Mediterranean diet for breast cancer prevention and treatment in postmenopausal women

Elżbieta Potentas, Anna Maria Witkowska, Małgorzata Elżbieta Zujko

Department of Food Commodities Science and Technology, Medical University of Białystok, Poland

Abstract

Breast cancer has become a big oncological concern both in Poland and most countries around the world. Epidemiological studies show that women who are directly in danger of suffering from breast cancer are mainly postmenopausal women. Due to the seriousness of the problem more attention is devoted to preventative measures that should be undertaken. That is why, Mediterranean diet and its beneficial effects on health started to be discussed. This diet contains antioxidants and shows anti-inflammatory properties which are crucial in breast cancer prevention. Its components are fish, olive oil, unrefined cereals, herbs, fruits and vegetables. In 1960s there was research done on the influence of low fat diet, as a preventative measure, on coronary artery disease. In 1980s, an interest in this diet grew and there was a great come-back to the origins of the diet. It led to estimation of its influence on cardiological and cancer diseases. Many positive effects were observed among people living in the Mediterranean area as far as health qualities of the diet are concerned. Mediterranean diet was compared with high fat diet of people living in Northern Europe and the USA. It seems to create new dietary recommendations as a preventative measure in breast cancer disease. The following article presents most recent data on the importance of Mediterranean diet as a prevention against breast cancer.

Key words: Mediterranean diet, breast cancer, antioxidants.

Introduction

Breast cancer, after lung cancer, is the second most commonly diagnosed malignancy in women both in Poland and most countries around the world. According to epidemiological data, in 2007, about 1.3 million occurrences of breast cancer were diagnosed and four hundred thousand cases led to death of a patient. Breast cancer patients account for about 34% of all women living with cancer. Analysis of the epidemiological data shows a steady increase in the incidence of breast cancer, especially in developed countries, but also developing countries. The cause of this phenomenon is believed to be a result of reduced physical activity, reproductive behavior change, as well as widespread use of hormone replacement therapy [1].

According to figures published by the Department of Epidemiology and Cancer Prevention Oncological Centre, Maria Skłodowska-Curie Institute, in 2008, 14,576 new cases of breast cancer were diagnosed and four hundred thousand cases led to death of a patient. Breast cancer patients account for about 34% of all women living with cancer. Analysis of the epidemiological data shows a steady increase in the incidence of breast cancer, especially in developed countries, but also developing countries. The cause of this phenomenon is believed to be a result of reduced physical activity, reproductive behavior change, as well as widespread use of hormone replacement therapy [1].

In 2011, the incidence of breast cancer accounted for 22.8% of all cancers, which placed this cancer in the first place in the classification of the incidence of all cancers; it was also the second most common cause of death from cancer [3].

Epidemiological data of 2012 show that the incidence of breast cancer cases in Poland was an average 52.9 per 100,000 with the mortality rate of 13.5/100,000 [3]. The prognosis for Poland for the year 2015 assumes the number of 17,500 cases of breast cancer, and in the year 2025 it will already be 21,100 cases [4].

Risk factors for breast cancer

Signs of breast cancer include pathological changes in milk ducts and lobules, and both locations include changes with mild hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ or the invasive cancer. Recognized risk factors for breast cancer include: age over 50 years of age, the family burden, endo- and exogenous sex hormones, obesity, low physical activity, alcohol abuse, exposure to ionizing radiation and...
diet. About 5-10% of breast cancer cases are hereditary. A 56-85% risk of developing breast cancer occurs in women with mutations of suppressor genes BRCA1 and BRCA2 [5, 6].

Another factor that may determine occurrence of breast cancer is primary immunodeficiencies, and especially ataxia telangiectasia syndrome which is characterized by mutations of the ATM gene [6].

The oral contraceptives usage and its direct association with breast cancer is still a matter of debate. But a number of studies has demonstrated an increase in the risk of developing breast cancer in women taking these hormonal therapies [7, 8].

Another factor increasing the risk of developing breast cancer is exposure to ionizing radiation, especially at a young age (numerous X-rays, radiation therapy in the treatment of dermatological lesions, radiation therapy in the treatment of cancer) [9].

