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Adherence to a Mediterranean Dietary Pattern and Risk of Breast and Endometrial Cancers: A Systematic Review

Mohammad Reza Mazandaranian, Arezoo Rezazadeh*, Alireza Bahrami

Department of Community Nutrition, National Nutrition and Food Technology Research Institute, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran.

ABSTRACT

Breast and endometrial cancers are the most prevalent cancers among women all over the world, with breast cancer being the first cause of cancer mortality in women. Major known risk factors for breast and endometrial cancers are obesity, low physical activity, and unhealthy and poor diet, contributing to about 30%-35% of cancer incidence. Recent evidence supports that adherence to a healthy dietary pattern such as the Mediterranean diet (MD) is associated with reduced risk of certain types of cancer, including breast and endometrial cancers. The data for the current review were identified through a systematic search on PubMed, Scopus, and Cochrane databases using the following search terms/keywords: "Mediterranean diet," "Mediterranean dietary pattern," "breast," "mammary," "endometrial," "cancer," "carcinoma," and "neoplasm." The reference lists of the included papers were also searched manually. Through the review process, eight case-control studies, four cohort studies, and one clinical trial were identified. The included studies were conducted among postmenopausal and premenopausal women in the United States and some European countries. The review suggests a protective role for the MD against breast cancer risk in both populations. According to the fact that there was insufficient research on the association of the MD pattern and endometrial cancer risk, its protective effect cannot be interpreted with certainty. Further studies in this area, especially interventional studies, are needed to determine causality.

Introduction

Breast and endometrial cancers are the most prevalent cancers among women all over the world. Breast cancer (BC) has the highest mortality rate in women compared with other cancers. Based on the report of Global Burden of Cancer Study (GLOBOCAN) 2012, about 6000 new cases of BC and 1500 new cases of endometrial cancer (EC) had been globally diagnosed in the five years [1-2]. Major known risk factors for breast and endometrial cancers are overweight and obesity, low physical activity, and poor nutrition, with an overall contribution of about 30%-35% to cancer incidence [3]. High consumption of processed foods high in saturated fats, salt, and sugar and low intake of fruit, vegetables, and whole-grain products (characteristics of Western dietary patterns) have been linked to a higher risk of cancers including BC and EC. However, following healthier dietary patterns (e.g., the Mediterranean diet [MD]) has been associated with reduced risk of certain cancers, including breast and endometrial cancers [4-5]. The MD is characterized by high consumption of fruits, vegetables, legumes, and nuts; low consumption of dairy and meat products, processed cereals, and monounsaturated fats; moderately high consumption of fish; and regular but moderate intake of alcohol (mostly from red wine) [6]. While some studies have reported the preventive influence of the MD on breast and endometrial cancers [4-5, 7-12], others have not found such associations [13-15]. Because of these

contradictory findings, the aim of the present study was to systematically review the association of the Mediterranean dietary pattern and risk of breast and endometrial cancers. Findings from this study may inform guidelines and future interventions aiming to reduce the risk of breast and endometrial cancers.

Methods

Data source and search strategy

Original data for this review were identified through a systematic search of PubMed (MEDLINE), Scopus, and Cochrane Library databases searched until March 2018. The following search terms were used in combination: "Mediterranean diet," "Mediterranean dietary pattern," "breast," "mammary," "endometrial," "cancer," "carcinoma," and "neoplasm" (Figure 1). The Medical Subject Headings (MESH) database was checked for selected keywords. Grey literature such as governmental and organizational published reports and the reference list of the selected studies (and previous systematic reviews in this topic) were also searched manually for relevant information and articles.
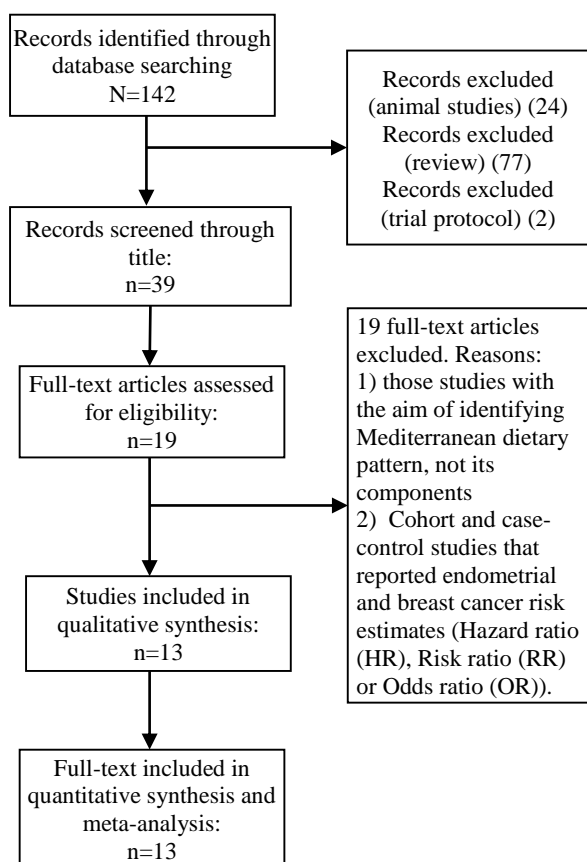
Studies were included if they (1) were cohort or case-control studies that reported endometrial and breast cancer risk estimates (hazard ratio [HR], risk ratio [RR], or odds ratio [OR]) and (2) identified the Mediterranean dietary pattern as one of the population's main dietary patterns. Only English-language studies were included.

