ORIGINAL ARTICLE

RISK PROFILE FOR BREAST CARCINOMA AND TUMOUR HISTOPATHOLOGY OF MEDICAL UNINSURED PATIENTS IN PAKISTAN

Uzma Raza, Aziza Khanam*, Meh-Jabeen, Mohammad Furqan, Saleem-ul-Haque**

Department of Biochemistry, Hamdard College of Medicine and Dentistry, Hamdard University, *University of Karachi, **Aziz Fatima Medical & Dental College, Faisalabad, Pakistan

Background: Breast carcinoma is an unpredictable disease in the sense that some patients may die at early disease stage due to wide-spread metastasis within six months to one year, while others may survive longer. This study was aimed to evaluate the risk factors for breast carcinoma occurrence and histopathological features of breast carcinoma developed in the social and economical conditions of Pakistan. **Methods:** A total of 224 female breast cancer diagnosed patients with uncovered medical insurance visiting at the Oncology clinic of a teaching hospital at Karachi, Pakistan were selected for the study. Two hundred and twenty-four (224) healthy female subjects free of any cancer diagnosis were selected as control from different areas of the city. Information on stress, occupation, life history, and life style was obtained through personal interviews. Breast tumour pathology was evaluated for histological grade, lymph node metastasis and hormone receptor status by using standard methods. Student's *t*-test, Chi-square test and ANOVA were used for comparison. **Results:** Breast cancer patients in significantly high percentage reported early marriages, abortion occurrence, stressful life style, family cancer history and past disease suffering from diabetes and hypertension. Life style including aerosol chewing and fat rich food intake was significantly high among the patients ($p<0.05$). On histopathological analysis, patients at the age of 40 years and below were identified in significantly high percentage with tumour grade III, 1–3 lymph node metastasis and hormone receptor negative type. Increasing age was associated with low tumour grade and less percentage of lymph node metastasis. Significantly high percentage of patients were presented with hormone receptor positive tumour ($p<0.05$). **Conclusion:** The contributing factors for breast carcinoma occurrence were related to life history and life-style of the patients. Medical insurance uncovered patients at initial diagnosis were presented in significantly high percentage with advanced disease including high tumour grade and lymph node metastasis due to less use of preventive and screening service which delays the diagnosis, effecting both survival and treatment cost.

Keywords: Pakistan, Risk Factors, Breast cancer, Women

INTRODUCTION

Breast cancer is the most common cancer and the second most common cause of cancer related deaths among North American and western European women.[1] Incidence data during the period of 1995–1997 from the population of Karachi south district reported 33.1% breast cancer incidence.[2] Most cancers of breast are invasive adenocarcinoma, but an increasing occurrence percentage of non-invasive forms was reported. There are some histological subtypes of invasive ductal adenocarcinoma that are associated with low risk of systemic dissemination.[3] Invasive ductal carcinoma is the most common type of invasive carcinoma presenting between 40% to 80% of all invasive types.[4] There are different types of risk factors. Some factors like a person's age or race can not be changed, whereas some factors are related to person's behaviour such as smoking, drinking and diet. It was reported earlier that family history of cancer, body mass index (BMI) and education were not significantly related to breast cancer risk.[5] It was reported that high fat content in the diet doubles the risk for breast carcinoma occurrence.[6] The study has reported that women with major life events, stress of daily activities and depression were at higher risk for breast cancer.[7] Association between occupation involving night shift work and breast cancer was documented earlier.[8]

Tumour histological features have both prognostic and therapeutic importance; this includes the number of lymph nodes involved in individual with breast carcinoma [9]. Patients with multiple unfavourable risk factors and histopathological features such as axillary lymph node metastasis, high nuclear grade, young age and large tumour size shows poor local control and disease free survival, so more aggressive treatment was suggested for these patients.[10] Circulating level of sex hormone was reported to have association with the risk of oestrogen receptor positive and progesterone receptor positive tumour.[11] Studies reported a better disease free survival for patients having hormone receptor positive breast tumour.[12] Previous studies reported that patients without medical insurance received less preventive and screening services. They were presented with advanced disease and delayed disease diagnosis.[13]

Aim of present study was to search out the risk factors responsible for breast carcinoma development in the country after considering the life history and life style

of Pakistani women. This study was also aimed to investigate the status of the disease of medically uninsured patients at initial diagnosis, so as to create a hub of clinician and government sector services providers to provide facility for disease awareness, early screening, treatment and prolonged management of disease.

