

Mediterranean Diet and Naltrexone/Bupropion Treatment for Weight Loss in Overweight and Obese Breast Cancer Survivors and Non-Cancer Participants: A Pilot Randomized Controlled Trial

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Introduction: The objective of this pilot randomized controlled trial was to investigate the combined effect of a Mediterranean diet and naltrexone/bupropion treatment on body weight, metabolic parameters, and quality of life in overweight or obese breast cancer survivors.

Methods: Forty-four breast cancer survivors were randomly assigned to receive the Mediterranean diet plus naltrexone/bupropion medication (breast cancer survivor MeDiet +NB group) or the Mediterranean diet alone (breast cancer survivor MeDiet-only group). Twenty-eight age-matched non-cancer patients were instructed to consume the Mediterranean diet plus naltrexone/bupropion medication (non-cancer MeDiet+NB group). After the 8-week intervention, changes in body weight, metabolic parameters, nutrient intake, and quality of life of the three groups were assessed.

Results: Significant weight loss of 2.8 kg was noted for the breast cancer survivor MeDiet +NB group, 1.8 kg for the breast cancer survivor MeDiet-only group, and 2.5 kg for the non-cancer MeDiet+NB group after 8 weeks ($P < 0.05$ versus baseline by Wilcoxon's signed-rank test). All three groups also exhibited significantly lower fasting glucose, insulin, and homeostasis model assessment of insulin resistance levels ($P < 0.05$). Quality of life as assessed by self-reported questionnaires showed improvement in all participants ($P < 0.05$). However, there were no significant differences of changes in body weights, metabolic parameters, and quality of life among the three groups or between the MeDiet+NB and MeDiet-only groups.

Conclusion: We found that the Mediterranean diet, with or without naltrexone/bupropion treatment, facilitates weight loss, improves metabolic parameters, and increases quality of life. The combination of the Mediterranean diet with naltrexone/bupropion treatment did not produce superior changes when compared to the Mediterranean diet alone.

Trial Registration: This trial was retrospectively registered on 10 July 2018 as NCT03581630 at ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/show/NCT03581630>).

Keywords: Mediterranean diet, naltrexone/bupropion, obesity, breast cancer survivors

Introduction

Breast cancer is a leading cause of cancer among women worldwide and the second most common cancer among women in Korea. From 1993 to 2015, the 5-year survival rate for breast cancer patients increased from 78.0% to 92.3% in Korea,¹ indicating the increased importance of health care for survivors. Overweight or obesity is associated with a higher risk for cancer recurrence and mortality among breast cancer survivors.^{2,3} Furthermore,

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obesity is associated with psychosocial problems, a low quality of life, and increased metabolic risk factors.^{4,5} Thus, the American Cancer Society and the American Society of Clinical Oncology recommend that cancer survivors achieve and maintain a healthy weight.⁶ Recent studies have begun examining the effect of weight loss intervention in overweight or obese breast cancer survivors.^{7,8} However, the bulk of these studies were conducted only in Western countries, and few have been conducted in Asian countries.

Weight loss intervention to address overweight or obesity should include comprehensive lifestyle modifications, and drug treatment for obesity is recommended as an adjunctive therapy.⁹ The Mediterranean diet, recently known as an effective alternative to low-fat or low-carbohydrate diets in terms of weight loss, is associated with a significant reduction in cardiovascular disease and total mortality, as well as body weight.^{10,11} Moreover, an updated meta-analysis pooling seven cohort studies reported an inverse association between the incidence of breast cancer and adherence to a Mediterranean diet.¹² In a secondary analysis of the PREDIMED (Prevención con Dieta Mediterránea) clinical trial, individuals consuming a Mediterranean diet supplemented with extra-virgin olive oil had a reduced incidence of breast cancer.¹³ These findings suggest that the Mediterranean diet would be an effective dietary intervention for overweight or obese breast cancer survivors.

With regard to pharmacological therapies to improve weight loss, the combination of the opioid receptor antagonist naltrexone and the norepinephrine-dopamine reuptake inhibitor bupropion (Contrave; Orexigen, La Jolla, CA, USA) was recently approved and shows long-term safety and efficacy. Bupropion's anorectic effect is the result of the stimulation of hypothalamic pro-opiomelanocortin neurons, whereas naltrexone blocks opioid-mediated autoinhibition of these cells.¹⁴ In addition, low-dose naltrexone inhibits tumor progression by upregulating the expression of opioid growth factor and its receptor.^{15,16} Furthermore, bupropion has been shown to improve sexual function in breast cancer patients.^{17,18} Therefore, the combination of naltrexone and bupropion may be beneficial for not only non-cancer obese people but also breast cancer survivors.

The aim of our study was to investigate the effect of the Mediterranean diet and naltrexone/bupropion treatment on body weight, metabolic parameters, and quality of life in breast cancer survivors who are overweight or obese. We also evaluated whether obesity drugs have an additional effect compared to the Mediterranean diet alone and

whether there are any differences in breast cancer survivors, compared to non-cancer obese people.

