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Risk factor assessment for breast cancer in North Cyprus: a comprehensive case-control study of Turkish Cypriot women

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Background/aim: This case-control study aims to assess the strength of associations between reproductive, lifestyle, sociodemographic, and dietary factors as well as other potential breast cancer risks and breast cancer (BC) in a North Cyprus population.

Materials and methods: The study includes 408 BC patients and 412 age-matched controls recruited from Near East Hospital and Dr. Burhan Nalbantoglu State Hospital in North Cyprus. Information regarding clinical and epidemiological characteristics was collected through a standardized interview. Age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression before and after adjusting for the potential confounders.

Results: In addition to various recognized BC risk factors, strong associations with BC were reported from women with fertility drugs used for >6 cycles (OR = 3.305, 95% CI 1.850–5.906, P < 0.001), depression (OR = 2.10, 95% CI 1.33–3.30, P < 0.001), exposure to radiation (OR = 1.74, 95% CI 1.02–2.98, P = 0.041), and excess consumption of oil (OR = 2.703, 95% CI 1.62–4.48, P < 0.001) and sugar (OR = 3.42, 95% CI 1.39–8.40, P = 0.007). Parental consanguinity (OR = 0.16, 96% CI 0.09–0.30, P < 0.001) and daily water intake of 1–2 L (OR = 0.36, 95% CI 0.19–0.66, P < 0.001) were strong protective factors.

Conclusion: Our results demonstrate the presence of classical as well as several additional BC risks. The findings will be of great benefit in establishing adequate evidence-based awareness and preventative measures in the North Cyprus population.

Key words: Breast cancer, risk factors, odds ratios, North Cyprus

1. Introduction

Breast cancer (BC) is the most frequent malignancy in women with an estimated 1.7 million cases and more than 0.52 million deaths in 2012 (1). Each year, 1 in 9 women are at risk of developing the disease (2). Numerous epidemiological studies over the last three decades have revealed a number of risk factors associated with BC (3).

The well-established environmental factors for BC include exogenous and endogenous exposure to hormones, reproductive factors, and lifestyle factors (smoking, exercise, alcohol use, etc.). In addition, an estimated 30% of germline genotypes have been associated with the heritability of BC (4). Furthermore, women with an affected first-degree relative have a twofold higher risk of developing the malignancy (5). The quantity of some dietary factors (oil, sugar, and water) has also shown some association with breast cancer risk (6).

Currently, it is believed that the environmental risk factors for BC are of far more significance than the mutations in the high-penetrance BC susceptibility genes *BRCA1* and *BRCA2* (7). If a related environmental factor is present, then women carrying certain genetic variants may have a higher risk of developing BC.

BC also exhibits a wide range of ethnic and geographical variations (8). A twofold difference in BC incidence is notable within Europe, where the highest rate is in northern countries, with an estimated 84.6 cases per 100,000 adult women, and the lowest is in East Europe, with 42.6 cases per 100,000 women. South Europe demonstrates intermediate rates (9).

North Cyprus, located in the Eastern Mediterranean, has a total population of 285,000 Turkish Cypriots and an average annual age-standardized BC incidence rate of 72 per 100,000 women (10). BC is the most common cancer among Turkish Cypriot women (11). The Mediterranean lifestyle of the North Cyprus population is rapidly changing towards a western style that has an increased impact on

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the health status of the region. Therefore, the study of risk factors attributed to BC in the Turkish Cypriot population, in particular, is crucial.

At present, the main risks for BC in Turkish Cypriot women are not known. This study is important as it evaluates risk factors for breast cancer comprehensively in Turkish Cypriot women. This case-control study aims to investigate the strength of the associations between the recognized risk factors and BC among the Turkish Cypriot female population. Furthermore, the study also evaluates other potential risk factors specific to the North Cyprus population (lifestyle, workplace or home environment, dietary factors, etc.).

2. Materials and methods

2.1. Recruitment of study participants and data collection

In this case-control study, participants were recruited from the medical oncology, radiation oncology, and general surgery departments of Near East Hospital and Dr. Burhan Nalbantoglu State Hospital in North Cyprus. A structured questionnaire was designed and face-to-face interviews were conducted to obtain information regarding the sociodemographic and potential risk factors. All study participants were given a written informed consent form in English or Turkish. Prior written permission was obtained from the North Cyprus Ministry of Health, as well as from the head of the Near East Hospital in Nicosia.

