The Effect of Diet on Breast Cancer Recurrence: The DIANA-5 Randomized Trial

Franco Berrino[1,2], Anna Villarini[3], Giuliana Gargano[1], Vittorio Krogh[1], Sara Grioni[1], Manuela Bellegotti[1], Elisabetta Venturelli[4], Milena Raimondi[1], Adele Traina[5], Maurizio Zarcone[5], Rosalba Amodio[5], Maria Piera Mano[6,7], Harriet Johansson[8], Salvatore Panico[9], Maria Santucci de Magistris[10], Maggiorino Barbero[11], Cristina Gavazza[12], Angelica Mercandino[13], Elena Consolaro[14], Rocco Galasso[15], Luciana Del Riccio[15], Maria Chiara Bassi[16], Milena Simeoni[17], Paolo Premoli[17], Patrizia Pasanisi[4], Bernardo Bonanni[8], and Eleonora Bruno[4]

ABSTRACT

Purpose: The DIANA-5 randomized controlled trial assessed the effectiveness of a diet based on Mediterranean and macrobiotic traditions (macro-Mediterranean diet) in reducing breast cancer recurrence.

Patients and Methods: The DIANA-5 study involved 1,542 patients with breast cancer at high risk of recurrence because of estrogen receptor–negative cancer, or metabolic syndrome, or high plasma levels of insulin or testosterone. Women were randomly assigned to an active dietary intervention (IG) or a control group (CG). Both groups received the 2007 American Institute for Cancer Research/World Cancer Research Fund recommendations for cancer prevention. The intervention consisted of meetings with kitchen classes, community meals, and dietary recommendations. Recommended foods included whole grain cereals, legumes, soy products, vegetables, fruit, nuts, olive oil, and fish. Foods to be avoided were refined products, potatoes, sugar and desserts, red and processed meat, dairy products, and alcoholic drinks. A compliance Dietary Index was defined by the difference between recommended and discouraged foods.

Results: Over the 5 years of follow-up, 95 patients of the IG and 98 of the CG developed breast cancer recurrence [HR = 0.99; 95% confidence interval (CI): 0.69–1.40]. The analysis by compliance to the dietary recommendations (IG and CG together) showed that the women in the upper tertile of Dietary Index change had an HR of recurrence of 0.59 (95% CI: 0.36–0.92) compared with women in the lower tertile.

Conclusions: The DIANA-5 dietary intervention trial failed to show a reduction in breast cancer recurrence, although self-reported diet at year 1 in IG and CG combined showed a protective association with the higher Dietary Index change.

See related commentary by McTiernan, p. 931

[1]Department of Epidemiology and Data Science, S.C. Epidemiology and Prevention, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy. [2]La Grande Via Foundation, Milan, Italy. [3]Department of Medicine and Surgery, Section of Hygiene and Public Health, University of Perugia, Perugia, Italy. [4]Department of Experimental Oncology, S.S.D. Nutrition Research and Metabolomics, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy. [5]Palermo and Province Cancer Registry, Clinical Epidemiology Unit with Cancer Registry, Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone", University of Palermo, Palermo, Italy. [6]Dipartimento Scienze Chirurgiche, Study University, Turin, Italy. [7]S.C. Epidemiologia dei Tumori, AOU Città della Salute e della Scienza, CPO Piemonte, Turin, Italy. [8]Division of Cancer Prevention and Genetics, IEO, European Institute of Oncology IRCCS, Milan, Italy. [9]School of Medicine, Federico II University, Naples, Italy. [10]A.O.U. Federico II, Naples, Italy. [11]Obstetrics and Gynecology Unit, Cardinal Massaia Hospital, Asti, Italy. [12]LILT, Associazione Provinciale di Asti O.D.V, Italy. [13]Fondazione Edo ed Elvo Tempia ONLUS, Biella, Italy. [14]ATS Insubria, Varese, Italy. [15]Unit of Regional Cancer Registry, Clinical Epidemiology and Biostatistics, IRCCS-CROB, Rionero in Vulture, Italy. [16]ATS Valpadana, Mantova area, Italy. [17]LUMEN Aps, San Pietro in Cerro (Piacenza), Italy.

A. Villarini and F. Berrino contributed equally as co-first authors and B. Bonanni and E. Bruno as co-last authors to this article.

Corresponding Author: Patrizia Pasanisi, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian, 1, Milano 20133, Italy. E-mail: patrizia.pasanisi@istitutotumori.mi.it

Clin Cancer Res 2024;30:965–74

doi: 10.1158/1078-0432.CCR-23-1615

Introduction

The incidence of breast cancer and the number of survivors continue to grow, with many countries including the United States, Canada, Australia, Japan, and several European countries reporting 85%–90% 5-year survival rates for women diagnosed between 2010 and 2014 (1). Despite these large and growing population benefits from novel interventions aimed at supporting health during treatments and survivorship, an important proportion of breast cancer women still die from it, and survivors suffer from comorbidities that affect not only the probability of dying from other causes but also of dying from breast cancer.

Prospective epidemiologic studies showed that overweight (2) and markers of insulin resistance such as high serum levels of glucose (3), insulin (4), and testosterone (5, 6) are associated with a significantly increased risk of breast cancer recurrence, both before and after menopause. Consistently, metabolic syndrome [defined as the presence of three or more of the following: abdominal obesity, hypertension, hyperglycemia, high triglycerides, and low high-density lipoprotein (HDL) cholesterol values] is associated with a higher recurrence rate in breast cancer women (6).

There is increasing observational and experimental evidence that improving diet and lifestyle favorably modifies these metabolic and hormonal prognostic factors for breast cancer. The Mediterranean diet, which is largely based on unrefined cereal products (mainly bread and pasta), pulses, vegetables, olive oil, nuts, fruit, moderate wine, occasionally fish and cheese and rarely other animal products, improves body composition, insulin sensitivity, lipid profile, and it is associated with a lower cumulative incidence of metabolic syndrome (7–10).

Translational Relevance

The results of the DIANA-5 dietary intervention trial did not confirm the hypothesis that a comprehensive dietary modification reduces breast cancer recurrence and metastases. However, observational analysis of the DIANA-5 cohort by compliance, showing a significantly better prognosis in the women in the upper tertile of dietary change, suggests that the hypothesis is not falsified. Our results point to the importance of obtaining in future dietary trials a better compliance to dietary recommendations and a sufficient differentiation between randomized groups.

Our previous DIet and ANdrogen (DIANA) randomized controlled trials showed that an insulin-lowering diet, which also involves increased phytoestrogen intake (macro-Mediterranean diet) significantly decreases bioavailable sex hormones, insulin-like growth factor-1 (IGF-1), body weight, and the main factors defining metabolic syndrome in both healthy postmenopausal women (DIANA-1; ref. 11) and in women with a previous diagnosis of breast cancer (DIANA-2; ref. 5). The DIANA-2 study, carried out on about 110 patients, also suggested that a decrease in testosterone may reduce breast cancer recurrence.

