

Breast cancer prevention: role of the Mediterranean Diet and its components

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Abstract: Breast cancer affects billions of people all over the world. Many factors contribute to the development of breast cancer, such as hormones, lifestyles, environmental factors, and diet patterns. According to the World Cancer Research Fund (WCRF), high consumption of fruits, vegetables and whole grains, as well as low intake of red and processed meat can lower cancer risk. As food items and nutrients are consumed in combination, dietary patterns have been successfully implemented as a tool to assess the additive or synergistic effect of food in nutritional epidemiology. The Mediterranean diet is a plant-based pattern characterized by high amounts of fruits, vegetables, nuts, legumes, fish, cereals including whole grains, and extra-virgin olive oil. Numerous studies have shown that the Mediterranean diet reduces the risk of breast cancer. Given the increasing severity and incidence of breast cancer, there is increasing interest in promoting prevention strategies to reduce incidence. The purpose of this paper is to provide an overview of the current evidence on the association between breast cancer and Mediterranean diet.

1. Introduction

According to Centers for Disease Control and Prevention (CDC), female breast cancer has become the top 1 cancer by rates of new cancer cases in 2018 (126.8%), also the top 2 cancer by rates of cancer deaths (19.8%) [1]. How to effectively prevent the increasing amount of breast cancer cases has become one of the major research areas nowadays. Most of the recognized risk factors for breast cancer, such as family history, age at menarche, age at menopause, and reproductive history, such as age at first birth and number of births, are generally not easily changed [2]. According to National Cancer Institute, long-term exposure of estrogen and progesterone are linked to the increased risk of breast cancer in women [3]. Many other factors also influence breast cancer development, such as exogenous hormone intake, diet, lifestyle, and alcohol [4, 5].

According to the World Cancer Research Fund (WCRF), high consumption of fruits, vegetables and whole grains, as well as low intake of red and processed meat can lower cancer risk. Dietary patterns are also associated greatly with the overall cancer risk and survival rate [6].

2. Dietary Pattern And Breast Cancer Risk

A meta-analysis involving 32 studies confirmed that there was a significant lower risk of breast cancer when the individual consumes a healthy dietary pattern (PR=0.93, 95%CI: 0.88, 0.98)[6]. Much research showed that the intake of dietary bioactive phytochemicals can have an effect in lowering the risk of breast cancer, as well as management of each stage of breast carcinogenesis [7].

Bioactive phytochemicals are found greatly in plant-based foods, such as vegetables, fruits, whole grains, and seeds. Among all the bioactive phytochemicals, food-derived polyphenols are found to be able to weaken the formation and virulence of breast cancer stem cells, which are the cells that are primarily responsible for tumor relapse, treatment-resistance, and metastasis [8]. Many phytochemicals have been linked with the potential anti-cancer activities, such as capsaicin from chili pepper, catechins from green tea, lycopene from tomatoes/papaya/pink guava/red carrots, isoflavone from soy/lentils/beans/chickpeas, piperlongumine from roots of long peppers, etc[15]. In a 10-year

prospective cohort study, result showed drinking 10 cups (120 mL/cup) of green tea everyday can respectively delay cancer onset by 7.3 years and 3.2 years in females and males [12].

3. THE Mediterranean diet Patterns

The Mediterranean diet is known to be one of the healthiest eating patterns in the world, which is the diet based on traditional cuisines of countries that border the Mediterranean Sea, such as Greece and Italy. Mediterranean diet emphasizes the intake of plant-based foods, such as olive oils, fruits and vegetables, whole grains, legumes and nuts, etc. Seafood and other lean-protein sources are consumed on weekly basis [9].

Due to the high consumption of plant-based foods, the Mediterranean diet include a high intake of polyphenols and other bioactive phytochemicals. These compounds are known to have anti-inflammatory and anti-thrombotic actions that can protect the cells from oxidative stress and potential mutations [10]. A hospital-based case-control study conducted in Italy and Switzerland also showed that the Mediterranean diet may lower the risk of breast cancer [16]. In this experiment, 3034 breast cancer cases and 3392 controls admitted to the same network of hospitals for acute and non-neoplastic, non-gynecologic diseases were studied, and using the Mediterranean Diet Score (MDS) to measure the adherence to the Mediterranean diet, which the score ranged from 0 (lowest adherence) to 9 (highest adherence). The estimated odds ratios (ORs) were conducted by using multiple logistic regression models. The result showed that for a MDS of 4-5, the ORs for breast cancer were 0.86 (95% CI, 0.76-0.98), when comparing to a MDS of 0-3; for a MDS of 6-9, the ORs were 0.82 (95% CI, 0.71-0.95) [16]. As a result, the Mediterranean diet was associated with a reduced breast cancer risk.

