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Breast Cancer in the Young: A 10-year Review of the Diagnosis, Treatment and Outcomes at the Philippine General Hospital

Sittie Aneza Camille A. Maglangit, MD, DPBS; Arjel D. Ramirez, MD, DPBS; Mark Richard C. Kho, MD, FPCS and Rodney B. Dofitas, MD, FPCS

Division of Surgical Oncology, Head and Neck, Breast, Skin and Soft tissue, and Esophagogastric Surgery, Department of Surgery, Philippine General Hospital, University of the Philippines Manila

Rationale: Breast cancer is the most prevalent cancer in the world. It is usually diagnosed in women 50 years old and older, but is also found in younger women. Its occurrence in young women led to questions with regards issues on its tumor biology, survival and fertility. There is insufficient local data to formulate treatment options relevant to this age group. This study reviews the data on breast cancer in young female patients seen in a tertiary institution.
Methods: This is a descriptive study involving a review of medical records of young female breast cancer patients (<35 years of age), seen at the Philippine General Hospital - Breast Care Center from January 2008 to December 2017.
Results: A total of 119 patients were included in the study. Of these young female patients, 29.4% presented with locally advanced disease (Stage IIIB) correlating with a high number of patients who underwent neoadjuvant chemotherapy (38.7%) and modified radical mastectomies with primary closure (62.18%).
Conclusion: Breast cancer in young females should be aggressively investigated as it commonly presents in an advanced stage.

Key words: breast cancer, screening, young female

Breast cancer ranks first (11.7%) in incidence worldwide and has surpassed lung cancer in the latest Global Cancer Observatory (Globocan) registry (2020).[1] It ranked fifth (6.9%) in mortality, following lung, colorectal, liver, and stomach cancers.[1] It is the most frequently diagnosed cancer in the Philippines, accounting for 17.7% of all new cases.[2] Approximately 10.7% of all cancer deaths are caused by breast cancer.[2] Based on these data, the authors can infer that breast cancer has always been a public health problem that continues to be a top priority in terms of prevention and treatment.

International studies have shown a significant difference in outcomes in breast cancer management in women diagnosed under 40 years of age as compared to those that developed breast cancer at a more advanced age. A younger age at breast cancer diagnosis, is an indicator of poor prognosis across all histologic subtypes and stages. Young women under 40 years of age treated for breast cancer have disproportionately high rates of second malignancies.[3] Poor prognosis was most strongly associated with young women who presented with axillary lymph node-negative breast cancer.[4]

The outcomes of young female breast cancer patients under 35 years of age, are less frequently studied. The studies of Fredholm and Han demonstrated that age has remained as an independent risk factor for breast cancer death in women under 35 years of age.[6,7] The scarcity of local literature demonstrating the status of breast cancer in this population has resulted in this retrospective study. The study aimed to determine the factors that contributed to unfavorable outcomes in this age group in our institution for a 10-year period. Specifically, to 1) describe the epidemiology of breast cancer in young female patients, 2) determine risk factors present in this population, 3) examine the clinical and pathological characteristics of the disease, 4) identify the treatment regimens administered such as type of surgery, chemotherapy, radiation, hormonal, and targeted therapies, whether for cure or palliation, and 5) determine corresponding outcomes (remission, recurrence, survival or death). The results from the study can become a source of data to improve the current existing practice

parameters on how to detect, manage and prevent breast cancer in this age group.

Methods

Study Design

This was a descriptive study involving a review of medical records of young female breast cancer patients seen at the Philippine General Hospital - Breast Care Center (PGH-BCC) from January 2008 to December 2017.

Inclusion criteria

Young female breast cancer patients under 35 years of age, regardless of stage and treatment received (± surgery, ± chemotherapy, and ± radiotherapy). Patients who died, whether from the disease or from other conditions, were included using the information available in the charts.

Exclusion criteria

Breast cancer in males, chest wall sarcoma, and patients whose charts could no longer be retrieved.