Several prospective studies showed that better overall dietary quality is associated with improved survival among patients with breast cancer (12). The effect of diet on breast cancer–specific mortality, however, is controversial. A recent study from Greece suggested a favorable prognostic effect of Mediterranean diet, with a significant improvement of disease-free survival (13). In the larger Nurses' Health Study and in the EPIC study, a higher Mediterranean diet score was associated with a lower risk of non-breast cancer death but was not significantly associated with breast cancer–specific mortality (14, 15). A meta-analysis of five studies showed that soy food intake was associated with reduced mortality in both estrogen receptor–negative (ER^-) and estrogen receptor–positive (ER^+) patients, and in both premenopausal and postmenopausal women (16). The two largest trials about diet and breast cancer survival, the Women's Intervention Nutrition Study (WINS; refs. 17–19), and the Women's Healthy Eating and Living (WHEL; refs. 20, 21), designed their dietary intervention mainly to lower the participants' fat intake respectively <20% and <30% of total calories. In the WHEL trial, the participants were also requested to increase their vegetable and fruit servings to improve fiber intake. However, only in the WINS study, a significant reduction in body weight and breast cancer recurrence were observed, confined to patients with ER^- tumors.

As for the lifestyle recommendations currently proposed for breast cancer women, the AICR/WCRF Decalogue suggest that breast cancer survivors should maintain healthy body weight, should engage in regular physical activity, achieve a dietary pattern high in vegetables, fruits, whole grains and legumes, and low in saturated fat and alcoholic beverages, and should increase the consumption of soy products (22). Much remains to be learned, however, about the diet–breast cancer survival relationship.

Here, we report the results of the DIANA-5 study, a randomized dietary intervention trial designed to test the hypothesis that a dietary change based on the macro-Mediterranean diet might prevent the development of recurrence in women with high-risk breast cancer.

Patients and Methods

Study design

Details of the study design, eligibility criteria, randomization procedures, and dietary intervention have been reported previously (23). Briefly, we have carried out a multi-institutional randomized controlled trial, the DIANA-5 study, to test the efficacy of dietary change to prevent the development of recurrence in breast cancer women surgically resected in the previous 5 years and considered at high risk of recurrence due to ER^- tumors, or because they had a metabolic syndrome, or high serum testosterone or insulin.

We randomized high-risk breast cancer women into two groups: the control group (CG) received general recommendations for cancer prevention (the 2007 AICR/WCRF Decalogue; ref. 24), while the intervention group (IG) received the same recommendations and was offered active support through kitchen courses, monthly community meals, and physical activity recommendations. All women were actively followed-up for 5 years. The study was conducted in full conformance with the principles of the Declaration of Helsinki.

Participants

Between 2008 and 2012, a total of 2,132 women surgically treated for stage I–III invasive breast cancer within the previous 5 years were enrolled in the DIANA-5 intervention study (NCT05019989; ref. 23).

At baseline, eligible women ranged between 35 and 70 years of age and showed no evidence of recurrence. Those who had undergone adjuvant treatments were recruited after the end of chemotherapy and during hormonal treatment. Eligible women were screened to select those at high risk of recurrence due to ER^- tumors, or because of the presence of one or more of the following endocrine/metabolic indicators: serum testosterone level ≥0.4 ng/mL (1.338 nmol/mL) or serum insulin ≥7 IU/mL (50 pmol/L) or presence of at least three factors defining the metabolic syndrome [waist circumference ≥80 cm; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, fasting plasma glucose ≥100 mg/100 mL (5.6 mmol/L) or previously diagnosed type II diabetes, triglycerides ≥150 mg/100 mL (1.7 mmol/L), high-density lipoprotein cholesterol <50 mg/100 mL (1.03 mmol/L)] or on the basis of receiving treatment for these parameters. On the basis of these criteria, 1,542 high-risk women were randomized into an active IG or a CG.

Eleven Italian institutions contributed patients to the study, 8 in Northern Italy and 3 in Southern Italy. Informed written consent was obtained from each subject before any trial-specific procedure or treatment.

The study was approved by the Institutional Review Board and Ethical Committee of the coordinating center (Fondazione IRCCS Istituto Nazionale dei Tumori of Milan) for all the other collaborating Institutions (INT 37/07).

Randomization and masking

High-risk women were randomly assigned (1:1) by means of an interactive system into an IG or CG. Randomization was stratified for age (≤50, >50 years), hormonal receptor status (ER^+, ER^-), nodal metastasis (N+, N−), and study center. Allocation was done centrally and blindly.

The randomization program was run from within the study's relational data base centralized at the coordinating center, with the group assignment immediately recorded in the database and was not subject to alteration.

Procedures

Dietary intervention

The DIANA-5 intervention consisted in a comprehensive qualitative dietary change based on the traditional Italian Mediterranean diet and, mainly to increase the phytoestrogen intake, we recommended to include several foods from the Japanese and macrobiotic traditions (macro-Mediterranean diet).

The goals of the intervention were:

- To control weight.
- To promote a healthy diet.

To achieve these goals, women randomized in the IG were encouraged:

- to include highly satiating foods such as whole grains, legumes, and high-fiber vegetables as major components of their diet, eat a vegetable soup or a vegetables salad before eating higher energy foods, choose fresh fruit rather than juice.
- to reduce high glycemic index foods [refined flour(s), potatoes, white rice, and corn flakes] and high insulinemic foods (sugar and milk). Nuts and legume flours were proposed in sweet and savory cookery recipes. Desserts were prepared without adding sugars, but using instead nuts, fresh fruit, and small amounts of dates, raisins, and dried apricots.
- to reduce foods rich in saturated fats (red and processed meat, milk, and dairy products) and to avoid sources of trans fatty acids [margarine(s) and industrial snacks and pastries]. Cold-pressed extra-virgin olive oil was the main source of fat. The consumption of nuts and seeds that help to control weight and glycemia was encouraged.
- to reduce animal products. Among animal foods, fish, especially cold-water fish (e.g., salmon, mackerel, and sardines), rich in omega-3 polyunsaturated fatty acids, was privileged.
- to include foods from the Japanese and macrobiotic traditions (soy milk, tofu, miso, soy sauce, tempeh, umeboshi, seaweeds, and fermented vegetables).

The IG women were invited to attend dietary activities, which consisted of thematic kitchen courses (i.e., "The healthy breakfast", "How to cook whole grain cereals", "How to cook legumes", "How to read a food label", "Sweets without sugar", etc.), community meals, once a month during the first year, and every few months in the subsequent 4 years (Supplementary Fig. S1). A registered nutritionist was always present during the kitchen courses and the community meals to ensure the necessary assistance to the cooks and to reinforce recommendations to the participants. Women did not receive a specific dietary plan with calorie count, but dietary recommendations, menus, recipes, and cooking instructions. However, the menus provided to participants were created not to exceed the 500 kcal in a meal (examples of menu are given in Supplementary Fig. S1). Only organic food was administered to women during cooking classes. Women were encouraged to participate in "Solidal buying groups" to facilitate their use of organic and macrobiotic foods at home. Agreements with organic food shops were reached to obtain discounts for the DIANA-5 participants.

The kitchen courses and community meals included up to 30 women and were designed to improve compliance and to share difficulties in following the dietary recommendations.

Physical activity recommendation

Beside the active dietary intervention, the women of the IG were recommended to reduce sedentary behavior and to achieve and maintain regular participation in a moderate intensity physical activity ($\sim$3 to 5 metabolic equivalents) for 210 minutes/week (30 minutes on average per day). They received a pedometer for free and were encouraged to walk at least 10,000 steps per day. We proposed monthly structured physical activity sessions, but the participation was very poor and after a few months we limited the structured physical activity program to small groups of volunteers (25, 26). However, we monitored physical activity levels in women of the IG and in a sample of CG. For a full week at baseline and after 1 year, the women wore a SenseWear Pro 3 Armband (BodyMedia), a multi-sensor device containing a two axial accelerometer and sensors that allow continuous recording of physiologic signals from the body, such as skin temperature, dissipated heat from the body (heat flux), galvanic skin response, and movement (27–29).