3.1 Olive Oil

Olive oil is the principal source of fat in the Mediterranean diet, which has been shown to be linked with lowering the risk of coronary heart disease and certain cancers. Extra-virgin olive oil also contains powerful antioxidants that can have potential biological activities that account for the health benefits of the Mediterranean diet.

The healthful properties of olive oils were thought to be related to the high monounsaturated fatty acid (MFA) content, mostly in the form of oleic acid, which ranges from 56 to 84% of total fatty acids. While oleic acid is largely found in animal products, such as pork and poultry; and the percentage of oleic acid intake in the Mediterranean diet is only slightly higher than the Western diets. As a result, oleic acid might not be the main contributor for the healthful effect of olive oils. Researchers then move their focus to the phytochemicals in olive oils.

Olives naturally contain a high number of phytochemicals. Plants obtain their phytochemicals from the stimulation of environmental stress, such as UV radiation and high temperature, which is a characteristic of the Mediterranean climate. These exposures stimulated the plants' need for different types of compounds to protect themselves, for example, they synthesize antioxidants in order to preserve their integrity from high UV radiation and high temperature environments. As a result, these highly bioactive phytochemicals help reduce the risk of several chronic diseases, such as cancer.

The main phytochemicals that contribute to the benefits of olive oils are phenols, which also contribute to a bitter and pungent taste of the olive oils. Olive oil phenolics have been associated with human health in both *in vitro* and *in vivo* studies. *In vitro* studies have showed that the antioxidant activity of olive oil phenolics, both hydroxytyrosol (HT) and oleuropein (OE) may inhibit copper sulfate-induced oxidation of LDL. HT and OE showed potential protection from DNA and amino acid modification. *In vivo* studies have showed an increased plasma antioxidant capacity after the administration of HT to rats [11].

3.2 Fruits and Vegetables

The Mediterranean diet also has a great focus on fresh fruits and vegetables daily. Numerous studies have concluded that potentially harmful chemicals that we are surrounded by everyday can have a

carcinogens effect on human bodies [13]. Fresh fruits and vegetables are naturally high in phytochemicals, and the active antioxidant activities can have crucial impact as primary chemopreventive agents in the initiation phase of carcinogenesis [14]. Resveratrol (RSV) is also a powerful antioxidant that is mainly found in grape skins and seeds, and red wines [18]. RSV has been shown to target steroid receptors, which is a potent inhibitor of quinone reductase 2 activity. RSV triggers the expression of a wide range of antioxidant enzymes, which may reduce the overall oxidative stress [17].

Another study documented 10911 invasive breast cancer cases, and the greater intake of total fruits and vegetables were associated with a lower breast cancer risk, especially the high intake of cruciferous and yellow/orange vegetables (>5.5 vs. <2.5 servings/day, HR=0.89, 95% CI=0.83-0.96; $p=0.006$). Intake of total vegetables was associated with lower risk of estrogen receptor negative tumors (HR per 2 additional servings/day as a continuous variable =0.84, 95% CI=0.77-0.93; $p=0.02$). Among molecular subtypes, higher consumption of total fruits and vegetables was most strongly associated with lower risk of human epidermal growth factor receptor 2 (HER2)-enriched (HR=0.79, 95% CI=0.67-0.93), basal-like (HR=0.84, 95% CI=0.72-0.97) and luminal A (HR=0.94, 95% CI=0.89-0.99), but not with luminal B tumors ($p=0.03$) [28].

