REVIEW

CURRENT EVIDENCE ON THE PROTECTIVE EFFECT OF DIETARY POLYPHENOLS ON BREAST CANCER

CONCETTINA FENGA[1]*, CHIARA COSTA[2], EMANUELA CARUSO[1], LUIGI RAFFA[1], CARMELA ALIBRANDO[1], SILVIA GANGEMI[1], ANCA OANA DOCEA[3], ARISTIDIS MICHAEL TSATSAKIS[4]

[1]*Department of Biomedical, Odontoiatric, Morphological and Functional Images, Occupational Medicine Section, University of Messina, Messina, 98125, Italy*
[2]*Department of Clinical and Experimental Medicine, University of Messina, Messina, 98125, Italy*
[3]*Department of Toxicology, Faculty of Pharmacy, University of Medicine and Pharmacy, Petru Rares Street, Craiova, 200349, Romania*
[4]*Laboratory of Toxicology, Medical School, University of Crete, Voutes, Heraklion, 71409, Crete, Greece*

**corresponding author: cfenga@unime.it*

Manuscript received: December 2015

Abstract

Epidemiological studies suggest that regular consumption of polyphenols, commonly contained in fruits and vegetables, is associated with a reduced risk of breast cancer (BC). Many epidemiological evidences suggest that the beneficial effect of a dietary pattern is attributable, at least in part, to phytochemicals which have antioxidant and antiproliferative activities. Since polyphenols are known to possess these properties, they have been hypothesized to contribute to the lower incidence of breast cancer. In this review the findings of 12 studies, including six case-control and six cohort studies are summarized and discussed. The results suggest that it is not yet possible to assess with certainty the effect of the Mediterranean diet (MD) on breast cancer (BC) risk in relation also to the individual characteristics such as genetic susceptibility, menopausal status, lifestyle and epigenetic modifications. Given the current evidences, further epidemiological studies on the relationship between polyphenols intake and BC risk are required.

Rezumat

Studiile epidemiologice sugerează că un consum constant de polifenoli, ce se găsesc în mod normal în fructe şi legume, este asociat cu un risc redus al dezvoltării cancerului de sân. Dovezile epidemiologice arată faptul că efectul benefic al regimului alimentar este atribuit, cel puţin în parte, conţinutului de fitocompuşi cu proprietăţi antioxidante şi antiproliferative. Având în vedere că polifenolii prezintă aceste proprietăţi, s-a emis ipoteza conform căreia aceştia ar contribui la scăderea incidenţei cancerului de sân. În această lucrare sunt prezentate pe scurt şi discutate concluziile a 12 studii, 6 studii de caz şi 6 studii de cohortă. Rezultatele evidenţiază că nu este încă posibil să se evalueze cu certitudine efectul dietei mediteraneene asupra riscului cancerului de sân raportat de asemenea la caracteristicile individuale, precum susceptibilitatea genetică, menopauza, modificări epigenetice şi ale stilului de viaţă. Potrivit dovezilor actuale sunt necesare pe viitor mai multe studii epidemiologice care să analizeze relaţia dintre ingestia de polifenoli şi riscul de apariţie a cancerului de sân.

Keywords: breast cancer (BC), polyphenol intake, Mediterranean diet (MD)

Introduction

The relationship between nutrition and health has been known since ancient times. Over the last 50 years, the impact of specific dietary patterns and foods of higher nutritional quality on the health and well-being of populations has been demonstrated with observational, case–control studies, prospective cohorts and randomized clinical trials. This considerable body of evidence has established that diet and dietary factors play strong roles in the prevention/ development of chronic diseases [69, 83].

The general worldwide mortality rate of breast cancer (BC) is 450,000 females annually, and each year about 1.4 million (20% female population) new cases of breast cancer are reported [26].

The highest incidence rates are observed in North America, Australia, New Zealand and Europe; conversely BC risk is very low in Asia and Africa. In Europe, it is known a north-south gradient: the incidence is higher in the Nordic countries as Belgium, Denmark and Netherlands and is lower in the Mediterranean area and in Eastern Europe [35].

In Italy, every year, BC affects about 35,000 women and it is the main cause of death in the age group between 35 and 44 years [3].

The same gradient has been recognised in Italy, as the incidence in the South including Sicily and Sardinia (93.1 cases per 100,000 women) is lower than in northern Italy (123.4 cases per 100,000 women) [75]. Historically, the incidence of overall

cancer was lower in Mediterranean countries compared to northern countries [76].
The cause of this is not clear, although it is likely to be related to reproductive factors (northern women have fewer children), nutrition and industrialization.
A number of risk factors have been recognized in the aetiology of BC, including: genetic background, endocrine hormones, menopausal status, environmental and occupational factors [1, 45].
Moreover, many studies have shown that some dietary factors such as fat, fruit, vegetable, some vitamins, dairy and soy intake may have an important role in BC risk. Despite the fact that the typical Mediterranean diet (MD) has been consumed in the Mediterranean basin for thousands of years, only in the 1960s Keys described its beneficial effect [39], assessing the protective role of MD against BC [50, 81].
MD is a healthy eating pattern, associated with reduced risk for metabolic [72], cardiovascular [22, 59] and neoplastic diseases [66], that has consistently been shown to provide a degree of protection against chronic degenerative diseases [23].
One of the most accredited hypotheses that explains this protection, is the high content in different beneficial compounds, such as polyphenols, largely present in Mediterranean foods like vegetables, fruits, olive oil and red wine. These have multiple biological effects including antioxidant activity, inhibition of inflammation, anti-mutagenic and anti-proliferative properties as well as an effect on cell signalling, cell cycle regulation and angiogenesis [6].
Studies demonstrated that plant polyphenols have an anticancer potential and could be used to develop food supplements that could have the same effects as these noticed for diet components [56, 71]. The intense research dedicated to this topic revealed the fact that food supplements with natural antioxidants have not only positive effects but are linked also to some problematic aspects, such as toxicological side effects when associated with classical synthetic drugs [49].
This review will focus on recent evidence about dietary factors affecting BC incidence with a specific focus on dietary polyphenols.

Dietary polyphenols and breast cancer

Polyphenols comprise a large class of antioxidants and include flavonoids, phenolic acid and its derivatives, lignans and stilbenes. These compounds are all derived from phenylalanine and contain an aromatic ring with a reactive hydroxyl group.

Flavonoids

Flavonoids (Figure 1) are a group of phenolic compounds with antioxidant activity; more than 4,000 distinct flavonoids have been identified in fruits and vegetables. They are classified as: flavonols (quercetin, kampferol, myricetin), flavanols (catechins), flavones (luteolin, apigenin), flavanones (hesperetin, naringenin), anthocyanidins and isoflavonoids (genistein, daidzein) [62].