Methods

Study Design

This 8-week, three-arm parallel-group, randomized controlled trial was conducted at Gangnam Severance Hospital (Seoul, South Korea) from July 2017 to July 2018. The study design and experimental protocol were approved by the Institutional Review Board of Gangnam Severance Hospital (IRB number 3–2017-0097) in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before screening and data collection. This trial was retrospectively registered at ClinicalTrials.gov (number NCT03581630).

Study Participants

Breast cancer survivors and age-matched non-cancer patients were recruited via poster and online advertisements at Gangnam Severance Hospital. All volunteers were initially screened by telephone. Women aged 20–65 years were eligible for inclusion if they had a body mass index (BMI) >25.0 kg/m² (obese for Asian populations, according to the World Health Organization¹⁹) or a BMI >23.0 kg/m² (overweight for Asian populations) in the presence of at least one metabolic risk factor (waist circumference ≥ 80 cm, triglyceride ≥ 150 mg/dL, high-density lipoprotein [HDL] cholesterol <50 mg/dL, fasting glucose ≥ 100 mg/dL, blood pressure $\geq 130/85$ mmHg, or a diagnosis of hypertension, type 2 diabetes mellitus, or dyslipidemia currently controlled with medications). Participants who were diagnosed with breast cancer stage I–III and completed cancer treatment, including surgery, adjuvant chemotherapy, radiotherapy, and/or hormonal therapy, were included in the breast cancer survivor group.

Participants who met any of the following criteria were excluded: uncontrolled hypertension, hepatic or renal disease, significant cardiovascular disease or stroke, history of seizures, serious psychiatric illness (such as bipolar disorder, schizophrenia, bulimia, anorexia nervosa, or suicidal ideation), taking medications such as monoamine oxidase inhibitors, opioid-containing medications, other naltrexone- or bupropion-containing medications, or tamoxifen, history of alcohol abuse or dependence, current smokers or use of nicotine replacement products in the previous 6 months, or women who were pregnant or breastfeeding. Participants with a history of breast cancer were excluded if they had

experienced cancer recurrence or metastasis. Women of child-bearing age were required to use effective contraception throughout the study period and up to 30 days after discontinuation of the study drug.

Randomization

Breast cancer survivors were randomly assigned to receive the Mediterranean diet plus naltrexone/bupropion medication (MeDiet+NB group) or the Mediterranean diet alone (MeDiet-only group). Participants were randomized using a computer-generated random number sequence with a block size of four. An independent statistician generated the allocation sequence, and the study coordinator assigned the participants to interventions in chronological order as the participants enrolled. Only outcome assessors were blinded to group allocation.

Intervention

Mediterranean Diet

All participants participated in the Mediterranean diet intervention and received dietary training from professional nutritionists at the baseline visit and samples of a Mediterranean diet for three times during the trial. To assess adherence to the Mediterranean diet, a 13-item questionnaire developed by the PREDIMED study group that modified the validated Mediterranean Diet Adherence Screener was used.²⁰ However, given the study population and evidence linking alcohol consumption with cancer,²¹ the item for wine consumption was excluded. The resulting modified scores ranged from 0 to 13, with scores higher than 9 defined as high adherence to the Mediterranean diet. Participants were educated to increase the scores by the following diet modifications: (i) abundant use of olive oil, sesame oil, or perilla oil for cooking and dressing; (ii) increased consumption of vegetables, fresh fruits, legumes, fish, nuts, white meat, and sauce made with tomato, onion, garlic, or olive oil; and (iii) avoidance of red or processed meat, butter or cream, sugar-sweetened beverages, and commercial sweets or pastries. Details of the modified Mediterranean diet score questionnaire are provided in the [online supporting material \(Table S1\)](#). Total calorie restriction of <1500 kcal per day was advised, which is a 500 kcal deficit from the daily recommended calories calculated according to the method presented by the Korean Diabetes Association.²² All participants were encouraged to communicate with the study researchers via mobile messenger by submitting their daily diet photographs and Mediterranean diet scores and receiving feedback ([Figure S1](#)).

Naltrexone/Bupropion Medication

Breast cancer survivors assigned to the MeDiet+NB group and all non-cancer patients were instructed to take naltrexone/bupropion. Participants took one extended-release tablet containing 8 mg naltrexone and 90 mg bupropion each morning for the first week. Then if tolerable, they increased the daily dose to two tablets, one in the morning and one in the evening for the next 7 weeks. Drug compliance was measured by the remaining pill count at week 1, 4, and 8. Noncompliant participants (compliance rate of less than 80%) were discontinued from the study.