The study group included 408 Turkish Cypriot women aged ≥45 years with histopathologically confirmed primary BC who had visited the hospitals between July 2016 and February 2017. Patients of less than 45 years of age were not included in the study due to the different etiology, mainly germline mutations in the breast and ovarian cancer susceptibility genes *BRCA1* and *BRCA2* in the case of early-onset BC (12).

The control group consisted of 412 age-matched Turkish Cypriot women without any known malignancy who had visited the hospital for routine health examinations.

An introductory letter about the aims and goals of the study was given to each of the patients and controls; those who were willing to participate in the study were interviewed by a trained interviewer.

2.2. Data analysis

For both case and control subjects, frequencies of categorical variables were calculated separately. The frequencies were cross-tabulated and variations in the respondent's characteristics between case and control subjects were analyzed by chi-square test. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for estimating the strength of the association between each hypothesized risk factor and BC risk. All model estimations were adjusted for age group, the only confounding variable we determined in our study. For all regression analyses (univariable and multivariable), we added age group as a confounding factor. Therefore, the model was adjusted for the confounding variable so that its effect was eliminated between study groups. A P-value of linear trend was noted in the case of ordered categorical variables. In the first step, the association between each hypothesized risk factor and BC was assessed by univariable logistic regression. Variables with $P > 0.25$ were disregarded and those with $P \leq 0.25$ were included in the multivariable logistic regression model. In the next step, all variables with $P > 0.05$ were disregarded and those with $P \leq 0.05$ were included in the final multivariable model. In all cases, the fit of the model was assessed on the basis of the Pearson chi-square or Hosmer–Lemeshow goodness-of fit statistics, which produced a nonsignificant result. SPSS 20 was used for statistical analysis (IBM Corp., Armonk, NY, USA).

2.3. Definitions

For the worldwide-recognized breast cancer risk prediction, a questionnaire similar to that previously used in the East Anglia breast cancer study was used in this study (13). The case subjects were asked to provide their age at diagnosis, while the control group was asked to provide their age at enrollment in the study. A gestational period of 24 weeks was considered pregnancy. The use of oral contraceptives and hormone replacement therapy (HRT) was considered for a minimum of 1 month. Premenstrual depression (PMD) was considered as an up to 4-days depression period before each menstruation for at least 1 year. Pesticide exposure was counted for at least one time, along with chemicals (dry-cleaning chemicals, alkyl phenol, mercury, lead, cadmium, etc.) Parental consanguinity was considered as marriages between second cousins or closer (first cousins, first cousins once removed, and second cousins) (14). Smoking was considered at least one cigarette a day for a minimum of 6 months. Any form of regular exercise for 3 h a week for the previous 6 months was considered.

For the dietary factors, a food frequency questionnaire, "Dietary Intake Questionnaire for the Quantitative Estimation of Adherence to Mediterranean Diet", was used with some modifications for this population (15), and habitual intakes over the previous year (date of interview for controls, date of diagnosis for cases) were considered. Sugar consumption was considered as anything containing added sugar (jam, frozen and nonfrozen desserts, candies, soft drinks, etc.), with a serving size of one teaspoon (5–7 g) and one glass of soft drink (250–300 g). For full-fat dairy products (FFDPs), a serving size of 100 g was considered. However, the respondents were asked for the frequency and not the quantity of olive oil consumed (15)

3. Results

The mean age at diagnosis of the study group case subjects was 57.7 ± 6.5 years, while the mean age of the control group was 57.5 ± 6.4 years.

On the basis of univariable analysis (Table 1), the variables (all with P > 0.25) dropped from the multivariable logistic regression model were the level of education, oral contraceptive use, butter consumption, olive oil consumption, and coffee consumption.

Although some variables, including rural/urban location, marital status, parity, number of children, breastfeeding history, HRT usage, pesticide exposure,

Table 1. Sociodemographic characteristics and age-adjusted odds ratios (95% CI) for BC comparing case and control subjects.

