Assessment Of Correlation Between Clinicopathological Features And Lymph Node Metastases In Breast Cancer

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Abstract

There were 177 cases (1 male) of breast cancer cases diagnosed at Hospital Pulau Pinang in 2003 and 2004 as reviewed from histopathology records. The female median age was 54 years with a peak age of 45 - 55 years. The highest incidence was seen in Chinese (62.5%) followed by Malay (26.7%) and Indian (10.2%) ethnic groups. Correlation of clinicopathological characteristics were analysed in surgically resected specimens of infiltrating ductal carcinomas. The mean tumour size was 3.75 cm and 50.4% of cases were of histologic grade 3. Lymph node metastasis was present in 57.6% patients who underwent axillary clearance. Ethnic group did not correlate with tumour size, histological grade or lymph node metastases. Nodal positivity correlated with histological grade and tumour size, but not with estrogen receptor or c-erbB-2 status.

The work was done at the Department of Pathology, Hospital Pulau Pinang, Penang, MALAYSIA.

INTRODUCTION

Breast cancer is the commonest cancer in Malaysian women with an incidence of 39.5 per 100,000 population and consisting of 31% of all female cancers, as reported in the Second Report of the National Cancer Registry, Malaysia ([1]). The disease is associated with high morbidity and mortality especially as we tend to see more advanced stages of breast cancer in our part of the world ([2], [3]). However data on breast cancer in Malaysia is still scarce and studies seem to be concentrated in the highly urban area around the capital city of Kuala Lumpur.

The aim of this study was to determine the pattern of breast cancer in Hospital Pulau Pinang and to compare it with other studies conducted in Kuala Lumpur. We also sought to determine the correlation, if any, between clinicopathological features of infiltrating ductal carcinoma and axillary lymph node metastases.

MATERIALS AND METHODS

The histopathology records of all newly diagnosed breast cancer cases in Hospital Pulau Pinang in 2003 and 2004 were retrospectively reviewed. Patients' age and racial group were documented. Tumour size was taken as the greatest dimension measured in mastectomy and lumpectomy specimens. The histological type of cancer and histological grade of invasive ductal carcinoma (using modified Bloom and Richardson histological grade) were determined in samples that had enough tissue for its assessment. Results of estrogen receptor and c-erbB-2 status using immunohistochemistry were documented. Lymph node status in specimens with axillary clearance was ascertained by routine grossing, followed by hematoxylin and eosin stain.

STATISTICAL ANALYSIS

Chi square was used to test the association between ethnic group, tumour size (categorized as ≤2 cm, >2 cm and ≤5 cm, and >5 cm), histological grade, estrogen receptor (ER) status, c-erbB-2 status and lymph node metastases. The level of significance was set at 5%. The difference in mean tumour size between the three ethnic groups was tested by Oneway Anova.

RESULTS

There were a total of 177 new cases (including 1 male) of breast cancer diagnosed at Hospital Pulau Pinang in 2003 and 2004. Of this 74 cases were diagnosed in 2003 and 103 cases in 2004. This represented an almost 40% increase in the number of cases in 2004 compared to 2003. The histological type of breast cancer comprised 137 infiltrating ductal carcinoma (not otherwise specified), 4 invasive lobular carcinoma, 3 papillary, 2 mucinous, one each of medullary, tubular and inflammatory carcinoma, 27 ductal

carcinoma in situ and 1 Non Hodgkin lymphoma.

All patients were female except for one male who had invasive ductal carcinoma. The median age for females was 54 years (range 29 to 90 years) with a peak age of 45 – 55 years. The racial breakdown comprised 110 Chinese (62.5%), 47 Malay (26.7%), 18 Indian (10.2%) and 1 Indonesian. When considering only patients who had mastectomy or lumpectomy, the racial breakdown was 65 Chinese (60.7%), 30 Malay (28.0%) and 12 Indian (11.2%) The mean tumour size of infiltrating ductal carcinoma as measured in mastectomy and lumpectomy specimens (n = 107) was 3.75 cm (range 0.6 cm to 9.8 cm). The size of infiltrating ductal carcinoma (IDC) tumours at presentation is tabulated in table 1 and the histological grade of IDC, in table 2. The mean tumour size for invasive lobular carcinoma was 4.5 cm, papillary carcinoma – 4.0 cm and mucinous carcinoma – 3.2 cm.

