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Estrogen and Progesterone Hormone Receptor Status in Pre-menopausal and Post-menopausal Women with Invasive Ductal Carcinoma in a Private Tertiary Hospital in Cebu City, Philippines: A Retrospective Study

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Objective: This study was conducted to determine the difference of hormone receptor status between pre-menopausal and post-menopausal women diagnosed with invasive ductal carcinoma in the local setting.

Methods: This retrospective descriptive study used data gathered from chart review of premenopausal and postmenopausal female patients diagnosed with invasive ductal carcinoma by tissue biopsy and underwent determination of hormone receptor status (estrogen and progesterone receptor) by immunohistochemical staining (ICA) using biopsy samples taken from June 2016 to December 2019 at Cebu Velez General Hospital, Cebu City. The significance of the difference in the hormone receptor status with menopausal status was analyzed using Fisher's exact test.

Results: Comparing the two groups, 25 (60%) of the pre-menopausal women and 37 (73%) of the post-menopausal women were determined as hormone sensitive, while 17 (40%) pre-menopausal women and 14 (27%) post-menopausal women were hormone resistant. The Fisher's exact test did not detect a statistically significant difference in the hormone receptor status of pre-menopausal and post-menopausal breast cancer patients.

Conclusion: There is no significant difference on the hormonal receptor status among pre-menopausal and post-menopausal women diagnosed with invasive ductal carcinoma. Thus, the need for hormone receptor status determination in these patients should be emphasized to aid in proper diagnosis, prognostication, and treatment planning.

Key words: Hormone receptor status, menopausal status, invasive ductal carcinoma, immunohistochemical staining

Introduction

Extensive studies on the etiology and pathophysiology of breast cancer have led to the development of a multimodal approach to the management of breast cancer, including surgical, chemotherapeutic, endocrine and targeted therapeutic approaches. Estrogen and progesterone receptors have been proven to play a role in breast carcinogenesis and have now become a target in preventing tumor growth and progression.

Estrogen receptor (ER) and progesterone receptor (PR) are intracellular steroid hormone receptors which have received substantial attention and have been proven to play a role in the growth of both normal breast tissue and aberrant breast tumor, expression of which has become the most important and useful predictive factors currently available for breast cancer.[1-4] Determination of ER and PR expression in tumor tissue is considered as a prerequisite for successful hormonal treatment of breast cancer. The degree of response to hormonal therapy is also significantly dependent on the presence of ER and PR in breast tumors: its efficiency is approximately 50% of ER positive tumors and 75% for tumors containing both ER and PR.[2] Thus, hormonal therapies offer many significant advantages to particular subsets of breast cancer patients and measurement of ER and PR levels in patients can select those tumors most likely to benefit from hormonal agents.[3]

It has been found that as many as 65% of breast tumors developing in women aged less than 50 years are ER positive, with figures increasing to 80% in women older than 50 years.[4] In a study by Faheem, et al., which included 1226 female Pakistani patients with breast cancer, significant association ($p < 0.05$) was found between ER and PR positivity, and Her 2 Neu over-expression with menopausal status, as well as tumor size, involvement

of skin, chest wall and lymph nodes and the presence of distant metastases. Both ER and PR positivity were found to be more common in postmenopausal women, with an incidence of 71.4% and 73.7% respectively, as compared to premenopausal women (56.3% and 55.5%, respectively).[5] Masood, in her study, agreed with these findings, noting that the frequency of positivity and the level of ER and PR increase with age, reaching their highest levels in postmenopausal women.[1]

According to the 2015 Philippine Cancer Facts and Estimates by the Philippine Cancer Society, more than 80% of Philippine families cannot afford out-of-pocket expenses needed for basic medical care,[6] In a developing country such as the Philippines, where majority of families are classified under the low-income class, diagnostic tools are not fully accessible by many patients due to financial constraints. With an estimated price of around Php 8,000 to over Php 12,000, hormone receptor status determination costs the same or almost twice over a month's minimum wage salary[7], making patients unable to afford these tests and consequently, may not seek medical attention entirely.

In the local setting, where burden of medical costs is significantly debilitating, many breast cancer patients are unable to comply to recommended diagnostic and treatment plans, hindering effective delivery of optimum patient care. As hormone receptor sensitivity is predictably higher in post-menopausal women, it may be reasonable to initiate hormonal treatment based on the patient's menopausal status despite a lack in definitive diagnostic testing for hormone receptor status, especially for patients who cannot comply with the prescribed diagnostics or treatment modalities, due to financial constraints.

