Original Article

Adherence to Mediterranean diet and the risk of breast cancer: a meta-analysis

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Background: For a long period of time, the Mediterranean diet (MD) has been regarded by many as a very healthy and balanced daily diet that may be related to the incidences of many types of cancer. However, the association between an MD and breast cancer risk remains inconsistent even though many studies about the topic have been conducted. Hence, we performed a meta-analysis to evaluate the relationship between an MD and breast cancer risk.

Methods: We searched PubMed, Medline, and EMBASE for relevant articles published earlier than May 2017. "Mediterranean diet" combined with "breast cancer" and "breast carcinoma" were used as search terms. The combined relative risk (RR) and corresponding 95% confidence interval (CI) were used to evaluate the association between an MD and breast cancer risk.

Results: A total of 18 articles were included in our meta-analysis; the studies spanned 11 years, ranging from 2006 to May 2017. Ten cohort and 8 case-control studies were included. Seven studies analyzed breast cancer incidence separately in premenopausal and postmenopausal women, whereas 6 studies were performed only in postmenopausal women, for a total of 13 analyses in postmenopausal women and 7 analyses among premenopausal women. Our meta-analysis revealed a significant and inverse association of the MD and breast cancer risk (RR: 0.92, 95% CI: 0.86, 0.99). Stratification analysis by study design and menopause status revealed a significant inverse association between the MD and breast cancer risk in case-control studies (RR: 0.85, 95% CI: 0.73, 0.99) and postmenopausal women (RR: 0.91, 95% CI: 0.85, 0.97) but not in cohort studies and premenopausal women.

Conclusions: Our meta-analysis revealed that an MD is significantly associated with a reduction of breast cancer risk in women, especially postmenopausal women. The MD can be suggested to women, especially postmenopausal women, as a healthy diet to reduce breast cancer risk.

Keywords: Mediterranean diet (MD); breast cancer; breast carcinoma; meta-analysis

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Introduction

Breast cancer is the most common cancer in women, but the incidence of breast cancer varies widely among different countries (1). Many reproductive factors are involved in the generation of breast cancer, such as the woman's age at full-term pregnancy, the number of births, menarche, and menopause (2). Physical activity is also involved in breast cancer incidence and recurrence (3-5). However, these factors cannot adequately explain the high incidence of breast cancer, suggesting that environmental factors such as nutrition might also be involved.

Previous studies have shown that diet influences the risk of breast cancer, but these studies are mainly focused on investigating the impact of a single nutrient or a certain food group; thus, the results are not conclusive (6-8).

For a long period of time, the Mediterranean diet (MD) has been regarded as a balanced and healthy daily diet. Although no gold standard exists, the MD is characterized by many conspicuous features, such as high intake of olive oil, which contains a large amount of monounsaturated fatty acids, vegetables, legumes, fruits, nuts, and unrefined cereals; low-to-moderate intake of dairy products (principally cheese and yogurt), seafood, and poultry; low intake of red meat; zero to four eggs weekly; and regular but moderate intake of alcohol (9).

According to a previous meta-analysis (10), the MD could reduce the overall risk of the incidence/mortality of many types of cancer by 10%; the risk of colorectal cancer could be reduced by 14%, and the risk of prostate cancer could be reduced by 4%. However, findings from studies of the MD and breast cancer risk have been inconsistent. A study that included 4,282 women aged 60–80 years old who underwent follow-up for 4.8 years showed that adherence to the MD was inversely associated with the risk of breast cancer [hazard ratio (HR) =0.43, 95% confidence interval (95% CI): 0.21, 0.88] (11). Similar results were reported in the cohort study by Cottet *et al.* (HR =0.85, 95% CI: 0.75, 0.95) (12), especially when tumors were estrogen receptor positive/progesterone receptor-negative. Numerous other cohort studies and case-control studies have reached a similar conclusion (13-15). Another study concluded that adherence to the MD was not associated with the risk of breast cancer. In February 2016, an epidemiology study that included 100,643 women who underwent follow-up from 1984 to 2006 did not observe any significant associations between the MD and the risk of breast cancer according to the molecular subtype (16). A case-control study from the UK that included 610 patients and 1,891 matched controls did not find that the MD was related to breast cancer (17). A similar observation was found in many other studies (18-20).

