

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. In the population of Polish women, breast cancer is the most common malignancy registered and represents 22.2% of all cancers. The largest number of malignant breast cancer cases is registered between the 50th and 69th year of life. After attaining the age of 45 years, the

number of deaths increases due to breast cancer and it is constant at the age of 50-79 years [2].

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

Corresponding author:

Małgorzata Zujko, Department of Food Commodities Science and Technology, Medical University of Białystok, 37 Szpitalna St., 15-295 Białystok, Poland, e-mail: malgorzata.zujko@umb.edu.pl

Submitted: 14.04.2015

Accepted: 27.10.2015

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 AT 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 diet 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 is, 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) eval-

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 Trichopoulou *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

Response Element (ARE) gene [48]. Lycopene competes with estrogen for estrogen receptors ER α and ER β , thus reducing transactivation of the Estrogen Response Element (ERE) contained in DNA [48]. The Mediterranean diet rich in fresh and processed tomatoes, prepared with the use of high temperatures and consumed in the form of sauces and as well as ingredients of many dishes, may be a preventative measure in reducing the risk of cancer.

Interest in the Mediterranean diet also resulted in research on the role of olive oil, which is the predominant fat in this diet. A special attention is drawn to its protective effect in cardiovascular diseases, but also in cancer [55]. Natural antioxidants in olive oil, such as phenols, sterols, carotenoids, tocopherol, squalene can protect the body from adverse effects caused by free radicals [56].

Effects of vitamin E, which is found in large quantities in olive oil, is primarily due to its antioxidant properties. This vitamin protects the human system against accumulation of lipid peroxides and free radicals. Lower concentrations of vitamin E promote an increase in the incidence of some cancers, because of lowered antioxidant potential [57]. Some studies showed that α -tocopherol inhibited premalignant stages of breast cancer in women [58].

The effect of olive oil in the prevention of breast cancer was observed in a study carried out in Spain in 2003-2009. The study involved 4282 women aged 60 to 80 years who were at a high risk of cardiovascular disease [59]. They were randomly assigned to three groups: 1) the Mediterranean diet with the addition of extra virgin olive oil, 2) Mediterranean diet supplemented with a variety of nuts or 3) control diet with a reduced fat content. After the average follow-up of 4.8 years, 35 confirmed cases of cancer of the breast were identified. The following indicators of morbidity for breast cancer have been observed: for every 1000 women using the Mediterranean diet with an increased amount of extra virgin olive oil, only 1.1 became sick within a year, while in a group with an increased amount of nuts, 1.8 and 2.9 in the control group. This was the first randomized controlled trial showing the effect of long-term dietary modification on the incidence of breast cancer. The results suggest a beneficial effect of Mediterranean diet with the addition of extra virgin olive oil in primary prevention of breast cancer [59].

In three independent population-based studies [27, 60-62] a significant correlation between the amount of fat in the diet and the risk of progression of hormone dependent breast cancer was observed. Previous research evaluated the risk of disease progression depending on the type of fat consumed in the form of saturated, monounsaturated and polyunsaturated fats. And so the greatest risk of disease progression was observed in female population, in whose diets saturated animal fats were prevalent [63], a phenomenon not

observed in groups of women eating monounsaturated or 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 phenomenal 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.

