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SYSTEMATIC REVIEWS AND META ANALYSIS

Effect of mediterranean diet on breast cancer: meta-analysis

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Abstract

Objective: In this meta-analysis, we have assessed the effects of Mediterranean Diet on breast cancer.

Methods: Case-control and cross-sectional studies were searched using PubMED, SpringerLink, and Taylor & Francis databases for inclusion in the meta-analysis. We confined our search to the studies conducted and published after year 2000. From all the included studies, geography, sample size, study design, study evaluation method, outcome, risk factors (lowest and highest limit and OR values), and 95% confidence interval data were extracted. Eleven studies with 26361 participants were included of which 10 were case-control studies and 1 was cross-sectional study.

Results: Following the analysis according to the random effects model, it was observed that compliance with the Mediterranean Diet or the high consumption amount of olive oil, seafood, whole grains, vegetables, and fruits in the Mediterranean Diet has a positive effect on breast cancer. The effect size was found to be OR 0.77 (0.68-0.88).

Conclusion: This meta-analysis, including the studies evaluating the effect of Mediterranean diet on breast cancer, concluded that the Mediterranean Diet has positive effects on breast cancer. The risk of breast cancer was found to be decreased with the increased compliance of the Mediterranean Diet.

Keywords: Breast Cancer, Cross-Sectional Study, Mediterranean Diet

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INTRODUCTION

Breast cancer is the second leading cause of death worldwide and is the most common cancer among women[1]. It accounts for over 2 million cases each year[2]. Breast cancer has multifactorial etiology which includes several factors such as age, genetic factors, hormonal factors, family history, use of alcohol, use of tobacco, obesity and physical inactivity[3,4]. Breast cancer cases are less observed in women of younger age and more in women of older age. Incidences of breast cancer have been found to sharply increase within the age group of 45 to 50[4].

Studies have shown that highest rate of breast cancer were observed in USA, and Northern Europe and lowest in Asia. Racial and ethnic differences also have an impact on the breast cancer incidences[5]. High incidences of breast cancer were observed in Caucasians than African Americans in women above the age of 50 years[6]. Family history has also been considered as an important risk factor for breast cancer but overall, less than 10% of all breast cancers have been found to be associated with inherited genetic mutations[7]. Hormonal factors such as increased level of estrogen hormone, post-menopausal hormonal therapy, birth control pills, fertility medications and increased levels of testosterone hormone in women have been strongly associated with risk of breast cancer[8].

Association of diet with breast cancer has been studied widely keeping in consideration food groups, single food and nutrients along with their effect on the survival of the patients[9]. The studies which have focused on the effect of individual foods and nutrients on the survival in cancer patients were able to provide restricted information on the effect of diet as they did not study interaction between the particular nutrient and other constituents of the diet. Therefore, regardless of many studies, the findings related to single nutrient or individual food have not given complete information on role of dietary pattern in the etiology of breast cancer. While it has been directly related to alcohol use[10,11], the evidence determined about some specific food and food groups is still controversial[12,13].

To overcome, the above said issues, it has been suggested to evaluate the effect of complete dietary patterns which are a combination of specific nutritional indicators on breast cancer. It would be helpful to therefore understand which dietary style in total could have a better effect on breast cancer survival. One such dietary pattern is Mediterranean diet which is considered to be a healthy dietary pattern. Mediterranean diet, which means “diaita” in Greek, meaning “lifestyle” includes high consumption of olive oil, olives, whole grains, vegetables and fruits, oil seeds, legumes and fish; with medium eggs, poultry and dairy products. It is a diet characterized by low levels of red meat and meat products. The Mediterranean diet, introduced by Ancel Keys in the 1960s, is one of the most widely researched and well-known dietary patterns worldwide. The traditional Mediterranean diet has its origins in the civilisations surrounding the Mediterranean Sea. This dietary pattern is therefore closely associated with the social behaviour and lifestyles of the Mediterranean region. The Mediterranean diet has been recognised as an ‘intangible cultural heritage of humanity’ by the United Nations Educational, Scientific and Cultural Organisation because it is deeply rooted in its geographical origins, has positive effects on health and has protective effects on the

environment. Since the 1960s, increasing evidence has demonstrated the potential positive effects of the Mediterranean diet on health[14].