	Cases (N = 408) %		Controls (N = 412) %		OR[1]	95% CI	P-value[2]
Sociodemographic factors							
Location							
Urban	222	54.4%	264	64.1%	1		0.007
Rural	186	45.6%	148	35.9%	1.471	1.114–1.954	
Income status							
<5000 TL	158	38.7%	174	42.2%	1		0.144
5000–10,000 TL	232	56.9%	229	55.6%	1.123	0.845–1.492	
>10,000 TL	18	4.4%	9	2.2%	2.257	0.984–5.180	
Education							
Primary	104	25.5%	115	27.9%			0.828
Secondary	189	46.3%	188	45.6%	1.110	0.795–1.550	
Tertiary	66	16.2%	61	14.8%	1.205	0.777–1.869	
University	49	12.0%	48	11.7%	1.184	0.731–1.919	
Marital Status							
Single (or widowed, divorced)	78	19.1%	43	10.4%	1		<0.001
Married	330	80.9%	369	89.6%	0.489	0.327–0.731	
BMI							
<25	38	9.3%	63	15.3%	1		P < 0.001
25–29.9	152	37.3%	198	48.1%	1.276	0.809–2.012	
≥30	218	53.4%	151	36.7%	2.375	1.509–3.738	
Family history							
No	180	44.1%	282	68.4%	1		P < 0.001
Yes	228	55.9%	130	31.6%	2.713	2.038–3.613	
Reproductive factors							
Menarche age							
≤12 years	329	80.6%	79	44.2%	1		<0.001
>12 years	182	19.4%	230	55.8%	0.186	0.136–0.255	
Age at menopause							
No menopause	7	1.7%	27	6.6%	1		<0.001
≤50 years	193	47.3%	246	59.7%	2.898	1.229–6.830	
>50 years	208	51.0%	139	33.7%	5.487	2.311–13.028	
Parity							
No	173	42.4%	87	21.1%	1		<0.001
Yes	235	57.6%	325	78.9%	0.363	0.267–0.494	
Age at FFP							
≥30 years	77	18.9%	27	6.6%	1		<0.001
<30 years	158	38.7%	298	72.3%	0.184	0.114–0.297	
Nil	173	42.4%	87	21.1%	0.693	0.416–1.154	
No. of children							
No children	173	42.4%	89	21.6%	1		<0.001
Up to 2	128	31.4%	121	29.4%	0.536	0.375–0.767	
More than 2	107	26.2%	202	49.0%	0.271	0.191–0.383	

Table 1. (Continued).

Breastfeeding							
Never	236	57.8%	143	34.7%	1		<0.001
Less than 1 year	114	27.9%	170	41.3%	0.406	0.296–0.557	
More than 1 year	58	14.2%	99	24.0%	0.359	0.244–0.527	
Oral contraceptive use							
No	191	46.8%	207	50.2%	1		0.340
Yes	217	53.2%	205	49.8%	1.143	0.868–1.505	
HRT							
Never used	249	61.0%	302	73.3%	1		0.002
Up to 5 years	96	23.5%	67	16.3%	1.702	1.188–2.439	
>5 years	63	15.4%	43	10.4%	1.726	1.127–2.643	
Fertility drug usage							
Never	282	69.1%	356	86.4%	1		<0.001
≤6 cycles	44	10.8%	23	5.6%	2.389	1.408–4.053	
>6 cycles	82	20.1%	33	8.0%	3.115	2.017–4.809	
General health-related factors							
History of FBD							
No	160	39.2%	212	51.5%	1		<0.001
Yes	226	55.4%	142	34.5%	2.108	1.569–2.832	
Don't know	22	5.4%	58	14.1%	0.502	0.294–0.856	
History of past biopsy							
No	344	84.3%	370	89.8%	1		0.023
Yes	64	15.7%	42	10.2%	1.621	1.068–2.460	
Consanguinity							
None	328	80.4%	260	63.1	1		< 0.001
Consanguineous	80	19.6%	152	36.9%	0.42	0.302–0.569	
PMD							
No	177	43.4%	236	57.3%	1		<0.001
Yes	231	56.6%	176	42.7%	1.745	1.322–2.304	
History of radiation exposure							
No	67	16.4%	123	29.9%	1		<0.001
1 to 2 times	143	35.0%	149	36.2%	1.801	1.235–2.626	
3 or more times	198	48.5%	140	34.0%	2.60	1.795–3.752	
Residential and workplace exposure factors							
Night-shift work							
No	390	95.6%	386	93.7%	1		0.236
Yes	18	4.4%	26	6.3%	0.688	0.371–1.277	
Pesticide exposure							
No	269	65.9%	299	72.6%	1		0.029
Yes	139	34.1%	113	27.4%	1.395	1.034–1.883	
Other chemical exposure							
No	225	55.1%	250	60.7%	1		0.089
Yes	183	44.9%	162	39.3%	1.274	0.964–1.683	
Lifestyle factors and diet-related factors							
Smoking							
No	173	42.4%	241	58.5%	1		<0.001
Yes	235	57.6%	171	41.5%	1.904	1.442–2.514	