Outcome Measurements

Body weight (nearest 0.1 kg) of participants, wearing light-weight clothing, was measured along with their height (nearest 0.1 cm) by using an automatic extensometer (BSM 330; Biospace, Seoul, South Korea). BMI was calculated as the ratio of weight (kg) to height squared (m²). To assess body composition, skeletal muscle mass, fat mass, and fat percentage were measured using a bioelectrical impedance analyzer (ACCUNIQ BC720; SELVAS Healthcare Inc., Daejeon, South Korea). Waist circumference was measured at the horizontal plane midway between the lowest ribs and the iliac crest with the participant in a standing position.

Fasting blood samples were collected from an antecubital vein to assess metabolic parameters at baseline and after the 8-week intervention. White blood cell (WBC) counts were quantified with an XN-9000 hematology analyzer (Sysmex, IL, USA). Fasting glucose, high-sensitivity C-reactive protein, total cholesterol, triglyceride, and HDL cholesterol levels were measured with the ADVIA 1650 Clinical Chemistry system (Siemens Medical Solutions, Tarrytown, NY, USA). Unless triglycerides were >400 mg/dL, low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald equation as follows: LDL cholesterol = total cholesterol – HDL cholesterol – triglyceride/5.²³ Fasting insulin was measured by an electrochemiluminescence immunoassay using an Elecsys 2010 instrument (Roche, Indianapolis, IN, USA). Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) method by applying the following formula: HOMA-IR = fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405.²⁴

At baseline and after the intervention, participants completed six questionnaires. The 24-h dietary recall method was used to calculate the intake of total calories and specific nutrients. The above-mentioned modified Mediterranean Diet Adherence Screener was used to assess adherence to the

Mediterranean diet. The Godin Leisure-Time Exercise Questionnaire was used to calculate the quantity of physical activity in metabolic equivalent-hours per week. Quality of life was measured using three common questionnaires: the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), the obesity-related problems (OP) scale, and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale. The EORTC QLQ-C30 comprises 30 items, including global health status, five functional scales, and eight symptom scales.²⁵ High scores on global health status and five functional scales indicate a better quality of life. The OP scale primarily focuses on the impact of obesity on psychosocial functioning, and higher scores indicate more problems.²⁶ The FACIT-F subscale uses 13 items to measure fatigue-related difficulty in managing daily activities, with higher scores indicating less fatigue and a better quality of life.²⁷

Safety assessments consisted of evaluations of treatment emergent adverse events, concomitant medications, vital signs (recorded at each visit), and clinical laboratory measures (recorded at baseline and at week 8), including serum creatinine and liver function tests.

Statistical Analysis

All data are presented as the medians (interquartile ranges). Differences in baseline characteristics between the

intervention groups were analyzed on the intention-to-treat population using the Kruskal–Wallis test. The primary and secondary endpoints were analyzed on the per-protocol population. Within-group differences after the intervention were analyzed by the Wilcoxon’s signed-rank test, and differences between groups postintervention were analyzed using the Quade’s rank analysis of covariates, adjusted for age and initial BMI. A *P* value of < 0.05 was considered statistically significant. All analyses were performed using SPSS for Windows (version 23.0; SPSS Inc., Chicago, Ill., USA). The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Results

Baseline Characteristics

A total of 75 candidates were screened for eligibility, and 72 participants (44 breast cancer survivors and 28 non-cancer patients) were enrolled in the study. The rate of study discontinuation was 22.2% (MeDiet+NB, 29.4%; MeDiet-only, 4.8%). In total, 56 participants finally completed the study (Figure 1). The baseline characteristics of participants are shown in Table 1. We found no significant differences between the groups with regard to age, body weight, or metabolic parameters at baseline. However, BMIs differed at baseline