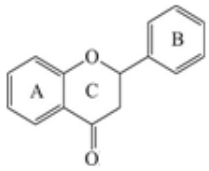

Figure 1.
Basic structure of a flavonoid

BC is hormone-dependent and its development and growth can be highly influenced by the expression of oestrogen receptor (ER) [36]. Most BC consists of both ER-positive and ER-negative cells, consequently agents which possess an inhibiting effect on both ER-positive and ER-negative cells can have a strategic role against tumour [32]. There is evidence that flavonoids can have such dual activity. In particular, naringenin contained in citrus fruits showed a similar cytotoxic effect in human BC cell lines both expressing and not ER. Moreover, a high intake of flavones, present in aromatic plants, has been correlated with a lower risk of BC [66].
Epidemiological studies performed on human populations mainly focus on genistein and daidzein, concluding that soy foods, which are particularly rich in these isoflavones, are protective against BC risk [33, 42]. These active principles are classified as phytoestrogens, which are plant-derived non-steroidal compounds with oestrogen-like biological properties [54]. A high intake of isoflavones has been hypothesized to contribute to the lower incidence of BC in Asian countries, where soy foods are habitually consumed in large amounts [15, 19], compared with western countries [53].
Several biological mechanisms have been proposed to explain how isoflavones may reduce the risk of BC [52]. Isoflavones and human oestrogen share similar chemical structures; given the consequent binding affinity of isoflavones to ER, they may act as oestrogen agonists and antagonists that compete for estradiol at the ERα/β receptor complex [40] (Figure 2). Isoflavones may also have an influence by altering the biosynthesis, metabolism and bioavailability of endogenous hormones [10, 47].
In this regard, isoflavones have been shown to inhibit aromatase and 17β-hydroxysteroid dehydrogenase Type I (17β-HSD1) through interaction with the receptor [84], as well as to increase the synthesis of Sex Hormone Binding Globulin (SHBG) [10].

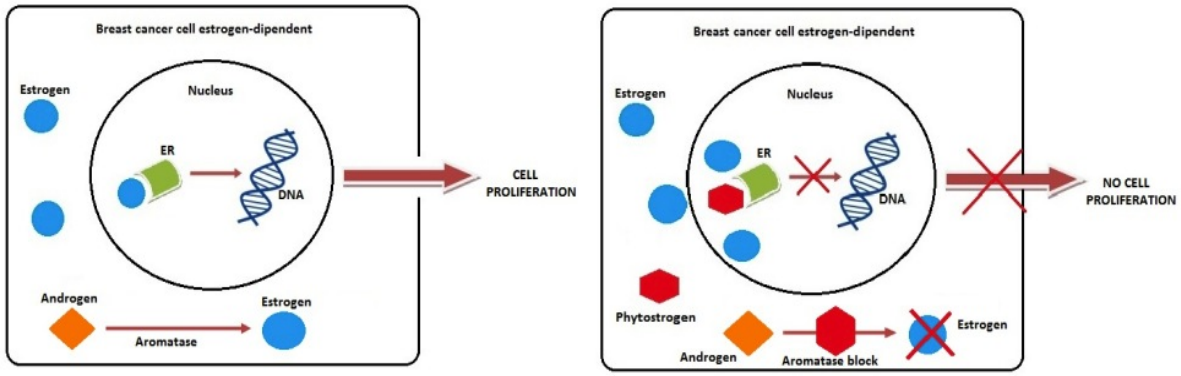

Figure 2.
Probable mechanism of phytoestrogens in preventing breast cancer in premenopausal women

Phenolic acids

Phenolic acids (Figure 3) can be classified into two groups: hydroxycinnamic acids and hydroxybenzoic acids derivatives.

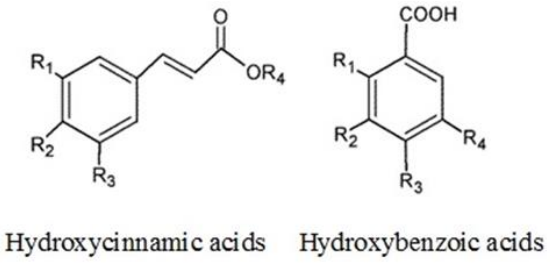

Figure 3.
Structures of phenolic acids

The hydroxybenzoic acid content of edible plants is generally very low, with the exception of certain red fruits, black radish and onions, which can have concentrations of several tens of milligrams per kilogram fresh weight [67]. Tea is an important source of gallic acid: tea leaves may contain up to 4.5 g/kg fresh weight [74]. Furthermore, hydroxyl-benzoic acids are components of complex structures such as hydrolysable tannins [16].

The hydroxycinnamic acids are more common than hydroxybenzoic acids and consist mainly of *p*-coumaric, caffeic, ferulic and sinapic acids [48].

These acids are rarely found in the free form, except in processed food that has undergone freezing, sterilization or fermentation. The bound forms are glycosylated derivatives or esters of quinic acid, shikimic acid and tartaric acid [16].

The richest sources are coffee (drink), lettuce, carrots, blueberries, blackberries, cranberries, sweet potatoes (whole, cooked, and raw), prunes, peaches, orange juice, apples, tomatoes, grapes, and grape products [8, 31].

The most abundant phenolic acid, representing between 75% and 100% of the total hydroxyl cinnamic acid content of most fruits, is caffeic acid, both free and esterified [70].

Other phenolic acid derivatives

The most common phenolic acid derivatives are lignans and stilbenes [48]. Lignans are diphenolic compounds that contain a 2, 3-dibenzylbutane structure derived by the dimerization of two cinnamic acid residues (Figure 4).

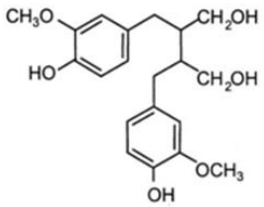

Figure 4.
Structure of lignin

The richest dietary source of lignin is linseed, which contains secoisolariciresinol and low quantities of matairesinol [2]. Other cereals, grains, fruits and certain vegetables also contain traces of the same lignans, but concentrations in linseed are about 1,000 times as high as concentrations in these other food sources [24].

Recent *in vitro*, animal and epidemiological studies suggest that dietary lignans may be chemo-preventive, anti-angiogenic, pro-apoptotic [80], potentially through anti-estrogenic and anti-oxidant mechanisms [1, 73].

Lignans were evaluated for their abilities to inhibit aromatase enzyme activity in ER-positive human breast cancer cells [31].

Lignans act as very weak oestrogens and may block ER in mammary gland from stronger cancer-stimulating oestrogens similarly to Tamoxifen [10].

Within the subclass of stilbenes, resveratrol (Figure 5) and the analogue spiceatannol and pterostilbene have been found in several edible natural products such as grapes (*Vitis spp.*), peanuts (*Arachis spp.*) [65], berries (blueberries, cranberries and lingonberries, all *Vaccinium* spp.) [61] and rhubarb (*Rheum spp.*) [60].

Resveratrol belongs to a class of defence molecules called phytoalexins that protect against infection and damage from exposure to ultraviolet irradiation [34].

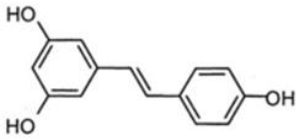

Figure 5.
Structure of resveratrol

Resveratrol was first reported to exert anti-tumour activities in 1997 [34]. Since then, the antioxidant, anti-inflammatory, anti-proliferative and anti-angiogenic effects of resveratrol have been widely studied [7, 14, 37, 65].

Resveratrol has been demonstrated to interact with molecular targets affecting apoptosis (P53, Bax/Bcl-2, Survivin; Caspase-9, 8, 7, 3, PARP), cell cycle (P21, Cyclins, cdks), protein kinases (MAPK, PI3K/AKT, JAK, Wnt), transcription factors (NF-κB, AP-1, Nrf-2), metastasization and invasion (MMP-2, 7, 9, VEGF) [44]. Subsequent reports have shown that resveratrol suppresses proliferation, induces apoptosis and suppresses metastasization and invasion of several types of cancers, such as colon, breast, pancreas, prostate, ovarian and endometrial cancers, as well as lymphoma through effects on different molecular targets [1, 4, 5, 30, 63].

Methods

In the present review, studies were identified by using a comprehensive search in PubMed, Google Scholar and Scopus databases until December, 2015.

