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Adherence to Mediterranean Diet and Metabolic Syndrome in *BRCA* Mutation Carriers

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Abstract

Background. Insulin resistance is associated with higher breast cancer (BC) penetrance in *BRCA* mutation carriers. Metabolic syndrome (MetS), an insulin resistance syndrome, can be reversed by adhering to the Mediterranean diet (MedDiet). In a dietary intervention trial on *BRCA* mutation carriers, we evaluated adherence to the MedDiet, and the association with the MetS, by analyzing data from the Mediterranean Diet Adherence Screener (MEDAS). *Methods. BRCA* mutation carriers, with or without BC, aged 18 to 70 years, were eligible for the trial. After the baseline examinations, women were randomized to a dietary intervention or to a control group. Both groups completed the MEDAS at baseline and at the end of the dietary intervention. *Results*. A total of 163 women completed the 6 months of dietary intervention. Compared with controls, the women in the intervention group significantly reduced their consumption of red meat ($P < .01$) and commercial sweets ($P < .01$) and their MEDAS score rose significantly (+1.3 vs +0.55, $P = .02$). The number of MetS parameters decreased with increasing points of adherence to the MEDAS score ($P = .01$). In the intervention group, there was a significant association with the greater reduction of MetS. *Conclusion. BRCA* mutation carriers in the intervention group experienced greater improvement in their MedDiet and MetS parameters.

Keywords

metabolic syndrome, Mediterranean diet, *BRCA* mutation carriers, dietary intervention trial, breast cancer

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Introduction

Lifestyle factors linked to insulin resistance such as high serum levels of insulin and IGF-I (insulin-like growth factor–I), abdominal adiposity, high energy intake, milk consumption, and low levels of physical activity have been associated with higher penetrance of breast cancer (BC) in *BRCA* mutation carriers.[1,2] The metabolic syndrome (MetS), an insulin resistance syndrome, is defined as a clustering of risk factors of metabolic origin, such as abdominal obesity, high blood pressure, dyslipidemia, and high fasting glycemia.[3] The etiology of MetS is considered to involve a complex interaction between genetic, metabolic, and environmental factors.[4-6] MetS increases the risk of type 2 diabetes, cardiovascular diseases[7-9] and several cancers, including BC.[10] Postmenopausal status is associated with a 60% increase in the risk of MetS.[6] Antihormonal treatments for BC and/or risk-reducing surgery (prophylactic adnexectomy) may affect the risk of MetS in *BRCA* mutation carriers. Dorum and colleagues[11] found that patients with bilateral oophorectomy before 50 years of age had a higher prevalence of MetS than age-matched controls. Similarly, a controlled observational study showed that bilateral oophorectomy for breast and ovarian cancer prevention was significantly associated with MetS in *BRCA* mutation carriers.[12]

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The Mediterranean Diet (MedDiet) is a low-protein diet involving high consumption of unrefined cereal products (in Italy mainly bread and pasta made with durum wheat), pulses, vegetables, olive oil, nuts, fruit, moderate amounts of wine, occasionally fish and cheese, and rarely other animal products. The MedDiet has recently emerged as a healthy dietary pattern that reduces insulin resistance.[13]

Prospective studies have shown an inverse relationship between adherence to the MedDiet and MetS.[14,15] Randomized intervention trials showed that MetS can be reversed by following the MedDiet, with a reduction of MetS prevalence of up to 69% after 2 years of diet.[16-18]

As part of a demonstration project on *BRCA* mutation carriers, we are conducting a randomized controlled trial to test whether a dietary intervention based on the MedDiet and macrobiotic recipes significantly reduces IGF-I and other markers of insulin resistance (IRm).[2] Preliminary results suggest that women in the intervention arm significantly lost weight, with lower hip circumference, triglycerides, and IGF-I than control women (unpublished data).

We investigated whether the *BRCA* mutation carriers increased their adherence to the MedDiet by analyzing the data from the Mediterranean Diet Adherence Screener (MEDAS).[19] Another aim was to study the relation between adherence to the MedDiet and MetS.

Subjects and Methods

This study is part of a more comprehensive project on 600 *BRCA* mutation carriers aimed at (1) whether a dietary intervention significantly reduced IGF-I and other IRm (randomized trial); (2) whether carriers with a diagnosis of BC had higher IGF-I than carriers without BC (case-control study); (3) whether IGF-I and its changes over time affected the subsequent BC incidence and prognosis (cohort follow-up). The study was approved by the Ethics Committee of the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan. The study is ongoing and recruitment is still open.

