Original Article

Variation in the Use of Advanced Imaging at the Time of Breast Cancer Diagnosis in a Statewide Registry

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BACKGROUND: Although national guidelines do not recommend extent of disease imaging for patients with newly diagnosed early stage breast cancer given that the harm outweighs the benefits, high rates of testing have been documented. The 2012 Choosing Wisely guidelines specifically addressed this issue. We examined the change over time in imaging use across a statewide collaborative, as well as the reasons for performing imaging and the impact on cost of care. **METHODS:** Clinicopathologic data and use of advanced imaging tests (positron emission tomography, computed tomography, and bone scan) were abstracted from the medical records of patients treated at 25 participating sites in the Michigan Breast Oncology Quality Initiative (MiBOQI). For patients diagnosed in 2014 and 2015, reasons for testing were abstracted from the medical record. **RESULTS:** Of the 34,078 patients diagnosed with stage 0-II breast cancer between 2008 and 2015 in MiBOQI, 6853 (20.1%) underwent testing with at least 1 imaging modality in the 90 days after diagnosis. There was considerable variability in rates of testing across the 25 sites for all stages of disease. Between 2008 and 2015, testing decreased over time for patients with stage 0-IIA disease (all $P < .001$) and remained stable for stage IIB disease ($P = .10$). This decrease in testing over time resulted in a cost savings, especially for patients with stage I disease. **CONCLUSION:** Use of advanced imaging at the time of diagnosis decreased over time in a large statewide collaborative. Additional interventions are warranted to further reduce rates of unnecessary imaging to improve quality of care for patients with breast cancer. ***Cancer* 2017;123:2975-83**. © *2017 American Cancer Society.*

KEYWORDS: breast cancer, CT scan, PET scan, bone scan, cost analysis, health care quality assessment, diagnostic imaging.

INTRODUCTION

In 2012, the American Society of Clinical Oncology, in conjunction with the American Board of Internal Medicine Foundation, released the first of a series of guidelines called Choosing Wisely to educate patients and providers about unnecessary procedures.[1] One of the so-called "Top 5" for oncology recommended against the use of advanced imaging with positron emission tomography (PET), computed tomography (CT), and radionuclide bone scans in asymptomatic patients with newly diagnosed early stage (stage I and II) breast cancer for the purpose of detecting metastatic disease.

The American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) also both recommend against use of advanced imaging for assessment of patients with stage I and II breast cancer if they have no signs or symptoms concerning for metastatic disease.[2,3] The rationale behind these recommendations is the low likelihood of the presence of metastatic disease in asymptomatic patients with newly diagnosed stage I and II breast cancer.[4-7] In contrast, the NCCN guidelines recommend considering assessment with advanced imaging for patients with clinical stage III disease given the higher prevalence of distant metastatic disease in these patients.

In addition to a low potential for benefit from imaging in asymptomatic patients with stage I and II breast cancer, considerable harm can be done. Advanced imaging generally requires radiation, and cumulative radiation exposure can increase the risk of second malignancies.[8] In addition, there are often false-positive or indeterminate findings on extent of disease evaluation, which can cause anxiety and can lead to the need for invasive biopsies as well as subsequent scans for further evaluation. Other potential harms from imaging includes delays in care and increased health care costs. It is therefore essential to minimize the inappropriate use of advanced imaging in this patient population.

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To evaluate the variation in use of CT chest, abdomen, and pelvis, PET, and bone scan imaging across a single state over time, the Michigan Breast Oncology Quality Initiative (MiBOQI) collected data regarding use of advanced imaging in a prospective registry of 25 participating hospitals. In addition, clinical and nonclinical factors associated with test usage were examined. We hypothesized that use of advanced imaging over time has decreased, especially since the publication of the Choosing Wisely initiative.

PATIENTS AND METHODS

Patient Characteristics

MiBOQI is a Blue Cross Blue Shield of Michigan/Blue Care Network–supported Collaborative Quality Initiative comprising 25 hospital systems that abstract comprehensive demographic, clinical, and pathologic data on patients with newly diagnosed breast cancer. The members of the collaborative conduct quality initiative projects, with the goal of improving the care of patients with breast cancer across the state of Michigan. Data from patients with stage 0-II breast cancer who were diagnosed between 2008 and 2015 and treated at 1 of the 25 participating MiBOQI hospitals were abstracted from the medical record and included in the registry. If a patient was treated with primary systemic therapy, the staging was based on clinical stage at presentation. If a patient was treated with primary surgery, the staging was based on pathologic stage.

