

RESEARCH ARTICLE

Breast Cancer in Young Women from a Low Risk Population in Nepal

Bibhusal Thapa¹, Yogendra Singh^{1*}, Prakash Sayami¹, Uttam Krishna Shrestha¹, Ranjan Sapkota¹, Gita Sayami²

Abstract

Background: The overall incidence of breast cancer in South Asian countries, including Nepal, is low compared to Western countries. However, the incidence of breast cancer among young women is relatively high. Breast cancer in such cases is characterized by a relatively unfavorable prognosis and unusual pathological features. The aim of this study was to investigate clinico-pathological and biological characteristics in younger breast cancer patients (<40 years) and compare these with their older counterparts. **Materials and Methods:** Nine hundred and forty four consecutive female breast cancer patients, admitted to the Department of Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal between November 1997 and October 2012, were retrospectively analyzed. **Results:** Out of the 944 female breast cancer patients, 263 (27.9%) were <40 years. The mean age was 34.6±5.0 years among younger patients compared to 54.1±9.9 for those ≥40 years. The mean age at menarche was also significantly lower (13.5±1.5 vs 14.2±1.5 years p=0.001) while the mean duration of symptoms was significantly longer (7.6 vs 6.5 months p=0.004). Family history of breast cancer was evident in 3.0% of the young women versus 0.3% in the older one. Mammography was performed less frequently in younger patients (59.7%), compared to older (74.4%), and was of diagnostic benefit in only 20% of younger patients compared to 85% of older ones. At diagnosis, the mean tumor diameter was significantly larger in young women (5.0±2.5 vs 4.5±2.4cm, p=0.005). Axillary lymph nodes were positive in 73% of younger patients and 59% of older patients. In the younger group, the proportion of stage III or IV disease was higher (55.1% vs 47.1%, p≤0.05). The proportion of breast conserving surgery was higher in young patients (25.1% vs 8.7%) and a higher proportion of younger patients receive neoadjuvant chemotherapy (9.9% vs 2.8%). The most common histological type was ductal carcinoma (93.1% vs 86%). The proportion of histological grade II or III was higher in younger patients (55.9% vs 24.5%). Similarly, in the younger group, lymphatic and vascular invasion was more common (63.2% vs 34.3% and 39.8% vs 25.4%, respectively). Patients in the younger age group exhibited lower estrogen and/or progesterone receptor positivity (34.7% vs 49.8%). Although statistically not significant, the proportion of triple negative tumors in younger age group was higher (22.4% vs 13.6%). **Conclusions:** Breast cancer in young Nepalese women represents over one quarter of all female breast cancers, many being diagnosed at an advanced stage. Tumors in young women exhibit more aggressive biological features. Hence, breast cancer in young women is worth special attention for earlier detection.

Keywords: Advanced stage - breast cancer - tumor biology - young women

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Introduction

Breast cancer is the most frequent cancer in women worldwide with 1.38 million new cases diagnosed every year, and represents over 23% of all cancers among females (Ferlay et al., 2008). However, breast cancer is still relatively infrequent in developing countries as compared to the developed western countries (Jemal et al., 2011). Although there is heterogeneity amongst breast cancer risks within the South Asian region, lower incidence of breast cancer may be due to a predominantly young population pyramid, lower intake of animal meat, and lower utilization of health services (McCormack et al., 2004; Gathani et al., 2010). The incidence of breast

cancer in young women is low in developed countries (Brinton et al., 2008). However, the incidence of breast cancer among young women in the low risk population of the South Asian countries including Nepal is much higher (Pradhananga et al., 2009; Kakarala et al., 2010). When breast cancer is detected in young women, prognosis is often worse than for older women (Maggard et al., 2003). Younger women are often less likely to seek early medical advice, leading to later detection often at more advanced stages. In addition, the majority breast cancer in young women presents with more aggressive tumor biology than in older women (Tichy et al., 2013). The aim of this study was to investigate clinicopathological and biological characteristics in young patients (<40 years of age) with

¹Departments of Surgery, ²Departments of Pathology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal *For correspondence: yp_singh@hotmail.com

breast cancer and compared with their older counterparts, in a tertiary care center in Nepal.

Materials and Methods

Nine hundred and fifty four consecutive breast cancer patients were admitted to the Department of Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal between November 1997 and October 2012. Ten patients were male. A retrospective analysis was carried out based on the data retrieved from the surgical records of all female breast cancer patients. Data collection included demography, medical history, clinical management such as mode of presentation, diagnosis, surgical treatment and neoadjuvant chemotherapy given; prognostic markers, such as tumor size, histological type, tumor grade, lymph node status, presence of lymphovascular invasion, estrogen (ER) and progesterone receptors (PR) status and HER2 status, and analyzed.