The trial component of the study has been previously described.[2] Eligible subjects were women aged 18 to 70 years, either unaffected or affected with BC, without metastases or previous ovarian cancer, who underwent genetic counseling and fulfilled high-risk selection criteria for genetic testing based on personal and/or family history and resulted carriers of deleterious *BRCA* mutations (BRCA1, BRCA2, or both). Unaffected *BRCA* mutation carriers with bilateral prophylactic mastectomy were not included.

Women were fully informed about the study and gave signed informed consent.

At baseline, all women provided a copy of their clinical notes, gave a postprandial blood sample (to measure IGF-I, IGFI-BP3, insulin, and metabolic parameters) and completed questionnaires on BC risk factors. Height and body weight were measured without shoes and heavy clothes, waist circumference was recorded with a measuring tape at the midpoint between the lowest rib and the iliac crest in expiration. Blood pressure was taken using an electronic device. The same measurements were repeated at the end of the 6 months of dietary intervention. All participants received general recommendations for the dietary prevention of cancer.[20]

After the baseline examinations, women were randomized to an active dietary intervention or to a control group that continued observing the baseline recommendations. Women in the intervention group were invited to participate in 6 full days of lifestyle intervention activities over the subsequent 6 months. These activities included 6 cookery courses followed by lunch, 6 physical activity sessions (walking for 45 minutes) and 6 conferences. Since the main objective of the trial was to reduce serum levels of IGF-I and insulin resistance the recommendations for women in the intervention group included

- reducing protein intake, mainly milk and animal protein (except fish), down to 10% to 12% of total calorie intake;
- reducing calorie intake, through the preferred consumptions of highly satiating foods, such as unrefined cereals, legumes, and vegetables;
- reducing high–glycemic index food, such as refined flours, potatoes, white rice, corn flakes, and high-insulinemic foods, such as sugar and milk, preferring instead whole grain rice, barley, millet, oat, spelt, quinoa and buckwheat, legumes, vegetables (any type except potatoes);
- reducing sources of saturated fat (red and processed meat, milk and dairy products), preferring instead unrefined vegetable fats, such as olive oil, nuts, and oleaginous seeds;
- eating mostly food of plant origin, with a wide variety of seasonal products.

These recommendations are basically those of the MedDiet.

MEDAS Questionnaire

The intervention and control groups both completed the validated 14-point MEDAS[19] at baseline and at the end of the 6 months of dietary intervention. MEDAS consists of 12 questions on food consumption frequency and 2 on eating habits: Do you use olive oil as the main source of fat for cooking? Do you prefer chicken, turkey, or rabbit instead of beef, pork, hamburgers, or sausages?—considered characteristics of the Mediterranean diet.

Each question is scored 0 or 1. One point is given for using olive oil as the principal source of fat for cooking, preferring white meat over red meat, or for consuming: (1) 4 or more tablespoons (1 tablespoon = 13.5 g) of olive oil/

day (including that used in frying, salads, meals eaten away from home, etc); (2) 2 or more servings of vegetables/day; (3) 3 or more pieces of fruit/day; (4) less than one serving of red meat or sausages/day; (5) less than one serving of animal fat/day; (6) less than one cup (1 cup = 100 mL) of sugar-sweetened beverages/day; (7) 7 or more servings of red wine/week; (8) 3 or more servings of pulses/week; (9) 3 or more servings of fish/week; 10) fewer than 2 commercial pastries/week; (11) 3 or more servings of nuts/week; or (12) 2 or more servings/week of a dish with a traditional sauce of tomatoes, garlic, onion, or leeks sautéed in olive oil.

Definition of the MetS

Various investigators have used different definitions of MetS. In the present study, we defined MetS on the basis of the presence of at least 3 components out of 5, according to the threshold proposed by the International Diabetic Federation[21]: systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, triglycerides ≥150 mg/100 mL, high-density lipoprotein (HDL) <50 mg/100 mL, waist circumference ≥80 cm. The exception was blood glucose for which we used the threshold of 120 mg/100 mL or more instead of 100 mg/100 mL or less, because blood was sampled an hour and a half after a standard meal.

Laboratory Methods

Blood samples were collected at baseline and after the 6-month intervention 90 minutes after a standard meal (miso soup, brown rice seasoned with sesame seeds and salt, vegetables and legumes, 50 g uncooked). Women were asked to give 20 mL of blood; we prepared 8 samples of serum (4), plasma (2), red blood cells (1), and buffy coat (1). Serum samples were aliquoted and stored at −80°C.

