Research Article

Cancer Epidemiology, Biomarkers & Prevention

Can Dietary and Physical Activity Modifications Reduce Breast Density in Postmenopausal Women? The DAMA Study, a Randomized Intervention Trial in Italy

Giovanna Masala[1], Melania Assedi[1], Francesco Sera[1,2], Ilaria Ermini[1], Daniela Occhini[1], Maria Castaldo[1], Elena Pierpaoli[1,3], Saverio Caini[1], Benedetta Bendinelli[1], Daniela Ambrogetti[3], and Domenico Palli[1]

Abstract

Background: Few randomized trials have been carried out to evaluate the effect of lifestyle modifications on mammographic breast density (MBD). The randomized 2 × 2 factorial Diet, physical Activity and MAmmography trial aimed to evaluate whether MBD can be reduced in postmenopausal women with high baseline MBD by a 24-month dietary and/or physical activity (PA) interventions.

Methods: We randomized healthy postmenopausal women, attending the Florence (Italy) mammographic screening program, ages 50 to 69 years, nonsmokers, with MBD > 50% and no recent hormone therapy, to (i) a dietary intervention focused on plant foods, with a low glycemic load, low in saturated fats and alcohol; (ii) a PA intervention combining daily moderate intensity activities and one weekly supervised session of more strenuous activity; (iii) both interventions; (iv) general recommendations. We evaluated changes in MBD based on Volpara estimates comparing baseline and follow-up digital mammograms by an intention-to-treat-analysis.

Results: MBD measures were available for 226 participants. An interaction emerged between treatments and thus we run analyses by arms. A decrease in volumetric percent density emerged for women in the dietary intervention (ratio 0.91; 95% CI, 0.86–0.97; $P = 0.002$) and in the PA intervention arm (0.93; 95% CI, 0.87–0.98; $P = 0.01$) in comparison with controls. No clear effect emerged in the double intervention arm.

Conclusions: This intervention trial suggests that a 24-month dietary or PA intervention may reduce MBD in postmenopausal women.

Impact: A modification of dietary habits or an increase in PA in postmenopausal women may reduce MBD. Further studies are needed to confirm these findings for planning breast cancer preventive strategies.

Introduction

Most factors that modulate breast cancer risk, including age and reproductive and family history, cannot be modified. However, potentially modifiable lifestyle risk factors have been identified as well (1, 2), suggesting specific strategies to reduce breast cancer incidence in the general female population or in subgroups at increased risk.

The extent of mammographically detected fibroglandular breast tissue, or mammographic breast density (MBD), is a strong and independent risk factor for breast cancer (3). MBD has been consistently associated with increased breast cancer risk in studies using different methods of MBD evaluation ranging from subjective evaluation by trained radiologists, to fully automated methods allowing to obtain quantitative measures of breast density, and in studies based either on films or digital mammograms (3, 4). Recent studies evaluating the association between the Breast Imaging Reporting and Data System (BI-RADS) classification of MBD, the most widely used in clinical settings, reported at least a 2-fold increase in risk in women with breast density >50% (5, 6).

Most established risk and protective factors for breast cancer act in the same direction in modulating MBD, except age and body mass index (BMI) for which associations are in the opposite direction. It is well known that MBD declines with increasing age, particularly during the menopausal transition, while BMI is inversely associated with MBD. Studies including MBD assessment should collect information on anthropometry, particularly longitudinal studies in which weight changes occur (7, 8).

MBD may be modified by hormonal aspects (9, 10) and the reduction of MBD was associated in some studies with reduced risk of breast cancer development or recurrence (10, 11, 12), thus suggesting the possibility to use MBD as a biomarker of the effect of interventions aimed to decrease breast cancer risk.

[1]Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy. [2]Department of Social and Environmental Health Research (SEHR), Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK. [3]Breast Cancer Screening Branch, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy.

Corresponding Author: Giovanna Masala, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Padiglione 28 A Mario Fiori Pontenuovo Via delle Oblate 4, Florence 50141, Italy. Phone: 39-055-7972546; Fax: 39-055-7972588; E-mail: g.masala@ispro.toscana.it

doi: 10.1158/1055-9965.EPI-18-0468

Lifestyle habits have also been investigated as possible modulators of MBD. Studies aimed to investigate the role of dietary habits and physical activity (PA) have been mostly observational, with a cross-sectional design, and have shown mixed results, possibly in relation to differences in study design, study population, timing of the exposure, and MBD assessment (13, 14).

Randomized intervention trials in which behavioral changes in dietary and PA habits are proposed to participants, with an adequate control group for comparison, can help in understanding the potential modifying effect on MBD and contribute to evaluate the role of lifestyle habits in lowering breast cancer risk. So far, few and mostly short-term intervention trials have been carried out mainly aimed to evaluate specific lifestyle aspects (15–19).

We have designed and carried out the DAMA (Diet, physical Activity and MAmmography) study, a 24-month randomized 2 × 2 factorial trial aimed at investigating whether a dietary intervention based on plant foods, with a low glycemic load, low in saturated fats and alcohol, and rich in antioxidants, and/or a PA intervention based on an increase of moderate PA levels, were able to reduce MBD in postmenopausal women with high MBD (>50%; ref. 20).

Materials and Methods

Study design and hypothesis

The DAMA study is a single-center, randomized intervention trial with a 2 × 2 factorial design (Trial Registration ID: ISRCTN28492718). We have already described the study protocol in detail (20). Briefly, the hypothesis tested in this study is that MBD can be reduced in healthy postmenopausal women with high MBD (>50%) by modifying their dietary habits and/or PA level in a 24-month intervention period.

The DAMA trial was approved by the Ethics Committee of the Local Health Authority in Florence (Italy). All study participants signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki.

Selection of study participants

We selected study participants among women attending the local screening program in Florence (21). Women potentially eligible were ages between 50 and 69 years, had a negative screening mammogram showing an MBD of 50% or more, as assessed routinely in the screening program applying the BI-RADS classification (22). We excluded from the study women selected for a second-stage diagnostic procedure after a screening mammogram, regardless of the final outcome of the diagnostic process.

Exclusion criteria included: premenopausal - or perimenopausal status (at least one menstrual cycle during past 12 months); recent (past 12 months) hormone therapy use; being a current smoker (or a former smoker for less than 6 months); a previous diagnosis of cancer (except nonmelanocytic skin cancer); diabetes or other major comorbidities, including major cardiovascular and neurologic diseases, severe hip or knee osteoarthritis, able to hamper an active participation in the study. We recruited participants between February 2009 and March 2010.

Baseline visit and randomization

Trained personnel measured weight, height, and hip and waist circumference through standardized procedures and collected information on dietary habits and lifestyle including PA using questionnaires previously used in the frame of the EPIC study (European Prospective Investigation into Cancer and Nutrition). The Food Frequency Questionnaire (FFQ), specifically validated for the Italian dietary habits, allowed to collect data on frequency of consumption of a large variety of food items and the quantity of the food consumed through the selection of an image of a food portion, or considering a standard portion when no image was provided. The consumption of alcoholic beverages was also collected (23).