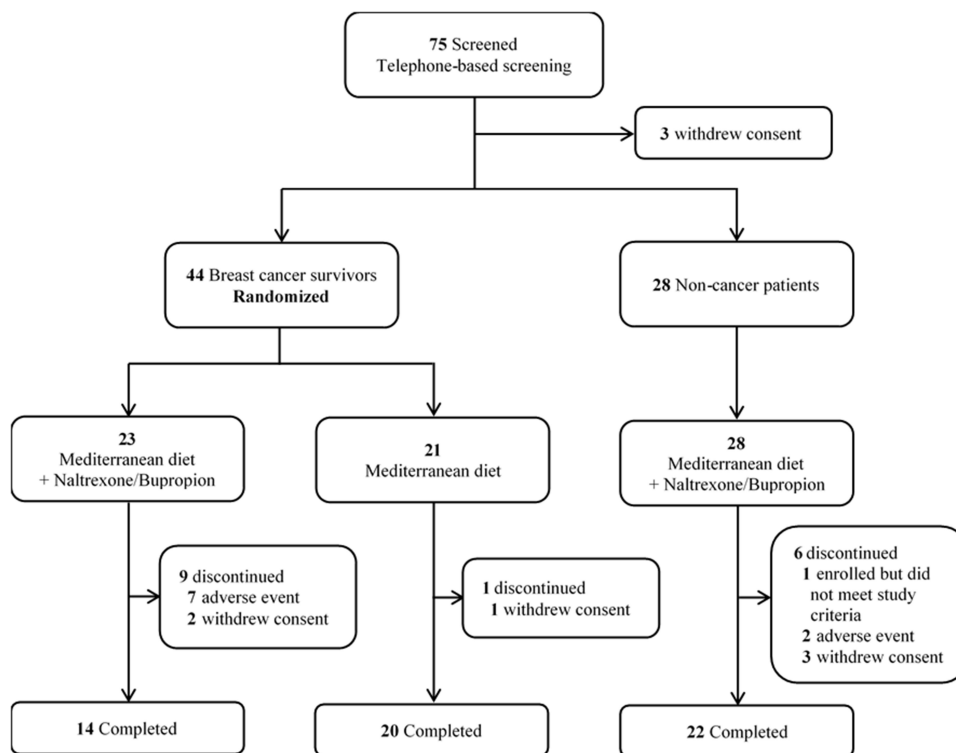


Figure 1 Flow chart of study participant selection.

between the groups; therefore, we analyzed the outcomes after adjusting for initial BMI.

Adherence to the Dietary Intervention

After the 8-week intervention, the percentages of participants with high adherence to the Mediterranean diet (score of ≥ 9) increased in all three groups (Figure 2). Changes in nutrient intake measured by 24-h dietary recall method are listed in Table 2. Monounsaturated fatty acid/saturated fatty acid ratio and dietary fiber intake increased after 8 weeks ($P = 0.046$ and $P < 0.001$, respectively), and the median total calorie intake decreased to <1500 kcal per day, which reflects high adherence to the Mediterranean diet. The comparison of changes in nutrient intake among the study groups revealed no significant differences, since the same dietary intervention

was advised to all three groups (Online supplementary Table S2). In addition, physical activity increased after 8 weeks in all participants ($P < 0.001$) (Table 2), although the changes did not differ among groups (Table S2).

Endpoints

Table 3 shows the changes in body weight, body composition, and metabolic parameters after the intervention. Body weight, BMI, and fat mass decreased in all three groups after 8 weeks ($P < 0.05$ versus baseline by Wilcoxon's signed-rank test). Quade's rank analysis of covariates, adjusted for age and initial BMI, was performed to estimate the statistical differences between groups. However, there were no significant differences among the three groups or between the MeDiet+NB and MeDiet-only groups.

Table 1 Baseline Characteristics of the Study Participants

Characteristics	Breast Cancer Survivors		Non-Cancer Patients	P value ^a
	MeDiet+NB	MeDiet Only	MeDiet+NB	
	(n = 23)	(n = 21)	(n = 28)	
Age (years)	56.0 (52.0, 57.5)	55.0 (50.5, 58.8)	53.5 (49.5, 57.0)	0.329
Body composition				
Weight (kg)	66.7 (63.1, 71.1)	65.7 (61.7, 69.1)	72.0 (64.5, 80.1)	0.076
BMI (kg/m ²)	27.6 (25.7, 28.6)	26.2 (24.9, 27.4)	29.2 (25.7, 31.4)	0.025
Skeletal muscle (kg)	22.7 (21.1, 23.9)	22.0 (21.4, 22.8)	23.1 (21.1, 25.9)	0.459
Fat mass (kg)	24.8 (22.9, 28.5)	23.6 (21.0, 28.6)	29.1 (23.3, 32.3)	0.083
Fat percentage	37.1 (36.3, 41.2)	37.1 (34.7, 42.4)	38.7 (35.2, 43.5)	0.329
WHR	0.91 (0.90, 1.00)	0.91 (0.87, 0.98)	0.92 (0.88, 1.00)	0.604
Diet and physical activity				
Total calorie (kcal/day)	1744.8 (1188.7, 2068.0)	1653.8 (1321.6, 1883.4)	1449.8 (1295.2, 1999.8)	0.901
Mediterranean diet score	8.0 (5.5, 10.0)	8.0 (7.0, 9.8)	7.0 (4.5, 9.0)	0.259
GLTEQ score (MET-h/wk)	9.0 (0.0, 26.5)	6.0 (3.0, 14.5)	4.8 (0.0, 17.5)	0.642
Metabolic parameters				
WBC count (no./ μ L)	5.55 (4.93, 6.19)	5.15 (4.40, 5.78)	5.25 (4.46, 6.26)	0.597
Fasting glucose (mg/dL)	88.0 (82.5, 105.5)	85.5 (79.0, 97.5)	86.0 (82.0, 97.5)	0.643
Insulin (μ U/mL)	7.50 (5.15, 12.00)	7.45 (5.33, 9.58)	7.90 (5.05, 9.80)	0.880
HOMA-IR	1.52 (1.08, 2.78)	1.49 (1.19, 2.25)	1.70 (1.06, 2.51)	0.804
Total cholesterol (mg/dL)	196.0 (153.5, 209.5)	196.5 (182.3, 219.0)	193.0 (165.5, 207.5)	0.478
Triglyceride (mg/dL)	136.0 (121.0, 186.5)	124.0 (92.5, 193.5)	112.0 (87.0, 145.5)	0.140
HDL cholesterol (mg/dL)	56.6 (49.8, 59.5)	54.0 (47.5, 64.1)	64.0 (47.7, 71.7)	0.262
LDL cholesterol (mg/dL)	109.9 (63.5, 130.1)	113.5 (99.0, 132.7)	110.1 (84.8, 124.3)	0.537
Vital signs				
Systolic BP (mmHg)	121.0 (117.5, 125.5)	127.5 (119.8, 140.8)	123.0 (116.5, 133.5)	0.173
Diastolic BP (mmHg)	79.0 (77.5, 84.0)	87.0 (77.3, 97.3)	79.0 (74.0, 85.0)	0.143
Heart rate (beats/min)	72.0 (66.5, 83.5)	75.0 (68.3, 80.8)	75.0 (67.0, 84.0)	0.812