3.3 Whole Grains

Whole grains are also emphasized in the Mediterranean diet [19]. A meta-analysis that includes four cohort and seven case-control studies suggested that high consumptions of whole grains are inversely associated with the risk of breast cancer (RR=0.84; 95% CI=0.74-0.96; $P=0.009$; $I^2=63.8\%$) [20]. A case-controlled study from Greece also suggested that for women between 44-68 years old, eating more than seven servings of whole grains per week was associated with a 51 percent lower risk of breast cancer (OR=0.49; 95% CI=0.29-0.82) [21]. The whole grain phytochemicals and fibers may be the main contributors for the anti-breast-cancer property [7]. Whole grains are a rich source of many phytochemicals, such as phenolic acids, carotenoids, alkylresorcinols, phytosterols, lignans, anthocyanins, vitamin E members, and polysaccharides [7, 22].

Different whole grains may have different effects on types of breast cancers due to the specific mechanisms. For example, germinated wheat flour can reduce the risk of human breast cancer (ER-positive, MCF-7 & TNBC, MDA-MB-231) because of the up-regulation of apoptosis; young barley and its methanolic effect on human breast cancer MCF-7 also shows a reduced risk of breast cancer because of the up-regulation of apoptosis, through lower metabolic activity, inhibition of proliferation, and cell cycle arrest in S phase; total phenolic extracts reduce the risk of human breast cancer (MDA-MB-231) through proliferation inhibition [23-25].

Whole grains may contribute to the reduced breast risk in multiple ways. Firstly, the dietary fiber in whole grains promotes satiation and satiety, as a result, may improve the obese situation. Fibers also control insulin resistance and insulin-like growth factors expression, which can reduce the risk for cancers. Dietary fiber in whole grains may also decrease circulating estrogen concentration by suppressing bacterial beta-glucuronidase activity, raising transient time and peristaltic activities in the gut, which inhibits the reabsorption of estrogens in the colon and increases the excretion of estrogens in feces [7].

3.4 Fish

In the Mediterranean diet, fishes are emphasized and consumed weekly. Regular intake of fishes and other seafoods provide abundant omega-3 fatty acids, which is an essential fatty acid that human body can't synthesize, and must be obtained from diet. Omega-3 polyunsaturated fatty acids consumption are a lot higher when comparing to the Western diet due to the high seafood intake.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are common types of omega-3 fatty acids found abundantly in cold-water fishes, such as tuna and salmon. Daily intake of EPA and DHA have been shown to have cardioprotective, anti-inflammatory, immunoregulatory, antioxidant and anticancer activities [18]. Omega-3 fatty acids show a strong anti-inflammatory and anti-cancer properties, which are crucial in breast cancer preventions. A study that investigated the role of DHA in triggering pyroptosis activation in breast cancer cells showed that DHA induces pyroptosis

programmed cell death in breast cancer cells[26].Moreover,the combination of omega-3 fatty acids with hydroxytyrosol and curcumin may also potentially reduce the inflammation in patients with breast cancers and can reduce their pain with aromatase-induced musculoskeletal symptoms.The clinical trial study involved 45 post-menopausal breast cancer patients with elevated C-reactive protein (CRP) taking predominantly aromatase inhibitors to receive a combination of hydroxytyrosol,omega-3 fatty acids,and curcumin for 1month.CRP,other inflammation-associated cytokines,and pain scores on the Brief Pain Inventory were measured before,at the end of the therapy,and 1 month after completion of the therapy [27].

3.5 Legumes and Nuts

Legumes,nuts,and seeds are encouraged in theMediterranean diet.They can not only bring deliciousness to the cuisines,but also provide plant-based proteins and other healthful nutrients.In a population-based case-control study,350 newly developed breast cancer and 700 controls were matched with cases in terms of age and socioeconomic status.Dietary intake of the participants was assessed using the food frequency questionnaire.Legume intake included the consumption of lentils,peas,chickpeas,red beans,and pinto beans;while nuts intake included the consumption of mixed nuts,almond,peanut,walnut,and hazelnut.Mean consumption of legume and nuts among cases and controls were 14.7 ± 15.0 and 2.3 ± 5.6 , respectively.A significant inverse association was found between legume intake and breast cancer (OR=0.41,95%CI: 0.30–0.57);participants in the top tertial of legume intake had 46% lower odds of breast cancer compared with those in the bottom tertial (OR=0.54,95%CI: 0.36–0.88).For nuts intake,it was also inversely associated with odds of breast cancer (OR=0.16,95%CI: 0.11–0.23).The result of the study suggests an inverse association of legume and nuts intake with odds of breast cancer [29].

