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Promotion of the mediterranean diet incancer long-survivors by means of the Med-Food Anticancer Program: a pilot study

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Abstract

Background. *The intervention "Med-Anticancer Food Program" has proven to be effective in promoting the Mediterranean Diet, significantly increasing the Mediterranean Adequacy Index in healthy subjects. There are no studies that have investigated the effectiveness of this intervention in individuals who have had a diagnosis of cancer.*

Objective. *To perform a pilot study to assess the opportunity of employing the methodology of the Med-Anticancer Food Program in order to encourage "long-term cancer survivors" to adhere to the Mediterranean Diet, as well as healthy people, and this in order to apply the program to larger groups.*

Methods. *From the residents' register of Foggia, a city in southern Italy, forty adults of both sexes, over 25 years of age, were recruited at random and assigned (1:1) as follows:*

- Twenty healthy subjects to the intervention-1 group

- Twenty long-term cancer survivors to the intervention-2 group

The Med-Anticancer Food Program was applied to both groups with an articulated intervention 11 weeks long, followed by a 52-week period of follow up. By means of a food diary of the last 3 days, the Mediterranean Adequacy Index values were calculated before intervention (T0), after a period of 11 weeks of interventions (T1) and at the end of the 52 weeks of follow-up period (T2). The H0 hypothesis of the study was that there are no differences between the two interventions in reaching by T1, and maintaining at T2, values of Mediterranean Adequacy Index around 7, considered the optimum for adherence to the Mediterranean diet.

Results. *Out of the subjects assigned to the intervention-1 group (n = 20), 11 subjects have completed the 52-months follow-up (55.0%); for intervention-2, 16 (80%) out of 20 have completed it. The average age of subjects was 52.1 years. The Mediterranean Adequacy Index, of intervention-1 group significantly increased from 2.8 (T0) to 9.2 (T1) and to 9.0 (T2) ($p < 0.0001$); whereas, in the intervention-2 group, Mediterranean Adequacy Index moved from 2.4 (T0) to 10.2 (T1) and to 9.3 (T2) ($p < 0.0001$). The difference of Mediterranean Adequacy Index between the two study groups at T1 and T2 was not significant. Such non-significance persists also after the stratification by sex and age obtained with Mantel-Haenszel procedure.*

The performance of the values of the laboratory parameters considered (folic acid, total cholesterol, alkyl resorcinol) was similar in the subjects of both intervention 1 and 2, without any difference, while considered at a basal level T0, at T1 and at the end of the follow-up period (T2).

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Conclusions. *The results of our work suggest the feasibility of conducting the Med-Anticancer Food Program in long-term cancer survivors. The results of the pilot study show that such intervention, carried on a small number of long term cancer survivors, is adequate to assess its feasibility but, due to the limited size of our study, a confirmation is required through larger nutritional prevention intervention studies*

Introduction

The Mediterranean Diet (MD) model is recommended for the prevention of tumors in both healthy subjects (primary prevention), and in those who have had a diagnosis of cancer (relapse prevention) (1-2). However, the general Italian population's adherence to MD is limited (3). The "Food Hygiene and Nutrition Service" of the "Local Health Authority" of Foggia, Italy (abbreviated as FG SIAN-ASL), in southern Italy, has designed and conducted the project called "Med-Anticancer Food Program" (M-AFP) (4-5), which had proven effective in healthy subjects in increasing adherence to the MD, estimated according to the Mediterranean Adequacy Index (MAI) (6-7). So far, the M-AFP was conducted only in healthy subjects. The aim of our further pilot study was to assess (a) whether the M-AFP could be effective in promoting the MD grip even in individuals who have had a diagnosis of cancer, and (b) whether there was any difference in response between them and the healthy subjects.To this end, two interventions of M-AFP were conducted, the former with healthy subjects and the latter with long-term cancer survivors, still alive 5 years after receiving their diagnosis, also called "long-term survivors". The *null hypothesis* of the study was that no differences are present between the two interventions in achieving the completion of the 11-week program and in maintaining - after a follow-up of additional 12 months - the MAI value equal to or greater than 7, which is considered the optimum for the adherence to the Mediterranean diet.

Methods

Sample size and recruitment

To calculate the sample size in relation to the null hypothesis H0 of no difference in the MAI to the end of the intervention of the M-AFP at 11 weeks (T1) and the follow-up period of 12 months (T2), to be assessed using the t-test for independent data, the following parameters were considered: alpha error = 0.5; power = 0.80; expected difference between groups = 4.0 with a sd = ± 3. Therefore, taking into account these parameters, the sample size results 13 persons for each intervention group; however, anticipating a 50% of drop-out, the number of subjects to be assigned to each of the two interventions should be 20. The study was conducted according to a cohort design.