Comparative Statistical Tests were performed with SPSS 15.0 for Windows statistical software. The Chi-squared test, Fisher's exact test and t-test were used to assess differences in clinical and pathological features between these two groups of patients (<40 and ≥40 years of age). Results were presented as the mean±SD, unless otherwise stated.

Results

The number of breast cancer patients increased each year from 44 in 1998 to 62 in 2012. Out of the 944 female breast cancer patients, 263 (27.9%) patients were <40 years. The youngest patient was 15 years old and the oldest was 95. The most common age group of women with breast cancer was 41-50 years (34%). Out of the young women diagnosed with breast cancer, the mean age was 34.6±5.0 years compared to 54.1±9.9 years for those ≥40 years (Table 1). Approximately half of the patients were from each of two major ethnic groups (Indo-Aryan 456

and Tibeto-Burman 488). Younger patients were more likely to be of Tibeto-Burman origin (58.2%) than their older counterparts (49.2%). The proportion of the patients coming from rural and urban areas was equal. However, more <40 patients came from urban areas (56.7% vs 47.4% p=0.051). The mean age at menarche was significantly lower in the <40 group (13.5±1.5 vs 14.2±1.5 years p=0.001).

The majority of breast cancer patients (82%) presented with painless breast lump. Other common presenting features were a breast lump with pain or ulceration (12%), and abnormal nipple discharge, followed by nipple disappearance (3%). The duration of symptoms varied from two weeks to three years before seeking medical attention. The mean duration of symptoms was significantly longer in younger women (7.6 vs 6.5 months p=0.004). 96% of women were married. The number of children ranged from one to eleven. A family history of breast cancer was evident in eight (3%) of the young women versus two (0.3%) of the older women. Bilateral cancer was identified in six (2.3%) and four (0.6%) of the <40 and ≥40 year groups, respectively. Two women were diagnosed with breast cancer during pregnancy.

Mammography was performed in 157 young patients (59.7%), compared to older patients 507 (74.4%), and was of diagnostic benefit in 53 (20.1%) young patients compared to 579 (85%) older patients. Fine needle aspiration cytology (FNAC) was used as a diagnostic tool in both groups (90.8% vs 95.3%). The mean tumor diameter decreased from 5.8cm in 1998 to 3.6cm in 2012. At diagnosis, the mean tumor diameter was significantly larger in younger women (5.0±2.5 vs 4.5±2.4cm, p=0.005). The axillary lymph node was positive in 192 (73%) young patients and 402 (59%) older patients. Out of 944 female breast cancer patients, stages 0, I, II, III, and IV were 0.6%, 6.7%, 40%, 40%, and 8%, respectively. The stage of the disease was unknown in 4.7% of the cases. In the younger group of patients, the proportion of stage III or IV disease was higher (55.1% vs 47.1%, p≤0.05). The majority of the patients (857 out of 944) underwent surgical treatment. Potentially curative surgery was done in 804 (85.2%) patients. The most common surgery was mastectomy with axillary level I and II lymph node dissection in 575 (60.9%) patients. Breast conserving surgery (BCS) was performed in only 125 patients (13.2%). The proportion of BCS was higher in younger patients (25.1% vs 8.7%). However, both younger and older patients who underwent BCS were given radiotherapy. Adjuvant chemotherapy was more often given to younger patients (54.5%) than older patients (33.9%) after BCS. The use of neoadjuvant chemotherapy was higher in young patients (10.3% vs 2.8%).

The most common histological type was ductal carcinoma (88%). Medullary carcinoma, lobular carcinoma and other types were 4.5%, 2.7% and 4.8%, respectively. Ductal carcinoma was more common in younger patients (93% vs 86%). Only 394 histological reports included histological grade, lymphatic and vascular invasion factors. The grade I, II, and III were 20.3%, 57.9%, and 20.8%, respectively. In the younger patients the number of histological grade II or III was higher (55.9% and 24.5%,