To identify in literature the relationship between dietary polyphenols and BC, we used the terms "Mediterranean diet", "polyphenols", "fruit and vegetables", "dietary phytochemicals", "cancer", "breast cancer", "breast cancer risk" as key words. All articles published up to the end-date of the search were included for the review. Only original epidemiologic studies employing intake of polyphenols and the association between a diet including fruits, vegetables, soy or its derivatives and BC, were selected. Studies that assessed dietary patterns through factor analysis techniques and/or principal components analysis and that reported risk estimates of BC (odds ratio [OR]) with a 95% confidence interval (CI) or standard error (SE) were included. According to our inclusion criteria, 12 studies were identified: six case-control studies and six cohorts.

Case-control studies

Table I shows six case-control studies describing the beneficial effect of the MD; in particular the intake of polyphenols has been found to be associated with a lower incidence of BC in pre and postmenopausal women.

Table I
BC risk in case-control studies

Author	Country	Cases/controls	Controlled covariates	OR/HR	95% CI	Protective effect of diet against BC
Castello et al., 2014	Spain	1,017/1,017	Alcohol consumption, BMI from self-reported, average physical activity in the past year, smoking, education, previous history of breast disease other than cancer, family history of breast cancer (BC), age at menarche, age at first delivery and menopausal status, fruit, vegetables, nuts and soy.	Pre-menopausal OR = 0.58 Post-menopausal OR = 0.54	Pre-menopausal (0.38, 0.91) Post-menopausal (0.34, 0.86)	Yes Max ER-, PR- and HER2-
Karimi et al., 2013	Iran	100/174	Age at menarche, age at first full-term pregnancy, smoking status, oral contraceptive drug use, BMI, physical activity, family history of BC and relative accuracy of energy reporting.	Pre-menopausal OR = 0.46 Post-menopausal OR = 0.47	Pre-menopausal (0.13, 1.55) Post-menopausal (0.08, 2.60)	Yes
Demetriou et al., 2012	Cyprus	935/817	Age at interview, family history, age at FFTP, HRT use, exercise, age at menarche, height, BMI in postmenopausal women.	OR = 0.63	(0.77, 1.53)	Yes Max ER- and PR-
Wu et al., 2009	USA	1,248/1,148	Age, BMI, education, physical activity, use of hormones, menopausal status, alcohol, ethnicity, birthplace, years of residence in USA, parity.	OR = 0.72	(0.54, 0.96)	Yes
Murtaugh at al., 2008	Spain	Hispanic women 757/867 Non-Hispanic white women 1,524/1,598	Age, education, family history of breast cancer, smoking, total activity, calories, dietary fibre, dietary calcium, height, parity, recent hormone exposure, interaction of recent hormone exposure and BMI.	Pre-menopausal OD = 0.76 Post-menopausal OD = 0.58	Pre-menopausal (0.63, 0.92) Post-menopausal (0.37, 0.90)	Yes
Cui et al., 2007	China	1,446/1,549	BMI, menopausal status, hormonal receptors, education, personal history of fibro-adenoma, physical activity, family history.	OR = 1.3	(1.0, 1.7)	Yes Max ER+

Below are reported in detail the results from each study.

Castello *et al.* (2014) published a case-control study, in which a total of 1,017 incident BC cases and 1,017 healthy women were recruited. Study population, including pre and postmenopausal women showed that adherence to MD pattern was associated with a lower risk of BC and no differences were observed between pre (top vs bottom quartile OR = 0.58, CI: 0.39, 0.91) and

postmenopausal women (OR = 0.54, CI: 0.34, 0.86) [13]. Dietary intake in the previous 5 years was estimated using a 117-item semi-quantitative Food Frequency Questionnaire (FFQ) [81] adapted to and validated in different Spanish adult populations [79]. Three major existing dietary patterns were identified: a Western pattern (rich in high-fat dairy products, processed meat, refined grains, sweets and caloric drinks and sauces) associated with OR for the top *vs.* bottom quartile of 1.46 (95% CI 1.04-1.31); an intermediate Prudent pattern characterized by an OR for the top vs bottom quartile of 1.09 (95% CI 0.79-1.50); and finally a Mediterranean pattern (denoting high intake of fish, vegetables, fruits and olive oil) implying a lower BC risk with a top vs bottom quartile of 0.56 (95% CI 0.40-0.79).

The results confirm the harmful effect of a Western diet on BC risk along with the protective effect of polyphenols intake on BC risk; moreover, they add new evidence on the benefits of a diet rich in these compounds for preventing all BC subtypes, particularly triple-negative tumours ER-, Progesterone Receptor (PR-) and Human Epidermal Growth Factor 2 (HER2-) [13].

Karimi *et al.* (2013), in a study conducted in Tehran province (Iran), analysed 100 women aged 30-65 years with BC and 174 controls to assess the relationship between dietary patterns and BC risk. Two major dietary patterns were identified by a FFQ. Study results suggested that BC risk had a 75% decrease (OR = 0.25, 95% CI: 0.08- 0.78) in women closely following a healthy dietary pattern (rich in vegetables, fruits, low fat dairy products, vegetables, olive and vegetable oils, fish, poultry, pickles, soya and whole grains); whereas those with unhealthy diet (with high intake of soft drinks, sugars, tea and coffee, French fries and potato chips, salt, sweets and desserts, hydrogenated fats, red and processed meat) had a significantly increased BC risk (OR = 7.78, 95% CI: 2.31-26.22). This study did not find significant differences in BC risk between pre and postmenopausal woman (p = 0.99) and in dietary pattern of premenopausal and post-menopausal women in relation of BC risk (p = 0.23 for interaction with healthy dietary pattern, p = 0.14 for interaction with unhealthy pattern). The results confirm that the cancer-protective effect of a healthy dietary intake may be related to the higher fibre and antioxidant vitamins consumption. Specifically, the low intake of green vegetables and an unhealthy diet could result in folic acid deficiency which could reduce the availability of S-adenosyl methionine for DNA methylation and thereby influence gene expression [18, 38].

Demetriou *et al.* (2012) showed that a dietary pattern including polyphenols intake might favourably influence the risk of BC in postmenopausal women. In this study, 935 postmenopausal women aged 40 - 70 years old that had a confirmed diagnosis of BC were recruited and compared with 817 healthy women selected as controls from the general population. A higher consumption of vegetables, fish and olive oil was independently associated with decreased BC risk. In addition, the Principal Component Analysis (PCA) performed to derive the patterns better describing the diet of study population, indicated that a diet characterized by vegetables, fruits, fish and legumes significantly reduced the risk of BC (ORs across quartiles of increasing levels of consumption: 0.89 with 95% CI: 0.65-1.22, 0.64 with 95% CI: 0.47-0.88, 0.67 with 95% CI: 0.49-0.92, p trend < 0.0001), even after adjustment for relevant confounders. PCA reduces a set of inter-correlated variables (food groups) into a smaller set of principal components, i.e. dietary patterns. Dietary intake of each of the 32 food and beverage items in food frequency questionnaire (FFQ) was considered and study results indicated that adherence to a Mediterranean dietary pattern rich in vegetables, fish, legumes and olive oil may favourably influence the risk of BC in postmenopausal women. Moreover, authors high-lighted that despite the weak individual effect estimated for each component, the combination of healthy foods into a dietary pattern results in a synergism enhancing protection against BC [20].