Table 1. (Continued).

Physical activity							
No	239	58.6%	182	44.2%	1		<0.001
Yes	169	41.4%	230	55.8%	0.564	0.428–0.745	
Alcoholic consumption							
Never	277	67.9%	332	80.6%	1		
≤300 mL/day	44	10.8%	28	6.8%	1.90	1.123–3.060	<0.001
>300 mL/day	87	21.3%	52	12.6%	2.04	1.397–2.990	
Oil consumption							
<20 mL	89	21.8%	135	32.8%	1		
20–40 mL	124	30.4%	184	44.7%	1.037	0.729–1.475	<0.001
>40 mL	195	47.8%	93	22.6%	3.251	2.254–4.689	
Butter consumption							
Never	99	24.3%	86	20.9%	1		
≤60 g	165	40.4%	185	44.9%	0.779	0.543–1.116	<.37
>60 g	144	35.3%	141	34.2%	0.893	0.615–1.296	
Margarine							
Never	117	28.7%	119	29%	1		
≤60 g	189	46.3%	156	38%	1.217	0.872–1.697	0.018
>60 g	102	25.0%	137	33.3%	0.752	0.523–1.081	
Sugar consumption (servings/day)							
≤3	11	2.7%	52	12.6%	1		
4–6	140	34.3%	189	45.9%	3.645	1.831–7.256	<0.001
>6	257	63.0%	171	41.5%	7.415	3.752–14.655	
Water intake							
<1 L	93	22.8%	44	10.7%	1		
1–2 L	148	36.3%	177	43.0%	0.39	0.255–0.593	=0.001
>2 L	167	40.9%	191	46.4%	0.40	0.267–0.614	
FFDP use							
Never	33	8.1%	30	7.3%	1		
1–3 servings	313	76.7%	290	70.4%	0.980	0.582–1.649	=0.035
≥4 servings	62	15.2%	92	22.3%	0.62	0.339–1.107	
Olive oil							
Never	49	12.0%	45	10.9%	1		
Sometimes	183	44.9%	190	46.1%	0.879	0.558–1.384	=0.856
Daily	176	43.1%	177	43.0%	0.903	0.572–1.425	
Coffee consumption							
Never	35	8.6%	31	7.5%	1		
1–2 cups	224	54.9%	227	55.1%	0.878	0.523–1.474	=0.868
≥3 cups	149	36.5%	154	37.4%	0.867	0.508–1.480	
Black tea consumption							
Never	42	10.3%	28	6.8%	1		
1–2 cups	240	58.8%	254	61.7%	0.644	0.386–1.073	=0.239
≥3 cups	126	30.9%	130	31.6%	0.668	0.389–1.146	

[1]Univariable odds ratios adjusted for age group. [2]P-values for difference between binary variables or P-value for linear trend across ordinal categorical variables.
OR: Odd ratios, BMI: body mass index, FFP: first full-term pregnancy, HRT: hormone replacement therapy, FBD: fibrocystic breast disease, PMD: premenstrual depression, FFDP: full-fat dairy product.

physical activity, margarine use, FFDP use, and alcohol use, were significant in the univariable model, their effects were markedly attenuated in the multivariable adjusted model, as none of them attained statistical significance in the adjusted multivariable logistic regression model. The risk profiles associated with income status, night shift work, chemicals, and black tea intake were less affected as these remained insignificant in the adjusted multivariate model as well (Table 2).

