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Research Article

The Correlation of Magee Equations and Oncotype DX Recurrence Score in Mexican Patients Diagnosed with Early Breast Cancer

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Abstract

Purpose: Magee equations (MEs) can adequately predict Oncotype Dx (ODX) recurrence scores among specific patients with early stage breast cancer (EBC). Nonetheless, MEs have never been previously assessed in Hispanic patients in Latin America. The objective of this study was to evaluate the correlation between MEs and ODX among a cohort of Mexican patients with EBC. **Methods**: We performed a single-center retrospective cohort among patients with invasive EBC treated between January 2008 and December 2022. Patients with 0-3 lymph nodes, positive hormone receptors, and negative HER2 who had an ODX RS on file were included. Data was collected from medical files to calculate MEs and correlate with ODX score. **Results:** 98 patients fulfilled the criteria and were included in the analysis. Mean age was 57.8 years (S.D. 11.13); most patients had clinical stage IA (43.9%) and IIA (47.9%) disease. The median ODX RS was 15, and most patients were catalogued as low and intermediate risk (N=85; 86.7%). Meanwhile, mean MEs score was 16.6 for all participants. Concordance using the MES average was 79.6%, sensitivity was 93.3% and specificity 34.8%. Interestingly, concordance increased to 86.7% when using only the result from the ME3 equation, with 95.0% sensitivity and 50% specificity. **Conclusion:** In Mexican patients with early EBC, the results from MEs correlate with ODX score, highlighting these as a potential tool to discriminate between cases which require genetic profiling and those which can forego testing. This data warrants validation in prospective studies amongst patients with BC in Latin America.

Keywords: Hispanics; Magee equations; recurrence score; oncotype; early invasive breast cancer.

Introduction

Breast cancer (BC) continues to represent the most common neoplasm diagnosed in women, and currently accounts for 10% of all cancer diagnoses made yearly [1]. Early-stage breast cancer (EBC) is defined as localized disease which has not spread beyond the breast or the axillary lymph nodes (clinical stages I-IIB [2] and is the most frequently diagnosed form of BC. Treatment for invasive EBC requires a multimodal approach, and includes local therapy with surgery +/- radiation therapy, as well as systemic therapy which is offered to the majority of patients in addition to local control [3].

Determining the correct sequence and type of therapy in this clinical context remains a challenge, and several prognostic and predictive markers have been developed to aid in the correct stratification of patients [4]. Among these, the multigene panel Oncotype Dx (ODX) is one of the most widely used strategies to assess patient prognosis, but also to aid in making decisions regarding chemotherapy among patients with hormone receptor (HR) positive/HER2 negative EBC subtypes. The 21-gene assay is designed to estimate the risk of distant recurrence by providing a score (RS) which was initially used to stratify patients as low risk (RS 0 - <18), intermediate risk (RS 18 - 30) and high risk (RS ≥ 31), with an average recurrence rate of 7%, 14% and 30% respectively.

In 2018 the Trial Assigning Individualized Options for Treatment (TAILORx) prospectively evaluated the benefits of chemoendocrine therapy for patients with a mid-range recurrence score, showing outcomes were non-inferior compared with patients receiving endocrine therapy alone. The trial redefined the risk categories, stratifying as low, intermediate and high risk for recurrence patients with scores ranging from 0-10, 11-25 and 26 or higher, respectively [5]. Other prospective studies have provided further evidence to support the use of ODX in the decision-making process. Nonetheless, one important limitation of the ODX, and other similar gene assays, is the associated cost, rendering limited access for populations living in low- and middle-income countries. In Mexico, costs for the ODX assay are estimated at MXN 56,739.76 (considering $3,416 USD and the current change rate from USD to MXN). If we take into account that in Mexico the minimum wage is 248.93 MXN, this will mean that a person might need to work 228 days in order to afford one ODX assay, which despite having evidence of cost-effectiveness [6] will remain inaccessible to a considerable proportion of the population affected by BC.

