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BREAST CANCER: INCIDENCE (THIRTEEN YEAR DATA ANALYSIS) AND ONE YEAR CLINICOPATHOLOGICAL DATA OF PATIENTS IN A TERTIARY CARE CANCER HOSPITAL

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ABSTRACT

Breast cancer is the commonest type of malignancy in the female population of Pakistan. The rationale of this study is to present the institution based breast cancer incidence in last 13 years and pattern of breast lumps to evaluate the association between tumor grade, metastasis in lyph nodes and other predictive aspects like tumor size and appearance of estrogen, progesterone (ER/PR) receptors and Her2/neu in one year.

Out of 28487 cancer patients 5667 were registered as breast cancer patients at KIRAN from 1st January 2000 to 31 December 2012. Male breast cancers accounted for 93 (1.64%) and female breast cancers were 5574 (98.3%). The age standardized rate (ASR) of female breast cancer is 37.13 which are highest among all cancers and the ratio is highest in the region.

One year prospective analysis of 568 breast cancer patients studied for their clinicopathological profile in which 554 (97.5%) were female and 14 (2.4%) were male patients. TNM classification indicates that majority of patients were at stage III and IV (6% at stage I, 20 % at stage II, 50 % at stage III and 23 % at stage IV). Majority of the cases (84%) have infiltrating ductal carcinoma (IDC) followed by in infiltrating lobular carcinoma (ILC) (11.4%) and only 4.4 % are rare carcinomas. Tumor grade I comprised only 5.6% and grade II was 59% and grade III was 35%. Hormone receptors (ER/PR) are positive in 50% of cases (ER/PR positive in 300 cases, only ER positive in 65 cases and only PR positive in 35 cases while ER/PR negative in 104 cases). Her2/neu showing high grade nuclei is positive in 226 cases while negative in 230 cases.

Since majority of patients present late with advanced disease, there is a great need for breast health awareness to decrease the burden of advanced disease.

Key words: Breast cancer, Clinicopathological data, Her2/neu, ER/PR, cancer incidence

INTRODUCTION

Breast carcinoma is the most prevalent malignancy in women worldwide (Ferlay *et al.*, 2010). According to one According to one report appear in lancet that over 1.6 million breast cancer cases obtained every year among women globally in 2010 (Forouzanfar *et al*., 2011). From nine Pakistani Punjab cities it is projected that 1 in 9 women will develop breast carcinoma during their life in Pakistan (Shami *et al.,* 1989). We know that in developed countries the concept of national cancer registries exist where every newly detected cancer patient is registered which is very helpful for the understanding of epidemiology and other contributory factors of cancer. Whereas in developing countries like Pakistan no comprehensive database or registries are available that gives the exact figure of the patients reported with the diagnosis of breast cancer (Bhurgri *et al*., 2006).

Pakistani women have the highest risk of breast cancer among all Asian populations (Shami *et al.,* 1989) which is already reported by several authors.

Previously, we have reported nine year cancer data from KIRAN, Karachi in which breast cancer cases were 3275 (Hanif *et al*., 2009) and in next five years we have 2392 more cases of breast cancer.

Breast carcinoma is thought to be a frequent cancer in the developed countries, whereas death toll is very high in developing countries. This concluded that although breast cancer incidence is high in the developed countries and low in under developed countries (Ferlay *et al*., 2011; IARC, 2008). Breast cancer incidence has increased worldwide in the last decades, with the exponential multiplication in many of the under developed countries (IARC, 2008). Several factors including reproductive health as well as differences in life style, exercise, weight, diet and excessive use of alcohol, are main differences in two classes (Allen *et al*., 2009).

Female breast cancer mortality rate is homogenous across the regions of the world, largely due to good survival rate in the developed countries (ranging from 6 per 100,000) as compared to 19 per 100,000 in Southern and Western Africa in 2008 (Ferlay *et al*., 2011; Ferlay *et al*., 2010). Almost 460,000 deaths were reported in 2008 and is the most common cause of cancer related deaths (Ferlay *et al*., 2011). In advanced countries, due to cancer registries every diagnosed cancer is being registered which helps in understanding the epidemiology of cancer. Whereas in developing countries like Pakistan no comprehensive database or registries are available that gives the

exact figure of the patients reported with the diagnosis of breast cancer (Bhurgri *et al.*, 2006).The condition become worst when breast cancer patients present with metastasis, a situation which significantly raises the tumor burden often resulting in fatal outcome.