Figure 1

Table 1: Size of primary breast tumour

Mean tumour size	Number of cases (Percentage of total) (n= 107)
≤ 2cm	26 (24.3%)
> 2cm, ≤ 5cm	60 (56.1%)
>5cm	21 (19.6%)

Figure 2

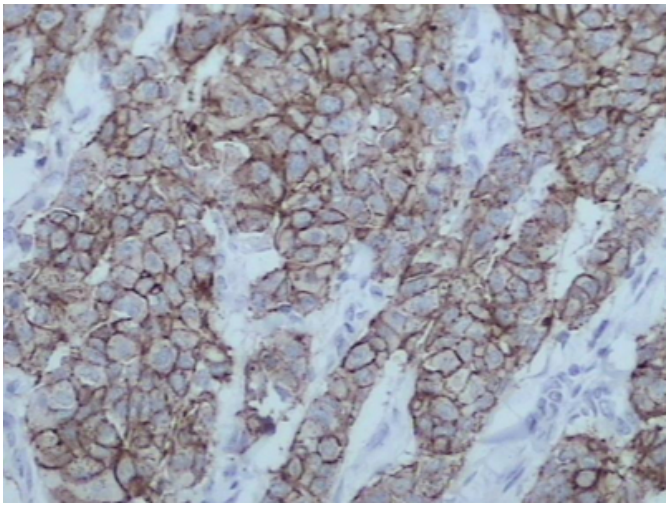
Table 2: Histologic grade of invasive ductal carcinoma (modified Bloom-Richardson)

Histologic grade	Number of cases (Percentage of total) (n= 123)
1	14 (11.4%)
2	47 (38.2%)
3	62 (50.4%)

Of a total of 102 cases stained for estrogen receptor and c-erbB-2, 43 (42%) were ER-positive and 39 (38%) were c-erbB-2 positive. ER-positive was seen in 27 of 63 Chinese patients, 10 of 30 Malays and 6 of 12 Indians, while c-erbB-2 was positive in 25 Chinese, 11 Malays and 3 Indian patients (Figure 1).

Figure 3

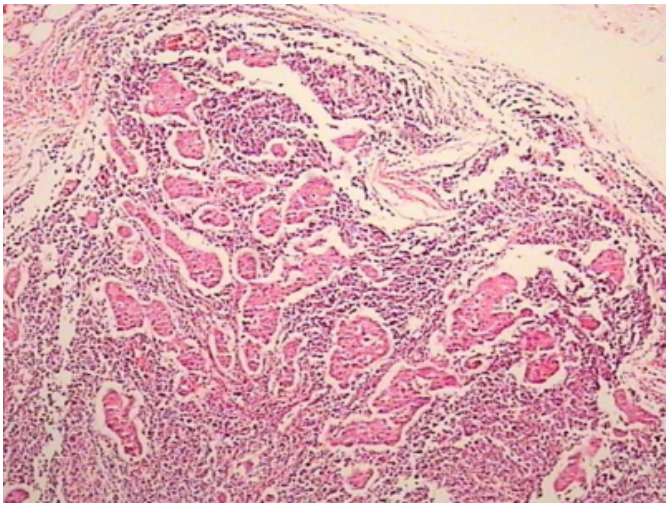
Figure 1: Immunohistochemistry showing c-erbB-2 positive membrane staining of breast cancer cells, x 200 magnification.



Fifty three (57.6%) of the 92 patients who underwent mastectomy and axillary clearance demonstrated histological evidence for nodal metastases. The total number of lymph nodes retrieved from surgically resected specimens during grossing ranged from 4 to 39 lymph nodes with the number of positive nodes varying from 1 to 28. On average, half of the lymph nodes sampled contained metastatic deposits (Figure 2).

Figure 4

Figure 2: Histology showing metastatic deposits in lymph node from a primary breast cancer, x 40 magnification.



STATISTICAL ANALYSIS

For statistical analysis, only the 107 cases where a mastectomy or lumpectomy was done were included. There was no correlation between ethnic group and tumour size

(categorized or mean size), histological grade or lymph node metastases. Lymph node metastases correlated significantly with tumour histologic grade (p = 0.050) but not with estrogen receptor or c-erbB-2 status. When tumour size was categorized into 3 groups (as in table 1), there was no association between lymph node metastases and tumour size (p = 0.067). However there was a significant association with lymph node metastases when tumour size was categorized into ≤2 cm or >2 cm (p = 0.032). There was no significant association between race and ER or c-erbB-2 status.