However, in a cohort study from Greece (21), conformity to the MD was not associated with breast cancer risk in the entire cohort (HR =0.88, 95% CI: 0.75, 1.03) or in premenopausal women (HR =1.01, 95% CI: 0.80, 1.28) but was inversely associated with breast cancer risk in postmenopausal women (HR =0.78, 95% CI: 0.62, 0.98), suggesting that menopausal status differentially impacts the relationship between the MD and breast cancer. Nevertheless, a cohort study conducted by British researchers (22) found a nonsignificant inverse association of adherence to the MD and breast cancer risk in both premenopausal women (HR =0.65, 95% CI: 0.42, 1.02) and postmenopausal women (HR =1.30, 95% CI: 0.83, 2.05). Thus, the correlation among the MD, breast cancer risk and menopausal status has not been determined.

Therefore, a meta-analysis was conducted to reassess the correlation between the MD and breast cancer risk by reviewing all of the inconsistent results that were collected from previously published articles. Additionally, we evaluated the influence of menopausal status on breast cancer risk in women who adhered to the MD through subgroup analysis. We attempted to produce the best possible evidence regarding the correlation between the MD and breast cancer risk in all and pre- or postmenopausal women.

Methods

Literature search strategy

We searched PubMed, Medline, and EMBASE for relevant articles published earlier than May 2017. The following search terms were used: "Mediterranean diet" combined with "breast cancer" and "breast carcinoma". The search terms were used in all fields. Moreover, we manually searched the references of relevant articles. When necessary, we contacted the authors of the original articles for useful information.

Study selection

We included studies that met the following criteria: (I) the study design was a cohort or case-control study; (II) the exposure was the MD or an MD-style dietary pattern, and the assessment method of the dietary pattern was validated by the Food Frequency Questionnaire (FFQ) or factor analysis posteriori; (III) the outcome was the incidence or risk of breast cancer; (IV) the diagnosis of breast cancer was performed by pathological biopsy or other standard methods; (V) the specific relative risk (RR), odds ratio (OR) or HR and corresponding 95% CI were reported; (VI) studies were written in English.

First, relevant studies were screened by searching the titles and abstracts. If the relevance was in doubt, the whole text of the paper was assessed, and any disagreements were discussed.

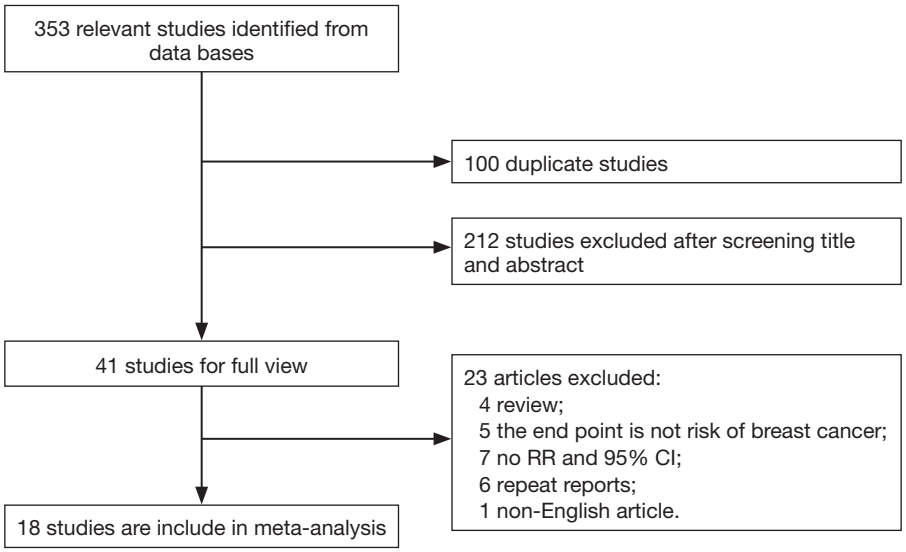

Figure 1 Flow chart of study selection.

Data extraction and quality assessment

Two independent investigators extracted key data, including: the last name of the first author, geographic area, publication year, study design, number of cases for participants or controls, age range or average age, menopausal status, hormone receptor status, follow-up time, dietary assessment method, end point of observation, diagnostic criteria/grade of cancer, results, RR/OR/HR (95% CI) for the highest *vs.* the lowest score for the MD and variables used in a multivariate model.