A clear risk factor for endometrial cancer and breast cancer in postmenopausal women is overweight. Epidemiological studies suggest that there are links between fat intake and breast cancer. It was hypothesized that the high-fat or high-calorie diets, leading to an increase in the fat content in the body, can affect the development of breast cancer. This is done by raising the circulation levels of certain hormones, prolactin and estrogen, which may facilitate the development of breast cancer. It is believed that food fat or fat contained in the body adversely affects the immune system, which becomes less efficient in combating emerging cancer cells [10].

Studies show a link between obesity and risk of breast cancer in postmenopausal women. Most cases of breast cancer in postmenopausal women are sensitive to estrogen, and estrogen produced in adipose tissue is conducive to the formation of a tumor [11]. Obesity causes secretion of inflammatory factors that stimulate aromatase enzyme responsible for the steroid hormone biosynthesis [11]. This affects the conversion of androgens into estrogen in adipose tissue. Neuhouser et al. [12] also confirm that obesity is closely linked with the growth of invasive breast cancer in postmenopausal women compared to women of normal weight.

Mediterranean diet

The Mediterranean diet, which is a traditional dietary pattern of the inhabitants of the Mediterranean countries, is considered to be one of the healthiest diets rich in many nutrients. This is not only due to its taste, but also a varied menu based on a large amount of fresh vegetables and fruits, fish, legumes, whole grains, olive oil and herbs. However, the main cause of the promotion of the Mediterranean diet is its health-related properties. The research has shown its impact on diminishing the risk of coronary and cancer diseases.

Fundamentals of the Mediterranean diet have been formulated on the basis of eating habits of people living in the Mediterranean countries. The following common features have been found in their diet:

- high consumption of fruits, vegetables, potatoes, legumes, nuts, whole grains,
- high consumption of olive oil as the main source of fat,
- high consumption of spices such as oregano, garlic, basil, thyme, rosemary, sage,
- moderate consumption of fish and seafood,
- moderate consumption of milk and dairy products (mainly cheese and yoghurt),
- moderate consumption of wine, mainly for meals,
- low consumption of meat and meat products,
- consumption of local, seasonal fresh produce [13].

Health properties of a traditional Mediterranean diet result from consumption of large quantities of vegetable products that are a source of bioactive components. These components have anti-cancer properties that include carotenoids, antioxidant vitamins (vitamin C, E, A), lycopene, resveratrol, flavonoids, polyphenols and dietary fiber. The Mediterranean diet is characterized by a favorable ratio of polyunsaturated fatty acids of omega-6 family to omega-3, which is about 2 : 1. In other European countries and the United States, this ratio is 10 : 1 and 20 : 1, respectively [14].

Interest in the Mediterranean diet dates back to the early sixties of the last century, when the American researcher Ancel Keys has published a report which presented a study on the effect of low fat diet on the reduced risk of coronary heart disease [14]. In 1980s, the diet gained widespread recognition and in 1995 a questionnaire was developed, based on the detailed characteristics of the individual components of the Mediterranean diet [15]. This allowed for an assessment of its impact on the risk of developing the condition and mortality, especially in cardiac diseases and cancer [16-23].

On the basis of the above questionnaire, first research assessing the influence of eating habits on the development and progression of hormone-dependent breast cancer among postmenopausal women was conducted [24]. The authors of the study observed the relationship between use of the Mediterranean diet, in which consumption of each characteristic product was evaluated with the help of the Mediterranean Diet Score (MDS), and a reduction in the incidence of breast cancer disease in the examined population. European research evaluated the impact of the Mediterranean diet on the development of breast cancer both in countries where this diet is traditional, and in the countries of Northern Europe, where higher amounts of red meat and saturated fat are consumed. Assessment of compliance with the recommendations of the Mediterranean diet was made on the basis of a questionnaire, in which the 10-point scale (0-9) evalu-
uated the contribution of each of its components in the menu of the surveyed people [16]. The results were counted on the basis of 9 characteristic food products. 0 or 1 points correspond to diet products such as vegetables, legumes, fruits, nuts, cereals, fish and seafood and a high content of unsaturated fatty acids. One point is given for moderate alcohol consumption in a daily dose from 5 up to 25 g. The total scoring balances ranged between 0 – no participation of the components of the diet and 9 – maximum saturation of the diet with components typical for the Mediterranean diet.