4. Conclusions

Breast cancer is a fast-developing disease that affects billions of people around the world. While the treatments are being researched, using medical nutrition therapy to lower the risk of breast cancer is critical in lowering the population with breast cancer and improve the overall quality of life of cancer patients.A large body of clinical and epidemiological studies have observed the protective effect of the MedDiet on cardiovascular disease, diabetes, obesity as well as cancer.The reason may be that the Mediterranean diet reduces the risk of breast cancer by providing powerful antioxidants,such as phenols, from various plant-based foods,and also acts as an anti-inflammatory diet by providing high levels of omega-3 fatty acids combined with other plant-based foods.The Mediterranean diet should be advocated clinically to reduce the risk of breast cancer.

References

- [1] CDC, <https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/>
- [2] Xiao, Yunjun et al. “Associations between dietary patterns and the risk of breast cancer: a systematic review and meta-analysis of observational studies.” *Breast cancer research: BCR* vol. 21,1 16. 29 Jan. 2019, doi: 10.1186/s13058-019-1096-1
- [3] NIH, <https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones>
- [4] Chen, Lu et al. “Milk and yogurt intake and breast cancer risk: A meta-analysis.” *Medicine* vol. 98, 12 (2019): e14900. doi:10.1097/MD.00000000000014900
- [5] De Cicco, Paola et al. “Nutrition and Breast Cancer: A Literature Review on Prevention, Treatment and Recurrence.” *Nutrients* vol. 11,7 1514. 3 Jul. 2019, doi: 10.3390/nu11071514
- [6] Hou, Ruixue et al. “Healthy dietary patterns and risk and survival of breast cancer: a meta-analysis of cohort studies.” *Cancer causes & control: CCC* vol. 30,8 (2019): 835-846. doi: 10.1007/s10552-019-01193-z

- [7] Xie, Mingsi et al. “Whole Grain Consumption for the Prevention and Treatment of Breast Cancer.” *Nutrients* vol. 11,8 1769. 1 Aug. 2019, doi:10.3390/nu11081769
- [8] Gu, Hao-Feng et al. “Prevention of breast cancer by dietary polyphenols-role of cancer stem cells.” *Critical reviews in food science and nutrition* vol. 60,5 (2020): 810-825. doi:10.1080/10408398.2018.1551778
- [9] Guasch-Ferré, M, and W C Willett. “The Mediterranean diet and health: a comprehensive overview.” *Journal of internal medicine* vol. 290,3 (2021): 549-566. doi:10.1111/joim.13333
- [10] Detopoulou, Paraskevi et al. “Micronutrients, Phytochemicals and Mediterranean Diet: A Potential Protective Role against COVID-19 through Modulation of PAF Actions and Metabolism.” *Nutrients* vol. 13,2 462. 30 Jan. 2021, doi:10.3390/nu13020462
- [11] Visioli, Francesco, and Claudio Galli. “Biological properties of olive oil phytochemicals.” *Critical reviews in food science and nutrition* vol. 42,3 (2002): 209-21. doi:10.1080/10408690290825529
- [12] Fujiki, H.; Sueoka, E.; Watanabe, T.; Suganuma, M. Primary cancer prevention by green tea, and tertiary cancer prevention by the combination of green tea catechins and anticancer compounds. *J. Cancer Prev.* **2015**, *20*, 1–4.
- [13] Liskova, Alena et al. “Dietary phytochemicals as the potential protectors against carcinogenesis and their role in cancer chemoprevention.” *Clinical and experimental medicine* vol. 20,2 (2020): 173-190. doi:10.1007/s10238-020-00611-w
- [14] Kapinova A, Stefanicka P, Kubatka P, et al. Are plant-based functional foods better choice against cancer than single phytochemicals? A critical review of current breast cancer research. *Biomed Pharmacother.* 2017; 96:1465–77.
- [15] Ranjan, Alok et al. “Role of Phytochemicals in Cancer Prevention.” *International journal of molecular sciences* vol. 20, 20 4981. 9 Oct. 2019, doi:10.3390/ijms20204981
- [16] Turati, Federica, et al. “Mediterranean Diet and Breast Cancer Risk.” *Nutrients*, vol. 10, no. 3, Mar. 2018, p. 326. *Crossref*, <https://doi.org/10.3390/nu10030326>.
- [17] Khan, A.; Chen, H.-C.; Wan, X.-X.; Tania, M.; Xu, A.-H.; Chen, F.-Z.; Zhang, D.-Z. Regulatory effects of resveratrol on antioxidant enzymes: A mechanism of growth inhibition and apoptosis induction in cancer cells. *Mol. Cells* **2013**, *35*, 219–225.
- [18] Augimeri, Giuseppina, et al. “Nutraceuticals in the Mediterranean Diet: Potential Avenues for Breast Cancer Treatment.” *Nutrients*, vol. 13, no. 8, July 2021, p. 2557. *Crossref*, <https://doi.org/10.3390/nu13082557>.
- [19] Valeria Tosti, MD, Beatrice Bertozzi, PhD, Luigi Fontana, MD, PhD, Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms, *The Journals of Gerontology: Series A*, Volume 73, Issue 3, March 2018, Pages 318–326, <https://doi.org/10.1093/gerona/glx227>
- [20] Farvid, M.S.; Eliassen, A.H.; Cho, E.; Liao, X.; Chen, W.Y.; Willett, W.C. Dietary Fiber Intake in Young Adults and Breast Cancer Risk. *Pediatrics* **2016**, *137*, e20151226.
- [21] Mourouti, N.; Kontogianni, M.D.; Papavagelis, C.; Psaltopoulou, T.; Kapetanstrataki, M.G.; Plytzanopoulou, P.; Vassilakou, T.; Malamos, N.; Linos, A.; Panagiotakos, D.B. Whole Grain Consumption and Breast Cancer: A Case-Control Study in Women. *J. Am. Coll. Nutr.* **2016**, *35*, 143–149
- [22] Makarem, N.; Bandera, E.V.; Lin, Y.; McKeown, N.M.; Hayes, R.B.; Parekh, N. Associations of Whole and Refined Grain Intakes with Adiposity-Related Cancer Risk in the Framingham Offspring Cohort (1991–2013). *Nutr. Cancer* **2018**, *70*, 776–786.

