

## Breast Cancer: Impact of Modifiable and Non-Modifiable Risk Factors Among Premenopausal Women of Karachi, Sindh

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### ABSTRACT

**Objective:** The goal of present study was to probe the interplay between modifiable and non-modifiable factors and breast cancer (BC) risk.

**Methodology:** Two hundred and twenty-eight (228) BC cases and 503 healthy volunteers with 20-45 years of age without history of BC were recruited from tertiary hospitals located in Karachi, a metropolitan city of Pakistan. Major risk factors for the BC were evaluated using pretested self-structured questionnaire.

**Results:** The adjusted regression analysis showed that Balouchi (OR=12.93, 95%CI=4.26-39.17) and Sindhi (OR=9.41, 95%CI=4.72-18.77) ethnicity, familial history of BC (OR=1.83, 95%CI=1.16-2.91), low socio-economic status (OR=26.81, 95%CI=17.56-40.94), marital age >30yrs (OR=20.99, 95%CI=4.15-106.24), hormone replacement therapy (OR=1.95, 95%CI=1.03-3.69), being obese (OR=1.589, 95%CI=1.03-2.46), high waist-to-Hip ratio (WHR) (OR=2.69, 95%CI=1.67-4.32), apple shape body (OR=2.62, 95%CI=1.63-4.21), consanguineous marriages (OR=1.62, 95% CI=1.15-2.29) and sun exposure <1 hr/day (OR=7.56, 95%CI=3.002-19.04), daily intake of beef (OR = 1.544, 95%CI=1.004-2.373), dry fruits (OR=1.922, 95%CI=1.233-2.996), rice (OR= 2.412, 95%CI=1.17-4.973), tea and coffee (OR=2.299, 95%CI=1.246-4.24) and less consumption of milk (OR=1.942, 95%CI=1.344-2.807) and fruits (OR=2.952, 95%CI=1.505-5.792) were increased the BC risk among premenopausal women. Conversely, first pregnancy <24yrs (OR=0.53, 95%CI=0.33-0.85), WHR <0.85 (OR=0.296, 95%CI=0.15-0.59), avocado body shape (OR=0.31, 95%CI=0.16-0.61), excessive chicken (OR=0.403, 95%CI=0.206-0.791) and eggs (OR=0.479, 95%CI=0.304-0.755) consumption were considered a protective factor.

**Conclusion:** Ethnicity, SES, marital age, HRT, breast cancer family history, overweight and obesity, intermarriages and sun exposure may be the major risk factors for BC among premenopausal women of Sindh, Pakistan. Diet may also play a role in developing BC.

**KEYWORDS:** Breast cancer; risk factors; modifiable; non-modifiable; premenopausal

### INTRODUCTION

Breast cancer (BC) is the leading women's health problem among rural and urban settings and the 2nd most frequently diagnosed cancer overtaking lung

incidence rates of breast cancer have evidently risen.<sup>1</sup> In Karachi city, BC constitutes about 52.4% of all diagnosed cancer among women which may be caused by the postmenopausal age, middle socioeconomic class, change in anthropometric profile and mutations in genes.<sup>1</sup> However, the results vary with environmental and ethnic differences. Some reproductive and dietary factors are eminent among Pakistani whereas other may not be fully applicable to our population where higher rates of fertility, early first gestational age, increase childbirths and increase lactation are the norm.<sup>2</sup> The BC risk factors can be categorized into non-modifiable, modifiable and controversial factors. Older age, female gender, family history of cancers, premature menarche, late menopause and breast cancer ½ genes are the non-modifiable factors.

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Whereas nulliparity, lack of breast feeding, hormonal variations, obesity, diet, oral contraceptives (OC), delayed first birth, hormone replacement therapy (HRT), and sedentary lifestyle are the modifiable factors. Other factors such as exposure to hazardous chemicals and pesticides have controversial effects.<sup>3</sup>

The international variations in the BC burden revealed that there were variations in the risk factors pattern among different environment. In the milieu of Southern Pakistan, the eminent factors in BC were not clearly reported, and it is apparent that unrecognized exposures specific to females of Southern Pakistan may have a role in the BC development. Therefore, this study was aimed to reconnoiter the association between modifiable and non-modifiable factors and BC risk in premenopausal women of Karachi, Pakistan.

