Systematic Review

Adherence to Mediterranean Diet and Risk of Breast Cancer in Premenopausal and Postmenopausal Women

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Abstract

Background: Mediterranean diet (MD) has long been suspected to impact on health promotion. Epidemiologic studies reveal the protective role of adherence to this dietary pattern on cancer incidence. However, its association with breast cancer risk remains unclear. Therefore, we aimed to investigate whether adherence to Mediterranean dietary pattern influence on breast cancer risk in postmenopausal and premenopausal women.

Methods: We performed an electronic search of published studies earlier than Apr 2015 using Pubmed, Google scholar, Cochrane and Scopus databases. The search terms included: breast neoplasm, breast tumors, mammary carcinoma, mammary neoplasm, breast cancer, and Mediterranean diet. Study inclusion criteria were: 1) written in English; 2) with a study arm of MD intervention or MD style assessment; 3) reported the BC risk in premenopausal and postmenopausal women.

Results: We summarized the findings of 8 studies in this review, including five cohorts and three case-control studies. Although, cohort studies reported controversial results in this field, case-control studies resulted inverse relation between this Mediterranean dietary pattern and breast cancer risk in pre or/and postmenopausal women.

Conclusions: It seems that there is no sufficient data to reach a conclusion about the effect of MD on breast cancer risk in pre and postmenopausal, but there are some evidences suggesting the protective association. More cohort studies in different parts of the world are needed to confirm these results.

Keywords: Breast cancer, Mediterranean diet, premenopausal women, postmenopausal women

Cite this article as: 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.

Introduction

Cancer is a leading cause of death worldwide.[1] The most usual kind of cancer among women in developing and developed countries is breast cancer (BC) that is an important general concern threatening the health of women in the world.[2] Each year about 1.4 million new cases of BC are recognized worldwide. Also, the general mortality rate of breast cancer is 450,000 females annually.[3] BC etiology is multifactorial and some risk factors comprise: genetic background, environmental factors, endocrine hormones and menopausalstatus.[4] Also, 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.[5] However, it is important to regard that individuals do not eat single foods. So, it is beneficial to investigate the association between dietary patterns and BC risk that express different aspects of dietary intake and food item concurrently. One such beneficial dietary pattern is Mediterranean diet (MD) characterized by elevated consumption of fruits, vegetables, olive oil, legumes, nuts, fish, minimally processed cereals, low intake of alcohol and low to moderate intake of red or white wine, as well as infrequent intake of red meat that has been accepted as a well-balanced diet.[5–8] Epidemiological evidences suggested that the MD could reduce the risk of BC[9,10] and lower incidence of this cancer among Mediterranean population has been attributed to the traditional MD adherence.[11] Several mechanisms have been proposed for protective effects of this diet against BC risk. Since, increased levels of endogenous estrogen are associated with an increased risk of BC,[12] MD can decrease endogenous estrogens and help to increased level of sex hormone binding globulin (SHBG).[13] Additionally, MD have phytoestrogens that display estrogens -like effects and may compete with estrogens in binding to estrogen receptors, so it has the ability to exert antiestrogenic effects.[9] Furthermore, MD contains high amount of phytochemicals with antioxidant properties and low amount ruminate animal-derived phytanic acid which may explain other protective effects.[13–15] Also, its lipid composition (olive oil) suppresses over expression of human epidermal growth factor receptor 2 (HER2) oncogene, that plays an important role in the development and progression of certain aggressive type of BC at the transcriptional level.[16,17]

However, studies that examine the beneficial effects of MD on postmenopausal and premenopausal BC risk have reported contradictory results.[6,18] So, we conducted this systematic review to investigate whether adherence to Mediterranean dietary pattern influence on BC risk in postmenopausal and premenopausal women.