Plasma glucose, triglycerides, total, low-density lipoprotein (LDL), and HDL cholesterol were measured using routine laboratory techniques. The technicians analyzing the serum samples were blinded to the intervention or control status of the patients.

Statistical Analysis

The distributions of each parameter, tested for normality by a graphic method, were normally distributed. The data were expressed as mean ± standard deviation (SD) or percentage. Body mass index (BMI) was defined as body weight in kilograms/height in meters squared (BMI = kg/m^2). The MEDAS score depended on the answer to each item., each scored 0 or 1. If the condition is not met, 0 points are recorded for the category. The final MEDAS score, ranging from 0 to 14, was the sum of all the points.

At baseline, the means of continuous metabolic variables in the intervention group were compared with the control group using Student's t test. A χ^2 test was used to compare frequencies. The Wilcoxon rank-sum test was used to compare food consumption in the intervention and control group at baseline.

Statistical analysis focused on changes in food intake and the metabolic parameters under study, calculated for each woman as the difference between values at the end of the study (sixth month) and baseline. We used the nonparametric Wilcoxon rank-sum test to compare baseline and 6-month food consumptions in the 2 groups. Analysis of variance for repeated measures (RM-ANOVA) was used to check for interactions between the 2 independent variables (group and time) and the dependent variable (factors under study). The model took into account time as the within-subjects factor and group as between-subjects factor. We analyzed the magnitude of changes in food consumption and metabolic variables using the difference (delta, Δ) between the end of the study and baseline for each woman in the two groups, and controlled for age (quintiles), BMI at baseline (quintiles), weight change (quartiles) and education (none or primary school, high school, degree or more).

The association between MetS and the MEDAS score was studied with a regression model. The reduction of the MetS parameters associated with the improvement of the MEDAS score was calculated using a multiple regression model including age (quintiles), BMI at baseline (quintiles), education (none or primary school, high school, degree or more), menopausal status and randomization group as model covariates.

A P value <.05 was taken as significant. All statistical tests were 2-sided. All analyses were done with the STATA 12 statistical package.

Results

At the time of writing 219 women had been properly randomized, 115 in the intervention and 104 in the control group. After randomization 2 women relapsed and 2 became pregnant so they did not start the active dietary intervention. Two others decided to drop out at the beginning of the dietary intervention, by choice. Therefore, data for 213 participants were available for this analysis, 122 women with a *BRCA1* mutation, 87 with a *BRCA2* mutation and 2 with both.

At baseline, the 2 groups were fairly homogeneous for anthropometric, hormonal, and metabolic variables (Table 1); 73.6% of women in the intervention arm and 65.5% in the control arm were menopausal at the time of recruitment (P = .19), but only 11% (in the intervention group) and 7% (controls) had a natural menopause. Two-thirds of the women (73/110) in the intervention arm and 64/103 controls had developed a BC (P = .91).

Food consumption was substantially similar in the 2 groups (Table 2). Intervention and control women both used

Table 1. Baseline Characteristics of the Study Population.[a]

	Intervention (n = 110)	Control (n = 103)
Age, y	46.9 ± 1.1	44.6 ± 9.7
Education		
First level	12.8	13.8
Second level	45.0	43.1
Third level	42.2	43.1
Menopause	65.4	73.6
Natural menopause	11.0	7.0
Metabolic syndrome		
1-2 factors	53.0	49.0
≥3 factors	14.0	7.0
Body mass index, kg/m^2	23.8 ± 4.5	23.9 ± 4.8
Waist circumference, cm	75.9 ± 9.9	77.2 ± 11.7
Hip circumference, cm	100.2 ± 11.4	110.2 ± 89.3
Systolic blood pressure, mm Hg	128.6 ± 18.7	126.9 ± 14.5
Diastolic blood pressure, mm Hg	81.0 ± 11.7	81.2 ± 9.6
Glycemia, mg/dL	112.1 ± 21.2	109.1 ± 23.1
Total cholesterol, mg/dL	199.8 ± 38.8	205.9 ± 36.4
High-density lipoprotein cholesterol, mg/dL	67.9 ± 15.9	73.3 ± 18.7
Low-density liprotein cholesterol, mg/dL	110.3 ± 33.1	115.4 ± 34.6
Triglycerides, mg/dL	107.2 ± 82.9	91.4 ± 47.1
IGF-I, ng/mL	171.3 ± 72.8	167.3± 62.4
Insulin, mU/mL	30.8 ± 19.4	26.2 ± 17.5