Table 2. Odds ratios (95% CIs) of BC by respondent's characteristics, adjusted for the effects of age and all other factors.

Variable		OR[1]	95% CI	P-value[2]
Sociodemographic factors				
Location	Urban	1		0.136
	Rural	1.375	0.905–2.091	
Income status	<5000 TL	1		0.806
	5000–10,000 TL	0.867	0.565–1.332	
	>10,000 TL	0.870	0.260–2.909	
BMI	<25	1		0.004
	25–29.9	1.734	0.876–3.433	
	>30	2.936	1.473–5.850	
Family history	No	1		0.000
	Yes	2.285	1.494–3.493	
Reproductive factors				
Menarche age	12 or less	1		0.000
	12 and above	0.204	0.129–0.324	
Age at menopause	No menopause	1		0.006
	≤50 years	6.726	1.825–24.789	
	>50 years	7.991	2.203–28.988	
Marital status	Single	1		0.367
	Married	0.694	0.313–1.536	
FFP	Yes	1		0.439
	No	3.717	0.134–1.03	
Age at FFP	≥30 years	1		0.000
	<30 years	0.183	0.113–0.296	
	Nil	0.697	0.418–1.160	
No. of children	No children	1		0.720
	Up to 2	0.600	0.022–16.314	
	More than 2	0.490	0.018–13.560	
Breast feeding duration	Never	1		0.338
	≤1 year	0.744	0.388–1.426	
	>1 year	0.571	0.271–1.204	
HRT	Never used	1		0.135
	Up to 5 years	1.566	0.919–2.669	
	>5 years	1.622	0.852–3.087	
Fertility drugs used	Never	1		0.000
	≤6 cycles	1.820	0.814–4.070	
	>6 cycles	3.779	2.010–7.106	
General health-related factors				
History of FBD	No	1		0.000
	Yes	2.366	1.488–3.761	
	Don't know	0.733	0.332–1.617	

Table 2. (Continued).

Past biopsy	No	1		0.001
	Yes	3.357	1.599–7.046	
Consanguinity	Nonconsanguineous	1		0.000
	Consanguineous	0.176	0.095–0.325	
PMD	No	1		0.009
	Yes	1.896	1.177–3.054	
Radiation exposure	No radiation	1		0.006
	1 to 2 times	1.759	0.993–3.118	
	3 or more times	2.529	1.432–4.465	
Residential and workplace exposure factors				
Night-shift work	No	1		0.981
	Yes	1.011	0.409–2.501	
Pesticide exposure	No	1		0.148
	Yes	1.375	0.894–2.117	
Other chemical exposure	No	1		0.463
	Yes	1.168	0.772–1.767	
Lifestyle factors and diet-related factors				
Smoking	No	1		0.020
	Yes	1.657	1.084–2.534	
Physical activity	No	1		0.165
	Yes	0.740	0.484–1.132	
Oil consumption	<20 mL			0.000
	20–40 mL	1.074	0.637–1.812	
	>40 mL	2.861	1.668–4.910	
Margarine	Never	1		0.375
	≤60 g	0.730	0.435–1.224	
	>60 g	0.700	0.404–1.214	
Sugar consumption, servings/day	≤3	1		0.001
	4–6	3.072	1.187–7.952	
	>6	5.236	2.042–13.423	
Water intake	<1 L	1		0.005
	1–2 L	0.392	0.204–0.751	
	>2 L	0.349	0.183–0.666	
Other FFDPs	Never	1		0.079
	1–3 servings	0.804	0.385–1.682	
	≥4 servings	0.451	0.192–1.061	
Alcohol consumption	Never	1	1	0.917
	≤300 mL/day	0.914	0.436–1.914	
	>300 mL/day	1.090	0.620–1.915	
Black tea consumption	Never	1		0.093
	1–2 cups	0.475	0.218–1.038	
	≥3 cups	0.393	0.169–0.911	

[1]Multivariable odds ratios adjusted for age group. [2]P-values for difference between binary variables or P-value for linear trend across ordinal categorical variables.
OR: Odd ratios, BMI: body mass index, FFP: first full-term pregnancy, HRT: hormone replacement therapy, FBD: fibrocystic breast disease, PMD: premenstrual depression, FFDPs: full-fat dairy products.