Intensive unit

1. ***Training Phase***, 3 meetings (1 per week), 2 hours each. The aim of this step was to explain the Mediterranean diet, the benefits of physical activity and list theMediterranean foods with high anti-cancer action.

2. ***Experiential Phase***, 2 meetings (1 per week), 2 hours each. In this phase the participants actively learn, through sensory experiences, the basic topics covered in the training phase.

3. ***Final Phase***, 2 syncretic meetings (1 per week), 2 hours each. Learning at this stage is accomplished by simultaneously living sensory, emotional and motor experiences, according to the model implemented in the laboratory of taste, observing the preparation

of dishes and courses in accordance with the principles set out in the training phase. The experiences are then fused together through the direct participation in the preparation of dishes of the Mediterranean diet, alongside with the weekly programs of physical activity.

Resilient unit

The resilient unit, namely for consolidation, aims to reinforce the skills acquired in the intensive unit. It is divided into 4 sessions (2 behavioral and 2 cognitive), 1 a week of 2 hours each. The purpose of each session is to consolidate the changes, to strengthen the subjects' motivation to change their eating habits and to get engaged in physical activity, analyzing any obstacles, adapting the program to themselves (tailoring).

Subjects

Twenty healthy subjects and 20 long-term cancer survivors, all of them of both sexes and > 25 y old, have been randomly recruited from the Foggia residents' register. The healthy subjects have been assigned to the intervention group-1 and the long-term cancer survivors to the intervention group-2. The inclusion criteria for group-2 was to have had a diagnosis of cancer five or more years before; the exclusion criteria were, for both groups: chronic diseases (except cancer for group 2, of course), pregnancy, lactation, vegetarian or vegan diets, regular intake of drugs, milk enzymes or algae, tobacco smoking habit, higher than usual intake of fruit and vegetables (>2 servings of fruit a day and >3 servings of vegetables/day), regular physical activity (>2 hours/week), taking dietary supplements and drinking alchol.

Both interventions were conducted by the same team of FG SIAN-ASL according to the M-AFP methodology, in accordance with the conduct of M-FAP: the 11 weeks of the intervention-1 and intervention-2 were divided into an *intensive unit* (phase of theoretical training, experiential and syncretic) and a *resilient unit*.

Using the food diary of the last three days of the MAI, values were calculated before the interventions (T0), at the end of the interventions (T1), and lastly after the follow-up period of 52 weeks (T2). At T0, T1, and T2 also BMI was measured and MAI calculated.

Biochemical analysis

Blood samples were taken after overnight fasting in the week before study entry (T0), upon completion of the 11 weeks of the two interventions (T1) and at the end of the 52-week follow-up period (T2). The plasma folic acid and beta-carotene have been measured to estimate the consumption of fruit and vegetables; the plasma cholesterol to estimate the consumption of animal products and the plasma alkylresorcinols with regard to the whole-grain cereals consumption (8), while the CRP (C reactive protein) has been measured to evaluate chronic inflammation (9-10).

Statistics

Data were analyzed using Excel®. The normality of the data and the variables' distribution were tested using the Kolmogorov-Smirnov test. The data have been presented as an average ± sd. The differences within the groups at different times have been analyzed by using paired student's t-tests; the differences between groups on the same point were analyzed with unpaired Student's tests. All reported p-values are two-sided with a cut-off value of 0.05. The stratification by sex and age, considered as confounding variables, has been undertaken both for the evaluation of CRP and for the MAI, by means of the Mantel-Haenszel procedure.

Results

Out of 40 subjects assigned to the intervention-1 group (n = 20) or to the

Table 1 - Demographic, anthropometric, and metabolic characteristics of subjects in intervention-1 group and in intervention-2 group

Variables	Intervention-1				Intervention-2			
	Basal T0	After 11-w T1	After 52-w T2	*P value (T2 vs T0)*	Basal T0	After 11-w T1	After 52-w T2	*P value (T2 vs T0)*
Sex (M/F)	5/6				6/10			
Age (y)	51.4 ± 14.06				52.6 ± 15.01			
BMI (Kg/m^2)	25.4± 3.76	25.1 ± 3.36	24.7 ± 2.87	< .0001	27.7± 3,63	27.1 ±3.28	25.6 ±2.40‡	< .0001
MAI	2.8 ± 0.82	9.2 ± 1.60*	9.0 ± 1.57	< .0001	2.4 ± 0.81	10.2 ± 1.41*	9.3 ± 1.46‡	< .0001
CRP (mg/L)	12.4± 4.21	3.0 ± 1.02*	3.1 ± 1.17	< .0001	14.0 ± 3.54	3.2 ±1.33*	3.2 ±1.20‡	< .0001
Serum Folic acid (nmol/L)	9.0 ± 3.45	15.5 ± 2.47*	14.8 ± 2.71	< .0001	10.1 ±2.98	14.4 ±2.85*	14.39 ±3.18‡	< .0001
Total serum cholesterol (mg/dL)	196 ± 12.4	180 ± 15.5*	175 ± 11.6	< .0001	201± 12.1	168 ± 13.8*	175±15.4‡	< .0001
Total plasma alkylresorcinols (nmol/L)	59± 29.7	219 ± 38.3*	196 ± 34.8	< .0001	55 ± 27.0	219 ±38.9*	207 ±44.5‡	< .0001