The quality of the involved studies was assessed using the Newcastle-Ottawa Scale (NOS), for which the scores range from 0–9 stars. Any studies that were ranked 4 stars or lower were excluded, while studies that were graded 6 stars or higher were regarded as good quality.

Data analysis

We conducted the meta-analysis by combining the multivariable adjusted RRs, HRs or ORs of the highest compared with the lowest MD adherence category based on a random-effects model using the Der Simonian-Laird method. This method consisted of both within and between study variabilities. To assess the weighting of each study, we calculated the standard errors for the logarithm of the RR/OR/HR of every study; these were regarded as the estimated variance of the logarithm of the RR/OR/HR, and an inverse variance method was used accordingly (23). In addition, we used the STATA version 12.0 software to analyze the data. A random-effects model was used to compute the combined RR and the 95% CI to assess the association between the MD and the risk of breast cancer. The Q statistic and I^2 statistic were used to determine the heterogeneity among the studies. Subgroup analysis was used to identify the association between the risk of breast cancer and menopausal status or study design. A sensitivity analysis was conducted to assess the influence of a single study on the overall risk estimate. Begg's and Egger's tests were used to detect the publication bias. A P value less than 0.05 was considered statistically significant.

Results

Literature search and study characteristics

Initially, we collected 353 related articles from the databases, including 100 duplicate studies. After the titles and abstracts were screened, 212 of the 253 remaining articles were excluded. Then, we reviewed the full texts of the remaining 41 articles. Finally, a total of 18 articles (11-22,24-29) were included in our meta-analysis. *Figure 1* shows a flow chart of the study selection.

The NOS scores of the 18 included studies were greater than 6 stars, and most studies were performed in Europe. The studies spanned 11 years, from 2006 to May 2017. Ten cohort and eight case-control studies were included. Seven studies analyzed breast cancer incidence separately

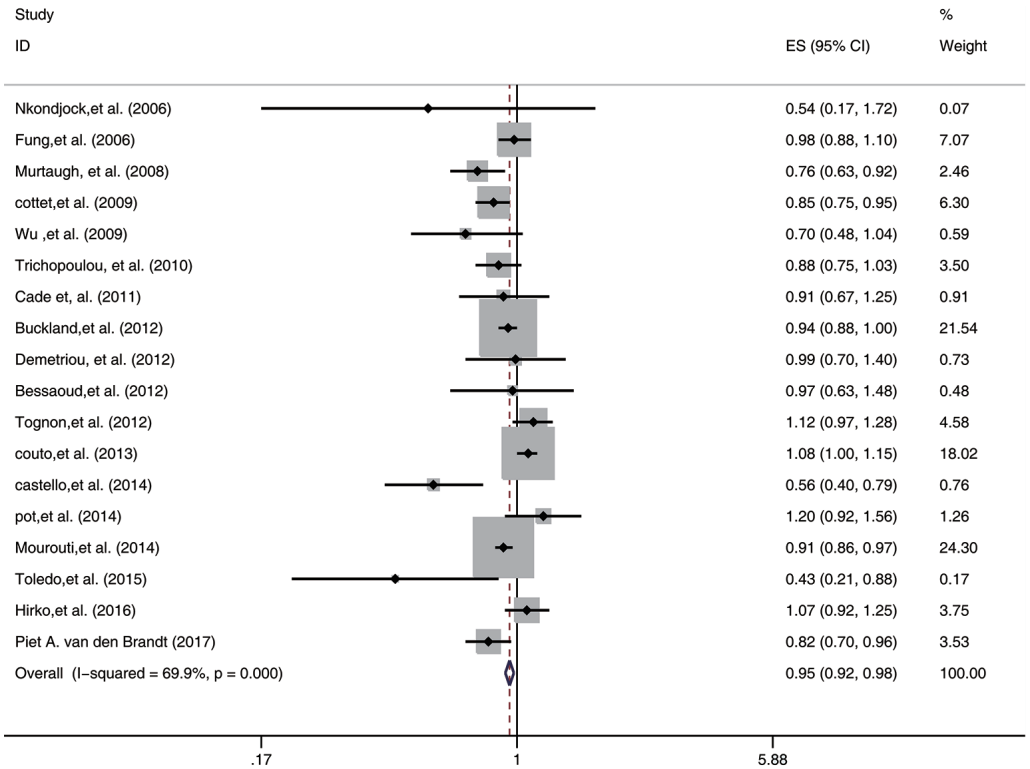

Figure 2 Forest plot for the relationship between MD and breast cancer risk. MD, Mediterranean diet.

in premenopausal and postmenopausal women, whereas 6 studies were performed only in postmenopausal women, for a total of 13 analyses in postmenopausal women and 7 analyses of premenopausal women. *Table S1* summarizes the basic characteristics of the 18 included studies.