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Accepted for publication: 2 September 2015

Methods

Search strategies

Original data for this review were identified through searches of the Pubmed, Google scholar, Cochrane and Scopus databases. We used search terms, "breast neoplasm", "breast tumors", "mammary carcinoma", "mammary neoplasm", "breast cancer", and "Mediterranean diet" as key words. The search terms were used for words in title or abstract on Medical Subject Heading (MESH). We conducted a literature search of published studies earlier than April 2015.

Selection of studies

Initial systematic search in above mentioned databases resulted in 109 articles. Studies that fulfilled the following criteria were eligible for selection: 1) written in English; 2) with a study arm of MD intervention or MD style assessment; and 3) reported the BC risk in premenopausal or/and postmenopausal women.

Two authors independently screened titles and abstracts of studies for potential eligibility. Full texts of potentially eligible studies were retrieved and two authors applied inclusion criteria to identify relevant studies to be included in the review. Disagreements were resolved through discussion; if necessary, a third reviewer involved. A total of 66 studies were excluded on the basis of the title and abstract. Then 35 studies were left out because they were not associated with our subjects. Finally, 8 papers were selected that were found to meet the aforementioned criteria in accordance items for systematic reviews (PRISMA). Also, we manually searched through the references from relevant articles where necessary. The details of selected articles are shown in the Figure 1.

Data extraction

Two independent investigators extracted key data, including country of study, the number of participants, population characteristics, dietary assessment method, adjustment for confounders, hormone receptor and menopausal status, year, study design, events followed and results. Characteristic of various studies are shown in Table 1.

Results

Through the review process, we identified five cohorts and three case-control studies. Overall, six studies in post and premenopausal and two studies in postmenopausal women were conducted. In four studies, favorite effects of MD in the post and premenopausal women were reported. Two and one of them show similar results only in postmenopausal and premenopausal women respectively. Also, five studies were performed in Mediterranean countries.

Among these researches, two and six studies use posteriori and priori approach to identify the MD patterns and BC risk in pre and postmenopausal women.

Cohort studies

One cohort article showed that adherence to MD pattern had an inverse association with significant reduction in the risk of BC among postmenopausal women. When individuals were classified according to estrogen and progesterone receptor, this association among BC cases with ER+/PR- became stronger. Also, in women with energy intake below the median (2,037 Kcal/day), this dietary pattern was conversely associated with this risk. In this study, MD was characterized by a high intake of fish, fruit,