The Magee equations (MEs), which emerged after studies showing a correlation between ODX RS and routinely reported pathology parameters, represent a set of multivariable models that can estimate the RS [3]. The 3 equations take into account different combinations which can include the Nottingham score, tumor size, and some semiquantitative scores for estrogen receptors (ER), progesterone receptors (PR), HER2 neu and Ki67. The result provides a reasonable estimate of actual RS, and can therefore be used to identify cases which will not require ODX testing, with the benefit of lowering costs and facilitating decision-making by clinicians. The Magee Decision Algorithm (MDA) has been established as a validated tool which can be used to discriminate between cases that require molecular testing and those which do not, and different studies have established their utility in patient cohorts with classification accuracy of 95.1% [7].

The objective of this study was to evaluate the correlation between the results obtained from the ODX RS and the MEs among Mexican women diagnosed with EBC. We hypothesized that patients with an ME score < 18 and mitosis score of 1 would be catalogued as low risk both by ME and ODX RS, and that women with an ME score of > 31 would be grouped as high risk by both assessments.

Materials and Methods

Study design

This study was designed as a retrospective, descriptive analytical cohort. Patients who were diagnosed with invasive early-stage breast cancer, with 0-3 positive lymph nodes, with positive HR and negative HER2 who were treated at the American British Cowdray Medical Center in Mexico City between January 2008 and December 2022 were eligible to participate in the study. Additional inclusion criteria were patients aged 18 years or older, with a full pathology report, including Nottingham score, cuantitative expression of hormone receptors, HER2 status and Ki 67. Patients with incomplete pathology reports or with duplicate records were excluded from the study. This protocol was reviewed and approved by the Research and Ethics Committee at the American British Cowdray Medical Center in Mexico City (CMABC-24-19).

Data acquisition

A board-certified oncologist reviewed patient records retrieved from the study period and extracted all data to construct an anonymized database which included all the information. All cases with available ODX RS were identified from the pathology section of the medical electronic records. Variables included baseline demographic characteristics, tumor grading information (Nottingham score), tumor size, semiquantitative immunohistochemical results for ER, PR, HER2 and Ki-67, ODX RS, and risk categorization as per ODX RS.

The pathology department at the ABC Medical Center reports the information from H&E-stained slides and immunohistochemistry based on analysis by a board-certified breast pathologist. ER, PR, HER-2 and Ki-67 are manually interpreted from samples prepared using approved kits and clones. The Nottingham score is reported as calculated following the Nottingham Combined histologic grade from the modification of the Bloom-Richardson system, according to the National Comprehensive Cancer Network Guidelines version 2.2024 [8]. Cases which lacked complete information on either NS, ER, PR, HER-2 or tumor size were excluded from the study. The database was encrypted with a password and stored in one computer.

Risk categories as assessed by the ODX RS using the cutoff points established in the TAILORX study were established for each patient (low 0-10; intermediate 11-25; high >25) (5). The MEs were used as published by Klein et al. (Magee equation 1: Recurrence score=15.31385+Nottingham score*1.4055+ERIHC*(−0.01924)+PRIHC*(−0.02925)+(0 for HER2 negative, 0.77681 for equivocal, 11.58134 for HER2 positive)+tumor size*0.78677+Ki-67 index*0.13269; Magee equation 2: Recurrence score=18.8042+Nottingham score*2.34123+ERIHC*(−0.03749)+PRIHC*(−0.03065)+(0 for HER2 negative, 1.82921 for equivocal, 11.51378 for HER2 positive)+tumor size*0.04267; Magee equation 3: Recurrence score=24.30812+ERIHC*(−0.02177)+PRIHC*(−0.02884)+(0 for HER2 negative, 1.46495 for equivocal, 12.75525 for HER2 positive)+Ki-67*0.18649 [9].

This study was conducted in compliance with the Declaration of Helsinki and with the International Conference on Harmonization

on Good Clinical Practice Guidelines. Approval was obtained for the retrospective collection of clinical, pathological and molecular data.

Statistical Analysis

A descriptive exploratory analysis was initially performed to determine data distribution for each one of the variables and perform internal quality controls. Variables were identified as having a normal or non-normal distribution using central and dispersion tendency measures, and assessed using parametric or non-parametric tests, accordingly. The clinical and pathologic data were then summarized using percentages and descriptive statistics (mean, S.D., frequencies).