All patients who present to a participating site within 180 days of diagnosis of a new breast cancer and who undergo surgery and/or systemic therapy at that institution are included in the registry, except for patients who are men, are under the age of 18 years, or have a history of a nonbreast invasive malignancy diagnosed within 90 days of breast cancer diagnosis. If a patient receives treatment at 2 MiBOQI institutions, she is included in the cohort where she received her first cancer-directed treatment.

Diagnosis of breast cancer was based on the date of the initial biopsy that demonstrated cancer. Data elements that were abstracted included demographic characteristics, pathologic findings, and treatments administered. In addition, dates of all CT, PET, and bone scans performed within 90 days after diagnosis of breast cancer were abstracted, except for scans that were performed for reasons deemed by the data abstractor to be unrelated to the diagnosis and evaluation of breast cancer. Scans performed before the date of diagnosis were excluded because the intent was to capture only those scans done as a result of the breast cancer diagnosis. For the cohort of patients diagnosed in 2014 and 2015, reasons for testing were abstracted from the medical record using a predefined list of reasons. These reasons were divided into reasons considered concordant or nonconcordant with guidelines by the authors of the manuscript before data analysis; the data abstractors were not aware of the classification of each reason.

Statistical Analysis

All data were analyzed using the statistical package R, version 3.2.3. Overall stage was based on a combination of clinical and pathologic stage. For those patients who underwent primary surgical resection, pathologic staging (including T and N stage) was used. In contrast, for those patients who received treatment with primary systemic therapy, clinical staging was used.

All patient characteristics were summarized as proportions, and the statistical significance of how scan utilization varied with patient characteristics was assessed using univariate and multivariate logistic regression. Cost savings were computed using scan costs for 2011 listed by the Centers for Medicare & Medicaid Services (CMS) (average costs: CT, $400; PET, $1075; bone scan, $290) applied to scan totals per 1000 patients observed in our data in 2010-2011 and 2015. Statistical significance was defined as $P < .05$.

RESULTS

Use of Advanced Imaging Studies

Of the 34,078 patients who were diagnosed with stage 0-II breast cancer between 2008 and 2015 and were included in the registry, 6853 (20.1%) underwent imaging with CT, PET, and/or bone scan for any reason within 90 days after diagnosis of breast cancer (Supporting Fig. 1). The percentage of those who underwent testing with at least 1 imaging modality increased with increasing stage (Fig. 1A). Similarly, the number of scans performed per patient increased with increasing stage (Supporting Fig. 2). In particular, almost 25% of patients with stage IIB disease underwent at least 3 advanced imaging tests, compared with approximately 12% for patients with stage IIA disease and less than 5% for stages 0 and I. Use of each type of imaging modality varied. CT scan was used most commonly, with 4953 (14.5%) patients undergoing at least 1 scan within 90 days after diagnosis of breast cancer. At least 1 bone scan was used for the assessment of 3268 (9.6%) patients. PET scans were used least often, with 1602 (4.7%) patients undergoing at least 1 scan in the 90 days after diagnosis.