The EPIC Lifestyle Questionnaire (LSQ) includes a section, aimed to assess PA at work and during leisure time, validated in *ad hoc* studies (24). PA at work was classified according to the following categories: sedentary, standing, manual, or heavy manual work. Information on leisure time activities includes recreational activities (walking, biking, and fitness activities) and household activities (hours spent in do-it-yourself activities, gardening, and house cleaning).

After completion of the baseline visit, we randomized each woman to one of the four arms of the study (diet, PA, diet + PA, control) through permuted-block randomization stratified by age (50–59 years and 60–69 years) and BMI category (<25 and $\geq$25 kg/m^2), with a constant block size ($n = 4$).

Intervention

Dietary intervention (arm 1). Each woman was asked to gradually adopt a diet mainly based on plant food, with a low glycemic load, low in saturated- and *trans*-fats and alcohol and rich in antioxidants. Overall, the aim of the intervention was to change the composition of diet in an isocaloric context (without specific advices on the quantity of food to be consumed). The intervention objectives were: (i) substitution of refined grains with wholegrains; (ii) consumption of at least one portion of raw and one portion of cooked vegetables at each meal; (iii) consumption of fish at least two to three times weekly; (iv) consumption of fresh and processed red meat reduced to less than 1 time/week considering all types; (v) at least three to four portions/week of legumes and pulses; (vi) consumption of two to three portions/day of fruit; (vii) cakes and desserts reduced to a maximum of 1 portion/week; (viii) no more than 1 portion/day of milk or yogurt and 2 portions/week of cheese, exclusion of full fat varieties; (ix) extra-virgin olive oil as the only dressing and cooking fat; (x) no more than one glass of wine per day, at meals, if already used to drink wine (20).

After an initial individual counseling, participants were requested to attend six group meetings and eight cooking classes during the 2 years of the study. The aim of both group sessions and cooking classes was to clarify the details of what was being requested from study participants and to enhance their motivation and adherence to instructions received.

PA intervention (arm 2). The aim was to increase moderate daily recreational activities up to 1 hour/day, corresponding to about 3 MET-hours/day (MET = Metabolic Equivalent) to be combined with a more strenuous activity accounting for 6 to 10 MET-hours/week. Each woman assigned to this arm discussed how to adapt requested changes in levels of PA to her lifestyle and daily schedule during an initial individual counseling session with a PA expert.

Suggested activities to be included in the daily routine were walking at moderate pace, biking, etc. We also provided some equipment for home exercises. Women were also requested to attend weekly a 1-hour session led by trained PA experts in an appropriate fitness facility (up to a maximum of 97 sessions over the 24-month period). The study protocol also included participation to six group sessions and six collective walks supervised by the study team (20).

Dietary + PA intervention (arm 3). Participants were asked to change both their dietary and PA habits by combining arm 1 and 2 protocols and activities as described above.

We requested study participants assigned to any of the intervention arms to keep five written 1-week diaries on diet (arm 1), PA (arm 2), or both (arm 3). The study personnel reviewed the diaries in order to monitor the achievement of study objectives and to discuss individually the difficulties encountered by participants.

Control group (arm 4). Women in this arm received general advices on healthy dietary and PA patterns according to the WCRF 2007 recommendations. We organized a group meeting within the first 6 months of the study and distributed *ad hoc* printed material.

Final visit

We invited all women for a visit 24 (±3) months after their enrolment into the study in the same period in which they underwent their routine screening mammographic examination. We applied the same protocol including the FFQ and the LSQ and the anthropometric measurements.

Outcome measures

The change in volumetric percent density (VPD) between baseline and the end of the study was the main outcome of the DAMA study. We planned to perform the follow-up mammogram in a specific time window (24 ± 3 months after randomization). Both baseline and follow- up mammograms were performed in the frame of the local screening program with the same digital mammography equipment (GE Senographe 2000D).

VPD was measured on the raw data from full-field digital mammograms collected in the study using the fully automated Volpara density software (version 3.1, Matakina Technology). The technical characteristics of Volpara system has already been described in detail previously (25). Briefly, the algorithm computes the thickness of dense tissue at each pixel using the X-ray attenuation of an entirely fatty region as an internal reference. The thickness values over the whole breast region are integrated to obtain the absolute dense volume (cm^3). Total breast volume (cm^3) is obtained by multiplying the breast area by the recorded breast thickness, corrected for the breast edge. VPD is then obtained from the ratio of the two measures. In the present study, we used the average VPD obtained from mediolateral oblique and craniocaudal views of the right and left breasts.

Sample size

According to the original factorial design with this sample size we estimated to be able to detect, with a two-sided 0.05 alpha level and a power of 0.90, percent MBD difference of 0.43*SD between either intervention and control groups (e.g., with a SD = 10.0%, we estimated to be able to identify a difference of 4.3%).

Statistical analyses

We compared the main characteristics of the study participants at baseline by arms, including data on dietary habits and PA habits obtained through the FFQ and LSQ, respectively, using analysis of variance (ANOVA) for quantitative variables. The χ^2 test was utilized for categorical variables.

The main outcome analysis was performed on an intention-to-treat basis. The factorial design allows evaluating separately the effect of dietary or PA intervention comparing the two groups receiving the same treatment with the two groups not receiving that treatment. Therefore, to evaluate the effect of dietary intervention, we compared subjects randomized to arms 1 and 3 versus arms 2 and 4 while we evaluated the effect of the PA intervention comparing subjects randomized to arms 2 and 3 versus arms 1 and 4.

VPD values were log transformed in order to normalize the distribution. For each treatment group, the ratio and 95% confidence intervals of follow-up VPD value in comparison with the control group were estimated through a general linear model with log-transformed follow-up VPD values as outcome, treatment groups as exposure, and the baseline mammographic VPD measure (on log scale), weight changes occurred in the intervention period, and the randomization block variables (age and BMI) as covariates.

We evaluated the presence of an interaction between the two treatments considered in the factorial design and we run a secondary analysis by arms as suggested by McAlister and others (26, 27).

We evaluated changes in selected food consumption and in PA habits between end of study and baseline between each intervention arm and control arm using questionnaire data through a general linear model analysis. The analyses were performed using SAS (SAS/STAT version 9.2).

Results

We recruited and randomized 234 women (18.4% of women selected from the screening mammographic files and 30.4% of the women defined as eligible after a specific interview). The most frequent reasons given by women who refused to participate were lack of time or lack of interest in the proposed intervention (Fig. 1).

All randomized women performed the planned screening mammogram at the end of the intervention period. The mean interval between this mammogram and the baseline mammogram was 2.2 (SD, 0.2) years. We identified both baseline and end-of-study mammograms of all women; however, for eight of them it was impossible to retrieve the raw data for the Volpara measurements due to technical problems in imaging storage system. Therefore, the present analysis is based on 226 women for which raw data of both baseline and end-of-study digital mammograms were available. For all these women, information collected at baseline and end-of-study visits were available and the mean interval between the two visits was 2.0 years (SD, 0.1).