This situation more commonly occur in developing countries like Pakistan where due to inadequate diagnostic resources most of the women present with advanced or metastatic breast cancer leading to poor outcome (Gilani *et al*., 2010). Hence, early diagnosis and therefore early management of breast cancer can progress the survival rate as well as the quality of life. The situation is worst in Pakistani women where the number is more than that and no systemic and scientific approach has been employed to combat the situation. The accurate occurrence, death rates, number of new cancer cases and casualty rate annually for Pakistan are not documented. No comprehensive database/registries existing regarding any disease as well as cancer in Pakistan and the only data on hand is hospital based (Hanif *et al*., 2009). In Pakistan the scenario of BC is miserable and approximately 90,000 women suffer from BC every year. The incidence of breast cancer in Karachi was 69.1 per 100,000 from 1998-2002 (Parkin and Fernandez, 2006)

Clinicopathological features have prognostic significance in breast cancer like cancer subtypes, tumor grade, lympho vascular invasion, ER and PR receptor, Molecular markers, peptide hormones, growth hormonal factors and their receptors, oncogenes, and tumor suppressor genes (Alahwal, 2006). Breast cancers are classified in different forms regarding their origin, grading, staging and receptor status. Each of the type influences the prognosis and affects treatment response. According to Tiwari histopathological analysis is a gold standard mode of diagnosis and also for follows up and fine needle aspiration cytology (FNAC) of breast lumps is an essential part of triple assessment (Clinical examination, imaging and Fine Needle Asoiration cytology (FNAC) of palpable breast lumps (Tiwari, 2007). FNAC is also useful in predicting tumor factors – like hormones receptor status (Gupta *et al*., 1993). The effectiveness of fine needle aspiration in the conclusion of breast lump in the female patients who attended the KIRAN out patients and day care departments has been studied. We also studied the cytological and histopathological association in the diagnosis of breast lesions and most of the predictive factors like, size of the tumor, grade, and lymphnodal metastasis, expression of ER, PR and HER2/neu by the tumor cells.

In this report we review the main demographic characteristics and clinicopathological presentation in 568 breast cancer patients in KIRAN. The aim of this study was to find out the cytological and histopathological association in the diagnosis of breast cancer and aspects including, tumor size, grade, metastasis in lymph nodes, and Estrogen receptor, Progesterone receptors and HER2/neu expression.

MATERIALS AND METHODS

Patients data including age, sex, and diagnosis of cancer based on histopathology and/ or Radiology reports (CT/MRI reports and biopsy reports,) or other diagnostic reports confirmed by concerned Doctors were recorded on first visit of the patients at KIRAN Hospital and updated subsequently (Data collection and case recording was similar and reported earlier (Hanif *et al*., 2009).

Examining physician record the patient's data on the patient's file and fill the feedback form which include patients age; marital status; residential address; Breast feeding or lactation, use of contraceptive pills and/or hormonal treatment; and consanguinity or family history of breast cancer. Data on tumor size and lymph nodal status were also obtained by the duty doctor and by examination of the tissue biopsies. Abdominal scans and chest X-rays were carried out to workup metastasis, and when indicated a bone scan was performed. All the diagnostic and staging work carried out according to international protocols and International classification of Disease-oncology (ICD'O) Codes.

First part of the study is a retrospective analysis of the breast cancer patients to determine frequencies of breast cancer (in all age groups and both genders) recorded at KIRAN Hospital from Jan. 2000 to Dec. 2012. Specific Performa of patient registry based on (ICD'O) codes using LAN for radiotherapy department of KIRAN for record buildup & investigation were used.

For clinicopathological analysis we have studied 568 patients during January to December 2012. Carcinoma type was determined following the WHO classification (Edge *et al*., 2010), TNM (tumor, node, metastasis) staging system of the (AJCC) was used to find out the clinical stage of the disease (American Joint Committee on Cancer 2002). Scarff, Bloom and Richardson (Rosai, 2004) recommendations were followed for grading of ductal and lobular carcinoma. Tumor grade and tumor size and its relation with the lymphnodal metastasis were also studied.

RESULTS

Out of 28487 cancer patients, 5667 were registered as breast cancer patients at KIRAN during the last 13 year. Only 93 (1.64%) cases were registered as male while female cancers were 5574 (98.3%). The age standardized rate/100,000 (ASR) of female breast cancers is 37.13 which are highest among all cancers in both genders.