In contrast, BMI, family history, menarche age, age at menopause, age at first full-term pregnancy (FFP), fertility drug use, smoking, fibrocystic breast disease (FBD), history of past biopsy, consanguinity, PMD, exposure to radiation, and the quantity of oil (all types other than olive oil), sugar, and water consumption were significant ($P \leq 0.05$) predictors of BC risk for the North Cyprus population in the adjusted multivariable analysis (Table 3).

Table 3. Odds ratios (95% CIs) of BC by respondent's characteristics, adjusted for the effects of all other significant variables.

Variables		OR[1]	95% CI	P-value[2]
BMI	<25	1		
	25–29.9	1.604	0.852–3.017	0.143
	≥30	2.831	1.490–5.379	<0.001
Family history	No	1		<0.001
	Yes	2.299	1.535–3.441	
Menarche age	≤ 12 years	1		<0.001
	>12 years	0.226	0.148–0.344	
Age at menopause	No menopause	1		
	≤ 50 years	5.491	1.669–18.061	0.005
	> 50 years	7.215	2.197–23.693	<0.001
Age at FFP	≥ 30 years	1		
	< 30 years	0.267	0.171–0.416	<0.001
	Nil	1.210	0.623–2.352	0.574
Fertility drugs used	Never	1		
	≤ 6 cycles	1.465	0.698–3.077	0.313
	> 6 cycles	3.305	1.850–5.906	0.000
Smoking	No	1		0.009
	Yes	1.695	1.142–2.515	
History of FBD	No	1		
	Yes	2.292	1.493–3.519	<0.001
	Don't know	0.692	0.320–1.496	0.349
History of past biopsy	No	1		
	Yes	3.306	1.643–6.655	0.001
Consanguinity	No	1		
	Yes	0.169	0.095–0.302	<0.00
PMD	No	1		
	Yes	2.104	1.339–3.305	0.001
Radiation exposure	No	1		
	1 to 2 times	1.747	1.024–2.981	0.041
	3 or more	2.546	1.504–4.309	0.001
Oil consumption/day	<20 mL	1		
	20–40 mL	1.031	0.631–1.685	0.902
	>40 mL	2.703	1.627–4.488	<0.001
Sugar consumption, servings/day	≤3	1		
	4–6	3.422	1.393–8.409	0.007
	>6	5.420	2.224–13.208	<0.001
Water intake	<1 L	1		
	1–2 L	0.36	0.194–0.666	0.001
	>2 L	0.36	0.199–0.677	0.001

[1]Multivariable odds ratios adjusted for age group. [2]P-values for difference between binary variables or P-value for linear trend across ordinal categorical variables.
OR: Odd ratios, BMI: body mass index, FFP: first full-term pregnancy, FBD: fibrocystic breast disease, PMD: premenstrual depression.

A 2.8-fold increase in BC risk was associated with being obese (OR = 2.83, 95% CI 1.490–5.379, P < 0.001), and a 2.3-fold increased risk (OR = 2.299, 95% CI 1.535–3.441, P < 0.001) was associated with family history of BC (first- and second-degree relatives combined) (Table 3).

In the case of reproductive factors, menarche at age greater than 12 years was associated with a 77% decrease in BC risk (OR = 0.226, 95% CI 0.148–0.344, P < 0.001), while nonmenopausal woman had an approximate 5.5-times decreased BC risk compared to women who had reached menopause at the age of 50 years or less (OR = 5.49, 95% CI 1.66–18.06, P = 0.005) and as much as 7.2-fold decreased BC risk compared with women who had reached menopause over the age of 50 (OR = 7.215, 95% CI 2.197–23.693, P < 0.001). Similarly, a 73% decreased BC risk was associated with women with FFP before 30 years of age (OR = 0.267, 95% CI 0.171–0.416, P < 0.001), and the use of fertility drugs for more than 6 cycles was associated with a 3.3-fold increased BC risk in the final multivariate model (OR = 3.305, 95% CI 1.850–5.906, P < 0.001) (Table 3).