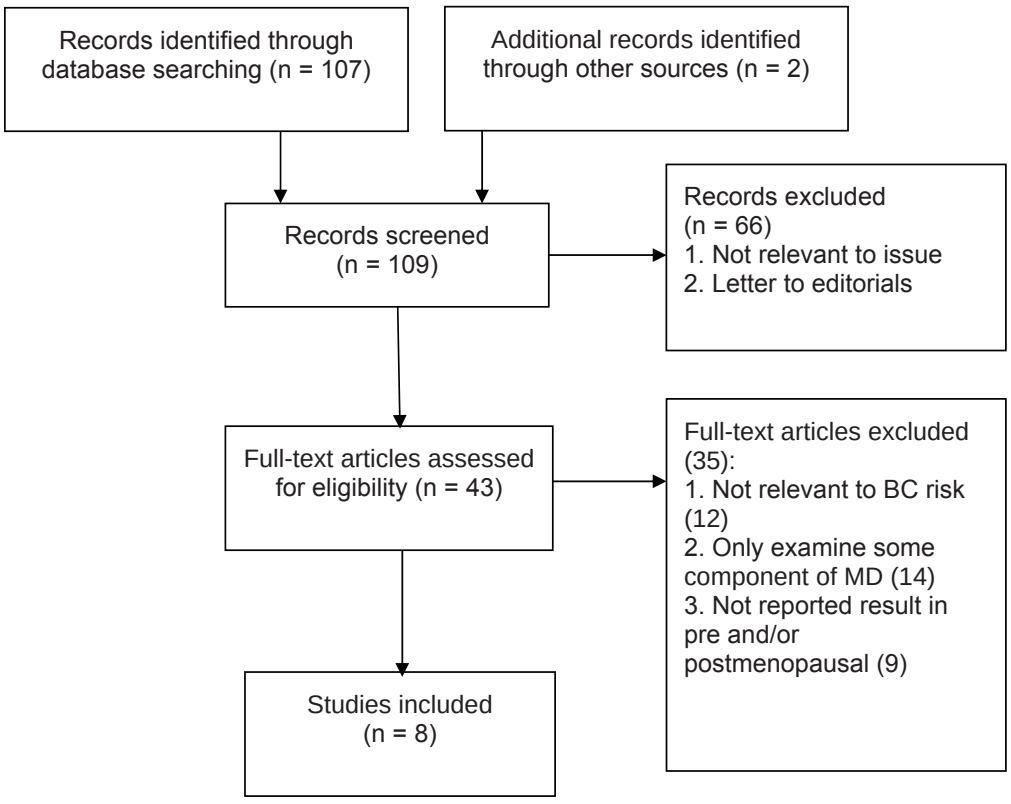

Figure 1. Flow chart of systematic literatures search

Table 1. Characteristics of included studies

Author	Year	Design	Region	Follow up duration	Sample size	Age	Adjust	OR/ HR/ *P*-value	Events followed	Diagnostic criteria/ grade cancer	outcome	Menopausal status	Hormone receptor status	MD[1] compliance assessment method
Castello, et al.	2014	Case-control	Spain	- - -	2034	- - -	total calories, alcohol consumption, body mass index (BMI) from self-reported weight and height (BMI¼kgm_2), 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	pre-menopausal 0.58 (0.38–0.91) post-menopausal 0.54 (0.34–0.86)	Risk of BC	- - -	Decrease BC risk	pre and post-menopausal	- - -	MD score (0–8) priori
Couto, et al.	2013	Cohort	Sweden	16 year	44‹840	30–49	History of BC[5] in mother and/or sister, personal history of benign breast disease, smoking, BMI, height, age at first birth and number of children, educational level, age at menarche, energy intake, intake of beverages, potatoes, sweets, eggs	All women OR = 1.08, CI: (1.0,1.15) pre-menopausal OR = 1.10, CI: (1.01,1.21) post- menopausal OR = 1.02, CI: (0.91,1.15)	BC incidence	ICD, 7th revision, code 170.0	Not related with BC risk	pre and post-menopausal	ER+/PR- ER-/PR+ ER-/PR- ER+/PR+	MD score (0–9) priori
Demetriou, et al.	2012	Case-control	Cyprus	3 year	2‹286	40–70	Age at interview, family history, age at FFTP, HRT, exercise, age at menarche, height, BMI in postmenopausal women	OR = 0.63, CI: (0.77,1.53) *P*-value for trend = 0.61	Risk of BC	- - -	Not related with BC risk	post-menopausal	Not reported	MD score by panagiotakos priori
Buckland, et al.	2012	Cohort	10 European countries	11 year	335‹062	35–70	BMI, height, educational level, physical activity, smoking, menopausal status, age at menarche, OCP use, breastfeeding, age at first FFTP[7],HRT, saturated fat intake, alcohol intake, energy intake, mutually adjusted for the arMED component	All women OR = 0.94, CI: (0.89,1.00) pre-menopausal OR = 0.94, CI: (0.88,0.99) post-menopausal OR = 0.99, CI: (0.84,1.18)	BC incidence	ICD-10 codes C50.0-C50.9/ invasive	Pre: not related with BC risk Post: decrease BC risk	pre and post-menopausal	ER-/PR- ER+/PR+	arMED[6] (0–16) priori
Cade, et al.	2011	Cohort	British	9 year	33‹731	35–69	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, CI: (0.42,1.02)post-menopausal HR = 1.30, CI: (0.83,2.05)	BC Incidence	ICD89 and 10	Pre: decrease BC risk Post: not related	pre and post-menopausal	Not reported	MD score (0–10) priori

