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Original Research

Dietary factors modify post-menopausal breast cancer risk: a case-control study from Turkish Cypriot population

Ruqiya Pervaiz[1,5], Özgür Tosun[2], Hasan Besim[3], Nedime Serakinci[1,4,*]

[1]Near East University, Faculty of Medicine, Department of Medical Genetics, Nicosia, North Cyprus

[2]Near East University, Faculty of Medicine, Department of Biostatistics, Nicosia, North Cyprus

[3]Near East University, Faculty of Medicine, Department of General Surgery, Nicosia, North Cyprus

[4]Near East University, Faculty of Art and Sciences, Department of Molecular Biology and Genetics, Nicosia, North Cyprus

[5]Abdul Wali Khan University, Faculty of Animal Sciences, Department of Zoology, Mardan, Pakistan

***For correspondence:**

nedimeserakinci@gmail.com

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Abstract

Background: Being potentially modifiable risk factor of breast malignancy, the role of diet in the development of breast cancer (BC) is of great concern. As up to 40 % of cancers can be prevented through dietary strategies; therefore, this case-control study is conducted with the aim to investigate the effects of frequently used dietary factors and postmenopausal BC risk in Turkish Cypriot population. **Material and method:** Total 786 postmenopausal women including 401 histologically confirmed BC cases and 385 control, recruited from two hospitals i.e. Near East Hospital and Doctor Burhan Nalbantoglu State Hospital Nicosia, Turkish Republic of Northern Cyprus, between the month of July to December 2016. A standardized interview procedure is used and the information is collected using a structured questionnaire from participants after giving informed consent form. For data analysis, SPSS version 20 software is used. Age-adjusted odds ratios (OD) and 95% confidence interval (CI) were calculated by logistic regression before and after adjusting for potential confounding effects of other factors. **Results:** The multivariable adjusted model confirmed a 3-fold increased BC risk with daily oil use of ≥ 40 mL (OR = 3.22, 95%CI 2.01-5.17, p<0.001). And 4.1-fold increased risk was associated with 4 to 6 daily servings of sugar intake (OR = 4.19, 95%CI 1.79-9.80, p = 0.001), this risk increased to 7.5-folds (OR = 7.5, 95%CI 3.25-17.32, p<0.001) when the consumption of sugar was increased to > 6 servings per day.

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Daily 1 to 2-liter water intake was associated with 64% decreased BC risk (OR = 0.36, 95%CI 0.20-0.63, p = 0.001). While, no significant association were observed between consumption of full-fat dairy products (FFDP), olive oil, coffee intake and BC risk. Interestingly, daily 3 or more cups of tea intake were associated with 54% decreased risk of BC (OR = 0.46, 95% CI 0.22-0.98, p = 0.043). **Conclusion:** The study suggests that the risk of BC can be reduced by limiting the consumption of oil and sugar and increasing daily water intake more than a liter.

Keywords

Breast cancer, Dietary factors, Odds ratio, North Cyprus

Introduction

Breast cancer is the most prevalent malignancy in Turkish Cypriot women (Pervaiz et al., 2017). There are various established risk factors for BC worldwide including, exogenous and endogenous hormonal exposure, various reproductive factors (early menarche, late menopause, late pregnancy, not breastfeed, and being non-parous) and lifestyle factors (smoking, alcohol and exercise) in addition to high penetrant gene variants i.e. BRCA1&2, ATM, PALB2, and CHEK2) (Rudolph et al., 2016).

The role of diet in the aetiology of BC is also noteworthy as large international variations exist in BC incidence rates (Horn-Ross et al., 2002). These variations might be ascribed to the antioxidant properties of certain selected nutrients that influencing DNA mutation, DNA repair, growth factors stimulations. These nutrients may also have some anti-estrogenic effects and metabolic detoxification (Potter and Potter, 1997).