Dietary assessment

Dietary assessment methods and women's compliance with the DIANA-5 dietary recommendations have been reported previously (30). Briefly, participants had to self-complete a 24-hour food frequency diary at baseline (before any dietary recommendations), before starting the dietary intervention, once a month during the first year, at the end of the first year ($\pm$2 months), and every few months in the subsequent years.

The 24-hour food frequency diary contains a list of 65 foods or food group items, without any information on portion size or weight, or on recipes. The women had to indicate whether, on the previous day, they had eaten or not eaten the specified food at breakfast, lunch, dinner, and breaks.

We did not ask portion size but for each dietary item we counted the number of portions consumed per day. The list of foods was established on the basis of what is usually consumed in Italy, and on the foods whose consumption we wanted to encourage.

For the analysis, we created an *a priori* classification of recommended or discouraged foods (30), but the 24-hour food frequency diary form did not include this information.

Recommended foods:

- Whole-grain products (whole bread, whole rice, other whole grain cereals, unsweetened muesli, oat flakes);
- Unsweetened beverages (vegetable milk, tea, barley coffee);
- Vegetables (all vegetables except potatoes);
- Fruit (all kinds of fruit);
- Legumes and soy products (legumes, tofu/tempeh);
- Recommended animal protein products (fish, molluscs, and crustaceans);
- Dried fruit (apricots, raisins, plums);
- Nuts and seeds (hazelnuts, almonds, walnuts, nut creams, and oilseeds);
- Vegetable oils (extra virgin olive oil, seeds oil);
- Spices and seasonings (miso, tamari, spices);

Discouraged foods:

- Sugary beverages (sugary beverages, animal milk);
- Alcoholic drinks (wine, beer, spirits);
- Sweets and cakes (white sugar, artificial sweeteners, chocolate, candies, biscuits, ice creams, brioches);
- Refined cereals (white bread, white rice, egg noodles, corn flakes, sweetened muesli);
- Discouraged animal products (red meat, processed meat);
- Discouraged vegetable protein products (seitan);
- Dairy products (all kind of fresh or seasoned cheese, including pizza or pasta);

- Starchy vegetables (potatoes, mashed potatoes, French fries);
- Butter and other discouraged seasonings (Butter, lard cream, margarine, ready sauces, mayonnaise, ketchup).

White meat, eggs, coffee, unsweetened citrus juices, and unsweetened fruit juices were considered as neutral foods (not recommended but not discouraged).

We constructed a healthy Dietary Index by adding one point for every portion of recommended foods and subtracting one point for every portion of discouraged foods consumed in the day (30).

In our previous paper on the DIANA-5 participants' compliance to the dietary recommendations (30), the change in the Dietary Index over the first year proved to be a strong predictor of the change in body weight and in metabolic parameters.

Laboratory analysis

Each study center measured plasma levels of glucose, triglycerides, and HDL cholesterol by routine biomedical techniques. As regards insulin and testosterone measurements, collaborating centers, following appropriate processing for serum, plasma, erythrocyte and buffy coat fractions, sent cryovials on dry ice to the coordinator center, where they are stored in freezer at -80°C

Insulin levels were measured using an immunoradiometric kit (Immunotech, Prague, Czech Republic), which showed an interassay coefficient of variation of 8.6%, with a mean insulin value of 10 μU/mL. Serum testosterone levels were evaluated using commercial RIA kits (CisBio Bioassy). The interassay coefficients of variation was 10.6% for mean testosterone titers of 0.253 ng/mL. Baseline and 1-year patient serum samples were tested in the same analytical batch. The personnel who analyzed the samples were blinded about patients' randomization group.

Outcomes

The primary outcome of the DIANA-5 study is breast cancer recurrence, which includes the development of a new breast primary, ipsilateral or contralateral, local/regional cancer recurrence or distant recurrence/metastasis. In seven cases, the only follow-up information available was death for breast cancer and in this case we assumed that the date of recurrence was the date of death. Carcinoma *in situ* is not considered a study outcome, but its occurrence was recorded.

Outcome events were ascertained during semiannual meetings or telephone interviews with study participants. Information regarding hospitalizations or medical diagnoses was recorded. For any reported recurrences, copies of relevant medical notes were collected; they were first reviewed by the study center clinical coordinator and then, blindly, by the study pathologist from the coordinating center, who had the final responsibility to adjudicate the outcome. DIANA-5 also relied on the routine oncological follow-up at the institution where the patient was treated. To prevent loss to follow-up, moreover, we also used regional cancer registries, available for four collaborating centers, and hospital discharge diagnosis information systems, available in all Italian regions, as well as death certificates.

Sample size and power computation

On the basis of the available recurrence and survival data for patients diagnosed in the late 1990s (31, 32) and the relative risk of recurrence associated with metabolic syndrome (6, 11) as well as high insulin and testosterone levels (5, 6), we estimated that the 5-year cumulative recurrence rate of high-risk patients could be of the order of 25%. To estimate the likely effect of the proposed lifestyle intervention, we used data from several epidemiologic studies focused on prognosis and lifestyle (6, 19). We hypothesized that a comprehensive dietary intervention plus physical activity recommendations would reduce breast cancer recurrence rate by at least 25%. As for power analysis, we determined that a sample size of 1,200 high-risk patients, 600 patients per arm, would guarantee an 80% chance of getting a significant difference in recurrence rate with 25% reduction, considering a 90% compliance in the IG and a 10% contamination of the CG. During the course of the study, however, we realized that the incidence of recurrences was lower than expected from our review of literature, and the sample size was increased to reach at least 1,500 breast cancer women.

Statistical analysis

The metabolic and dietary characteristics of the 1,542 breast cancer women at high risk were summarized by randomization group using mean and SD and they were compared by using *t* tests. The frequencies of histologic and clinical parameters by randomization group were compared by using χ^2 test.

We analyzed the magnitude of changes in anthropometric, metabolic, and dietary variables by using the difference between the 1 year and the baseline measurements for each woman in the two groups. This analysis did not include the women who relapsed in the first year, who did not performed blood examination and clinical visit.

The main analysis of the effect of intervention on incidence of recurrence was based on the intention-to-treat principle, that is, it was based on assigned treatment at the time of randomization. We computed relapse-free survival. The statistic test was a two-sided log-rank test with a significance level $\alpha = 0.05$. HRs and confidence intervals (CI) were computed by Cox proportional hazards model to evaluate the effects of the intervention while adjusting for key covariates such as age, study center, tumor size (T1-T4), presence of positive axillary nodes (metastatic/total examined), histology type (ductal, lobular, mucinous, mixed ductal/lobular, others), chemotherapy, hormonal therapy, number of metabolic syndrome components (included in the models because slightly more altered in the IG than in the CG).

In accordance to the study protocol, we also carried out an observational analysis by compliance in the whole cohort (IG and CG together). We classified the participants on the basis of change in Dietary Index between baseline and the first year. Most women who had a breast cancer event during the first year (52) did not filled out the 24-hour frequency diary at 1 year (either because died or ill) and were excluded from the analysis. Moreover, a few women (31) were excluded from the observational analysis because the 24-hour food frequency diary were incomplete (missing data on recommended and/or discouraged foods).

Data availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restriction.