The mean age of participants was 58.7 years (SD 5.2), with 42% reporting a high school degree. Most participants were never smokers and with a BMI <25. Among women with a paid work (57.5%) most reported a sedentary work. Approximately 69% reported to have never used hormone therapy (Table 1).

The randomized groups were similar at baseline for these and other listed variables including those related to dietary and PA

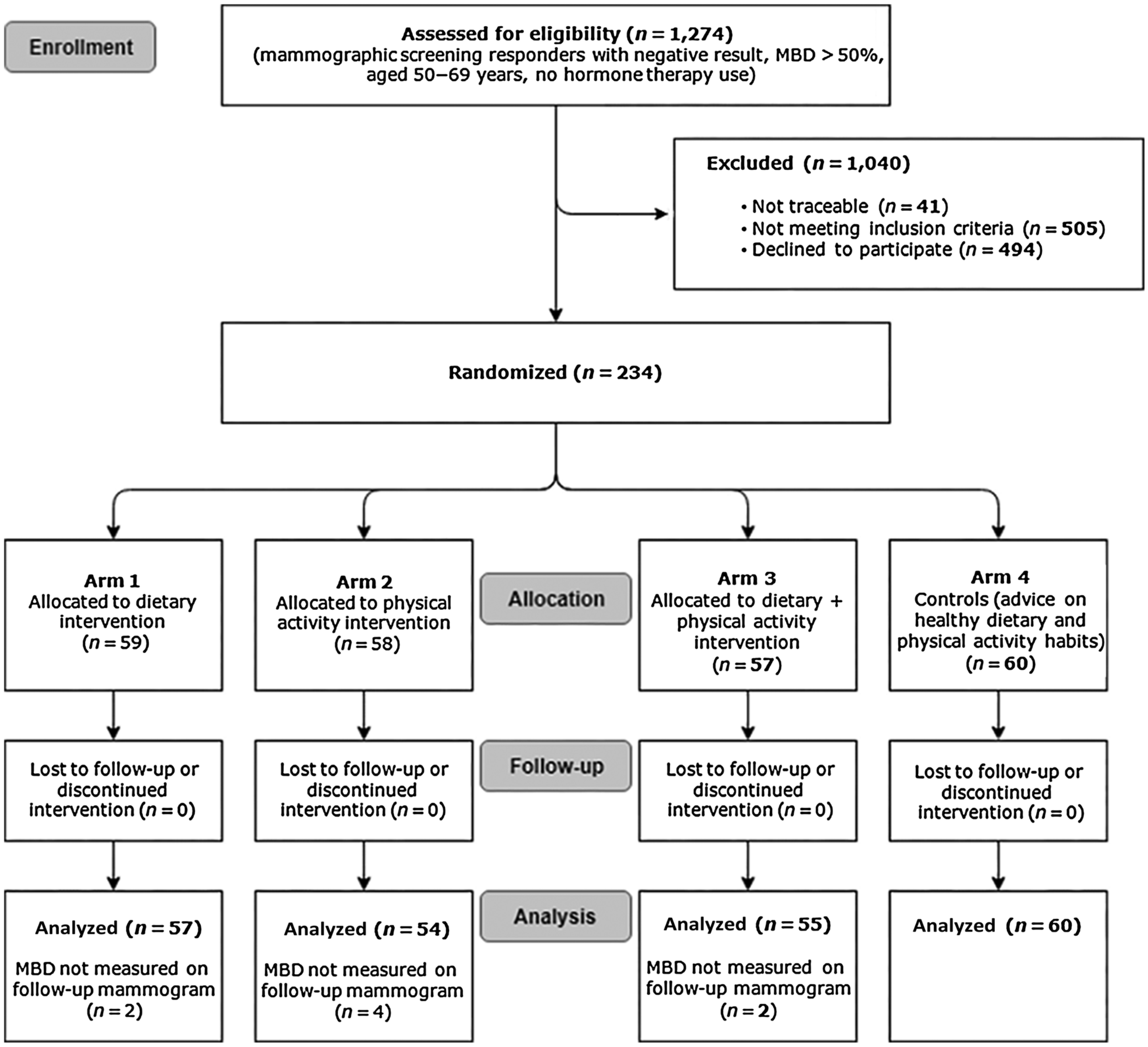

Figure 1.
Recruitment of participants, randomization, and follow-up in the DAMA intervention trial. CONSORT flow diagram showing procedures of selection among eligible women and participants with complete data available.

habits at baseline except some differences in reported consumption of a few selected items (cheese and cakes).

Based on data obtained in the baseline and final visits, we first evaluated if any change in weight, potentially affecting breast density measures, occurred. Overall participants experienced an average weight loss of approximately 0.38 kg (SD, 2.9); the weight loss was more evident in the PA + dietary intervention arm (0.54 kg; SD, 2.6) and less evident in the control arm (0.20 kg; SD, 2.6). However, no significant differences between arms emerged.

At baseline, 202 women (89.3%) were classified in BI-RADS category 3 (51%–75% fibroglandular tissue) and 24 (10.7%) in BI-RADS category 4 (>75% fibroglandular tissue) by the local screening radiologists. No differences in BI-RADS classification distribution emerged by arms ($P = 0.39$). Overall, the median VPD at baseline automatically estimated through Volpara software was 14.0% (IQ 10.3–18.9) and the mean was 15.0% (SD, 5.6). No significant differences emerged by arms, although we observed a lower mean VPD value in women randomized to the double intervention arm (mean, 13.9%; SD, 5.8).

Main outcome results

Analyses by the two main treatments showed no statistically significant effect, although there was some evidence of a modest reduction in VPD. However, a clear interaction between the two treatments emerged ($P = 0.01$), supporting the need for analyses by single arms. In Fig. 2, we show the unadjusted geometric means of VPD in each arm at baseline and follow-up. We observed a percent reduction in VPD measured in follow-up mammograms

Table 1. Distribution (categorical variables) or mean and standard deviation (continuous variables) at baseline of selected characteristic, dietary, and PA habits of participants, overall and by study arm (the DAMA intervention trial, Florence, Italy)

