Correlation Between Obesity and High Density Lipoprotein Cholesterol (HDL-C) in Breast Cancer Patients of Southern Rajasthan

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Abstract Despite advances in management of breast cancer, etiology is still elusive. Diet, obesity and other life style factors have been implicated in its etiology. We assessed the role of obesity and HDL-C levels in patients with rural background in etiology of breast cancer. To know the relation between obesity and incidence of breast cancer in local population. Also to know serum HDL-C level in breast cancer and its correlation with breast cancer. A nested pilot study of 50 breast cancer patients was done and matched with 50 healthy women as controls. Obesity was measured by weight, height, BMI (Body Mass Index), waist circumference (WC), Hip Circumference (HC), WC/HC ratio, and Serum High Density Lipoprotein Cholesterol (HDL-C) was measured in patients and in controls. There was no significant difference in distribution of weight ($p=0.298$), height ($p=0.653$), BMI ($p=0.459$) and WHR ($p=0.052$) among cases and controls. HDL-C level was observed to be significantly lower in cases than control group ($p=0.017$). Breast cancer patients of pre menopausal age had significantly low Weight ($p=0.037$) and BMI ($p=0.011$) than post menopausal patients. In our study population only low HDL-C level had significant correlation with breast cancer and none of the other anthropometric measurements were associated with breast cancer. However, large population based case control and cohort studies are needed to identify low serum HDL-C as an independent predictor of increased risk of breast cancer.

Keywords Breast cancer · Obesity · High density lipoprotein cholesterol · Body mass index · Waist hip ratio

Introduction

Breast cancer has emerged as a rapidly growing cancer in India and has already replaced cervical cancer as the most common cancer affecting Indian women. Even though advances have been made in early detection of breast cancer, less radical primary therapy and use of radiation therapy and adjuvant chemotherapy, the etiology of breast cancer still remains elusive. It continues to be a health care issue of epidemic proportion but no significant advances have been made to identify people at high risk of developing this cancer. It is considered as disease of opulence which usually funnels to high fat consumption and obesity. Weight gain and obesity causing breast cancer remains unsolved mystery. Weight gain, obesity and HDL-C levels are correlated with development of breast cancer in women to explore their possible role prevention of breast cancer.

Patients and Methods

We conducted a pilot study of 50 clinico-pathologically diagnosed breast cancer patients registered at The Breast clinic, in the Department of Surgery, R N T Medical College Udaipur which is the only tertiary care hospital in Southern Rajasthan. In the present study patients were staged according to the tumor node metastasis (TNM) classification and an informed consent was taken. In order to prevent confounding and allow comparability and matching among cases and controls patients with known diabetes, hyperlipidemia, pregnancy, thyroid disease which altered serum HDL-C were not

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included in the study. Equal number of healthy matched controls were selected among patient's relatives.

Obesity was measured by body weight in kilograms (kg), height in centimeters (cm), waist circumference (cm), and hip circumference (cm) and expressed in terms of BMI {weight/ (height)²} and waist-hip ratio (WC/HC). Waist circumference was measured just above the level of lateral iliac crest and below lowest rib. Hip circumference was measured under the inferior rim of symphysis pubis in midline. HDL-C levels was estimated by taking fasting venous blood samples and samples were sent to biochemical laboratory in Department of Biochemistry, R N T Medical college, Udaipur. Serum HDL-C was measured by new technique known as Direct Homogenous Assay Method that is based on selective solubilizing effect of proprietary detergent to the different lipoprotein. The kit contained no magnesium salt, thus avoiding mechanical problem and used automated analyzer giving accurate measurement of HDL-C. As the recommendation for low cut off values of BMI for Asian population have not been accepted uniformly we adhered to standard World Health Organization (WHO) classification [1]. According to WHO standards the normal BMI was taken to be between 18.50–24.99, underweight <18.5, overweight ≥ 25.00 and obesity ≥ 30.00 . Waist Hip ratio >0.9 was considered abnormal in study and HDL-C levels <40 mg/dl were considered low with normal range between 40 to 60 mg/dl [2].

Statistical Analysis

We used Pearson Chi-Square test, Continuity Correlation and Independent sample t test to assess the significance of Weight, BMI and Serum HDL-C levels between breast cancer patients and controls. As the cohort size was small expert statistician opinion was taken to arrive at results. Sample t test which is most appropriate in small sample was applied and accordingly p value <0.05 was accepted as significant and <0.01 as highly significant. As comparisons were made between only two groups at a time corrections for multiple comparison were not applied. In Chi square test not more than 20% cells had expected values less 5 and hence gave accurate results. Data were analyzed using computerized statistical software SPSS version 16.

Results

A total of hundred women were included in the study with 50 histologically proven cases of breast cancer and 50 healthy matched controls. In our study 59% patients were rural and 41% were urban. Mean age of cases were 48.32 ± 10.94 years and controls was 49.96 ± 9.94 years respectively ranging from

25 years to 73 years. The distribution was almost equal among cases and controls. Age at diagnosis was 40 years in pre menopausal patients compared 56 years in post menopausal women. The characteristics of study population are shown in Table 1.

Majority of patients (22/50, 44%) presented in stage II of breast cancer and 32% in stage III and 24% patients presented in stage IV and none were in stage I indicating that in rural set up patients presented in advanced stages. Mean weight of cases was 52.38 kg and controls was 55 kg and distribution was almost similar ($p=0.298$) (Table 2).