Demographic data showed that 98.7% of breast cancers were in the age range of 16-75 years (80% among 31-60 years) (Table 1). Out of 5667 patients 2288 were in age group 31-45 and other 2069 patients in age group 46-60 years. Age-standardized rate/100,000 (ASR) of these breast cancer female patients was 37.13.

Among 568 breast cancer patients who presented with breast lumps during January to December 2012 (One year prospective analysis) and studied for their clinicopathological profile, 554 (97.5%) were female and 14 (2.4%) were male patients (Table 2).

TNM classification of these patients indicated that majority of patients were at stage III and stage IV (6% at stage I, 20 % at stage II, 50 % at stage III and 23 % at stage IV) (Table 3).

Table 1. Demographic data in all 5667 breast cancer patients in thirteen years.

Demographic data in all 5667 breast cancer patients in thirteen years										
Total No. of Breast cancer patients	Male	ASR*	Female	ASR	Age Groups					
					0-15	16-30	31-45	46-60	61-75	>75
5667	93	1.64	5574	37.13	6	519	2288	2069	708	77

ASR, age-standardized rate/100,000

Table 2. Demographic data in 568 breast cancer patients from Jan-Dec. 2012.

Demographic data in 568 breast cancer patients during one year										
Total No. of Breast cancer patients	Male	ASR*	Female	ASR	Age Groups					
					0-15	16-30	31-45	46-60	61-75	>75
568	14	1.64	554	37.13	2	63	180	168	86	71

ASR, age-standardized rate/100,000

Histopathology indicated that majority of the cases (84%) had infiltrating ductal carcinoma (IDC) followed by in infiltrating lobular carcinoma (ILC) (11.4%) and only 4.4 % are rare carcinomas (mucinous, papillary, lymphomas, squamous cell carcinoma etc.) (Table 3).

Tumor grade I (well differentiated) comprised only 5.6% and grade II (moderately differentiated) was 59% which is highest in all and grade III (poorly differentiated) was 35% (Table 3).

Expression of hormone receptors (ER&PR) showing low grade nuclei were positive in 50% of cases (ER/PR both positive in 300 cases, only ER positive in 65 cases and only PR positive in 35 cases while ER/PR both negative in 104 cases) (Table 3).

Her2/Neu showing high grade nuclei was positive in 226 cases while negative in 230 cases. Rests (112 cases) are either unknown or not done (Table 3).

Relationship of tumor rating and expression of hormonal receptors and Her2/neu were also studied. Among 568 cases of Breast carcinoma (BC), 32 were of grade I, out of which 10 were ER/PR negative, 18 were ER/PR positive, and 8 were HER2/neu positive. Three hundred and thirty six BC tumors were grade II, out of which 225 were ER/PR negative, 90 were ER/PR positive, and 170 were HER2/neu positive. Out of 200 BC cases having grade III tumors, 110 were ER/PR negative, 80 is ER/PR positive, and 48 are HER2/neu positive. Mostly grade I tumors were ER, PR positive, and majority of grade III tumors were ER, PR negative, and HER2/neu positive.

Table 3. Clinicopathological data in 568 breast cancer patients from Jan-Dec. 2012.

Stage of disease at diagnosis (TNM)	Nos.	%
I	36	6
II	114	20
III	286	50
IV	132	23
Tumor grade		
Grade I	32	5.6
Grade II	336	59
Grade III	200	35
Tumor types		
Infiltrating ductal carcinoma (IDC)	478	84
Infiltrating lobular carcinoma (ILC)	65	11.4
Other types	25	4.4
Stage IV metastasis		
Bony mets	340	60
Liver mets	159	28
Pulmonary mets	47	8
Mets on more than one site	22	4
Hormone receptor phenotypes		
ER+/PR+	300	50
ER+/PR-	65	11.4
ER-/PR+	35	6
ER-/PR-	104	18
Unknown/not done	64	11.2
Her2/Neu tumor expression		
Positive	226	39
Negative	230	40.4
Unknown/not done	112	19.7

AJCC: Classified according to the American Joint Committee on Cancer Staging System=568

Table 4. Tumor grade and expression of hormones.