The initial systematic search identified 39 potential articles. Two authors independently screened the titles and abstracts based on eligibility criteria. Next, the full text of potential articles was reviewed. Disagreements over the eligibility of papers were resolved by including a third author. Figure 1 shows the study selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The methodology of this systematic review has been registered at the International Prospective Register for Systematic Reviews (CRD42018088587).

Data extraction and quality assessment

Two independent investigators extracted key data including the name of the first author, year and country of study, the number and mean age of participants, study design, dietary assessment method, the MD diet compliance assessment method (the method of extraction of Mediterranean diet score [MDS] and components of the score), confounders, events followed, and outcomes (adjusted OR, HR, and 95% CIs). The "checklist of items to consider in data collection" from Cochrane Handbook for Systematic Review of Interventions was used in the process of data extraction [16].

Results

A total of 13 studies (8 case-control studies, 4 cohort studies, and 1 clinical trial) met the inclusion criteria. The included studies had been conducted among post- and pre-menopausal women in the United States and some European countries. The summary of findings by cancer type is presented in Tables 1 and 2.

Breast cancer

One case-control study was conducted across four states of the United States to assess BC risk among women of white and Hispanic ethnicity. Food consumption was recorded using the Diet History Questionnaire, and dietary patterns were identified using factor analysis. Food items were categorized into 69 groups such as low-fat and high-fat dairy, red meat, poultry, etc. The results showed that both Western (OR, 1.32; 95% CI,

Figure 1.

Selection of studies

Table 1. The association of Mediterranean diet score/dietary pattern with breast cancer

Authors	Year	Design	region	Sample size	Age	Follow-up duration	MD compliance assessment method	Adjustment	Results	Outcome
Murtaugh, et al.	2008	Case-control	USA	Case=2281 Control=2465	25-79	-	MDS	age, center, education, family history of breast cancer, smoking, total activity, calories, dietary fiber, dietary calcium, height, parity, recent Hormone exposure, BMI, and interaction of recent hormone exposure and BMI.	(0.76; 0.63, 0.92; P for trend < 0.01	lower risk of best cancer
Cade, et al.	2011	Cohort	Britain	33.731	35-69	9	MDS	Use of hormone therapy, age, BMI, physical activity, smoking status, calorie-adjusted fat intake, the age of menarche, oral contraceptive use, parity, ethanol, total days breastfeeding, socioeconomic class and level of education.	(95%CI; P (trend) = 0.4)	No significant association was seen
Buckland, et al.	2012	Cohort	Denmark, France, Germany, Greece, Holland, Italy, Norway, United Kingdom, Spain and Sweden	335,062	50.8(9.8)	6	arMED	Menopausal status, age, education, BMI, family history of breast cancer, physical activity, smoking status, the age of	(95% CI; 0 and 12%)	Decreased incidence of BC