The list of patients was extracted from the Integrated Surgical Information System (ISIS) database of the Department of Surgery – Philippine General Hospital. The search terms "breast cancer" or "breast carcinoma" and "modified radical mastectomy" were used. The search was then narrowed down to include only young female patients. Records from the PGH-BCC and the Outpatient Department (OPD) Medical Records Section were also used for the search. Individual patient records were reviewed, and the following data were obtained:

- Basic sociodemographic information: age, age at diagnosis, BMI, use of oral contraceptives, high animal fat diet, and family history of breast cancer
- Clinical and pathological characteristics of the disease: histologic type, TNM stage, nuclear grade, lympho-vascular invasion (LVI), hormone receptor and human epidermal growth receptor (HER2neu) status
- Treatment administered: type of surgery, chemotherapy, radiation, hormonal, and targeted therapy. Indication for treatment, whether for cure or palliation
- Treatment outcomes: remission, recurrence, survival, or death

Information was recorded using a standard data collection form. Histopathologic and immuno-histochemistry (IHC) results not readily available in the chart were retrieved from the Department of Pathology, as well as from records kept by the Department of Health Breast Cancer Medicines Access Program (BCMAP), the government section at the Philippine General Hospital that provided free chemotherapy drugs to eligible breast cancer patients (Stage I-IIIB). Data collected were kept confidential and patients were assigned with control numbers that served as their only identifiers.

Data Analysis

Patients' characteristics were expressed as frequency and percentages. Recurrence was estimated from the date of initial treatment to the date when the recurrence was recorded in the chart or the presence of recurrent disease by imaging.

Results

A total of 119 patients were included in the study. The demographic and clinical profiles of patients are shown in Table 1. The average age was 31 years old with a range of 23-34. There were no patients under 20 years of age. Breast cancers were mostly located on the right breast (51.3%).

With regards the BMI, almost 40% were within the ideal weight range, 19.3% were overweight, 6.7% were obese, and 5% were underweight. The patients' heights and weights were not recorded in 29.4% of the charts. Eight percent of the patients (8%) had a history of oral contraceptive pill (OCP) use and 8% had an early menarche. Five percent (5%) had a smoking history, 4.2% had a known BRCA mutation, and a very small number of patients had prior history of breast cancer and

uterine bleeding. One patient was pregnant at the time of her breast cancer diagnosis. Hypertension, obesity, and bronchial asthma were the most common illnesses indicated in the charts.

Table 1. Demographic and clinical profile of mastectomy patients (N = 119)

Patient-related Factors	Frequency (Percentage)
Age at diagnosis:	
20-35 years (mean)	31
<20 years	0
Laterality:	
Left	58 (48.7%)
Right	61 (51.3%)
Body mass index (BMI):	
Underweight	6 (5%)
Ideal weight	47 (39.5%)
Overweight	23 (19%)
Obese	8 (6.7%)
Not known	35 (29.8%)
Risk factors:	
High animal fat diet	0
Use of oral contraceptives	9 (7.76%)
Early menarche	9 (7.76%)
Smoking	6 (5.04%)
BRCA mutation	5 (4.2%)
Prior history of breast cancer	2 (1.68%)
History of uterine bleeding	3 (2.52%)
Pregnancy	1 (0.84%)
Comorbidities:	
Obesity	6 (5.04%)
Hypertension	7 (5.88%)
Diabetes mellitus	2 (1.68%)
Bronchial asthma	3 (2.52%)
Thyroid disease	2 (1.68%)
PTB	2 (2.68%)
Previous surgeries:	
Excision of breast mass	34 (28.6%)
Incision biopsy	1 (0.84%)
Left oophorectomy for ovarian cyst	1 (0.84%)
Suction curettage for hydatidiform mole	1 (0.84%)
Modified radical mastectomy for contralateral breast cancer	1 (0.84%)
Low section caesarian section	1 (0.84%)
Not indicated	80 (67.2%)
Family history of breast cancer:	
Yes	16 (13.44%)
No	65 (54.62%)
Unknown	38 (31.93%)

Thirty-four patients (28.6%) reported having previous excision of breast masses, which turned out to be mostly fibroadenomas. Five patients each reported a history of incision biopsy of breast mass, left oophorectomy for ovarian cyst, suction curettage of hydatidiform mole, modified radical mastectomy for the contralateral breast, and cesarean section. Thirteen percent had a family history of breast cancer, 54% had no recorded family history for breast cancer, and 32% did not indicate a family history of breast cancer.