Wu *et al.* (2009), studied Asian American women, a group experiencing rapid increases in BC incidence. 1,248 were BC cases and 1,148 healthy women. Women who were high consumers of meat/ starch and low consumers of the vegetables and soy diet showed the highest risk (OR: 2.19; 95% CI: 1.40, 3.42; p for trend = 0.0005). Conversely, it was observed an inverse association for the vegetables and soy dietary pattern with higher consumption of vegetables, fruits, soy, milk, chicken and fish (OR = 0.72, CI: 0.54, 0.96).The results suggest that a MD diet both including or not soy is associated with a reduced risk of BC in Asian Americans; furthermore, this finding cannot be explained by the effect of soy because a MD pattern excluding soy intake had similar beneficial effects on BC risk [83].

Murtaugh *et al.* (2008) examined Hispanic women (757 BC cases and 867 controls) and non-Hispanic white women (1524 BC cases and 1598 controls) from the Four-Corners Breast Cancer Study (Arizona, New Mexico, Colorado and Utah) to assess the association of dietary patterns (Western, Prudent, Native Mexican, Mediterranean and Dieter) with BC risk. Native Mexican pattern included Mexican cheeses, soups, meat dishes, legumes, and tomato-based sauces; Dieter pattern was associated with avoiding high-fat dairy

products and salad dressing, cola beverages and butter and with using low-fat dairy, margarine, low-fat but high-sugar desserts, diet beverages and sugar substitutes. Study results suggested that the Western (OR for highest *versus* lowest quartile = 1.32; 95% CI: 1.04-1.68) and Prudent (OR = 1.42; CI: 1.14-1.77) dietary patterns were positively associated with BC risk in different strata by ethnicity and menopausal status. These data agree with other studies concluding that the Western dietary pattern is associated with an increase of BC risk [34, 55].
The Native Mexican (OR = 0.68; CI: 0.55-0.85) and Mediterranean (OR = 0.76; CI: 0.63-0.92) dietary patterns were associated with a decrease in BC risk in all women examined, irrespective of ethnicity and menopausal status. This decrease in risk was most evident among postmenopausal Hispanic women in the highest quartile of the Mediterranean pattern (OR = 0.58; 95% CI: 0.37-0.90; p for trend < 0.01). The Dieter pattern was associated with lower breast cancer risk among premenopausal Hispanic women only (p for trend < 0.01) [55].

A case-control study performed by Cui *et al.* (2007) in Asian populations living in China included 1,446 cases and 1,549 controls. Two patterns emerged in PCA (principal component analysis): a "vegetable-soy" pattern (tofu, cauliflower, beans, bean sprouts, green leafy vegetables) and a "meat-sweet" pattern (shrimp, chicken, beef, pork, candy, desserts).
The results showed no overall association of BC risk with the vegetable/soy pattern but the risk was increased in the highest quartile of the meat/sweet pattern (OR = 1.3; 95% CI, 1.0-1.7; p trend = 0.03). In stratified analyses, the meat/sweet pattern resulted significantly associated with an increased risk of ER-positive BC among postmenopausal women, specifically in the subset with the body mass index (BMI) > 25. These findings indicate that a western diet increases BC risk in postmenopausal Chinese women [19].

Cohort studies

Table II shows six cohort studies analysing evidence regarding the protective role of dietary polyphenols.

Table II

BC incidence in cohort studies

Author and follow up duration	Country	Study population	Controlled covariates	OR/HR	95% CI	Protective effect of diet against BC
Kyro et al., 2015 6 years	10 European countries	367,903	BMI, Age, height, weight, educational level, smoking status, physical activity, use of hormones, menopausal status, alcohol, stage of tumour, polyphenols and lignans intake.	Pre-menopausal HR = 1.26 Post-menopausal HR = 0.83	Pre-menopausal (1.05,1.51) Post-menopausal (0.72,0.69)	Yes
Zamora et al., 2013 11.5 years	10 European Countries	334,850	Age, height, weight, BMI, educational level, smoking status, physical activity, use of hormones, menopausal status, alcohol, flavonoids, isoflavones and lignans intake.	All women HR = 0.97 Pre-menopausal HR = 0.98 Post-menopausal HR = 0.96	All women (0.90, 1.04) Pre-menopausal (0.84, 1.15) Post-menopausal (0.86, 1.06)	No
Buckland et al., 2012 11 years	10 European Countries	335,062	BMI, height, educational level, physical activity, smoking, menopausal status, age at menarche, breastfeeding, age at first FFTP, HRT, fruit and vegetables intake, saturated fat intake, alcohol intake, energy intake, mutually adjusted for the arMED component.	All women OR = 0.94 Pre-menopausal OR = 0.94 Post-menopausal OR = 0.99	All women (0.89, 1.00) Pre-menopausal (0.88, 0.99) Postmenopausal (0.84, 1.18)	Yes Max ER-, PR-
Cade et al., 2011 9 years	British	33,731	Age, energy intake, menopausal status, calorie-adjusted fat, BMI, physical activity, use of OCP, HRT, smoking, parity, age at menarche, ethanol, breast feeding, socioeconomic class, level of education.	Pre-menopausal HR = 0.65 Post-menopausal HR = 1.30	Pre-menopausal (0.42, 1.02) Post-menopausal (0.83, 2,05)	Yes
Fung et al., 2005 16 years	USA	3,026	Age, MD, weight, menopausal status, smoking, fruit and vegetables in polyphenols intake, alcohol intake, socioeconomic class.	OR = 0.62	(0.44, 0.87)	Yes ER-
Sieri et al., 2004 5 years	Italy	8,984	BMI, height, educational level, consumption of alcoholic beverages, cooked vegetables intake, pasta, and physical activity.	OR = 0.66	(0.46, 0.94)	Yes

The European Prospective Investigation into Cancer and Nutrition (EPIC) is an ongoing multi-centre prospective cohort study designed to investigate the relationship between nutrition, lifestyle, environmental factors and cancer, with the potential for studying other chronic diseases as well. EPIC investigators assessed adherence to the Mediterranean diet through a simple scoring system and have documented, in a series of papers, that closer adherence to this diet is associated with reduced overall mortality as well as incidence of and mortality from cardiovascular diseases and cancer.

The study currently includes 519,978 participants (366,521 women and 153,457 men, mostly aged 35-70 years) in 23 centres located in 10 European countries, to be followed for cancer incidence and cause-specific mortality for several decades. At enrolment, which took place between 1992 and 2000 at each of the different centres, information was collected through a non-dietary questionnaire on lifestyle variables and through a dietary questionnaire addressing usual diet. EPIC represents the largest single resource available today world-wide for prospective investigations on the aetiology of cancers (and other chronic diseases) that can

integrate data on lifestyle and diet, biomarkers of diet and of endogenous metabolism (e.g. hormones and growth factors) and genetic polymorphisms [60].

A multicentre study performed with EPIC cohort focused on polyphenol intake and BC survival investigating the association between pre-diagnostic intakes of polyphenol classes (flavonoids, lignans, phenolic acids, stilbenes, and other polyphenols) in 367,903 women. The cohort comprised 23 centres in Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Most participants were recruited from the general population. At recruitment (years 1993 - 1999), lifestyle and dietary questionnaires were collected from the participants. 11,782 women were followed since the date of diagnosis of BC for a median of 6 years. During this time, 1,482 women died including 753 deaths due to BC. For pre-menopausal women, no association was observed between polyphenols classes and all-cause or BC-specific mortality, except for the lignans class where higher intakes were non-significantly with higher risk of BC-specific mortality (adjusted model: HR = 1.24, 95% CI: 0.98-1.58). Conversely among postmenopausal women, intake of lignans was associated with lower risk of BC-specific mortality (adjusted model: HR = 0.83, 95% CI: 0.72-0.96), and no association was found for any of the other polyphenol classes; no association was found for other polyphenol classes [41].

