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Original Investigation

Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial
A Randomized Clinical Trial

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IMPORTANCE Breast cancer is the leading cause of female cancer burden, and its incidence has increased by more than 20% worldwide since 2008. Some observational studies have suggested that the Mediterranean diet may reduce the risk of breast cancer.

OBJECTIVE To evaluate the effect of 2 interventions with Mediterranean diet vs the advice to follow a low-fat diet (control) on breast cancer incidence.

DESIGN, SETTING, AND PARTICIPANTS The PREDIMED study is a 1:1:1 randomized, single-blind, controlled field trial conducted at primary health care centers in Spain. From 2003 to 2009, 4282 women aged 60 to 80 years and at high cardiovascular disease risk were recruited after invitation by their primary care physicians.

INTERVENTIONS Participants were randomly allocated to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat).

MAIN OUTCOMES AND MEASURES Breast cancer incidence was a prespecified secondary outcome of the trial for women without a prior history of breast cancer (n = 4152).

RESULTS After a median follow-up of 4.8 years, we identified 35 confirmed incident cases of breast cancer. Observed rates (per 1000 person-years) were 1.1 for the Mediterranean diet with extra-virgin olive oil group, 1.8 for the Mediterranean diet with nuts group, and 2.9 for the control group. The multivariable-adjusted hazard ratios vs the control group were 0.32 (95% CI, 0.13-0.79) for the Mediterranean diet with extra-virgin olive oil group and 0.59 (95% CI, 0.26-1.35) for the Mediterranean diet with nuts group. In analyses with yearly cumulative updated dietary exposures, the hazard ratio for each additional 5% of calories from extra-virgin olive oil was 0.72 (95% CI, 0.57-0.90).

CONCLUSIONS AND RELEVANCE This is the first randomized trial finding an effect of a long-term dietary intervention on breast cancer incidence. Our results suggest a beneficial effect of a Mediterranean diet supplemented with extra-virgin olive oil in the primary prevention of breast cancer. These results come from a secondary analysis of a previous trial and are based on few incident cases and, therefore, need to be confirmed in longer-term and larger studies.

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Breast cancer, the most frequently diagnosed malignant tumor and the leading cause of cancer death among women, has increasing incidence rates. In 2012, 1.7 million women received a diagnosis of breast cancer. Since the 2008 estimates, breast cancer incidence has increased by more than 20% worldwide, while mortality has increased by 14%.[1] In European countries, breast cancer is the most common incident cancer and the first or second (after lung cancer) malignant neoplasm implicated in mortality among women.[2]

Diet has been extensively studied as a modifiable component of lifestyle that could influence breast cancer development. Epidemiological evidence on the effect of specific dietary factors is still inconsistent, and the only convincing evidence relates to an increased risk in women with high alcohol consumption.[3]

The inconsistent association between foods or nutrient consumption and breast cancer risk may be partly due to the fact that individuals do not consume foods or nutrients in isolation but mixtures of foods with different nutrient constituents that may interact synergistically to influence biological pathways leading to or protecting from cancer. Thus, assessing diet as a whole, based on overall dietary patterns, provides more useful information on the role of diet in breast cancer risk. The Mediterranean dietary pattern has attracted considerable attention because, historically, breast cancer rates have been lower in Mediterranean countries than in Northern or Central European countries or the United States.[4,5] The Mediterranean diet (MeDiet) is characterized by an abundance of plant foods, fish, and especially olive oil.[5] In the Lyon Diet Heart Study, participants allocated to a cardioprotective Mediterranean-type diet showed a 61% lower risk of cancer (all subtypes) than those participants allocated to a control diet close to the step 1 American Heart Association prudent diet.[6] Recent prospective cohort studies have evaluated the association between adherence to a MeDiet pattern and specifically breast cancer risk.[7,8] However, the epidemiological evidence is still limited and conflicting.[9,10] Moreover, no randomized trial has ever assessed the effect of the MeDiet on the primary prevention of breast cancer.

To further examine the effects of the MeDiet on breast cancer risk, we have analyzed the effect of the MeDiet supplemented with extra-virgin olive oil (EVOO) or nuts in the randomized intervention of the PREDIMED trial on the incidence of breast cancer.