								menarche, the age of menopause, breastfeeding, age at full-term pregnancy, saturated fat intake, total energy, and alcohol intake, Use of hormone therapy, oral contraceptive use	
Demetriou, et al.	2012	Case-control	Greece	Case=935 Control=817	40-70	2	MDS	age at interview, family history, age at FFTP, HRT use, exercise, age at menarche, height and BMI in post-menopausal women	(OR=1.00-95%CI: 0.96-1.04	Mediterranean diet score was not associated with lower risk of BC
Couto, et al.	2013	cohort	Sweden	49,258	30-49	16	MDS	history of breast cancer in mother and/or sister(s), personal history of benign breast disease, smoking status, BMI, height, age at first birth and the number of children, educational level, age at menarche, total energy intake, consumption of beverages, potatoes, sweets, and eggs.	(RR:0.93. 95%CI; 0.87-0.99);	consuming Dairy products was significantly associated with reduced risk of breast cancer
Mourouti, et al.	2014	Case-control	Greece	Case=250 Control=250	56 (12)		Med Diet Score	Menopausal status, age, education, BMI, family history of breast cancer, physical	(P-value<0.005; 95% CI: 0.84, 0.93).	Decreased BC risk

								activity, smoking status, the age of menarche, the age of menopause		
Castello´, et al.	2014	Case-control	spain	Case=1017 Control=1017	25	-	aMED	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.	(95%CI;0.69-0.89)	Decreased BC risk
Toledo, et al.	2015	Randomized controlled clinical trial	Spain	Control=1391 Case1=1476 Case2=1285	60-80	4.8	Med Diet score	Use of hormone therapy, age, BMI, family history of breast cancer, baseline adherence to Mediterranean diet, physical 2activity, smoking status, total energy intake, the age of menopause, prevalent diabetes mellitus, use of statins	(95% CI; 0.16-0.87).	BC incidence was lower in med diet+EVOO

| Castello, et al. | 2017 | Multicase-control | Spain | Case=1124 Control=1589 | 24-85 | 5 | Mediterranean dietary pattern | Menopausal status, age, education, BMI, age at first delivery, family history of breast cancer, physical activity, smoking status, calorie, and alcohol intake | (95%CI;0.69-0.89) | Decreased BC risk |
| Turati, et al | 2018 | Case-control | Italy and Switzerland | Case=3034 Control=3392 | Case=55 Contro=56 | 17 | MDS | study center, age, education, body mass index, physical activity, smoking, parity, menopausal status, oral contraceptive use, hormone-replacement therapy use, diabetes, family history of breast cancer, non-alcohol energy intake; | p-value=(0.008) ,(OR=0.95; 95% CI 0.92–0.99) | Decreased risk of BC |

Table 2. Results of endometrial cancer studies

Authors	Year	Design	region	Sample size	Age	Follow-up duration	MD compliance assessment method	Adjustment	Results	Outcome
Dalvi, et al.	2007	Case-control	USA	Case=647 Control=633	35-79	-	MDS	age, race/ethnicity, age at menarche, OC use, parity, average daily caloric intake, average weekly physical activity, and the joint effects of menopausal status, HT use, and BMI	(95%CI; 059-1.4 for the highest versus lowest quintile)	No association
George, et al.	2015	cohort	USA	161,808	50-79	22	aMDS	age, energy intake, ethnicity, education,	(HR: 0.98, 95% CI: 0.82-1.17)	with the lower risk of

							Adjusted for		Outcome
							metabolic equivalent of task hours per week leisure-time physical activity, diabetes status, postmenopausal Hormone replacement therapy use, oral contraceptive use, age at first birth, a participant in the observational study, a participant in HT trial, a participant in DM trial.		endometrial cancer
Ricceri, et al	2017	Case-control	Italy	Case=297 Control=307	Case=31 Control=60	-	Mediterranean diet index	age, parity, menopausal status, hormone replacement therapy use, oral contraceptive use, body mass index, age at menarche, physical activity, education, smoking status, and total energy intake	p-value=0.004 (adjusted OR: 0.51, 95% CI 0.39-0.86)	Decreased risk of EC