This study aimed to determine if hormone receptor status differs between pre-menopausal and post-menopausal women diagnosed with invasive ductal carcinoma in the local setting. Conclusions of this study may aid in adjusting the treatment strategies for Filipino women diagnosed with breast cancer.

Methods

The study is a retrospective descriptive study using data gathered at Cebu Velez General Hospital, Cebu City, Cebu, Philippines. from June 2016 to December 2019.

Inclusion Criteria

The participants of the study were all patients that were seen at Cebu Velez General Hospital, Cebu City, Cebu, Philippines between June 2016 and December 2019, who fulfilled the following criteria:

1. Female
2. Diagnosed with invasive ductal carcinoma by tissue biopsy (via core needle biopsy or open biopsy)
3. Underwent determination of hormonal receptor status (estrogen and progesterone receptor) by immunohistochemical assay (ICA), using biopsy samples taken from June 2016 to December 2019
4. With a recorded menopausal status (i.e., age of menopause)

Exclusion Criteria

1. Patients with no official results of hormone receptor status determination and biopsy results found on chart review or on laboratory records
2. Patient with no recorded date or age of menopause

The sample population was collected via three pathways:

1. Breast Care Clinic
   In the hospital's Breast Care Clinic, a comprehensive chart review of all patient consults seen from June 2016 to December 2019 was made. Those who fulfilled the inclusion criteria were included in the study. (Figure 1)
2. Medical Records Database
   All charts of admitted patients with a discharge diagnosis of invasive ductal carcinoma were reviewed. Patients with official records of biopsy results and hormone receptor status were included in the study. (Figure 2)

3. Laboratory Database
   All patients with laboratory records of hormone receptor determination and results of invasive ductal carcinoma from breast biopsies were recorded. This list was cross-referenced with existing patient charts in both the Breast Care Clinic and the Medical Records. (Figure 3)

Operational Definitions

Tissue sampling method – technique used to obtain tissue sample used for the determination of hormone receptor status. This may be performed by Core Needle Biopsy (CNB) or Open Biopsy using the following methods: punch biopsy, incisional biopsy, excisional biopsy, biopsy from mastectomy specimen

Post-menopausal – patients with self-reported age of menopause as reflected in chart records

Pre-menopausal – patients with no recorded age of menopause and with a recent menstrual cycle in reference to date of chart entry

Hormone Receptor Sensitivity – interpretation of positive for estrogen receptors on immunohistochemical assay

Hormone Receptor Resistance – interpretation of negative for estrogen receptors on immunohistochemical assay

Estrogen and Progesterone Receptor Positivity – nuclear staining on 1% or more of tumor cells, based on ASCO/CAP guidelines[8]

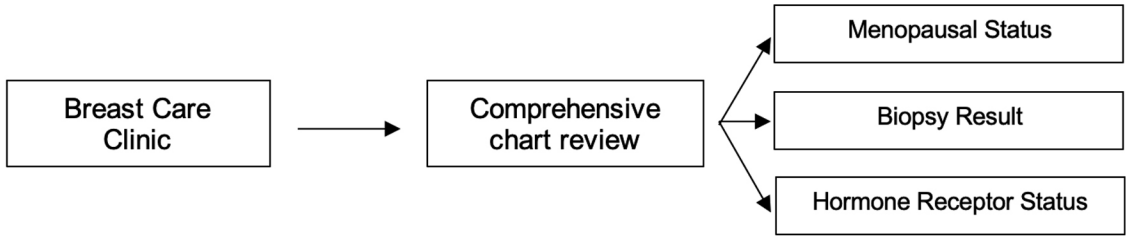

Figure 1. Patient inclusion pathway from the Breast Care Clinic.

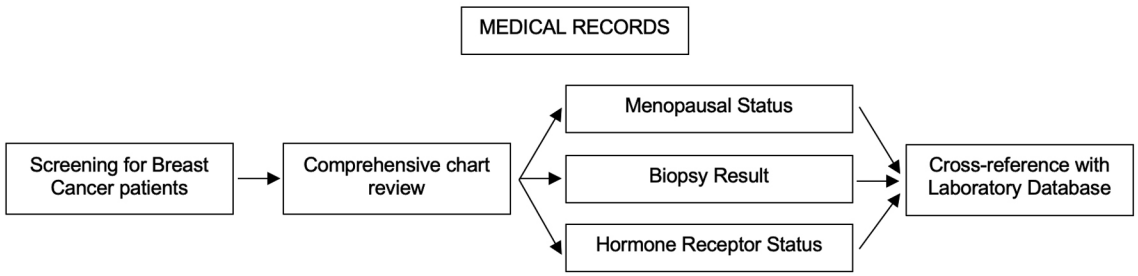

Figure 2. Patient inclusion pathway from the Medical Records Database.

