

# Exploring the Association of Serum Lipids, Plasma Glucose, Obesity and Demographic Factors on Breast Cancer Risk in Bangladeshi Female: A Case Control Study

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## Abstract:

**Background:** The fifth most prevalent cause of cancer-related death worldwide and the most frequently diagnosed malignancy is breast cancer. Breast cancer is the second most prevalent neoplasm in Bangladesh and it is rising alarmingly among females. Ignorance and illiteracy are contributing factors to mortality due to delayed presentation. This study was aimed to evaluate the association of obesity, serum lipids, plasma glucose and demographic factors with breast cancer risk in Bangladeshi females.

**Materials and Methods:** This was a case-control study designed using a population of 60 females (30 in each group). The analysis involved a comparison of both the socio-demographic data and the blood samples collected from the participants in the study. Samples were collected over a one-year period from the Department of Surgery at Bangladesh Medical College and Hospital, as well as from the Departments of Surgery and Oncology at Bangabandhu Sheikh Mujib Medical University, Bangladesh. Statistical analysis was performed with SPSS version 26.

**Results:** Mean body mass index (BMI) of case group is 29.4 ( $\pm$  2.8) and control group is 25.5 ( $\pm$  3.4) where P value is significant ( $<0.001$ ). Significant differences ( $P$ -value  $\leq 0.05$ ) were observed in triglycerides (TG), low density lipoprotein (LDL) cholesterol, and total cholesterol (TC) level between cases and controls. Though there were no significant differences observed between the groups in fasting plasma glucose (FPG), plasma glucose- 2 hours after breakfast (PG-2HABF), haemoglobin A1c (HbA1c), high density lipoprotein (HDL) cholesterol, and serum creatinine level.

**Conclusion:** TC, TG and LDL cholesterol level as well as BMI are independent predictors of breast cancer risk among Bangladeshi females.

**Key Word:** Breast cancer, Hyperglycemia, Hyperlipidemia, Lipid profile, Obesity.

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## I. Introduction

Breast cancer is the most common cancer among females globally. In terms of prevalence, it ranks as the leading type of cancer affecting females across the world. Every year, 76,000 women in South Asia, including Bangladesh, India, Nepal, Myanmar, Pakistan, Tibet, and other countries, pass away from breast cancer<sup>1</sup>. The Global Cancer Observatory (GLOBOCON) estimates that it will be responsible for 6.9% of cancer-related fatalities and 11.7% of new cancer cases in 2020. By 2040, incident cases are predicted to rise by more than 47%<sup>2,3</sup>. Despite having a lower prevalence of breast cancer than their Western counterparts, the disease is growing quickly in developing nations<sup>2,3</sup>. A recent estimate states that Southeast Asia has a 41.2% incidence and 15% fatality rate<sup>2</sup>. A few reports exist on Bangladesh's breast cancer epidemiology and risk factors. Based on a study conducted by the National Institute of Cancer Research and Hospital (NICRH), 5255 cases of breast cancer were detected between 2005 and 2010, with an average age of presentation of 42 years<sup>4,5</sup>. Numerous

research have been conducted to better understand the disease's characteristics, causative relationships, and appropriate treatments to address this public health issue in light of the rise in reported cases and deaths.

A number of environmental factors are critical to the underlying mechanism, in addition to known dangers such as being non-Hispanic white, having a greater chronological age, and genetic influence<sup>6,7,8</sup>. Recently, there has been a growing understanding of the impact that weight and diet have on plasma lipids and lipoproteins, and how these factors influence the incidence of breast cancer<sup>9,10</sup>. It has been discovered that estrogen receptor-positive breast cancer cells proliferate and spread more easily when exposed to the cholesterol metabolite 27-hydroxycholesterol<sup>11,12</sup>. Inhibiting apoptosis and promoting the growth and migration of cancer cells may be related to the activation of several inflammatory pathways by lipoprotein oxidation and HDL glycation<sup>13</sup>. By reducing elevated cholesterol, apolipoprotein A-I mimetics and cholesterol-lowering medications are thought to be promising therapeutics for the prevention of breast cancer<sup>9</sup>. Millions of women who are at risk of breast cancer due to changed lipid levels now have hope because to lipid-lowering medications. Regretfully, there is still no agreement on the impact of dyslipidemia on the risk of breast cancer due to conflicting and ambiguous study findings. In fact, total cholesterol has been linked to an increased risk of breast cancer in one human study<sup>14</sup>, however results from multiple other investigations show different conclusions<sup>10,15,16</sup>. There is less evidence to support the idea that total cholesterol and breast cancer risk are inversely correlated<sup>17</sup>. On the other hand, there is a growing recognition that type 2 diabetes mellitus (T2DM) and breast cancer (BC) occur together in the same patient population with high mortality rates<sup>18</sup>. Overall survival and disease-specific survival are significantly worse in diabetic BC patients compared to non-diabetic BC patients, suggesting a correlation between T2DM and cancer progression<sup>19</sup>.