1.04-1.68; p for trend < 0.01) and prudent dietary patterns (OR, 1.42; 95% CI, 1.14-1.77; p for trend < 0.01) were associated with a higher risk of BC, but adherence to a Mediterranean dietary pattern was associated with a lower risk of BC (OR, 0.76; 95% CI, 0.63-0.92; p for trend < 0.01), especially in postmenopausal Hispanic women (OR, 0.58; 95% CI, 0.37-0.90; p for trend < 0.01) [10]. Mammography Simulation Tool for design Optimization Studies (MASTOS) was a case-control study that was carried out from 2004 to 2006. Cases were 1109 and controls were 1177 women aged 40-70. Cases had a confirmed BC between 1999 and 2005. The participants' dietary intakes and adherence to the MD were assessed using a food frequency questionnaire (FFQ) and an MDS measurement tool. MDS was not associated with lower risk of BC (OR, 1.00; 95% CI, 0.96-1.04). However, higher intake of some components of this pattern such as vegetables (OR, 0.95; 95% CI, 0.92-0.99), fish (OR, 0.88; 95% CI, 0.79-0.98), and olive oil (OR, 0.95; 95% CI, 0.92-0.99) were associated with lower risk of BC [9]. In another study, conducted in Greece over 18 months, with 250 cases and 250 controls, dietary intake was measured using a semi-quantitative 86-item FFQ. Results showed that one unit increase in MDS was associated with 12% lower likelihood of BC (OR, 0.88; 95% CI, 0.84-0.93). In this study, the most protective components of the MD were nonrefined cereals, followed by vegetables, fruit, and alcohol, and red meats and their products were the most nonprotective components [7]. The Spanish Breast Cancer Research Group case-control study was performed among Spanish female population. They recruited 1017 incident cases of BC and assessed their dietary intake using a 117-item self-administered FFQ. The results revealed that one unit increase in MDS was associated with 21% lower risk of BC in all women (OR, 0.79; 95% CI, 0.69-0.89) [8]. One case-control study that was conducted on a sample of 1124 cases and 1589 controls used a 154-item FFQ for dietary assessment, and the results showed that BC patients had more adherence to the Western

dietary pattern (OR, 1.53; 95% CI, 1.15-2.02), with no difference between cases and controls in MDS [13]. In another study in Italy and Switzerland, 3034 BC cases and 3392 controls were included, and a 78-item FFQ was used for dietary intake analysis. MDS and modified MDS (excluding alcohol) were calculated, and it was found that for every point increase in MDS, the risk of BC decreased by 5% (OR, 0.95; 95% CI, 0.92-0.99) [17].

In a large cohort study with 35,372 British women aged 35-69 years between 1995 and 1998, diet was assessed using a 219-item self-administered FFQ, and MDS was used to assess the level of adherence to the Mediterranean dietary pattern. No significant association was seen between the Mediterranean dietary pattern and risk of BC (HR, 0.65; 95% CI, 0.42-1.02; p for trend = 0.9) [15]. The European Prospective Investigation into Cancer and Nutrition study, involving 23 centers across 10 European countries, analyzed dietary data collected via a self-administered semi-quantitative FFQ for 335,062 women who were mostly 30-75 years old. An adapted relative MDS, excluding alcohol use, was used to measure the level of adherence to the MD. The result shows that higher adherence to the MD was associated with a 6% lower risk of BC (OR, 0.94; 95% CI, 0.88-1.00) [11]. The Swedish Women's Lifestyle and Health cohort study analyzed dietary data for around 49000 women aged 30 to 49 years recruited in 1991-1992. Dietary intake was assessed using an 80-item FFQ and MDS was used to assess the level of adherence to the MD. Examining the components of the MD revealed that consuming dairy products was significantly associated with reduced risk of BC (RR, 0.93; 95% CI, 0.87-0.99); this kind of association was not seen for other components [12].

In a study that took place among women in the Prevention with Mediterranean Diet trial during 2003 to 2009, 4282 women were randomly allocated into 3 equal intervention groups: an MD supplemented with extra-virgin olive oil, an MD supplemented with mixed nuts, and a control diet (advised to reduce dietary fat). During the time of the trial, 35 confirmed incident cases of malignant BC were identified. Women consuming an MD supplemented with extra-virgin olive oil had a 62% lower risk of malignant BC compared with women in the control diet group (95% CI, 0.16-0.87); however, the difference in BC risk was not significant between the MD supplemented with nuts and the control diet (OR, 062; 95% CI, 0.29-

1.36) [5].

Endometrial cancer

A study conducted in San Francisco, US, recruited 647 cases and 633 controls and assessed dietary intake using a 103-item FFQ. No association was seen between a Mediterranean dietary pattern and EC risk (95% CI, 0.59-1.4 for the highest versus lowest quintile) [14].

However, in another study with 297 incident cases of EC and 307 controls in northern Italy, the risk of EC in women with high adherence to the MD was half the risk in women with low adherence to the MD (adjusted OR, 0.51; 95% CI, 0.39-0.86) [18].