Results

Out of 1,542 women at high risk, 769 (mean age 52.0 ± 8.5 SD) were randomized into the IG and 773 (mean age 51.7 ± 8.3 SD) into the CG (**Fig. 1**, CONSORT trial flow diagram). The adherence to DIANA-5 activities and appointments for both randomized groups together was of 87% in the first year of the study and reduced to about 60% from the third to fifth year.

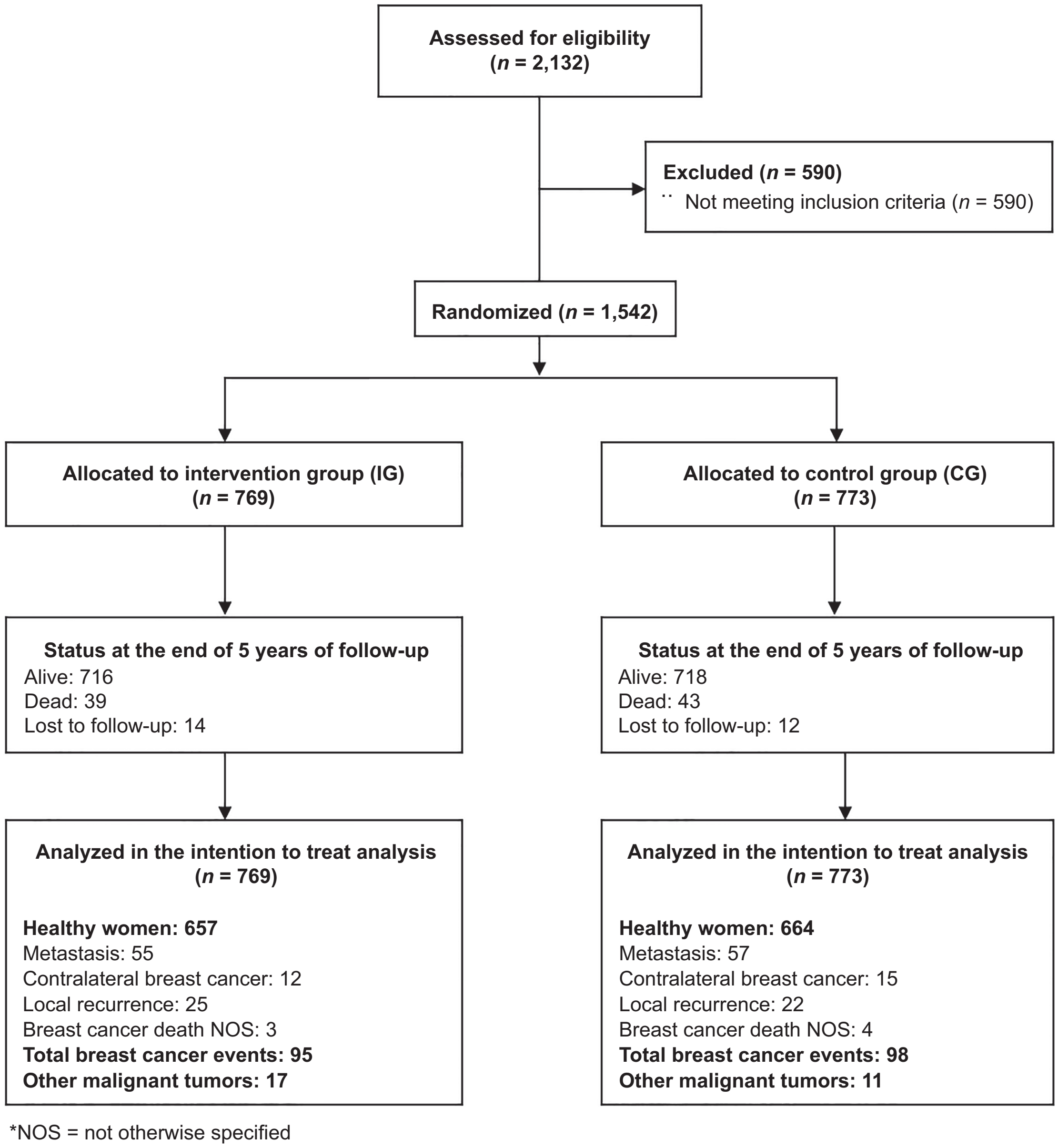


Figure 1.
CONSORT trial flow diagram.

Table 1 shows the distribution of the baseline clinical variables by randomization group. On average, both randomized groups had received a breast cancer diagnosis around 1.8 years prior to recruitment, with a homogeneous distribution for each year of the 5-year diagnosis–enrolment window. Considering the distribution of pathologic variables at the time of diagnosis, the randomization achieved highly comparable groups regarding tumor types, tumor size (T), nodal metastasis, cytologic grading (G), and hormone receptor status.

As for the metabolic, anthropometric, and dietary characteristics of the DIANA-5 population, we did not observe any significant difference between the study groups. Data from the baseline 24-hour food frequency diary showed a homogeneous consumption of recommended foods, with a slightly higher consumption of discouraged foods and a lower Dietary Index in the CG, without, however, any significant difference. At baseline the range of consumption per day of the recommended foods was 0–47 (median value 9), of discouraged foods consumption was 0–19 (median value 6), and the Dietary Index ranged from −11 to +33 (median value 3.6).

Changes in anthropometric and metabolic parameters by randomization group after 1 year's intervention showed a significant improvement in both groups, but the IG showed somewhat greater changes in all the parameters under study (Supplementary Table S1). The IG lost weight ($P < 0.001$), body mass index (BMI; $P < 0.001$), and decreased waist circumference ($P < 0.001$), glycemia ($P = 0.04$), and triglycerides ($P = 0.01$) significantly more than the CG. Consistently, the reduction of the metabolic syndrome parameters was significantly higher in the IG compared with the CG ($P < 0.001$). Overall, the IG improved the consumption of recommended foods (+2.8 vs. +0.9; $P < 0.001$) more

Table 1. Baseline characteristics of DIANA-5 study.

	IG (*N* = 769)	CG (*N* = 773)
Age at recruitment (years)	52.0 ± 8.5	51.7 ± 8.3
Study center		
Northern Italy		
Milan (NCI)	193 (25.1%)	191 (24.7%)
Milan (European Institute of Oncology)	86 (11.2%)	87 (11.2%)
Asti	47 (6.1%)	48 (6.2%)
Biella	36 (4.7%)	36 (4.7%)
Busto Arstizio	27 (3.5%)	25 (3.2%)
Mantova	24 (3.1%)	26 (3.4%)
Piacenza	16 (2.1%)	12 (1.6%)
Turin	95 (12.4%)	98 (12.7%)
Southern Italy		
Palermo	141 (18.3%)	145 (18.8%)
Naples	65 (8.5%)	64 (8.3%)
Rionero in Vulture	39 (5.1%)	41 (5.3%)
Years from diagnosis to randomization (mean ± SD)	1.84 ± 1.3	1.82 ± 1.3
Tumor size (T)		
1	488 (61.4%)	474 (61.3%)
2	239 (31.1%)	236 (30.5%)
3	13 (1.7%)	24 (3.1%)
4	5 (0.7%)	12 (1.6%)
n.s	25 (3.0%)	26 (3.5%)
Nodal metastasis (yes)	324 (42.1%)	328 (42.4%)
Histology		
Ductal	591 (77.4%)	600 (78.2%)
Lobular	84 (11.0%)	76 (9.9%)
Other	94 (11.6%)	97 (11.9%)
Grading[a]		
G1	104 (13.9%)	85 (11.3%)
G2	336 (44.9%)	360 (48.0%)
G3–G4	310 (41.2%)	305 (40.7%)
HER2 positive[b]	226 (30.3%)	218 (28.9%)
ER^-	170 (22.1%)	166 (21.5%)
PR^-	228 (29.6%)	225 (29.1%)
Weight (kg)	68.9 ± 13.0	68.3 ± 12.8
Waist circumference (cm)	87.5 ± 12.4	86.8 ± 12.3
Systolic pressure (mm/Hg)	127.5 ± 18.5	126.4 ± 18.6
Diastolic pressure (mm/Hg)	82.4 ± 11.4	81.6 ± 11.9
Glycemia (mg/dL)	94.3 ± 18.1	94.0 ± 16.1
HDL (mg/dL)	60.3 ± 15.6	61.5 ± 15.5
Triglycerides (mg/dL)	113.8 ± 68.0	109.4 ± 61.3
Insulin (μU/mL)	10.0 ± 5.8	10.0 ± 8.4
Testosterone (ng/mL)	0.35 ± 0.2	0.35 ± 0.2
HOMA index	2.4 ± 1.7	2.4 ± 2.2
RFC(frequencies day)[c]	10.1 ± 5.2	9.9 ± 5.2
DFC(frequencies day)[c]	6.0 ± 3.3	5.9 ± 3.3
DI (RFC-DFC)/day[c]	4.1 ± 6.4	4.0 ± 6.3