[a]Data are presented as mean ± or as percentages.

olive oil as main cooking fat, in moderate quantities (about 5 teaspoons/day) and consumed about 2 portions of vegetables per day. At baseline, intervention women ate slightly more fruit ($P = .38$), red meat ($P = .23$), legumes ($P = .11$), and fish ($P = .29$), and white meat rather than red meat ($P = .35$) than controls. Control women consumed slightly more pasta and wine than those in the intervention arm (Table 2). At baseline, both groups had good scores for adherence to the MedDiet (average MEDAS scores 7.9 and 7.4, $P = .13$). No significant differences in baseline foods consumption or in the MEDAS score emerged by comparing women with and without BC.

So far, 163 women (80 in the intervention and 83 in control group) have completed the 6 months of dietary intervention. The before/after analysis of MEDAS indicated that in both groups most of the indicators of the MedDiet improved but the intervention women made changes with greater impact on health. They significantly reduced their consumption of red meat ($P < .001$), butter ($P = .04$) and commercial sweets ($P < .001$) and significantly increased the consumption of legumes ($P < .001$) and nuts ($P < .001$). They also significantly reduced their consumption of pasta ($P = .01$). The control women significantly improved their consumption of legumes ($P = .02$), fish ($P = .01$), and nuts ($P = .02$) and significantly reduced the consumption of commercial sweets ($P = .04$). Both groups had nonsignificant increases in vegetable and fruit consumption. Both BC affected and unaffected women improved the indicators of the MedDiet in a similar way.

After the 6 months of dietary intervention, the MEDAS score increased by 1.3 in the intervention ($P < .001$) and 0.55 in controls ($P = .01$). The "delta" analysis of differences (intention to treat analysis) in food consumption between the 2 groups (Table 3) showed that intervention women reduced their consumption of red meat and commercial sweets significantly more than controls. Intervention women also had a significantly larger increase in consumption of legumes than controls and a borderline significant increase of nuts. Controlling the analysis for age, BMI at baseline, weight change, and education (ANOVA), the differences remained significant for the consumption of red meat and commercial sweets. Comparing the 2 groups, the difference in the MEDAS score improvements was borderline significant ($P = .05$). Controlling the analysis for age, BMI at baseline, weight change, and education, the results became significant ($P = .02$).

Stratifying the analysis for the presence or the absence of a previous BC, the "delta" analysis of differences showed that affected women increased slightly more the consumption of legumes compared with the unaffected ($P = .04$). Controlling the analysis for randomization group, age, BMI at baseline, weight change, and education (ANOVA), this result remained significant. Comparing affected and unaffected women, the difference in the MEDAS score improvements was not significant either in the crude or in the adjusted analysis.

As regards the metabolic pattern of the 163 *BRCA* mutation carriers, only 12% (13% in the intervention and 9% in the control group) had a MetS at baseline. However, 37% of the intervention arm and 30% of controls had at least 2 or more factors of the MetS ($P = .56$). Among these women, 89% were menopausal (15% natural menopause, 73% induced by BC treatment, and 12% due to bilateral prophylactic adnexectomy). After the 6 months of dietary intervention, most of the metabolic and anthropometric parameters significantly improved in both groups, but women in the intervention group significantly lost weight, with lower BMI, hip circumference, and triglycerides (unpublished data). Women in the intervention group had significantly less MetS ($P = .01$) and significantly fewer MetS factors ($P < .001$) while controls achieved only small changes (P for comparison = .02).

The MetS and adherence to the MedDiet were inversely correlated. The multiple regression model reported a significant association between reduction of the MetS parameters and improvements in the MEDAS score. The number

Table 2. Mediterranean Diet Adherence Screener (MEDAS) Food Consumption at Baseline.