		Study arm				
	Whole study sample ($n = 226$)	**Diet ($n = 57$)**	**PA ($n = 54$)**	**Diet + PA ($n = 55$)**	**Control group ($n = 60$)**	P^a
Level of education						
None/primary school	64 (28.3%)	18 (31.6%)	15 (27.8%)	12 (21.8%)	19 (31.7%)	
High school	96 (42.5%)	25 (43.9%)	24 (44.4%)	24 (43.6%)	23 (38.3%)	
University	66 (29.2%)	14 (24.5%)	15 (27.8%)	19 (34.6%)	18 (30.0%)	0.85
Smoking						
Former	98 (43.4%)	25 (43.9%)	23 (42.6%)	28 (50.9%)	22 (36.7%)	
Never	128 (56.6%)	32 (56.1%)	31 (57.4%)	27 (49.1%)	38 (63.3%)	0.48
General characteristics						
Age (years)	58.7 (5.2)	58.6 (5.6)	58.6 (4.7)	58.8 (5.1)	58.8 (5.4)	0.99
Height (cm)	159.2 (9.4)	159.2 (6.6)	159.5 (5.6)	159.5 (4.8)	158.5 (7.1)	0.77
Weight (kg)	61.9 (9.5)	62.1 (8.2)	62.9 (9.7)	63.0 (10.6)	60.0 (9.2)	0.29
BMI (kg/m^2)	24.4 (3.5)	24.5 (3.1)	24.8 (4.0)	24.6 (3.1)	24.7 (3.2)	0.57
BMI (groups)						
<25	142(62.8%)	35 (61.4%)	34 (63.0%)	36 (65.5%)	37 (61.7%)	
≥25	84 (37.2%)	22 (38.6%)	20 (37.0%)	19 (34.5%)	23 (38.3%)	0.97
Waist circumference (cm)	76.6 (7.7)	77.4 (7.1)	77.7 (7.9)	76.4 (7.6)	75.6 (8.0)	0.44
Waist circumference (groups)						
<88	207 (91.6%)	54 (94.7%)	48 (88.9%)	50 (90.9%)	55 (91.7%)	
≥88	19 (8.4%)	3 (5.3%)	6 (11.1%)	5 (9.1%)	5 (8.3%)	0.73
Hormonal and reproductive history						
Hormone therapy use						
Never	157 (69.5%)	43 (75.4%)	36 (66.7%)	34 (61.8%)	44 (73.3%)	
Ever	69 (30.5%)	14 (24.6%)	18 (33.3%)	21 (38.2%)	16 (26.7%)	0.38
Contraceptive pill use						
Never	102 (45.1%)	30 (52.6%)	20 (37.0%)	23 (41.8%)	29 (48.3%)	
Ever	124 (54.9%)	27 (47.4%)	34 (63.0%)	32 (58.2%)	31 (51.7%)	0.36
Number of children						
0	39 (17.3%)	13 (22.8%)	10 (18.5%)	8 (14.5%)	8 (13.3%)	
1	92 (40.7%)	20 (35.1%)	19 (35.2%)	30 (54.5%)	23 (38.3%)	
2+	95 (42.0%)	24 (42.1%)	25 (46.3%)	17 (31.0%)	29 (48.3%)	0.20
Breastfeeding						
Never	37 (19.8)	12 (27.3)	6 (13.6)	10 (21.3)	9 (17.3)	
Ever	150 (80.2)	32 (72.7)	38 (86.4)	37 (78.7)	43 (82.7)	0.41
Age at first child (years)	28 (5.1)	27 (3.9)	27 (5.7)	28 (5.4)	28 (5.3)	0.65
Age at menarche (years)	12.5 (1.4)	12.4 (1.4)	12.3 (1.2)	12.5 (1.6)	12.9 (1.4)	0.09
Age at menopause (years)	49.9 (4.1)	49.6 (4.7)	50.4 (3.2)	50.3 (3.2)	49.3 (4.8)	0.45
Diet						
Total vegetables (g/day)	198.5 (94.5)	188.6 (70.7)	203.8 (110.0)	203.3 (81.6)	198.9 (110.4)	0.82
Leafy vegetables (g/day)	35.5 (22.1)	35.3 (22.0)	35.8 (27.2)	33.1 (17.0)	37.7 (21.5)	0.74
Fruit (g/day)	328.4 (168.3)	298.9 (154.5)	324.4 (143.8)	329.2 (158.7)	359.4 (204.8)	0.28
Nuts, seeds, and dried fruit (g/day)	2.6 (4.2)	2.2 (4.0)	2.8 (4.0)	2.9 (5.3)	2.4 (3.4)	0.77
Legumes (g/day)	19.2 (14.6)	20.1 (19.4)	15.1 (11.1)	21.3 (14.5)	20.1 (11.4)	0.12
Red and processed meat (g/day)	77.1 (43.2)	74.7 (36.8)	85.3 (53.6)	74.8 (38.9)	74.1 (42.2)	0.47
Cheese (g/day)	45.8 (34.2)	38.9 (22.8)	42.6 (25.1)	58.2 (43.1)	43.8 (38.7)	0.02
Cakes and cookies (g/day)	41.7 (50.1)	31.5 (40.3)	39.5 (35.6)	61.4 (74.1)	35.3 (36.8)	0.01
Wine (g/day)	73.9 (100.2)	77.6 (104.3)	67.0 (97.2)	69.5 (95.2)	80.5 (105.4)	0.87
Extra-virgin olive oil (g/day)	27.5 (12.9)	26.2 (9.6)	29.2 (14.0)	27.5 (11.8)	27.3 (15.4)	0.67
Kcal	2,065.5 (635.5)	1,925.4 (506.3)	2,068.0 (650.1)	2,226.5 (753.1)	2,048.6 (595.7)	0.09
PA levels						
Nonoccupational PA[b] (MET-hours/week)	89.2 (46.2)	83 (37.3)	85.7 (48.4)	90.4 (49.7)	97.0 (48.4)	0.38
Household PA (MET- hours/week)	63.1 (40.3)	59.2 (34.5)	60.5 (42.2)	64.8 (44.6)	67.7 (40.0)	0.65
Recreational PA (MET-hours-week)	26.0 (20.2)	23.8 (15.4)	25.2 (20.4)	25.6 (18.9)	29.3 (24.6)	0.50
At work (N)	130 (57.5%)	34 (59.6%)	32 (59.2%)	31 (56.4%)	33 (55.0%)	0.96
PA at work						0.61
Sedentary	79 (60.8%)	24 (70.6%)	18 (56.2%)	20 (64.5%)	17 (51.5%)	
Standing	34 (26.1%)	6 (17.6%)	10 (31.3%)	7 (22.6%)	11 (33.3%)	
Manual	17 (13.1%)	4 (11.8%)	4 (12.5%)	4 (12.9%)	5 (15.2%)	
Total PA index[c]						0.74
Inactive	60 (26.5%)	19 (33.3%)	15 (27.8%)	16 (29.1%)	10 (16.7%)	
Moderate inactive	57 (25.2%)	11 (19.3%)	12 (22.2%)	15 (27.3%)	19 (31.7%)	
Moderate active	91 (40.3%)	22 (38.6%)	23 (42.6%)	20 (36.4%)	26 (43.3%)	
Active	18 (8.0%)	5 (8.8%)	4 (7.4%)	4 (7.3%)	5 (8.3%)	

[a] *P* values were calculated from GLM for continuous variables and from χ^2 test for categorical variables.
[b] Including household and recreational activities.
[c] The total PA index is categorized into four levels based on a cross-tabulation of occupational activity by the combined household and recreational activities in quartiles.