Methods

Trial Design

This study was conducted within the frame of the PREDIMED (Prevención con Dieta Mediterránea) trial (ISRCTN35739639) (http://www.predimed.es).[11,12] Briefly, PREDIMED is a large, multicenter, randomized trial designed to test the effects of the traditional MeDiet on the primary prevention of cardiovascular disease (CVD). The protocol (Supplement 2) was approved by the institutional review boards at all study locations. The trial was stopped in December 1, 2010, after a median follow-up of 4.8 years because of evidence of early cardiovascular benefit of both MeDiet groups compared with the control group.

Participants

Eligible participants for the PREDIMED trial were men aged 55 to 80 years and women aged 60 to 80 years free of CVD at enrollment, who had either type 2 diabetes mellitus or at least 3 of the following major cardiovascular risk factors: smoking, hypertension, elevated low-density lipoprotein cholesterol level, low high-density lipoprotein cholesterol level, overweight or obesity, or family history of premature coronary heart disease.[11] Study candidates were selected from databases of primary health care facilities. Of 8367 candidates meeting enrollment criteria, 89% agreed to participate and provided written informed consent.

Randomization, Masking, Interventions, and Measurements

During the period October 2003 through June 2009, 7447 participants were enrolled in the PREDIMED trial, of whom 4282 were women. Participants were randomly allocated in a 1:1:1 ratio to the 3 intervention groups: MeDiet supplemented with EVOO, MeDiet supplemented with mixed nuts, or control diet (advice to reduce dietary fat). The coordinating center constructed a computer-generated randomization table. Allocation was concealed by opaque, sequentially numbered, and sealed envelopes and stratified by sex and age. For the present study, 1 woman was excluded because of a prior diagnosis of breast cancer and 7 other women were excluded because of probable (not confirmed as malignant) breast tumors. Investigators assessing the occurrence of new breast cancer cases were blinded to the intervention.

Participants in the 2 intervention groups were given supplementary foods for free: EVOO (1 L/wk for the participant and their families) or mixed nuts (30 g/d: 15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds) according to their randomization group. The purpose of supplementation was both to ensure a high consumption of these key components of the traditional MeDiet and to promote a better overall adherence to the intervention.

At baseline and quarterly thereafter, dieticians ran individual and group sessions, with up to 20 participants, separately for each group. In the appropriate individual sessions, a 14-item dietary screening questionnaire was used to assess adherence to either of the MeDiets, and a 9-item dietary screening questionnaire was used to assess adherence to the control diet. The answers to the questionnaires were used as a tool to personalize the intervention for each participant and to negotiate changes to upgrade adherence to either the MeDiet or the control diet.

Participants in the control group also received dietary training at the baseline visit and completed the 14-item dietary screener used to assess baseline adherence to the MeDiet. Thereafter, during the first 3 years of the trial, they received a leaflet explaining the low-fat diet on a yearly basis. However, the realization that the more infrequent visit schedule and less intense support for the control group might be limitations of the trial prompted us to amend the protocol in October 2006. Thereafter, participants assigned to the control diet received

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personalized advice and were invited to group sessions with the same frequency and intensity as those in the MeDiet groups, with the use of a separate 9-item dietary screener. During the study, participants in the control group received gifts of nonfood items as incentives. Attained changes in diet are shown in the eTable in Supplement 1.

Energy restriction was not specifically advised, nor was physical activity promoted in any group. The intervention did not target drug prescriptions; thus, it was implemented within the regular medical care of the participants.

Outcome

Cases were defined as the first invasive breast cancer (*International Classification of Diseases for Oncology* codes C50.1-C50.9). Availability of results from a cytological or histological examination was considered as confirmation. Even though information on biological parameters was not requested for a case to be accepted, medical records were reviewed to extract this information. Incident cases through December 1, 2010, were identified from 2 sources: review of all the medical records of each participant by a panel of physicians (masked to the intervention), both at the primary health care level and at the hospital level, and death certificates (*International Classification of Diseases, Ninth Revision,* code 174 or *International Classification of Diseases, 10th Revision,* code C50). A clinical events committee blinded to the intervention and the dietary information of participants adjudicated all end points using prespecified criteria.

Cancer incidence was defined as a secondary outcome in the original study protocol. Five specific cancer locations were always included as relevant outcomes in all interim analyses and in all reports prepared every year for the Data and Safety Monitoring Board of the PREDIMED trial: breast cancer, lung cancer, prostate cancer, colorectal cancer, and gastric cancer. These results on breast cancer are the first results for any cancer that have been analyzed and submitted for publication in the PREDIMED trial.