Recently, a randomized control trial among women at high risk of cardiovascular disease has provided the first evidence about the reduction of BC incidence by diet intervention. Women were randomly assigned to Mediterranean diet patron which is generally rich in plant food, fish and olive oil. About half of these women were as likely to develop invasive BC as those who were only assigned to a diet with only reduce fat intake (Toledo et al., 2015).

Dietary factors have been thought to be the main modifiable risk factors for cancer and it is estimated that up to 40% of cancers could be prevented through dietary strategies (Surh, 2003). The risk of BC is supposed to increase with

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various food nutrients that increase the circulation level of oestrogens and growth factors including insulin-like growth factors I (Potter and Potter, 1997).

In TRNC population, The Mediterranean dietary patron is increasingly changing to the western dietary patron, leading to the rise of diseases incidence including cancer. As to enhance general health and reduce the risk of BC, women can alter their diet successfully. Therefore, the purpose of this case- control study is to assess the strength of association between the consumption of various commonly used diet factors including oil, sugar, water, dairy products, olive oil, alcohol, coffee and black tea and BC risk in this part of the island. To the extent of our knowledge, this is the first epidemiological investigation on BC risk and dietary factors in this population.

Materials - Methods

Study Subjects

This case-control study was carried out in connection with our previous study on BC risk factors in North Cyprus population. The analysis comprised of total 786 menopausal women; 401 BC cases and 385 control healthy women without any malignancy. Both cases and control were recruited from two hospitals of the island i.e. Near East Hospital Nicosia and Doctor Burhan Nalbantoglu State Hospital Nicosia, TRNC between the month of July to December 2016.

Data collection

A standardized interview procedure was used for both cases and control and information regarding sociodemographic factors and the various commonly used dietary factors were collected on a detailed questionnaire after giving informed consent form. From control, questions about diet intake in the previous year were asked, while from cases in the previous year before diagnosis were asked. Furthermore, age at the time of interview of control women is noted and for cases, age at the time of diagnosis is noted.

In addition to the questions about the quantity of specific dietary factors consumption i.e. oil or fat, sugar, olive oil, water, full fats dairy products (FFDP), coffee and tea intake, questions about age, weight, height, education, income status, marital status, family history of BC, age at menarche and menopause, parity, age at first full-term pregnancy (FFP), number of children, breastfeeding (at least 1 month), oral contraceptive and HRT use, smoking status and exercise were included in the questionnaire. All information was self-reported except BMI which was based on actual measurement. The exercise was considered a 30 minutes' walk or physical activity for at least four times a week. Smoking was considered one cigarette a day for at least 6 months. A gestation period of 24 weeks or more is considered pregnancy, oral contraceptive used and HRT was

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considered the use for at least one month. Sugar consumption was considered as anything containing added sugar i.e. jam, jelly, syrup, frozen desserts, non-frozen desserts, candies, chocolate and soft drinks etc. for a serving size of 1 teaspoon (5-7grammes) and one glass of soft drink (250-300 grammes) was indicated. For FFDP i.e. butter, cheese, full-fat milk etc. serving size of 100 grammes is considered. Only frequency and not the quantity of olive oil use were asked in the food frequency questionnaire.

Analysis

The difference between socio-demographic characteristics, dietary factors and cases and control were first assessed by cross-tabulation and chi-square test. In order to assess the degree of association of potential risk from dietary factors and BC, unconditional logistic regression model before and after adjusting for potential confounders are used. The fit of the model is assessed on the basis of Pearson chi-square or Hosmer-Lemeshow goodness-of-fit statistics. Age group is not used as a potential risk for BC but is used as a confounder in the uni- and multivariable regression models. The statistical analysis was performed using SPSS statistical software version 20.

Results

The analysis confirmed that more cases than control were obese (BMI ≥ 30), single, with family history of BC, with earlier menarche, late menopause, with no parity, with no or ≤ 2 children, never breastfeed, used HRT, were smokers, physically inactive, and consumed more fatty food, more sugar and less water, less FFDP, and more likely to use alcohol. But, no significant difference was reported for education, income status, age at FFP, oral contraceptive used, olive oil used, daily coffee and black tea intakes in cases and control (**Table 1**).