Table 2 showed the clinicopathologic characteristics of the disease described in terms of histologic type, pathologic stage, nuclear grade, presence or absence of LVI and presence or absence of estrogen and progesterone receptors (ER/PR) as well as HER2neu overexpression. The most common histologic type was invasive mammary carcinoma in 89%. The remaining histologic types were mucinous carcinoma (5%), unknown histology (3.5%), and metaplastic carcinoma (1.7%). The highest number of breast cancer patients was in the locally-advanced stage (stage IIIB, 29.4%) followed by early breast cancer (stage IIA-IIB, 24.3% and 16.8%, respectively).

The histologic nuclear grade of the breast cancers were found to be as follows: grade 2 (35.3%), grade 3 (23.5%), grade 1 (5%) and 36% of the reports did not indicate the histologic grade. Lymphovascular invasion was found in 23.1% of patients, 29% had no recorded LVI and 48% of the histopathology reports did not indicate the presence or absence of LVI.

The most common hormone receptor in the breast cancer specimens were ER positive/PR positive in 22.7%, ER negative/PR negative in 15% and more than half (57%) of the charts did not report the ER/PR status. The presence of the HER2neu gene was reported in 4.2% of patients, absent in 10% and 85.8% had no HER2neu report.

The different treatment modalities can be seen in Table 3. The most frequent surgical treatment done was a modified radical mastectomy with primary closure in 62%, modified radical mastectomy with split thickness skin grafting in 11.75% and a modified radical mastectomy with primary closure with concomitant bilateral salpingo-oophorectomy in 9.24%. Other operations reported were modified radical mastectomy with breast reconstruction in 3.36%, breast-conserving surgery (BCS) with axillary

Table 2. Clinicopathologic characteristics of breast cancer in young females (N = 119)

Tumor Factors	Frequency (Percentage)
Histologic type	
Invasive ductal carcinoma	102 (86%)
Invasive lobular carcinoma	0 (0%)
Invasive mammary carcinoma	4 (3.5%)
Metaplastic carcinoma	2 (1.7%)
Mucinous carcinoma	6 (5.0%)
Not known	4 (3.5%)
Stage	
0	0
IA	5 (4.2%)
IB	0
IIA	20 (16.8%)
IIB	29 (24.3%)
IIIA	14 (11.8%)
IIIB	35 (29.4%)
IIIC	7 (6.0%)
IV	8 (6.7%)
Nuclear grade	
1	6 (5%)
2	42 (35.3%)
3	28 (23.5%)
Not known	43 (36.2%)
Lymphovascular invasion	
Positive	28 (23.5%)
Negative	34 (28.6%)
Not known	57 (47.9%)
Hormonal status	
ER positive-PR positive	27 (22.7%)
ER positive-PR negative	5 (4.2%)
ER negative-PR positive	1 (0.84%)
ER negative-PR negative	18 (15.12%)
Not known	68 (57.14%)
HER2neu positive	5 (4.2%)
HER2neu negative	12 (10%)
Not known	83 (85.8%)
Pathologic complete response (no residual tumor after neoadjuvant chemotherapy)	12 (10.08%)

lymph node dissection (ALND) in 2.5%, total mastectomy with sentinel lymph node biopsy (SLNB) in 1.68%, one patient had a BCS and SLNB, and another patient had a radical mastectomy with rib resection. Eight percent of the 119 charts did not indicate the type of surgery performed.

Table 3. Treatment patterns in young females with breast cancer (N = 119).