Follow-up ended at the time of diagnosis of an invasive breast cancer, death, last follow-up contact, or December 1, 2010, whichever occurred first.

Covariates

At baseline and once yearly during follow-up, a validated 14-item MeDiet screener,[13] a general medical questionnaire, a 137-item validated food frequency questionnaire,[14] and the Minnesota Leisure-Time Physical Activity Questionnaire[15,16] were administered. Information from the food frequency questionnaire was used to calculate intake of energy and nutrients. Other lifestyle-related variables such as smoking, health conditions, and sociodemographic variables were assessed by a 47-item general questionnaire.[12] In addition, trained study personnel directly measured weight, height, and waist circumference.

Sample Size

Sample size was estimated for the primary end point, namely, CVD. It was reassessed in 2008 and set at 7400 participants with the assumption of a 6-year follow-up and underlying CVD event rates of 8.8% and 6.6% in the control and intervention groups, respectively.[12]

Statistical Analysis

Our main analyses were performed on an intention-to-treat basis. We used Cox regression models with robust estimates for the variance to assess the effect of the intervention on malignant breast cancer incidence. First, we fitted a crude model, and then we adjusted for age (3 groups: ≤60, >60 to 70, and >70 years), recruitment center, baseline body mass index (calculated as weight in kilograms divided by height in meters squared, categorized into quartiles), waist-to-height ratio (dichotomous), use of hormone therapy, leisure-time physical activity (categorized into quartiles), total energy intake (categorized into quartiles), alcohol consumption (categorized into quartiles), age at menopause (dichotomous), smoking habit, diabetes mellitus, use of statins, family history of cancer, and baseline adherence to the MeDiet (high vs low). In an ancillary analysis, we merged both MeDiet groups and assessed their effect compared with the control group. For the primary analysis, we excluded 7 women with a non-pathologically confirmed incident breast cancer. In sensitivity analyses, we included these women as cases or as noncases. We repeated our analyses after excluding women who received a diagnosis of malignant breast cancer during the first year of follow-up and considering only malignant neoplasms positive for estrogen receptors (ERs). We did subgroup analyses stratifying by age, smoking status, alcohol intake, prevalent type 2 diabetes, obesity, use of hormone therapy, family history of cancer, and baseline adherence to the Mediterranean diet. However, the small number of cases in some of the strata precluded fitting the models for some of these subgroups. Analyses were repeated with Poisson regression models with robust estimates for the variance. Finally, we also completed a per-protocol analysis in which we used time-dependent Cox models to assess the association between attained consumption of EVOO during follow-up (cumulative mean across all the available food frequency questionnaires) and subsequent incidence of breast cancer.

Results

From October 2003 through June 2009, 4282 women were randomly assigned to 1 of the 3 intervention groups (eFigure in Supplement 1). Their baseline characteristics are presented in **Table 1**. The mean (SD) age of participants was was 67.7 (5.8) years, and mean (SD) body mass index was 30.4 (4.1). Most women underwent menopause before 55 years, and less than 3% used hormone therapy. Baseline characteristics were well balanced in the 3 groups.

During a median (SD) follow-up time of 4.8 (1.7) years, we identified 35 confirmed incident cases of malignant breast cancer. Among them, 33 had available information on ER status and 31 were positive. Of 27 cases with information on progesterone receptor status, 21 were positive, and of 21 with information on ERBB2 receptors, 12 were positive. For 122 participants, no information for breast cancer incidence during follow-up was available.

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Table 1. Baseline Characteristics of Female PREDIMED Trial Participants by Intervention Group