MATERIAL AND METHOD

The study was conducted on 224 female breast cancer patients with infiltrating ductal carcinoma. Breast carcinoma was proved by biopsy. Patients were selected from the oncology clinic of a teaching hospital at Karachi, Pakistan. Breast carcinoma of all patients was proved by biopsy. Patients selected had primary breast carcinoma in one breast. The patients were with uncovered medical insurance. Control selected were healthy females without any cancer history. Patients and control subjects using contraceptives and hormonal therapy for menopausal symptoms were excluded from the study. Females included in the study were from the low and middle income class. Patients included were involved in professional and domestic activities till late night. This life pattern was followed by them with the average of three years. Information was obtained through personal interviews and questionnaire. Questionnaires included questions on life history including past health status, age at marriage, abortion occurrence, menopausal status, family cancer history and life style including stress, occupational activity and dietary habits. Breast cancer females reported depression and stress in their life. Histopathological features to assess the extent of disease at the time of initial diagnosis included nuclear grade, lymph node involvement and hormone receptor positivity. Metastasis was excluded by bone scan, chest x-ray and abdomen ultrasound.

Histopathology of the tumour tissue included, tissue processing tissue fixation followed by Harris's Haematoxylin and Eosin Staining Method.[14] Microscopic grading of breast carcinoma was according to Nottingham Modification of the Bloom-Richardoson system.[15]

Paraffin sections of the tumour tissue were stained by monoclonal antibodies against oestrogen and Progesterone by Envision Technique, (Dakocytomation Envision+ System, peroxidase-HRP method). Chemicals were supplied by Dakocytomation Denmark DK-2600 Glostruo Denmark. The oestrogen and progesterone receptors were scored according to total score given below:

Total Score<75	(Negative)
Total Score 75–99	(Weak Positive)
Total Score 100–119	(Intermediate Positive)
Total Score 120 and above	(Strong Positive)

For data analysis SPSS-11 was used. The results were given in the text as number and percentage for qualitative/categorical variable like occupation, stress, past disease history, family history of cancer, hormone receptor positivity, lymph nodes involvements and tumour nuclear grade to compare proportion/ percentage of qualitative/categorical variables in breast cancer cases and controls. Chi-square test/test proportion was applied. Means and standard deviations of quantitative/continuous variables in breast cancer cases and control was analysed by Student's *t*-test and ANOVA. In all statistical analysis, $p<0.05$ were considered significant. Body Mass Index (BMI) was calculated by the following formula:

$$\text{BMI= Weight (Kg)/[(Height(meter)]}^2$$

RESULTS

The study was conducted on 224 breast carcinoma women who were attending the outdoor cancer department of Liaquat National Hospital, Karachi, Pakistan. Two hundred and twenty-four control female subjects having no signs and symptoms of carcinoma were also included in the study. Personal data was collected through questionnaire and was updated after 6 months. Patients selected were with uncovered medical insurance and had primary tumour in one breast. Patients were without metastasis to distant organs at the time of disease diagnosed, 148 patients had axillary lymph node metastasis whereas 76 patients were without axillary lymph node metastasis.

Table-1 shows that significantly high percentage of breast cancer patients as compared to control subjects were involved in occupational activities and were suffering stress. Significantly high percentage of breast cancer patients as compared to control subjects were in the habit of cigarette smoking, aerosol chewing and fatty food intake.

Table-2 shows that in breast patients, age at marriage and percentage of subjects having children was significantly low whereas percentage of subjects, having abortion was significantly high as compared to control subjects. No significant change in BMI was observed in the two groups.

Table-3 shows that percentage of hormone receptor positive breast cancer patients with past abortion history was significantly high as compared to hormone receptor negative patients. Significantly low percentage of hormone receptor positive patients were without abortion history.

Table-4 shows that the history of cancer among the family members of breast cancer patients was significantly high as compared to control subjects. Whereas past disease history of diabetes and hypertension was found in significantly high percentage in hormone receptor positive breast cancer patients as compared to control subjects.

