Influence of health insurance status on inclusion of HER-2/neu testing in the diagnostic workup of breast cancer patients

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Abstract

Objectives. To assess the prevalence of HER-2/neu testing in a community-based health care system shortly after the approval of several laboratory kits for HER-2/neu testing for diagnostic purposes by the US Food and Drug Administration and to discern the best discriminating variables for inclusion of the test in the diagnostic workup of breast cancer patients.

Design. A retrospective cross-sectional study was designed to analyze data for the period beginning 1 January 1999 and ending 31 December 2000.

Setting. Henry Ford Health System, the largest health care system in southeastern Michigan, is a comprehensive, self-contained system.

Study participants. Four hundred and fifty-one women diagnosed with primary invasive breast cancers were consecutively sampled from the tumor registry of the Henry Ford Health System.

Results. The proportion of women tested for HER-2/neu increased by 2-fold during year 2 of the observation. Absence of estrogen receptors (OR = 1.96, 95% CI 1.15–3.21), physicians with specialty in surgery (OR = 6.21, 95% CI 2.88–13.33, P = 0.0001), and having a capitated insurance (OR = 1.59, 95% CI 1.06–2.44, P = 0.027) were associated with HER-2/neu testing.

Conclusion. Absence of estrogen receptors was the only pathological characteristic associated with HER-2/neu testing. The effect of specialization in surgery on the increased likelihood of HER-2/neu testing can be explained mostly by the 'patient volume effect'. The observed disparity in the delivery of innovative diagnostic approaches to cancer patients was influenced by the type of health insurance. Implementation of institutional policies can improve in providing universal quality of care for all patients regardless of their health insurance.

Keywords: biomarker, breast cancer, health insurance, HER-2/neu

Introduction

Recent advances in biotechnology have made the concept of the formulation of molecular targeted adjuvant therapy a reality [1]. The human epidermal growth factor receptor-2 (HER-2/neu) is a well-characterized biomarker in the biology of breast cancer which has had immediate impact on clinical medicine. The HER-2/neu biomarker is an independent prognostic marker and is associated with a relative resistance to anthracycline-based chemotherapy and possibly tamoxifen therapy [2–6]. HER-2/neu testing among women diagnosed with stage IV breast cancer identifies potential candidates for Herceptin adjuvant antibody treatment [6].

In 1998, the US Food and Drug Administration approved several laboratory kits for evaluation of the HER-2/neu biomarker in clinical settings [7–9]. Two years later, the College of American Pathologists and the American Society of Clinical Oncology issued a series of recommendations regarding the significance of HER-2/neu testing in the diagnostic workup of breast cancer patients [10,11]. Despite extensive data indicating the value of HER-2/neu testing in clinical settings, the availability of approved laboratory kits, and recommendations from the two organizations, it was not until 2001 that several large health care facilities took initiatives to implement institutional policies to incorporate testing for the HER-2/neu biomarker in the diagnostic workup of breast cancer patients.

To our knowledge, no systematic investigation has been conducted to assess the variables that discriminate the inclusion of a novel biomarker with diagnostic value in the clinical workup of breast cancer patients. We undertook a retrospective
cross-sectional study to evaluate the proportion of women who were tested for HER-2/neu and to determine the variables that were associated with HER-2/neu testing of a woman at the initial clinical presentation of her breast cancer.

Methods

Study population

The study participants were patients at the Henry Ford Health System, the largest health care provider in southeastern Michigan. About 60% of the patient population at the Henry Ford Health System are insured through the Health Alliance Plan, a large, not-for-profit, mixed-model health maintenance organization. The remaining 40% have coverage through the traditional fee-for-service insurance, Medicare, or Medicaid.

We identified women diagnosed with primary breast cancers from the tumor registry of the Henry Ford Health System. The other eligibility criteria were: (i) date of diagnosis of the first primary breast cancer between 1 January 1999 and 31 December 2000; (ii) patients received treatment and post-treatment follow-up at either the main hospital campus of the Henry Ford Health System or one of its satellite hospitals or clinics; and (iii) pathological diagnosis of stage I, II, III, or IV. Women diagnosed with stage 0 breast cancer were excluded from the study since HER-2/neu testing does not influence clinical decisions about their course of treatment. Women diagnosed with recurrent breast cancer were excluded to reduce the potential confounding effect of disease severity.