Characteristic	MeDiet With EVOO (n = 1476)	MeDiet With Nuts (n = 1285)	Control Diet (n = 1391)
Age, mean (SD), y	67.6 (5.8)	67.4 (5.6)	68.1 (6.0)
Smoking, No. (%)			
Never	1276 (86.5)	1123 (87.4)	1216 (87.4)
Former	88 (6.0)	68 (5.3)	78 (5.6)
Current	112 (7.6)	94 (7.3)	97 (7.0)
Body mass index, mean (SD)	30.4 (3.9)	30.2 (4.1)	30.7 (4.2)
Waist to height ratio, mean (SD)	0.64 (0.07)	0.63 (0.07)	0.64 (0.07)
Hypertension,[a] No. (%)	1269 (86.0)	1114 (86.7)	1197 (86.1)
Type 2 diabetes mellitus,[b] No. (%)	701 (47.5)	533 (41.5)	618 (44.4)
Dyslipidemia,[c] No. (%)	1112 (75.3)	1003 (78.1)	1065 (76.6)
Family history of premature coronary heart disease,[d] No. (%)	392 (26.6)	328 (25.5)	372 (26.7)
Family history of cancer, No. (%)	807 (54.7)	680 (52.9)	709 (51.0)
Use of hormone therapy, No. (%)	42 (2.9)	34 (2.7)	37 (2.7)
Age at menopause >55 y, No. (%)	102 (6.9)	62 (4.8)	78 (5.6)
Physical activity, mean (SD), METs-min/wk	179 (168)	177 (165)	161 (166)
MeDiet adherence score,[e] mean (SD)	8.7 (1.9)	8.7 (1.9)	8.4 (1.9)
Total energy intake, mean (SD), kcal/d	2163 (568)	2184 (565)	2100 (539)
Alcohol consumption, No. (%)			
Abstainers	765 (51.8)	594 (46.2)	760 (54.6)
>0 to <15 g/d	645 (43.7)	642 (50.0)	575 (41.3)
≥15 g/d	66 (4.5)	49 (3.8)	56 (4.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EVOO, extra-virgin olive oil; MeDiet, Mediterranean diet; MET, metabolic equivalent.

[a] Defined as systolic blood pressure at least 140 mm Hg, diastolic blood pressure at least 90 mm Hg, or use of antihypertensive therapy.

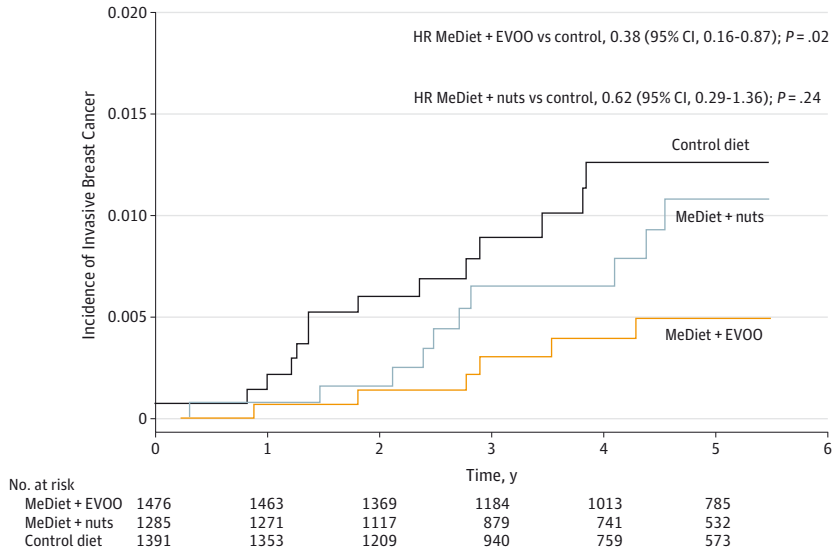
[b] Defined as fasting blood glucose level at least 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) on 2 occasions, 2-h plasma glucose level at least 200 mg/dL after a 75-g oral glucose load, or use of antidiabetic medication.

[c] Defined as low-density lipoprotein cholesterol level greater than 160 mg/dL (to convert to millimoles per liter, multiply by 0.0259), high-density lipoprotein cholesterol level no more than 40 mg/dL in men or 50 mg/dL in women, or use of lipid-lowering therapy.

[d] Defined as diagnosis of coronary heart disease in a male first-degree relative before the age of 55 y or in a female first-degree relative before the age of 65 y.

[e] On a scale of 0 to 14.

Figure 1. Incidence of Invasive Breast Cancer, According to the Intervention Group



Hazard ratios were obtained from Cox regression models.
EVOO indicates extra-virgin olive oil; HR, hazard ratio; MeDiet, Mediterranean diet.