Tumor grade	No. of cases	ER/PR negative	ER/PR positive	HER2/neu positive
Grade I	32	10	18	8
Grade II	336	225	90	170
Grade III	200	110	80	48

DISCUSSION

Earlier we have reported nine year cancer patients data of KIRAN in which breast cancers cases were 3275 (Hanif *et al*., 2009) and in next five years we have 2392 more cases of breast cancer. In KIRAN Breast cancer is the most frequent cancer in females (38.2% of the total female cancers). In Karachi cancer registry also reported highest (Bhurgri *et al*., 2006) and also in many other reports from Pakistan (Aziz *et al*. 2003). BC incidence is the highest reported from several Asian countries, apart from Jews in Israel (Parkin *et al*, 1993; Bhurgri *et al*., 2000). Almost one third of the female cancers are breast cancer.

Among third world countries Pakistan suffers from a high load of breast cancer. According to a recent report of Karachi Cancer Registry the ASR of breast cancer in Pakistan is 69.1 per 100,000, almost equal to European and North American ASR (Banning *et al*., 2009).

In west breast cancer is supposed to be frequent in old age whereas it is more common at a young age in Pakistan (Mahmood *et al*., 2006). In Pakistan, due to its socio- religious taboo late stage presentation being a common feature and is the main cause of high cancer burden.

The cause of very high breast cancer rate in region (amongst all Asian countries except Jews in Israel) is the increasing population rate and socioeconomical and political instability as more than 90,000 women victim of breast cancer per annum (Daily Times 2007, Liede *et al*., 2002). All Asian countries except Pakistan have breast cancer

rates of not as much of 41 ASR (Liede *et al.*, 2002). Shaukat Khanum Memorial Cancer Hospital and Research Center in Lahore, Pakistan is one of the biggest cancer hospital in public sector has reported 42% of total female malignancies treated was breast cancer (Badar *et al*., 2005). Thus, we can imagine the heavy burden of breast cancer in Pakistan because of being third world nation and because of having no cancer registry at national level.

There are many reasons we have discussed earlier for the comparatively high rates of the BC and the ovarian cancer in Pakistan but they are in fact not on record and the specific factors have not been identified including life style and reproductive factors. Genetic factor such as BRCA1 and BRCA2 mutations in the breast and ovarian cancer vulnerability genes may add a major proportion of breast and ovarian cancer susceptibility. Moreover cousin marriages which are highest in the world may also contribute for the multiplication of these genes (Hashmi, 1997). The trend of cousin marriages is 60-76% in Pakistan (Hashmi, 1997). Similarly, family marriages also play important role for this much boost in the risk of diseases caused by mutations in these recessive genes. No information available on the probable role that these recessive genes take part in adult cancers specifically breast cancers. Shami et al., has described an association between consanguinity and risk of BC in Pakistan (Shami *et al*., 1989) Reproductive age BC reported from Pakistan is the highest (Bhurgri *et al*., 2006). Early marriages, multiple births and extended breast-feeding are the norm but these cannot be considered as the major risk factors. Similarly reproductive age, menopausal age and effect of reproductive hormones may possibly be risk factors along with nutritional factors and obesity.

Morries *et al*., (2002) have stated that triple test i.e. examination by medical specialist, radiography imaging and histopathology (Biopsy / FNAC) all in combination are the best clinical approach for the diagnosis and the management of patients with breast lesions. AJCC guidelines says that the investigative precision of these three tests taken together approach to 100 % (AJCC, 2002). In KIRAN all the diagnostic and staging work was according to international protocols and International classification of Disease-oncology (ICD'O) Codes. A total of 568 cases of malignant BC lesions were studied in one year, out of which 478 (84.15%) cases were diagnosed as infiltrating ductal carcinoma (IDC). Biopsy of all these cases was consistent with cytological diagnosis. Sixty five cases (11.4%) were diagnosed as infiltrating lobular carcinoma (ILC) of breast and only 25 (4.4 %) are rare carcinomas (mucinous, papillary, lymphomas, squamous cell carcinoma etc).

Cytologically ductal carcinoma showed 100% consistency where as other types of BC showed discrepancy in the cytohistological relationship.

We use grading system (Simplified Black) into the low and high grade cytologically; accordingly all 478 cases of invasive ductal carcinoma into the low and high grade. Among 478 cases of ductal carcinomas, 247 were histologically diagnosed as low grade, and 231 cases were graded as high grade, out of which, 32 were graded as Grade-I and 336 were graded as Grade –II and 200 as Grade –III tumors. Majority of the cases in this study were the grade - II tumors.