Main analysis

A random-effects model was used to analyze the data of the 18 studies to assess the association between the MD and the risk of breast cancer. We found that the MD could markedly reduce the risk of breast cancer (RR: 0.92, 95% CI: 0.86, 0.99). Strong evidence of heterogeneity was detected among these studies (I^2=69.9%, P=0.000). *Figure 2* shows the results of our meta-analysis.

Subgroup analysis

We conducted a subgroup analysis to identify the source of heterogeneity according to menopausal status and study design. Adherence to the MD significantly decreased the risk of breast cancer, showing an inverse association between the MD and breast cancer in postmenopausal women (RR 0.91, 95% CI: 0.85, 0.97) but not in premenopausal women (RR 0.91, 95% CI: 0.85, 0.97). Study design analysis showed that adherence to the MD significantly decreased the risk of breast cancer in case-control studies (RR 0.85, 95% CI: 0.73, 0.99) but not in cohort studies (RR 0.85, 95% CI: 0.73, 0.99). Nevertheless, evidence of heterogeneity was also found across the four subgroups (premenopausal: I^2=67.5%, P=0.005; postmenopausal: I^2=59.9%, P=0.003; case-control: I^2=61.0%, P=0.012; cohort studies: I^2=71.3%, P=0.000), suggesting that other factors were involved. *Table 1* shows the results of the subgroup analysis.

Sensitivity analysis and publication bias

Removal of each study individually showed that the combined RRs were similar, and no single study obviously modified the combined results, which implied that our results were statistically stable and reliable. *Figure 3* shows the results of the sensitivity analysis. In addition, Begg's and Egger's regression tests showed a low probability of publication bias (P=0.121) (*Figure 4*).

Table 1 Subgroup analysis of Mediterranean diet and breast cancer risk

Study group	No. of study	RR (95% CI)	P for heterogeneity	I^2 (%)
All	18	0.92 (0.86, 0.99)	0	69.9
Menopause statues				
Premenopause	7	0.93 (0.83, 1.05)	0.005	67.50
Postmenopause	13	0.91 (0.85, 0.97)	0.003	59.90
Study design				
Cohort	10	0.95 (0.88, 1.03)	0.000	71.30
Case-control	8	0.85 (0.73, 0.99)	0.012	61.00

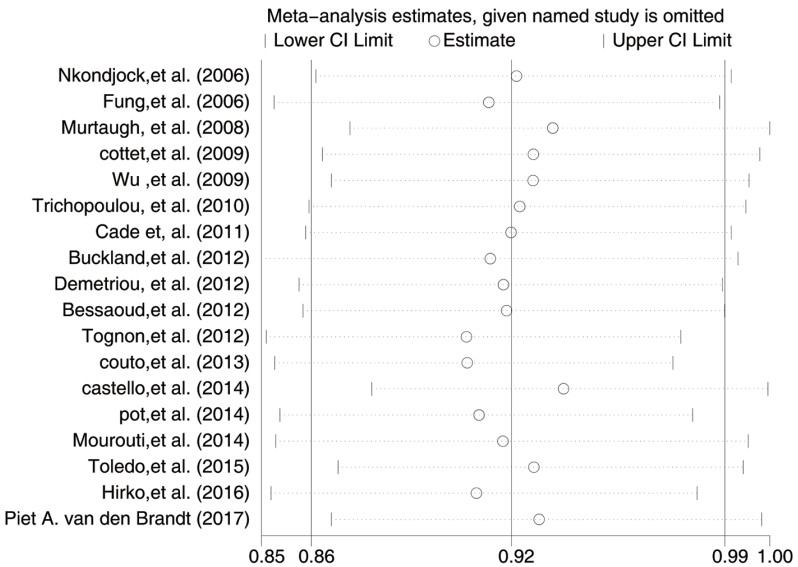

Figure 3 Sensitive analysis.

