and treatments.^[90] Surprisingly, an average of 5-6% of CRC patients is linked to germline gene disorders.^[91] Furthermore, 70% of CRC tumors are only observed infrequently and in small numbers.^[92] This information implies that there may be important treatment options for CRC. Diet can either reduce or raise the risk of CRC as a treatment method.^[93] Several prospective studies

have examined the link between MD adherence and CRC. According to certain research, following MD is linked to a significantly lower risk of CRC.^[57,94,95] Women who follow MD may have a lower incidence of CRC and rectal cancer, according to a cohort study of women.^[96] Case-control research conducted in Italy similarly found a connection between greater MD adherence and a lower risk of cancer.^[97] Even when prospective sociodemographic factors were taken into account, MD used after a CRC diagnosis resulted in higher survival.^[98] Bioactive substances found in MD-specific fruits and vegetables may help to reduce the incidence of CRC. It was found that 3,3'-diindolylmethane from cruciferous and sulforaphane prevented the development of cancer cells with its effect of stopping the cell cycle.^[99,100] Fruit extracts rich in anthocyanin contained in red wine, olive oil, and various fruits and procyanidins have been shown to inhibit the growth of cancer cells.^[101,102]

PROSTATE CANCER

Prostate cancer (PCa) is second in incidence among men worldwide and fourth among causes of mortality.^[90] PCa, an abnormal growth disease, is significantly affected by cellular growth signals. Many neoplasias, including PCa, are linked to metabolic syndrome and insulin resistance, which is thought to be a key dietary determinant in this group of disorders.^[103-105] The incidence and death of PCa were found to be lower in nations that have traditionally adopted the MD lifestyle, particularly in Southern European countries.^[106,107] MD, which is high in fiber and includes vegetables, seafood, and olive oil, has been linked to a decreased risk of PCa, death, and progression.^[108-111] According to the findings, lifestyle and diet were found to be major factors in the treatment of deadly prostate cancer patients.^[112] Components such as animal fats, dairy products, and calcium were discovered to have a deleterious effect on PCa incidence.^[113,114] A study on aggressive PCa found that higher MD scores were inversely proportional to PCa.^[115] Higher adherence to MD was not associated with PCa prognosis but was associated with greater adaptation to MD after non-metastatic PCa diagnosis and lower overall death of olive oil consumption (22-31%).^[116] Larger prospective studies also found that MD was associated with a similar decrease in overall mortality.^[117,118]

GASTRIC CANCER

Gastric cancer (GC) is a multi-factor disease in which various environmental and genetic factors

play a role.^[119] Current statistics see GC as the leading cause of cancer deaths worldwide with a survival rate of fewer than 12 months for advanced stage.^[120] The presence of *Helicobacter pylori* is the main risk factor for GC.^[121] With correct nutrition, early diagnosis, and suitable therapy, GC can be decreased and prevented.^[122] In case-control research, it was discovered that those with a high a priori score, which is defined by poor fruit and vegetable consumption and a high starch diet consumption, had a higher risk of GC.^[123] For vegetables, fruits, and legumes, which cover a substantial amount of MD, it was found to be inversely proportional to the risk of GC.^[124,125] Olive oil has also been shown to protect against the effects of GC.^[33] Other MD ingredients, such as seafood, dairy products, and red wine, were found to be less consistently linked to a risk of stomach cancer.^[126,127] GC mortality was lower in the south of Italy, where MD was more frequent than in the north.^[128] According to the findings of the cohort trial, higher compliance with MD reduced the incidence of GC by 33%.^[129]

LUNG CANCER

More than two million new cases of lung cancer were detected worldwide in 2018. This number of diagnosed cases contributes 12.3% to all cancers. For men, this rate ranked first with 15.5%, while for women it was third with 8.8%. Tobacco is the leading cause of lung cancer. In addition, passive smoking is a cause of lung cancer. A history of emphysema, chronic bronchitis, tuberculosis, and pneumonia has been associated with an increased risk of lung cancer. Cancer-causing compounds in cigarette smoke, coal tar, and other inhaled particles such as asbestos can directly affect the DNA of lung cells. Since the entire lung is exposed to these inhaled substances, it can cause multiple cancers in various regions.^[75] In addition, red meat, processed meat, and alcohol increase the risk of cancer. While not smoking is the first step in preventing lung cancer, consuming foods containing retinol and carotenoids, which MD also contains abundantly, can reduce the risk of lung cancer. A diet rich in vitamin C can reduce the risk of lung cancer in those who still smoke.^[130,131] Even though Poland is not a Mediterranean country, a study on the effects of MD on breast and lung cancer found that the control group had a greater risk of cancer and that MD had a protective effect.^[132] In an Italian study of smokers, strong adherence to MD was linked to a decreased risk of lung cancer in asymptomatic heavy smokers. In addition, heavy smokers with a high red meat intake and a low adherence to MD were found to have a higher risk of lung cancer.^[133] Several studies

have also found that adherence to MD reduces the risk of lung cancer.^[134-136]

In conclusion, cancer has become one of the world's most common diseases and one of the most pressing issues of our time. It is one of the world's top causes of death. Among the alternative approaches to cancer prevention, the diet has proven to be one of the most effective variables. A nutritional strategy has been employed to prevent various ailments in recent years. The Mediterranean diet is widely regarded as the healthiest eating pattern. There is a restricted amount of meat, sweets, and red wine in addition to olive oil, a substantial amount of vegetables, fruits, grains, and modest fish and dairy products. MD protects and prevents neoplasia by including different bioactive substances like antioxidants, carotenoids, flavonoids, fiber, and monounsaturated fatty acids, which are plentiful in the MD. MD is effective in cancer stages by providing protection against free radicals, helping to modulate DNA damage. This review summarizes current cancer data and the effect of MD on the most common types of cancer in the world. Although there are extensive studies on the protective effect of the MD in the literature, there is a need in the future for diet adaptation and other neoplasia types outside the Mediterranean region.

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