Breast cancer has also been linked to risk factors such as obesity and BMI<sup>20</sup>, socio-demographic characteristics<sup>21,22</sup> and obstetric variables<sup>23</sup>. Obesity is defined as having excess body fat based on body mass index (BMI)<sup>20</sup>. Obese individuals (OB) have a BMI of 30 kg/m<sup>2</sup> or greater and are more likely to develop chronic diseases such as cancer, particularly breast cancer. Women who are overweight or obese are at an increased risk of developing breast cancer<sup>24</sup>, particularly those who have gone through menopause<sup>25</sup>.

The incidence of breast cancer cases and related fatalities is increasing in Bangladesh. Hence, understanding the risk factors associated with the disease might aid in the prevention and management of this malignant condition. Therefore, the study was designed to assess the relationship among BMI, serum lipid profile, plasma glucose and demographic risk factors with breast cancer among Bangladeshi females.

## **II. Material And Methods**

This case-control study was carried out in the Department of Anatomy, Bangabandhu Sheikh Mujib Medical University (BSMMU) hospital. The patients were recruited from the Department of Surgery, Bangladesh medical college, and hospitals and the Department of Surgery and the Department of Oncology, BSMMU.

**Study Design:** Case-control study

**Study Location:** Department of Anatomy, Bangabandhu Sheikh Mujib Medical University (BSMMU) hospital

**Study Duration:** March 2018 to January 2020.

**Sample size:** A convenient sampling technique was used for this study. Thirty females in each group was included for this pilot study.

**Subjects & selection method:**

**Inclusion criteria:**

1. Female
2. Age range 30 to 70 years
3. Diagnosed breast cancer patient by an oncologist
4. Willing to adhere to the protocol requirements and to provide written informed consent

**Exclusion criteria:**

1. History of heavy smoking
2. Symptoms of respiratory tract infection, digestive tract disease, thyroid hormonal dysfunction, coronary artery disease, and stroke
3. Usage of antibiotics and anti-inflammatory drugs (Ibuprofen, Ketorolac, Etoricoxib, and steroids), anti-neoplastic drugs (Methotrexate), and hormones (Progesterone and Estrogen) within the last two months
4. Current pregnancy or breastfeeding

**Procedure methodology:**

A semi-structured data sheet was developed to gather information from the study participant. The data collected from participants included socio-demographic information, diagnostic reports of breast cancer, and personal details such as menstrual history, age of menarche, dietary habits, lifestyle choices, family history of the disease, and the participants' medical history. BMI assessment and categorization participant weight (in kilograms) was measured using a digital bathroom scale (Model: Meb 9370, Miyako Electronics Ltd., Bangladesh) and height (in meters) was measured using a standard measuring tape. Then BMI was calculated using standard formula. The WHO recommended Asian criteria for BMI categorization was used for this study<sup>26</sup>. A BMI  $\geq 23$  was considered overweight and/or obese and a BMI between 18.5 and 22.9 was considered normal weight.

**Laboratory procedure:**

Analysis of blood samples from cases and their matched controls were done in same batches but in random order. Serum lipid, plasma sugar and other biochemical assays were carried out at the Department of Biochemistry and Molecular Biology, BSMMU. Serum lipid measures were standardized with the Centers for Disease Control (CDC, Atlanta, GA) Lipid Standardization Program. Five milliliters of fasting (at least 12 hr) venous blood was collected. serum was separated by centrifugation and analyzed on the same day by the enzymatic method in an automated analyzer (Beckman Coulter-AU680) for lipid profiles comprising TC, TG, LDL and HDL.

