Original Article

Role of food choice for breast cancer prevention in developing societies: A pilot case–control study in the women North Cyprus

ABSTRACT

Background: Breast cancer incidence is increasing in developing societies. The Mediterranean eating regimen has been suggested to play a preventive role in reducing breast cancer risk.

Objective: This study investigated the preventive role of fruits and vegetables, eggs, fish, olives and olive oil, and fresh potatoes consumption similar to western Mediterranean diets on breast cancer development in the women of North Cyprus.

Materials and Methods: This case–control study was carried out in Dr. Burhan Nalbantoglu Devlet Hastanesi, Lefkosa, North Cyprus. The study group was 305 women with confirmed cases of breast cancer and the control group was 302 women without breast cancer. Due consent to participate in the study was obtained. Information on dietary intake was collected, which included age, menopausal status, breast density, age at menarche, and dietary consumption of fresh potatoes, fruits and vegetables, olives and olive oil, fish, and eggs. Logistic regression model was used to analyze the link between the dietary intake and breast cancer risk.

Results: Consumption of fruits and vegetables, olives and olive oil 5 or more servings per day, and fish 2 servings per week showed an odd ratio (OR) = 0.09 (0.04–0.18), 0.06 (0.03–016), and 0.04 (0.02–0.10), respectively, with the 4–6 eggs per week and 4 or more servings of fresh potatoes per week OR = 0.10 (0.54–0.20) and 0.15 (0.08–0.28), respectively.

Conclusion: The consumption of olives and olive oil 5 or more times, and fish 2 or 1 times weekly played a more significant role in reducing the risk of breast cancer in women. Investigating at a larger scale in the study population is yet to be done.

Keywords: Breast cancer, breast cancer prevention, developing societies, Mediterranean diets

INTRODUCTION

Breast cancer is the most predominant malignancy among the women of North Cyprus[1] as well as in similar developing societies.[2] Yearly, worldwide deaths from breast cancer are about 327,000. It is estimated that 1.35 million new cases will be observed each year and in 2020, 1.7 million cases are going to be diagnosed with more than 50% of the cases in developing regions.[3]

The increase in breast cancer risk is suggested to be due to changes in lifestyle, reproductive factors, increased life expectancy,[4,5] genetic factors, race, environmental conditions, physical activity, socioeconomic status, body mass index, and nutrition.[6]

Among all primary preventions for breast cancer in developing societies, the consumption of the

Ceasar Dubor Danladi, Nedime Serakinci

Department of Molecular Biology, Faculty of Art and Sciences, Cyprus International University, Nicosia, Turkish Republic of North Cyprus

Address for correspondence: Dr. Ceasar Dubor Danladi, Department of Molecular Biology, Faculty of Art and Sciences, Cyprus International University, Nicosia, Turkish Republic of North Cyprus.
E-mail: danladiceasar@ymail.com

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right foods is the most cost-effective cancer preventive intervention.[7]

Inter-societal differences in response to dietary consumption and breast cancer risk maybe linked to genetics.[8] There are polymorphisms in the interactions of diets intake and gene, that may influence epigenetics and further modify the expression of genes that influence the risk of breast cancer.[9]

A French cohort study reported, that there was an inverse relationship with breast cancer risk following the intake of "healthy/Mediterranean diet" consisting of fruits, raw or cooked vegetables, fish and crustaceans, olive oil, and sunflower oil in postmenopausal women especially those with estrogen receptors positive/progesterone receptors negative tumors[10] and breast cancer was also observed to decrease in Latino and non-Latino Caucasian women in a study carried out in the United States to investigate the function of Mediterranean diets such as alcoholic beverages, chicken, seafood, vegetables, green salads, olive oil, and salad oil among this group.[11] Although the study by Bessaoud et al. reported no association between breast cancer risk and the intake of fruits, raw and cooked vegetables, fish, and olive oil in France,[12] Demetriou *et al.* in another study observed a positive relationship between the consumption of the Mediterranean diet and breast cancer risk in women.[13] Further investigation on the Mediterranean dietary intake and breast cancer risk carried out among Greek-Cypriot women, reported that the adherence to a dietary pattern rich in vegetables, fish, legumes, and olive oil may favorably influence the risk of breast cancer.[14] The foods consumed in the Mediterranean reduce breast cancer risk[15] and diets of a sort conventional in Mediterranean societies are portrayed by a high intake of vegetables, fruits, fish, olive oil, and moderate consumption of protein, which are thought to present health advantages.[15]