Table 1. Features of Breast Cancer in Women <40 and ≥40 Years of Age

	<40 yrs	≥40 yrs	p value
No. of patients (%)	263 (27.9)	681 (72.1)	
Mean age (y)*	34.6±5	54.1±9.9	
Tibeto-Burman decent (%)	153 (58.2)	335 (49.2)	0.045
Urban residents (%)	149 (56.7)	323 (47.4)	0.051
Mean age at menarche (y)*	13.5±1.5	14.2±1.5	0.001
Mean duration of symptoms (m)*	7.6±6.5	6.5±5.7	0.004
Family history of breast cancer (%)	8 (3)	2 (0.3)	0.004
Bilateral breast cancer (%)	6 (2.6)	4 (0.6)	0.057
Mammographic diagnosis (%)	53 (20.1)	579 (85)	0.001
Fine Needle Aspiration diagnosis (%)	239 (90.8)	649 (95.3)	0.056
Mean tumor diameter (cm)*	5±2.5	4.5±2.4	0.005
Axillary Lymph node positivity (%)	192 (73)	402 (59)	0.002
Stage III or IV (%)	145 (55.1)	321 (47.1)	0.049
Breast conserving surgery (%)	66 (25.1)	59 (8.7)	0.001
Neoadjuvant chemotherapy (%)	27 (10.3)	19 (2.8)	0.001
Ductal carcinoma (%)	245 (93.1)	586 (86)	0.004
Histological grade II or III (%)**	147 (55.9)	167 (24.5)	0.002
Lymphatic invasion (%)**	249 (63.2)	135 (34.3)	0.010
Vascular invasion (%)**	157 (39.8)	100 (25.4)	0.020
ER &/or PR positivity (%)	17 out of 49 (34.7)	106 out of 213 (49.8)	0.050
HER2 positivity (%)	13 out of 49 (26.5)	50 out of 213 (23.5)	0.600
Triple negative tumors (%)	11 out of 49 (22.4)	29 out of 213 (13.6)	0.120

*Data presented=Mean±SD; **Out of 394

respectively). Moreover, the lymphatic and vascular invasion were also higher (63.2% vs 34.5% and 40.0% vs 25.5%). Only 262 patients' tumors (49 younger and 213 older patients) were immunohistochemically analyzed for hormonal receptors and HER2 status. The status of ER, PR and HER2 was not statistically different between two groups, but patients in the younger age group exhibited lower ER and/or PR positivity (34.7% vs 49.8%) and higher HER2 positivity (26.5% vs 23.5%). The proportion of triple negative tumors (ER, PR and HER2- Negative) in the younger age group was higher (22.4% vs 13.6%, statistically not significant).

Discussion

Breast cancer is the most common cancer in women and its incidence has been increasing worldwide. Regional variations are pertinent and the rate of increase is remarkable especially in Asian countries. Potential contributors to this increase are rapid urbanization, increasing life expectancy and life style changes including decreased physical activity, and westernized dietary habits (Poter, 2008; Agrawal et al., 2009). As such, there is a wide variation in the incidence of breast cancer in different cities of India and broader Asia (Stanley et al., 2010).

Breast cancer can affect any age, race and ethnic group. However, breast cancer accounts only for 6.6% of all breast cancer in women <40 years of age (Tichy, et al., 2013). Its incidence and mortality vary among different ethnic groups. The incidence of breast cancer in women <40 years in South Asian population (Indian/Pakistani) is 16.2% compared to 6.2% in Caucasian women (Kakarala et al., 2010). In the present study, breast cancer accounted for 27.9% in patients <40 years old, which is comparable to a report of 26% in younger than 35 years olds from Northern India (Nandakumar et al., 2004). There are two major ethnic groups in Nepal; those of Indo-Aryan decent and those of Tibeto-Burman decent and these ethnic groups account for 60% and 40% of the Nepal population, respectively. This study found that breast cancer in women <40 years old was more common in Tibeto-Burman decent than Indo-Aryan descent.

The higher physical activity of rural residents may positively influence the incidence of breast cancer, as it affects hormones and weight gain in addition to delaying menarche (Dorgan, 1998). In our present study, the age at menarche in the older patients was one year later than the younger group. Menarche at a relatively early age is associated with an increased risk for breast cancer (Das et al., 2012). Moreover, breast cancer was more common in young women of urban areas perhaps due to adaptation of a more sedentary life style. The reproductive factors like nulliparity, and late age at first full-term pregnancy have been associated with a high risk of breast cancer (Pisani, 1992). In contrast, Nepalese breast cancer cases are seen at young age with early first full-term pregnancy and long duration of lactation (Singh et al., 2002).

Positive family history of breast cancer is a known breast cancer risk factor (Pisani, 1992). In young patients, genetically inherited susceptibility to breast cancer has been well described. Indeed, in the present series younger

women were likely to have a family history than women in the older group (3% vs 0.3%). Although we do not know the genetic status of our patients, approximately 5% of young patients had a germ-line BRCA1 mutation and a 3% BRCA2 mutation (Malone et al., 2000).