Trichopoulou, et al.	2010	Cohort	Greek	9.8 year	14،807	20–86	Age, educational level, smoking, BMI, height, metabolic equivalents of task hours per day, energy intake, age at menarche, parity, age at first delivery, menopausal status, age at menopause hormone replacement therapy, interaction term for the BMI by menopausal status	Overall HR = 0.88, CI: (0.75,1.03) pre-menopausal HR = 1.01, CI: (0.80,1.28) post-menopausal HR = 0.78, CI: (0.62,0.98)	BC incidence	ICD code C50	Pre:not related with BC risk Post: decrease BC risk	pre and post-menopausal	Not reported	MD score (0–9) priori
Cottet, et al.	2009	Cohort	France	9.7 year	65،374	51–55	Age, educational level, region at baseline, BMI, height, family history of BC, age at menarche, age at FFTP combined with number of live births, menopausal hormone therapy, history of benign breast disease use of OCP, life time duration of breast feeding, physical activity, smoking, energy intake excluding alcohol, current use of phytoestrogen supplements and vitamin/ mineral supplement	HR = 0.85, CI: (0.75,0.95)	BC incidence	ICD codes C50-C50.6 and C50.8-C50.9/ invasive (88%)	Decrease BC risk	Post-menopausal	ER+/PR- ER-/PR+ ER-/PR- ER+/PR+	factor analysis posteriori
Murtaugh, et al.	2008	Case-control	Arizona, New mexico, Colorado, Utah	5 year	4،119	25–79	Age, center, education, family history of BC, smoking, activity, calories, dietary fiber and calcium, height, parity, recent hormone exposure, BMI, interaction of recent hormone exposure and BMI	White non- Hispanic pre-menopausal OR = 0.86, CI: (0.55,1.32), *P* trend = 0.56 post-menopausal OR = 0.86, CI: (0.64,1.16) *P* trend = 0.24, Hispanic pre-menopausal OR = 0.70, CI: (0.42,1.16), *P*- trend = 0.11 post-menopausal OR = 0.58, CI: (0.37,0.90), *P*-trend < 0.01	Risk of BC	ICD sites C50-C50.6 and C50.8-C50.9/ in situ or invasive	Decrease BC risk	pre and post-menopausal	Not reported	posteriori

[1]MD: Mediterranean Diet; [2]BMI: Body Mass Index; [3]HRT: Hormone Replacement Therapy; [4]OCP: Oral Contraceptive; [5]BC: Breast Cancer; [6]arMED: Adapted relative Mediterranean Diet; [7]FFTP:First full-term pregnancy; [8] ICD: International Classification of Diseases.

vegetables and olive oil.[19] Similar results were obtained by another study among postmenopausal women. Also, after examination the component of MD, fish intake appeared to be positively related to BC risk among premenopausal women which probably due to chance on account of multiple comparisons in statically method. Diet was evaluated each year through the FFQ and conformity to MD was assessed through a score (range = 0 – 9). For this analysis, fruit and vegetables, legumes, cereals, fish and sea foods, nuts, dairy products, olive oil, monounsaturated and saturated lipids, and ethanol were considered. Lack of information on estrogen/progesterone receptor status was one of the limitations of this study.[13]

In 2011, another cohort study that was conducted among pre and postmenopausal healthy women reported an inverse association between MD pattern and incidence of tumor breast only among premenopausal women. In this study, hormone receptor status was not reported. Compliance to MD was based on a MD score (0 – 10 score).[20]

The Swedish cohort study investigated the association between MD with BC risk in pre and postmenopausal women aged 30 – 49 years that were followed up during 16 years. Intake of food and beverages was measured by using a food frequency questionnaire (FFQ). MD score (0 – 9 points) was constructed based on the intake of fish, vegetables, fruits, cereals, legumes, alcohol, the ratio of unsaturated fat to saturated fat, meat and dairy products. Although, 290 g dairy products consumption along with this regime caused a statistically significant reduction in BC risk, Mediterranean style diet didn't have a beneficial effect on the risk of BC among these women.[6]