## METHODOLOGY

The present study is a case-control study conducted at the University of Karachi on the premenopausal women of Karachi, a metropolitan city of Pakistan, where populations from different areas are resided. The sample size was calculated using online sample size calculator open Epi with 95% confidence interval and 80% statistical power. Total 731 women (228 BC patients and 503 age-matched healthy volunteers) were enrolled during 2012-2015 with age brackets of 20-45 years. All cases were diagnosed histopathologically with breast cancer recruited from the public hospitals of Karachi. All controls were healthy females having a good physical condition with no prior disease history and age matched to cases. All controls were recruited from the general populations by simple random sampling. All participants who were <20 years and >45 years and all those who suffer from major medical illness other than breast cancer were excluded. The detailed criteria for the selection of participants are described in Figure 1.

The approval of this study was given by the Bioethics committee and BASR, UoK (01178/2010) according to the standard Helsinki Declaration. Printed informed consent was given to all participants for signing. The interviews were then conducted by the investigator.

All relevant facts and figures were collected through face-to-face interviews by an interviewer. The pre-tested self-structured questionnaire was

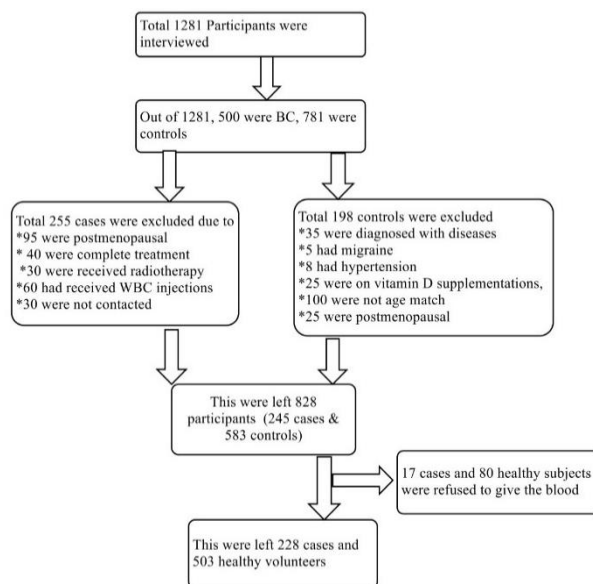


Figure 1: Selection of Participants

given to all participants to fill it properly. The information which was not provided were also filled by telephonic conversation. The parameters in the questionnaire included information on socio-demographic characteristics (women's age, racial/ethnic group, profession, socio-economic status (SES), marital status, age at time of marriage, intermarriages), reproductive history (no. of pregnancies, breast feeding, early gestational age, menarche, length of menstrual cycle, OC and HRT), family history, environmental exposures (sunlight, perfumes and insecticide) and diet. The histopathological parameters of patients were obtained from the medical record.

Body dimensions including height in meters, weight in kilograms, waist and hip circumference was measured. Body mass index (BMI) was calculated as the body weight (Kg) is divided by height (m<sup>2</sup>). Cut-off values of BMI were taken according to the WHO defined criteria (2004) for Asians. Categories of BMI was underweight (<18.5 kg/m<sup>2</sup>), healthy weight/normal (18.5-<23 kg/m<sup>2</sup>), overweight (23-<25 kg/m<sup>2</sup>) and obese (>25 kg/m<sup>2</sup>).<sup>4</sup> Waist-to-Hip ratio (WHR) was measured by taking the ratio of waist and hip circumference. The WHR values <0.8 is considered as good, 0.8-0.85 is average and >0.85 is unacceptable.<sup>5</sup> However, the women with WHR <0.80 are classified as pear body shape, 0.80-0.90 as avocado shape and >0.90 as apple body shape. The body fat% (BF%) was measured using Eiken-type Skin Fold Caliper (TK-11258, Ogawa Seiki Co.,

LTD, Tokyo, Japan). The score of BF% was classified as 10-20% (essential body fat), 21-24% (fitness), 25-31% (acceptable) and more than 31% (obese). Moreover, a self-structured 31 food items food frequency questionnaire was prepared to determine the association between diet and BC risk. **Statistical analysis:** The collected information was analyzed using SPSS version-23.0 software and the data was taken as significant with p-value <0.05. All qualitative variables are taken in terms of frequencies (percentages for categorical variables and mean  $\pm$  standard deviation for continuous variables). The likelihood ratio test for the interaction of modifiable and non-modifiable risk factors with premenopausal BC risk was calculated using Pearson  $\chi^2$  test. Crude/unadjusted (UORs) and adjusted odds ratios (AORs) and 95% confidence interval (95% CI) were calculated using binary unconditional logistic regression analysis.