Risk categories used by the ODX RS were applied to the modified Magee RS, and then these were compared with their paired ODX RS for concordance. Accuracy was compared between all combinations and the highest selected for further analysis. Sensitivity was defined as the number of individuals correctly classified as having a low/intermediate ODX RS risk category and who received a low risk RS when using the MEs RS, over the total number of patients assessed as having a low risk score using the MEs. Specificity was defined as the number of individuals who were classified as low/intermediate risk using the ODX RS, but were classified as having an intermediate RS using the MEs, divided by the total number of patients assessed as having an intermediate RS as per the MEs. Predictive positive value (PPV) was defined as the number of individuals with a low/intermediate ODX RS and a low RS as per MEs, divided by the total number of individuals with a low/intermediate ODX RS. Negative predictive value (NPV) was defined as individuals with a high ODX RS who were also classified as intermediate risk using the MEs, divided by the total number of individuals classified as having a high ODX RS. Correlations were evaluated using Pearson´s correlation coefficient. Finally, a $\chi 2$ test of independence was performed to assess statistical significance. Statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using Microsoft® Excel® for Microsoft 365 MSO (version 2403 compilation 16.0.17425.20124).

Results

From January 2008 to December 2022 a total of 101 patients diagnosed with HR(+)/HER2 (-) EBC were identified and assessed for eligibility. Among these, N=98 patients had the complete pathological data available on their electronic records and were therefore included in the analysis. Mean age among the study population was 57.8 years (S.D. 11.13). Clinical stage was IA in 43.9% (N=43), IIA in 47.9% (N=47) and IIB in 8.2% (N=8). Node negative patients were in 64.3% (N=63) and the most frequent tumor subtype was ductal carcinoma in 80.6% of cases (N=79). The median ODX RS was 15, and 86.7% of all included patients were catalogued as low/intermediate risk as per oncotype RS. Mean Magee score was 16.6 (S.D. 4.7). A summary of clinicopathologic characteristics is presented in Table 1.

Characteristic	**N=98 (%)**
Age, mean, S.D.	57.8, 11.2
Female sex, %	97 (99%)
Clinical stage	
IA	43 (43.9%)
IIA	47 (47.9%)
IIB	8 (8.2%)
Surgery	
Conservative	34 (34.7%)
Total	24 (24.5%)
NA	40 (40.8%)
Lymph nodes	
0	64 (65.3%)
1	28 (28.6%)
2	4 (4.1%)
3	2 (2.0%)
Tumor subtype	
Ductal	79 (80.6%)
Lobular	16 (16.3%)
Other	3 (3.1%)
Ki67	
<=20%	75 (76.5%)
>20%	23 (23.5%)
ODX RS, median	15
Oncotype risk	
Low	27 (27.6%)
Intermediate	58 (59.2%)
High	13 (13.3%)
score, mean (S.D.)	
AVG Magee	17.2 (4.7)
M1 Magee	17.2 (4.9)
M2 Magee	18.0 (5.3)
M3 Magee	16.4 (4.6)

Table 1: Baseline patient demographics and disease characteristics.

When considering the average score for the MEs 1-3, the overall concordance was 79.6% between the ME RS and the ODX RS.

Sensitivity was 93.3%, specificity was 34.4%, positive predictive value was 82.4% and negative predictive value was 61.5%. When assessing the ME3 RS concordance with ODX RS increased to 86.7%, sensitivity was 95.0%, and specificity was 50%. Positive predictive value increased to 89.4% and negative predictive value to 69.2%. There was a significant association between both the ODX RS and the average MEs RS (p=0.0005) and the ODX RS and the ME3 RS (p=0.00000036).

The correlation between Nottingham score (0.219), tumor size (0.067), ER (-0.119), PR (-0.438), Ki-67 (0.346), mitosis score (0.210) is summarized in Table 2. The correlation coefficient for the ME3 and the ODX RS was 0.501 (Figure 1).