	Criterion[a]	Intervention (n = 110)	Control (n = 103)	P[b]
Do you use olive oil as main cooking fat?	Yes	98.7%	96.4%	.33
How much olive oil do you consume in a day (including oil for frying, on salads)?	≥4 tablespoons	4.69 ± 2.53	4.66 ± 2.56	.92
How many vegetable servings do you eat per day? (1 serving ~ 200 g)	≥2	1.90 ± 0.86	1.91 ± 0.90	.97
How many fruit units do you eat per day? (1 serving ~ 100-150g)	≥3	2.04 ± 1.33	1.86 ± 1.61	.38
How many servings of red meat, hamburger, or meat products do you eat per day?	<1	0.71 ± 1.01	0.57 ± 0.72	.23
How many servings of butter, margarine, or cream do you eat per day? (1 serving = 12 g)	<1	0.16 ± 0.45	0.12 ± 0.32	.48
How many sweet beverages do you drink per day?	<1	0.35 ± 0.88	0.33 ± 0.69	.82
How much wine do you drink per week? (glass)	≥7	1.30 ± 2.22	1.94 ± 2.76	.07
How many servings of legumes do you eat per week? (1 portion = 150 g)	≥3	2.54 ± 2.27	2.11 ± 1.50	.11
How many servings of fish or shellfish do you eat per week? (1 portion = 150 /200 g)	≥3	1.91 ± 1.1.20	1.67 ± 1.12	.14
How many times per week do you eat commercial sweets or pastries (not homemade)?	<2	3.27 ± 2.63	3.81 ± 2.75	.16
How many servings of nuts do you eat per week? (1 portion = 30 g)	≥3	2.88 ± 2.65	2.76 ± 2.75	.76
Do you preferentially eat chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes	77.5%	71.1	.35
How many times per week do you eat pasta?	≥2	3.47 ± 2.18	3.77 ± 2.20	.33
MEDAS score		7.9 ± 2.1	7.4 ± 2.0	.16

[a]Criterion to score 1 point. Otherwise, 0 recorded.
[b]*P* of Wilcoxon rank-sum test.

of MetS parameters fell slightly on increasing the points of adherence of the MEDAS score ($P = .01$), controlling for age, BMI, menopausal status, education, and randomization group. Menopausal status appeared to have no significant effect. Belonging to the dietary intervention group was significantly associated with a greater reduction of the MetS.

Discussion

Women with highly penetrant BRCA mutations have a 55% to 60% risk for BC.[22-24] However, since penetrance rates are not 100%, it can be postulated that some risk-modulating factors do exist. The MetS considerably influences sporadic BC risk and prognosis[25] and rare retrospective data suggest that lifestyle factors linked to insulin resistance and IGF-I might be important for *BRCA* mutation carriers.[1] However, there are no prospective studies in this context. We therefore designed a demonstration project to examine whether a dietary intervention, emphasizing the Mediterranean diet, leads to a reduction of IGF-I and other markers of insulin resistance (randomized trial) and to investigate whether the intervention leads to a reduction of BC incidence and BC mortality in BRCA1 and BRCA2 mutation carriers (prospective cohort study).

The preliminary findings from the MEDAS questionnaires suggest that women in the intervention group showed substantial improvement in most of the indicators of the MedDiet and significantly raised their MEDAS score, by 1.3. Compared with controls, the women in the intervention group had a significantly greater reduction of consumption of red meat and commercial sweets. The control group also showed some improvement in the indicators of the MedDiet. The public awareness and the easy access to information about the benefits of the MedDiet led to the control group making some adjustments just to be on the safe side (the drop-in effect). Furthermore, this "contamination" was expected by design, because at baseline all women received the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR0 recommendations for cancer prevention[20] and the central recommendation of the WCRF/AICR is also the basic characteristic of the MedDiet ("Eat mostly food of plant origin, with a variety of non-starchy vegetables and of fruit every day and with unprocessed cereals and/or pulses within every meal"). These recommendations and the participants' vigorous motivation probably resulted in changes in the dietary habits of control women too and reduced the potential overall result.

Table 3. "Delta, Δ" Analysis of Differences (Intention to Treat Analysis) in Food Consumption Between the 2 Groups.