Greek studies evaluated the influence of the Mediterranean diet on progression of breast cancer [25]. Oncological diagnosis was established on the basis of the guidelines by the International Classification of Diseases for Oncology [26]. The research initially qualified 16,172 women, but the final assessment excluded 520 women who did not undergo long-term observations on specific stages of evaluation, and another 845 women, who, in the course of observation, among others changed their dietary habits. Finally, 14,807 women were examined, and the period of the study ranged from 9.8 to 15.8 years. In the rated group, 240 women were diagnosed with breast cancer. In this particular group, an impact of the diet was measured by MDS index on the progression of the disease. Significant differences in disease progression were observed only in the group of older postmenopausal women. In the subgroup that did not stick to the diet the progression of the disease was visibly faster than in the group that complied with the recommendations of the Mediterranean diet (p < 0.03) [25].

Epidemiological studies were launched in 1993 under the auspices of the International Agency for Research on Cancer (IARC) and World Health Organization in order to assess the impact of diet on the development and progression of cancer in terms of practical aspects and the promotion of healthy dietary habits [27]. The European coordinators of the research were experts in the European Prospective Investigation into Cancer and Nutrition European Prospective Study: cancer and nutrition (EPIC) [28]. The study involved 521,468 people, including 366,521 women aged from 39 to 69 years. The study was performed in 10 countries and 23 centers from the countries that were involved: Germany, Denmark, the Netherlands, Norway, Sweden, Great Britain, France, Spain, Italy, and Greece. The examined group included 24,195 people, 7272 men and 16,923 women with the diagnosed cancer. Among women who took part in the research, there were 7119 women diagnosed with breast cancer.

For the purposes of the survey, a questionnaire was developed, in which the presence of 260 foodstuffs in the diet was evaluated. The first results of a comparative study were published in 2002. Participation in the diet of plant products, inter alia, such as fruits and vegetables was analyzed. As expected, based on the knowledge of eating habits, the smallest consumption of these products was observed in Sweden and Norway, the largest in Spain. In the next stage of the study, the effect of diet on cancer development was examined. In the conducted analysis, the variable correlation between the progression of malignant breast cancer and the presence of saturated fat in the diet was observed. For the purposes of the interpretation of the results obtained, two working hypotheses to explain the observed phenomenon were tested. The first of them was that the supply of fats stimulates the synthesis of endogenous estrogen, and this, as we all know, affects the progression of changes in the course of a malicious hormone-dependent breast cancer [29-31]. Another hypothesis was that limiting consumption of saturated fat can affect the reduction of concentration and decrease the activity of sex hormones, which translates, in effect, to slow progression of the disease [32-34].

Another observation was made regarding participation of vegetable products in the diet. And so it has been observed that their greater supply correlated with slowing down the progression of colorectal cancer, and in turn, a greater share of meat in the diet, especially red meat, resulted in increased progression of the cancer process [35]. Similar results were obtained in a study conducted in the United States, where a negative correlation between supply of vegetable products, as well as nuts and seeds, grains and progression of cancer in women was found. Such relations were not observed in the case of breast cancer in women and prostate cancer in men [36, 37].

In 1991-1992, a large-scale, population-based study was launched in Scandinavia to assess the impact of diet, among other things, on the risk of developing breast cancer in a group of 96 thousand women aged 30 to 49 years. The observation period included 16 years and assessed finally 44,840 women, with 1278 diagnosed with breast cancer. The influence of the Mediterranean diet on the risk and progression of breast cancer, both hormone dependent as well as hormone independent, was examined [38]. The contribution of individual components of the diet was evaluated according to the MDS score developed by Trichopoulos et al. [39]. In conclusion, the study observed no particular relationship between the use of typical products for the Mediterranean diet and the risk and progression of breast cancer, both hormone dependent and hormone independent. The only risk factor for low-impact strength, however, was alcohol consumption.