## RESULTS

Total 228 BC cases and 503 healthy controls were enrolled in this study. The affected side of breast cancer in majority of the women was right (53.9%) side. Invasive ductal carcinoma (93.4%) with grade-II (71.9%) is the common histological type of BC in Pakistani women. Moreover, most of cases had ER+ (55.3%), PR+ (50%) and Her2neu+ (42.9%).

The mean age of BC cases and healthy controls were  $37.6 \pm 7.5$  and  $35.2 \pm 7.2$  years respectively. Ethnicity and familial BC history were more frequent among cases than controls (Table 1). However, premenopausal BC risk was increased with Balouch and Sindhi ethnic groups and positive familial BC history (Table 1).

Working/professional females, Low SES, unmarried females' status, marital age, lower no. of previous pregnancy, Age at first pregnancy, abortion, HRT, higher WHR, apple body shape, vigorous physical activity, walking, intermarriages and lower sun exposure shows significant association with premenopausal breast cancer (Table 2). However, lower SES, marital age >30yrs, HRT, obesity, high WHR, apple body shape, consanguineous marriages and sun exposure <1 hr/day were significantly increasing premenopausal BC risk (Table 2). Those having their first full term pregnancy <24 years, WHR <0.85 and avocado body shape have protective effects (Table 2).

**Table 1. Association between potential non-modifiable elements and premenopausal BC risk**

Non-modifiable factors	Cases/controls (n 228/503)	Pearsons $\chi^2$	Crude/auor (95%CI)	Baor (95%CI)
<b>Demographics</b>				
<b>Age:</b>				
20-26	20/58	1.58	Reference	-----
27-33	34/78		1.26 (0.66-2.42)	
34-40	110/225		1.42 (0.81-2.48)	
41-45	64/142		1.31 (0.73-2.35)	
<b>Ethnicity</b>				
Urdu Speaking	94/252	97.13**	Reference	Reference
Punjabi	20/104		0.52 (0.30-0.88)*	0.52 (0.31-0.89)*
Balouch	19/4		12.73 (4.22-38.42)*	12.93 (4.26-39.17)*
Sindhi	41/12		9.16 (4.61-18.18)*	9.41 (4.72-18.77)*
Pakhtoon	18/47		1.03 (0.57-1.86)	0.99 (0.55-1.81)
Others	36/84		1.15 (0.73-1.81)	1.17 (0.74-1.85)
<b>Reproductive</b>				
<b>Menarcheal Age (Years)</b>				
12-14	186/423	2.02	Reference	Reference
>14	28/45		0.91 (0.48-1.73)	0.91 (0.48-1.74)
<12	14/35		1.415 (0.86-2.34)	1.39 (0.84-2.30)
<b>Familial history</b>				
<b>Breast cancer history</b>				
No	191/455	6.824*	Reference	Reference
Yes	37/48		1.84 (1.16-2.91)*	1.83 (1.16-2.91)*
<b>Other cancers history</b>				
No	199/442	4.495	Reference	Reference
Yes	29/61		1.06 (0.66-1.69)	1.067 (0.67-1.71)

aUOR is unadjusted ORs/Crude OR

bAOR is adjusted ORs which is adjusted to the age (1:2).

\*p<0.05, \*\*p<0.01

**Table 2. Association between potentially modifiable elements and premenopausal BC risk**

Modifiable factors	Cases/controls (n 228/503)	Pearsons $\chi^2$	Crude/auor (95%CI)	Baor (95%CI)
<b>Demographics</b>				
<b>Profession</b>				
House-hold	211/366	36.96**	Reference	Reference
Working	17/137		0.21 (0.13-0.37)*	0.21 (0.12-0.35)*
<b>Socio economic status</b>				
Middle	49/424	314.28**	Reference	Reference
Lower	177/58		26.41 (17.37-40.14)*	26.81 (17.56-40.94)*
Upper	2/21		0.82 (0.19-3.62)	0.84 (0.19-3.68)
<b>Marital status</b>				
Married	208/363	33.39**	Reference	Reference
Unmarried	20/140		0.25 (0.15-0.41)*	0.14 (0.07-0.27)*
<b>Marital age (Years)</b> (N 208/363)				
<20	105/244	20.69**	Reference	Reference
20-30	95/117		1.89 (1.32-2.58)*	3.34 (2.16-5.18)*
>30	8/2		9.29 (1.94-44.51)*	20.99 (4.15-106.24)*