A new treatment modality of systemic adjuvant therapy in which treatment was given before surgery was also evaluated. More rapidly metastatic tumors are more likely to react to chemotherapy than low grade tumors (slightly slow in growth), with assessment of biological assertiveness of cancer. Fine needle aspiration cytology grading also allows sequential estimation to see how treatment modulate grade of the tumor.

Among important prognostic parameters axillary lymph node metastasis is considered significant in view of sizes and numbers. This parameter help to determine survival rate as well as the intensity of the axillary node involvement and the total number (less than 4 versus 4 or more), the total of metastasis tumor, the existence or nonexistence of extra nodal increase and the destroyed vessels.

In this study out of 478 cases of ductal carcinomas 200 cases were considered, out of which 170 patients had major mastectomy together with Lymph nodal removal. Grading was as per Bloom Richardson grading and was evaluated for metastasis (nodal) and for the prognosis (data not shown).

In group I (histological grade – I), <4 lymph node association and in group II (grade – II and Grade – III), showed > 4 lymph node association. Grade – III tumors had >4 lymph node association (maximum number) and Grade - I tumors show less than 4 lymph node association. In this study the grade I tumors showed generally < 4 lymph node association and majority of tumors which were in grade III showed > 4 lymph node association, similar results were reported in a study done by Gurjeet *et al*. (2008) and Arisio *et al*. (2000) showing that lymph node metastasis associated remarkably with the tumor histological grade.

Correlation between hormonal expression (Her2/neu) and tumor grade were also studied (Table 4). Among 568 cases of ductal/lobular carcinoma, 32 tumors were classified as grade I (ten were ER/PR negative, 18 were ER/PR positive, and 8 were HER2/neu positive). Similarly 336 tumors were grade II, (225 were ER/PR negative, 90 were ER/PR positive, and 170 were HER2/neu positive). Among 200 cases of grade III tumors, (110 were ER/PR negative, 80 were ER/PR positive and 48 are HER2/neu positive). Majority of grade I tumors were ER, PR positive, and grade III tumors were ER, PR negative, and HER2/neu positive showing good association with the studies of

Gurjeet *et al*. (2008) and Arisio *et al*. (2000) who also illustrate that grade-I tumors had excellent prognosis with ER and PR by the tumor cells and grade III tumors with bad prognosis with HER2/neu positive and ER, PR negative.

In conclusion, tumors of grade-I mostly showed ER and PR positive and most of the grade III tumors showed negative value for ER and PR expression and positive for HER2/neu expression which is parallel with the studies done by Gurjeet *et al*., (2008) and Arisio *et al*. (2000).

In conclusion, we can say that the tumor size, involvement of lymph nodes, grade, expression of ER/PR and Her2/neu are significant parameter and are very useful for best management and treatment followup of breast cancer patients.

Clinical staging according to AJCC showed that the majority of BC patients (50%) were in stage III, followed by Stage II, I and IV at the time of diagnosis (p=0.0001). The findings of our study regarding grade and stage of tumor indicate another time that in our region patients are presenting late in the course of BC and the tumor acquire higher grade and stage by the time the patients reaches the clinician. These findings are inconsistent with many other studies (Bhurgri *et al*., 2006; Banning *et al.*, 2009; Banning *et al.*, 2009) reported from different countries and point to that majority of the cases with BC usually present earlier before the tumor progressed to advanced grade and stage. Reason for this late presentation in our region may be lake of awareness, ignorance and deficiency of health facilities at primary health care level. (25) (Aziz *et al.*, 2010).

REFERENCES

Alahwal, M.S. (2006). HER-2 positivity and correlations with other histopathologic features in Breast Cancer patients– hospital based study. *J Pak Med Assoc*., 56: 65-8.

Allen, N.E., V. Beral, D. Casabonne, S.W. Kan, G.K. Reeves, A. Brown and J. Green (2009). Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst*., 101(5): 296-305.

American Joint Committee on Cancer (2002). The breast. In: *7. AJCC cancer staging manual*, 6th ed. New York, Springer, pp.171–180.

Arisio, R., A. Sapino, P. Cassoni *et al*. (2000). What modifies the relation between tumor size and lymph node metastasis in T1 breast carcinoma?: *J Clin Pathol.*, 53: 846– 850.

Aziz, Z., S. Sana, S. Saeed *et al.* (2003). Institution based tumor registry from Punjab: five year data based analysis. *J Pak Med Assoc*., 53: 350-3.