Treatment Factors	Frequency (Percentage)
Surgery	
BCS with SLNB	1 (0.84%)
BCS with ALND	3 (2.52%)
Mastectomy with SLNB	2 (1.68%)
MRM with primary closure	74 (62.18%)
MRM with reconstruction	4 (3.36%)
MRM with BSO	11 (9.24%)
MRM with STSG	14 (11.75%)
Radical mastectomy with rib resection	1 (0.84%)
Not known	9 (7.56%)
Neoadjuvant chemotherapy	46 (38.7%)
Complete pathologic response	not determined
Adjuvant chemotherapy	10 (8.4%)
Palliative chemotherapy	5 (4.2%)
Radiotherapy	14 (11.76%)
Hormonal therapy	9 (7.56%)
Targeted therapy	2 (1.68%)

BCS – breast conservation surgery, SLNB – sentinel lymph node biopsy, MRM - modified radical mastectomy, BSO – bilateral salpingoophorectomy, STSG – split thickness skin graft

Radiation therapy was reported to be given in 11.76% of patients. Neoadjuvant chemotherapy was given in 38.7% of patients, although the pathologic complete response (pCR) from neoadjuvant treatment could not be determined due to the lack of reporting in the charts reviewed. Although pCR may not have been reported, it can still be inferred from the findings in the final histopathology report of "no residual tumor following neoadjuvant therapy", which was found in 12 (10.08%) specimens.

Adjuvant chemotherapy was given in 8.4% of patients. Of the 8 patients who had documented metastatic disease and were eligible for palliative chemotherapy, only 5 patients (62.5%) received palliative chemotherapy. Thirty three patients (27.7%) were considered candidates for hormonal therapy, but only 9 patients (27.3%) received hormonal therapy. Of 5 known patients who were HER2-positive, 2 patients (40%) received targeted therapy. Fifty-seven per cent and 85% of the total patients had unknown ER/PR and HER2neu values, respectively.

Treatment outcomes were determined by using the reported local recurrence and onset of distant metastases and second primary cancers. Local recurrence in the ipsilateral breast was reported in 8.4%, 11.76% had distant metastases in the form of bone, lung, and liver metastases, and 1.68% was documented to have had second primary cancers. Only one patient was reported to have died from a pulmonary complication.

Discussion

Majority of international studies define breast cancer in young women as breast cancer diagnosis on or before 35 or 40 years of age.[3] Approximately 7% of women with breast cancer are diagnosed before 40 years of age, and this disease accounted for more than 40% of all cancers in women in this age group.[3] In a retrospective study by Makanjuola, the prevalence rate was 3.5 per 1000 primary cancer occurring in the symptomatic population studied and that 4 in every 100 primary cancers were diagnosed in women younger than 30 years.[13] This is consistent with the data from the present study, where majority of the patients were diagnosed under 35 years and were locally advanced at presentation. Although relatively rare, breast cancer diagnosed before 35 years of age needs special emphasis as it tends to be diagnosed at a later stage, is more aggressive, has a higher mortality rate and with higher risk of metastatic recurrence. Breast cancer in this age group is mostly being detected at a later stage because of the low index of suspicion from both the patient and the primary care physician.[5]

The peak age of breast cancer in Asians was much younger than that in Western countries such as the United States, as approximately half of Asian breast cancer patients were premenopausal as compared to 15−30% in the West.[8] In the study by Shoemaker, there was an increased incidence of breast cancer in the young population for Asian or Pacific Islander women and white women.[10] Simpson study showed that Filipinos who moved to Canada were diagnosed with breast cancer at a younger age as compared to women from other parts of East Asia or Caucasians.[9] They were also more likely to be diagnosed with a more aggressive form of cancer.[9]

Risk Factors

Non-modifiable risk factors such as family history and genetic mutations do account for increased risks of breast cancer in premenopausal women.[8] In the study, only 4.2% had BRCA mutations, and 13.4% had a family history of breast cancer. To be able to address the highly aggressive nature of breast cancer in young women, performing a risk assessment during clinical encounters and genetic counseling for BRCA1/BRCA2 carriers could identify those who would benefit from preventive strategies such as prophylactic bilateral mastectomies.

A review of modifiable risk factors showed that long-term use of oral contraceptives, low BMI, and high animal fat diet consumption were associated with increased risk of premenopausal breast cancer. In a prospective cohort study from Denmark in women younger than 35 years, there was one additional case of invasive breast cancer for every 50,000 women who used hormonal contraception.[14] Recent OCP use was related to a higher risk of breast cancer in contrast to the risk among females who had no OCP use.[14] With the limited sample gathered from the available charts, the authors could not safely presume that the 9 patients (~8%) documented to have prior OCP use have a higher risk of breast cancer. A bigger sample of patients is necessary to document OCP as a risk factor for the development of breast cancer in young females.