**Table 2. Association between potentially modifiable elements and premenopausal BC risk (Continue)**

Modifiable factors	Cases/controls (n 208/363)	Pearsons $\chi^2$	Crude/auor (95%Ci)	Baor (95%CI)
<b>Anthropometric Indices</b>				
<b>Quetelet index</b>				
Healthy weight	56/157	6.63	Reference	Reference
Underweight	22/64		0.96 (0.54-1.71)	0.97 (0.54-1.72)
Overweight	79/158		1.402 (0.93-2.11)	1.38 (0.91-2.09)
Obese	71/124		1.61 (1.05-2.45) *	1.59 (1.03-2.46)*
<b>WHR</b>				
Good	27/92	82.96**	Reference	Reference
Average	15/173		0.29 (0.15-0.58) *	0.296 (0.15-0.59) *
High	186/238		2.66 (1.66-4.26) *	2.69 (1.67-4.32) *
<b>Body shape</b>				
Pear	27/91	79.003**	Reference	Reference
Avocado	16/172		0.31 (0.16-0.61) *	0.31 (0.16-0.61) *
Apple	185/240		2.598 (1.62-4.16) *	2.62 (1.63-4.21) *
<b>Reproductive</b>				
<b>No. of pregnancies</b>				
>5	60/82	6.772*	Reference	Reference
0	22/24		1.25 (0.64-2.44)	1.13 (0.57-2.24)
<5	126/257		0.67 (0.45-0.99) #	0.58 (0.39-0.88) #
<b>Breast feeding</b>				
Yes	186/339	2.8 07	Reference	Reference
No	22/24		1.67 (0.91-3.06)	1.67 (0.901-3.107)
<b>Age at first live birth (years)</b>				
<20	49/63	14.003**	Reference	Reference
20-24	81/118		0.49 (0.31-0.78) *	0.53 (0.33-0.85) *
25-29	39/115		0.58 (0.307-0.78)	0.62 (0.33-1.18)
>29	17/43		1.13 (0.709-1.81)	1.22 (0.75-1.97)
<b>Length of menstrual period (days)</b> (N 228/503)				
3-7	193/446	14.003**	Reference	Reference
<3	23/32		1.66 (0.95-2.91)	1.73 (0.98-3.05)
>7	12/25		1.109 (0.55-2.25)	1.14 (0.56-2.33)
<b>OC use</b> (N 228/503)				
No	197/454	2.39	Reference	Reference
Yes	31/49		1.46 (0.90-2.36)	1.47 (0.91-2.38)
<b>HRT</b> (N 228/503)				
No	209/481	4.65*	Reference	Reference
Yes	19/22		1.99 (1.05-3.75) *	1.95 (1.34-3.69) *

<b>BF%</b>				
Fitness	20/57	7.18	Reference	Reference
Essential fat	5/18		0.79 (0.26-2.41)	0.81 (0.263-2.47)
Acceptable	64/174		1.05 (0.58-1.88)	1.05 (0.58-1.92)
Obese	139/254		1.56 (0.9-2.703)	1.599 (0.8-2.91)
<b>Life Style Factors</b>				
<b>Sleeping time</b>				
>8 hrs	74/191	2.07	Reference	Reference
<8 hrs	154/312		1.274 (0.915-1.773)	1.26 (0.904-1.756)
<b>Consanguineous marriages</b>				
No	149/381	8.503**	Reference	Reference
Yes	79/122		1.656 (1.178-2.328)*	1.619 (1.146-2.287)*
<b>Sun exposure</b>				
Yes (>1 hour/day)	5/73	24.98**	Reference	Reference
No (<1 hour/day)	223/430		7.572(3.016-19.006)*	7.56 (3.002-19.04)*
<b>DIET</b>				
<b>Animal based food</b>				
<b>Beef</b>				
Rarely/None	70/148	14.64**	Reference	Reference
Monthly	10/23		0.907 (0.409-2.009)	0.884 (0.398-1.961)
Weekly	83/244		0.709 (0.486-1.036)	0.69 (0.471-1.009)
Daily	65/88		1.541 (1.003-2.366)*	1.544 (1.004-2.373)*
Total	228/503			
<b>Chicken</b>				
Daily	30/32	74.77**	Reference	Reference
Weekly	26/72		0.396 (0.202-0.775)*	0.403 (0.206-0.791)*
Monthly	99/351		0.301 (0.174-0.519)*	0.3 (0.173-0.518)*
Rarely/None	73/48		1.622 (0.875-3.007)	1.64 (0.883-3.047)
Total	228/503			
<b>Dairy Food Items</b>				
<b>Egg</b>				
Rarely/None	84/129	17.84**	Reference	Reference
Monthly	39/60		0.983 (0.603-1.602)	0.988 (0.605-1.613)
Weekly	66/191		0.522 (0.353-0.774)*	0.532 (0.359-0.79)*
Daily	39/123		0.479 (0.305-0.754)*	0.479 (0.304-0.755)*
<b>Milk</b>				
Daily	78/186	39.97**	Reference	Reference
Weekly	26/135		0.454 (0.277-0.746)*	0.453 (0.275-0.746)*
Monthly	16/50		0.755 (0.405-1.406)	0.767 (0.41-1.432)
Rarely/None	108/132		1.93 (1.337-2.786)*	1.942 (1.344-2.807)*