The Mediterranean diet has been found to have a protective effect on breast cancer because of the nature of its constituents. It is rich in antioxidants, carotenoids, vitamins, flavonoids, squalene found in extra virgin olive oil and dietary fiber. This diet model prevents DNA damage by decreasing endogenous estrogen level[15], increasing sex hormone binding globulin levels[16], and showing a positive response to the harmful effects of free radicals[17,18]. Various studies have shown that this dietary pattern can reduce the risk of breast cancer by reducing the oxidative risk[19,20].

Worldwide, breast cancer incidences differ drastically from each other[21]. Due to lack of evidence-based studies, the association between the Mediterranean diet and breast cancer is still under debate. According to the EPIC (European Prospective Investigation into Cancer) study, when the effects of the Mediterranean diet was examined on all types of cancer, it showed protective effect against various types of cancer, especially breast cancer[22].

Another important study, PREDIMED randomized study, showed that the Mediterranean diet had a preventive effect against breast cancer especially on post-menopausal breast cancer. This study concluded that extra virgin olive oil, which is included in the Mediterranean diet, has a very potential effect in primary prevention of breast cancer. Long-term and comprehensive studies are needed to further ascertain the positive effects of the Mediterranean diet on breast cancer[23].

Herein, we conducted a meta-analysis of available cross sectional and case control studies which have assessed the association between the adherence to a Mediterranean diet and breast cancer, in order to establish the effect of adherence to a Mediterranean diet on breast cancer.

METHOD

Literature Search Study

An electronic literature search was conducted to identify relevant studies published in English between 2000-2020 from PubMed, SpringerLink, and Taylor & Francis databases with the following keywords. “Mediterranean Diet” OR “olive oil” OR “whole grain” OR “seafood” OR “vegetable and fruit” AND “breast cancer”. We did not keep the restriction of age of the participants for selecting studies for this meta-analysis. In addition, references cited in the original studies were manually searched.

Inclusion Criteria

Titles and abstracts of the publications on the relationship between the Mediterranean Diet and breast cancer incidences were reviewed. The full texts of the articles whose abstracts were found appropriate were downloaded and deemed eligible for this meta-analysis if they fulfilled the following inclusion criteria: 1-) case-control and cross-sectional studies; 2-) studies that yield results on breast cancer; 3-) Studies including Odd Ratio (OR), 95% confidence interval (CL) data; 4-) Studies after 2000.

Exclusion Criteria

Comments, reviews, cohort studies, and unpublished studies were excluded from the analysis. A total of 940 articles were found in

the first search. Thirty potentially relevant articles were dropped after duplication analysis, summary and title screening, removal of studies prior to 2000, and exclusion of non-breast cancer studies and studies with breast cancer recurrence. Nineteen of these articles were not included in the study due to the lack of appropriate statistical data. After all these exclusion criteria, a total of 11 studies were left for the meta-analysis. The articles reviewed were tagged as "Mediterranean Diet[21-24]," "olive oil[22,25]," "healthy[26,27]," "dietary pattern[28]," "whole grain[29]," "fatty fish[30]," "Western diet[31]." Healthy diet is characterized by the consumption of vegetables and fruits, seafood, poultry. The Western diet is a diet characterized by refined grains, red meat, processed meat, high-fat foods and sweets. The flow diagram of the steps of the article selection process for meta-analysis is given in Figure 1.

