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Can dietary and physical activity modifications reduce breast density in postmenopausal women?
The DAMA study, a randomized intervention trial in Italy.

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Abbreviations list: BI-RADS: Breast Imaging Reporting and Data System; BMI: Body Mass Index; DAMA study: Diet, physical Activity and MAMmographic study; EPIC: European Prospective Investigation into Cancer and Nutrition; FFQ: Food Frequency Questionnaire; LSQ: Lifestyle Questionnaire MBD: Mammographic Breast Density; MET: Metabolic Equivalent; PA: Physical Activity; VPD: Volumetric Percent Density.

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Abstract

Background: Few randomized trials have been carried out to evaluate the effect of lifestyle modifications on mammographic breast density (MBD). The randomized 2x2 factorial DAMA trial aimed to evaluate whether MBD can be reduced in post-menopausal women with high baseline MBD by a 24-months dietary and/or physical activity (PA) interventions.

Methods: We randomized healthy post-menopausal women, attending the Florence (Italy) mammographic screening program, aged 50-69 years, non-smokers, with MBD>50% and no recent hormone therapy, to: a) a dietary intervention focused on plant-foods, with a low glycemic load, low in saturated fats and alcohol; b) a PA intervention combining daily moderate intensity activities and one weekly supervised session of more strenuous activity; c) both interventions; d) 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-months 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, 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 two 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.

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 behavioural 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-months randomized 2x2 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 post-menopausal women with high MBD (>50%) (20).

Material and Methods

Study design and hypothesis

The DAMA study is a single-centre, randomized intervention trial with a 2x2 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 post-menopausal women with high-MBD (>50%) by modifying their dietary habits and/or PA level in a 24-months 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 programme in Florence (21). Women potentially eligible were aged between 50 and 69 years, had a negative screening mammogram showing a MBD of 50% or more, as assessed routinely in the screening programme 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: pre- or peri-menopausal 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 non-melanocytic skin cancer); diabetes or other major co-morbidities, including major cardiovascular and neurological 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, 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, 60-69 years) and Body Mass Index category ($< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$), 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: a) substitution of refined grains with wholegrains; b) consumption of at least one portion of raw and one portion of cooked vegetables at each meal; c) consumption of

fish at least two-three times weekly; d) consumption of fresh and processed red meat reduced to less than 1 time/week considering all types e) at least three-four portions/week of legumes and pulses; f) consumption of two- three portions/day of fruit; g) cakes and desserts reduced to a maximum of 1 portion/week; h) no more than 1 portion/day of milk or yogurt and 2 portions/week of cheese. Exclusion of full fat varieties; i) extra-virgin olive oil as the only dressing and cooking fat; j) no more than one glass of wine per day, at meals, if already used to drink wine (20).

After an initial individual counselling, participants were requested to attend six group meetings and eight cooking classes during the two 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.

Physical activity 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 6-10 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 counselling session with a PA expert.

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

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

We requested study participants assigned to any of the intervention arms to keep five written one-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 six 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 \pm 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, Wellington, New Zealand). The technical characteristics of Volpara system has been already described in details (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 (cm³). Total breast volume (cm³) is obtained by multiplying the breast area by the recorded breast thickness, corrected for the breast edge. Volumetric percent density (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 $0.43 \times SD$ 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 chi-square test was utilized for categorical variables.

The main outcome analysis was performed on an intention-to-treat basis. The factorial design allows to evaluate 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 (Figure 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 year (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 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 Figure 2 we show the unadjusted geometric means of volumetric percent density in each arm at baseline and follow-up. We observed a percent reduction in VPD measured in follow-up mammograms 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 arm 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-months 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.

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, 33, 34, 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, 40, 41,42). Some studies reported an inverse association with an increasing level of recreational activities (43,44,45), but others studies did not (46,47, 35). 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 five years after the assessment of lifestyle habits.

To our best knowledge only one trial evaluated the effect of a PA intervention in post menopausal 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% to 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 (16,17,18)

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 two years 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 programmes with a radiological 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.