Note: Data are presented as mean ± SD or percentage.
Abbreviations: DFC, Discouraged Food Consumption; DI, Dietary Index; RFC, Recommended Food Consumption.
[a]Data available for 750 women (IG) and 750 (CG).
[b]Data available for 755 women (IG) and 724 (CG).
[c]Data available for 696 women (IG) and 701 (CG).

than the CG and significantly reduced the consumption of discouraged foods (−3.4 vs. −1.9; $P < 0.001$) compared with the CG (Supplementary Table S1). Consistently, the IG significantly improved the Dietary Index compared with the CG. The Dietary Index remained higher in the IG also in the subsequent years (Supplementary Fig. S3). The average Dietary Index difference between the IG and the CG during the 5 years of the study was 3.1.

Analysis by intention to treat

All patients except 26 were successfully followed up for 5 years. The cumulative incidence of new breast cancer events over 5 years of follow-up was of 95 events in the IG and 98 events in the CG (**Fig. 1**, CONSORT trial flow diagram). Besides, the incidence of distant metastasis was quite similar (55 and, respectively, 57). **Figure 2** shows that the survival curves without recurrence of the two randomized groups are quite superposed (HR = 0.99; CI: 0.69–1.40). The figure also reports the HRs for each individual year.

The intention-to-treat analysis by subgroups (ER^+ and ER^- tumors, premenopausal and postmenopausal women, years from diagnosis, Northern and Southern Italy recruitment centers, different hormonal treatments) did not show any significant effect modification (data not shown). The subgroup analysis involving the 498 participants enrolled within 1 year from diagnosis showed a nonsignificant lower HR of recurrence (adjusted HR = 0.58; 95% CI: 0.24–1.42; 61 recurrences).

Observational analysis of the whole cohort (IG and CG together) by compliance

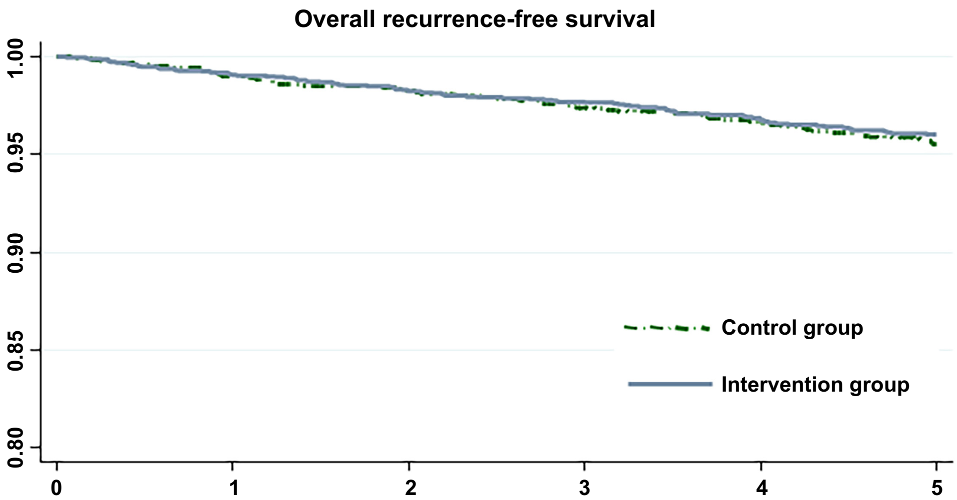
Table 2 shows the HR associated with the change in the Dietary Index during the first year of the study. Improvement in the Dietary Index was associated with a significantly better prognosis: the women with improvements above the upper tertile (Dietary Index > +6.8) experienced a 41% reduction of new breast cancer events. The HR for women classified above the upper tertile of change versus those classified under the lower tertile was 0.59; 95% CI: 0.36–0.92; $P_{trend} =$ 0.04. HRs for each follow-up year were 0.98, 0.69, 0.52, 0.45, and 0.63 (comparing the upper vs. the lower tertile), all with large CIs. The Dietary Index change was computed by subtracting the Dietary Index of the baseline 24-hour food frequency diary from the Dietary Index of the 24-hour food frequency diary filled-out after 1 year, but the result did not materially change using instead the sum of the 24-hour food frequency diaries filled-out in the first year. **Figure 3** shows the recurrence-free survival curves by tertiles of dietary change. The average Dietary Index change was +11.1 in the upper tertile, +4.4 in the middle tertile, and −1.8 in the lower tertile, where several women worsened their diet. Interestingly, the difference between the average Dietary Index change above the upper tertile and below the lower tertile was four times greater (12.9) than the overall Dietary Index difference between the IG and the CG (3.1; Supplementary Fig. S3).

HRs associated with the tertile of change in metabolic and anthropometric variables during the first year of follow-up were investigated (Supplementary Table S2). Except for blood pressure, the improvement of metabolic syndrome parameters was not associated with a better prognosis.

Discussion

The DIANA-5 randomized trial failed to show a reduction in breast cancer recurrence and metastasis. The main analysis, based on the intention-to-treat principle (i.e., based on the assigned treatment at the time of randomization), did not elicit any difference between the IG and the CG: 95 versus 98 new breast cancer events, HR = 0.99 (95% CI: 0.69–1.14), either because changing the diet and improving physical activity recommendations has no effect or because the difference achieved by the intervention is too small to elicit any difference in disease-free survival.

The DIANA-5 intervention aimed to improve hormonal and metabolic factors that previous studies suggested as important prognostic factors for breast cancer, including body weight, metabolic syndrome parameters, insulin, and testosterone levels.



Number at risk

IG	769	710	654	597	533	408
CG	773	734	663	609	563	409
HR/year (95% CI)		1.03 (0.47–1.45)	1.02 (0.53–1.95)	0.75 (0.37–1.51)	1.21 (0.59–2.47)	0.87 (0.44–1.73)

Recurrence/Years	1st year	2nd year	3rd year	4th year	5th year	HR (95% CI) Unadjusted	HR (95% CI) Adjusted
IG (*n*) CG (*n*)	28 28	20 18	14 20	18 14	15 18	1.03 (0.74–1.43)	0.99 (0.69–1.40)

HR Adjusted for age, center, tumor size (T1-T4), positive auxiliary nodes (metastatic/total examined), histology (ductal, lobular, mucinous, mixed ductal/lobular, others), chemotherapy, hormonal therapy, number of metabolic syndrome components at baseline.