In the multivariable adjusted logistic regression model, more than 3–fold increased risk of BC were reported for daily oil consumption of ≥ 40ml (OR = 3.22, 95%CI 2.01-5.17, p<0.001). A 4.1-fold increased risk were associated with 4 to 6 daily serving of sugar (OR = 4.19, 95%CI 1.79-9.80, p = 0.001), this risk increased to more than 7-folds (OR = 7.5, 95%CI 3.25-17.32, p<0.001) when daily sweets consumption was increased to > 6 servings. However, daily 1 to 2-liter water intake were found to associated with 64% decreased BC risk (OR = 0.36, 95%CI 0.20-0.63, p = 0.001) in multivariable logistic regression model. While, no significant association were observed between consumption of FFDP, olive oil, coffee intake and BC risk. Interestingly, daily 3 or more cups of tea intake were associated with 54% decreased risk of BC (OR = 0.46, 95% CI 0.22-0.98, p = 0.043) (**Table 2, Fig. 1**).

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Table 1. Socio-demographic features and potential risk factors among cases and control

Variable	Cases (n = 401)		Control (n = 385)		P-value[1] for chi-square
	n	%	n	%	
Age group					**P= 0.377**
45-54	149	37.2%	161	41.8%	
55-65	193	48.1%	170	44.2%	
≥65	59	14.7%	54	15%	
Education					**P= 0.231**
Primary	104	25.9%	110	28.6%	
Secondary	183	45.6%	178	46.2%	
Tertiary	65	16.2%	58	15.1%	
University	49	12.2%	39	10.1%	
BMI					**P< 0.001**
<25	37	9.2%	59	15.3%	
25-29.9	152	37.9%	190	49.4%	
≥ 30	212	52.9%	136	35.3%	
Income status					**P= 0.174**
< 5000TL	157	39.2%	163	42.3%	
5000-10,000 TL	226	56.4%	213	55.3%	
> 10,000TL	18	4.5%	9	2.3%	
Marital status					
Single (widow divorced)	77	10.6%	41	10.6%	**P= 0.001**
Married	324	80.8%	344	89.4%	
Family History					
No	174	43.4%	260	67.5%	**P< 0.001**
Yes	227	56.6%	125	32.5%	
Menarche Age					
12 or less	322	80.3%	166	43.1%	**P< 0.001**
> 12	79	19.7%	219	56.9%	
Age at Menopause					

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≤ 50	193	48.1%	246	63.9%	**p< 0.001**
> 50	208	51.9%	139	36.1%	
Full term pregnancy					
No	165	41.1%	83	21.6%	**p< 0.001**
Yes	236	58.9%	302	78.4%	
Age at 1st pregnancy (FFP)					
≥30 years	77	19.2%	25	6.5%	**P= 0.133**
<30 years	159	39.7%	277	71.9%	
Nil	165	41.1%	83	21.6%	
No. of Children					
No children	166	41.4%	84	21.8%	**p< 0.001**
Up to 2	128	31.9%	112	29.1%	
More than 2	107	26.7%	189	49.1%	
Breast Feeding					
Never	229	57.1%	133	34.5%	**p< 0.001**
Yes	172	42.9%	252	65.5%	
Oral Contraceptive use					
No	189	47.1%	201	52.2%	**P= 0.155**
Yes	212	52.9%	184	47.8%	
HRT					
No	244	60.8%	280	72.7%	**p< 0.001**
Yes	157	39.2%	105	27.3%	
Smoking					
No	170	42.4%	229	59.5%	**P< 0.001**
Yes	231	57.6%	156	40.5%	
Exercise					
No	233	58.1%	162	42.1%	**P< 0.001**
Yes	168	41.9%	223	57.9%	
Oil/fats consumption/day					
< 20ml	88	21.9%	123	31.9%	**P< 0.001**
20-40 ml	121	30.2%	173	44.9%	