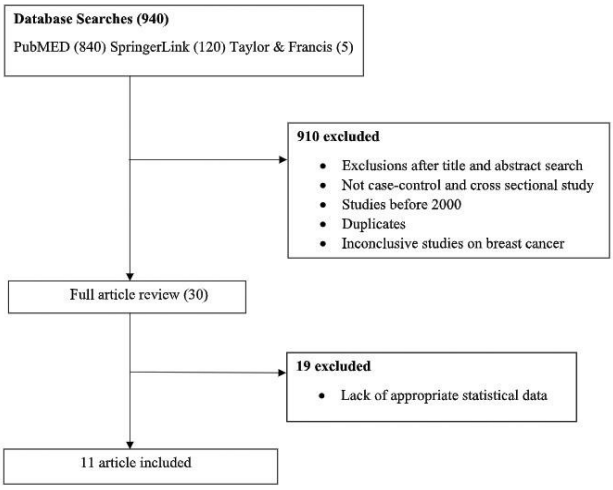

Figure 1. Flow diagram showing the steps of the article selection process for meta-analysis

Data Extraction

We extracted the following data from all the included studies; authors, year of publication, geography of the study, sample size, study design, age range of the participants, study evaluation method, outcome, risk factors (lowest and highest limit and OR values) and 95% confidence interval.

The quality of the studies included in the meta-analysis was evaluated with the Newcastle-Ottawa Scale.

Statistical Analysis

Comprehensive Meta Analysis (CMA) license software was used for the data analysis. The data of all articles meeting the inclusion criteria and decided to be included in the study was entered into the CMA program. CMA program was used to obtain the general effect sizes, forest plot, funnel plot graphics.

The heterogeneity of the articles was evaluated. Q statistics is used to calculate the effect size in meta-analysis studies, to decide on the fixed and random effect model and to measure the heterogeneity between the studies. In the analysis of the Q statistics, it is tested whether all the studies show the overall effect. As a result of the analysis, if the significance value (p) is below the critical value, it could be interpreted as not all the studies show the same effect. In this case, it can be said that there is heterogeneity between the studies[24,25]. The I^2 statistics provides information about the ratio of this heterogeneity. If the individual study results included in the meta-analysis are homogeneous, the fixed effect model is used, and in the case of heterogeneous, the random effects model is used[32].

Publication bias in the studies was examined with a funnel plot. There should be symmetry in the funnel plot, when there is no spring bias. If there is a bias in the publications included in the study, this situation causes an asymmetrical appearance in the graphic and one corner of the graphic is emptier than the

other corner[26].

RESULTS

Total 940 articles were obtained from the literature search; of which, 11 articles, including a total of 26,361 participants, which evaluated the relationship between the Mediterranean Diet and breast cancer were included in the study. 10 of these articles were case-control studies and 1 article was across-sectional study. The main characteristics of these studies (type of study, participant age range, sample size, country of study, evaluation criteria and other features) have been shown in Table 1.

Table 1. General characteristics of the studies included in the meta-analysis

Author/ Year	Place	Ages of Participants	Study Type	Number of Participants	Diet Assessment Method	Assessment	Adjustment
Turati et al. 2008	Italy Switzerland	23-78	Case-Control	3034 cases 3392 controls	78-item FFQ (Food Frequency Questions)	Med Diet Score	Anthropometric measurements, smoking and alcohol consumption, family history, hormone replacement therapy (HRT) use, personal medical history, menopausal status, education, BMI, oral contraceptive use
Garcia-Arenzana et al. 2013	Spain	45-69	Cross-Sectional	3548 post and perimenopausal	117-item FFQ	Mammography	BMI, menopausal status, educational status, socioeconomic status, hormone replacement therapy, physical activity, smoking habit, alcohol consumption, mammographic density
Demetriou et al. 2012	Cyprus	40-70	Case-Control	935 cases 817 controls	32-item FFQ	MedDiet Score by Panagiotakos MedDiet Score by Martinez-Gonzalez	Level of education, marital status, BMI, physical activity status, smoking habits, alcohol consumption, family history of breast and ovarian cancer, hormone replacement therapy, age at pregnancy and menarche, gestation period, parity, breastfeeding, age at first and last pregnancy
Garcia-Segovia et al. 2006	Canary Islands	25-85	Case-Control	291 cases 464 controls	88-item FFQ		Chronic diseases, sociodemographic variables, smoking habits (age at onset, age at quitting, smoked per day, type of tobacco), alcohol consumption (amount of alcohol consumed per day, drinking patterns), physical activity, menstrual and reproductive events and nutritional beliefs, opinions and attitudes, family history of diseases,
Mourouti et al. 2014	Greece	44-68	Case-Control	250 cases 250 controls	86-item FFQ	Med Diet Score And IPAQ (International Physical Activity Questionnaire)	Educational level, financial status, BMI, physical activity, smoking habits, family history of breast and ovarian cancer, gynecological medical history (age of menopause, age of menarche, and use of hormone replacement therapy)