The defensive role of Mediterranean foods on breast cancer is biologically plausible with the Mediterranean diet rich in fiber, antioxidants such as flavonoids, vitamins, carotenoids, and squalene, and the diets might modulate breast cancer risk by diminishing endogenous estrogens,[16] increasing sex-hormone binding globulin levels,[17] neutralizing free radicals and preventing deoxyribonucleic acid damage,[18,19] lessening oxidative stress,[20,21] and genetic modification.[22]

Previous studies on Mediterranean foods and breast cancer have provided mixed results. North Cyprus has a typical western Mediterranean way of life with living conditions and diets that ought to be ideal for healthy wellbeing.[23,24] Culture may drive the consumption of certain types of foods in high amounts based on local availability.[25] Limited evidence exists that supports the probable causal role of Western

Mediterranean diets. Finding the specific foods that have a significant impact on breast cancer risk will allow for a targeted consumption to achieve maximum benefits.

Furthermore, an awareness on the pivotal role of Mediterranean foods should be encouraged, most especially in the population vulnerable to micronutrients deficiencies[26,27] such as in developing societies.

The purpose of our study was to investigate the potential positive impact of the Western Mediterranean dietary lifestyle through investigating the significance of the varying amount of intake of fruits and vegetables, fish, olives and olive oil, fresh potatoes (cooked), and eggs on breast cancer risk among the women of North Cyprus.

MATERIALS AND METHODS

General study details

This was a hospital-based case–control study. The study was carried out in Dr. Burhan Nalbantoglu Devlet Hastanesi, Lefkosa, North Cyprus, between January 2018 and November 2018. Ethical approvals were obtained from Near East University, North Cyprus ethical community with approval number YDU/2018/55-523 and the ethical community of Dr. Burhan Nalbantoglu Devlet Hastanesi, Lefkosa, North Cyprus with approval number YTK.1.01.

Informed consent was obtained from participants before the study was carried out.

There was no form of funding received for this study.

The study was conducted according to ethical guidelines established by the Declaration of Helsinki and other guidelines such as Good Clinical Practice Guidelines and those established by the ICMR.

Participants

From sampling the women enrolled were as follows:

Case group = 305 women with confirmed cases of breast cancer.

Hospital-based control groups = 302 women without breast cancer attending the cancer hospital for other reasons. Women between the ages of 18–69 years were included in the whole study group. Women with confirmed cases of breast cancer were included in the case group, while women with a history of lobular and ductal carcinoma *in situ* were excluded from the control group. Hospital-based controls were used to obtain a more reliable data.

The sampling size was based on the following calculations:

$$n = \frac{N \times t^2 \, p \times q}{(N-1)\, d^2 + t^2 \times p \times q}$$

Equation 1: Equation 1 was used to determine how many women are needed to get results that reflect the target population as precisely as possible. $N = 121{,}257$ women population size, $t = t$-table value $= 1.96$ (a $=0.05$), $P =$ (prevalence rate) $= 91/100{,}000 = 0.00091$ (expected frequency). This is the proportion of the population affected by BC, $q = 1 - p = 0.99909$. This is the proportion of the population not affected by BC, $d =$ (acceptable margin of error) $=0.001$. The margin of error is the amount of error that can be tolerated. A lower margin of error requires a larger sample size. Following the calculations, the required sample size was 317.8 women.

Objectives
The influence of the Mediterranean diets in the prevention of breast cancer among the women of North Cyprus was studied.

Study methodology
Breast cancer cases were approached while waiting for their oncologist appointment or while receiving chemotherapy. Patients with breast cancer were selected as diagnosed pathologically based on the international classification of diseases for oncology 3rd edition (C50.0–C50.9)[28] and registered with the cancer center's database.

The hospital-based controls were women attending the hospital for other reasons and had no history of breast cancer. The goals of the study were explained clearly to them and due consent to participate was verbally obtained or by filling a consent form. The controls were asked questions about their dietary intake in the past 5–10 years, while the cases were also asked the same questions about their dietary intake 5–10 years before diagnosis.