Another study based on EPIC cohort and published in 2013 by Zamora *et al.* [85] investigated the dietary flavonoid and lignan intake and BC risk according to menopause and hormone receptor status. The study, conducted in 10 European countries, considered a cohort of 334,850 women between 35 and 70 years old and has registered 11,576 new BC cases in 11.5 years. No association between total flavonoids, isoflavones and lignans intake was observed on the overall BC risk. Total flavonoid intake was not associated with BC overall (HR = 0.97, CI: 0.90-1.04), in pre-menopausal women (HR = 0.98, CI: 0.84, 1.15) or in post-menopausal women (HR = 0.96, CI: 0.86-1.06). The results obtained for total lignan or flavonoid subclasses (including isoflavones) did not show any association either.

A study lasting 11 years conducted by Buckland *et al.* (2012), in 10 European countries within the EPIC cohort, investigated the association between adherence to MD and risk for BC among 335,062 women recruited from 1992 to 2000. The cohort included 9,009 postmenopausal and 1,216 premenopausal women affected by first primary incident invasive BC diagnosed during the follow-up period. Validated country-specific FFQ were used to record the usual diet, while adherence to MD was estimated through an adapted relative MD (arMED) score, based on the score designed by Trichopoulou *et al.* [76]. Results showed that adaptation to a MD excluding alcohol was associated to a modest reduced risk of BC in postmenopausal women (high *vs.* low arMED score; HR = 0.93; 95% CI: 0.87-0.99; p_{trend} = 0.037), and this association was stronger in ER-/PR- tumours (HR = 0.80; 95% CI: 0.65-0.99). The arMED score was not associated with BC in premenopausal women. The results support the potential scope for BC prevention through dietary modification: in fact the diet reduced the risk of BC by 6% overall and by 7% in postmenopausal women; but the risk was reduced by 20% in ER-/PR- tumours in post-menopausal women [11].

A study conducted by Cade in 2011 in a cohort of healthy pre- and postmenopausal British women reported an inverse association, though not significant, between adherence to MD and incidence of BC only in premenopausal women. In postmenopausal women, no clear trends were observed. This analysis included 828 incident cases of BC in 33,731 women with a mean follow-up of 9 years. There were no statistically significant associations between either the MD pattern or the World Health Organization Healthy Diet Index (WHO HDI) and risk of BC. Maximal adherence to the MD was associated with HR = 0.65 (CI: 0.42-1.02) compared with minimal adherence [12].

Fung *et al.* (2005) measured the risk associated with food consumption in 3,026 incident cases of postmenopausal BC, using a subsample of the Nurse's Health Study cohort. This study, lasting 16 years, has shown no overall association between dietary pattern and BC risk. However, a Western-type diet may increase the risk of BC among smokers, and a prudent diet may protect against ER- tumours. The last is characterized by a higher intake of fruits and vegetables rich in polyphenols, while the Western pattern is characterized by higher intakes of red and processed meats, refined grains, sweets and desserts and high-fat dairy products. Food intake information was collected by a FFQ and dietary patterns have been identified by PCA.

Neither of the patterns was associated with overall risk of postmenopausal BC. Western pattern score was positively associated with smokers at baseline (RR = 1.44; CI = 1.02-2.03). The prudent pattern was inversely associated with ER- cancer (RR = 0.62; CI = 0.45-0.88). Among the major food groups, higher consumptions of fruits (RR for 1 serving/day increase = 0.88; 95% CI = 0.80-0.97) and vegetables (RR = 0.94; 95% CI = 0.88-0.99) were significantly associated with decreased risk for ER (-) BC [28].

Sieri *et al.* (2004) in an Italian cohort analysing 8,984 women with 207 incident cases of BC, showed that a diet rich in raw vegetables and olive

oil protects against BC risk. The cohort was recruited from 1987 to 1992 from residents in Northern Italy who filled a FFQ. Four dietary patterns, which explained 30% of the variance, emerged: salad vegetables (mainly consisting of raw vegetables and olive oil); western (mainly consisting of potatoes, red meat, eggs and butter); canteen (pasta and tomato sauce); and prudent (cooked vegetables, pulses, and fish, with negative loading on wines and spirits). After adjustment for potential confounders, only the salad vegetables pattern was associated with significantly lower (34-35%) BC incidence (RR = 0.66, 95% CI: 0.47-0.95). The relationship was stronger for subjects with a BMI < 25 (RR = 0.39, 95% CI: 0.22-0.69); whereas women with body mass index ≥ 25 had no protective effect from the consumption of raw vegetables [68].

Discussions

There are many epidemiological studies that investigated the relationship between BC incidence and dietary patterns characterized by vegetable, fruit, soy and its derivatives, and suggest the possibility to decrease BC risk by following a MD [21, 48, 58, 77]. In fact, this model contains nutritional compounds rich in polyphenols that could have anti-cancer activities, since they exhibit antioxidant properties and interfere with molecular events involved in the initiation, promotion, and progression of stages of tumour, suggesting chemo-preventive and therapeutic capacity of dietary polyphenols against BC. Many studies indicate a positive correlation [7, 25, 29, 86], while others suggest no association [9, 43]. While a number of *in vitro* experiments have suggested that poly-phenols may influence carcinogenesis and tumour development [21, 51, 58, 77], very few clinical trials have been conducted regarding the role of polyphenols in BC prevention, incidence or mortality [17]. However, association between various dietary patterns with BC risk remains unclear.

In the present review, referred to studies published between 2004 and 2015, case-control studies indicated that MD could reduce BC risk, mostly in post-menopausal women with receptor negative tumours. Conversely, cohort studies reported conflicting results. In fact between the studies conducted within the large EPIC cohort, Buckland *et al.* [11] indicated a modest BC risk reduction only in post-menopausal women with receptor negative tumours, while Kyro *et al.* [41] confirmed this association only in postmenopausal women characterized by a high intake of lignans but not for other polyphenol subclasses; Zamora *et al.* [85] did not find a reduction in BC risk with any polyphenol subclass. However, other authors [28, 68] suggested a protective effect of a diet rich in polyphenols. Moreover, Cade *et al.* [12] indicated a not significant association, only in premenopausal subjects.

The most valid hypotheses on the causal relationship of MD adherence on breast cancer were connected to the hormonal pathway and hormone receptor status that could be involved in the heterogeneity of these results.

Hormonal risk factors are strongly important in the genesis of BC, and may be strongly associated to the risk of ER+, PR+ or HER+ breast tumours that depend on the presence of these hormones for ongoing proliferation. In contrast, non-hormonal risk factors, such as diet, may be more related with BC not expressing hormone receptors [24].

If the association between diet and BC is modest, it could be harder to identify in hormone receptor-positive tumours where hormonal factors, in particular oestrogen, already have such a strong influence. On the other hand, the effect of diet on BC may be clearer in hormone receptor-negative tumours where hormonal factors are not so relevant. Moreover, the protective effect of this dietary pattern on receptor-positive BC may be related to a hormonal pathway via decreasing the concentration of circulating oestrogens [18]. In fact plant-based food, such as fruits and vegetables, which contains significant amounts of bioactive phytochemicals, usually act by mimicking the hormones [17].

In addition the protective effect of the MD on cancer risk may be explained through multiple biological effects of flavonoids, including antioxidant activity, inhibition of inflammation, anti-mutagenic and antiproliferative properties as well as the involvement in cell signalling, cell cycle regulation and angiogenesis [66]. It is difficult to determine which components of a healthy dietary pattern explain the inverse association with breast cancer risk. Although some components of fruits and vegetables, such as folates, lignans and polyunsaturated fatty acids, have been inversely associated with postmenopausal breast cancer risk, a protective effect of fruits and vegetables has not been solidly established. Though individual effect estimate of single food components can be weak, when healthy foods are combined in a dietary pattern, outcomes estimates are usually stronger and suggest that they may act synergistically to confer their potent antioxidant and anticancer activities [44, 18]. This partially explains why no single antioxidant can replace the complex mixture of natural phytochemicals in fruit and vegetables and realize their health benefit [46].