In their study, Buckland, et al. assessed pre and postmenopausal healthy women for 11 years in 10 European countries. Validated country-specific questionnaires were used to record the usual diet; semi-quantitative FFQ combined with a food record. Diet history questionnaires administered through a personal interview. Adherence to MD estimated through an adapted relative MD (arMED) scores (0 – 16 points). The original score considered fruit and vegetables, legumes, cereals, alcohol, olive oil and fish. The scoring was inverted for meat and dairy products presumed to not fit MD. The finding showed arMED was inversely associated with BC risk only in postmenopausal women especially for estrogen/progesterone receptor negative (ER-/PR-) persons.[9]

Case-control studies

A case-control study among pre and postmenopausal women showed adherence to MD pattern associated with lower risk of BC and no differences were observed between pre- and postmenopausal women. This dietary pattern loaded high in fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil, and low in juices. Dietary intake was estimated using a 117-item semi-quantitative FFQ. A total of 1017 incident BC cases and 1017 matched healthy controls of similar age (±5 years) without a history of BC were recruited.[21]

According to another case-control report, a dietary pattern including fruit, vegetables, fish, legumes, and olive oil that was resembled the MD guide might be favorably influence the risk of BC in postmenopausal women. In the case group, 935 postmenopausal women aged 40 – 70 years old that had a confirmed diagnosis of BC were recruited. Also, 817 healthy women were selected as controls from the general population. FFQ and Principal Component Analysis (PCA) were used to determine dietary patterns in this study.[8]

Also, another study confirmed a significant protective role of MD on incidence of BC in pre and postmenopausal Hispanic women and non-Hispanic white women. These cases had a histologically confirmed diagnosis for either in situ or invasive BC. Controls were healthy women that frequency-matched by ethnicity, BMI and menopausal status with cases. Food intake was reported by using a computerized, interviewer-administered dietary history questionnaire and PCA.[22]

Discussion

Although there was insufficient evidence to reach a conclusion about the effect of MD on BC risk in pre and postmenopausal women, case-control studies demonstrated that MD could reduce this risk in pre and postmenopausal women.[8,22] However, the design of these studies are susceptible to recall and selection bias and often show stronger diet-diseases associations than other studies. In addition, cohort studies reported conflicting results. Whereas, one study suggested reliance on MD lead to lower postmenopausal BC risk,[13] another study showed this result only in premenopausal women.[20] It was assumed that a hormonal pathway and hormone receptor status could be involved in the heterogeneity of these results. Hormonal risk factors, such as exposure to exogenous and endogenous hormones are strongly important in the cause of BC, and may be more associated to the risk of hormone receptor-positive breast tumor that depends on the presence of certain hormone for ongoing proliferation. In contrast, non-hormonal risk factors, such as diet, may be more related with hormone receptor-negative BC, refers to BC that does not express the hormone receptor.[6] However, few studies have assessed the association between the MD compliance and the risk of specific breast tumor characteristics, such as ER and PR status.[9,19] In hormone receptor-positive tumors, where hormonal factors have a strong influence, identify relation between MD and BC risk is difficult. On the other hand, although the effect of MD on BC may be clear in hormone receptor-negative tumors where hormonal factors have not an influence, the protective effect of this dietary style on receptor-positive BC[19] may be related to hormonal pathway via decreasing the concentration of circulating estrogens.