Badar, Farhana, Zia S. Faruqui, Ammar Ashraf and Najam Uddin (2007). Third World Issues in Breast Cancer. *J Pak Med Assoc*., 57: 137-40.

Banning, Maggi, Haroon Hafeez, *et al.* (2009). The Impact of culture and sociological and psychological issues on muslim patients with breast cancer in Pakistan. *Cancer Nursing*, 32: 1-8.

Bhurgri, Y., A. Bhurgri,S.H. Hassan *et al.* (2000). Cancer incidence in Karachi, Pakistan: first results from Karachi Cancer Registry. *Int J Cancer*, 85: 325-9.

Bhurgri, Y., A. Bhurgri, S. Nishter *et al.* (2006). Pakistan – country profile of cancer and cancer control 1995-2004. *J. Pak Med Assoc*., 56: 124-30.

Daily Times (2007). "90,000 Breast Cancer Cases Annually in Pakistan." Daily Times, Lahore, 28 Oct. 2007.

Edge, S.B., D.R. Byrd, C.C. Compton *et al*., eds (2010). Breast In: IAJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347-76.

Shin, H.R., F. Bray, D. Forman, C. Mathers and M.D. Parkin (2010). DM.GLOBOCAN 2008 v1.2, *Cancer Incidence and Mortality Worldwide*: IARC Cancer Base No. 10 : International Agency for Research on Cancer, 2010. Available from: http://globocan.iarc.fr. Accessed May 2011.

Ferlay, J., H.R. Shin, F. Bray, D. Forman, C. Mathers and M.D. Parkin (2010).). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, 127(12): 2893-2917.

Forouzanfar, M.H., K.J. Foreman, A.M. Delossantos *et al*. (2011). Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet*. 378(9801): 1461-84.

Kaur, G., R. Ismail, L. S. Kam *et al*. (2008). Assessment of correlation between clinicopathological features and lymph node metastases in breast cancer. *Internet Scientific publications* LLc, 1996 to 2008.

Gilani SI, Khurram M, Mazhar T, Mir ST, Ali S, Tariq S, et al. *J Pak Med Assoc* 2010;60(3):205-208.

Gupta, R.K., A.G. Hutchison, C.S. Dowlow *et al.* (1993). Fine needle aspiration in cytodiagnosis of breast masses in pregnant and lactating women and its impact on management. *Diagn. Cytopathol*., 9: 156–159.

Hashmi, M. (1997). Frequency of consanguinity and its effects on congenital malformation: a hospital based study. *J Pak Med Assoc*., 47: 75-8.

IARC (2008). *World Cancer Report 2008*. Lyon, Int. Agency for Research on Cancer.

Liede, Alexander, Imtiaz A. Malik, Zeba Aziz, Patricia De los Rios, Elaine Kwan, and Steven Narod (2002). "Contribution of BRCA1 and BRCA2 Mutations to Breast and Ovarian Cancer in Pakistan." *Am. J. Hum. Genet*. 71: 595-606.

Mahmood, S., T.F. Rana and M. Ahmad (2006). Common determinants of Ca Breast–a case control study in Lahore. *Ann King Edward Med Coll*, 12: 227-8.

Morris, K.T., J.T. Vetto, J.K. Petty, Lumss *et al*. (2002). A new score for the evaluation of palpable breast masses in women under age 40. *American Journal of Surgery*, 184: 245–247.

Hanif, H. P. Zaidi, S. Kamal and A. Hameed (2009). 'Institution based cancer incidence in a local population in Pakistan: Nine year Data analysis' . *Asian Pacific journal of Cancer Prevention*, 10: 225-228.

Parkin, D.M. and L.M. Fernandez (2006). Use of statistics to assess the global burden of breast cancer. *Breast J*., 12: S70-80.

Parkin, D.M., P. Pisani and J. Farlay (1993). Estimates of worldwide incidence of 18 major cancers in 1985. *Int J Cancer*, 54: 594-606.

Rosai, J. (ed). (2004). *8. Rosai and Ackerman's surgical pathology: breast*, 9th ed, Vol. II. St. Louis, Mosby, 2004:1763–1839.

Shami, S.A., L.H. Schmitt and A.H. Bittles (1989). Consanguinity related prenatal and postnatal mortality of populations of seven Pakistani Punjab cities. *J Med Genet*, 26: 267-271.

Tiwari, M. (2007). Role of Fine needle Aspiration cytology in diagnosis of breast lumps. *Kathmandu University Medical Journal*, 5(2): 215-217.

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