Women allocated to the MeDiet supplemented with EVOO showed a 62% relatively lower risk of malignant breast cancer than those allocated to the control diet (95% CI, 0.16-0.87) (**Figure 1**). Participants in the MeDiet supplemented with nuts showed a nonsignificant risk reduction compared with women in the control group (hazard ratio [HR], 0.62 [95% CI, 0.29-1.36]). When both MeDiet groups were merged together, we observed a 51% relative risk reduction (95% CI, 0.25-0.94) (**Table 2**). When we excluded women who received a diagnosis of malignant breast cancer during the first year after enrollment, the results hardly changed. Similarly, the results did not substantially change after including women with breast cancer with no cytological or histological confirmation either as cases or as noncases or when we considered only ER-positive malignant neoplasms. In the stratified analyses, all but 2 point estimates showed an inverse association between the MeDiet plus EVOO intervention and the incidence of breast cancer (**Table 3**).

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Table 2. Risk of Invasive Breast Cancer According to the Intervention Group[a]

	Hazard Ratio (95% CI)			
	Control Diet (n = 1391)	Mediterranean Diet With EVOO (n = 1476)	Mediterranean Diet With Nuts (n = 1285)	Both Mediterranean Diets (n = 2761)
Cases/person-years	17/5829	8/7031	10/5492	18/12 523
Rate, per 1000 person-years	2.9	1.1	1.8	1.4
Crude rate ratio	1 [Reference]	0.38 (0.16-0.87)	0.62 (0.29-1.36)	0.49 (0.25-0.94)
Multivariable adjusted rate ratio[b]	1 [Reference]	0.32 (0.13-0.79)	0.59 (0.26-1.35)	0.43 (0.21-0.88)
After excluding women with follow-up <1 y[c]				
Crude rate ratio	1 [Reference]	0.37 (0.15-0.90)	0.64 (0.28-1.45)	0.48 (0.24-0.98)
Multivariable adjusted rate ratio[b]	1 [Reference]	0.33 (0.13-0.85)	0.65 (0.27-1.53)	0.46 (0.22-0.96)
After including nonconfirmed cases as cases				
Crude rate ratio	1 [Reference]	0.38 (0.16-0.87)	0.62 (0.29-1.36)	0.49 (0.25-0.94)
Multivariable adjusted rate ratio[b]	1 [Reference]	0.32 (0.13-0.79)	0.59 (0.26-1.35)	0.43 (0.21-0.88)
After including nonconfirmed cases as noncases				
Crude rate ratio	1 [Reference]	0.38 (0.16-0.87)	0.62 (0.29-1.36)	0.49 (0.25-0.94)
Multivariable adjusted rate ratio[b]	1 [Reference]	0.32 (0.13-0.79)	0.59 (0.26-1.35)	0.43 (0.21-0.88)
Including only estrogen receptor–positive malignant neoplasms				
Crude rate ratio	1 [Reference]	0.31 (0.11-0.85)	0.65 (0.27-1.57)	0.46 (0.22-0.98)
Multivariable adjusted rate ratio[b]	1 [Reference]	0.24 (0.08-0.71)	0.58 (0.23-1.47)	0.38 (0.17-0.86)

Abbreviation: EVOO, extra virgin olive oil.

[a] Results obtained from Cox regression models.

[b] Adjusted for age (3 groups), study site (continuous), body mass index (quartiles), waist to height ratio (dichotomous), use of hormone therapy, leisure-time physical activity (quartiles), total energy intake (quartiles), alcohol consumption (quartiles), age at menopause (<55 vs ≥55 y), and baseline adherence to the Mediterranean diet (high vs low).

[c] Four cases were excluded: 1 in the Mediterranean diet with EVOO group, 1 in the Mediterranean diet with nuts group, and 2 in the control group.

When we assessed the 3 trial groups together in a per-protocol analysis, participants who attained a higher EVOO consumption during follow-up exhibited the lowest risk (HR for 5th vs 1st quintile, 0.18 [95% CI, 0.06-0.57]) (**Figure 2**). In these analyses with yearly cumulative updated dietary exposures, the HR was 0.72 (95% CI, 0.57-0.90) for each additional 5% of calories from EVOO.

Discussion

In this secondary analysis of the PREDIMED trial, we found a significant inverse association between consumption of a MeDiet supplemented with EVOO and breast cancer incidence. A high consumption of EVOO (≥15% of total energy intake) seems to be instrumental for obtaining this significant protection. A nonsignificant risk reduction was observed with the MeDiet supplemented with nuts.