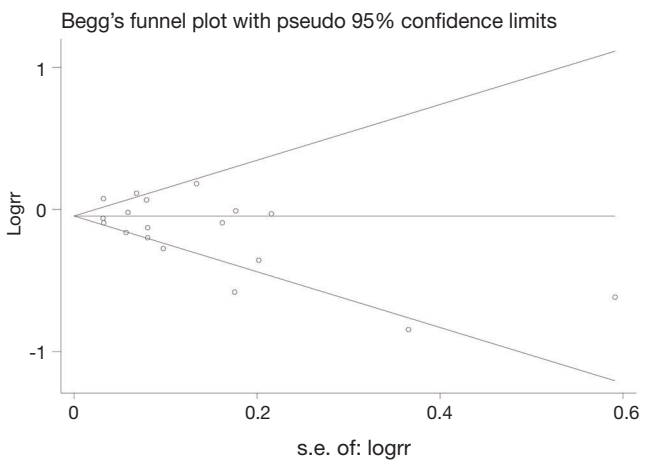

Figure 4 Forest plot for publication bias.

Discussion

Many studies have investigated the association between the MD and breast cancer risk in the past 10 years (11-16), including prospective cohort studies and retrospective case-control studies. However, those studies did not reach a precise conclusion regarding whether the MD could reduce the risk of breast cancer. Our meta-analysis included 18 studies on the association of the MD and breast cancer published from 2006 to May 2017 and found a statistically significant inverse association, i.e., the MD could reduce the risk of breast cancer. This conclusion is consistent with that of a previous meta-analysis (30), in which adherence to the MD was shown to reduce the risk, incidence

and mortality of many cancers, including breast cancer. Moreover, stratification analysis by menopausal status revealed a significant inverse association between the MD and breast cancer risk in postmenopausal women but not in premenopausal women, which is consistent with the results of many other studies (31).

The MD is characterized by increased consumption of vegetables, fruits, nuts, and cereals. The flavonoids contained in these types of food may contribute to cancer prevention through multiple biological effects, including antioxidant activity, inhibition of inflammation, and antimutagenic and antiproliferative properties (32).

The main source of fat of the MD is olive oil, which contains abundant oleic acid, a monounsaturated fatty acid, and squalene. Oleic acid can suppress overexpression of the HER2 oncogene and in turn promotes apoptosis in tumor cells (33). Squalene can play an anticancer role by reducing oxidative DNA damage and inhibiting beta-hydroxy-beta methylglutaryl-CoA-reductase, which affects cellular signal transduction and proliferation in human mammary cells (34).

Seafood, such as fish and shrimp, is an important component of the MD. The anticarcinogenic effects of seafood are mainly due to n-3 polyunsaturated fatty acid, which inhibits the transformation of arachidonic acid into eicosanoids, which are proinflammatory signaling molecules, and regulates gene expression, transcription and activities of molecules related to the signal transduction for cell growth (35).

The reduced consumption of red meat, dairy products and alcohol in the MD may also contribute to its anticarcinogenic effect. Red meat and dairy products contain abundant saturated fat, which has been demonstrated to be an independent carcinogenetic factor likely due to increased energy balance and insulin resistance. Red meat is also a source of some known mutagenic compounds, such as heterocyclic amines and polycyclic aromatic hydrocarbons, which are related to the breast cancer etiology (36,37). The MD can be classified as a traditional or an adapted pattern. The former, but not the latter, includes regular but moderate intake of alcohol (38). It is well known that alcohol consumption is a risk factor for breast cancer (39). However, a case-control study (40) conducted in France reported a lower risk of breast cancer among women consuming 10–12 g/d of wine compared with non-wine drinkers. This result was explained because red and white wine contain resveratrol, an anticarcinogenic polyphenol (41). In addition, regardless of the health benefits of the traditional MD, the total daily calorie content must be controlled to avoid obesity, which is a risk factor for breast cancer (42).

Our results showed that adherence to the MD is associated with a significant reduction of breast cancer risk in postmenopausal women but not in premenopausal women. One of the possible causes may be that with age, postmenopausal women focus more on their diet than premenopausal women to maintain their health.

Because strong evidence of heterogeneity was observed in our meta-analysis, we used a random-effects model to calculate the combined RR and maintain the stability of the results.