Table 1.(countinue) General characteristics of the studies included in the meta-analysis

Bessaoud et al. 2008	France	25-85	Case-Control	437 cases 922 controls	59-item FFQ	Healthy and Unhealthy diet model	Reproductive and menstrual factors, demographic characteristics, oral contraception, family history of cancer, hormone replacement therapy anthropometric factors, physical activities, and smoking habits.
Buck et al. 2011	Germany	50-74	Case-Control	2884 cases 5509 controls	176-item FFQ	Healthy and Unhealthy diet model	Menstrual status, demographic characteristics, hormone replacement therapy, family history of breast cancer, breastfeeding, smoking, and alcohol consumption, BMI
Kim et al. 2009	South Korea	25-77	Case-Control	358 cases 360 controls	103-item FFQ	IPAQ MET (metabolic equivalent of task)	Demographics and lifestyle factors (alcohol consumption, smoking habits, and physical activity), age at menarche, age at menopause, menopause status, menopausal status, postmenopausal hormone use
Zhang et al. 2010	China	25-70	Case-Control	438 cases 438 controls	81-item FFQ	Healthy and Unhealthy diet model	Sociodemographic characteristics, weight, height, BMI, menstrual and reproductive history, menopausal status, use of contraceptive drugs, use of exogenous hormones, history of benign breast disease, family history of breast cancer, physical activity, smoking habits, alcohol consumption, and prior disease history.
Mourouti et al. 2015	Greece	44-68	Case-Control	250 cases 250 controls	86-item FFQ	Med Diet Score IPAQ	Educational level, BMI, smoking habits, physical activity, alcohol consumption, family history of breast cancer, gynecological medical history, hormone replacement therapy
Castelló et al. 2014	Spain	Women of similar age (± 5)	Case-Control	1017 cases 1017 controls	117-item FFQ	aMED (alternate Mediterranean Diet) AHEI (Alternative Healthy Index)	Demographic characteristics and anthropometric characteristics, personal and family history of breast cancer, physical activity and diet, smoking habits, alcohol consumption

The age range of the study participants varied between 23 and 85 years. Four of the studies were conducted among post- and perimenopausal women. Studies had been conducted in Italy, Spain, Cyprus, Greece, Canary Islands, France, Germany, South Korea and China.

MedDiet Score was used in 5 of the studies and adherence to the Mediterranean Diet was evaluated. Alternative assessment methods were used in other studies. Food frequency questionnaires were used to evaluate the dietary patterns of the participants. The International Physical Activity Questionnaire (IPAQ) was used to evaluate their physical activity.

When the heterogeneity test results were examined, it was observed that the effect sizes of the studies included in the meta-analysis were heterogeneously distributed and the heterogeneity was high (Q: 56 I^2: 82).

While the part indicated in the form of black squares next to each study in the forest chart used in meta-analysis indicated the effect size of that study in the present meta-analysis, the lines on both sides of the black square indicated that the effect size of that study was in the 95% confidence interval. The rhombus at the bottom of all the squares showed the overall effect size of all the studies. In meta-analysis studies, a general conclusion is reached based on the effect size of each study. Eleven studies conducted to examine the effect of the Mediterranean Diet on breast cancer were included in the meta-analysis and the effect sizes for all the included studies were calculated and the overall effect size was reached.