Data were collected with the use of a specially designed questionnaire through a standardized interview. The questionnaire included information on age, menopausal status, age at menarche, and breast density. In addition, a diet interview was conducted on each subject using a food frequency questionnaire designed to capture the consumption of 5 food items selected from previously validated questionnaires,[29,30] and commonly consumed by the people of North Cyprus. The frequency of intake of the 5 food items was categorized as follows: eggs intake: 4–6/week, 1–3/week and none; fruits and vegetables intake: 5 or more servings per day, 3–4 servings per day, 2 servings per day and none; olives and olive oil intake: 5 or more servings per day, 3–4 servings per day, 2 servings per day and none; fish intake: 2 servings per week, 1 serving per week, and never; and fresh potatoes: 4 or more servings per week, 2–3 servings per week, and 1 serving or none per week. Only the completely answered questionnaires were analyzed [Table 1].

Table 1 shows the standard used for the servings of each studied Mediterranean food.[31-33] A serving is equal to the quantity per meal and this can be cooked, fresh, or dried.

Statistical analysis
Women's age, menopausal status, breast density, age at menarche, and dietary intake between cases and controls were first analyzed by cross-tabulation and Chi-square test. The statistical significance was $P < 0.05$. To analyze the link between the frequency of dietary intake and breast cancer risk, a multivariable logistic regression model was used and only diet consumption frequency was analyzed. No confounding variables were used in the analysis. The fit of the model was assessed on the basis of Pearson's Chi-square or Hosmer–Lemeshow goodness of fit. The statistical analysis was carried out using IBM SPSS (IBM, Armonk, NY, USA).
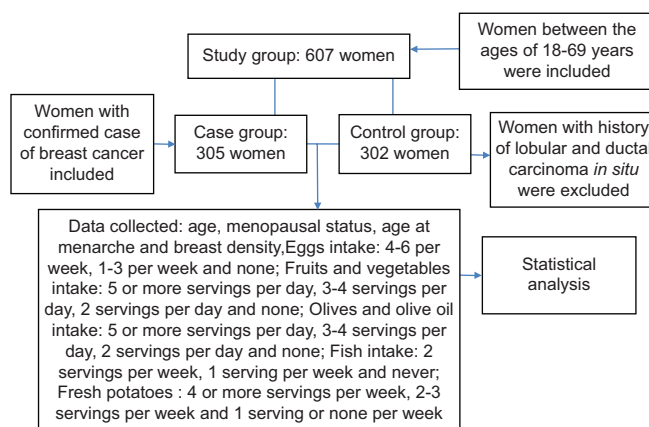
RESULTS

Study flow diagram

Table 1: The standard serving of the studied foods

Foods	Amounts
1 serving of vegetables	1 cup of raw leafy vegetables, 1/2 a cup of raw or cooked vegetables
1 serving of potatoes	1 cup of diced, mashed or medium-sized boiled potato
1 serving of fruits	1 cup of chopped fruits, 125 mL (1/2 cup) of fruit juice (no added sugar) and ½ cup dried fruits
1 serving of fish	1 can of fish, 1 cup of sliced fish, or 1 fish
1 serving of egg	1 egg
1 serving of olive oil	1 tablespoon per meal
1 serving of olives	5 olives per meal

A total of 305 breast cancer cases and 302 hospital-based controls were studied.

The age range of the participants studied was between 18 and 69 years, with a mean age of 45.60 years.

The highest number of 221 women in the menarche group were premenopausal women with 13 years of age at menarche, while the following are 163 postmenopausal women in the same category. The lowest, which is 29 premenopausal women had their menarche at age = <12 years. Fifty postmenopausal women had their menarche at age = <12 years. The women with menarche at age = >14 were 88 premenopausal women and 56 postmenopausal women.

201 women, with heterogeneously dense breast were premenopausal, followed by 155 postmenopausal women with almost entirely fatty breast and 7 postmenopausal women with extremely dense breast. Fifty-two premenopausal women had extremely dense breast [Table 2].

As shown in Table 3, more women in the hospital-based control group consumed fruits and vegetables 5 or more servings per day ($n = 161$) with less women in the breast cancer group consuming the same amount ($n = 106$).

Olives and olive oil were highly consumed in the hospital-based controls group with 49 women consuming 5 or more servings per day and 41 women in the breast cancer cases group. The number of women not consuming olives and olive oil increased in the breast cancer cases group while the reverse was the case in the hospital-based control group.