Data collection

When a patient is first seen at any of the Henry Ford Health System facilities for any reason, he/she is assigned a permanent and unique lifetime medical record number and entered into the Master Patient Index, which serves as the central data repository for each patient. The Master Patient Index database is useful in obtaining demographic and health insurance data. The electronic medical records contain notes from physicians, radiology and pathology records, and clinical laboratory results.

The data collection of this project was exempt from requiring written informed consent, stipulated by the US Department of Health and Human Services regulation 45 CFR 46, Nos. 3 and 5. Data were collected from existing databases and no study participant was contacted. The Institutional Review Board at Henry Ford Health System approved this study (IRB # 1369).

We abstracted data on (i) patient characteristics, (ii) tumor characteristics, and (iii) results of HER-2/neu testing, date of request and specialty of physician who had submitted the request. Insurance plans were then categorized into fee-for-service, capitated insurance, Medicare, or Medicaid. If patients with Medicare Part A had supplemental policies, then their insurance was classified as fee-for-service or capitated, depending on its type. Patients with fee-for-service insurance were self-referred, whereas patients with capitated insurance were referred by a primary care physician to a surgeon or medical oncologist.

Statistical methods

We used descriptive statistics to summarize the characteristics of the study population. The variable ‘age at the time of diagnosis’ was categorized into six age groups: <40, 40–49, 50–59, 60–69, 70–79, and 80 years and older. We classified breast cancers based on their expression of the estrogen receptor status into two phenotypes: positive and negative. Cancer stage was classified as I–IV and nuclear grades as 1–3. Axillary nodal involvement was classified into four groups: (i) lymph nodes were not evaluated, (ii) evaluated but negative for metastasis, (iii) only sentinel node positive for metastasis, and (iv) sentinel and axillary lymph nodes positive for metastasis. Finally, we dichotomized the study participants into two groups ‘evaluated for HER-2/neu’ and ‘not evaluated for HER-2/neu’.

We applied multivariate logistic regression to determine the variables associated with inclusion of HER-2/neu testing in the diagnostic workup of patients. In developing the best fitted model, we first estimated the individual effect of each variable on HER-2/neu testing. Correlations between different variables were estimated and the multi-collinearity effect was prevented by including in the model only variables with coefficient values of ≤0.70 [12]. Variables with a P-value of <0.10 from the univariate analysis were considered candidate variables. Interactions between variables were also tested at P ≤ 0.1. The initial model was built using the forward selection approach. The final model contained only variables that were significant at P ≤ 0.05 and interaction terms that remained significant at P ≤ 0.10. We adjusted the final model for the year of diagnosis to account for time effects. Finally, we used the combination of logistic regression and the receiver operating characteristic (ROC) curve to detect the best discriminative factors for inclusion of HER-2/neu testing at the time of diagnosis [13,14]. The curve is a graphic display of predictive accuracy of the logistic model with the area under the curve equal to the C-index. A C-index of 0.8 or greater suggests that the model has some utility in predicting outcomes in clinical settings [15]. The Statistical Analysis System (SAS, Cary, NC, USA), version 8.2 was used to conduct the statistical analyses.

Results

We identified a total of 482 women from the tumor registry at Henry Ford Health System. After reviewing medical records, we excluded 31 women from the study because: (i) of electronic restriction on accessing medical records (n = 16, 3%), (ii) of recurrent cancers (n = 2, 0.4%), (iii) date of diagnosis was prior to 1999 (n = 1, 0.1%), (iv) patients were metastatic at the time of diagnosis and refused any medical intervention (n = 4, 0.8%), (v) patients opted to be treated elsewhere (n = 4, 0.8%), and (vi) referral to Henry Ford Health System for a second opinion (n = 4, 0.8%). A total of 451 women remained in the study.