Notes: Data are expressed as medians (interquartile ranges). ^aP values calculated by the Kruskal–Wallis test.

Abbreviations: BMI, body mass index; BP, blood pressure; GLTEQ, Godin Leisure-Time Exercise Questionnaire; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of assessment-insulin resistance; LDL, low-density lipoprotein; MeDiet, Mediterranean diet; MET-h/wk, metabolic equivalents-hour/week; NB, naltrexone/bupropion; WBC, white blood cell; WHR, waist-hip ratio.

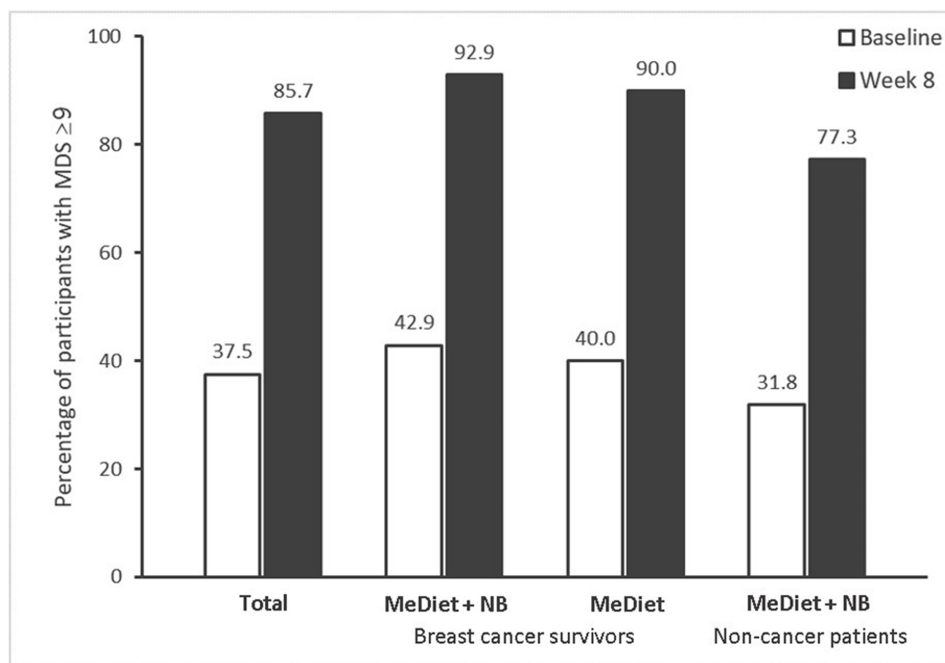


Figure 2 Percentages of participants with a Mediterranean diet score (MDS) ≥ 9 by group.

Among measures of metabolic parameters, fasting glucose, insulin, and HOMA-IR significantly decreased in all three groups ($P < 0.05$ versus baseline by Wilcoxon’s signed-rank test) (Table 3). In addition, WBC count, total cholesterol, triglyceride, and LDL cholesterol were slightly reduced in all three groups, some with statistically significant

within-group changes. Among the groups, only triglyceride levels were significantly different ($P = 0.025$ by Quade’s rank analysis of covariates). Other metabolic parameters were not significantly different among the three groups or between the MeDiet+NB and MeDiet-only groups.