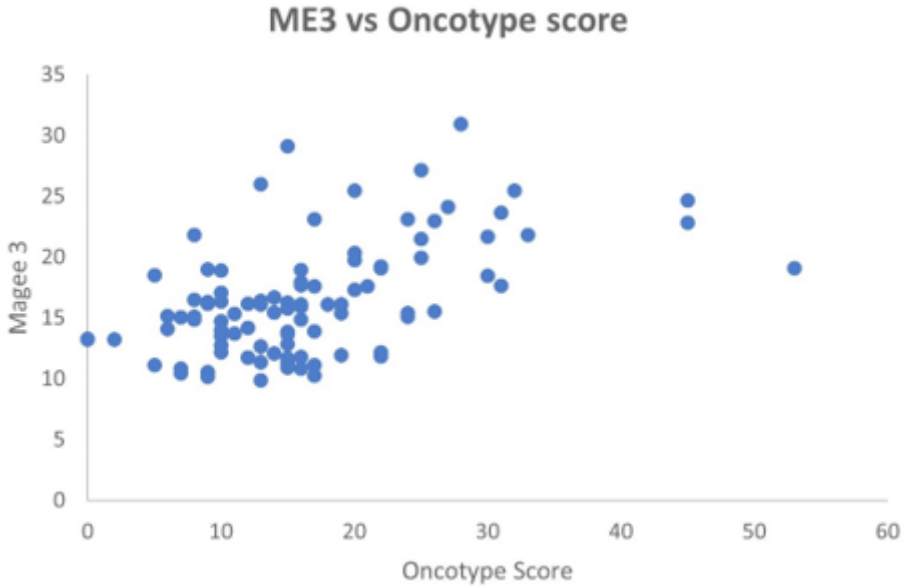

Figure 1: ME3 vs Oncotype score.

	Oncotype score
Nottingham Score	0,219
Tumor size	0,067
Estrogen receptors	- 0,119
Progesterone receptors	- 0,438
Ki67	0,346
Mitosis	0,210
ME1	0,486
ME2	0,381
ME3	0,501
Used ME	0,501
Max Me	0,448

Table 2: Correlation score for selected variables and ODX RS.

We performed a subgroup analysis in which patients were stratified according to age. Concordance was higher when considering women aged <50 years (92%) compared with women aged ≥50 years (85%). Both groups showed a statistically significant association between ODX RS and MEs (p=0.0057 and p=0.000015, respectively). When considering patients by clinical stage, concordance was 81%, 89% and 100% among women with clinical disease stage IA, IIA and IIB, respectively. All subgroup analyses showed statistically significant associations between ODX RS and MEs.

Discussion

The global burden of breast cancer in terms of mortality has steadily increased for the last decade. There are several potential explanations for these observations, including an aging population as well as exposure to risk factors associated with western lifestyles. Globally, BC is the most frequently diagnosed neoplasm in women and accounts for 1 in every 4 new cancer cases and 1 in every 6 deaths [10], highlighting the need to implement novel strategies which decrease mortality among this patient subgroup.

Guidelines for standard of care treatment among patients with BC have changed considerably over the past 2 decades. Particularly, the advent of molecular testing and its widespread implementation in the last 10 years has changed the landscape of therapeutic decisions among women with HR+/HER2- BC. Early in 2000, the conventional course of action included offering chemotherapy to all women diagnosed with BC who had lymph node metastases or with primary tumors larger than 1 cm. Although the intention of this intervention was to provide a potential benefit to all patients, it also induced toxicity and incurred in associated costs without evidence of a significant benefit for all treated patients. Molecular tests, including ODX RS, have aided in the decision-making process by generating accurate risk stratification strategies which can then be used to make informed decisions as to which patients are likely to benefit from receiving chemotherapy based on the risk of recurrence. Despite the global acceptance of these molecular strategies, their associated costs are still prohibitory in some world regions. This is particularly alarming when considering that mortality rates due to BC have been decreasing in many high human developmental index (HDI) countries, but have consistently increased among low HDI countries [10]. As a result, the populations living in these areas face the challenges of higher mortality and lower availability of typing tools to aid in selecting appropriate treatment.