As seen in Figure 2, as a result of the analysis made according to the random effects model, it was observed that compliance with the Mediterranean Diet or the high consumption amount of olive oil, seafood, whole grains, vegetables and fruits in the Mediterranean Diet had a positive effect on breast cancer. Moreover, it could be stated that the incidences of breast cancer were lower in women who were on this diet. The effect size of the Mediterranean Diet on breast cancer was found to be OR 0.77 (0.68-0.88).

The funnel plot that gives information about whether there is publication bias in the studies included in the meta-analysis has been shown in Figure 3. As evident from the funnel plot in the figure, 6 of the studies included in meta-analysis were between the axis and 4 were outside the axis. Accordingly, it was determined that 4 studies did not have an effect size, yet a significant number of other studies were at a level to contribute to the effect size. When the funnel plot was examined, it was seen that the effect sizes of the studies included in the meta-analysis had been distributed close to symmetry. Therefore, it could be inferred that there was no publication bias in the study.

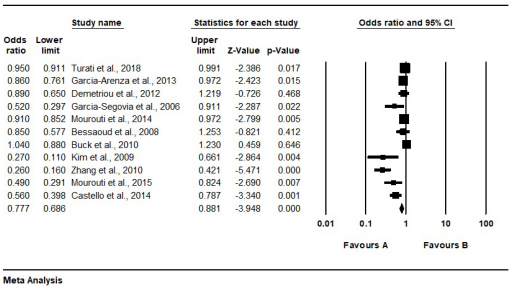

Figure 2. Forest chart showing the effect sizes of the studies

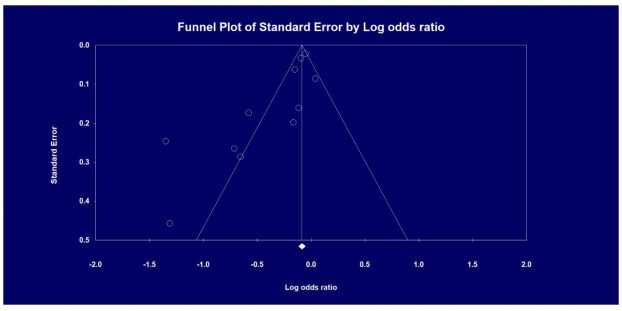

Figure 3. Funnel plot showing publications bias in CMA program

DISCUSSION

Various studies have been conducted to investigate the association between Mediterranean diet and breast cancer in last decade[16,23,27,29] which included retrospective case-control studies, prospective cohort studies as well as cross-sectional studies. However, till date, there is no precise conclusion regarding the association of

Mediterranean diet in reducing the risk of breast cancer. Our present meta-analysis included 11 studies based on inclusion and exclusion criteria, which were focused on the association of Mediterranean diet and breast cancer published since year, 2000. We had found strong evidence for high heterogeneity among the studies used for this meta-analysis, therefore we used random-effects model in this study to calculate RR and maintaining the stability of the results.

In this meta-analysis study, 11 effect sizes belonging to 11 studies were calculated. While a statistically significant difference was found in 10 studies, no significant difference was found in 1 study. This study aimed to examine the effect of the Mediterranean Diet and the consumption of olive oil, fish, whole grains, vegetables and fruits, which are the basic foods of the Mediterranean Diet, on breast cancer and breast density with meta-analysis method

As per the analysis conducted in this data based on available literature, it was concluded that the Mediterranean Diet reduced the risk of breast cancer, and the incidence of breast cancer in women decreased with the increase in compliance with the Mediterranean Diet [OR 0.77 (0.68-0.88)]. In line to our findings, a case-control study conducted in Italy and Switzerland, which evaluated the effect of Mediterranean diet on breast cancer using MedDiet Score, it was found that the highest adherence score to the Mediterranean Diet was associated with lower breast cancer[31]. These results were also consistent with a previously conducted meta-analysis wherein it was shown that adhering to Mediterranean diet reduced the risk, incidences and mortality related to many types of cancer, including breast cancer[33]. A stratification analysis conducted by menopausal age showed that a significant inverse association between the risk of breast cancer and Mediterranean Diet[22].