The strengths of this study are its randomized design, the achieved changes in the participants' dietary habits according to the intervention,[17] little residual confounding with almost no changes in estimates after adjustment for many potential confounders, and the thorough and blind revision of medical information to assess outcomes. The adjudication committee, whose members were blinded to the intervention group, assessed the events with specific criteria, dispelling potential misclassification biases. We also acknowledge some limitations. First, breast cancer was not the primary end point of the PREDIMED trial. Thus, the present work is only a prespecified secondary analysis of a large nutritional intervention trial and we cannot warrant that all women had mammograms free from suggestive findings at baseline. However, the randomization was able to yield well-balanced and comparable groups, and, given the large sample size, a balance in other characteristics can be safely assumed. Second, the number of observed breast cancer cases was small. The potential for missing some incident breast cancer cases is basically null regarding clinically relevant events. In any case, this possibility will affect only women lost to follow-up, and most of them belonged to the control group. Therefore, undetected cases of breast cancer would more likely have increased even further the rate in the control group. Accordingly, our results would tend to underestimate the beneficial effect of the intervention. The low rate of breast cancer among women in the PREDIMED trial should not be surprising. If the MeDiet is actually protective against breast cancer, a low incidence is to be expected in a study with these characteristics, especially when overall adherence to the MeDiet was good already at baseline. Third, we do not have information on an individual basis on whether and when women in our trial underwent mammography. Potentially, cancers could be missed without mammograms. However, because of the randomized design and the large sample size, we believe that we can safely assume an even distribution of subclinical cases in the 3 groups under the null hypothesis. Also, we prioritized specificity in our protocol for case ascertainment and we believe that our protocol for confirmation of cases

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Table 3. Risk of Invasive Breast Cancer by Intervention Group in Subgroup Analyses[a]

Variable	No.	Cases/ Person-years	Hazard Ratio (95% CI) vs Control Diet		
			Mediterranean Diet With EVOO	Mediterranean Diet With Nuts	Both Mediterranean Diets
Age					
≤67 y	2095	15/9099	0.16 (0.04-0.68)	0.16 (0.04-0.71)	0.16 (0.05-0.50)
>67 y	2057	20/9254	0.56 (0.15-2.03)	1.52 (0.53-4.39)	0.92 (0.34-2.47)
Smoking					
Never	3615	31/16 082	0.33 (0.13-0.86)	0.63 (0.27-1.49)	0.46 (0.22-0.96)
Ever	537	4/2271	…	…	…
Alcohol intake					
≤25 g/d	2119	22/9460	0.35 (0.11-1.12)	0.84 (0.32-2.20)	0.54 (0.22-1.29)
>25 g/d	2033	13/8893	0.30 (0.07-1.30)	0.34 (0.08-1.45)	0.32 (0.10-1.06)
Diabetes mellitus					
No	2300	16/9967	0.37 (0.10-1.37)	0.49 (0.13-1.81)	0.42 (0.15-1.20)
Yes	1852	19/8385	0.22 (0.05-0.88)	0.61 (0.18-2.00)	0.37 (0.13-1.07)
BMI					
<30	1995	17/8809	0.32 (0.09-1.09)	0.27 (0.07-1.16)	0.29 (0.11-0.83)
≥30	2157	18/9543	0.28 (0.07-1.12)	0.99 (0.35-2.81)	0.57 (0.22-1.49)
Use of hormone therapy					
No	4039	33/17 905	0.31 (0.12-0.80)	0.64 (0.28-1.46)	0.44 (0.21-0.92)
Yes	113	2/448			
Family history of cancer[b]					
No	1702	10/7558	0.19 (0.05-0.70)	0.10 (0.004-2.25)	0.15 (0.03-0.70)
Yes	2196	22/9658	0.37 (0.11-1.21)	0.78 (0.29-2.12)	0.53 (0.22-1.30)
Baseline adherence to the Mediterranean diet[c]					
Low	1936	21/8398	0.31 (0.10-0.96)	0.39 (0.12-1.26)	0.34 (0.14-0.86)
High	2216	14/9955	0.33 (0.07-1.63)	1.00 (0.25-4.03)	0.62 (0.16-2.33)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ellipses, insufficient sample size for comparison; EVOO, extra-virgin olive oil.