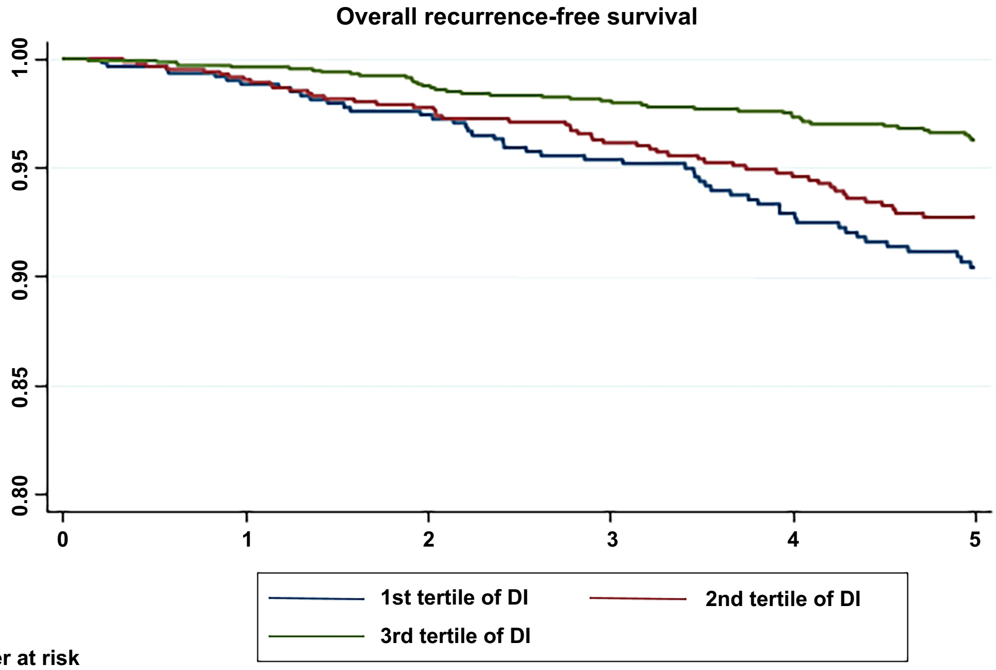
Figure 2.

Kaplan–Meier plot describes the overall recurrence-free survival between the groups assigned at the time of randomization. The two lines represent overall recurrence-free survival over time (5 years) by randomization group. The blue line is for IG. The dashed green line is for the CG. For each year, the number of patients with breast cancer at risk and HRs are represented. The horizontal axis represents the time of observation. The vertical axis represents the HRs.

Table 2. Observational analysis: HR of subsequent breast cancer events by Dietary Index change between 1 year and baseline.

	Breast cancer events (*n*)	Dietary Index change: 1st Tertile ($<+2$)	Dietary Index change: 2nd Tertile ($+2$ to $+6.8$)	Dietary Index change: 3rd Tertile ($>+6.8$)	P_{trend}	Continuous
Total population	142/1,300	**1.00**	**0.86 (0.58- 1.29)**	**0.59 (0.36–0.92)**	**0.04**	**0.77 (0.60–0.96)**
ER^-	29/265	1.0	2.58 (0.67–8.66)	2.25 (0.58–8.74)	0.81	1.45 (0.77–2.77)
ER^+	113/1,045	1.0	0.68 (0.42–1.09)	**0.42 (0.26–0.77)**	**0.003**	**0.65 (0.49–0.86)**
ER^+ and tamoxifen treatment	71/606	1.0	**0.45 (0.24–0.85)**	**0.30 (0.15–0.60)**	**<0.001**	**0.54 (0.38–0.77)**
ER^+ and aromatase inhibitors	42/444	1.0	1.26 (0.56–2.84)	1.09 (0.42–2.98)	0.62	1.06 (0.66–1.70)
ER^+ and premenopausal at diagnosis	66/625	1.0	**0.60 (0.32–1.10)**	**0.24 (0.11–0.54)**	**<0.001**	**0.51 (0.35–0.74)**
ER^+ and postmenopausal at diagnosis	47/412	1.0	0.99 (0.46–2.14)	1.27 (0.24–3.24)	0.63	1.13 (0.71–1.71)

Note: HR adjusted for age, center, tumor size (T1-T4), positive auxiliary nodes (metastatic/total examined), histology (ductal, lobular, mucinous, mixed ductal/lobular, others), chemotherapy, hormonal therapy, and Dietary Index (DI) at baseline.



Number at risk

1st tertile of DI	474	450	414	385	350	255
2nd tertile of DI	454	427	399	362	325	239
3rd tertile of DI	464	449	415	389	359	292

HR/year (95% CI)		1st year	2nd year	3rd year	4th year	5th year
1st tertile of DI		1	1	1	1	1
2nd tertile of DI		0.88 (0.18–4.35)	1.81 (0.52–6.32)	0.75 (0.29–1.99)	0.75 (0.25–2.31)	0.92 (0.37–2.29)
3rd tertile of DI		0.98 (0.11–8.30)	0.69 (0.17–2.82)	0.52 (0.16–1.62)	0.45 (0.14–1.50)	0.63 (0.22–1.79)

HR adjusted for age, center, tumor size (T1-T4), positive auxiliary nodes (metastatic/total examined), histology (ductal, lobular, mucinous, mixed ductal/lobular, others), chemotherapy, hormonal therapy, and Dietary Index (DI) at baseline.

Figure 3.

Kaplan–Meier plot describes the recurrence-free survival by Dietary Index (DI) changes. Participants were classified on the basis of change in DI between baseline and the first year. The blue line describes participants in the first tertile of DI change. The red line describes participants in the second tertile of DI change. The green line represents participants in the third tertile of DI change. The horizontal axis represents the time of observation. The vertical axis represents the HRs.

The overall success of the DIANA-5 study was relatively poor with respect to other studies on overweight/obese patients with a specific goal of weight loss and based on calorie restriction (33, 34). However, DIANA-5 women were not selected on the basis of their body weight (actually 42% of them had a BMI less than 25) and did not receive a specific dietary plan with calorie count, but only dietary recommendations. Despite the fact that the meals proposed during cooking classes did not exceed the 500 calories, participants were probably not able to reproduce a similar calorie restriction at home. Furthermore, the DIANA-5 study did not achieve the same improvement of insulin, testosterone, and glycemia as in our previous DIANA trials (always based on a qualitative dietary change). In the DIANA-1 and 2 studies, however, we offered participants dietary activities more frequently (twice a week and, respectively fortnightly) than in DIANA-5 (once a month).

Notwithstanding the effort of the investigators of the different study centers, we have not been able to ensure sufficiently strong differentiation between treatment groups. The intervention was successful in significantly reducing several negative prognostic factors in the IG, but also the CG improved their parameters and the delta between the average reduction in the IG and CG was small: −1.5 kg for body weight, −0.6 cm for waist circumference, −1.2 mg/dL for glycemia and −5.8 mg/dL for triglyceridemia, −0.6 for insulinemia (Supplementary Table S1). Such differences are not likely to cause any clinically significant biological effect. We estimated that the Dietary Index of the IG, on average, was 3.1 points higher than the index of the CG.

However, this apparent difference may be an overestimate because a participant repeatedly advised to change diet may overstate compliance to please the investigative team.