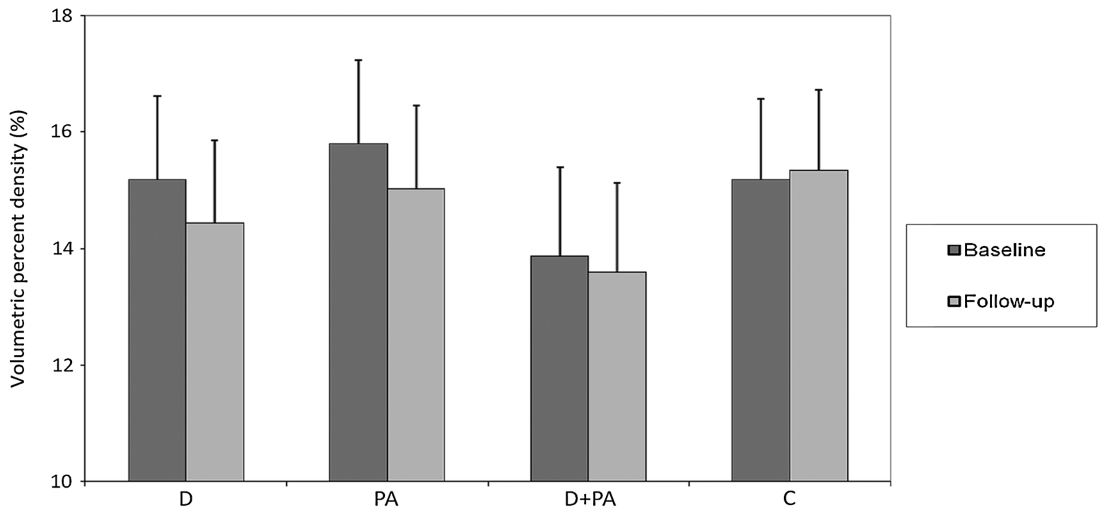

Figure 2.
The main outcome in the DAMA trial. Geometric mean (+ SD) of VPD measured at baseline and follow-up mammographic examination in women randomized to dietary (D), physical activity (PA), and double intervention arms (D + PA) and in controls (C).

in comparison with baseline in the dietary and in the PA intervention arms (4.7% and 5.1%, respectively; see also Table 2).

When analyses were carried out in comparison with the control arm by a model including terms for baseline VPD log-transformed, weight changes occurred in the intervention period and the randomization block variables (age and BMI) as covariates, a VPD reduction of approximately 9% for the dietary (ratio 0.91; 95% CI, 0.86–0.97; $P = 0.003$) and of 7% for the PA arm (ratio 0.93; 95% CI, 0.87–0.98; $P = 0.01$) emerged. Women in the PA + diet arm showed a lower reduction in VPD ($P = 0.08$; Table 2).

No adverse effects related to the intervention protocols were reported.

Compliance with the proposed interventions

The changes in reported dietary and PA habits are shown in Table 3. An increase in vegetable and legumes consumption and a decrease in red meat and cakes consumption emerged in arms 1 and 3 in comparison with the control group. We also found an increase in reported hours/ week of all recreational activities, particularly walking and fitness activities in both arms 2 and 3 in comparison with the controls. We performed an evaluation of the adherence to the protocol activities by arms. We observed a reduced participation to the supervised PA weekly sessions among women randomized to the double intervention arm in comparison with women randomized to the PA arm (45.7% vs. 57.3%; $P = 0.02$). No statistically significant differences emerged in participation to all other protocol activities, although, overall, participation of women randomized to the double intervention arm was lower in comparison with those in the single intervention arms.

Discussion

In this randomized factorial trial aimed to investigate the effect of a 24-month dietary and/or PA intervention in reducing breast density in healthy postmenopausal women with baseline high breast density, we did not find a significant effect of the two main treatments. When we considered the effects by single arms, a significant reduction in VPD measures clearly emerged in women randomized to the dietary intervention and in women randomized to the PA intervention. Overall, our results suggest that, in comparison with the control group, the women randomized to the dietary or the PA intervention arm experienced a reduction in VPD between 9% and 7%. In contrast, in women randomized to the double dietary and PA interventions the reduction was lower and failed to reach the statistical significance.

Table 2. Analysis according to single intervention arms compared with control arm (the DAMA intervention trial, Florence, Italy)

Volumetric percent density	Dietary intervention arm $n = 57$ Geometric mean (95 % CI)	PA intervention arm $n = 54$ Geometric mean (95% CI)	Dietary and PA intervention arm $n = 55$ Geometric mean (95% CI)	General recommendations (control) arm $n = 60$ Geometric mean (95% CI)
Baseline	15.22 (13.85–16.74)	15.83 (14.41–17.38)	13.87 (12.47–15.42)	15.20 (13.86–16.68)
Follow-up (at 24 months)	14.51 (13.14–16.02)	15.01 (13.61–16.57)	13.64 (12.26–15.19)	15.35 (14.01–16.82)
Follow-up adjusted[a]	13.54 (12.94–14.18)	13.76 (13.14–14.41)	14.06 (13.41–14.73)	14.84 (14.24–15.47)
Ratio[b] (95% CI)	0.91 (0.86–0.97)	0.93 (0.87–0.98)	0.95 (0.89–1.00)	1
P	$P = 0.003$	$P = 0.01$	$P = 0.08$	—

[a]Adjusted for weight change, VPD log-transformed at baseline, randomization block variables.
[b]Ratio of the adjusted geometric means at follow-up.

Table 3. Estimated changes in consumption of selected food (g/day) and kilocalories and in leisure time PA (MET-hours/week) at the end of the intervention in comparison to baseline by arms (the DAMA intervention trial, Florence, Italy)