Smoking was positively associated with BC risk as approximately 70% increased BC risk was associated with smoking (OR = 1.695, 95% CI 1.142–2.515, P = 0.009) in the final multivariable model.

The history of FBD was associated with a twofold increased BC risk (OR = 2.29, 95% CI 1.49–3.52, P < 0.001). History of past biopsy was related with more than 3-fold increased BC risk (OR = 3.306, 95% CI 1.643–6.655, P = 0.001) (Table 3).

Furthermore, consanguinity was associated with an 83% decrease risk of BC (OR = 0.169, 95% CI 0.095–0.302, P < 0.001). PMD was associated with more than 2-fold increased risk (OR = 2.10, 95% CI 1.339–3.305, P < 0.001). Similarly, exposure to diagnostic radiations (chest X-rays) on at least one occasion after puberty was also significantly related with 70% increased BC risk (P < 0.001) (OR = 1.747, 95% CI 1.024–2.981, P = 0.041) in the multivariable final model (Table 3).

In the case of dietary products, the quantity of oil consumption (>40 mL per day) indicated an association of 2.7-fold increased BC risk. For sugar consumption, the risk increased significantly in subcategories with the increase in the quantity of sugar consumption (P < 0.001). However, daily water intake of 1–2 L was found to decrease the BC risk by almost 64% (OR = 0.36, 95% CI 0.19–0.66, P < 0.001) (Table 3).

4. Discussion

The main aim of this study was to evaluate the strength of the associations of the globally recognized and other potential risk factors for BC in the North Cyprus female population. Apart from BMI, all of the factors investigated were self-reported and a standardized interview procedure was used for collecting information from case and control subjects.

The differences between the rural and urban incidences of BC are thought to be due to the greater distance from health care facilities and the lower socioeconomic conditions in the rural population. However, the variations in the rural/urban lifestyle and income status are not drivers in North Cyprus. Furthermore, marital status has no direct role in BC risk modification; this is the association of reproduction with a marital status that possibly affects the BC risk.

The literature has indicated that obesity is associated with a decreased BC risk in premenopausal women and an increased risk in postmenopausal women (16). Our results are in concordance with the literature as, due to the specific age group (45 years and above) of our sample, most of our study participants (96%) were postmenopausal women, while only 4% were premenopausal.

The positive relationship between family history and BC risk in this population corresponds to the findings of other case-control and cohort studies in different geographical regions and different populations. Pooled analysis of 38 studies reported a 2.1% relative risk of BC with first- and second-degree relatives with BC (5).

The positive relation of the increased risk of developing BC and various reproductive factors are in concordance with the published literature (3,17). Similarly, the strong univariable association of BC risk with the number of children and breastfeeding duration is attenuated in the multivariable adjusted model, indicating that the observed association was confounded by other reproductive factors. Furthermore, no or only weak associations of BC risk were observed with oral contraceptive use and HRT. The inverse association between HRT and BC risk did not persist in the final adjusted model. Surprisingly, a direct association with BC risk was observed with the history of fertility drug usage (for the treatment of polycystic ovary syndrome and/or for inducing ovulation), as an insignificant BC risk of 46% was associated with fertility drugs used for 6 or fewer cycles; however, this risk increased to OR = 3.3 (95% CI 1.85–5.90) when the drugs were used for more than 6 cycles. This is an unexpected result because most of the published literature has shown a negative relation between the history of fertility drugs usage and BC risk; nonetheless, a relative risk of BC ranging between 2.7 to 3.8 has been reported by past studies from women using human menopausal gonadotropin for at least 6 cycles (18).

Smoking (current or past) was the only significant lifestyle factor with a 69% increased BC risk. Biological data are available that link active smoking at a young age with breast carcinogenesis, in which twenty different compounds found in tobacco smoke were identified to

induce mammary carcinogenesis (19).