The consumption of olive oil, which protects against many diseases, especially cardiovascular diseases with its monounsaturated fatty acids, is quite high in the Mediterranean Diet and is basically the main source of fat. It contains abundance of Oleic acid. Oleic acid is known to suppress the overexpression of oncogene HER2 and thereby promote the apoptotic death in tumor cells[34]. This suggests that olive oil used in Mediterranean diet could have a positive impact on breast cancer suppression. In a study on olive oil, the relationship between olive oil consumption and mammographic breast density was investigated, and it was reported that the prevalence of breast density decreased with high olive oil consumption [OR 0.86 (0.76-0.96)][35]. Since high mammographic breast density is one of the major risk factors associated with breast cancer, reduced breast density after olive oil consumption indicates that it could modulate mammographic breast density which is an important risk bio-marker for breast cancer. Few other studies also supported that olive oil has a protective role on breast cancer [OR 0.52 (0.30-0.92)][36]. In a meta-analysis study, wherein relationship between olive oil intake and breast cancer was evaluated, it was found that there might be an inverse relationship between olive oil intake and breast cancer[37]. However, more extensive studies with long-term follow up are needed to ascertain these findings.

Fish, an example of good quality protein, is one of the frequently consumed foods in the

Mediterranean Diet. Some epidemiological studies and meta-analyses have indicated that ω-3 fatty acid supplementation has positive effects on various cancers[38,39]. In a study investigating the risk of breast cancer with fish consumption, it was shown that w-3 fatty acids were inversely related to postmenopausal breast cancer [OR 0.27 (0.11-0.66)][40]. The anti-carcinogenic potential of fish and other seafoods is mainly due to the presence of n-3 polyunsaturated fatty acid which acts by inhibiting the transformation of arachidonic acid into eicosanoids, thereby regulating signaling for cell growth[38]. This further proves the importance of another component of Mediterranean diet in reducing the risk of breast cancer.

Whole grains included as the basic foods of the Mediterranean Diet have low glycemic index, increased satiety, rich fiber content, and contain phytochemicals and are found to be protective against cardiovascular diseases. In a study investigating the relationship of whole grain consumption with breast cancer risk, whole grain consumption was found to be associated with lower breast cancer risk [OR 0.49 (0.29-0.82)][41].

The Western Diet is characterized by the consumption of high calorie, high protein and high fat foods. It is very low in fiber and usually contains fried foods. A study compared the western diet style with the Mediterranean Diet, and it was observed that the compliance with the Western Diet was associated with a high risk of breast cancer [OR 1.46 (1.06-2.01)], and compliance with the Mediterranean Diet was associated with a lower risk of breast cancer [OR 0.56 (0.40-0.79)][42]. Likewise, in another study investigating the effect of the Mediterranean and Western Diet on breast density, women who were highly dependent on Western diet had higher breast density than those with low breast density [OR 1.25 (1.03-1.52)], but this study did not find any significant association between the Mediterranean Diet and breast cancer risk [OR 0.99 (0.81-1.21)][43].

Although many studies found a relationship between the Mediterranean diet and low breast cancer risk, and Western diet and high breast cancer risk, there are some studies which did not show this effect. In a study, it was reported that both the Healthy diet [OR 1.04 (0.88-1.23)] including the Mediterranean Diet components and the Unhealthy diet [0.96 (0.81-1.13)] models containing the Western Diet components had no relationship with the breast cancer[44]. Similar result was obtained in a meta-analysis with cohort studies. In this study, it was stated that there was no relationship between the adherence to the Mediterranean Diet and the incidence of breast cancer [RR 1.01 (95% CI, 0.88-1.16)][45].