While 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 a analysis by arms (26,27). While we can not 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 counselling. 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 programme, a well-known and long-standing organized program thus assuring 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 chemioprevention trial women on tamoxifen who experienced a 10% or greater reduction in percent breast density in 12-18 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 programmes. The DAMA trial suggests a potential effect of physical activity 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 programmes.

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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).

	Whole study sample (n=226)	Study arm				p-value ^a
		Diet (n=57)	Physical activity (n=54)	Diet + physical activity (n=55)	Control group (n=60)	
Level of education						
none/primary school	64 (28.3%)	18 (31.6%)	15 (27.8%)	12 (21.8%)	19 (31.7%)	0.85
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%)	
Smoking						
former	98 (43.4%)	25 (43.9%)	23 (42.6%)	28 (50.9%)	22 (36.7%)	0.48
never	128 (56.6%)	32 (56.1%)	31 (57.4%)	27 (49.1%)	38 (63.3%)	
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
Body Mass Index (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
Body Mass Index (groups)						
<25	142(62.8%)	35 (61.4%)	34 (63.0%)	36 (65.5%)	37 (61.7%)	0.97
≥25	84 (37.2%)	22 (38.6%)	20 (37.0%)	19 (34.5%)	23 (38.3%)	
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%)	0.73
≥88	19 (8.4%)	3 (5.3%)	6 (11.1%)	5 (9.1%)	5 (8.3%)	
Hormonal and reproductive history						
Hormone therapy use						
never	157 (69.5%)	43 (75.4%)	36 (66.7%)	34 (61.8%)	44 (73.3%)	0.38
ever	69 (30.5%)	14 (24.6%)	18 (33.3%)	21 (38.2%)	16 (26.7%)	
Contraceptive pill use						
never	102 (45.1%)	30 (52.6%)	20 (37.0%)	23 (41.8%)	29 (48.3%)	0.36
ever	124 (54.9%)	27 (47.4%)	34 (63.0%)	32 (58.2%)	31 (51.7%)	
Number of children						
0	39 (17.3%)	13 (22.8%)	10 (18.5%)	8 (14.5%)	8 (13.3%)	0.20
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%)	

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) (Cont'd)

		Whole study sample (n=226)	Study arm			p-value	
			Diet (n=57)	Physical activity (n=54)	Diet + physical activity (n=55)		Control group (n=60)
Breastfeeding							
	never	37 (19.8)	12 (27.3)	6 (13.6)	10 (21.3)	9 (17.3)	0.41
	ever	150 (80.2)	32 (72.7)	38 (86.4)	37 (78.7)	43 (82.7)	
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		2065.5 (635.5)	1925.4 (506.3)	2068.0 (650.1)	2226.5 (753.1)	2048.6 (595.7)	0.09
Physical activity levels							
Non occupational physical activity ^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 physical activity (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 physical activity (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		130 (57.5)	34 (59.6)	32 (59.2)	31 (56.4)	33 (55.0)	0.96
Physical activity at work							
	sedentary	79 (60.8%)	24 (70.6%)	18 (56.2%)	20 (64.5%)	17 (51.5%)	0.61
	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 physical activity index^c							
	inactive	60(26.5%)	19 (33.3%)	15 (27.8%)	16 (29.1%)	10 (16.7%)	0.74
	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 X² test for categorical variables; ^b including household and recreational activities; ^c the total physical activity index is categorized into four levels based on a cross-tabulation of occupational activity by the combined household and recreational activities in quartiles.

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

	Dietary intervention arm N=57	Physical activity intervention arm N=54	Dietary and physical activity intervention arm N=55	General recommendations (control) arm N=60
Volumetric percent density	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	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 value	p = 0.003	p = 0.01	p = 0.08	-

^aAdjusted for weight change, volumetric percent density (VPD) log-transformed at baseline, randomization block variables

^bRatio 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)		Physical activity (n=54)		Diet + physical activity (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)

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) (Cont'd)

	Diet (n=57)		Physical activity (n=54)		Diet + physical activity (n=55)		Control group (n=60)
	Difference (%)	p	Difference (%)	p	Difference (%)	p	Difference (%)
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 physical activity	2.9 (4.3)	0.44	10.4 (12.0)	0.09	16.9 (18.7)	0.01	-3.0 (3.1)
- Household physical activity	2.1 (3.5)	0.27	-1.4 (2.3)	0.63	2.4 (3.7)	0.26	-4.3 (6.3)
- Recreational physical activity	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.