[a] Results obtained from Cox regression models. Adjusted for age (3 groups), center, body mass index (quartiles), waist to height ratio (dichotomous), use of hormone therapy, leisure-time physical activity (quartiles), total energy intake (quartiles), alcohol consumption (quartiles), age at menopause (<55 vs >55 y), and baseline adherence to the Mediterranean diet (high vs low).

[b] Information was not available for 254 women.

[c] Scored on a scale of 0 to 14 points, dichotomized into low adherence (0-8 points) and high adherence (9-14 points).

ensures a high degree of specificity.[18(p359)] Fourth, our participants were white postmenopausal women at high cardiovascular risk. Thus, our results may not be generalizable to other age groups or ethnicities. Fifth, information on reproductive factors known to be associated with breast cancer risk was not available for further adjustment. Nevertheless, because of the randomized allocation of participants, it is not likely that these factors may have introduced substantial confounding. Fifth, our study cannot disentangle whether the observed beneficial effect was attributable mainly to EVOO or to its consumption within the context of the traditional MeDiet. Sixth, according to the study event definitions, we collected information on malignant tumors. Thus, we did not register noninvasive tumors such as in situ tumors. Therefore, we cannot include noninvasive cases in our analyses. Seventh, up to October 2006 when the study protocol was amended,[12] the intervention in the control group was less intense than in the intervention group. Consequently, some differences in social support, positive expectations, and empowerment could have existed between the intervention and the control groups. Nevertheless, only 5 cases of breast cancer had been identified up to that date. In addition, it seems unlikely that the magnitude of the risk reduction in breast cancer can be explained only in terms of increased social support.

No prior nutrition intervention trial has addressed the effect of the MeDiet specifically on breast cancer. In the Lyon Diet Heart Study, a randomized trial, a protective effect of a cardioprotective Mediterranean-type diet against overall cancer incidence was observed, supporting the hypothesis of an anticancer effect of the MeDiet.[6] The potential beneficial effect of the MeDiet may be explained by several mechanisms,[19] for example, a reduction in DNA oxidative damage.[20] Specifically for breast cancer, results from observational studies have been inconsistent. A recent meta-analysis[21] reported no association between adherence to the MeDiet and breast cancer incidence in cohort studies, revealing a pooled estimate risk ratio of 1.01 (95% CI, 0.88-1.16), whereas results from case-control studies suggested an 18% risk reduction (95% CI, 0.69-0.97). However, most cohort studies[8-10,22] included in this meta-analysis were conducted outside the Mediterranean geographical area and it cannot be assumed that a proper MeDiet was followed outside this region. The EPIC study is the only large cohort study that has included countries from the Mediterranean area.[7] In that study, the HR for postmenopausal women was 0.93 (95% CI, 0.87-0.99) when comparing high (10-16 points) vs low (0-5 points) adherence to the MeDiet. If this information (as a prior) were integrated with our present results using a simple Bayesian approach recommended in

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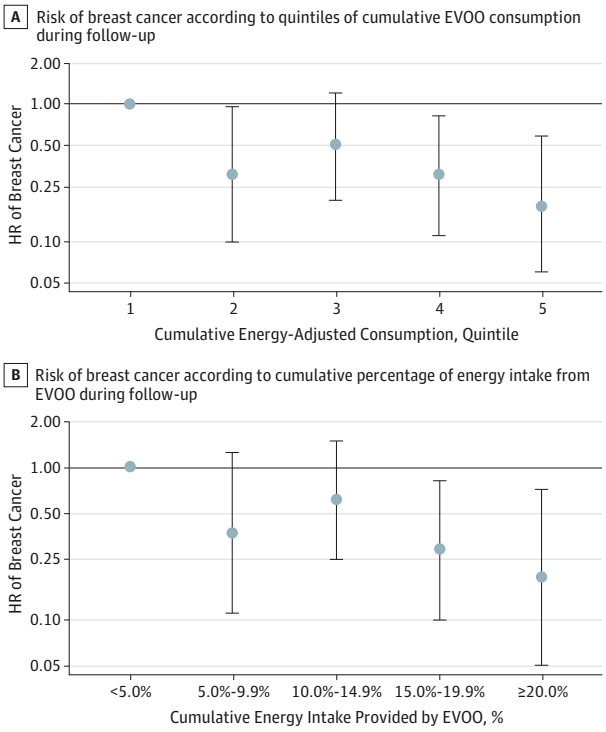
Figure 2. Incidence of Breast Cancer, According to Attained Consumption of Extra-Virgin Olive Oil (EVOO) During Follow-up