- [23] Zhang, L.Z.; Liu, R.H. Phenolic and carotenoid profiles and antiproliferative activity of foxtail millet. *Food Chem.* **2015**, *174*, 495–501
- [24] Cho, K.; Lee, C.W.; Ohm, J.-B. In Vitro Study on Effect of Germinated Wheat on Human Breast Cancer Cells. *Cereal Chem.* **2016**, *93*, 647–649.
- [25] Kubatka, P.; Kello, M.; Kajo, K.; Kruzliak, P.; Vybohova, D.; Smejkal, K.; Marsik, P.; Zulli, A.; Gonciová, G.; Mojzís, J.; et al. Young Barley Indicates Antitumor Effects in Experimental Breast Cancer In Vivo and In Vitro. *Nutr. Cancer* **2016**, *68*, 611–621
- [26] Pizato, N., Luzete, B.C., Kiffer, L.F.M.V. *et al.* Omega-3 docosahexaenoic acid induces pyroptosis cell death in triple-negative breast cancer cells. *Sci Rep* **8**, 1952 (2018). <https://doi.org/10.1038/s41598-018-20422-0>
- [27] Martínez, N., Herrera, M., Frías, L. *et al.* A combination of hydroxytyrosol, omega-3 fatty acids and curcumin improves pain and inflammation among early stage breast cancer patients receiving adjuvant hormonal therapy: results of a pilot study. *Clin Transl Oncol* **21**, 489–498 (2019). <https://doi.org/10.1007/s12094-018-1950-0>
- [28] Farvid, M.S., Chen, W.Y., Rosner, B.A., Tamimi, R.M., Willett, W.C. and Eliassen, A.H. (2019), Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up. *Int. J. Cancer*, *144*: 1496-1510. <https://doi.org/10.1002/ijc.31653>
- [29] Yaser Sharif, Omid Sadeghi, Sanaz Benisi-Kohansal, Leila Azadbakht & Ahmad Esmailzadeh (2021) Legume and Nuts Consumption in Relation to Odds of Breast Cancer: A Case-Control Study, *Nutrition and Cancer*, *73*:5, 750-759, DOI: 10.1080/01635581.2020.1773874