Figure Legends

Figure 1

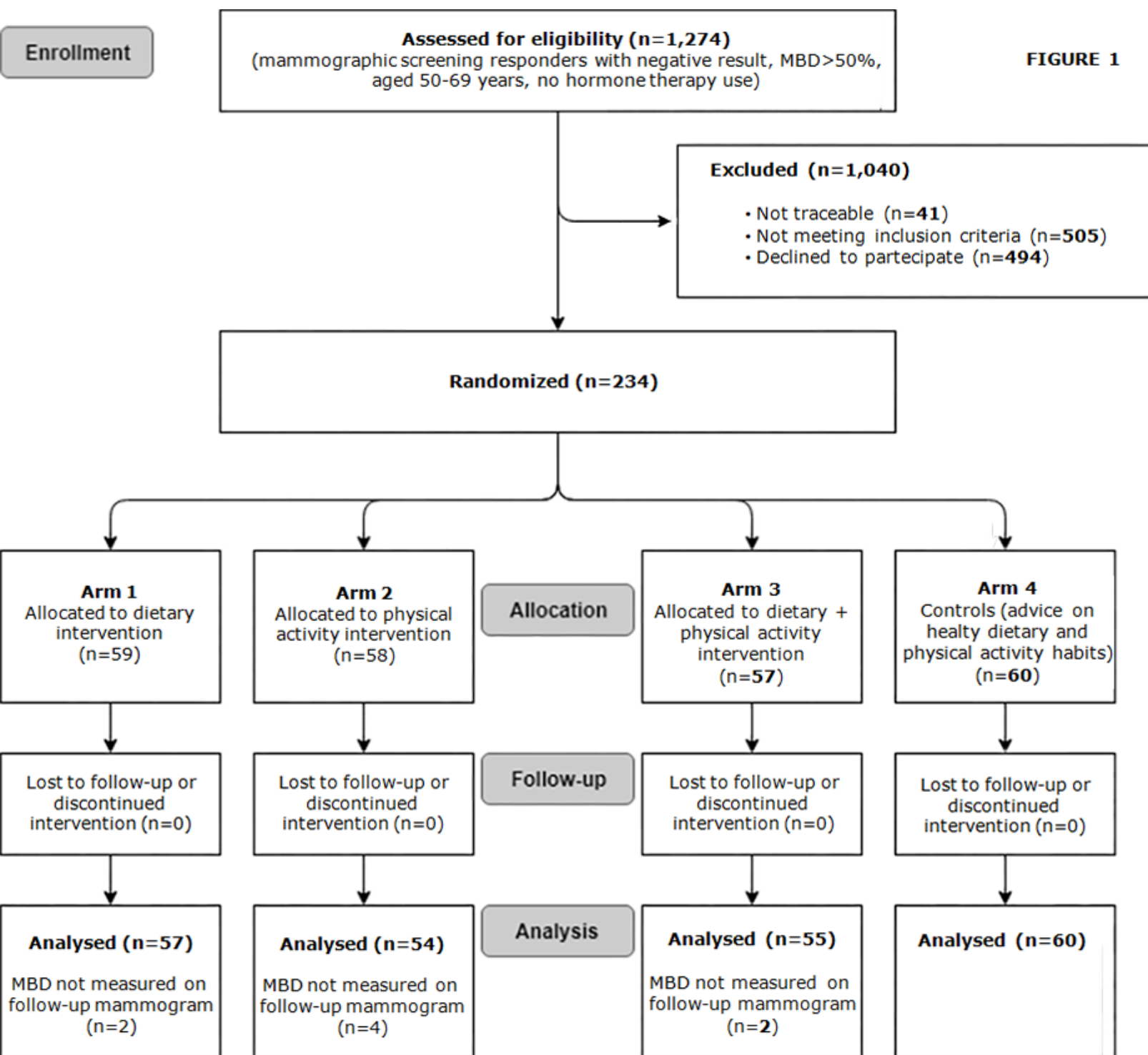
Recruitment of participants, randomization and follow-up in the DAMA intervention trial.