Eighty-three breast cancer cases consumed 2 or more servings per week of fish while 160 hospital-based controls consumed the same amount. One hundred and nineteen breast cancer cases and 132 hospital-based controls consume fish once in a week.

The breast cancer cases that consumed 4 or more servings per week of fresh potatoes were 59 with 134 women observed in the hospital-based control group. Ninety-eight and 117 women consumed 2–3 servings per week of fresh potatoes (cooked) in the breast cancer cases and hospital-based control groups, respectively.

4–6 eggs and 1–3 eggs were consumed per week by 154 and 50 breast cancer cases respectively, while 225 and 49 women with the same consumption rate were observed in the hospital-based control group.

Table 2: The distribution of characteristics in the study population

Variables	Breast cancer patients	Hospital-based controls	Significant
Age (years)			
0–29	6	109	<0.05
30–39	41	67	
40–49	54	52	
50–59	93	48	
60–69	111	26	
Breast density			
Extremely dense	25	34	<0.05
Heterogeneously dense	179	129	
Almost entirely fatty	101	139	
Menopausal status			
Premenopausal	117	221	<0.05
Postmenopausal	188	81	
Age at menarche (years)			
≤12	73	6	<0.05
13	170	214	
14	62	82	

Table 3: The dietary consumption of the study population

Diets	Breast cancer patients	Hospital-based controls	Significant
Eggs			
4–6 per week	154	225	<0.05
1–3 per week	50	49	
None	101	28	
Fruits and vegetables			
5 or more servings per day	106	161	<0.05
3–4 servings per day	48	58	
2 servings per day	45	65	
None	106	18	
Olives and olive oil			
5 or more servings per day	41	49	<0.05
3–4 servings per day	52	86	
2 servings per day	115	150	
None	97	17	
Fish			
2 servings per week	83	160	<0.05
1 serving per week	119	132	
Never	103	10	
Fresh potatoes (cooked)			
4 or more servings per week	59	134	<0.05
2–3 servings per week	98	117	
1 or none per week	148	51	

A multivariable logistic regression model was used to analyze the food intake frequency, the least frequency of intake was used as the reference [Table 4]. The omnibus test of model, coefficients was significant ($P < 0.05$). Cox and Snell $R^2 = 0.442$ and Nagelkerke $R^2 = 0.590$. The Hosmer and Lemeshow test was also significant ($P < 0.05$). From the regression analysis, the intake of fruits and vegetables 5 or more servings/week and 2 servings/

Table 4: The logistic regression analysis of food intake frequency of the study group

Diets	B	Significant	OR	95% CI		P %
				Lower	Upper	
Fruits and vegetables						
Never (reference)		0.00	1.00			
5 or more servings/day	−2.4	0.00	0.09	0.04	0.18	7
3–4 servings/day	−2.3	0.00	0.10	0.04	0.20	9
2 times/day	−2.0	0.00	0.12	0.06	0.27	10
Eggs						
Never (reference)		0.00	1.00			
4–6/week	−2.2	0.00	0.10	0.05	0.20	9
1–3/week	−2.1	0.00	0.11	0.05	0.25	10
Olives and olive oil						
Never (reference)		0.00	1.00			
5 or more servings/day	−2.7	0.00	0.06	0.03	0.16	5
3–4 servings/day	−2.3	0.00	0.10	0.04	0.21	8
2 servings/day	−1.9	0.00	0.16	0.08	0.32	13
Fish						
Never (reference)		0.00	1.00			
2 servings/week	−3.1	0.00	0.04	0.02	0.10	3
1 serving/week	−2.7	0.00	0.06	0.03	0.15	5
Fresh potatoes (cooked)						
Never (reference)		0.00	1.00			
4 or more servings/week	−1.9	0.00	0.15	0.08	0.28	13
2–3 servings/week	−1.7	0.00	0.18	0.10	0.33	15

OR: Odds ratio, CI: Confidence interval

week had an odd ratio (OR) = 0.09 and 0.12, respectively. The OR = 0.10 and 0.11 was observed for the intake of 4–6 eggs/week and 1–3 eggs/week, respectively. Olives and olive oil intake 5 or more servings/week was 0.06, while the OR of 1 serving of fish/week was 0.06, Intake of 2 servings/week of fish OR = 0.04. Fresh potatoes 4 or more servings/week OR = 0.15.