The proportion of women whose cancers were evaluated for HER-2/neu was 51.9% (n = 234). Of these women, 72 (30.8%) were evaluated for HER-2/neu in 1999 and 162 (69.2%) in 2000, an ~2-fold increase (Table 1). On average women who were tested for HER-2/neu were younger (57.8 ± 13.4 years)
HER-2/neu testing and health insurance

Oncologists and surgeons requested testing of HER-2/neu for 11 (4.8%) and 220 (95.2%) patients, respectively. About 60% \( (n = 141) \) of women with capitated insurance coverage and 40% \( (n = 93) \) of women with fee-for-service insurance were tested for HER-2/neu. Among women tested for HER-2/neu, 30% \( (n = 69) \) were estrogen receptor negative. Of women who were not tested for HER-2/neu, 19% \( (n = 41) \) were diagnosed with cancers not expressing estrogen receptors \( (P = 0.03) \). Finally, of the women who were tested for HER-2/neu, 45% \( (n = 106) \) were diagnosed with poorly differentiated nuclear grade cancers, compared with 30% \( (n = 65) \) of women who were not tested. This difference was statistically significant \( (P = 0.008) \).

**Multivariate logistic regression modeling**

Results from the multivariate logistic regression modeling are presented in Table 2. Type of health insurance, estrogen receptor status, and specialty of physician in charge of the patient’s treatment were the best indicators for HER-2/neu testing. Women who were insured through a fee-for-service type insurance were less likely to be tested for HER-2/neu relative to those who were insured through a capitated insurance \( (OR = 0.55, 95\% \text{ CI } 0.36–0.85, P = 0.008) \). The likelihood of HER-2/neu testing increased by almost 2-fold if a woman was diagnosed with estrogen receptor negative cancer \( (OR = 1.92, 95\% \text{ CI } 1.15–3.21, P = 0.013) \). Finally, the likelihood of a woman being evaluated for HER-2/neu increased by almost 6-fold \( (OR = 6.2, 95\% \text{ CI } 2.88–13.33, P = 0.0001) \) if the referral physician was specialized in surgery. Results of the ROC analysis yielded C-indexes of 0.799, indicating a moderate discriminative model.

**Discussion**

We conducted a retrospective analysis to assess the proportion of women who were tested for HER-2/neu shortly after the availability of standardized laboratory kits for use in the clinical...
setting. During the period of 1999 and 2000, testing for HER-2/neu status was based on the discernment of the physician in charge of the patient’s treatment; thus, we evaluated the variables that best discriminated for inclusion of the test in the diagnostic workup of breast cancer patients. Women whose cancers were characterized by the absence of estrogen receptor were more likely to be tested. Our finding concurs with the clinical correlative studies and laboratory experimental studies describing an inverse association between the HER-2/neu biomarkers and the presence of estrogen receptors [2–4,16].

We report that the differential in testing of the HER-2/neu biomarker could have been in response to the physicians’ learning process, the associated diagnostic costs, and patients’ health insurance coverage. Between 1999 and 2000, the proportion of women who were tested for HER-2/neu increased by almost 2-fold. We attribute this increase to the learning curve phenomenon. Our literature search of the Medline database yielded a >1.5-fold increase in the scientific coverage of HER-2/neu laboratory testing between 1999 and 2000. This increase might have been an influencing factor for accepting the validity and reliability of the kits for diagnostic purposes. Also, in 2000, a series of recommendations regarding HER-2/neu testing, one of which was that the routine testing of HER-2/neu should be a component of the diagnostic workup for every woman diagnosed with breast cancer, was published [10,11]. Finally, patients’ knowledge about HER-2/neu testing might have been another reason for the observed increase. Within this study population, two women were evaluated for HER-2/neu despite having excellent prognoses (well differentiated tumor grade, stage I, no nodal involvement and positivity for hormonal receptors). An in-depth review of their medical records indicated that these patients were self-educated about the issue of HER-2/neu testing and had requested that their cancers be tested for HER-2/neu.