Results obtained from Cox regression models. Adjusted for age, use of hormone therapy, physical activity, body mass index, alcohol consumption, baseline adherence to the Mediterranean diet, age at menopause, total energy intake, smoking status, prevalent diabetes mellitus, family history of cancer, and use of statins. Error bars show 95% confidence intervals. HR indicates hazard ratio.

epidemiology,[18] the posterior relative risk would be 0.92 (95% CI, 0.87-0.98). The differential effects of the 2 MeDiet interventions on breast cancer may be attributed to a higher consumption of EVOO among participants allocated to the MeDiet supplemented with EVOO as our ancillary analyses showed (Figure 2). Consumption of EVOO accounted for 22% of total caloric intake in the MeDiet supplemented with EVOO, whereas nuts represented 10% of the total calories in the MeDiet supplemented with nuts. The stronger inverse association with EVOO consumption may also be ascribed to its high polyphenol content.

Epidemiological studies on the association between EVOO consumption and breast cancer incidence are scarce. A meta-analysis of case-control studies concluded that olive oil consumption, including not only EVOO but also other common types of olive oil (with a lower content of bioactive polyphenols), was inversely associated with breast cancer incidence.[23] These case-control studies have been conducted in Mediterranean countries, and they consistently found an inverse association between olive oil consumption and breast cancer risk. This finding, however, was not replicated in the EPIC cohort.[24] Nonetheless, it is noteworthy that none of these studies differentiated between types of olive oil. Several biological mechanisms could explain the putative anticarcinogenic properties of EVOO. All types of olive oil provide a high supply of monounsaturated fatty acids, mainly oleic acid, as well as squalene, whereas EVOO also contains various biologically active compounds, such as the polyphenols oleocanthal, oleuropein, hydroxytyrosol, and lignans. In vitro studies have suggested that oleic acid has an antiproliferative effect by affecting the expression of human oncogenes.[25] The hydrocarbon squalene has been reported to exert a beneficial effect on intracellular oxidative stress and DNA oxidative damage in mammary epithelial cells.[26] Olive oil polyphenols may have a potential role in breast cancer prevention.[27] Oleocanthal has been associated with inhibition of tumor growth and proliferation, migration, and invasiveness of breast cancer cells in in vitro or in vivo breast cancer models.[28] Oleuropein has been associated with increased apoptosis of cultured breast cancer cells through different pathways.[29,30] Also, hydroxytyrosol has been reported to reduce intracellular reactive oxygen species in human breast epithelial cells and to prevent oxidative DNA damage in both human breast epithelial cells and human breast cancer cells.[31] Lignans are phytoestrogens whose consumption has been associated with a lower risk of breast cancer in postmenopausal women.[32]

In the PREDIMED trial, participants in the control group did not reduce their total fat intake substantially—albeit their saturated fat intake stayed less than 10% during follow-up—even though they were advised to follow a low-fat diet. This result can be ascribed to the rooted tradition of adherence to the MeDiet, particularly among older people. On the other hand, several prospective studies have suggested that higher fat intakes, especially animal fat, may be associated with a higher risk of breast cancer.[33-36] Moreover, in the Women's Health Initiative study, total fat consumption was associated with a higher risk of breast cancer.[37] Also, in the Women's Health Initiative study, women who reported the highest levels of fat intake at baseline and therefore may have achieved the greatest reduction in fat intake showed a significantly lower risk of breast cancer.[38] Among women with early-stage breast cancer in the Women's Intervention Nutrition Study, lower fat intakes were associated with lower estrogen-negative breast cancer recurrence.[39] Taking all this evidence into account, greater reductions in the incidence of breast cancer could have been observed in the control group had these women followed a truly low-fat diet.

Conclusions

The results of the PREDIMED trial suggest a beneficial effect of a MeDiet supplemented with EVOO in the primary prevention of breast cancer. Preventive strategies represent the most sensible approach against cancer. The intervention paradigm implemented in the PREDIMED trial provides a useful scenario for breast cancer prevention because it is conducted in primary health care centers and also offers beneficial effects on a wide variety of health outcomes.[40] Nevertheless, these results need confirmation by long-term studies with a higher number of incident cases.

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