The presentation of breast cancer in young women may differ from older women in many respects. The majority of the Nepalese women tend to believe that painless lumps are harmless. Young women ignore mild breast symptoms. Only 10% of women from the capital city of Nepal undergo clinical examination of the breast (Bhatta et al., 2011). In the present series, younger women presented late compared to older women (7.6 months vs 6.5 months). Young women seek medical advice only when the disease is very obvious and the younger patients often have a longer history of breast lump (Ashley et al., 1989). Poor symptom knowledge and recognition are important issues in developing countries, where cancer awareness will be the remedy (Taib et al., 2011). Limited mammographic screening is possible in younger women. Moreover, clinical and radiological examinations in younger women have a limited accuracy, which might lead to a delay in the diagnosis (Di Nubila et al., 2006).

In general, Asian women have denser breast tissue which can obscure cancers on mammography (del Carmen et al., 2007). At present, mammography is not available even in all regional hospitals of Nepal and mammographic screening is not feasible in our country (Sidhartha et al., 2008). Mammogram was performed less frequently in younger women than older women. In the present series, only 20.1% of the younger patients had mammographically proven breast cancer. In younger women, the mammographic sensitivity is low because of the dense breast tissue of this age group (Foxcroft et al., 2004). Using combing mammography and ultrasonography, the accuracy of detection can be increased in young women (Houssami et al., 2002). FNAC is a useful evaluation for both palpable breast masses and non-palpable breast lesions detected on mammography (Pinappel et al., 2004). The accuracy rate of FNAC in diagnosing breast cancer is more than 90%, which was consistent with our report in both groups of patients (Ariga et al., 2002).

Younger women with breast cancer present with larger tumor sizes, and more extensive lymph node involvement than older women (Guerra et al., 2003). Moreover, breast cancer in young Asian women is more aggressive than in Caucasians (Tea et al., 2013). In the present study, younger patients presented with higher stage of the disease than the older patients.

There are specific issues associated with the diagnosis of breast cancer in young women. These issues arise during treatment of such patients with potentially aggressive tumor biology, larger tumor size and psychosocial factors unique to young women. BCS produces an acceptable cosmetic appearance, therefore less anxiety, depression, improved body image and sexuality when compared with mastectomy (Al-Ghazal et al., 2000). In this study also, younger patients had more BCS than in older age group. As modified radical mastectomy treats the breast with axilla adequately in one operation, it avoids the need of

adjuvant radiotherapy in all cases and is associated with a very low locoregional recurrence rate. Moreover, patients underwent mastectomy if they wanted neither BCS nor post-operative radiotherapy.

Adjuvant therapy is routinely recommended to breast cancer patients as it increases survival and decreases the chances of recurrences (Early Breast Cancer Trialists' Collaborative Group, 1992). Selection of the chemotherapy regimen is determined by prognostic factors. Preoperative or neoadjuvant chemotherapy can downstage locally advanced diseases and make them operable and also increases the chance of BCS rather than mastectomy (Gonzalez-Anquolo et al., 2008). The younger women in the study were given more preoperative or postoperative chemotherapy than the older women. As chemotherapy has shown benefit younger patients than older patients (Menard et al., 2000).

Breast cancers in young women are more likely to be hormone receptor-negative and of higher grade (Colleoni et al., 2002). In addition, HER2-positive disease is more common in young women. Like in our series, it was more likely to have more triple negative breast cancer (estrogen receptor-negative, progesterone receptor-negative and HER2-negative) in young women than in older counterparts (Lee et al., 2011). The triple negative breast cancer subtype or basal-like subtype is higher in African-American women, and is associated with aggressive histology and poor clinical outcome (Ihemelandu et al., 2007). In this study the features of aggressive tumor biology in younger patients might be expected to result in a poorer prognosis.

Special care is needed for breast cancer in women below the age of 40 years. There are specific issues in this age group like fertility and contraception, pregnancy after cancer and cancer during pregnancy (Rodrigues-Walberg and Oktay, 2012). Moreover, younger women may need more psychosocial support than older women (Howard-Anderson et al., 2012).

In conclusions, more than one quarter of the breast cancer diagnosed in Nepal is in young females, many being diagnosed at an advanced stage. Younger women may be less likely to seek early medical attention, leading to late detection. Tumors in young women have more aggressive biological features. Hence, there is an urgent need to raise breast cancer awareness among this population. Early risk assessment, annual clinical breast examination and screening, should be done from a younger age. Further study is warranted to investigate survival and post treatment recurrence in the younger women with breast cancer.

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