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> 40ml	192	47.9%	89	23.1%	
Sugar consumption, servings/day					
≤ 3	11	2.7%	52	13.5%	**P< 0.001**
4-6	137	34.2%	170	44.2%	
> 6	253	63.1%	163	42.3%	
Water consumption/day					
<1 litre	89	22.2%	39	10.1%	**P= 0.010**
1-2 litre	148	36.9%	168	43.6%	
> 2 litre	164	40.9%	178	46.2%	
FFDP* use/day					
Never	30	7.5%	25	6.5%	**P= 0.031**
1-3 servings	309	77.1%	275	71.4%	
≥4	62	15.5%	85	22.1%	
Olive oil use/day					
Never	49	12.2%	44	11.4%	**P= 0.959**
Some time	179	44.6%	177	46.0%	
Daily	173	43.1%	164	42.6%	
Alcohol consumption/day					
Never	274	68.3%	314	81.6%	**P< 0.001**
≤ 300 ml	44	11.0%	27	7.0%	
> 300 ml	83	20.7%	44	11.4%	
Daily Coffee consumption/day					
Never	34	8.5%	29	7.5%	**P= 0.829**
1-2 cups	218	54.4%	213	55.3%	
≥3 cups	149	37.2%	143	37.1%	
Daily black tea consumption /day					
Never	40	10.0%	26	6.8%	**P = 0.209**
1-2 cups	236	58.9%	231	60.0%	
≥3 cups	125	31.2%	128	33.2%	

Notes: 1. *P-value of the chi-square test for independence.*
** Full fats dairy Products.*

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Table 2. Uni- and multivariable logistic regression and adjusted odds ratios with 95% CI.

Variables	Univariable		p-value[2]	Multivariable		p-value[2]
	OR1	(95% CI)		OR3	(95% CI)	
Oil/fats consumption/day						
(≤ 20ml)	1					
(21-40 ml)	0.99	(0.69-1.42)		0.98	(0.62-1.54)	0.83
(> 40ml)	3.08	(2.12-4.48)	<0.001	3.22	(2.01-5.17)	<0.001
Sugar consumption, servings/day						
≤ 3	1					
4-6	3.92	(1.96-7.81)		4.19	(1.79-9.80)	0.001
> 6	7.60	(3.84-15.03)	<0.001	7.50	(3.25-17.32)	<0.001
Water consumption/day						
<1 litre	1					
1-2 litre	0.38	(0.24-0.58)		0.36	(0.20-0.63)	
> 2 litre	0.39	(0.25-0.61)	<0.001	0.37	(0.21-0.64)	0.001
FFDP* use/day						
Never	1					
1-3 servings	0.94	(0.54-1.64)		0.94	(0.47-1.89)	0.86
≥4	0.61	(0.32-1.14)	0.06	0.53	(0.24-1.17)	0.119
Olive oil use/day						
Never	1					
Some time	0.90	(0.57-1.42)		1.13	(0.62-2.06)	0.67
Daily	0.78	(0.59-1.48)	0.89	1.37	(0.75-2.51)	0.30
Daily Coffee intake						
Never	1					
1-2 cups	0.87	(0.51-1.49)		0.67	(0.34-1.36)	0.27
≥3 cups	0.90	(0.52-1.55)	0.89	0.61	(0.29-1.26)	0.18
Daily black tea intake						

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Never	1					
1-2 cups	0.67	(0.40-1.14)		0.51	(0.25-1.01)	0.057
≥3 cups	0.65	(0.37-1.14)	0.30	0.46	(0.22-0.98)	0.043

***Note: 1**. Univariable odds ratios adjusted for age. 2. P values for the difference between binary variables or p value for linear trend across ordinal categorical variables. 3. Multivariable odds ratios adjusted for age, BMI, family history, menarche age, age at menopause, parity, Breast feeding, smoking, exercise and HRT. * Full fats dairy Products.*