Table-5 shows that significantly high percentage of hormone receptor negative patients are in the age group of 40 years and below. Significantly high percentage of hormone receptor positive patients were in the age group of 51–70 years and above. Patients with 1–3 lymph node metastasis were significantly high in the age group of 40 years and below. Patients with tumour Grade III were significantly high in the age group of 40 years and below. Patients with tumour Grade I were significantly high in the age group of 41–50 years.

Table-1: Life style of control and breast cancer female subjects

Subjects	Educated (%)	Occupational Women (%)	Occupational/ Household Women Under Stress (%)	Habits (Percentage)	
				Cigarette Smoking/ Aerosols Chewing (%)	Fatty Food/ Spicy Food Intake (%)
Control (n=224)	129 (57.58)	78 (34.82)	48 (21.42)	34 (15.17)	3 (1.33)
Breast cancer patients (n=224)	124 (55.35)	95 (42.41)*	173 (77.23)*	68 (30.35)	37 (16.51)*

*p<0.05 compared to Controls

Table-2: Life history of control and breast cancer female subjects

Subjects	Age at disease presentation (years)	Age at marriage (years)	Percentage of subjects having children	Percentage of subjects having abortions	Body Mass Index (Kg/m^2)
Control	43.98±0.76	23.08±0.32	88.39 (198)	14.73 (33)	20.08±0.22
Breast cancer patients	44.61±0.82	*20.44±0.53	*79.01 (177)	*54.01 (121)	20.09±0.21

*p<0.05 compared to controls

Table-3: The frequency of abortion in breast infiltrating ductal carcinoma patients

Breast Carcinoma Type	Without Abortion	Number of abortions in percentage			
		1	2	>2	Total abortion (%)
Percentage of hormone receptor negative (IFDC) patients (n=89)	67.41 (60)	23.59 (21)	8.98 (8)	-	32.58 (29)
Percentage of hormone receptor positive (IFDC) patients (n=135)	*31.85 (43)	*48.88 (66)	13.33 (18)	5.92 (8)	*68.14 (92)

*p<0.05 compared to hormone receptor negative breast carcinoma patients

Table-4: Family cancer history and past disease history of control and Breast Cancer female subjects.

Subjects	Family Cancer History (%)	Past Disease History Percentage				
		Hypertension/ Heart Problem	Diabetes	Jaundice	Arthritis/ Bone Disease	Total Past Disease History
Control (n=224)	7.14 (16)	0.44 (01)	2.67 (06)	1.78 (04)	5.35 (12)	10.26 (23)
Percentage of hormone receptor positive(IFDC) (n=135)	[a]20.74 (28)	[a]13.33 (18)	[a]11.11 (15)	2.96 (04)	5.18 (07)	[a]32.59 (44)
Percentage of hormone receptor negative (IFDC) (n=89)	[a]17.97 (16)	8.98 (08)	7.86 (07)	4.49 (04)	3.37 (03)	24.71 (22)

*p<0.05 compared to controls

Table-5: Age-wise distribution of breast cancer patient on the basis of hormone receptor and lymph node positivity and tumour grade

Breast Carcinoma type	Age (years)					
	<30	31–40	41–50	51–60	61–70>	Total
Patients with hormone receptor positive breast carcinoma	3.70 (5)	21.50 (29)	39.30 (53)	[n]21.50 (29)	[n]14.10 (19)	[n]60.27 (135)
Patients with hormone receptor negative breast carcinoma	*22.50 (20)	*41.60 (37)	25.80 (23)	6.70 (6)	3.40 (3)	39.73 (89)
Patients without lymph node metastasis breast carcinoma	5.26 (4)	19.73 (15)	40.78 (31)	22.36 (17)	11.84 (9)	33.92 (76)
Patients with 1–3 lymph node metastasis breast carcinoma	[a]16.10 (19)	[a]36.44 (43)	27.11 (32)	12.71 (15)	7.62 (9)	[a]52.6 (118)
Patients with ≥4 lymph node metastasis breast carcinoma	6.66 (2)	26.66 (8)	43.33 (13)	10.00 (3)	13.33 (4)	13.39 (30)
Patients with Grade I breast carcinoma	-	7.89 (3)	[c]52.63 (20)	23.68 (9)	15.78 (6)	16.96 (38)
Patients with Grade II breast carcinoma	8.92 (10)	28.57 (32)	32.14 (36)	17.85 (20)	12.50 (14)	[c]50.00 (112)
Patients with Grade III breast carcinoma	[b]20.27 (15)	[b]41.89 (31)	27.02 (20)	8.10 (6)	2.70 (2)	33.03 (74)

p<0.05: *compared to hormone receptor positive breast carcinoma patients, [a]compared to patients without lymph node metastasis and ≥4 lymph node metastasis, [b]compared to patients with tumour Grade I and II, [c]compared to patients with tumour Grade II and III, [n]compared to hormone receptor negative patients