When we compared the distribution of height, both cases and controls were of almost similar height (152.24 cm and 153 cm respectively) and distribution was not significant ($p=0.653$). BMI of cases was 22.8 kg/m^2 and controls was 23.8 kg/m^2 and there was no significant correlation ($p=0.459$). Comparison between weight and BMI with stage of disease is shown in Tables 3 and 4. Breast cancer patients of pre menopausal age had significantly low Weight ($p=0.037$) and BMI ($p=0.011$) than post menopausal patients. Distribution characters between pre menopausal and post menopausal patients are shown in Table 2. Majority (83.3%) of pre menopausal and 60% of post menopausal patients presented with advanced disease in our study. When Waist hip ratio which is another parameter to assess obesity was studied it was observed that both cases and controls (0.81 and 0.83 respectively) had normal WHR and distribution was not significant ($p=0.053$).

When serum HDL-C levels which is important component of metabolic syndrome was compared it was seen that even though mean HDL-C among cases and controls (41.83 mg/dl and 46.1 mg/dl respectively) was in normal range, serum HDL-C levels of cases was significantly lower than controls ($p=0.017$) suggesting that breast cancer had comparatively low HDL-C levels (Fig. 1)

Discussion

Breast cancer is one of the most important causes of cancer related morbidity and mortality all over the world and

Table 1 Selected characteristics of breast cancer Cases ($N=50$) and Controls ($N=50$)

Variables	Controls	Cases	<i>p</i> value
Mean age (in years)	49.9	48.3	0.435
Mean weight (in kg)	55	52	0.298
Height (cm)	153	152.2	0.653
BMI	23.8	22.8	0.459
W/H ratio	0.836	0.816	0.052
HDL (mg/dl)	46.1	41.8	0.017

Table 2 Selected characteristics in pre menopausal ($N=24$) and post menopausal women ($N=26$)

Variables	Premenopausal	Postmenopausal	<i>p</i> value
Mean weight (in kg)	48.5	55.8	0.04
Height (in cm)	154.1	150.5	0.196
BMI	20.4	25.1	0.012
W/H ratio	0.809	0.822	0.425
HDL (in mg/dl)	41.6	41.9	0.899

Indian subcontinent is not an exception. Although many non modifiable risk factors like age of menarche, age of first child, menopausal status, and genetic risk have been implicated, there are also modifiable risk factors like high fat intake, lack of physical activity, use of hormone replacement therapy which can be altered to reduce incidence of breast cancer.

Anthropometric indices have been proposed to be associated with development of breast cancer [3]. BMI, WHR, height and body weight have been reported to be significantly associated with breast cancer development however, relation appears to be complex. Case control study have suggested positive association between weight, BMI and breast cancer risk in pre and post menopausal women but the results of cohort studies are equivocal and inconclusive. BMI has been shown to having positive and inverse association in post and pre menopausal patients' respectively [3]. But in our present nested study none of the anthropometric parameters have been found to be associated with breast cancer ($p>0.05$).

Proposed mechanism for cancer development appears to be one of the three pathways mainly Estrogen pathway, insulin pathway and leptin pathway. In postmenopausal women increased risk is due to increased circulating level of estradiol and reduced level of sex hormone binding globulin and conversion of androgens to estrone in adipose tissue [4–6]. However the role in pre menopausal women is inconsistent [3, 7–9] or inverse relation due to anovulatory and irregular cycles due to obesity [9]. Not only this several

Table 3 Comparison of BMI with Stage of disease ($N=50$)

		Stage of disease		Total
		early	advanced	
BMI	<18	10	12	22
	18–25	20	28	48
	25–30	14	2	16
	>30	6	8	14
Total		50	50	100

$P=0.013$

Table 4 Comparison of Weight with Stage of disease ($N=50$)

		Stage of disease		Total
		early	advanced	
Weight	<50 kg	15	12	27
	>50 kg	15	8	23
Total		30	20	50

$p=0.487$

endocrine changes induced by obesity like increased leptin, insulin, insulin like growth factor-I, androgens and progesterone have been proposed to be underlying factors [4, 10]. One important component of metabolic syndrome is HDL-C that has recently been related to increased risk of breast cancer in obese and overweight women [11–19]. Because HDL-C is better marker of metabolic status than total serum cholesterol [20] we included it in our study to know whether serum levels correlate with breast cancer development. In our study serum levels of HDL-C in cases was substantially lower than controls and is statistically significant ($p=0.017$) and thus has significant correlation with breast cancer. Our finding is supported by observations of HDL-C in several retrospective studies [21–23]. However there was no significant distribution of HDL-C levels in pre and post menopausal patients ($p=0.899$). This comparatively low HDL-C level seen in our study is whether is due to breast cancer itself or is there a causal relationship between the two needs to be established by large population based case control and cohort studies. If it is proved to be useful biomarker then it could provide useful means for identifying women at increased risk of development of breast cancer so that preventive strategies could be instituted at early stage there by bringing down incidence of this global pandemic.

The main drawback of our study was limited number of patients enrolling in the study and lack of follow up of patients treated. At rural level lack of specialists and limited therapeutic options and ignorance of disease among patients are further deterrent to study. Because

Fig. 1 Serum HDL-C levels (mg/dl) in cases ($N=50$) and controls ($N=50$)

of this it becomes difficult to conduct case control study as follow up of patients is difficult. However with available resources we tried to arrive at some conclusion and intended to move in direction where there is ray of new hope.

Conceptually cancer is degenerative disease and therefore its incidence increases with increasing life span. Breast cancer in this region seems to defy this hypothesis with dominance in middle age. It clearly alludes that neither obesity nor affluence are directly related to breast cancer in this region. Breast cancer patients are leaner than controls. Height weight BMI and WHR are not associated significantly with breast cancer in local population. However serum HDL-C levels are significantly lower among breast cancer patients than among controls raising a question whether low levels correlate with subsequent chance of developing breast cancer there by serving as biomarker of breast cancer in our patients.

Conflict of interest The authors due not have any disclosable interest.

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