	Diet ($n = 57$)		PA ($n = 54$)		Diet + PA ($n = 55$)		Control group ($n = 60$)
	Absolute difference (%)	P^a	Absolute difference (%)	P	Absolute difference (%)	P	Absolute difference (%)
Food groups (g/day)							
Total vegetables	40.0 (21.2)	0.06	−14.7 (−7.2)	0.17	45.8 (22.5)	0.01	8.7 (4.4)
Leafy vegetables	8.8 (24.9)	0.29	1.9 (5.3)	0.63	14.6 (44.1)	0.02	4.1 (10.9)
Fresh fruit	24.8 (8.3)	0.72	13.9 (4.3)	0.70	−20.8 (6.3)	0.39	−12.0 (3.3)
Nuts, seeds, and dried fruit	2.9 (131.8)	0.16	−0.1 (3.6)	0.12	1.9 (65.5)	0.73	1.5 (62.5)
Legumes	19.8 (98.5)	<0.0001	4.5 (29.8)	0.94	14.3 (67.1)	0.0008	2.0 (10.0)
Red and processed meat	−41.6 (55.7)	<0.0001	−26.2 (30.7)	0.49	−43.2 (57.8)	<0.0001	−20.5 (27.7)
Cheese	−13.3 (34.2)	0.40	−8.3 (19.5)	0.98	−21.4 (36.8)	0.03	−8.2 (18.7)
Cakes and cookies	−13.4 (42.5)	0.006	−8.4 (21.3)	0.04	−32.6 (53.1)	0.004	17.9 (50.7)
Wine	−13.6 (17.5)	0.25	0.2 (0.3)	0.60	−21.6 (31.1)	0.02	−4.4 (5.5)
Extra-virgin olive oil	4.6 (17.5)	0.22	−2.9 (9.9)	0.10	4.3 (15.6)	0.16	1.4 (5.1)
Kilocalories	−162.6 (8.4)	0.10	−107.1 (5.2)	0.27	−294.6 (13.2)	0.005	12.3 (0.6)
Leisure time physical activity (MET-hours-week)							
Overall leisure time PA	2.9 (4.3)	0.44	10.4 (12.0)	0.09	16.9 (18.7)	0.01	−3.0 (3.1)
Household PA	2.1 (3.5)	0.27	−1.4 (2.3)	0.63	2.4 (3.7)	0.26	−4.3 (6.3)
Recreational PA	0.8 (3.4)	0.89	11.8 (46.8)	0.01	14.5 (56.6)	0.002	1.3 (4.4)

[a]P values were calculated from GLM comparing each intervention arm with the control arm.

Studies on the modulating effects of diet and PA on breast density have been mostly observational and results are mixed. Some studies suggested positive associations with high intake of saturated fatty acids (28, 29), proteins and carbohydrates (30, 31), alcohol (32–35), consumption of sweet foods (36), and with the adherence to a Western-style diet (37). An inverse association with fiber and carotenoids (28), vitamin D, and calcium (38, 35) emerged in some studies, but these findings were not confirmed by others (39–42). Some studies reported an inverse association with an increasing level of recreational activities (43–45)′ but others studies did not (35, 46, 47). We have previously reported the results of a longitudinal study of 1,600 healthy women, carried out in the frame of the EPIC Florence cohort, showing that a low alcohol intake and a diet with a low glycemic load, rich in vegetables, olive oil as dressing fat (48, 49) and a moderate PA (50) were associated with a lower mammographic density pattern in a negative mammogram obtained 5 years after the assessment of lifestyle habits.

To the best of our knowledge, only one trial evaluated the effect of a PA intervention in postmenopausal women on breast density. In the ALPHA trial, a parallel group randomized trial, sedentary postmenopausal women ($n = 320$) were randomized to aerobic exercise (45 minutes at 70%–80% heart rate reserve, 5 days per week) or to a control group requested to maintain the usual PA level for 1 year. The intervention included both facility-based and home-based sessions. Overall, moderate to intense aerobic activities were proposed. Changes in breast density measures, assessed in digitized mammograms obtained at baseline and 1 year after, were not significantly different between the two groups (15). In the ALPHA trial, the intervention appeared to be more structured, with more intense activity sessions and quite strictly monitored, while in our study women were invited to specific supervised session 1 hour/week and were requested to perform at least 1 hour/day of moderate intensity activity without supervision, with group walks and periodic diaries. Additional differences with our study also include selected characteristics of the study populations, the duration of intervention period and different methods to assess breast density.

Trials aimed to evaluate the effect of dietary modification on MBD in postmenopausal women are scanty and mostly aimed to evaluate the effect of specific foods or food components rather than to evaluate the effect of a more comprehensive modification of dietary pattern. Randomized trials aimed to evaluate the effect of supplementation of soy isoflavones (16–18) did not find any effect on various MBD measures in postmenopausal women. No effect on MBD emerged in a recently published randomized double-blind placebo-controlled trial aimed to evaluate the effect of a green tea extract in healthy postmenopausal women with high MBD at baseline, although in younger women (50–55 years) randomized to the green tea extract supplementation arm, there was some evidence of a reduction in MBD (19).

The effect of a 2-year low-fat and high-carbohydrate diet in an isocaloric context in comparison with the usual American diet was evaluated in a multicenter randomized trial involving healthy women participating to mammographic screening programs with a radiologic breast density in more than 50% of the breast area. A reduction in the area of density emerged and was particularly evident in women in menopause transition (51).

We carried out a dietary intervention aimed to a modification of diet informed by updated recommendations for the prevention of cancer, providing indication on food choices and frequency of consumption. It is difficult to compare our study to the previously described studies, although basically our intervention pointed to reduce animal fats and proteins, to increase the consumption of foods rich of antioxidants and fiber, and to replace highly refined carbohydrate-based foods with wholegrain products.

Although we supported an isocaloric change in diet focusing on quality rather than on quantity of foods and the PA intervention was based mainly on moderate activities, participants experienced some weight reduction, more evident in the intervention groups. Being aware of the possible effect of changes in weight on MBD measures, although the entity of these changes was not significantly different between arms, we adjusted for individual change.

Although we observed a reduction in VPD in both dietary and PA single intervention arms, we found only a modest reduction in VPD in the double intervention arm. Overall, these findings emerged as an interaction between the two treatments, thus supporting the need of an analysis by arms (26, 27). Although we cannot exclude the role of chance, it is also possible that the heavier involvement requested to women randomized to the double PA and dietary intervention arm might have resulted in a reduced adherence to the protocols as suggested by the lower attendance to the weekly fitness supervised session among these women in comparison with women randomized to the PA intervention arm. Another aspect to be considered is that in the double intervention arm, weight loss tended to be more pronounced, and this aspect might have spuriously affected VPD measures.

Strengths of the DAMA trial include an approach aimed to obtain a general modification of dietary and PA habits in the daily life for a relatively long period through practical activities, group meetings and individual counseling. We monitored the compliance of participants, although the use of self-reported dietary and PA information represents a limit of this study in comparison to more objective measures.

Our trial targeted postmenopausal women enrolled from the local mammographic screening program, a well-known and long-standing organized program, thus ensuring high quality and comparability of mammograms (21). The evaluation of MBD assessed on digital mammograms through an automated software is an additional characteristics of this trial in comparison with others published so far in the same field.

High breast density is an established risk factor for breast cancer. MBD has been considered as a possible intermediate endpoint in randomized trials aimed to evaluate the efficacy of specific interventions aimed to reduce breast cancer risk.

In the case–control study nested in the IBIS-I chemoprevention trial women on tamoxifen who experienced a 10% or greater reduction in percent breast density in 12 to 18 months have a 63% reduction in breast cancer risk (10). Studies in breast cancer patients on endocrine therapies suggested an effect on specific mortality and recurrence rates for MBD reductions ranging from approximately 10% to more than 20% (11, 12, 52). Notably, all the studies previously cited used two-dimensional MBD measures based on film mammograms, while we used volumetric breast density measures based on digital examinations. These measures were obtained on different scales and therefore comparisons are difficult. A recent observational study in breast cancer patients showed an association between endocrine therapies and reduction on digitally obtained volumetric breast density (53) but no data are available so far, on the magnitude of the effect with a prognostic significance.