Other than the above epidemiological assessment results were obtained by the Spanish researchers who observed the impact of the Mediterranean diet on progression of disease in 1017 women diagnosed with breast cancer [40]. The observation which was carried out for 5 years, assessed consumption of 117 food.
products. Because the alcohol consumption has been recognized as a promoting factor of the development and progression of cancer processes [41, 42], it was excluded from being evaluated in the diet. In the studies, a correlation has been found between the use of food products typical for the "Western diet" (red meat, saturated fats, white bread) and progression of breast cancer. Such relation was observed more strongly in postmenopausal women.

Other relations were found in a group of women consuming a Mediterranean diet rich in fruits, vegetables and unsaturated fats. In this study group, the use of food products typical for this diet did not correlate with a reduction in the degree of progression of breast cancer, especially in the case of hormone independent cancers [43]. In conclusion, the study attempted to interpret the observed phenomenon [43]. And so the hypothesis tested was that the probable mechanism explaining the phenomenon of the impact of the Mediterranean diet to slow the progression of breast cancer in women, is high content of antioxidants in plant foods. In the examined cases, a hypothetical influence of antioxidants manifested itself in an inhibition of the synthesis and activity of growth factors that promote development of cancer cells, starting from activation of carcinogens, through regulating the cell cycle, to the process of angiogenesis and promotion of the local inflammatory response.

Rich sources of antioxidants, for example, are whole grain cereals commonly found in the Mediterranean diet; in turn, in the "Western diet", cereal grains are generally in the form of highly processed flour products. Whole grains contain carbohydrates with a low glycemic index (GI), while high GI products, in this case highly processed grains, stimulate increased insulin and the insulin-like growth factor (IGF) synthesis with a proven impact on the promotion of the risk of developing tumors [44]. The effect of IGF in the development of cancer manifests itself, inter alia, by inhibiting the apoptosis induced by gamma radiation, cytotoxic factors and proinflammatory cytokines as TNF, induction of production of vascular endothelial growth factor (VEGF) dependent on hypoxia-inducible factor-1 (HIF-1), which is one of the primary mechanisms for promoting the process of angiogenesis. IGF stimulates the signaling pathway of beta-catenin that initiates the development of cancer [44]. It also stimulates the synthesis of the factors promoting the proliferation and activation of cells, for example estrogen, which in the case of hormone-dependent breast cancers seems to have a fundamental importance in initiating and sustaining the cancer process.

Polyphenols are compounds common in plants, but only recently returned to account as healthy ingredients of a diet. As natural antioxidants they can protect the body against reactive oxygen species (ROS) and reactive nitrogen species (RNS). They also have the ability of chelation of iron ions and copper and may intensify the activity of other antioxidants. Polyphenols have a sealing as well as vasodilatory ability. They also show antibacterial, antiviral, anti-inflammatory and anti-thrombotic properties [45, 46]. Polyphenols are considered to be one of the most effective substances that prevent cardiovascular and oncological disease [47, 48].

Resveratrol is a natural phytoalexin, which is found in skins of red fruits, including grapes. It is also present in high concentrations in the wine, mostly red. This compound has a wide range of biological activity, including cytotoxic activity, antifungal, antimicrobial, antiviral and cytoprotective activity, and also protects against the development of neurodegenerative processes. Resveratrol is found in two forms of cis-and trans-isomers. Trans-resveratrol is a stilbenoid present in common grape vine Vitis vinifera [49]. The second form of resveratrol, cis-resveratrol, is formed as a result of isomerization of trans-resveratrol and after the dissolution of the polymer molecule of resveratrol of grape skins during fermentation, by the action of UV rays and high pH [50].

In conditions conducive to the emergence of obesity, which is the consumption of high-fat, high-calorie diet, resveratrol affects the regulation of energy balance, which can prevent the diet-dependent obesity and related metabolic disorders. This is due to the activation of protein SIRT1 by resveratrol. SIRT1 is the enzyme that regulates appetite, a member of the sirtuin family of proteins, which is capable of regulating the activity of certain transcription genes [51]. Resveratrol plays an important role in the prevention of cancer by blocking the process of initiation, promotion and progression. As a phytoestrogen it regulates the expression of numerous genes associated with the development of breast cancer, including a tumor suppressor BRCA1 gene [52]. It has been shown that resveratrol induces apoptosis of breast cancer cells by the action of protein p-53 [53].