**Ethical consideration**

The study protocol was approved by the Institutional Review Board (IRB), BSMMU (reference number: BSMMU/2018/14574(A); Date: 18.12.2018). Written informed consent was obtained from the participants before inclusion.

**Statistical analysis**

Socio-demographic and biochemical data were analyzed using the One-way ANOVA test in Statistical Package for Social Science (SPSS) version 26.0 (IBM Corporation, Released 2015, IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY). Risk factor analysis of variables by logistic regression analysis comparing breast cancer patients to healthy controls.

**III. Result**

Demographic characteristics of the controls and cases are shown in table 1. The age of female breast cancer patients ranged from 30 to 65 years. The age group of 40 to 51 years represents the highest (46.67%) in the study population. The frequency of below 35 years of age was 3.33% and the same for above 60 years of age. The age of the controls ranged from 22 to 63 years. 70% of the cases had the onset of breast cancer before 50 years of age.

**Table no 1: Demographic characteristics of the controls and cases**

Parameter	Control mean ( $\pm$ SD)	Breast cancer mean ( $\pm$ SD)	P-value
Age in years	37.3 ( $\pm$ 12.5)	46.7 ( $\pm$ 8.2)	<b>0.001*</b>
Weight in kg	61.9 ( $\pm$ 8.2)	71.6 ( $\pm$ 6.9)	0.285
Height in m	1.6 ( $\pm$ 0.08)	1.55 ( $\pm$ 0.06)	<b>&lt;0.001*</b>
BMI, kg/m <sup>2</sup>	25.5 ( $\pm$ 3.4)	29.4 ( $\pm$ 2.8)	<b>&lt;0.001*</b>

\* indicates the level of significance

The BMI of the cases ranged from 23.3 kg/m<sup>2</sup> to 36.45 kg/m<sup>2</sup> and 20.38 kg/m<sup>2</sup> to 30.50 kg/m<sup>2</sup> for cases and controls respectively. Among all of the cases, 50% had a BMI of 30 kg/m<sup>2</sup> or above. Mean BMI of case group is 29.4 ( $\pm$  2.8) and control group is 25.5 ( $\pm$  3.4). The P value is considered significant.

Biochemical characteristics of the controls and cases are shown in table 2. Significant differences (P-value  $\leq$  0.05) were observed in TG, LDL cholesterol, and TC level between cases and controls.

There were no significant differences observed between the groups in FPG, PG- 2HABF, HbA1c, HDL cholesterol, and serum creatinine level.

**Table no 2: Biochemical characteristics of the controls and cases**

Parameter	Control mean (± SD)	Breast cancer mean (± SD)	P-value
Plasma Glucose (mmol/L)			
Fasting	5.1 (±0.67)	5.2 (±2.9)	0.991
2 hours after breakfast	6.5 (±0.74)	7.5 (±4.8)	0.26
HbA1c (%)	5.5 (±0.5)	6.2 (±1.5)	0.13
Lipid profile (mg/dL)			
Triglycerides	115.4 (±33.9)	167.7 (±72.6)	<b>0.001*</b>
HDL Cholesterol	49.1 (±8.3)	44.9 (±9.8)	0.078
LDL Cholesterol	106.8 (±17.3)	130.5 (±36.9)	<b>0.002*</b>
Total Cholesterol	164.4 (±20.7)	209.9 (±54.5)	<b>0.001*</b>
Serum creatinine (mg/dL)	0.83 (±0.22)	0.89 (±0.24)	0.43

\* indicates the level of significance

Among the cases, 56.67% had a history of menarche before 11 years of age and 13.3% of the controls had a history of menarche before 11 years of age, 63.3% of the female breast cancer patients were postmenopausal, and the majority had a history of menopause between 40-50 years.

Among all the females, 96.6% of cases and 83.3% of control were married. Among cases 6.6% were nulliparous. The majority (82.0%) of the cases had their first live pregnancy below 21 years.