Vegetables and fruits				
Vegetables				
Daily	170/301	27.26**	Reference	Reference
Weekly	18/83		0.384 (0.223-0.661)*	0.389 (0.225-0.673)*
Monthly	17/86		0.35 (0.201-0.609)*	0.353 (0.203-0.614)*
Rarely / None	23/31		1.314 (0.742-2.326)	1.307 (0.738-2.315)
Fruits				
Daily	12/45	83.44**	Reference	Reference
Weekly	7/134		0.187 (0.069-0.506)*	0.188 (0.069-0.508)*
Monthly	27/93		1.04 (0.482-2.247)	1.035 (0.478-2.238)
Rarely / None	182/231		2.823 (1.447-5.51)*	2.952 (1.505-5.792)*
Dry Fruits				
Daily	85/171	28.41**	Dry Fruits	Reference
Weekly	78/245		0.633 (0.44-0.911)*	0.635 (0.44-0.917)*
Monthly	6/26		0.459 (0.182-1.157)	0.47 (0.186-1.189)
Rarely / None	59/61		1.923 (1.235-2.994)*	1.922 (1.233-2.996)*
Other Items				
Pulses				
Daily	122/135	50.56**	Reference	Reference
Weekly	89/301		0.322 (0.229-0.453)*	0.325 (0.231-0.458)*
Monthly	6/29		0.226 (0.091-0.562)*	0.22 (0.088-0.55)*
Rarely / None	11/38		0.316 (0.154-0.645)*	0.308 (0.15-0.631)*
Rice				
Daily	10/38	61.78**	Reference	Reference
Weekly	4/80		0.18 (0.053-0.612)*	0.181 (0.053-0.615)*
Monthly	13/84		0.557 (0.224-1.387)	0.56 (0.225-1.395)
Rarely / None	201/301		2.404 (1.167-4.954)*	2.412 (1.17-4.973)*
Tea / Coffee				
Daily	14/67	16.59**	Reference	Reference
Weekly	0/13		NC	NC
Monthly	17/21		3.759 (1.588-8.896)*	3.964 (1.658-9.477)*
Rarely / None	197/402		2.275 (1.246-4.155)*	2.299 (1.246-4.24)*

aUOR is unadjusted ORs/Crude OR

baOR is adjusted ORs which is adjusted to the age (1:2).

\*p<0.05, \*\*p<0.01

Diet also plays a significant role in breast cancer. Daily intake of beef, dry fruits, rice, tea and coffee and less consumption of milk and fruits increase BC risk. However, high consumption of chicken and eggs has protective effect (Table 2).

## DISCUSSION

The goal of present study was to probe the interplay between modifiable and non-modifiable elements and risk of BC among premenopausal women of Karachi, Pakistan. Ethnicity seems to have a pivotal role in BC development. Results analyzed that Balouchi and Sindhi racial groups were significantly related with BC risk which agrees with another report.<sup>2</sup>

Consistent with the findings of Shiyabola 6, Aro significant difference was witnessed between family history and premenopausal BC.

Socioeconomic status is the considered factor for BC among women. In line with the report 7, our study found that poor premenopausal women have an association with susceptibility of having BC.