Table 2 Changes in Nutrient Intake and Physical Activity After Intervention

Nutrient Intake	Baseline	Week 8	P value ^a
Total Calorie (kcal)	1653.8 (1308.1, 1967.0)	1386.2 (1133.0, 1614.9)	0.001
Carbohydrate (%)	54.5 (42.8, 62.3)	54.6 (47.5, 60.9)	0.519
Protein (%)	15.9 (14.2, 17.7)	15.9 (13.9, 20.2)	0.405
Total fat (%)	28.3 (22.4, 34.7)	28.4 (24.1, 35.2)	0.807
SFA (%)	5.2 (3.2, 7.2)	5.7 (4.0, 7.2)	0.967
MUFA (%)	6.5 (4.8, 9.1)	8.3 (5.6, 10.5)	0.267
PUFA (%)	8.2 (4.8, 10.7)	9.0 (4.8, 13.4)	0.332
n-3 PUFA (%)	0.43 (0.05, 0.84)	0.57 (0.12, 1.31)	0.209
n-6 PUFA (%)	2.39 (0.65, 5.13)	3.17 (0.79, 6.67)	0.212
MUFA/SFA ratio	1.24 (1.09, 1.51)	1.35 (1.13, 1.84)	0.046
PUFA/SFA ratio	1.75 (0.90, 2.45)	1.64 (1.02, 2.28)	0.832
Dietary fiber (g/1000 kcal)	13.5 (8.8, 17.9)	18.2 (11.9, 23.3)	<0.001
GLTEQ score	7.1 (2.0, 18.0)	15.8 (4.7, 30.0)	<0.001

Notes: Data are expressed as medians (interquartile ranges). ^aP values calculated by Wilcoxon’s signed-rank test.

Abbreviations: MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; GLTEQ, Godin Leisure-Time Exercise Questionnaire.

In all participants, quality of life as assessed by self-reported questionnaires improved after the intervention (Figure 3). Global health status and five functional scales, as assessed by the EORTC QLQ-C30, significantly increased after 8 weeks ($P < 0.05$ by Wilcoxon’s signed-rank test). The FACIT-F subscale also increased ($P = 0.002$) and OP scale decreased ($P = 0.031$), indicating quality of life improvements. No significant differences in quality of life were found among the groups (Online supplementary Table S3).

Safety and Tolerability

Vital signs, including blood pressure and heart rate, were in the normal or prehypertension range at baseline in all three groups (Table 1). After 8 weeks, systolic blood pressure significantly decreased in the cancer survivor MeDiet-only group and the non-cancer MeDiet+NB group ($P < 0.05$ by Wilcoxon’s signed-rank test, data not shown). Diastolic blood pressure significantly decreased only in the non-cancer patient group, and heart rate showed no significant change in all three groups. Clinical laboratory measures, including serum creatinine and liver function tests, showed no evidence of treatment-related hepatotoxicity or nephrotoxicity (data not shown).

Table 3 Changes in Body Weight, Body Composition, and Metabolic Parameters After Intervention

Parameters	Breast Cancer Survivors		Non-Cancer Patients	P value ^a	P value ^b
	MeDiet+NB	MeDiet Only	MeDiet+NB		
	(n = 14)	(n = 20)	(n = 22)		
Weight (kg)	-2.8 (-3.6, -1.9)*	-1.8 (-3.3, -0.6)*	-2.5 (-4.2, -1.8)*	0.394	0.209
BMI (kg/m ²)	-1.1 (-1.5, -0.7)*	-0.7 (-1.4, -0.2)*	-1.0 (-1.7, -0.7)*	0.404	0.212
Skeletal muscle (kg)	-0.1 (-0.8, 0.3)	-0.4 (-0.8, 0.6)	-0.2 (-1.2, 0.1)*	0.938	0.867
Fat mass (kg)	-1.7 (-3.2, -0.8)*	-1.8 (-2.7, -0.6)*	-2.3 (-3.0, -0.1)*	0.771	0.469
Fat percentage (%)	-1.4 (-3.6, 0.3)*	-1.4 (-2.7, 1.1)	-1.6 (-2.9, -0.4)*	0.623	0.393
WHR	-0.02 (-0.05, 0.01)*	-0.01 (-0.04, 0.02)	-0.01 (-0.04, -0.01)*	0.386	0.169
WBC count (no./μL)	-0.01 (-0.69, 0.78)	-0.66 (-0.94, 0.10)*	-0.01 (-0.74, 1.06)	0.503	0.241
Fasting glucose (mg/dL)	-10.0 (-18.5, -6.0)*	-7.0 (-13.0, -3.0)*	-12.0 (-15.0, -6.5)*	0.627	0.332
Insulin (μIU/mL)	-2.60 (-4.15, 0.25)*	-1.10 (-2.10, -0.10)*	-1.70 (-2.85, -0.05)*	0.467	0.455
HOMA-IR	-0.65 (-1.09, -0.13)*	-0.40 (-0.50, -0.17)*	-0.41 (-0.99, -0.14)*	0.589	0.595
Total cholesterol (mg/dL)	-23.0 (-32.5, -0.5)*	-5.0 (-23.0, 7.0)	-18.0 (-24.0, 3.5)*	0.461	0.245
Triglyceride (mg/dL)	-41.0 (-59.0, -23.0)*	-25.0 (-57.0, 8.0)*	-4.0 (-26.0, 28.0)	0.025	0.703
HDL cholesterol (mg/dL)	0.4 (-1.2, 6.2)	0.4 (-2.2, 7.8)	-0.7 (-5.0, 8.6)	0.735	0.763
LDL cholesterol (mg/dL)	-16.6 (-24.9, 5.2)	-7.7 (-17.6, 9.1)	-10.4 (-27.2, -0.2)*	0.274	0.139