The use of already available standard histopathologic variables to provide comparable risk stratification without incurring in expenses from molecular tools has been achieved through the advent of the MEs. The readily and freely available MEs can calculate a recurrence score with data which is routinely generated in each standard pathology report. Using this information, MEs can estimate a RS in BC cases which significantly correlates to the RS obtained from ODX analysis. Furthermore, the use of MEs has derived in the creation of the Magee Decision Algorithm, which aims to safely determine which patients will require ODX testing and which patients are unlikely to reap benefits from molecular testing [7].

To the best of our knowledge, this study represents the first cohort to assess the use of MEs amongst an exclusively Hispanic population of women with EBC. Several publications have emerged since 2013 which assess the correlation between MEs and ODX RS, and these have been summarized in a previous study by Glasgow et al. in 2020 [11]. In the initial study by Klein et al. a total of 817 cases were used to create the original ME and three other MEs which gave concordance values ranging from 54.3%-54.4%. Importantly, this model was further validated in this stud using 255 cases. In a follow up study by Turner et al. 283 BC cases were used in order to correlate MEs and ODX RS using an average modified ME equation set. In this study, concordance rose to 70% when using this modification, reaching a Pearson´s correlation coefficient of 0.6644 [12]. It is important to note that both of these studies used the traditional cutoff values which were applicable in the pre-TAILORx era. More recently, in 2019, Turner et al. published an additional study in order to validate the use of their model using the Rochester Modified Magee algorithm (RoMMa). In this study, Pearson´s correlation coefficient rose to 0.6996 when using this modified algorithm, and authors concluded that the use of such strategies could represent health system savings for up to $100,000,000 USD [13]. Other studies published have reached concordance values for MEs and ODX RS ranging from 63.3% [11], 57.6% [14], and 66.4% [15]. In our study, we report concordance values which range from 79.6% when using the average of ME1-3, 84.5% when using the average of ME1 and ME3, and reaching 86.7% when using ME3 alone to perform risk stratification. As is, this data showcases that the use of MEs among Hispanic women, namely patients from Mexico diagnosed with BC, is not only feasible but could potentially outperform their use in other populations. It is important to underscore that ME3 is an equation that includes only semiquantitative data for ER, PR, HER2 and Ki67, and thus it is also possible that these results are partly due to the expertise of the pathology team and the single-center nature of the current study. Nonetheless, our results showcase that 8 out of 10 patients within this subpopulation of BC can be adequately catalogued using MEs, thus generating potential healthcare savings comparable or higher to those reported in other studies.

It is important to note that this study has several strengths, including a single-center design which aids in providing a homogeneous population in order to obtain comparable data, also the availability of pathology data from a single pathology center which also aids in narrowing inter-institutional protocols and equipment which could provide varying results in important variables which are reported in a semiquantitative manner. Nonetheless, the information should also be interpreted in light of the limitations of this study, which include a retrospective design and the consequent possibility of missing values for some important variables during the database construction. The results do however highlight the potential usefulness of the MEs among Hispanic populations and can aid in generating hypothesis which should be tested in future studies

with robust prospective designs and adequate follow-up to assess patient outcomes.

Conclusion

In Mexican patients with invasive early stage, HR+/HER2- EBC, the results from MEs correlate with ODX score, highlighting these as a potential tool which can help discriminate between cases which require genetic profiling and those which can forego testing. This data warrants further prospective studies to strengthen he conclusions amongst patients with BC in Latin America.

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by CN. The first draft of the manuscript was written by CN and AM commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Antonio Maffuz-Aziz: conceptualization, formal analysis, investigation, methodology, resources, supervision, validation, visualization, writing, review and editing.

Jorge E Monges-Jones: conceptualization, formal analysis, investigation, methodology, resources.

Gabriela Estefanía Aguilar Guerrero: conceptualization, data curation, investigation, methodology, software, validation, writing the original draft.

Cecilia Nehmad-Misri: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, resources, supervision, validation, visualization, writing the original draft, writing, review and editing.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to general policy regarding patient data but are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of ABC medical center (CMABC-24-19).

Consent to participate

Due to the retrospective nature and minimal risk of this study the Ethics Committee of ABC Medical Center waived the requirement to obtain any informed consent.

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