Values are mean ± SD; MAI = Mediterranean Adequacy Index, is calculated by dividing the sum of the percentage of total energy from typical Mediterranean
food by the sum of the percentage of total energy from non-typical Mediterranean food groups, and is expressed as mean value ± SD; P values are two-sided
and were calculated by paired and non-paired Student's t-test.
P < .05 versus basal; † P < .05 versus T0 (intervention-1); ‡ P < .05 versus T1 (intervention-1).

intervention-2 group (n = 20), 11 (55%) and 16 (80%), respectively, have completed the 12-month follow-up. The duration of the study numbered a total of 63 weeks: 11 weeks of intervention and 52 of follow-up. Table 1 shows for both steps the characteristics of the subjects: at baseline (T0), after 11 weeks of intervention (T1) and after 52 weeks of follow-up (T2).

Out of the intervention-1 group, 5 males (45.5%) and 6 females (54.5%) have completed the study; out of intervention-2 group, 6 males (37.5%) and 10 females (62.5%) have completed the study. The mean age of the 27 subjects was 52.1 (± 11.93) years, in particular: in the intervention-1 it was 51.4 (± 14.06) years of age , in intervention-2, 52.6 (± 15.01) years of age, with no significant difference between the two groups in the study.

The MAI for the subjects of intervention-1 has significantly ($p < 0.0001$) increased from 2.8 (± 0.82) at T0, to 9.2 (± 1.60) at T1 and 9.0 (± 1, 57) at T2; while for subjects of intervention-2 it has increased significantly ($p < 0.0001$) from 2.4 (± 0.81) at T0, to 10.2 (± 1.41) at T1 and up to 9.3 (± 1.46) at the end of the follow-up period (T2). At the end of the study, there was not a significant difference between the two study groups in MAI score, even after the stratification by sex and age by means of the Mantel-Haenszel procedure. In subjects of the intervention-1 group the CRP was considerably reduced from 12.4 (± 4.21) at T0, to 3.0 (± 1.02) at T1 and to 3.1 (± 1.17) at T2; while, for the intervention-2

Table 2 - Means and SD of MAI at the end of the study, stratified by sex and age

Sex	Age (years)	Measures	Intervention-1 Group	Intervention- 2 Group
Males	<50	mean	8.3	8.9
		SD	0.99	1.83
		n	2	3
	51 - 70	mean	7.3	9.0
		SD	0.06	0.29
		n	3	3
Females	<50	mean	10.8	9.0
		SD	1.50	1.18
		n	3	5
	51 - 70	mean	8.6	9.7
		SD	0.75	1.47
		n	3	5

SD = standard deviation
n = number of subjects
MAI= Mediterranean Adequacy Index

group, CRP was reduced from 14.0 (± 3.54) recorded at T0 to 3.2 (± 1.33) at T1 and to 3.2 (± 1.20) at T2. At the end of the study, there was not a significant difference between the two study groups in the CRP values, even after stratification by sex and age by means of the Mantel-Haenszel procedure, with $\chi^2_{M\text{-}H}$ = 1.93 (P = 0.1651).

The Folic acid value of the intervention subjects-1 significantly increased from 9.0 (± 3.45) at T0, to 15.5 (± 2.47) at T1 and to 14.8 (± 2.71) at T2; In intervention subjects-2 Folic acid has risen significantly (p < 0.0001) from 10.1 (± 2.98) to T0, 14.4 (± 2.85) at T1 and by the end of the follow-up period (T2) it has risen to 14.39 (± .3.18)

The total cholesterol of the intervention-1 subjects decreased significantly (p <.0001) from 196 (± 12.4) at T0 to 180 (± 15.5) at T1 and to 175 (± 11.6) at T2; in intervention-2 people folic acid decreased significantly (p < 0.0001) from 201 (± 12.1) at T0, to 168 (± 13.8) at T1 and, by the end of the follow-up period (T2), increased to 175 (± 15.4).

The total plasmatic alkyl resorcinol of intervention-1 subjects increased significantly from 59 (± 29.7) at T0 to 219 (± 38.3) at T1 and 196 (± 34.8) at T2; In intervention-2 people the total alkyl resorcinol plasma significantly increased (P < 0.0001) from 55 (± 27.0) at T0 to 219 (± 38.9) at T1 and - by end of the follow-up period (T2) - it reached 207 (± 44.5).