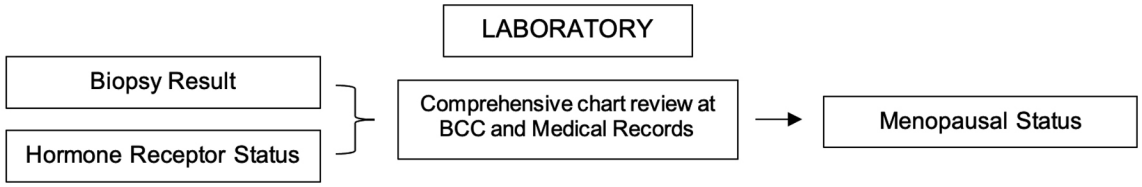

Figure 3. Patient inclusion pathway from the Laboratory Database.

Estrogen and Progesterone Receptor Negativity – nuclear staining in < 1% of tumor cells, based on ASCO/CAP guidelines[8]

Data Analysis

Data gathered from charts reviewed included age of patient, self-reported menopausal status (or age of menopause), tissue biopsy result and hormone receptor status. The data for each patient was tabulated in Excel (Version 16.39, Microsoft).

The hormonal receptor status and menopausal status were cross-tabulated and analyzed using Fisher's exact test in Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.)

Ethical Considerations

Depersonalization of data was observed in the conduct of this study by assignment of numerical codes to each patient. Only the number codes, age, menopausal status, tissue sampling method, and hormone receptor status were recorded in the study. After conclusion of the research, data was stored and secured electronically at the Breast Care Clinic of CVGH. An approval from the CIM-CVGH Institutional Review Board was obtained.

Results

A total of ninety-three (93) females diagnosed with invasive ductal carcinoma using a variety of tissue sampling methods were included in the study. Of the 93 females, 42 (45%) were pre-menopausal women and 51 (55%) were post-menopausal women. The mean age of the pre-menopausal group was 42 years old while the mean age of the post-menopausal group was 59 years old. A majority of the women were both ER and PR positive while about a third were ER and PR negative. Among the pre-menopausal women, 29 underwent core needle biopsy while 13 had open biopsy. Among the post-menopausal women, 29 underwent core needle biopsy, while 22 underwent open biopsy. (Table 1)

Table 2 summarizes the menopausal status against hormonal status of this cohort of breast cancer patients. The Fisher's exact test did not show any statistical difference in the hormonal status between pre-menopausal and post-menopausal patients (p=0.102).

The tissue sampling method (Core Needle vs Open Biopsy) was also cross-tabulated against hormone receptor status (Table 3). The Fisher's exact test likewise did not detect any statistical difference between hormonal status and the techniques of biopsy (p=0.671).

Discussion

Estrogen receptor (ER) and progesterone receptor (PR) are the most widely studied markers in breast tissue. Compared with hormone receptor negative tumors, hormone receptor–positive breast cancers exhibit stronger clinical responses to hormonal treatment and incidence rates that rise continuously with aging after menopause. However, many of the studies that have compared risk factors for receptor-positive and receptor-negative tumors have led to debate.[9]

Table 1. Patient data summary.

	Data	
Total	93	
Mean Age (sd)	51.86 (sd=11.88)	
Menopausal Status		
Pre-menopausal	42	
Post-menopausal	51	
Biopsy Technique		
Core Needle Biopsy (CNB)	58	
Open Biopsy	35	
Excision Biopsy		7
Incision Biopsy		4
Lumpectomy		1
Mastectomy		23
Hormone Receptor Status		
ER-PR-	51	
ER+PR-	11	
ER-PR+	1	
ER+PR+	30	

Table 2. Cross-table of menopausal status vs hormone receptor status. (ER: estrogen receptor, PR: progesterone receptor).

	ER-PR-	ER+PR-	ER-PR+	ER+PR+	Total
Pre-menopausal	16	7	1	18	42
Post-menopausal	14	4	0	33	51
Total	30	11	1	51	93

Table 3. Cross-table of tissue sampling methods vs hormone receptor status. (ER: estrogen receptor, PR: progesterone receptor, CNB: core needle biopsy, Open Biopsy includes excision, incision, lumpectomy and mastectomy)

	ER-PR-	ER+PR-	ER-PR+	ER+PR+	Total
CNB	27	10	1	20	58
Open Biopsy	24	1	0	10	35
Total	51	11	1	30	93

Several studies have also been done in an attempt establish a specific correlation between hormone receptor status and menopausal status on females diagnosed with breast cancer among different races, with varying results.