DISCUSSION

Cancer is the leading cause of death throughout the world and is second to cardiac disease in mortality figure. In Pakistan since 1997 the frequency of malignant tumour has varied from year to year between 6–12% and male to female ratio was 1.37:1.[16]

Culture and life style of any nation reflects their health conditions. There is remarkable variation in the incidence of breast cancer between different countries. In western countries rates of disease occurrence is more as compared to Asia or black African.[17] Life style is an important factor reflecting the health status of any nation and dietary habits are also an important factor reflecting the life style. This study shows that significantly high percentage of patients was in the habit of traditional food intake, rich in fat contents. It has been suggested that low incidence of breast cancer in Japan may be due to the very low

dietary fat intake thus reducing the cancer incidence.[17] Oral intake habits of patients which include chewing of beetle leaves, beetle nuts, tobacco and *Gutka* (aerosol mixture) was significantly high in this study (Table-1). These aerosols are rich in chemicals, tannins and alkaloids. It has been reported earlier that organic solvents are genotoxic and act directly or indirectly through their metabolite. Organic solvents are lypophilic and are readily absorbed and distributed through the body by blood stream, since there is limited detoxification of highly reactive metabolites. Breast parenchyma is embedded in fat depot capable of storing lypophilic xenobiotics. It is conceivable that organic solvent and their metabolites once stored in the fat tissues migrate to the breast parenchyma and are then transferred to the mammary lobules through continuous apocrine secretions. These secretions may remain in the ductular system, for long time and the effect exerted by the solvents and their bio-activated metabolites can be determined.[18] The study conclude that dietary and oral intake habits play a significant role in the development of breast carcinoma in Pakistani culture.

In the present study, significantly high percentage of breast cancer patients were involved in different occupations such as nursing, beauticians, doctors, teachers, maids, tailoring and marketing. Percentage of patients experiencing life stress including household and occupational stress was significantly high as compared to control subjects. Increased risk of breast cancer has been reported in occupational women and the role of job stress in carcinogenesis have been reported previously.[19] Chronic stress has been associated with a depressed immune response that may promote cancer.[20] It was reported that stressful events increase the levels of stress hormones such as cortisol and the catecholamine, as well as endogenous oestrogen levels; high levels of oestrogen are strongly associated with increased breast cancer risks.[21,22] In this study stress emerges as the significant risk factor for breast carcinoma incidence which includes not only in occupational but also household females, indicating that disease occurrence is significantly related to stress, excluding stress source. In considering the effect of job stress on women's health, it is important to consider the interaction between work stress and home stress caused by additional responsibilities in the home. Patients included in the study through questionnaire reported that they were not involved in any physical exercise due to shortage of time; however, their occupational and domestic activities were often extended till midnight, without physical exercise. Women working on rotating night shifts with at least three nights per month in addition to days and evenings in that month, appear to have moderately increased risk of breast cancer. As previously reported, late night work requires light exposure and light exposure during night suppresses melatonin production. Melatonin has anti cancer activity.[23]

Life history of control female subjects was compared with breast carcinoma patients. This study reports that in breast cancer patients the age at marriage and the percentage of the patients having children was significantly low as compared to control subjects. Percentage of abortion occurrence was significantly high in breast cancer patients as compared to control subjects. This study does not establish any significant relation between breast cancer occurrence and body mass index (BMI). Earlier studies reported that relationship between the body weight and breast cancer is dependent on age. In women with age under 50 years there is little correlation between body weight and breast cancer risk however in the age group of 60–69 years, increase in body weight increases the risk for breast cancer.[17]

Previous studies have reported that women without children are at higher risk of breast cancer occurrence[18] and the protective effects of full term pregnancies against cancer was also reported[17]. High percentage of abortions was seen in hormone receptor positive breast carcinoma patients as compared to hormone receptor negative breast carcinoma patients. In the earlier studies it was suggested that pregnancy protects the female against the oestrogen and in turn prevents the breast cancer occurrence, since oestrogen is produced during the pregnancy to stimulate the breast growth; if abortion takes place in that period of pregnancy then the female is exposed to high concentration of oestrogen.[24]