Although our statistical data showed that an MD could reduce the risk of breast cancer in women, especially in postmenopausal women, three limitations of our meta-analysis should be addressed. First, the contents of the MD were not identical in different studies, and the methods used to assess the MD were also not identical. Some studies used the validated FFQ a priori, and the others used the factor analysis posteriori. Second, the heterogeneity was still high after subgroup analysis by study design and menopausal status, indicating that other factors also contribute to the heterogeneity, such as hormone receptor status, age of menarche, oral contraceptive use, full-term pregnancy, number of births, family history, related genetic mutations and the determination of menopausal status. Third, the studies included in this meta-analysis were mainly conducted in Europe; therefore, further validation is required for the conclusions to be applied to other populations.

Conclusions

This meta-analysis revealed that the MD is significantly associated with a reduction of breast cancer risk in women, especially in postmenopausal women. The MD can be suggested to women, especially postmenopausal women, as a healthy dietary pattern to reduce breast cancer risk.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.10.13). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 General characteristics of included studies

Study	Country	Year	Study design	The number of participants (case/control)	Age (years)	Menopausal status	Hormone receptor	Follow-up (years)	Dietary assessment method	End point	Diagnostic criteria/ grade cancer	Results	OR/HR/P value	Adjustment
Nkondjock, *et al.*	Canada	2006	Case-control	183 (89/94)	<65	Not reported	Not reported	Not reported	Validated FFQ, MD score (0–9) priori	Risk of BC	Not reported	Not related	OR =0.54, 95% CI = (0.17,1.72), P=0.491	Age, place of residence, education, smoking, menopausal status, height, weight and history of weight change, female reproductive history, breast feeding, practice of breast self-examination, tamoxifen use, age at menarche, parity, oral contraceptive use, hormone replacement therapy, marital status, physical activity
Fung, *et al.*	USA	2006	Cohort	71,058	30–55	Postmenopausal	ER+, ER–	18	Validated FFQ, MD score (0–9) priori	BC incidence	Self-report in the biennial questionnaire	Overall and ER+: not related; ER–: decrease	Overall: RR =0.98, 95% CI = (0.88,1.10), P=0.69;ER–: RR =0.79, 95% CI = (0.60,1.03), P=0.03; ER+: RR =1.05,95% CI = (0.91,1.18), P=0.23	Age, smoking habit, BMI, multivitamins, energy intake, physical activity, family history of breast cancer, personal history of benign breast disease, age at menopausa, hormone therapy, BMI at age 18, weight change since age 18
Murtaugh, *et al.*	4 states: Arizona, new Mexico, Colorado, Utah	2008	Case-control	4,746 (Hispanic: 757/867; non-Hispanic: 1,524/1,598)	25–79	Pre/ postmenopausal	Not reported	5	Factor analysis posteriori	Risk of BC	ICD codes C50-C50.6 and C50.8-C50.9/*in situ* or invasive	Decrease BC risk	Overall: OR =0.76, 95% CI = (0.63, 0.92); Hispanic pre: OR =0.70, 95% CI = (0.42, 1.16). Post: OR =0.58, 95% CI = (0.37, 0.90); non-Hispanic: pre: OR =0.86, 95% CI = (0.55, 1.32). Post: OR =0.86, 95% CI = (0.64, 1.16)	Age, medical center, education, smoking, total activity, calories, dietary fiber, dietary calcium, height, parity, recent hormone exposure, reference year BMI, interaction of BMI, recent hormone exposure across quartiles of dietary patterns.
Cottet, *et al.*	France	2009	Cohort	65,374	51–55	Postmenopausal	ER+/PR–, ER+/PR+, ER–/PR–, ER–/PR+	9.7	Factor analysis posteriori	BC incidence	ICD codes C50-C50.6 and C50.8-C50.9/ invasion (88%)	Decrease BC risk	HR =0.85, 95% CI = (0.75,0.95)	Age, education, geographic area, BMI, height, family history of breast cancer, age at menarche, age at full-term pregnancy, number of livebirths, menopausal hormone therapy, personal history of benign breast disease, oral contraceptive use, breastfeeding, physical activity, smoking, energy intake, phytoestrogen supplement, vitamin/mineral supplement