Contrary to our *a priori* expectations, the improvement in metabolic syndrome parameters was not associated with a better prognosis, and, actually, the trend was in the opposite direction. Also insulin sensitivity was not associated with a better prognosis. We suspect that these unforeseen results may be linked to the fact that the majority of DIANA-5 women had undergone chemotherapy and were under hormonal treatment upon recruitment. Hormonal treatments and chemotherapy, in fact, improve prognosis and may cause metabolic imbalance (35, 36), thus confounding the prognostic effects of metabolic factors. However, adjusting for treatment (chemotherapy yes or no, tamoxifen yes or no, aromatase inhibitors yes or no) did not materially modify the results. Other factors may be at stake.

When we planned the study, we were aware that contamination of the CG was built into the study design. Both randomized groups, in fact, received the leaflet with the AICR/WCRF recommendations for the prevention of cancer. On the one hand, we judged that it would have been unethical not to inform at all the women of the CG, and, on the other hand, we considered that it would have been unpractical to keep them into the study for 5 years, filling-out questionnaires and accepting clinical examinations and the donation of blood samples, without receiving some motivating information. We were confident that the difficulty of a lifestyle change without counseling and enforcement would have permitted a sufficient differentiation between groups. Because of this CG contamination problem, we also planned a secondary analysis to assess the effect of the intervention by applying a compliance score.

The Dietary Index, an indicator of compliance with dietary recommendations (recommended foods – discouraged foods), proved to be significantly associated to breast cancer prognosis. The joint analysis of the IG and the CG showed that women with the best improvement in the Dietary Index (above the upper tertile) decrease the risk of recurrence by 41% (95% CI: 8–64). The fact that the difference in the average Dietary Index change between the upper and lower tertiles is significantly higher than the Dietary Index difference between the IG and the CG corroborates the hypothesis that the negative result of the intention-to-treat analysis was due to insufficient differentiation of the randomized groups. While in the intention-to-treat analysis of the trial, we did not see any significant difference between premenopausal and postmenopausal women, nor between ER^+ and ER^- tumors, in the observational analysis the effectiveness of the dietary change appears to be confined to premenopausal ER^+ cases, or to ER^+ cases treated with tamoxifen (as the vast majority of premenopausal patients are treated with tamoxifen, we cannot establish if the effect modification is due to age or treatment). One might hypothesize that the dietary modification increases the anticancer effect of tamoxifen. A similar effect of dietary change, indeed, was recently observed in a preclinical model of breast cancer treated with tamoxifen or fulverstrant (in this case, the dietary intervention was intermittent fasting or fasting mimicking diet; ref. 37). The effect modification of cancer treatment, however, was not an *a priori* hypothesis and it might have occurred by chance.

A limit of our study is that we did not use any dietary instrument to estimate the women's nutrient intake. However, 24-hour food frequency diaries are highly efficient in describing and comparing the average consumption of specific foods and dietary patterns between populations, in line with our aim (38). When we planned the study, we considered that successful epidemiologic studies into diet and health relay more on dietary pattern than on the accurate quantification of nutrients. In the case of breast cancer, for instance, with the exception of alcohol, prospective epidemiologic studies failed to find any significant relationship with accurately measured specific foods and nutrients (21). Several studies, on the contrary, detected significant relationship with dietary patterns, such as Mediterranean diet and the adherence of AICR/WCRF recommendations (39).

A further limit of our study is that the Dietary Index developed for this trial is still unvalidated. In our previous article (30), we observed that the Dietary Index shows a predictive validity, but we did not conduct a dedicated validation study.

In conclusion, similar to previous dietary trials aimed at reducing the incidence of chronic diseases (MRFIT, WHI/DM, WHEL; ref. 40), the DIANA-5 randomized trial did not achieve sufficient differentiation in the recommended dietary goals to test the hypothesis that macro-Mediterranean diet may improve breast cancer prognosis. The observational analysis of the DIANA-5 cohort, however, seems to confirm that this is the case, at least for ER^+ breast cancer. Further trials should invest much more than a monthly meeting and kitchen class to obtain a satisfactory dietary change.

Authors' Disclosures

R. Galasso reports grants from Italian Ministry of Health during the conduct of the study. L. Del Riccio reports grants from Italian Ministry of Health during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

F. Berrino: Conceptualization, funding acquisition, investigation, methodology, writing–original draft, project administration, writing–review and editing. **A. Villarini:** Conceptualization, data curation, investigation, project administration. **G. Gargano:** Resources, data curation. **V. Krogh:** Formal analysis, supervision, methodology, writing–review and editing. **S. Grioni:** Resources, data curation. **M. Bellegotti:** Resources. **E. Venturelli:** Resources. **M. Raimondi:** Resources. **A. Traina:** Resources, investigation. **M. Zarcone:** Resources. **R. Amodio:** Resources. **M.P. Mano:** Resources, investigation. **H. Johansson:** Resources, writing–review and editing. **S. Panico:** Investigation, writing–review and editing. **M. Santucci de Magistris:** Resources. **M. Barbero:** Investigation. **C. Gavazza:** Resources. **A. Mercandino:** Resources. **E. Consolaro:** Resources. **R. Galasso:** Investigation. **L. Del Riccio:** Resources. **M.C. Bassi:** Resources, investigation. **M. Simeoni:** Investigation. **P. Premori:** Resources. **P. Pasanisi:** Conceptualization, data curation, formal analysis, supervision, methodology, writing–original draft. **B. Bonanni:** Supervision, investigation, writing–review and editing. **E. Bruno:** Resources, data curation, formal analysis, methodology, writing–original draft.

Acknowledgments

The study was supported by the Italian Department of Health, Programma Integrato Oncologia (PIO, RFPS-2006-1-339715), Associazione Italiana per la Ricerca sul Cancro (AIRC, IG-2011-11942), and Vita e Salute Foundation.

This research was also supported by Italian Ministry of Health "Ricerca Corrente" funds.

The authors give special thanks to Mrs. Patrizia Curtosi, Dr. Claudio Lanfranco, Mrs. Rita Carretto, Mrs. Dina Calosso, Dr. Vicki Rabino, Dr. Tania Cunzolo, Dr. M. Luisa Amerio, Dr. Daniela Piccillo, Dr. Annalisa Alessiato, Dr. Stefania Sterpetti, Dr. Raffaella Ravera, Dr. Simona Feira, Dr. Ildegarda Campisi, Dr. Cecilia Dolcemascolo, and Dr. Rosalba Staiti for contribution in recruitment activities. We thank the association Salute Donna Onlus and Cristina Piccarolo, Antonella Maule, and Angela Angarano for the lifestyle activities. We thank Adalberto Cavalleri for the support in the biological bank. Finally, the authors would like to acknowledge with much appreciation all the volunteers who participated in the study.

The publication costs of this article were defrayed in part by the payment of publication fees. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received May 31, 2023; revised August 2, 2023; accepted October 13, 2023; published first October 17, 2023.