A prospective cohort study followed a sample of 84,415 postmenopausal women from the Women's Health Initiative Clinical Trials and Observational Study for a mean period of 13.3 years, during which 1392 cases of EC were documented. Dietary intake was analyzed using a 122-item FFQ. Results showed no association between adherence to an MD pattern and risk of EC (HR, 0.98; 95% CI, 0.82-1.17) [4].

Discussion

In the present systematic review, most of the studies investigated the association between the MD and BC. Data from cohort and case-control studies revealed that higher adherence to the MD was inversely associated with BC risk, a finding that is consistent with the results of a randomized controlled trial. However, due to the scarcity of data on the relationship between the MD and EC, the findings are still inconclusive and need further investigation [4, 7-13].

The protective effects of the MD are due to the antioxidative and anti-inflammatory properties [19-21] together with blood pressure–lowering effect [22] of this dietary pattern. The antioxidant capacity of the MD can be attributed to its richness in vitamins C and E, carotenoids, phenols, and flavonoids. This dietary pattern seems to lower inflammation by reducing C-reactive protein, interleukin-6, homocysteine, and fibrinogen levels [23-25]. The special role of this diet is attributed to its high content of extra-virgin olive oil (EVOO), which has been shown to affect the stages of carcinogenesis, to improve immune function, to reduce oxidative stress, and to contribute to alterations in the hormonal status, cell membrane structure and function, cellular signaling pathways, and gene expression [7]. Carcinoprotective effects of EVOO is probably due to its particular fatty acid composition: it contains high amounts of oleic acid and

polyunsaturated fatty acids (PUFAs), a low ratio of n6:n3 PUFA, minor bioactive compounds such as squalene, and phenolic antioxidants such as oleocanthal, oleuropein, and hydroxytyrosol [5]. A clinical trial showed that consuming EVOO more than 15% of total energy intake is effective in reducing the risk of BC incidence [5]. In some studies, adherence to MD was not associated with a lower risk of BC in premenopausal women, which is probably due to genetic effects and early-life events that have a stronger role in premenopausal BC patients. Also, age-related changes in local tissue metabolism of sex steroid hormones, mainly estrogen, may explain the difference in BC risk between premenopausal and postmenopausal women [11].

Studies observed different results by tumor subtype (i.e., estrogen receptor [ER]+ vs ER-tumors), with the role of the MD being clearer in ER- tumors because hormonal factors do not have an essential role in cancer prognosis [8, 11]. Some studies did not provide any information on hormone receptor status [9, 10, 15]. Some studies found a more effective role for the MD in ER+ BC, which can be explained by the fact that hormonal pathways in ER+ BC are more involved and adhering to an MD pattern decreases endogenous estrogen and increases sex hormone–binding globulin levels, thereby decreasing the level of circulating hormone and lowering the BC risk [26-28].

The possible protective effect of the MD on EC is based on the richness of the diet in phytoestrogens, which have antiestrogenic effects. Vegetables, which are consumed in abundance in MD, have protective effects against EC as they can modulate steroid hormones concentration and their metabolism, activate antioxidant mechanisms, modulate detoxifying enzymes, and stimulate the immune system [18]. Also, vegetables and fruits, with high contents of flavonoids and carotenoids, may contribute to EC prevention [29]. Fiber richness in the MD and high consumption of plant foods also may have a role in the preventive effect of MD [30].

Some limitations of the studies included in the review included the heterogeneity of cases in terms of menopausal and tumor type status, recall bias, and healthy volunteer effect [7, 11, 13]. Also, other risk factors for BC, such as the age of menarche, physical activity, and smoking status, were not considered in some studies.

In conclusion, our review suggests the protective role of the MD against BC risk. Based on the collected evidence on the beneficial effect of the MD, it is suggested that adherence to a Mediterranean dietary pattern may lead to decreased breast and endometrial cancer risk for both premenopausal and postmenopausal women; however, due to scarcity of studies and insufficient data on the relation between an MD pattern and EC risk, its protective effect could not be ascertained yet, and further studies in this area are needed.

Conflict of interest

There is no conflict of interest regarding this review.

Authorship

MRM and AR designed the search method, MRM, AR and AB conducted the search and selection of studies. SK supervised the Prisma systematic review method; MRM drafted the manuscript. AR finalized the paper. All the authors read and approved the final manuscript.

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