References

- Kornafel J (ed.). Rak piersi. Centrum Medyczne Kształcenia Podyplomowego, Warszawa 2011.
- Wojciechowska U, Didkowska J, Zatoński W. Nowotwory złośliwe w Polsce w 2006 roku. Centrum Onkologii – Instytut im. Marii Skłodowskiej-Curie, Warszawa 2008.
- Didkowska J. Epidemiologia nowotworów złośliwych piersi w Polsce, Krajowy Rejestr Nowotworów Zakład Epidemiologii i Epidemiologii Nowotworów Centrum Onkologii – Instytut im. M. Skłodowskiej-Curie w Warszawie; available at: www.korektorzdrowia.pl/wp-content/uploads/5.-joanna.didkowska.pdf.
- Didkowska J, Wojciechowska U, Zatoński W. Prognozy zachorowalności i umieralności na nowotwory złośliwe w Polsce do 2025 roku, s.47. Publikacja wydana w ramach zadania „Rejestracja nowotworów złośliwych” Narodowego Programu Zwalczenia Chorób Nowotworowych, Warszawa 2009.
- Easton DF, Bishop DT, Ford D, et al. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *Am J Hum Genet* 1993; 52: 678-701.
- Struwing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997; 336: 1401-1408.
- Beral V. Collaborative Group on Hormonal Factors in Breast Cancer: Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997; 350: 1047-1059.
- Ursin G, Ross RK, Sullivan-Halley J, et al. Use of oral contraceptives and risk of breast cancer in young women. *Breast Cancer Res Treat* 1998; 50: 175-184.
- John EM, Kelsey JL. Radiation and other environmental exposures and breast cancer. *Epidemiol Rev* 1993; 15: 157-162.
- Willet WC. Diet and cancer. *Oncologist* 2000; 5: 393-404.
- Wang X, Simpson ER, Brown KA. Aromatase overexpression in dysfunctional adipose tissue links obesity to postmenopausal breast cancer. *J Steroid Biochem Mol Biol* 2015; 153: 35-44.
- Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. *JAMA Oncol* 2015; 1: 611-621.
- Trichopoulou A. Traditional Greek Mediterranean diet: an expression of culture, history and lifestyle. In: *Greek traditional cuisine*. O.T.E.K., Athens 2004; 16-19.
- Itsiopoulos C, Hodge A, Kaimakamis M. Collaborative Group on Hormonal Factors in Breast Cancer: Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Mol Nutr Food Res* 2009; 53: 227-239.
- Trichopoulou A, Kouris-Blazos A, Wahlgvist M, et al. Diet and overall survival in elderly people. *BMJ* 1995; 311: 1457-1460.
- Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003; 348: 2599-2608.
- Fung TT, McCullough ML, Newby PK, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr* 2005; 82: 163-173.
- Trichopoulou A, Orfanos P, Norat T, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ* 2005; 330: 991.
- Mitrou PN, Kipnis V, Thiébaud ACM, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population. Results from the NIH-AARP Diet and Health Study. *Arch Intern Med* 2007; 167: 2461-2468.
- Sofi F, Cesari F, Abbate R, et al. Adherence to Mediterranean diet and health status: eta-analysis. *BMJ* 2008; 337: a1344.
- Fung TT, Rexrode KM, Mantzoros CS, et al. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* 2009; 119: 1093-1100.
- Benetou V, Trichopoulou A, Orfanos P, et al. Conformity to traditional Mediterranean diet and cancer incidence: The Greek EPIC cohort. *Br J Cancer* 2008; 99: 191-195.
- Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. *Nutr Metab Cardiovasc Dis* 2006; 16: 559-568.
- Fung TT, Hu FB, McCullough ML, et al. Diet quality is associated with the risk of estrogen receptor-negative breast cancer in postmenopausal women. *J Nutr* 2006; 136: 466-472.
- Trichopoulou A, Bamia C, Lagiou P, Trichopoulos D. Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. *Am J Clin Nutr* 2010; 92: 620-625.
- World Health Organization. International classification of diseases for oncology. 2nd ed. WHO, Geneva 1990.
- Gonzalez CA. The European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* 2006; 9 (1A): 124-126.
- Kaaks R, Berrino F, Key T, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2005; 97: 755-765.
- Michels KB, Mohlajee AP, Roset-Bahmanyar E, et al. Diet and breast cancer: a review of the prospective observational studies. *Cancer* 2007; 109: 2712-2749.
- Kaaks R, Berrino F, Key T, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2005; 97: 755-765.
- Kaaks R, Rinaldi S, Key TJ, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Endocr Relat Cancer* 2005; 12: 1071-1082.
- Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. *Cancer Causes Control* 1990; 1: 81-97.
- Berrino F, Bellati C, Secreto G, et al. Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomized trial. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 25-33.
- Wu AH, Pike MC, Stram DO. Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. *J Natl Cancer Inst* 1999; 91: 529-534.
- Buckland G, Agudo A, Luján L, et al. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr* 2010; 91: 381-390.
- Thiebaut AC, Kipnis V, Chang SC, et al. Dietary fat and postmenopausal invasive breast cancer in the National Institutes of Health – AARP Diet and Health Study cohort. *J Natl Cancer Inst* 2007; 99: 451-462.