Wu, *et al.*	USA	2009	Case-control	2,396 (1,248/1,148)	25–74	Not reported	Not reported	6	Validated FFQ, MD score (0–10) priori	Risk of BC	Not reported	Decrease BC risk	OR =0.70, 95% CI = (0.48, 1.04), P=0.033	Age, specific ethnicity, education, age at menarche, parity, marital status, BMI, physical activity, total calories, menopausal status, type of menopausal, age at menopause
Trichopoulou, *et al.*	Greece	2010	Cohort	14,807	20–86	Pre/ postmenopausal	Not reported	9.8	Validated FFQ,MD score (0–-9) priori	BC incidence	ICD codes C50	Overall and pre: not related; post: decrease	Overall: HR =0.88, 95% CI = (0.75, 1.03); pre: HR =1.01, 95% CI =(0.8, 1.28); post: HR =0.78, 95% CI = (0.62, 0.98)	Age, education, smoking, physical activity, BMI, age at menarche, menopausal status, age at last menstrual cycle, parity status, age at first full term delivery, number of full term births, hormone replacement therapy
Cade, *et al.*	British	2011	Cohort	33,731	35–69	Pre/ postmenopausal	Not reported	9	Validated FFQ,MD score (0-–10) priori	BC incidence	ICD codes 9 and 10	Overall and post: not related; pre: decrease	Pre: HR =0.65, 95% CI = (0.42, 1.02), P=0.09; post: HR =1.30, 95% CI = (0.83, 2.05)	Age, total energy intake, BMI, physical activity, oral contraceptive use, hormone replacement use, smoking, parity, age at menarche, alcohol intake, breast feeding duration, education, national statistics socio-economic class
Buckland, *et al.*	10 European countries	2012	Cohort	335,062	35–70	Pre/ postmenopausal	ER+/PR+, ER–/PR–	11	arMED score (0–16) priori	BC incidence	ICD-10 C50.0-50.9/ Invasive	Overall and post: decrease; pre: not related	Overall: OR =0.94, 95% CI = (0.88, 1.00), P=0.048; post: OR =0.93, 95% CI = (0.87, 0.99), P=0.037; pre: OR =0.97, 95% CI = (0.81, 1.15), P=0.839	Age, BMI, height, education, technical or professional training, university, smoking, physical activity, age at menarche, oral contraception use, breastfed, age at first full-term pregnancy, menopausal status, saturated fat intake, alcohol intake, total energy intake
Demetriou, *et al.*	Cyprus	2012	Case-control	2,286 (1,109/1,177)	40–70	Postmenopausal	Not reported	3	Validated FFQ, MD score by Panagiotakos priori	Risk of BC	Not reported	Not related	OR =0.99, 95% CI = (0.70, 1.40), P=0.06	Age, marital status, education, BMI, exercise status, smoking, family history of breast cancer or ovarian cancer, hormone use, age at menarche, pregnancy, gestation period, parity, breast feeding, age at first and last pregnancy, weight, height
Bessaoud, *et al.*	France	2012	Case-report	1,359 (437/922)	25–85	Not reported	Not reported	2	Validated FFQ, principal component analysis (PVC)	Risk of BC	Not reported	Not related	OR =0.97, 95% CI = (0.63, 1.48)	Parity, age at first full-term pregnancy, breast feeding, duration ovulatory activity, education, BMI, oral contraception, hormone replacement therapy, family history of cancer, anthropometric factors, physical activities, smoking, total energy intake
Tognon, *et al.*	Sweden	2012	Cohort	77,151	30–70	Not reported	Not reported	9	Validated FFQ, MD score (0–8) priori	BC incidence	ICD 9 codes 140–208 or ICD 10 codes C00-C97	Not related	Female: HR =1.12, 95% CI = (0.97, 1.28); male: not reported	Sex, age, obesity, physical activity, smoking, education