It has been observed in a study that the risk of breast cancer increases by 56% for each additional 100g / day red meat consumption[45]. Reduced consumption of red meat in Mediterranean diet could also be one of the contributory factors for the anti-carcinogenic effect of this diet. Red meat serves as a source of few known mutagenic compounds like heterocyclic amines which have a relationship with the etiology of breast cancer[11,46].

Various other studies supported the finding of our study. In a study examining the relationship between nutrition and breast cancer among Korean women, it was reported that high intake of vegetables and seafood had an inverse relationship with breast cancer [OR 0.14 (0.08-0.25)][47], which are the main

constituents of Mediterranean diet.

A cohort study and meta-analysis was conducted which investigated the relationship between compliance with the Mediterranean Diet and the risk of breast cancer (and estrogen / progesterone receptor subtypes, ER / PR). This Dutch Cohort study conducted research on the diet and lifestyle changes of 62,573 women for 20.3 years. It was observed in this study that there was an inverse relationship between compliance with the Mediterranean Diet and the risk of receptor-negative breast cancer[48].

In a cross-sectional study in which alcohol consumption and adherence to the Mediterranean Diet were measured and their relationship with breast density was investigated, adherence to the Mediterranean Diet and the use of multivitamin-multiminerals were inversely related to breast density and could have a protective effect against breast cancer (OR 0.53; 95% CI 0.34-0.83), whereas high alcohol consumption was reported to cause an increase in breast density (OR 1.47; 95% CI 0.82-2.63)[49].

Study Strengths and Weaknesses: One of the main strengths of this meta-analysis is that it is a systematic review of the possible effects of the Mediterranean diet on breast cancer from a large pool of studies. An important advantage, especially in terms of understanding the relationship between diet and cancer, is that it brings together different studies and provides more robust and generalisable results. However, one of its weaknesses is the heterogeneity that was observed between the studies. Each of the studies analysed may have used different methods. For example, the definition of diet, the characteristics of the participants or the follow-up periods may have been different. One of the weaknesses is these methodological differences.

Study Limitations: Case-control and cross-sectional studies were screened for inclusion in the meta-analysis. PubMED, SpringerLink and Taylor & Francis databases were used. Our search was limited to studies whose publication date was after the year 2000.

CONCLUSION

Many studies have shown that olive oil, fish, whole grains, vegetables and fruits, which are the components of the Mediterranean Diet, are effective in reducing breast cancer. Thanks to these foods, fiber, antioxidants, flavonoids, vitamins, and carotenoids taken regularly in the Mediterranean diet which can reduce excess estrogens in a natural way and neutralize free radicals. In this way, the Mediterranean diet serves as a protective factor against the risk of breast cancer. At the same time, reduced consumption of red meat and refined foods in this dietary pattern that increase the risk of breast cancer are also supporting this effect. According to the results we obtained from the meta-analysis of the studies conducted with the Mediterranean Diet and its components, it has been observed that the Mediterranean Diet has positive effects on breast cancer, and the risk of breast cancer decreases with the increase of compliance with the Mediterranean Diet.

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Ethical Declaration: This study was conducted in accordance with the Declaration

of Helsinki and approved by the Ethics Committee of the Hurrem Sultan Hospital, Ethics Committee No: November 13, 2020-40.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Con-ceptualization, ÜD and AK; methodology, ÜD and RMK; software, RMK and ÇPF; vali-dation, RMK., ÇPF and AK; formal analysis, ÜD; investigation, AK resources, RMK and ÇPF; data curation, ÜD; writing—original draft preparation, ÜD and AK; writing—review and editing, RMK and ÇPF; visualization, ÜD; supervision, ÜD; project administration, ÜD and AK; funding acquisition, ÜD. All authors have read and agreed to the published version of the manuscript.

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