The percentage probabilities (*P*) of breast cancer linked to each dietary category was calculated as $P = \text{Exp}(B)/1 + \text{Exp}(B) \times 100$ and is represented in Table 4.

DISCUSSIONS

Nutrition has long been suggested to impact breast cancer etiology in about 35% of disease cases,[34] the sufficient consumption of foods containing essential nutrients is crucial to the modification of breast cancer risk in women.

The studied foods commonly consumed on the Mediterranean island of North Cyprus, which include, fresh potatoes, olives and olive oil, fruits and vegetables, eggs, and fish reduced the probability of breast cancer in all the women, proving that they are among the healthiest diets.[35] Interestingly, Table 5 shows the first quartile the intake of fish 2 or 1 times per week followed by 5 or more times of olives and olive oil provided the highest protection in reducing the probability of breast cancer disease in women.

Table 5: Classification tables of odds ratio of dietary intake across quartiles

Quartiles	OR	95% CI	Dietary intakes
1st	0.04	0.02–0.10	2 servings/week of fish
	0.06	0.03–0.15	1 serving/week of fish
	0.06	0.03–0.16	5 or more servings/day of olives and olive oil
2nd	0.09	0.04–0.18	5 or more servings/day of fruits and vegetables
	0.10	0.04–0.21	3–4 servings/day of olive and olive oil
	0.10	0.04–0.21	3–4 servings/day vegetables and fruits
3rd	0.10	0.05–0.20	4–6 eggs per week
	0.11	0.05–0.25	1–3 eggs per week
	0.12	0.06–0.27	2 servings/day of vegetables and fruits
4th	0.15	0.08–0.28	4 or more servings/week of fresh potatoes
	0.16	0.08–0.32	2 servings/day of olives and olive oil
	0.18	0.10–0.33	2–3 servings per week of fresh potatoes

OR: Odds ratio, CI: Confidence interval

A case–control study situated in Italy with 2569 breast malignant growth cases and 2588 controls found an inverse relationship with fish intake, especially among postmenopausal women[36] linked to the consumption of dietary marine n-3 polyunsaturated unsaturated fatty acids.[37]

While an epidemiological and experimental proof recommended that olive oil may decrease the risk of specific tumors, specifically breast cancer,[38] this may be due to the high monounsaturated fat content and concentration of poly-phenolic compounds in virgin and extra virgin olive oil.[39]

These are the main wellspring of lipids within the customary Mediterranean diet.[29] According to studies, Mediterranean dietary lipids have been shown to impact breast cancer.[40] These lipids play a significant role in the regulation of biological activity and are important components of the cell membrane.[41] However, when the concentration of polyunsaturated lipids in membranes is too high it may lead to an upsurge in fluidity and peroxidation.[42] Thus, moderate consumption of these lipids is effective in decreasing oxidation damage in the membranes.[43] The protective effect of the intake of Mediterranean dietary lipids on breast cancer may be through the signaling pathways such as receptor tyrosine-protein kinase ErbB4-truncated protein, which plays a part in mammary development and breast cancer and Ak strain transforming parthway linked to apoptosis.[44,45]

Mediterranean dietary lipids may decrease proliferation through the down surge of epidermal growth factor-2 signaling pathway as Ki-67 has been shown to decrease following the administration of lipids in malignant and benign breast neoplasm.[45-47] Dietary lipids influence the decrease of factor-kB nuclear translocation and signaling on peroxisome proliferation-activated gamma receptor and through the interaction with the G-protein receptor 120, which reduces apoptosis inhibitors and cytokines adhesion molecules.[48] Dietary lipids from Mediterranean foods are shown to partially and beneficially affect the expression of atherosclerosis-related genes,[49] Tumor suppressor gene p53 expression increased with the intake of fish-sourced docosahexaenoic acid (DHA).[50,51] Phenolic extracts from Brava extra virgin olive oil minimized cell viability and induced cell death in Michigan Cancer Foundation-7 breast cancer cells.[52] Breast cancer 1 and 2 genes also increased with exposure of breast cells lines to omega-3 polyunsaturated fatty acid (eicosapentaenoic acid and DHA) from fish.[53] An accompanied decrease in HER-2/neu an oncogene has been seen in BT-474 and SKBr-3 breast cancer cells treated with oleic acid supplements.[54] Gago-Dominguez et al. observed a 30% lower risk of breast cancer linked to glutathione-S-transferase T1 null genotype in postmenopausal Chinese women living in Singapore after the intake of marine dietary lipids from fish.[55] The benefits were more in postmenopausal women with glutathione transferase (GST) polymorphisms that led to low or no GSTT1, GSTP1, and GSTM1 activity.[55]

To be able to recommend the right nutrition for a given population, it is important to find the dietary intake that incorporates all the nutrients required[56] and when consumed in the right amounts will provide optimum benefits.