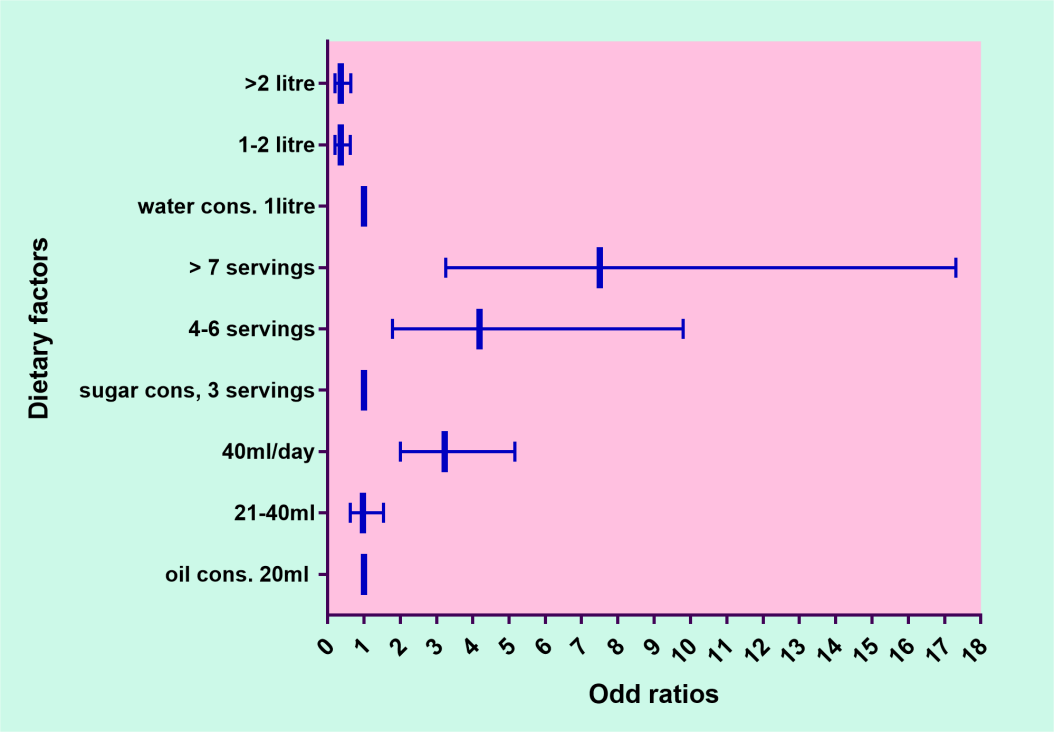

Figure 1. Odds ratios and 95% Wald confidence interval for BC risk.

Discussion

The key purpose of the present study was to evaluate the strength of association of various commonly used dietary factors and BC risk in TRNC. Only post-menopausal cases and control women were included in the study since diet has been indicated to have a different influence on pre and post-menopausal BC (Psaltopoulou et al., 2011). It is to be noted that all the factors used here are self-reported excluding BMI. Of the studied dietary factors, we found that consumption of excess oil/fats and sugar were associated with increased BC risk.

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Also, daily water intake of more than one liter was associated with reduced BC risk.