The number of patients found in this retrospective study who had early menarche proved to be consistent with the meta-analysis done by the Collaborative Group in UK which showed that breast cancer risk increases

by a factor of 1.05 (95% CI 1.044–1.057; p<0.0001) for every year younger at menarche.[15] Low BMI and a diet rich in animal fat were not identified as significant risk factors for breast cancer in the present study. Obesity and hypertension were the most common comorbidities present in the study population. Obese women with breast cancer tend to have worse disease-free and overall survival in comparison to non-obese women with breast cancer, despite provision of appropriate local and systemic therapies.[16] They reported more complications in treatment and have a higher risk for local recurrence in contrast to patients with normal BMI.[16]

Pathologic Factors

Breast cancer in young women is associated with adverse pathological factors, which include high grade tumors, hormone receptor negativity, and HER2 gene overexpression. Results of this retrospective study showed that majority of the patients had invasive mammary carcinoma as the most common histologic type (89%) and presented as a locally advanced breast cancer (stage IIIB, 29.4%) followed by early breast cancer (stage IIB, 24.3%) with majority having grade 2 disease.

ER-positive/PR-positive were the most common hormonal status in the present study population which is in direct contrast to the findings seen by the European Institute of Oncology where 185 premenopausal women with invasive breast cancer less than 35 years of age had a higher percentage of ER-negative (p <.001), PR-negative (p <.001), vascular or lymphatic invasion (48.6% υ 37.3%, p = .006), and pathologic grade 3 tumors (p <.0001) as compared with women 35-50 years of age.[3]

HER2 positive and triple-negative breast cancers were more likely to have a poorer prognosis in young women.[5,12,17] Despite insufficient data to corroborate this statement, present study showed that the most number of patients who had breast cancer was in the locally advanced stage. Unfortunately, this study was not able to show the outcomes of patients based on their subtypes due to the lack of ER/PR and HER2neu reporting in the charts. One of the identified limitations of this study included lack or absence of certain data for analysis, such as ER/PR, HER2neu, LVI, and histologic grade. Treatment outcomes were not entirely conclusive for the 119 patients included in the study.

Recurrence

In a retrospective study by Han, young age (<35 years) was found to be an independent risk factor for relapse in operable breast cancer patients.[7] Age under 40 years showed a worse prognosis among lymph node-positive patients (p < 0.001) and was a significant predictor of recurrence in multivariate analysis (p = 0.010).[7] Present study demonstrated a 5-year recurrence rate of 20%, locoregional recurrence in 8.4%, and distant recurrence in 11.8%. It is difficult to infer from the present local study, the likelihood of increased locoregional recurrences and distant spread contributing to poorer outcomes on young women with breast cancer.

Survival

According to Fredholm, et al., the cumulative 5-year relative survival ratio was lowest in women aged 20-34 years.[6] After correction for stage, tumor characteristics, and treatment, age remained as an independent risk factor for breast cancer death in women under 35 years of age.[6] Young women affected by breast cancer have a higher risk of dying as compared to their middle-aged counterparts even if diagnosed early and given intensive treatment. In a retrospective study in India, women less than 40 years of age were found to have more distant metastases from breast cancer.[11] Out of 372 patients, tumor relapse occurred in 131 cases, among which 84 patients died.[11] Of these deaths, 35 patients (26.31%) were less than 40 years of age, while 49 patients (20.50%) were more than 40 years, with an estimated median overall survival of 32 and 41 months, respectively.[11] It was then concluded that the biological behavior of breast cancer in the younger age group was associated with an aggressive nature and had worse clinical outcomes as compared to the older age group.[11] A cohort study by Brandt, et al showed that age under 40 years was positively associated with high breast cancer-specific mortality (BCSM) following invasive breast cancer.[4] This is also consistent with Han's study, which highlighted the greater probability of recurrence and death at all time periods.[7]

Conclusion

Breast cancer in young female patients were mostly locally advanced warranting neoadjuvant chemotherapy and eventual modified radical mastectomies with primary closure. Risk assessment during clinical encounters and counseling for young women with high genetic predisposition should be emphasized.

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