Notes: Data are expressed as medians (interquartile ranges). ^aDifferences among the three groups were calculated by Quade's rank analysis of covariates, adjusted for age and initial BMI. ^bDifferences between the MeDiet+NB and MeDiet-only groups were calculated by Quade's rank analysis of covariates, adjusted for age and initial BMI. *P value <0.05 vs baseline values by Wilcoxon's signed-rank test.

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of assessment-insulin resistance; LDL, low-density lipoprotein; MeDiet, Mediterranean diet; NB, naltrexone/bupropion; WBC, white blood cell; WHR, waist-hip ratio.

Of the 51 participants who received the naltrexone and bupropion treatment, 39 participants (76%) experienced adverse effects during the trial. Nausea was the most frequent adverse effect (39%), followed by dizziness (33%), dry mouth (25%), and constipation (22%). The symptoms were mostly mild to moderate in intensity. One serious adverse effect, syncope, occurred in the non-cancer patient group, which was considered unlikely related to the study drug. Nine participants discontinued the study due to adverse effects, including nausea (10%), urticaria (4%), dizziness (2%), and syncope (2%).

Discussion

This study is the first to report the combined effect of a Mediterranean diet and naltrexone/bupropion treatment on body weight, metabolic parameters, and quality of life in breast cancer survivors who are overweight or obese, known risk factors for cancer recurrence and mortality. The 8-week interventions reduced body weights, BMI, and fat mass, while improving metabolic parameters and quality of life in all participants. However, no significant difference among the three groups was observed.

Unexpectedly, we found no additional effect of naltrexone/bupropion medication on body weight and metabolic parameters despite evidence from previous studies showing effective weight reduction with these drugs.^{28,29} This discrepancy

may be due to the low dose of naltrexone/bupropion used in this study. Unlike previous studies using the approved maximum doses of naltrexone (32 mg) and bupropion (360 mg), only half of the doses were used in this study. The open-label aspect of the study without a placebo could also be a reason. An increase in physical activity was seen in the MeDiet-only group, which could suggest that the participants in this group made more efforts to achieve lifestyle modifications because they did not take the obesity drugs.

Although this pilot study could not accurately evaluate the effectiveness of the Mediterranean diet since there was no control group without the Mediterranean diet, our results are consistent with previous randomized clinical trials demonstrating the benefits of the Mediterranean diet for body weight and metabolic parameters.^{30,31} The PREDIMED study group reported reduced fasting glucose, insulin, and insulin resistance as short-term effects on cardiovascular risk factors of the Mediterranean diet, compared to a low-fat diet,³² which is in agreement with findings obtained in our study. Monounsaturated fats from olive oil, an important component of the Mediterranean diet, have been shown to help improve glucose metabolism and insulin sensitivity, as well as increase postprandial fat oxidation.^{33,34} The effects of the Mediterranean diet on body weight and composition are attributed to a low consumption of