A better understanding of MBD determinants might provide insight into the pathogenesis of breast cancer and clues to develop strategies for primary prevention, focused on high-MBD groups easily identifiable in large-scale mammographic screening programs. On the other hand, less than 40% of eligible women accepted to participate, thus suggesting caution in generalization of results and supporting the need of further research on strategies for sustainable lifestyle modifications programs. The DAMA trial suggests a potential effect of PA and dietary intervention in reducing MBD, while results related to the combined application of both strategies are less clear. Larger studies are needed to confirm these findings in order to better clarify the role of MBD in the complex pathway leading to breast cancer and the possible role of monitoring MBD in primary prevention programs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G. Masala, F. Sera, D. Palli
Development of methodology: G. Masala, F. Sera, S. Caini
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I. Ermini, D. Occhini, M. Castaldo, E. Pierpaoli, S. Caini, B. Bendinelli, D. Ambrogetti, D. Palli
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Masala, M. Assedi, F. Sera, E. Pierpaoli, D. Palli
Writing, review, and/or revision of the manuscript: G. Masala, M. Assedi, F. Sera, I. Ermini, D. Occhini, M. Castaldo, E. Pierpaoli, S. Caini, B. Bendinelli, D. Ambrogetti, D. Palli
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Assedi, S. Caini, D. Ambrogetti
Study supervision: G. Masala, D. Palli

Acknowledgments

The DAMA trial has been funded by the Istituto Toscano Tumori–ITT (grant 2009–2012 to G. Masala, supporting M. Castaldo and D. Occhini), the Ministry of Health (Programma Integrato Oncologia 2006 coordinated by D. Palli) and Associazione Italiana per la Ricerca contro il Cancro (AIRC) Milan, Italy (IG-2015 to D. Palli, supporting E. Pierpaoli, S. Caini, and B. Bendinelli).

The authors wish to thank all the participants of the DAMA trial and all the staff personnel involved in the different phases of the study. The technicians and all other personnel of the Florence mammographic screening are acknowledged for their collaboration. Members and volunteers of a Florence consumers cooperative (UNICOOP) are also acknowledged for their support to the study cooking activities.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 27, 2018; revised July 6, 2018; accepted July 27, 2018; published first August 1, 2018.

References

1. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. AICR, Washington, DC, 2007.
2. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer. 2017. Available at: wcrf.org/breast-cancer–2017.
3. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1159–69.
4. Eng A, Gallant Z, Sherpherd J, McCormack V, Li J, Dowsett M, et al. Digital mammographic density and breast cancer risk: a case control study of six alternative density assessment methods. Breast Cancer Res 2014;16:349.
5. Olson JE, Sellers TA, Scott CG, Schueler BA, Brandt KR, Serie DJ, et al. The influence of mammogram acquisition on the mammographic density and breast cancer association in the Mayo Mammography Health Study cohort. Breast Cancer Res 2012;14:R147.
6. Masala G, Ambrogetti D, Assedi M, Bendinelli B, Caini S, Palli D. Mammographic breast density and breast cancer risk in a Mediterranean