DISCUSSION

There is a dearth of data on breast cancer in Malaysia although it is recognized as the most common cancer and the leading cause of cancer deaths in women ([1]). Through a pubmed search there are only a few published reports on breast cancer in Malaysian women. The crude incidence is estimated at 39.5 per 100,000 population ([1]). There were a total of 177 newly diagnosed breast cancer cases in HPP in two years with a significant increase in the second year (103 cases) compared to the previous year (77 cases). The number of new cases of breast cancer diagnosed in two centres in Kuala Lumpur was approximately 120 to 200 cases per year ([2]). Our study showed a median age of 54 years and peak age of 45 to 55 years with approximately 40% of patients below 50 years old. This is comparable with data previously reported in Malaysia where the incidence of cases below 50 years old reached 50% ([1,2,3]). The significantly higher incidence of breast cancer in Chinese women (62.5% of patients) is in concordance with the Second Report of the National Cancer Registry, Malaysia though another study conducted in Kuala Lumpur Hospital found that breast cancer incidence was highest among the Malay ethnic group, followed by Chinese and Indians ([1,2, 3]). This difference reflects the local racial population in the different areas where the studies were conducted, Chinese being the major ethnic group in Penang state where HPP is the main government hospital.

The assessment of correlation between various clinicopathological features and lymph node metastases was done to gain a better insight into its prognostication in breast cancer, considering that nodal metastases is the best single prognostic indicator in breast cancer.

Tumour size is an important indicator for overall survival as clearly shown by its inclusion in the TNM Staging System for breast cancer ([4, 5]). Nodal positivity is significantly correlated with large tumour size (>10 mm). In our study the majority of infiltrating ductal carcinoma tumours was larger than 2 cm (75.7%) with a mean size of 3.75 cm at presentation. Almost 20% of cases were more than 5 cm in size. Though the average tumour size is smaller than that quoted in other studies in Kuala Lumpur (average tumour size of 4.2 cm to 5.4 cm), this still meant that the majority of cases are diagnosed at a locally advanced stage. Cancers were observed to be larger among the Malay ethnic group in previous reports though we could not substantiate it in our study ([2, 3]). There was a positive association between lymph node metastases and tumour size when the latter was categorized as ≤2 cm or >2 cm. Hence T2 breast cancer had a higher probability to metastasize to axillary lymph nodes compared to T1 stage tumours.

In our study about 50% of infiltrating ductal carcinomas was poorly differentiated (grade 3) with a tendency of higher grade tumours to metastasize to axillary lymph nodes. This suggests that histologic grade would be a valuable prognostic factor in breast cancer. However other reports show conflicting and inconclusive results which at the moment does not support the addition of histologic grade into the AJCC staging system for breast cancer ([6]).

Estrogen is a weak prognostic indicator but a good predictor of response to endocrine therapy ([7, 8]). They are found to some degree in 50-80% of breast tumours though studies done in Nigeria report a much lower frequency of 25% ([9, 10, 11]). In our study 42% of cases were ER-positive. The pathologists involved in the study set a low cut-off point for a positive interpretation of the assay and immunohistochemical staining was always done in tandem with controls. Therefore this result is a true value. It was interesting to note that higher grade tumours were associated with ER-negative assays (p=0.004). This is comparable with the studies done in Nigeria where high grade breast tumours were more likely to be ER-negative ([10, 11]).

The c-erbB-2/HER2 gene is usually reported to be amplified in about 10-30% of breast cancers ([12]). Its overexpression is more prevalent in higher grade tumours compared to low grade tumours ([10, 13]). Our study showed 38% of infiltrating breast carcinomas to be c-erbB-2 positive. Though not statistically significant, there was a higher frequency of positivity in grade 2 (41%) and grade 3 (40%) invasive breast cancer compared to grade 1 tumours (23%). It should be cautioned that there is subjectivity and a lack of

standardization in the interpretation of immunohistochemical staining of this receptor protein, even more so prior to the implementation of the more recent scoring system. This factor may have contributed to the higher than usual frequency of c-erbB-2 positivity.

Overexpression of c-erbB-2 and absent estrogen receptor status is often associated with aggressive tumours and poor prognosis ([8]). In our study lymph node metastases was not associated with these biological markers, as similarly reported by Arisio and colleagues who did not find any significant correlation between nodal positivity and ER, PR or c-erbB-2 status in invasive breast cancers of <2 cm size. ([14]). A negative relationship between ER and c-erbB-2 expression has been reported in other studies as well as in the authors personal experience, but this could not be substantiated in our study ($p = 0.97$) ([13]).

More than half of the patients (57.6%) in our study had evidence of lymph node metastases and thus constituted advanced stage, which again reiterates the late stage of presentation in Malaysian women.

CONCLUSION

The study shows a high incidence and predominance of breast cancer in Malaysian Chinese women. Majority of patients present at a locally advanced stage with cancers larger than 2 cm, and associated with poorly differentiated histology, estrogen receptor-negative and lymph node metastases. It is hoped that greater public awareness and future breast screening programmes will promote early detection of breast cancer.

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