The ability of a diet to provide prevention and reduction of diseases that are linked to it determines its nutritional sufficiency[57] and genotype may be determining factor on how these nutrients are made available for body use and function. The frequency of polymorphism differs with ethnicity this interplay needs to be studied to find out how breast cancer can be modified by food intake in relation to genotype[9] in this population. Most societies especially the developing societies can explore the advantages of Mediterranean diets through research that looks for diets that are affordable, effective, and locally available sources of sufficient micronutrients that can reduce the risk of breast cancer.

The long-term control of breast cancer can be achieved when the association between culture and nutritional selections is considered when making policies because most societies consider food as an essential part of their cultures, religious, and social experiences.

Policies and programs that advocate home farms and gardens can lead to the increased availability, affordability, and consumption of healthy foods such as potatoes, vegetables, fruits, eggs, fish, and olives in developing societies.

Also encouraging with incentives for people to set up neighborhood supermarkets and eateries that sell these foods will improve affordability and availability.

Agricultural subsidies in developing societies for producers of these foods will encourage others to start producing thus reducing cost and increasing availability.

Cultural festivals that promote and protect healthy foods are important in sustaining healthy eating.

Civil society organizations, such as farming and fishing cooperatives, religious groups, charitable organizations, and women's groups, should play a part in public policy creation and implementation.

Transnational food trade with proper regulations will enable the availability of a variety of healthy foods coming from across the borders.

Governments of developing societies that want to ensure that nutritional objectives are adhered to in order to improve the wellbeing of their citizens need to carry out school and public education campaigns on diets and engage the food and agriculture sectors.[7] The awareness of the pivotal role of these diets in breast cancer prevention will go a long way in increasing the implementation of policies and programs that target the right population.

Our study was carried out in a typical Mediterranean setting and reproducible. The cognitive impairment arising from illness and treatment may influence the answers provided by some breast cancer patients but to overcome this, patients were ensured to be in stable state by qualified medical practitioners before the interviews was conducted.

The case–control study method used has its limitations in the sense that the information collected is subject to recall bias. To minimize this a few food items were used in the food frequency questionnaire and the consumption categories were such that the participants could easily recall. However, such bias may not affect the results because the true effect may not be far from what was observed. The completeness of answers to the food items was used as a conformity test.

Despite the limitations considering that the dietary habits of the people of North Cyprus are similar to the traditional Mediterranean diets, an investigation of its effect on breast cancer risk is needed at the very moment because of the increase onset of the disease.

CONCLUSION

The Mediterranean diet has been shown to confer lots of health benefits and the intake of olives and olive oil 5 or more times daily, and fish 2 times weekly more significantly reduced the risk of breast cancer risk in the women of North Cyprus, the benefits of these foods can only be maximized when the appropriate policies that encourage the intake of healthy diet are established. The protection against breast cancer in comparison with other foods may be genotype related and calls for a need to study on a large scale the interplay between dietary intake in association with the genotype of this population.

Putting in perspective
Central question
1. What is the link between the intake of the Mediterranean diet and breast cancer prevention among the women of North Cyprus?

Key findings
1. The consumption of olives and olive oil 5 or more times, and fish 1 or 2 times weekly is significant in reducing the risk of breast cancer among the women of North Cyprus
2. There should be more awareness on the importance of the intake of the Mediterranean diets in breast cancer prevention.

Impact
1. The study will play a pivotal role in patient management and counseling on food intake
2. The study can be utilized in the creation of policies and programs that promote the production and consumption of healthy foods for the population of North Cyprus and other populations including the Indian population.

Further studies
1. There is a need for a larger study in the same population and other populations
2. The link between the dietary intake and the genotype of the population should be investigated.

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Conflicts of interest
There are no conflicts of interest.

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