	Intervention (n = 80)	Control (n = 83)	P^a	P^b
How much olive oil do you consume in a day (including oil used for frying, or salads)?	+0.94	+0.62	.99	.79
How many vegetable servings do you eat per day? (1 serving ~ 200 g)	+0.05	+0.05	.91	.87
How many fruit units do you eat per day? (1 serving ~ 100-150 g)	–0.16	+0.04	.65	.27
How many servings of red meat, hamburger, or meat products do you eat per day?	–0.54	+0.05	**<.01**	**<.01**
How many servings of butter, margarine or cream do you eat per day? (1 serving = 12 g)	–0.06	–0.02	.93	.59
How many sweet beverages do you drink per day?	–0.18	0.04	.62	.31
How much wine do you drink per week? (glass)	–0.18	0.40	.69	.08
How many servings of legumes do you eat per week? (1 portion = 150 g)	+1.19	+0.66	**.01**	.41
How many servings of fish or shellfish do you eat per week? (1 portion = 150/200 g)	+0.16	+0.39	.38	.38
How many times per week do you eat commercial sweets, or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	–1.83	–0.43	**<.01**	**<.01**
How many servings of nuts do you eat per week? (1 portion = 30 g)	+1.63	+0.96	.05	.06
How many times per week do you eat pasta?	–0.08	–0.42	.18	.43
MEDAS score	+1.3	+0.55	.05	**.02**

Abbreviations: MEDAS, Mediterranean Diet Adherence Screener.
[a]*P* of Wilcoxon rank-sum test (values in boldface indicate statistical significance).
[b]*P* of analysis of variance controlling for age (quintiles), body mass index at baseline (quintiles), weight change (quartiles), and education (values in boldface indicate statistical significance).

MetS is an insulin resistance syndrome. A recent study showed that *BRCA* mutation carriers with BC more frequently develop type-2 diabetes.[26] This is an interesting point because it suggests that the prediabetic condition, when insulin is typically very high, facilitates the development of mammary tumors in carriers of the *BRCA* mutation. MetS can be reversed by adhering to the MedDiet, with a reduction in its prevalence of up to 69% after 2 years of diet.[16-18] Our diet and androgen (DIANA) randomized controlled trials showed that an insulin-lowering diet based on traditional Mediterranean and macrobiotic recipes significantly reduced the main factors defining the MetS, body weight, and the bioavailability of sex hormones and IGF-I, in healthy postmenopausal[27,28] and in women with BC.[29]

This is the first dietary intervention trial based on the MedDiet and macrobiotic recipes in *BRCA* mutation carriers. We previously showed that women in the intervention group had significantly lower serum levels of IGF-I and a better IGF-I/IGFBP3 ratio (unpublished data). These results also suggest an inverse relation between the MetS parameters and adherence to the MedDiet. Compared with women whose MEDAS score did not change or got worse, women whose score improved achieved a greater reduction of the MetS factors. This reduction slightly increased on increasing the points of adherence to the MEDAS score. In our population, the prevalence of MetS at baseline was fairly low (12%) and, as expected, the metabolic disorders were more prevalent in women in menopause. However, the reduction of the number of MetS factors was not influenced by menopausal status but was significantly related to the randomization group (dietary intervention) and to improvement of the MEDAS score.

These findings, though encouraging, are still based on small numbers. Another prospective randomized controlled trial in *BRCA* mutation carriers is currently running, to demonstrate improvements in nutritional behavior (adherence to the Mediterranean diet), BMI, and physical fitness in the mutation carriers in the intervention group.[30] Both studies will assess the role of a lifestyle intervention program in a cohort of *BRCA* mutation carriers. A recent prospective study evaluated the impact of adherence to the prevention recommendations of the American Cancer Society on overall mortality in a high genetic risk population. Adherence to all 3 prevention recommendations (do at least 150 minutes of moderate-vigorous exercise/week, do not drink or drink at most one glass of alcoholic drink/day, keep your body mass index lower than 25 kg/m^2) was associated with a 44% reduction of mortality in high-risk healthy women and 53% in women already suffering from BC.[31]

Therefore, although one cannot overstate the importance of surgery and/or chemoprevention, along with surveillance for BRCA mutation carriers, we think that there is a need to be able to offer recommendations to women regarding lifestyle choices. It is conceivable that interventions to control body weight and insulin resistance or increase physical activity may help decrease cancer risk particularly among women who are not opting to undergo prophylactic surgery or who are delaying surgery. This is particularly relevant in

the context of genetic counselling, where the counsellor has the potential to significantly affect women's prevention options, specifically among those who opt to not undergo surgery or chemoprevention.

With structured exercise and dietary adaptations, mutation carriers will be able to play an independent role in cancer prevention, which will help reinforce their self-management.

Conclusions

This is the first dietary intervention trial based on the MedDiet and macrobiotic recipes in *BRCA* mutation carriers. The results are encouraging and open a new way of thinking about prevention in high-risk families. With structured exercise and dietary adaptations, mutation carriers will be able to play an independent role in cancer prevention, which will help reinforce their self-management.

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