The use of hormonal contraceptives was observed greater in cases than that in controls. The history of breastfeeding was present in 93% of the cases. About two-thirds of the patients had a duration of breastfeeding for over six months.

**Table no 3: Reproductive characteristics of the controls and cases**

Parameter	Control mean (± SD)	Breast cancer mean (± SD)	P-value
Age at menarche	12.4(±1.4)	11.7(±1.6)	0.096
Parity	1.5(±1.3)	2.1(±0.2)	<b>0.047*</b>
Age at first childbirth	24(±3.8)	18.6(±3.4)	<b>0.004*</b>
Age at menopause	43.3(±2.6)	42.3(±3.6)	0.447

\* indicates the level of significance

The logistic regression analysis comparing breast cancer patients to healthy controls reveals several insights. The model's Cox & Snell R Square (0.416) and Nagelkerke R Square (0.554) indicate that the independent variables account for a significant portion of the variance in breast cancer diagnosis. BMI shows a significant effect with a coefficient of -0.325 and a p-value of 0.002. TG also significantly influence the odds, with a coefficient of -0.020 and a p-value of 0.024, suggesting that higher TG levels are associated with slightly decreased odds of breast cancer. Overall, the model effectively distinguishes between breast cancer and healthy controls, with BMI and TG levels being the most significant predictors (Table 4).

**Table no 4: Risk factor analysis of variables by logistic regression analysis comparing breast cancer patients to healthy controls**

Variables	B	p-value	OR	95% C.I	
				Lower	Upper
BMI	-0.325	<b>0.002*</b>	0.723	0.588	0.888
TG	-0.020	<b>0.024*</b>	0.980	0.963	0.997
HDL	0.034	0.379	1.035	0.959	1.117
LDL	-0.008	0.694	0.993	0.956	1.030
TC	-0.020	0.177	0.981	0.953	1.009

#### IV. Discussion

In this study, all female breast cancer patients were under 65 years old, with the youngest patient being 30 years old. The mean age of cases was 46.7 (±8.2) years. The age ranging from 40 to 51 years represented the highest (46.67%). The mean age of female breast cancer patients was found very close (46 years) to a study in Bangladesh<sup>27</sup>. In a Bangladeshi study observed the mean age was 43.55 years<sup>28</sup>. So the mean age of the breast

cancer patients seems to be relative earlier in Bangladesh, though in another study in Bangladesh found the mean age at diagnosis was 37.5 years which was earlier than that found in other studies of this country<sup>29</sup>.

Among the South-Asian countries, a similar picture of early-onset was noted. The mean age of female breast cancer patients has been documented to be 47.9 years in India and 46.5 years in Nepal<sup>30,31</sup>. In contrast, the mean age was found higher (55-60 years) in Western countries<sup>28</sup>. In the United States, the mean age of female breast cancer patients was 70 years<sup>32</sup>.

In the present study, 50% of females among the cases are obese. The average BMI of the cases was 29.4 kg/m<sup>2</sup> and 50% of the controls had BMI within the range from 25 to 29.9 kg/m<sup>2</sup>. A study conducted among the Bangladeshi population found the mean BMI of a healthy adult married women was 20.8533. Iqbal et al. stated the BMI was greater than 25 kg/m<sup>2</sup> among the female breast cancer patients in the Bangladeshi population<sup>27</sup>. Obesity is a recognized risk factor for the development of breast cancer and recurrence even when patients have treated appropriately<sup>34</sup>. This may be due to the imbalance in the ratio between leptin and adiponectin produced by the adipocytes. The increase leptin-adiponectin ratio in obesity has been implicated in neoplastic transformation and tumor progression<sup>35</sup>. Though Singh et al. (2011) observed no differences in BMI between the case and control groups, in their study on the Indian population<sup>36</sup>. A strong association was found between weight gain after menopause with the occurrence of breast cancer in USA population-based study<sup>37</sup>.