The data about the effect of MD on BC risk in pre and post-menopausal women are controversial. Most of them show possible inverse associations between BC incidence and dietary patterns characterized by vegetable, fruit, soy and its

derivatives especially in postmenopausal subjects, and suggest the possibility to decrease BC risk by following a MD.

Intake of lignans before breast cancer diagnosis may be related to improved survival among postmenopausal women, but may on the contrary worsen the survival for premenopausal women [41]. This suggests that the role of phytoestrogens in BC is complex and may be dependent of the menopausal status. In fact menopausal status might be an important modifier of the effect of phyto-estrogens on the risk for BC because mechanisms that mediate the effect could involve the ovarian synthesis of sex hormones or the alteration of other menstrual cycle characteristics [85]. According to the WHO's "Global Strategy on Diet, Physical Activity and Health" [82] the MD is a promising strategy to prevent and enhance quality of life.

Recent studies have shown that phytochemicals have the potential of modulating various molecular processes, including signalling pathway involved in the development and progression of tumours. They can act directly on miRNAs and post-transcriptionally modulate gene expression affecting tumour development and progression or, alternatively, cause a synergistic effect when administered together with conventional drugs. A slight change in the expression of one miRNA can generate a signalling cascade that has the potential to involve many molecular networks and trigger various responses in the tumour cell, specifically in the cancer types that are hormone related such as BC [17, 78].

Conclusions

This scientific approach could play a pivotal role in the evaluation of dietary phytochemicals, which might be used as multifunctional agents capable of stopping or reversing transformation of premalignant cells or for the preservation of healthy cells [54]. In conclusion, the present review suggests that it is not yet possible to assess with certainty the effect of MD on BC risk in relation also to the individual characteristics such as genetic susceptibility, menopausal status, lifestyle, and epigenetic modifications. Given current evidences, further epidemiological studies on the potential association between polyphenols intake and BC risk should continuously be conducted.

References

1. Adlercreutz H., Mazur W., Phyto-oestrogens and Western diseases. *Ann. Med.*, 1997; 29: 95-120.
2. Adlercreutz H., Epidemiology of phytoestrogens. *Baillieres Clin. Endocrinol. Metab.*, 1998; 12: 605-623.
3. AIRTUM Working Group, Prevalence and cure of cancer in Italy. Italian Cancer Figures - Report 2014. *Epidemiol. Prev.*, 2014; 38 (6 Suppl 1): 1-144.
4. Androutsopoulos V.P., Ruparelia K.C., Papakyriakou A., Filippakis H., Tsatsakis A.M., Spandidos D.A., Anticancer effects of the metabolic products of the resveratrol analogue, DMU-212: structural requirements for potency. *Eur. J. Med. Chem.*, 2011; 46(6): 2586-2595.
5. Apostolou A., Stagos D., Galitsiou E., Spyrou A., Haroutounian S., Portesis N., Trizoglou I., Wallace Hayes A., Tsatsakis A.M., Kouretas D., Assessment of polyphenolic content, antioxidant activity, protection against ROS-induced DNA damage and anticancer activity of *Vitis vinifera* stem extracts. *Food Chem. Toxicol.*, 2013; 61: 60-68.
6. Barrea L., Balato N., Di Somma C., Nutrition and psoriasis: is there any association between the severity of the disease and adherence to the Mediterranean diet? *J. Transl. Med.*, 2015; 13: 18.
7. Benetou V., Orfanos P., Lagiou P., Trichopoulos D., Boffetta P., Trichopoulou A., Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC cohort study. *Cancer Epidemiol. Biomarkers Prev.*, 2008; 17: 387-392.
8. Betés-Saura C., Andres-Lacueva C., Lamuela-Raventos R.M., Phenolics in white free-run juice and wines from Penedes by high-performance liquid chromatography: changes during vinification. *J. Agric. Food Chem.*, 1996; 44(10): 3040-3046.
9. Botterweck A.A., van den Brandt P.A., Goldbohm R.A., A prospective cohort study on vegetable and fruit consumption and stomach cancer risk. *The Netherlands. Am. J. Epidemiol.*, 1998; 148: 842-853.
10. Brooks J.D., Thompson L.U., Mammalian lignans and genistein decrease the activities of aromatase and 17beta-hydroxysteroid dehydrogenase in MCF-7 cells. *J. Steroid Biochem. Mol. Biol.*, 2005; 94: 461-467.
11. Buckland G., Travier N., Cottet V., González C.A., Luján–Barroso L., Agudo A., Adherence to the Mediterranean diet and risk of breast cancer in the European prospective investigation into cancer and nutrition cohort study. *Int. J. Cancer*, 2013; 132: 2918-2927.
12. Cade J.E., Taylor E.F., Burley V.Y., Greenwood D.C., Does the Mediterranean dietary pattern or the healthy diet index influence the risk of breast cancer in a large British cohort of woman. *Eur. J. Clin. Nutr.*, 2011; 65: 920-928.
13. Castello A., Pollan M., Buijsse B., Ruiz A., Casas A.M., Spanish Mediterranean diet and other dietary patterns and breast cancer risk: case–control. *Epi. GEICAM study Br. J. Cancer*, 2014; 111: 1454-1462.
14. Catalgol B., Batirel S., Taga Y., Ozer N.K., Resveratrol: French paradox revisited. *Front Pharmacol.*, 2012; 3: 141.
15. Cho Y.A., Kim J., Shin A., Dietary patterns and breast cancer risk in Korean women. *Nutr. Cancer*, 2010; 62: 1161-1169.
16. Clifford M.N., Scalbert A., Ellagitannins - occurrence in food, bioavailability and cancer prevention. *J. Food Sci. Agric.*, 2000; 80: 1118-1125.
17. Cojocneanu Petric R., Braicu C., Raduly L., Zanoaga O., Dragos N., Monroig P., Dumitrascu D., Berindan-Neagoe I., Phytochemicals modulate carcinogenic signaling pathways in breast and