37. Kabat GC, Kim MY, Hollenbeck AR, Rohan TE. Attained height, sex, and risk of cancer at different anatomic sites in the NIH-AARP Diet and Health Study. *Cancer Causes Control* 2014; 25: 1697-1706.
38. Couto E, Sandin S, Löf M, et al. Mediterranean dietary pattern and risk of breast cancer. *PLoS ONE* 2013; 8: e55374.
39. Trichopoulos A, Kouris-Blazos A, Wahlgvist ML, et al. Diet and overall survival in elderly people. *BMJ* 1995; 311: 1457-1460.
40. Castello A, Pollan M, Buijsse B, et al. Spanish Mediterranean diet and other dietary patterns and breast cancer risk: case-control EpiGEICAM study. *Br J Cancer* 2014; 111: 1454-1462.
41. Hastert TA, Beresford SA, Patterson RE, et al. Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 1498-1508.
42. Fedirko V, Jenab M, Rinaldi S, et al. Alcohol drinking and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Ann Epidemiol* 2013; 23: 93-98.
43. Grosso G, Buscemi S, Galvano F, et al. Mediterranean diet and cancer: epidemiological evidence and mechanism of selected aspects. *BMC Surgery* 2013; 13 (Suppl 2): S14.
44. LeRoith D, Roberts CT Jr. The insulin-like growth factor system and cancer. *Cancer Lett* 2003; 195: 127-137.
45. Ullah MF, Khan MW. Food as medicine: potential therapeutic tendencies of plant derived polyphenolic compounds. *Asian Pac J Cancer Prev* 2008; 9: 187-195.
46. Potać I, Bobrowski M, Bijak M, et al. Związki polifenolowe i ich suplementacja u kobiet po menopauzie. *Prz Menopauzalny* 2011; 2: 157-162.
47. Kołodziejczyk J, Wachowicz B. Kurkumina jako naturalny antyoksydant chroniący układ krążenia. *Postępy Fitoterapii* 2009; 4: 239-244.
48. Terlikowska K, Witkowska A, Dobrzycka B, Terlikowski SJ. Likopen w chemoprolaktyce raka piersi. *Prz Menopauzalny* 2013; 17: 358-362.
49. Todaro A, Palmeri R, Barbagallo RN, et al. Increase of trans-resveratrol in typical Sicilian wine using β -glucosidase from various sources. *Food Chem* 2008; 4: 1570-1575.
50. Gu X, Chu Q, O'Dwyer M, Zeece M. Analysis of resveratrol in wine by capillary electrophoresis. *J Chromatogr A* 2000; 881: 471-481.
51. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 α . *Cell* 2006; 6: 1-14.
52. Le Corre L, Fustier P, Chalabi N, et al. Effects of resveratrol on the expression of a panel of genes interacting with the BRCA1 oncosuppressor in human breast cell lines. *Clin Chim Acta* 2004; 344: 115-121.
53. Laux MT, Aregullin M, Berry JP, et al. Identification of a p53-dependent pathway in the induction of apoptosis of human breast cancer cells by the natural product, resveratrol. *J Altern Complement Med* 2004; 10: 235-239.
54. Adams LS, Zhang Y, Seeram NP, et al. Pomegranate ellagitannin-derived compounds exhibit antiproliferative and antiaromatase activity in breast cancer cell in vitro. *Cancer Prev Res* 2010; 3: 108-113.
55. Harwood JL, Yaqoob P. Nutritional and health aspects of olive oil. *Eur J Lipid Sci Technol* 2002; 104: 685-697.
56. Fit M, de la Torre R, Covas M. Olive oil and oxidative stress. *Mol Nutr Food Res* 2007; 51: 1215-1224.
57. Kline E, Lawson KA, Yu W, et al. Vitamin E and cancer. *Vitam Horm* 2007; 76: 435-461.
58. Divisi D, Di Tommaso S, Salvemini S, et al. Diet and cancer. *Acta Biomed* 2006; 77: 118-123.
59. Toledo E, Salas-Salvadó J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. *JAMA Intern Med* 2015; 175: 1752-1760.
60. Wirfält E, Mattisson I, Gullberg B, et al. Postmenopausal breast cancer is associated with high intakes of 6 fatty acids (Sweden). *Cancer Causes Control* 2002; 13: 883-893.
61. Bingham SA, Luben R, Welch A, et al. Are imprecise methods obscuring a relation between fat and breast cancer? *Lancet* 2003; 362: 212-214.
62. Freedman LS, Potischman N, Kipnis V, et al. A comparison of two dietary instruments for evaluating the fat-breast cancer relationship. *Int J Epidemiol* 2006; 35: 1011-1021.
63. Boyd NF, Stone J, Vogt KN, et al. Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. *Br J Cancer* 2003; 89: 1672-1685.
64. Hwang D. Fatty acids and immune responses – a new perspective in searching for clues to mechanism. *Annu Rev Nutr* 2000; 20: 431-456.
65. Jump DB, Clarke SD. Regulation of gene expression by dietary fat. *Annu Rev Nutr* 1999; 19: 63-90.
66. Kaefer CM, Milner JA. The role of herbs and Spice in cancer prevention. *J Nutr Biochem* 2008; 19: 347-361.
67. González-Vallinas M, Molina S, Vicente G, et al. Modulation of estrogen and epidermal growth factor receptors by rosemary extract in breast cancer cells. *Electrophoresis* 2014; 35: 1719-1727.