Among breast cancer patients, significantly high percentage of patients reported family cancer history. Study evaluated significantly high relationship of family cancer history with hormone receptor positive tumour as compared to hormone receptor negative tumour. Higher breast cancer risk was reported when blood relative or first-degree relatives have this disease. If the relatives were affected with breast cancer at or before the age of 45, then risk was for both tumour types, hormone receptor positive and hormone receptor negative. When relative were affected after the age of 45 years then increased risk was for hormone receptor negative tumour.[25]

Before the occurrence of breast carcinoma significantly high percentage of patients were suffering from diabetes and hypertension. Percentage of past disease occurrence was low in hormone receptor negative breast carcinoma patients as compared to hormone receptor positive breast carcinoma patients. Stress may be related to cardiovascular diseases and the relationship between job stress and cardiovascular disease has been established earlier.[26] Pat disease sufferings may be co-related with the release of stress hormones[21,22].

Breast cancer is emerging as a serious problem in low and middle resources regions of the world. In countries with limited resources patients without medical insurance received less preventive services.[13] This study was conducted on patients without medical insurance to evaluate the disease stage when presented for initial diagnosis and utilized tumour grade, axillary nodal status and hormone receptor status to evaluate the disease stage. Previous studies have reported axillary nodal status, tumour size, histological grade and hormone receptor status as prognostic factors. Tumour occurance site in the breast was reported of not much prognostic importance.[17]

This study correlated the age groups with tumour Grades, lymph node metastasis and hormone receptor positivity. Highest percentage of Grade I patients were in the age group of 41–50 years. Highest percentage of Grade III patients were less than 40 years. In this study significant difference in the prognostic factor profile was observed for hormone receptor positive and negative breast cancer patients. Hormone receptor negative patients in significantly high percentage developed the disease at younger age. It was suggested earlier that high nuclear Grade is associated with low disease free survival.[27] Axillary lymph node metastasis has been identified as adverse prognostic factor for locoregional and distant recurrence, however the patients may benefit from adjuvant radiotherapy and aggressive systemic therapy regimens.[28]

Disease free survival, overall survival and disease free relapse are effected by axillary lymph node metastasis and high tumour grade, so the requirement of aggressive treatment for these patients is required.[28]

We conclude that in a low and middle income group of breast cancer patients the disease is diagnosed at an advanced stage with high tumour Grade and axillary lymph node metastasis, which affects the overall survival of the patients.

CONCLUSION

Disease occurrence can be reduced in the country by improving the risk factors included in the life style of the nation, which includes stress, late night work, fat rich diet and by excluding the chewing of beetle leaves, beetle nuts and tobacco. Medical insurance uncovered patients included in the study were presented with advanced disease at initial diagnosis with high tumour grade and axillary lymph node metastasis. Whereas the tumour occurrence at the age of above 40 years and hormone receptor positivity may be beneficial for treatment response and disease free survival. There is an urgent requirement to develop policies for medical insurance coverage, which will bring improvements in reducing disparities in breast cancer presentation and treatment.