hormone-related cancers. *Onco. Targets Ther.*, 2015; 8: 2053-2066.
18. Cottet V., Touvier M., Fournier A., Touillaud M.S., Lafay L., Clavel-Chapelon F., Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. *Am. J. Epidemiol.*, 2009; 170: 1257-1267.
19. Cui X., Dai Q., Tseng M., Dietary patterns and breast cancer risk in the Shanghai Breast Cancer Study. *Cancer Epidemiol. Biomarkers Prev.*, 2007; 16: 1443-1448.
20. Demetriou C.A., Hadjisavvas A., Loizidou M.A., Loucaides G., Neophytou I., Sieri S., The Mediterranean dietary pattern and breast cancer risk in Greek - Cypriot women: A case–control study. *BMC Cancer*, 2012; 12: 113.
21. Duthie S.J. Dobson V.L., Dietary flavonoids protect human colonocyte DNA from oxidative attack *in vitro*. *Eur. J. Nutr.*, 1999; 38: 28-34.
22. Esposito K., Di Palo C., Maiorino M.I., Petrizzo M., Bellastella G., Siniscalchi I., Long-term effect of mediterranean-style diet and calorie restriction on biomarkers of longevity and oxidative stress in over-weight men. *Cardiol. Res. Pract.*, 2011; 2011: 293916.
23. Esposito K., Giugliano D., Mediterranean diet for primary prevention of cardiovascular disease. *N. Engl. J. Med.*, 2013; 369: 674-675.
24. Farsinejad-Marj M., Talebi S., Ghiyasvand R., Miraghajani M., Adherence to Mediterranean diet and risk of breast cancer in premenopausal and postmenopausal women. *Arch. Iran Med.*, 2015; 18(11): 786-792.
25. Favero A., Parpinel M., Franceschi S., Diet and risk of breast cancer: major findings from an Italian case-control study. *Biomed. Pharmacother.*, 1998; 52: 109-115.
26. Ferlay J., Shin H.R., Bray F., Forman D., Mathers C., Parkin D.M., Cancer Incidence and Mortality Worldwide. For GLOBOCAN 2008 - IARC Cancer Base No 10 Lyon, France: International Agency for Research on Cancer; 2010.
27. Feskanich D., Ziegler R.G., Michaud D.S., Giovannucci E.L., Speizer F.E., Willett W.C., Colditz G.A., Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *J. Natl. Cancer Inst.*, 2000; 92: 1812-1823.
28. Fung T.T., Hu F.B., Holmes M.D., Dietary patterns and the risk of postmenopausal breast cancer. *Int. J. Cancer.*, 2005; 116: 116-121.
29. Gonzalez C.A., Pera G., Agudo A., Bueno-de-Mesquita H.B., Ceroti M., Boeing H., Schulz M., Del Giudice G., Plebani M., Carneiro F., Berrino F., Sacerdote C., Tumino R., Panico S., Berglund G., Siman H., Hallmans G., Stenling R., Martinez C., Dorronsoro M., Barricarte A., Navarro C., Quiros J.R., Allen N., Key T.J., Bingham S., Day N.E., Linseisen J., Nagel G., Overvad K., Jensen M.K., Olsen A., Tjonneland A., Buchner F.L., Peeters P.H., Numans M.E., Clavel-Chapelon F., Boutron Ruault M.C., Roukos D., Trichopoulou A., Psaltopoulou T., Lund E., Casagrande C., Slimani N., Jenab M., Riboli E., Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int. J. Cancer*, 2006; 118: 2559-2566.
30. González-Vallinas M., González-Castejón M., Rodríguez-Casado A., Ramírez de Molina A., Dietary phytochemicals in cancer prevention and therapy: a complementary approach with promising perspectives. *Nutrition Reviews*, 2013; 71(9): 585-599.
31. Heinonen S., Nurmi T., Liukkonen K., *In vitro* metabolism of plant lignans: new precursors of mammalian lignansenterolactone and enterodiol. *J. Agric. Food Chem.*, 2001; 49: 3178-3186.
32. Hsieh C.Y., Santell R.C., Haslam S.Z., Helferich W.G., Estrogenic effects oggenestein in the growt of estrogen receptor-positive human breast cancer (MCF-7) cells *in vitro* and *in vivo*. *Cancer Res.*, 1998; 58: 3833-3838.
33. Hui C., Qi X., Qianyong Z., Xiaoli P., Jundong Z., Mantian M., Flavonoids, Flavonoid Subclasses and Breast Cancer Risk: A Meta-Analysis of Epidemiologic Studies. PLoS ONE 8(1): e54318.
34. Jang M., Cai L., Udeani G.O., Slowing K.V., Thomas C.F., Beecher C.W., Fong H.H., Farnsworth N.R, Kinghorn A.D., Mehta R.G., Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*, 1997; 275: 218-220.
35. Jemal A., Center M.M., Desantis C., Ward E.M. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol. Biomarkers Prev.*, 2010; 19: 1893-1907.
36. Jemal J.D., Davidson N.E., Estrogen carcinogenesis in breast cancer. *N. Engl. J. Med.*, 2006; 354: 270-282.
37. Kaneuchi M., Sasaki M., Tanaka Y., Yamamoto R., Sakuragi N., Dahiya R., Resveratrol suppresses growth of Ishikawa cells through down-regulation of EGF. *Int. J. Oncol.*, 2003; 23: 1167-1172.
38. Karimi Z., Jessri M., Houshiar-Rad A., Mirzaei H.R., Rashidkhani B., Dietary patterns and breast cancer risk among women. *Public Health Nutr.*, 2014; 17(5): 1098-1106.
39. Keys A., Menotti A., Karvonen M.J., Aravanis C., Blackburn H., Buzina R., The diet and 15-year death rate in the seven countries study. *Am. J. Epidemiol.*, 1986; 124: 903-915.
40. Kuiper G.G., Lemmen J.G., Carlsson B., Interaction of estrogenic chemicals and phyto-estrogens with estrogen receptor beta. *Endocrinology*, 1998; 139: 4252-4263.
41. Kyrø C., Zamora-Ros R., Scalbert A., Tjønneland A., Dossus L., Johansen C., Pre-diagnostic polyphenol intake and breast cancer survival: the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Breast Cancer Res. Treat.*, 2015; 154(2): 389-401.
42. Lamartiniere C.A., Murril W.B., Manzolillo P.A., Ginestein alters the onotgenicity of mammary gland development and protects against chemically-induced mammary cancer in rats. *Proc. Soc. Exp. Biol. Med.*, 1998; 217: 358-364.
43. Larsson S.C., Andersson S.O., Johansson J.E., Wolk A., Fruit and vegetable consumption and risk of bladder cancer: a prospective cohort study.