Our study indicated that potential risk from the history of FBD as well as from previous biopsy was found to have significantly increased in the final model. A recent study provided details regarding benign breast disease and BC risk and estimated that more than 80% of these cancers are invasive, regardless of the type of benign histology categories (20).

Parental consanguinity appeared to protect against BC (84% reduced risk) in the North Cyprus population. In North Cyprus, consanguinity practice is infrequent. Nevertheless, marriages between second- and third-degree relatives are comparatively more common than between first-degree relatives. Therefore, consanguinity is observed to be a useful factor for the reduction of BC risk in this study for Turkish Cypriot women.

The analysis confirmed the association of 74% increased risk of BC and depression in the final adjusted model. Evidence from studies on experimental animals and human and clinical trials have suggested that depression may influence BC development through several mechanisms, such as interfering with the DNA repair mechanism and triggering the abnormal activity of the hypothalamic–pituitary–adrenal axis (21). Likewise, chest X-ray exposure after puberty was also found to be a significant risk for BC in North Cyprus women. The radiation damage caused by radiopharmaceuticals is generally through the formation of free radicals, which subsequently causes DNA damage (22).

No significant increased BC risks were reported in cases of exposure to pesticides in the adjusted model. As the carcinogenic effect of pesticides is strongest when exposure occurs before puberty when breast development starts, women at age 14 when exposed to DDT had significantly increased risks of BC (23).

The estimations confirmed that large amounts of oil and sugar consumption were significantly positively associated with BC risk, while daily water intake of approximately 1 to 2 L was found to reduce BC risk by up to 64%. However, the risk remains the same even after increasing water intake above 2 L per day. Other studies have also supported the beneficial effect of drinking water on various cancers including bladder cancer, colorectal cancer, and BC prevention (24). Water may play a role in the removal of cellular carcinogens as chronic dehydration may alter the intracellular water concentration, affect the enzymatic activity in metabolic regulations, and inhibit removal of carcinogens from cells (25). The relationship between oil or fat intake and BC is unclear; however, there is evidence that lower fat intake reduces the concentration of bioavailable serum sex hormones (26,27), which are the main risk factors for BC. Similarly, worldwide sugar consumption has increased threefold in the last 50 years (28). In addition to metabolic syndromes, excessive sugar consumption is associated with several types of cancers, including BC (29,30). High sugar consumption in addition to inactive lifestyle is also associated with the higher prevalence of obesity (31). An additional spoon of sugar consumed daily is thought to be associated with 14% increased risk of being overweight or obese (32). Sugars are found to enhance cell proliferation and migration, induce DNA damage, and increase inflammation (33). All these adverse effects are associated with cancer pathogenesis.

No significant association between BC risk and the consumption of butter, margarine, other FFDPs, coffee, and tea were reported in the final adjusted model. However, dairy products are a diverse group of foods, with different factors that can potentially influence the risk. Some dairy products, such as whole milk and some cheeses, have relatively high saturated fat content and may increase the risk. Additionally, several contaminants and growth factors, such as insulin-like growth factor I in dairy products, may have potential carcinogenic effects and could promote BC cell growth. However, the calcium and vitamin D contents in dairy products have been hypothesized to reduce the BC risk.

Our study has several limitations; first, the population of the study is predominantly postmenopausal, thus limiting the generalizability of the results to premenopausal women. Similarly, all the information except BMI was self-reported and therefore no information was available about breast density, which is a moderate independent risk factor. However, any potential bias is nondiscriminational as breast density is not routinely determined during breast screening in North Cyprus and would have affected all methods similarly. Furthermore, the genetic predisposition for BC (i.e. *BRCA1* and *BRCA2* gene mutation status) in case and control subjects was also unknown, except the information regarding family history for breast cancer. Therefore, further studies should focus on the mutation status of BC susceptibility genes in this population.

In this epidemiological investigation, a comprehensive range of factors was assessed. In addition to strong associations with various recognized factors, the BC risk in North Cypriot women was found to be associated with PMD, exposure to diagnostic radiation, and the quantity of oil and sugar consumed. However, consanguinity and adequate daily water intake were protective factors. The results of the study can help with the development of a risk assessment tool for the North Cyprus population in order to identify high-risk individuals that will improve the prevention of the disease.

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