REFERENCES

1. Lostumbo L, Carbine N, Wallace J. and Ezzo J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev 2004;18:CD 002748.
2. Bhurgri Y, Bhurgri A, Hassan S H, , Zaidi SH, Rahim A, Sankaranarayanan R, *et al*. Cancer incidence in Karachi, Pakistan: First results from Karachi cancer Registry. Int J Cancer 2000;85:325–29.
3. Ravdin PM. Prognostic factors in breast cancer. In: Textbook of breast cancer. A clinical guide to therapy. G. Bonadonna, G.N. Hortobagyil and A.M. Gianni (eds) London: Martin Duntz; 1997.p.35–63.
4. Rosen PP, Oberman HA. Atlas of tumor pathology. Tumours of the mammary gland. Washington, DC: Armed Forces Institute of Pathology; 1992.
5. Nichols HB, Trentham-Dietz A, Love RR, Hampton JM, Hoang Anh PT, Allred DC, *et al*. Differences in breast cancer risk factors by tumor marker subtypes among Premenopausal Vietnamese and Chinese women. Cancer Epidemiol Biomarkers 2005;14:41–7.
6. Gonzalez CA. The European prospective investigation into cancer and nutrition (EPIC). Public Health Nutr 2006;9:124–6.
7. Kruk J, Aboul-Enein HY. Psychological stress and the risk of breast cancer: a case control study. Cancer Detect Prev 2004;28:399–408.
8. Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. Night work and breast cancer risk: a systematic review and meta analysis. Eur J Cancer 2005;41:2023–32.
9. Kendal WS. Statical Kinematics of axillary nodal metastases in breast carcinoma. Clin Exp Metastasis 2005;22:177–83.
10. Kim KJ, Huh SJ, Yang JH, Park W, Nam SJ, Kim JH, *et al*. Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. J Clin Oncol 2005;35:126–33.
11. Missmer SA, Eliassen AH, Barbieri R, Hankinson SE. Endogenous estrogen, androgen and progesterone concentrations and breast cancer risk among post menopausal women. J Natl Cancer Inst 2004;96:1856–65.
12. Grann VR, Troxel AB, Zojwalla NJ, Jacobson JS, Hershman D, Neugut AI. Hormone receptor status and survival in a population-based cohort of patients with breast carcinoma. Cancer 2005;103:2241–51.
13. Helpern MT, Bian J, Ward EM, Schrag NM, Chen AY. Insurance status stage of cancer at diagnosis among women with breast cancer. Cancer 2007;110:403–11.
14. Ramnik S. Histopathology. In: Medical Laboratory Technology. New Delhi India: Jaypee Brothers Medical Publishers (P) LTD; 2006.p. 1031–4.
15. Breast: In: John DB, Marilyn G. (eds) Theory and Practice of histological techniques. China: Harcourt Publishers Limited; 2002. p. 1824–25.
16. National Nutritional Survey 1985–87 Report, Islamabad: National Institute of health, Government of Pakistan; 1988.
17. Michael JG. Cancer of the breast. In: Peter, JM, Ronald, AM (eds). Oxford Textbook of surgery. Vol-1. New York: Oxford University Press Inc; 1994.
18. Labreche FP, Goldberg MS. Exposure to organic solvents and breast cancer in women: A hypothesis. Am J Ind Med 1997;32:1–14.
19. Shelia Hoar Zahm SH, Blair A. Occupational cancer among women: Where have we been and where are we going? Am J Ind Med 2003;44:565–75.
20. Bauer ME, Perks P and Lightman SL, Shanks N. *et al*. Restraint stress is associated with changes in glucocorticoid immunoregulation. Physiol Behav 2001;73:525–32.
21. Bowman RE, Ferguson D, Luine VN. Effects of chronic restraint stress and estradiol on open field activity, spatial

memory, and monoaminergic neurotransmitters in ovariectomized rats. Neuroscience 2002;113:401–10.
22. Key T, Appleby P, Barnes I, Reeves G; Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in Postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
23. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, *et al*. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. J Natl Cancer Inst 2001;93:1563–8.
24. Parkins T. Does abortion increase breast cancer risk? Natl Cancer Inst 1993;85:1987–8.
25. Tutera AM, Sellers TA, Potter JD, Drinkard CR, Wiesner G, Folsom AR. Association between family history of cancer and breast cancer defined by estrogen and progesterone receptor status. Genet Epidemiol 1996;13:207–21.
26. Lee S, Colditz G and Berkman LF, Kawachi I. A prospective study of job strain and coronary heart disease in U.S. women. Int J Epidemiol 2002;31:1147–53.
27. Monteiro GI, Jorge M, Marques VP, Ortiz M, Ravasco P. The effect of locoregional recurrence on survival and distant metastasis after conservative treatment for invasive breast carcinoma. Clin Oncol 2005;17:111–7.
28. Truong PT, Berthelet E, Lee J, Kader HA, Olivotto IA. The prognostic significance of the percentage of positive/dissected axillary lymph nodes in breast cancer recurrence and survival in patients with one to three positive axillary lymph nodes. Cancer 2005;103:2006–14.

Address for Correspondence:

Dr. Uzma Raza, Department of Biochemistry, Hamdard College of Medicine and Dentistry, Hamdard University, Madinat-ul-Hikmah, Mohammad Bin Qasim Avenue, Karachi-74600, Pakistan. **Tel:** +92-21-36440169
Email: raza.uzma@hotmail.com