Cancer Epidemiol. Biomarkers Prev., 2008; 17: 2519-2522.
44. Larsson S.C., Hakansson N., Naslund I., Bergkvist L., Wolk A., Fruit and vegetable consumption in relation to pancreatic cancer risk: a prospective study. *Cancer Epidemiol. Biomarkers Prev.*, 2006; 15: 301-305.
45. Leonardi G.C., Rapisarda V., Marconi A., Scalisi A., Catalano F., Proietti L., Travali S., Libra M., Fenga C., Correlation of the risk of breast cancer and disruption of the circadian rhythm (Review). *Oncol. Rep.*, 2012; 28(2): 418-428.
46. Liu B.L., Zhang X., Zhang W., Zhen H.N., New enlightenment of French Paradox: resveratrol's potential for cancer chemoprevention and anti-cancer therapy. *Cancer Biol. Ther.*, 2007; 6: 1833-1836.
47. Longo V., Fontana L., Calorie restriction and cancer prevention: metabolic and molecular mechanisms. *Trends in Pharmacological Sciences*, 2010; 31(2): 89-98.
48. Manach C., Scalbert A., Morand C., Rémésy C., Jiménez L., Polyphenols: food sources and bio-availability. *Am. J. Clin. Nutr.*, 2004; 79(5): 727-747.
49. Margină D., Ilie M., Grădinaru D., Androutsopoulos V.P., Kouretas D., Tsatsakis A.M., Natural products-friends or foes? *Toxicol. Lett.*, 2015; 236(3): 154-167.
50. Michels K.B., Mohllajee A.P., Roset–Bahmanyar E., Beehler G.P., Moysich K.B., Diet and breast cancer: A review of the prospective observational Studies. *Cancer*, 2007; 109(12): 2712-2749.
51. Middleton E.Jr., Kandaswami C., Theoharides T.C., The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol. Rev.*, 2000; 52: 673-751.
52. Motoki I., Shoichiro T., Risk factors for breast cancer: epidemiological evidence from Japanese studies. *Cancer Sci.*, 2011; 102(9): 1607-1614.
53. Mousavi Y., Adlercreutz H., Genistein is an effective stimulator of sex hormone-binding globulin production in hepatocarcinoma human liver cancer cells and suppresses proliferation of these cells in culture. *Steroids*, 1993; 58: 301-304.
54. Murril W.B., Brown N.M., Zhang J.X., Manzolillo P.A., Barnes S., Lamartiniere C.A., Prepubertalgenestein exposure suppresses mammary cancer and enhances gland differentiation in rats. *Carcinogenesis*, 1996; 17: 1451-1457.
55. Murtaugh M.A., Sweeney C., Giuliano A.R., Herrick J.S., Hines L., Byers T., Baumgartner K.B., Slattery M.L., Diet patterns and breast cancer risk in Hispanic and non-Hispanic white women: the Four-Corners Breast Cancer Study. *Am. J. Clin. Nutr.*, 2008; 87(4): 978-984.
56. Olaru O.T., Venables L., van de Venter M., Nitulescu G.M., Margina D., Spandidos D.A., Tsatsakis A.M., Anticancer potential of selected *Fallopia adans* species. *Oncol. Lett.*, 2015; 10(3): 1323-1332.
57. Parasramka M.A., Ho E., Williams D.E., Dashwood R.H., MicroRNAs, diet, and cancer: new mechanistic insights on the epigenetic actions of phytochemicals. *Mol. Carcinog.*, 2012; 51(3): 213-230.
58. Plaumann B., Fritsche M., Rimpler H., Brandner G., Hess R.D., Flavonoids activate wild-type p53. *Oncogene*, 1996; 13: 1605-1614.
59. Rees K., Hartley L., Flowers N., Clarke A., Hooper L., Thorogood M., Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. *Cochrane Database Syst. Rev.*, 2013; 8: CD009825.
60. Riboli E., Hunt K.J., Slimani N., European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr.*, 2002; 5(6B): 1113-1124.
61. Rimando A.M., Kalt W., Magee J.B., Dewey J., Ballington J.R., Resveratrol, pterostilbene, and piceatannol in vaccinium berries. *J. Agric. Food Chem.*, 2004; 52: 4713-4719.
62. Rui Hai Liu, Potential Synergy of Phytochemicals in Cancer Prevention. *J. Nutr.*, 2004; 134: 3479S-3485S.
63. Sahpazidou D., Geromichalos G.D., Stagos D., Apostolou A., Haroutounian S.A., Tsatsakis A.M., Tzanakakis G.N., Hayes A.W., Kouretas D., Anti-carcinogenic activity of polyphenolic extracts from grape stems against breast, colon, renal and thyroid cancer cells. *Toxicol. Lett.*, 2014; 230(2): 218-224.
64. Sak K., Cytotoxicity of Dietary Flavonoids on Different Human Cancer Types. *Pharmacognosy Reviews*, 2014; 8(16): 122-146.
65. Sanders T.H., McMichael R.W., Hendrix K.W., Occurrence of resveratrol in edible peanuts. *J. Agric. Food Chem.*, 2000; 48: 1243-1246.
66. Schwingshackl L., Hoffmann G., Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies. *Int. J. Canc.*, 2014; 135: 1884-1897.
67. Shahidi F., Naczk M., Food phenolics, sources, chemistry, effects, applications. Lancaster, PA: Technomic Publishing Co Inc, 1995.
68. Sieri S., Krogh V., Pala V., Dietary patterns and risk of breast cancer in the ORDET cohort. *Cancer Epidemiol. Biomarkers Prev.*, 2004; 13: 567-572.
69. Signorelli P., Ghidoni R., Resveratrol as an anti-cancer nutrient: molecular basis, open questions and promises. J. Nutr. Biochem., 2005; 16(8): 449-466.
70. Sosulski F., Krygier K., Hogge L., Free, esterified, and insoluble-bound phenolic acids. 3 Composition of phenolic acids in cereal and potato flours. *J. Agric. Food Chem.*, 1982; 30: 337-340.
71. Stagos D., Amoutzias G.D., Matakos A., Spyrou A., Tsatsakis A.M., Kouretas D., Chemoprevention of liver cancer by plant polyphenols. *Food Chem. Toxicol.*, 2012; 50(6): 2155-2170.
72. Steffen L.M., Van Horn L., Daviglus M.L., Zhou X., Reis J.P., Loria C.M., Jacobs D.R., Duffey K.J., A modified Mediterranean diet score is associated with a lower risk of incident metabolic syndrome over 25 years among young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *The British Journal of Nutrition*, 2014; 112: 1654-1661.
73. Sunita P., Pattanayak S.P., Phytoestrogens in post-menopausal indications: A theoretical perspective. *Pharmacogn. Rev.*, 2011; 5(9): 41-47.
74. Tomas-Barberan F.A., Clifford M.N., Dietary hydroxybenzoic acid derivatives and their possible

role in health protection. *J. Sci. Food Agric.*, 2000; 80: 1024-1032.
75. Trichopoulou A., Mediterranean diet: the past and the present. *Nutr. Metab. Cardiovasc. Dis.*, 2001; 11: 1-4.
76. Trichopoulou A., Pagona L., Kuper H., Trichopoulos D., Cancer and Mediterranean Dietary Traditions. *Cancer Epidemiol. Biomarkers Prev.*, 2000; 9: 869.
77. van Erk M.J., Roepman P., van der Lende T.R., Stierum R.H., Aarts J.M., van Bladeren P.J., van Ommen B., Integrated assessment by multiple gene expression analysis of quercetin bioactivity on anticancer-related mechanisms in colon cancer cells *in vitro*. *Eur. J. Nutr.*, 2005; 44: 143-156.
78. Vanden Berghe W., Epigenetic impact of dietary polyphenols in cancer chemoprevention: lifelong remodeling of our epigenomes. Pharmacol. Res., 2012; 65(6): 565-576.
79. Vioque J., Navarrete-Munoz E.M., Gimenez-Monzo D., Garcia-de-la-Hera M., Granado F., Young I.S., Ramon R., Ballester F., Murcia M., Rebagliato M., Iniguez C., INMA-Valencia Cohort Study Reproducibility and validity of a food frequency questionnaire among pregnant women in a Mediterranean area. *Nutr. J.*, 2013; 12: 26.
80. Webb A.L., McCullough M.L., Dietary lignans: potential role in cancer prevention. *Nutr. Cancer*, 2005; 51(2): 117-131.
81. Willett W.C., Sacks F., Trichopoulou A., Drescher G., Ferro-Luzzi A., Helsing E., Mediterranean diet pyramid: a cultural model for healthy eating. *Am. J. Clin. Nutr.*, 1995; 61: 1402S-1406S.
82. World Health Organization, 2009.
83. Wu A.H., Yu M.C., Tseng C.C., Dietary patterns and breast cancer risk in Asian American women. *Am. J. Clin. Nutr.*, 2009; 89: 1145-1154.
84. Yager J.D., Davidson N.E., Estrogen carcinogenesis in breast cancer. *N. Engl. J. Med.*, 2006; 354: 270-282.
85. Zamora-Ros R., Ferrari P., Gonzalez C.A., Tjonneland A., Olsen A., Bredsdorff L., Dietary flavonoid and lignan intake and breast cancer risk according to menopause and hormone receptor status in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. *Breast Cancer Research and Treatment*, 2013; 139(1): 163-176.
86. Zhang S.M., Hunter D.J., Rosner B.A., Giovannucci E.L., Colditz G.A., Speizer F.E., Willett W.C., Intakes of fruits, vegetables, and related nutrients and the risk of non-Hodgkin's lymphoma among women. *Cancer Epidemiol. Biomarkers Prev.*, 2000; 9: 477-485.