This study found that the majority of the pre-menopausal (62%) and post-menopausal (73%) patients included the study demonstrated hormone receptor-positive tumors, with no significant difference between the two groups. This result is in conjunction with the findings of other studies done on various racial groups.[10-14] However, some studies contradict this finding, suggesting that hormone receptor sensitivity is significantly higher in the post-menopausal patients.[1,4,5]

In the local setting, Siguan, et al. noted that of the 45 breast cancer patients (36.6% of 123 patients in their study) subjected to estrogen receptor determination, 72% of the pre-menopausal patients and 78% of the post-menopausal patients were hormone receptor negative.[15] This observation is similar to the analysis by Dey, et al. among breast cancer patients in South India.[16]

In terms of the method of hormone receptor determination, a study done by Stierer, et al. demonstrated that ER-immunohistochemical assay (ICA) yielded a significant positive correlation with a trend towards higher positivity in post-menopausal women, but no significant association was found between PR-ICA and menopausal status.[17] Present study finding is inconsistent with this observation, as no difference was found between the two patient groups with ICA employed as the sole method of hormone receptor determination.

Differences in tissue sampling methods and variables in specimen processing have been shown to have an effect in hormone receptor status outcome. A local case series done by Uy, et al., at the Philippine General Hospital observed that core needle biopsy (CNB) specimens of pre-menopausal patients exhibited significantly higher rates of hormone receptor positivity compared to that of mastectomy specimens of the same patients, identifying difficulties in standardizing mastectomy specimen processing and delayed specimen fixation, among others, as factors influencing such finding.[18] An earlier local study done by the same group found that standardization of tissue specimen fixation procedures resulted in a higher proportion of hormone receptor positive tumors from mastectomy specimens, with a concurrent over-all increase in the frequency of hormone receptor positive cases[19], leading to the formulation of the center's protocol for standardized testing of estrogen receptor/progesterone receptor assay.[20]

Nofech-Mozes, et al., in their systematic review of hormone receptor testing, also found that core biopsies had higher hormone status positive rates, with high

median ER (95%) and PR (88.5%) concordance values, which were attributed to better fixation as compared to surgical specminens.[21] A meta-analysis by Chen, et al., examined the accuracy of hormone receptor status detection between core needle and open excision biopsy (OEB) in breast cancer patients and concluded that CNB had higher diagnostic accuracy in evaluating hormone receptor status compared to OEB.[22] Studies utilizing fine-needle aspiration cytology (FNAC) specimens subjected to alcohol-based fixation have also demonstrated excellent hormone receptor ICA concordance rates compared to the standard formalin-fixed paraffin-embedded (FFPE) specimen samples.[23,24] Contrary to above-mentioned data, no difference was found between hormone receptor status and method of biopsy in this study.

The variation in estrogen receptor expression in breast carcinomas between premenopausal and postmenopausal women may reflect different levels of circulating estrogens in both groups.[12] Since postmenopausal women have lower circulating estrogen levels, the higher estrogen receptor levels observed in these patients have been suggested to be due to an increase in unoccupied cytosolic receptor, rather than an increase in total hormone receptor.[13]

The result of this study may be attributed to the heterogeneity of the study population's patient and tumor characteristics. The present study was only limited to utilizing the patients' self-reported menopausal status and hormone receptor status determined using ICA. Several factors, such as tumor size, histopathologic type, nuclear grade, stage and nodal status on diagnosis, as well as patient's age on diagnosis, parity, and age at first childbirth, have variable associations with hormone receptor status.[5,9,10,12] Thus, inclusion of the aforementioned factors in future studies may lead to a more precise conclusion.

In its latest iteration, the National Comprehensive Cancer Network (NCCN) Guideline on Breast Cancer recommends the collection of biomarkers such as hormone receptor status (ER and PR assay) for all samples of invasive breast cancer.[25] In consonance, the latest evidence-based clinical practice guideline on the diagnosis and management of breast cancer by the Philippine College of Surgeons recommends that "hormone receptor status should be the main consideration in selecting the type of adjuvant treatment", in conjunction with the recommendation that "patients with invasive early breast cancer that are estrogen or progesterone-positive should be considered for adjuvant endocrine therapy regardless of patient age, menopausal status, …" However, the College also recommends that estrogen receptor assay may be determined first, and if the result is negative, progesterone receptor assay be done then, as sequential assays may be more practical and cost-effective.[26] This recommendation is prudent and encourages patients to undergo testing for at least one receptor assay, rather than none at all.

Conclusion

Menopausal status is not reliably associated with hormone receptor status in patients diagnosed with invasive ductal carcinoma. The need for hormone receptor status determination should be emphasized to these patients, as this is essential for the proper management and prognostication of the disease.

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