Surgeons were more likely to test their patients for HER-2/neu. We attribute this observation to the group of surgeons with a subspecialty of surgical oncology. There is no support in the literature for the effect of surgical specialty or clinical experience on HER-2/neu testing or other biomarkers with potential diagnostic value. However, others have reported improved survival of breast cancer patients when treated by surgical oncologists [17]. The effect of surgeon specialization on increased survival among breast cancer patients has been attributed to: (i) pure volume effect, (ii) surgical skills and (iii) more appropriate use of adjuvant therapies [17]. In this study, the observed higher percentage of requests for HER-2/neu testing by surgical oncologists might have been due to the ‘volume effect’. At the Henry Ford Health System, the majority of breast cancer patients are referred to surgical oncologists for confirmation of a suspicious mammogram or a palpable lump in the breast.

Women who were insured through a fee-for-service plan were less likely to be tested for HER-2/neu relative to those who had coverage through capitated insurance. There is no controversy regarding billing for HER-2/neu testing, however, reimbursement may vary by payer and by national region [18]. Participants in this study were from the same area; therefore, reimbursement variation by region could not have been an influencing factor. Also, since the participating physicians at Henry Ford Health System provide medical care to patients regardless of their insurance plan (fee-for-service, capitated, Medicare, or Medicaid), the variable ‘physician in charge’ was not a significant confounding factor. Our data indicate that insurance and the out-of-pocket costs might have been the reasons for the observed differences in HER-2/neu testing. Evaluation of the billing data and consultation with several individuals in the Department of Patient Financial Services and the Revenue Manager at the Department of Pathology suggested that between 1999 and 2000 the largest fee-for-service health insurance provider for this population accepted a maximum of $675.35 and $181.90 for HER-2/neu testing, depending on the type of laboratory testing. In contrast, capitated insurance covered the entire cost. Therefore, we propose that some physicians might have refrained from HER-2/neu testing simply to reduce the burden of out-of-pocket cost on

Table 2 | Variables best associated with HER-2/neu testing of breast cancer patients at the initial clinical presentation of cancer: results of the multivariate logistic regression analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tested for HER-2</th>
<th>Not tested for HER-2</th>
<th>OR1</th>
<th>95% CI2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capitated coverage</td>
<td>141</td>
<td>99</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fee-for-service</td>
<td>93</td>
<td>118</td>
<td>0.63</td>
<td>0.41–0.94</td>
<td>0.027</td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>163</td>
<td>175</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>69</td>
<td>41</td>
<td>1.96</td>
<td>1.15–3.21</td>
<td>0.013</td>
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<tr>
<td>Physician’s specialty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>11</td>
<td>45</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>220</td>
<td>173</td>
<td>6.21</td>
<td>2.88–13.33</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

1Odds ratio.
295% confidence interval.
3Adjusted for the year of diagnosis.
their patients. The disparity in the health service delivery and utilization of effective care between fee-for-service and capitated insurance has been reported [19–21]. One of the theoretical benefits of capitated insurance is the philosophy of reducing cost by emphasizing primary and secondary interventions and transferring the cost-saving initiatives to patients. However, others suggest that health care providers tend to increase utilization of services for patients whose insurance coverage has minimal or no out-of-pocket costs in order to recover the revenue losses caused by cost-sharing insurances [22]. The observed higher probability of HER-2/neu testing in the diagnostic workup of breast cancer patients with capitated insurance might have been to offset losses in revenue. Regardless of the reason, disparity in quality of care delivery due to the effect of health insurance exists and has been reported for medical conditions other than breast cancer [23]. In 2001, many institutions including the Henry Ford Health System implemented policies that testing for HER-2/neu should be a component of the diagnostic workup of any woman newly diagnosed with invasive breast cancer of any stage. Implementation of this policy has standardized the quality of care for every single breast cancer patient.

We acknowledge the limitations of the present study. Firstly, the scope of this study was limited to only one institution and one geographical region. Secondly, due to the relatively small sample size the study did not have adequate statistical power to discern the influence of socio-economic status on HER-2/neu testing.

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References


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