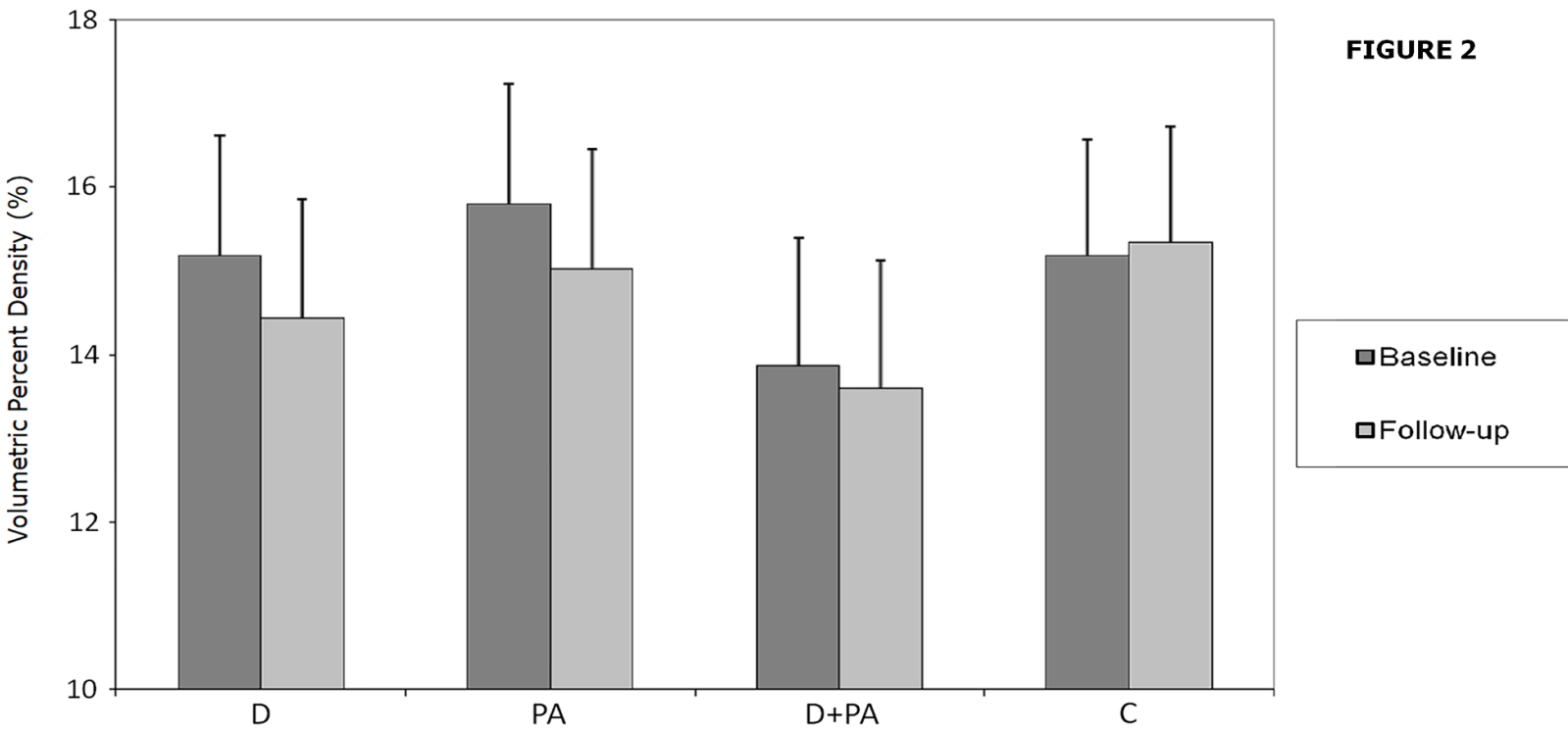
CONSORT Flow Diagram showing procedures of selection among eligible women and participants with complete data available.

Figure 2

The main outcome in the DAMA trial. Geometric Mean (+ SD) of Volumetric Percent Density 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).

FIGURE 1





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, Melania Assedi, Francesco Sera, et al.

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