This study revealed that marital age >30 years was associated with increased premenopausal BC risk which agrees with the previous observations.<sup>8</sup>

Pregnancies have a major impact on BC development as it was previously documented that long term BC risk reduces with a higher number of alive childbirths.<sup>9</sup>

In this study, first full-term live birth younger than 25 years was significantly related with reduced BC risk than those who were elder than 25 years which was consistent with another study.<sup>10</sup>

The biological explanation of this result may be explicated by the fact that, at the early first alive childbirth, the epithelial cells of mammary tissues have the highest degree of terminal differentiation which has the ability to metabolize the carcinogens and repair the DNA damage more efficiently.

Lactation has many health benefits and may protect against BC. Breast Cancer Health Disparities Study (BCHDS) observed that the mortality rate of BC was reduced by 16% among cases due to lactation.<sup>11</sup> In this study, a lack of significant relationship was observed between lactation and BC risk which might be caused by the excessive breast-feeding practice in our population.

HRT is a well-establish breast cancer contributing factor which increases the higher risk of having mammary cancer. This study found that HRT have a significant association with mammary cancer in

premenopausal females which is not in agreement with the previous report.<sup>12</sup>

The relationship between anthropometric measurements and BC risk is debatable. In this study, higher BMI was associated with increased BC risk which is in line with the previous literature.<sup>13</sup> Statistically, a significant association was also present in this study between WHR and BC risk. It was considered as an important factor like BMI in the development of breast cancer risk. Women with WHR >0.85 may increase the mammary cancer risk.<sup>14</sup> The most possible reason may be the presence of chronic low-grade inflammation in obese females which causes DNA damage and cancer development.

We have also observed the association between consanguineous marriages (cousin marriages) and premenopausal breast cancer risk. Cousin marriage is a social tradition in most of the region of Pakistan and the overall incidence of this type of marriages is 56% among Pakistani. This kind of marriages increase low penetrance mutations or single nucleotide polymorphisms (SNPs) that can affect breast cancer susceptibility. Positive association of consanguinity, particularly first cousin marriages, has been shown in the previous study to increase the BC risk.<sup>15</sup> This study also observed the association of sunlight exposure with BC risk. Sunlight exposure <1hr/day increased the breast cancer risk at an early age which is contrary to the finding of previous literature.<sup>16</sup> Sunlight exposure is necessary for the vitamin D synthesis which is actively involved to increase cellular differentiation, decrease proliferation, and induce apoptosis and thereby prevents breast cancer. Healthy diet has an essential role in the long-term management of BC. The results show that daily intake of beef, dry fruits, rice, tea and coffee and less consumption of milk and fruits are associated with the increase risk of BC. However, high consumption of chicken and eggs was associated with reduced risk of BC. A recent study among African American and European American women showed high beef consumption (prepared by grilling or oven-broiling) was associated with increased risk of BC. In contrast, weekly fish consumption was related with decrease risk of BC.<sup>17</sup> A Sister Study (US and Puerto Rico-based nationwide prospective cohort study) evaluated that red meat increase the BC risk, however, poultry meat reduces the BC risk.<sup>18</sup> The relationship of dry fruits and BC is not stated yet.

In the SUN (Seguimiento Universidad de Navarra) project, women who consume more than 1 cup coffee per day was associated with decrease BC risk, in contrast, consumption of 1 or <1 cup of coffee/day did not show the association among premenopausal women.<sup>19</sup> A meta-analysis on dairy products showed that dairy products can reduce the risk of breast cancer. However, dairy products having high-fat are detrimental to female population.<sup>20</sup>

### **Study's limitations**

The major limitations of our study are 1) Small sample size which may be overcome by the recruitment of a large number of participants, 2) Moreover, this study did not estimate the hormone profiles and genetic factors related to BC which will further support our findings.

### **CONCLUSION**

Balouchi and Sindhi ethnic background, lower SES, marital age>30years, no previous pregnancy, HRT, positive family history of breast cancer, BMI >27.5Kg/m<sup>2</sup>, WHR >0.85, avocado and apple body shape, consanguineous marriages and sun exposure <1hr/day may be the contributing risk factors for BC in premenopausal women of Karachi, Pakistan.

### **IMPLICATIONS**

It is strongly recommended for females with the modifiable risk factors to perform breast screening earlier and their BC risk can be overcome by changes their life style pattern.

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#### Author's Contribution

<b>Mehir un Nisa Iqbal</b>	Study conception and design, data collection, data analysis and interpretation and manuscript writing and approve it
<b>Syed Amir Maqbool</b>	Study conception and design, and manuscript writing and approve it
<b>Taseer Ahmad Khan</b>	Study conception and design, or critical revision for important intellectual content and final approval of the version to be published
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