Couto, *et al.*	Sweden	2013	Cohort	44,840	30–49	Pre/ postmenopausal	ER+/PR–, ER+/PR+, ER-/PR–, ER–/PR+	16	Validated FFQ, MD score (0–9) priori	BC incidence	ICD, 7th revision, code170.0	Overall: not related	Overall: OR =1.08, 95% CI = (1.00, 1.15); pre: OR =1.10, 95% CI = (1.01, 1.21); post: OR =1.02, 95% CI = (0.91, 1.15)	History of breast cancer in mother and/ or sister, personal history of benign breast disease, smoking, BMI, height, age at first birth, total number of children, education, age at menarche, total energy intake, consumption of beverages, potatoes, sweets and eggs
Castello, *et al.*	Spain	2014	Case-control	2,034 (1,017/1,017)	Not reported	Pre/ postmenopausal	ER–/PR–/ Her2–; Her2+/ ER (+. –), PR(+.-); ER+ or PR+/Her2–	Not reported	Validated FFQ, MD score (0–8) priori	Risk of BC	Not reported	Decrease BC risk	Overall: OR =0.56, 95% CI = (0.40, 0.79); post: OR =0.54, 95% CI = (0.34, 0.86); pre: OR =0.58, 95% CI = (0.38, 0.91).	Total calories, alcohol consumption, BMI, physical activity, smoking, education, history of breast disease, family history of breast cancer, age at menarche, age at first delivery, menopausal status
Pot, *et al.*	UK	2014	Case-control	2,501 (610/1,891)	Case: 57.2 (mean); control: 56.6 (mean)	Postmenopausal	Not reported	11	Validated FFQ, MD score (0–9) priori	Risk of BC	ICD, the 9 and 10 revision, codes CD174 or C50	Not related	Overall: OR =1.20, 95% CI = (0.92, 1.56); post: OR =1.10, 95% CI = (0.80, 1.51)	Age, parity, use of hormone replacement therapy, weight, height, physical activity, menopausal status, energy intake, family history of breast cancer, breastfeeding, education
Mourouti, *et al.*	Greece	2014	Case-control	500 (250/250)	56 (average)	Pre/ postmenopausal	Not reported	1.7	Validated FFQ, MD score (0–55) priori	Risk of BC	Not reported	Decrease BC risk	Overall: OR =0.91, 95% CI = (0.86, 0.97); pre: OR =0.94, 95% CI =(0.88, 1.00); post: OR =0.92, 95% CI = (0.86, 0.97)	Age, education, BMI, smoking, physical activity, family history of breast cancer, age at menarche, age at menopause, use of hormone replacement therapy, parity
Toledo, *et al.*	Spain	2015	Cohort:RCT	4,282	60–80	Postmenopausal	Not reported	4.8	Validated FFQ	BC incidence	ICD codes C50.1-C50.9	Decrease BC risk	MD with EVOO: HR =0.32, 95% CI = (0.13, 0.79); MD with Nuts: HR =0.59, 95% CI = (0.26, 1.35); both: HR =0.43, 95% CI = (0.21, 0.88)	Age, BMI, weight, height, hormone therapy, physical activity, total energy intake, alcohol consumption, age at menopause, smoking, diabetes mellitus, use of statins, family history of cancer
Hirko, *et al.*	USA	2016	Cohort	100,643	30–55	Not reported	Luminal A/ B, Her2 type, Basal-like, unclassified	22	Validated FFQ, MD score (0–9) priori	BC incidence	Not reported	Not related	Luminal A: HR =1.09, 95% CI = (0.91, 1.30); Luminal B: HR =1.02, 95% CI = (0.76, 1.37); Her2 type: HR =0.74, 95% CI = (0.42, 1.29), Basal-like: HR =0.78, 95% CI = (0.49, 1.26); unclassified: HR = 0.89, 95% CI = (0.41, 1.89)	Energy intake, physical activity, parity and age at first birth, age at menarche, duration of oral contraceptive use, family history of breast cancer, benign breast disease, menopausal hormone use, BMI at age 18 years, weight change since age 18
Piet A. van den Brandt	Maastricht	2017	Cohort	62,573	55–69	Postmenopausal	ER–, ER+, PR-, PR+, ER–/PR–, ER+/PR+	20.3	Alternate Mediterranean Diet Score (aMED) (0–8) priori	BC incidence	Nationwide Dutch Pathology Registry.	Decrease BC risk	Overall: HR =0.82, 95% CI = (0.70, 0.96); ER–: HR =0.60, 95% CI =(0.39, 0.93); ER+: HR =0.87, 95% CI = (0.69, 1.10); PR–: HR =0.72, 95% CI =(0.52, 1.05); PR+: HR =0.90, 95% CI = (0.69, 1.19); ER+/PR+: HR =0.91, 95% CI = (0.69, 1.21); ER–/PR–: HR =0.61, 95% CI = (0.36, 1.01)	Age, cigarette smoking, duration, body height, BMI, non-occupational physical activity, highest level of education, family history of breast cancer, history of benign breast disease, age at menarche, age at first birth, age at menopause, oral contraceptive use, postmenopausal hormone replacement therapy, energy intake, alcohol intake