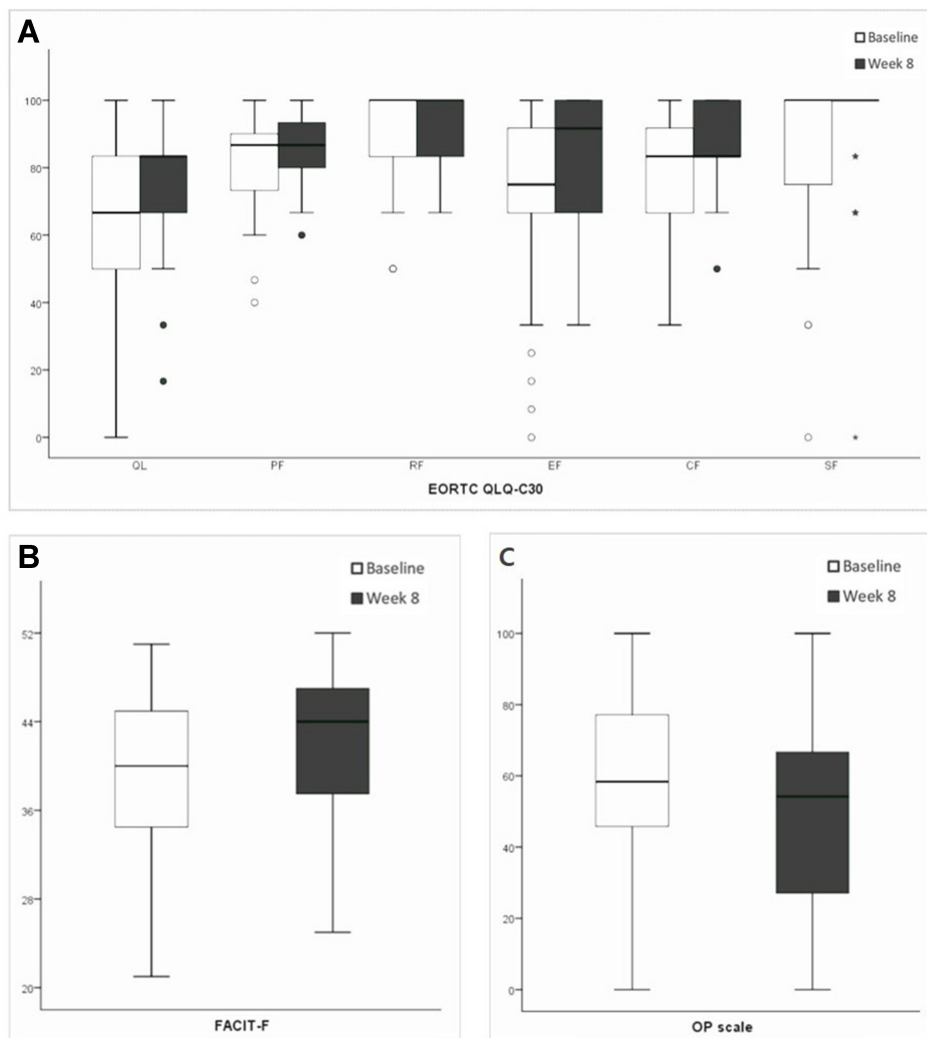


Figure 3 Changes in quality of life as assessed by questionnaires. **(A)** Global health status (QL) and five functional scales, namely, physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), and social functioning (SF), of EORTC QLQ-C30 at baseline and week 8. **(B)** FACIT-F subscale at baseline and week 8. **(C)** OP scale at baseline and week 8.

animal products and high consumption of vegetables, fruits, and legumes. This diet is not energy dense, has a low glycemic load, and has large amounts of vitamins and dietary fiber,³⁵ which was confirmed by our data.

In the present study, we also found that there were no differences in the results for breast cancer survivors and non-cancer obese people: only the dropout rate due to the adverse events of the obesity drug was higher in breast cancer survivors. This may be because the breast cancer survivors could feel more anxious about adverse events, such as nausea, than non-cancer people. To our knowledge, this is the first weight loss intervention using obesity drugs in breast cancer survivors, while the benefits of the Mediterranean diet for breast cancer patients are relatively well known. Oleic acid in olive oil has been shown to regulate oncogenes in human breast

cancer cells.³⁶ Moreover, oleocanthal, a polyphenol in olive oil, has been found to inhibit the proliferation, invasion, and growth of tumor cells in vitro and in breast cancer models in vivo.³⁷ Therefore, the Mediterranean diet appears to be helpful as a dietary intervention in breast cancer patients. Further studies about the choice of obesity drugs to breast cancer patients are warranted.

The present study has several limitations. First, the use of an 8-week intervention precluded investigations of the effectiveness of the intervention on weight maintenance or cancer recurrence. Second, we recruited non-cancer patients matched to survivors by age, not BMI. As a result, the baseline BMIs differed between groups, requiring adjustments for this factor in statistical analyses. Third, we relied on self-reported dietary intake using the

24-h dietary recall method, which may have recall bias. However, the increased monounsaturated fatty acid/saturated fatty acid ratio and dietary fiber measurements by 24-h dietary recall method were consistent with consumption of a Mediterranean diet. Finally, the rate of study discontinuation was higher than the anticipated dropout rate of 10%. Most of the participants reported dropping out due to the adverse effects of the naltrexone/bupropion medication.

Conclusions

In summary, we found that the Mediterranean diet, with or without naltrexone/bupropion treatment, facilitates weight loss, improves metabolic parameters, and increases quality of life in breast cancer survivors who are overweight or obese. The combination of the Mediterranean diet with naltrexone/bupropion treatment did not produce superior changes in outcomes when compared to the Mediterranean diet alone. Future studies should include a larger number of participants over a longer period of time to determine the effect of the Mediterranean diet on breast cancer recurrence or survival.

Abbreviations

BMI, body mass index; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; MeDiet, Mediterranean diet; NB, naltrexone/bupropion; OP, obesity-related problems; PREDIMED, Prevención con Dieta Mediterránea; WBC, white blood cell.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB number 3–2017–0097). Written informed consent was obtained from each participant before screening and data collection. All datasets intended for sharing are deidentified. All procedures

were conducted in accordance with the ethical standards of the 1975 Helsinki Declaration.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, substantially revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article will be submitted; and have agreed to take responsibility and be accountable for all aspects of the article.

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Disclosure

We declare no competing interests for this work.

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