Our results are in consistence with other studies. For instance, a prospective study on a large heterogeneous population of European women has shown the high fats diet to increase BC risk, particularly high saturated fat intake increases the risk of receptor-positive BC (Sieri et al., 2014). However prospective observational studies on association between fat consumption and BC risk have inconsistent findings, but many studies have confirmed that this association may be due to unspecific quantification of fat intake (Prentice et al., 2013) despite the fact that, other comprehensive study did not confirm this (Key et al., 2011), the cause of inconsistencies may be due to the fact that specific type of fat (not of the total fat) is linked only to some BC types. In nested case-control study within the French EPIC cohort, it is shown that trans fatty acids increase the risk of BC (Chajès et al., 2008). Evidence supports that the high fats intake increases the concentration of bio-available serum sex hormones (Parry et al., 2011), which is the main risk factor for BC. It also enhancing reabsorption in the intestine and increasing blood fatty acid level that may increase free estrogenic concentration in blood serum (Rock et al., 2004). The role of dietary fats in cancer tumor formation are given in a recent study in Nature. The study has shown the effects of high fats diet on the intestinal stem cells lineage and has established a mechanism by which progenitor cell when exposed to high fats diet become more stem cells like and prone to oncogenic transformation (Beyaz et al., 2016). Same is the case of dilatory sugar intake. Recently, in a multiple mouse model study, the impacts of dietary sugar on mammary gland tumor development and the mechanism involve were investigated, and found that sucrose intake comparable to the amount of western diet led to increasing tumor growth and metastasis by inducing 12-lipoxygenase signaling, when compared with non-sugar starch diet (Jiang et al., 2016). Furthermore, our study showed that daily 1-2 liter water intake decreased the risk up to 64%, an only small increase of 1% were observed with further increased water intake. Malignancies mostly studied in connection with water include bladder and colorectal cancers and only rarely with BC (Michaud et al., 1999). Conversely, a hospital-based study on diet and beverage consumption and BC risk by Stookey et al observed that water intake is significantly associated with 69% reduced BC risk (adjusted odds ratio of 0.31, 95%CI, 0.13-0.72) (Stookey et al., 1997).

No significant association between BC risk and consumption of FFDP and olive oil were reported. In contrast, the majority of case-control studies carried out in Mediterranean countries consistently concluded an inverse association of BC risk and olive oil consumption (Sieri et al., 2014). It is reported that the hydrocarbon squalene compound in olive oil, exerts a beneficial effect on oxidative stress and DNA damage in mammary epithelial cells (Warleta et al., 2010), polyphenols from olive oil may have a possible role in the prevention of BC (Casaburi et al., 2013). Being a part of Mediterranean island, olive oil and dairy products consumption are frequent in TRNC. Therefore, large follow-up study may

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provide an appropriate finding of the effect of olive oil and FFDP use on BC risk in this population.

Although coffee and tea consumption showed no significant association with BC risk in this study, it is reported that a daily 3 or more cups of black tea were found to associated significantly with decreased BC risk in the adjusted model. This association was not significant in the uni-variable model. As one of the most commonly proposed pathways leading to carcinogenesis is oxidative DNA damage which is strongly determined by body iron storage (Toyokuni, 2009), coffee and tea are supposed to inhibit iron absorption in the small intestine, and subsequently decreasing oxidative stress through reducing stored iron in the body (Morck et al., 1983). Recently it has been confirmed that coffee and not tea was associated with lower level of oxidative DNA damage and low body iron storage in women (Hori et al., 2014). There is inconsistency in the association of BC risk and intake of coffee and tea, in the published literature (Harris et al., 2012). Furthermore, a large meta-analysis indicated no association of black tea intake and BC risk (Nie et al., 2014).

Conclusion

It is concluded that there is a strong association between consumption of fats, sugar and BC risk. Water intake has beneficial effects on the primary prevention of BC. The most appropriate approach against cancer is the preventive strategies. To the best of our knowledge, this is the first report to validate an association of BC risk and dietary factors in this part of the island. Hopefully, these findings will give new insights in BC epidemiology. Nevertheless, these results need confirmation by long-term prospective studies.

Abbreviations

BC: Breast cancer

BMI: Body Mass index

CI: Confidence interval

FFDP: Full-fat dairy products

HRT: Hormonal replacement therapy

OD: Odds ratios

SPSS: Statistical Package for Social Sciences

TRNC: Turkish Republic of Northern Cyprus

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Author contribution

RP participated in the conception of the study, data acquisition, interpretation and drafting the manuscript. ÖT participated in the statistical analysis and revising the article. HB participated in the design of the study and revising the article. NS participated in the conception of the study and critically revising the article for important intellectual content.

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