The current study found that The cases and controls were significantly different in terms of TG, TC and LDL cholesterol levels ( $P \leq 0.001$ ). Chowdhury et al., 2021 found that breast cancer patients had significantly higher TC, LDL, and TG levels than both benign breast disease patients and healthy controls, while the HDL levels remain similar<sup>38</sup>. A concordant finding was reported by researchers in Ghana and India<sup>39,40</sup>. However, studies conducted in other regions have shown opposing findings. One study in Libya found significantly elevated TC and HDL levels in breast cancer patients compared with controls<sup>41</sup>, while LDL and TG levels remained unchanged in their study. Another study from the Middle East found significantly increased levels of TC and LDL among women with malignant tumors in comparison to the benign and control groups<sup>42</sup>. This was also reported by a Srilankan study<sup>43</sup>. A Nepalese study noted an elevation of HDL and a decrease in LDL in breast cancer patients<sup>44</sup>.

No correlation between breast cancer and plasma glucose, serum creatinine, and HbA1c level was found in the present study.

The present study shows mean age at menarche of female breast cancer patients was 11.43 (SD±1.5) years and the majority (56.67%) had menarche at and below eleven years of age. In another study by Jabeen et al., 2013, where they found 54% had menarche at eleven or below<sup>28</sup>.

South-East Asian countries including China (13.1 years), in Japan, it is below 16 years<sup>45</sup>. In a study done on Europe and North American female breast cancer patients, it was found that the breast cancer risk increased by a significantly greater factor for every year younger at menarche than for every year older at menopause<sup>46</sup>.

Regarding menopause, in this study 66.67% of cases were postmenopausal and their mean age at menopause was 43.7 years. Chakraborty et al., 2015 also noticed the dominance of breast cancer among postmenopausal females<sup>47</sup>. Despite in study by Jabeen et al., 2013, found premenopausal age group was predominant in female breast cancer patients<sup>28</sup>. A female's likelihood of developing breast cancer is associated with her exposure to hormones produced by her ovaries. Pregnancy and breastfeeding, which both reduce a female's lifetime number of menstrual cycles and thus her cumulative exposure to endogenous hormones, are associated with a decrease in breast cancer risk. This study founds 6.67% were nulliparous and 43% had had three or more birth. Parity reduces risk by bringing persistent changes in the mammary gland that reduces the susceptibility of carcinogenic effects on the breast<sup>48</sup>. But these findings go against the findings with the studies conducted on the Bangladeshi population as well as the current study.

In the present study, the mean age at first childbirth for female breast cancer patients is 18.6 years. This finding was more or less similar to Jebeen et al., 2013, where 82% of cases had a first child <21 years of age<sup>45</sup>. Iwasaki and Tsugane, 2011, have emphasized that nulliparity increases the risk of breast cancer. This might be due to early marriage among Bangladeshi females, the mean age at first marriage is 18.7 years<sup>33</sup>. Marriage at an early age and multiple births are the common features in Bangladeshi society. We cannot ignore the socioeconomic background of the females in the present study.

In 2013, a review of 32 studies concluded that the risk of having breast cancer was 14% lower among parous females who had ever breastfed compared with parous females who never breastfed have stated that a longer period of breast feeding reduces the risk of breast cancer<sup>47,49</sup>. These two findings were conflicting with the present study, where 93.33% of the female breast cancer patients were breastfed and duration was more than six months in the majority of cases.

In the present study, the frequency of breast cancer patients who used oral contraceptives is 56.7%, the majority (65%) of the patients used pills for less than five years. Similar to the current study that also have not

found any significant association between the use of oral contraceptives and the risk of developing breast cancer<sup>50</sup>.

It has also been observed two factors in our study (BMI and TG) are significant in logistic regression analysis as important predictors of breast cancer.

Limitations of the study includes a relatively small population. The present study did not include long-term follow-ups, and the effect of standard treatment for breast carcinoma on the serum lipid profile was not investigated. However, the need for these investigations to be included is recognized for future studies.

## V. Conclusion

The results of the above study showed that there is a significant association between BMI, elevated levels of TC, TG and LDL level and breast carcinoma among adult females in Bangladesh. BMI and TG levels being the most significant predictors among these. These findings are of importance for the prevention of breast cancer among females with dyslipidemia and overweight or obesity.

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