population: a nested case-control study in the EPIC Florence cohort. Breast Cancer Res Treat 2017;164:467–73.
7. Hart V, Reeves KW, Sturgeon SR, Reich NG, Sievert LL, Kerlikowske K, et al. The effect of change in body mass index on volumetric measures of mammographic density. Cancer Epidemiol Biomarkers Prev 2015;24: 1724–30.
8. Soguel L, Durocher F, Tchernof A, Adiposity DC. Breast density, and breast cancer risk: epidemiological and biological considerations. Eur J Cancer Prev 2017;26:511–20.
9. Byrne C, Ursin G, Martin CF, Peck JD, Cole EB, Zeng D, et al. Mammographic density change with estrogen and progestin therapy and breast cancer risk. J Natl Cancer Inst 2017;109(9). doi: 10.1093/jnci/djx001.
10. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst 2011;103: 744–52.
11. Nyante SJ, Sherman ME, Pfeiffer RM, Berrington de Gonzalez A, Brinton LA, Bowles EJ, et al. Longitudinal change in mammographic density among ER-positive breast cancer patients using tamoxifen. Cancer Epidemiol Biomarkers Prev 2016;25:212–6.
12. Li J, Humphreys K, Eriksson L, Edgren G, Czene K, Hall P. Mammographic density reduction is a prognostic marker of response to adjuvant tamoxifen therapy in postmenopausal patients with breast cancer. J Clin Oncol 2013;31:2249–56.
13. Yaghjyan L, Colditz GA, Wolin K. Physical activity and mammographic breast density: a systematic review. Breast Cancer Res Treat 2012;135: 367–80.
14. Ziembicki S, Zhu J, Tse E, Martin LJ, Minkin S, Boyd NF. The association between alcohol consumption and breast density: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2017;26:170–78.
15. Woolcott CG, Courneya KS, Boyd NF, Yaffe MJ, Terry T, McTiernan A, et al. Mammographic density change with 1 year of aerobic exercise among postmenopausal women: a randomized controlled trial. Cancer Epidemiol Biomarkers Prev 2010;19:1112–21.
16. Maskarinec G, Verheus M, Steinberg FM, Amato P, Cramer MK, Lewis RD, et al. Various doses of soy isoflavones do not modify mammographic density in postmenopausal women. J Nutr 2009;139:981–6.
17. Delmanto A, Nahas-Neto J, Traiman P, Uemura G, Pessoa EC, Nahas EA. Effects of soy isoflavones on mammographic density and breast parenchyma in postmenopausal women: a randomized, double-blind, placebo-controlled clinical trial. Menopause 2013;20:1049–54.
18. Verheus M, van Gils CH, Kreijkamp-Kaspers S, Kok L, Peeters PH, Grobbee DE, et al. Soy protein containing isoflavones and mammographic density in a randomized controlled trial in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2008;17:2632–8.
19. Samavat H, Ursin G, Emory TH, Lee E, Wang R, Torkelson CJ, et al. A randomized controlled trial of green tea extract supplementation and mammographic density in postmenopausal women at increased risk of breast cancer. Cancer Prev Res 2017;10:710–18.
20. Masala G, Assedi M, Caini S, Ermini I, Occhini D, Castaldo M, et al. The DAMA trial: a diet and physical activity intervention trial to reduce mammographic breast density in postmenopausal women in Tuscany, Italy. Study protocol and baseline characteristics. Tumori 2014;100:377–85.
21. Giorgi D, Ambrogetti D, Bianchi S, Catarzi S, Ciatto S, Morrone D, et al. Design and preliminary results of the Florence breast cancer screening programme (Progetto Firenze Donna). Eur J Cancer Prev 1994;3:29–34.
22. American College of Radiology. Breast Imaging Reporting and Data System (BI-RADS®). 4th ed. Reston, VA: American College of Radiology; 2003.
23. Palli D, Berrino F, Vineis P, Tumino R, Panico S, Saieva C, et al. A molecular epidemiology project on diet and cancer: the EPIC-Italy prospective study. Design and baseline characteristics of participants. Tumori 2003;89:586–93.
24. InterAct Consortium, Peters T, Brage S, Westgate K, Franks PW, Gradmark A, et al. Validity of a short questionnaire to assess physical activity in 10 European countries. Eur J Epidemiol 2012;27:15–25.
25. Highnam R, Brady M, Yaffe M, Karssemeijer N, Harvey J. Robust breast composition measures—VolparaTM. In: Martí J, Oliver A, Freixenet J, Martí R, editors. Lecture Notes in Computer Science: 10th International Workshop on Digital Mammography; 2010 Jun 16–18; Girona, Spain: Springer-Verlag; 2010. p. 651–8.
26. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. JAMA 2003;289:2545–53.
27. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. BMC Med Res Methodol 2003;3:26.
28. Brisson J, Verreault R, Morrison AS, Tennina S, Meyer F. Diet, mammographic features of breast tissue, and breast cancer risk. Am J Epidemiol 1989;130:14–24.
29. Nagata C, Matsubara T, Fujita H, Nagao Y, Shibuya C, Kashiki Y, et al. Associations of mammographic density with dietary factors in Japanese women. Cancer Epidemiol Biomarkers Prev 2005;14:2877–80.
30. Sala E, Warren R, Duffy S, Welch A, Luben R, Day N. High risk mammographic parenchymal patterns and diet: a case-control study. Br J Cancer 2000;83:121–26.
31. Tseng M, Byrne C, Evers KA, Daly MB. Dietary intake and breast density in high-risk women: a cross-sectional study. Breast Cancer Res 2007;9:R72.
32. Cabanes A, Pastor-Barriuso R, García-López M, Pedraz-Pingarrón C, Sánchez-Contador C, Vázquez Carrete JA, et al. DDM-Spain: alcohol, tobacco, and mammographic density: a population-based study. Breast Cancer Res Treat 2011;129:135–47.
33. Flom JD, Ferris JS, Tehranifar P, Terry MB. Alcohol intake over the life course and mammographic density. Breast Cancer Res Treat 2009;117: 643–51.
34. Castelló A, Prieto L, Ederra M, Salas-Trejo D, Vidal C, Sánchez-Contador C, et al. DDM-Spain research group. Association between the adherence to the international guidelines for cancer prevention and mammographic density. PLoS One 2015;10:e0132684.
35. Brand JS, Czene K, Eriksson L, Trinh T, Bhoo-Pathy N, Hall P, et al. Influence of lifestyle factors on mammographic density in postmenopausal women. PLoS One 2013;8:e81876.
36. Duchaine CS, Dumas I, Diorio C. Consumption of sweet foods and mammographic breast density: a cross-sectional study. BMC Public Health 2014;14:554.
37. Castelló A, Ascunce N, Salas-Trejo D, Vidal C, Sanchez-Contador C, Santamariña C, et al. Association between western and mediterranean dietary patterns and mammographic density. Obstet Gynecol 2016;128: 574–81.
38. Bérubé S, Diorio C, Verhoek-Oftedahl W, Brisson J. Vitamin D, calcium, and mammographic breast densities. Cancer Epidemiol Biomarkers Prev 2004;13:1466–72.
39. Bertone-Johnson ER, Chlebowski RT, Manson JE, Wactawski-Wende J, Aragaki AK, Tamimi RM, et al. Dietary vitamin D and calcium intake and mammographic density in postmenopausal women. Menopause 2010;17: 1152–60.
40. Qureshi SA, Couto E, Hilsen M, Hofvind S, Wu AH, Ursin G. Mammographic density and intake of selected nutrients and vitamins in Norwegian women. Nutr Cancer 2011;63:1011–20.
41. Tamburrini AL, Woolcott CG, Boyd NF, Yaffe MJ, Terry T, Yasui Y, et al. Associations between mammographic density and serum and dietary cholesterol. Breast Cancer Res Treat 2011;125:181–89.
42. Qureshi SA, Couto E, Hofvind S, Wu AH, Ursin G. Alcohol intake and mammographic density in postmenopausal Norwegian women. Breast Cancer Res Treat 2012;131:993–1002.
43. Marmara EA, Papacharalambous XN, Koulolias VE, Maridaki DM, Baltopoulos JP. Physical activity and mammographic parenchymal patterns among Greek postmenopausal women. Maturitas 2011;69:74–80.
44. Oestreicher N, Capra A, Bromberger J, Butler LM, Crandall CJ, Gold EB, et al. Physical activity and mammographic density in a cohort of midlife women. Med Sci Sports Exerc 2008;40:451–56.
45. Trinh T, Eriksson M, Darabi H, Bonn SE, Brand JS, Cuzick J, et al. Background risk of breast cancer and the association between physical activity and mammographic density. Breast Cancer Res 2015;17:50.
46. Conroy SM, Butler LM, Harvey D, Gold EB, Sternfeld B, Oestreicher N, et al. Physical activity and change in mammographic density: the Study of Women's Health Across the Nation. Am J Epidemiol 2010;171:960–68.
47. Reeves KW, Gierach GL, Modeugno F. Recreational physical activity and mammographic breast density characteristics. Cancer Epidemiol Biomarkers Prev 2007;6:934–42.
48. Masala G, Ambrogetti D, Assedi M, Giorgi D, Del Turco MR, Palli D. Dietary and lifestyle determinants of mammographic breast density. A longitudinal study in a Mediterranean population. Int J Cancer 2006; 118:1782–89.

49. Masala G, Assedi M, Bendinelli B, Ermini I, Occhini D, Sieri S, et al. Glycemic index, glycemic load and mammographic breast density: the EPIC Florence longitudinal study. PLoS One 2013: doi: 10.1371/journal.pone.0070943.
50. Masala G, Assedi M, Ambrogetti D, Sera F, Salvini S, Bendinelli B, et al. Physical activity and mammographic breast density in a Mediterranean population: the EPIC Florence longitudinal study. Int J Cancer 2009; 124:1654–61.
51. Boyd NF, Greenberg C, Lockwood G, Little L, Martin L, Byng J, et al. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: results from a randomized trial. Canadian Diet and Breast Cancer Prevention Study Group. J Natl Cancer Inst 1997;89: 488–96.
52. Kim J, Han W, Moon HG, Ahn S, Shin HC, You JM, et al. Breast density change as a predictive surrogate for response to adjuvant endocrine therapy in hormone receptor positive breast cancer. Breast Cancer Res 2012;14: R102. Erratum in: Breast Cancer Res 2012;14:403.
53. Engmann NJ, Scott CG, Jensen MR, Ma L, Brandt KR, Mahmoudzadeh AP, et al. Longitudinal changes in volumetric breast density with tamoxifen and aromatase inhibitors. Cancer Epidemiol Biomarkers Prev 2017;26:930–37.