Furthermore, some confounding factors such as, family history of BC, using hormone therapy and oral contraceptives, as well as some dietary intake might have an impact on this research results.[6]

Moreover, biological plausibility of difference between the effects of mentioned diet on the pre and postmenopausal BC incidence included some genetic factors such as, cytokine gene, BCAR1 gene, BC anti-estrogen resistance protein1,[23,24] as well as early life events such as age at menarche, age at menopause, parity, lactation and abortion.[25] These factors are stronger agents for incidence of premenopausal BC than influence of dietary pattern. In addition, age-related changes such as variation in sex hormone levels may also express some differences between BC risk and nutritional status in post and premenopausal women.[9]

Besides the mentioned factors, differences in the methods, posteriori and priori approach, applied to ascertain MD may explain the discrepancies in the results of these studies.[19,22] One limitation of this method is that the identified pattern is population-dependent, and may not use to other population. Other studies constructed an assumed score according to prior knowledge of the composition of the MD.[6,9,20] The composition of a specific component

may change from one population to another in this method. For example, in Mediterranean population olive oil is the main source of unsaturated fat, unlike in non-Mediterranean population. Also, in some studies usual diet of participant was different from studies conducted in Mediterranean countries. So, consumption threshold of MD useful components may not be reached in these studies.[6]

A number of physiological mechanisms can explain the preventive effects of the MD on breast malignancy. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses over expression of HER2 oncogene which in turn, promotes apoptosis in tumor cells.[26] Also, squalene, a major bioactive compound in olive oil, has an anti-tumor activity by decreasing DNA oxidative damage and beta-hydroxy-beta-methylglutaryl-coAreductase action as an enzyme that effects on cellular signal transduction and proliferation in human mammary cells.[27]

Low consumption of red meat in MD may also play an important role in reducing the incidence of BC. Red meat is a source of saturated fat and iron, which have independently been related to carcinogenesis. In general, the association between saturated fat and cancer are probably related to elevated levels of energy balance and insulin resistance, whereas iron generate free radicals and induce oxidative stress that results in activation some carcinogenesis pathway. Red meat is also a source of some known mutagenic compounds, including N-nitros compound, heterocyclic amines and polycyclic aromatic hydrocarbons that may be involved in the BC etiology.[28,29]

Due to the high quantity of marine foods in MD, the anticarcinogenic related mechanisms of marine n-3 poly unsaturated fatty acid can be described by inhibition of eicosanoid derived from arachidonic acid, as a pro-inflammatory signaling molecule, regulation of gene expression, transcription and activities of molecules related to the signal transduction of cell growth.[30]

Furthermore, MD has been characterized by low intake of alcohol. As whereas, alcohol inhibits the activity of 2-hydroxylase and sulfotransferase, enzymes involved in estrogen degradation, low levels of estrogens provided by this diet can lead to decreased risk of BC. In addition, alcohol is metabolized to acetaldehyde (AA) that is mutagenic and carcinogenic compound which binds to proteins and DNA, forming stable carcinogenic adducts. Also, AA can stimulate carcinogenesis pathway, reduces the anti-oxidative defense system and alter in directly epigenetic DNA and histone methylation.[31]

On the other hand, red wine polyphenol and resveratrol in MD can reduce localized estrogen production in BC cells. Resveratrol decreases the aromatase levels in malignant cells, an enzyme responsible for the biosynthesis of estrogens, and via these ways it can exert protective impact on breast tumor.[32]

We should note the limitation of this review study such as scarcity of studies. Furthermore, lack of the evaluation of hypothesized factors relating to breast cancer include breastfeeding, adiposity, physical activity, genetic background, insulin resistance, and chronic inflammation in mentioned research are other restrictions.

Also, only few studies investigated risk of BC in pre and postmenopausal separately. Due to inconsistent results and insufficient evidences, further well-designed and long term studies by considering the BC risk factors such as genetic background, hormone receptor status, habitual dietary pattern and physical activity level are needed. Moreover, components of the MD can act synergistically to reduction BC risk, so it is important that all components of the MD considered in studies.

In conclusion, our review suggests that there is no sufficient data to reach a conclusion about the effect of MD on breast cancer risk in pre and postmenopausal women. Given the possible beneficial effects, suggesting in some evidences, MD can be suggested to women as a healthy dietary pattern, which may contribute to a reduction in BC risk.

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