References

1. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018;391:1023–75.
2. Chan DSM, Vieira R, Abar L, Aune D, Balducci K, Cariolou M, et al. Post-diagnosis body fatness, weight change and breast cancer prognosis: global cancer update program (CUP global) systematic literature review and meta-analysis. Int J Cancer 2023;152:572–99.
3. Minicozzi P, Berrino F, Sebastiani F, Falcini F, Vattiato R, Cioccoloni F, et al. High fasting blood glucose and obesity significantly and independently increase risk of breast cancer death in hormone receptor-positive disease. Eur J Cancer 2013;49:3881–8.
4. Goodwin PJ. Obesity, insulin resistance and breast cancer outcomes. Breast 2015; 24:S56–9.
5. Berrino F, Pasanisi P, Bellati C, Venturelli E, Krogh V, Mastroianni A, et al. Serum testosterone levels and breast cancer recurrence. Int J Cancer 2005;113: 499–502.
6. Pasanisi P, Berrino F, De Petris M, Venturelli E, Mastroianni A, Panico S. Metabolic syndrome as a prognostic factor for breast cancer recurrences. Int J Cancer 2006;119:236–8.
7. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr 2010;92:1189–96.
8. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A, Basterra-Gortari FJ, Nuñez-Cordoba JM, Martinez-Gonzalez MA. Mediterranean diet inversely associated with the incidence of metabolic syndrome: the SUN prospective cohort. Diabetes Care 2007;30:2957–9.
9. Esposito K, Kastorini C-M, Panagiotakos DB, Giugliano D. Mediterranean diet and metabolic syndrome: an updated systematic review. Rev Endocr Metab Disord 2013;14:255–63.
10. Kastorini C-M, Panagiotakos DB, Chrysohoou C, Georgousopoulou E, Pitaraki E, Puddu PE, et al. Metabolic syndrome, adherence to the mediterranean diet and 10-year cardiovascular disease incidence: The ATTICA study. Atherosclerosis 2016;246:87–93.
11. Berrino F, Bellati C, Secreto G, Camerini E, Pala V, Panico S, et al. Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomized trial. Cancer Epidemiol Biomarkers Prev 2001; 10:25–33.
12. Castro-Espin C, Agudo A. The role of diet in prognosis among cancer survivors: a systematic review and meta-analysis of dietary patterns and diet interventions. Nutrients 2022;14:348.
13. Mantzorou M, Tolia M, Poultsidi A, Vasios GK, Papandreou D, Theocharis S, et al. Adherence to Mediterranean diet and nutritional status in women with breast cancer: what is their impact on disease progression and recurrence-free patients' survival? Curr Oncol 2022;29:7482–97.
14. Castro-Espin C, Bonet C, Crous-Bou M, Nadal-Zaragoza N, Tjønneland A, Mellemkjær L, et al. Association of Mediterranean diet with survival after breast cancer diagnosis in women from nine European countries: results from the EPIC cohort study. BMC Med 2023;21:225.
15. Kim EHJ, Willett WC, Fung T, Rosner B, Holmes MD. Diet quality indices and postmenopausal breast cancer survival. Nutr Cancer 2011;63:381–8.
16. Chi F, Wu R, Zeng Y-C, Xing R, Liu Y, Xu Z-G. Post-diagnosis soy food intake and breast cancer survival: a meta-analysis of cohort studies. Asian Pac J Cancer Prev 2013;14:2407–12.
17. Chlebowski RT, Rose D, Buzzard IM, Blackburn GL, Insull W, Grosvenor M, et al. Adjuvant dietary fat intake reduction in postmenopausal breast cancer patient management. The Women's Intervention Nutrition Study (WINS). Breast Cancer Res Treat 1992;20:73–84.
18. Chlebowski RT, Blackburn GL, Elashoff RE, Thomson C, Goodman MT, Shapiro A, et al. Dietary fat reduction in postmenopausal women with primary breast cancer: phase III Women's Intervention Nutrition Study (WINS). J Clin Oncol 23: 16s, 2005 (suppl; abstr 10).
19. Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from The Women's Intervention Nutrition Study. J Natl Cancer Inst 2006;98:1767–76.
20. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 2007;298:289–98.
21. Pierce JP, Faerber S, Wright FA, Rock CL, Newman V, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials 2002;23:728–56.
22. WCRF. Survivors of breast and other cancers; 2018. Available from: https://www.wcrf.org/wp-content/uploads/2021/02/Cancer-Survivors.pdf.
23. Villarini A, Pasanisi P, Traina A, Mano MP, Bonanni B, Panico S, et al. Lifestyle and breast cancer recurrences: the DIANA-5 trial. Tumori 2012;98:1–18.
24. World Cancer Research Fund/American Institute for Cancer Research. Second Expert Report – Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. WCRF/AICR, Washington; 2007.
25. Bruno E, Roveda E, Vitale J, Montaruli A, Berrino F, Villarini A, et al. Effect of aerobic exercise intervention on markers of insulin resistance in breast cancer women. Eur J Cancer Care 2018;27:e12617.
26. Giallauria F, Vitelli A, Maresca L, Santucci de Magistris M, Chiodini P, Mattiello A, et al. Exercise training improves cardiopulmonary and endothelial function in women with breast cancer: findings from the Diana-5 dietary intervention study. Intern Emerg Med 2016;11:183–9.
27. Fruin ML, Rankin JW. Validity of a multi-sensor armband in estimating rest and exercise energy expenditure. Med Sci Sports Exerc 2004;36:1063–9.
28. Jakicic JM, Marcus M, Gallagher KI, Randall C, Thomas E, Goss FL, et al. Evaluation of the SenseWear pro armband to assess energy expenditure during exercise. Med Sci Sports Exerc 2004;36:897–904.
29. van Hoye K, Mortelmans P, Lefevre J. Validation of the SenseWear Pro3 armband using an incremental exercise test. J Strength Cond Res 2014;28: 2806–14.
30. Bruno E, Krogh V, Gargano G, Grioni S, Bellegotti M, Venturelli E, et al. Adherence to dietary recommendations after one year of intervention in breast cancer women: the DIANA-5 trial. Nutrients 2021;13:2990.
31. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. Eur J Cancer 2009;45:931–91.
32. Allemani C, Storm H, Voogd AC, Holli K, Izarzugaza I, Torrella-Ramos A, et al. Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. Eur J Cancer 2010;46:1528–36.
33. Rock CL, Flatt SW, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA, et al. Results of the exercise and nutrition to enhance recovery and good health for you (ENERGY) trial: a behavioral weight loss intervention in overweight or obese breast cancer survivors. J Clin Oncol 2015;33:3169–76.
34. Ligibel JA, Barry WT, Alfano C, Hershman DL, Irwin M, Neuhouser M, et al. Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. NPJ Breast Cancer 2017;3:37.
35. Zimbalist AS, Caan BJ, Chen WY, Mittendorf EA, Dillon DAR, Quesenberry C, et al. Metabolic abnormalities and survival among patients with non-metastatic breast cancer. BMC Cancer 2022;22:1361.
36. Dieli-Conwright CM, Wong L, Waliany S, Bernstein L, Salehian B, Mortimer JE. An observational study to examine changes in metabolic syndrome components in patients with breast cancer receiving neoadjuvant or adjuvant chemotherapy. Cancer 2016;122:2646–53.
37. Caffa I, Spagnolo V, Vernieri C, Valdemarin F, Becherini P, Wei M, et al. Fasting-mimicking diet and hormone therapy induce breast cancer regression. Nature 2020;583:620–4.
38. Thomson CA, Giuliano A, Rock CL, Ritenbaugh CK, Flatt SW, Faerber S, et al. Measuring dietary change in a diet intervention trial: comparing food frequency questionnaire and dietary recalls. Am J Epidemiol 2003;157:754–62.
39. Hastert TA, Beresford SAA, Patterson RE, Kristal AR, White E. Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2013;22:1498–508.
40. Willett WC, Ludwig DS. Dietary trials on chronic disease: learning from the past to avoid repeating it. Am J Clin Nutr 2021;114:2119–20.