Another compound, which demonstrates breast cancer protective properties is urolithin B. It is a metabolite of ellagic acid in pomegranate, which is formed under the influence of the bacterial flora of the gastrointestinal tract. Urolithin B inhibits aromatase activity (the enzyme responsible for the conversion of androgens into estrogen) as well as the process of proliferation of tumor cells in the mammary gland in vitro [54]. The results of this research stress the protective role of ellagic acid as well as its metabolites in the prevention of hormone dependent breast cancer [54].

One of the natural antioxidant substances is lycopene, bright red carotenoid pigment found in tomatoes. Technological processes that use high temperature such as braising, baking, frying or steaming increase its bioavailability in the body. Lycopene shows antitumor activity, which is associated with antioxidant, anti-inflammatory and immunomodulatory properties and it is capable to affect the expression of the Antioxidant...
animal fats were prevalent [63], a phenomenon not served in female population, in whose diets saturated and monounsaturated and polyunsaturated fats. Interpretation of the research above seems to be difficult due to the difficulty in assessing the contribution of saturated and monounsaturated fats in diet due to their co-occurrence in a variety of food products, such as butter and margarine, beef or poultry, dairy products and cheese.

On the basis of meta-analyses carried out, the supply of saturated fat in the diet can be one of the causes of development and progression of the disease process in the case of malignant breast cancer in women [34, 64, 65]. In the summary of the above assessment, consideration was given to possible mechanisms for the impact of diet on the possible progression of the cancer process. According to the authors of the study, those mechanisms include stimulation of the synthesis of endogenous steroid hormones that modulate the immune system function in its anticancer response, and modulation of the gene expression in cancer cells, as well as expression of these genes, which stimulate the synthesis of sex hormones with a recognized impact on the development and progression of hormone dependent breast cancer [34, 64, 65].

For the preparation of dishes, in addition to the basic products, a variety of herbs and spices that enhance food flavor, but also have healing properties, are also used. They contain bioactive components with anticancer properties such as apigenin and quercetin (basil, oregano), rosmarinic acid (rosemary), curcumin (turmeric) and gingerol (ginger), allicin (garlic), and apigenin (basil, marjoram). The effect of anticancer herbs may result from their antioxidant, anti-inflammatory, and antimicrobial properties as well as from inhibition of bio-activation of carcinogens in the body [2, 66]. Supercritical fluid rosemary extract (SFRE) has shown antitumor activity against different subtypes of breast cancer by decreasing the expression of ER-α receptor HER2 (responsible for the signaling pathway of estrogen dependent ER+ breast tumors and showing HER2 expression). The rosemary extract increases the effect of anticancer drugs used in the treatment of breast cancer (tamoxifen, trastuzumab, paclitaxel). These results confirm the potential usefulness of SFRE as a complementary approach in the therapy of breast cancer [67].

Conclusions

Epidemiological data indicate a steady increase in the incidence of breast cancer, especially in developed countries, but also in developing countries. One of the risk factors for breast cancer is poor and high-fat diet. For this reason, there is an interest in the Mediterranean diet, which contains small amounts of saturated animal fats, considered one of the causes of development and progression of breast cancer. The Mediterranean diet is rich in antioxidants, which probably inhibit...
the synthesis as well as activity of growth factors that promote the development of cancer cells. It is thought that the phenominal feature of this diet is inhibition of breast cancer processes due to a high level of antioxidants it contains [43]. A review of the literature shows that the Mediterranean diet can also be utilized as a preventative measure in breast cancer, especially in postmenopausal women [17]. Further careful observations are conducted to examine the influence of this particular diet on breast cancer development. It may be the starting point to develop dietary recommendations for women at risk, as well as women suffering from breast cancer in order to slow down the progression of the disease.

Disclosure
Authors report no conflict of interest.

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