Discussions and conclusions

Our pilot study provides important evidence concerning the feasibility of promoting the Mediterranean Diet through M-AFP in long-term cancer survivors.

At the end of the 11-week intervention phase, both 11 out of the 20 healthy subjects and 16 of the long-term cancer survivors who completed the study showed

a significant reduction in BMI, CRP and serum cholesterol, and a significant increase in MAI, serum folic acid and total plasma alkylresorcinols, with no difference between the two groups. Such anthropometric, dietetic and bio-haematochemical improvements were also maintained at the end of the 52-week follow-up, with no significant difference between the two groups.

The fact that no difference has been detected between the two intervention groups may suggest that the M-AFP has an inherent capacity to motivate participants to join the Mediterranean Diet, regardless of having had cancer or not. This capacity probably lays in the particular character of the M-AFP, structured and conducted according to the indications suggested by the cognitive-social theory, widely validated in the literature and effective for short and long-term change.

Our findings therefore suggest that M-AFP increases adherence to the Mediterranean Diet in long-term cancer survivors, but we feel that such result should be confirmed in controlled and sufficiently extensive intervention studies in the field of nutritional prevention (11-12).

Riassunto

Promozione della dieta mediterranea nei soggetti lungo-sopravviventi al cancro mediante il med-food anticancer program: uno studio pilota

Background. L'intervento "Med-Food Anticancer Program" si è dimostrato efficace nella promozione della Dieta Mediterranea, incrementando significativamente l'Indice di Adeguatezza Mediterraneo nei soggetti sani. Non ci risultano studi che abbiano indagato l'efficacia del Med-Food Anticancer Program nei soggetti che hanno avuto una diagnosi di cancro.

Obiettivo. Valutare in un pilota la fattibilità di reclutamento, randomizzazione e delle procedure per l'utilizzo della metodologia del Med-Food Anticancer Program nell'incrementare l'aderenza alla Dieta Mediterranea sia dei soggetti sani che di quelli che hanno avuto una diagnosi di cancro da oltre 5 anni ("lungosopravviventi"), da applicare poi in uno studio di scala maggiore.

Metodi. Dal registro dei residenti della città di Foggia, in Italia meridionale, quaranta adulti di entrambi i sessi e di età superiore ai 25 anni sono stati reclutati random così come di seguito:

- venti soggetti sani, assegnati al gruppo di intervento-1 condotto secondo la metodologia del Med-Food Anticancer Program;
- venti soggetti lungosopravviventi, assegnati al gruppo di intervento-2 condotto secondo la metodologia del Med-Food Anticancer Program.

Ambedue gli interventi hanno avuto la durata di 11 settimane, seguite da un periodo di 52 settimane di follow-up. Mediante il diario alimentare degli ultimi 3 giorni sono stati calcolati i valori dell'Indice di Adeguatezza Mediterranea prima degli interventi (T0), dopo gli interventi di 11 settimane (T1) ed infine al termine del periodo di follow-up (T2). L'ipotesi Ho dello studio è stata quella di nessuna differenza tra i due interventi nel mantenere al T2 il valore uguale 7 dell'Indice di Adeguatezza Mediterranea, considerato l'optimum per l'aderenza alla dieta mediterranea.

Risultati. Dei 40 soggetti assegnati al gruppo di intervento-1 (n=20) o al gruppo di intervento-2 (n=20), hanno completato i 12-mesi di follow-up 11 soggetti dell'intervento-1 (55,0%) e 16 (80%) dell'intervento-2. L'età media dei soggetti era di 52,1 anni. L'Indice di Adeguatezza Mediterranea, nel gruppo-1, è aumentato significativamente da 2,8 (T0) a 9,2 (T1) e a 9,0 (T2) al termine del periodo di follow-up ($p<0,0001$); mentre, nel gruppo-2, da 2,4 (T0) a 10,2 (T1) e a 9,3 (T2) ($p<0,0001$). La differenza dell'Indice di Adeguatezza Mediterranea tra i due gruppi in studio al T1 e al T2 non era significativa. Tale non-significatività permane anche dopo stratificazione per sesso ed età operata con la stima di Mantel-Haenszel. L'andamento dei valori degli altri parametri di laboratorio considerati (acido folico serico, colesterolo totale e achilresorcinoli) è stato analogo sia nei soggetti dell'intervento-1 che in quelli dell'intervento-2, senza alcuna differenza tra i due gruppi nei tempi considerati a livello basale T0, al T1 e al termine del periodo di follow-up (T2).

Conclusione. Dai risultati dello studio pilota emerge la fattibilità e l'efficaciadell'intervento del Med-Food Anticancer Program applicato ad un piccolo numero di lungosopravviventi al cancro;questo risultato richiede mperò di essere confermato da studi controllati più ampi ampi di intervento di prevenzione nutrizionale.

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