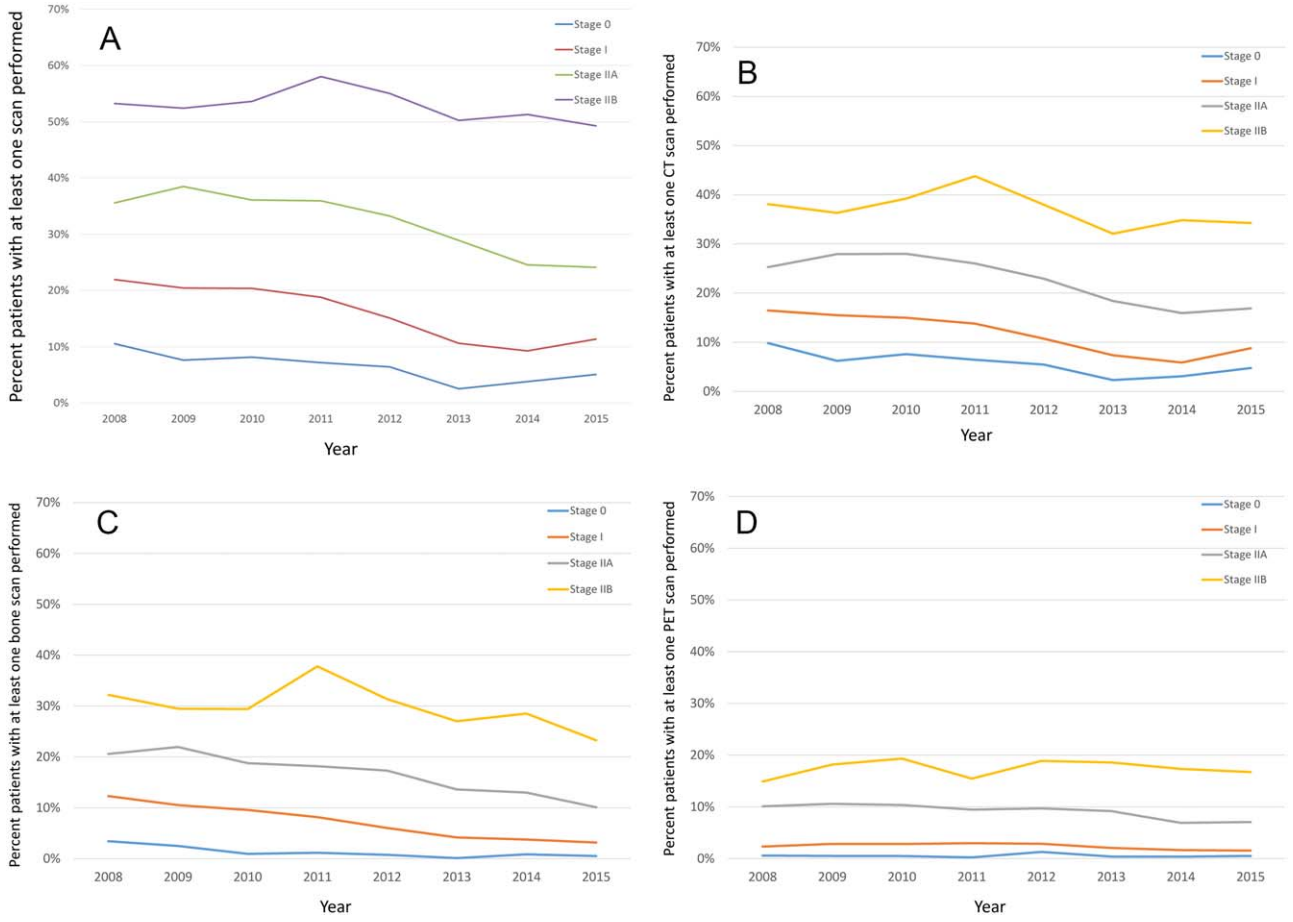

Figure 1. Percentage of patients who had at least 1 scan performed, by year. Each line represents a different disease stage (A: blue: stage 0, red: stage I, green: stage IIA, purple: stage IIB). (A) At least 1 scan of any imaging modality. (B) At least 1 CT scan. (C) At least 1 bone scan. (D) At least 1 PET scan (B-D: blue:stage 0, orange: stage I, gray: stage IIA, yellow: stage IIB).

The number of patients who underwent imaging with at least 1 diagnostic scan decreased over time from 2008 to 2015 for stage 0-IIA breast cancer (all $P < .001$) and remained stable for stage IIB disease ($P = .10$) (Fig. 1A, Supporting Table 1). When specific imaging modalities were examined, the number of patients who underwent imaging with at least 1 CT scan or at least 1 bone scan decreased for stage 0-IIA breast cancer ($P < .001$) (Fig. 1B,C). For PET scans, the number of patients who underwent imaging between 2008 and 2015 decreased for stages I and IIA breast cancer ($P = .001$) but there was no apparent significant decrease for patients with stages 0 and IIB disease (Fig. 1D).

Variability Across MiBOQI Sites

Across the 25 participating sites, there was considerable variability in the use of imaging tests (Fig. 2). When examining the number of patients with stage 0 disease who underwent any advanced imaging scan during the 90 days after diagnosis, rates of testing varied from 2.5% to 43.7%, with a median of 5.5%. For stages I, IIA, and IIB, the medians were 13.0% (7.6-55.9%), 30.4% (15.2-66.5%), and 53.1% (27.5-84.9%), respectively.

The majority of scans performed were CT scans. When examining the number of patients with stage 0 disease who underwent any CT scan, rates of testing across the sites varied from 1.3% to 43.7%, with a median of 4.6% (Supporting Fig. 3A). For stage I, IIA, and IIB, the medians were 9.5% (4.6-53.9%), 18.3% (8.3-61.5%), and 32.6% (10.6-69.9%), respectively (Supporting Fig. 3B-D).

Fewer patients underwent testing with bone scans or PET scans. When examining the number of patients with stage 0 disease who underwent a bone scan, rates of testing across the sites varied from 0% to 19.7%, with a median of 0.7% (Supporting Fig. 3A). For stage I, IIA, and IIB,

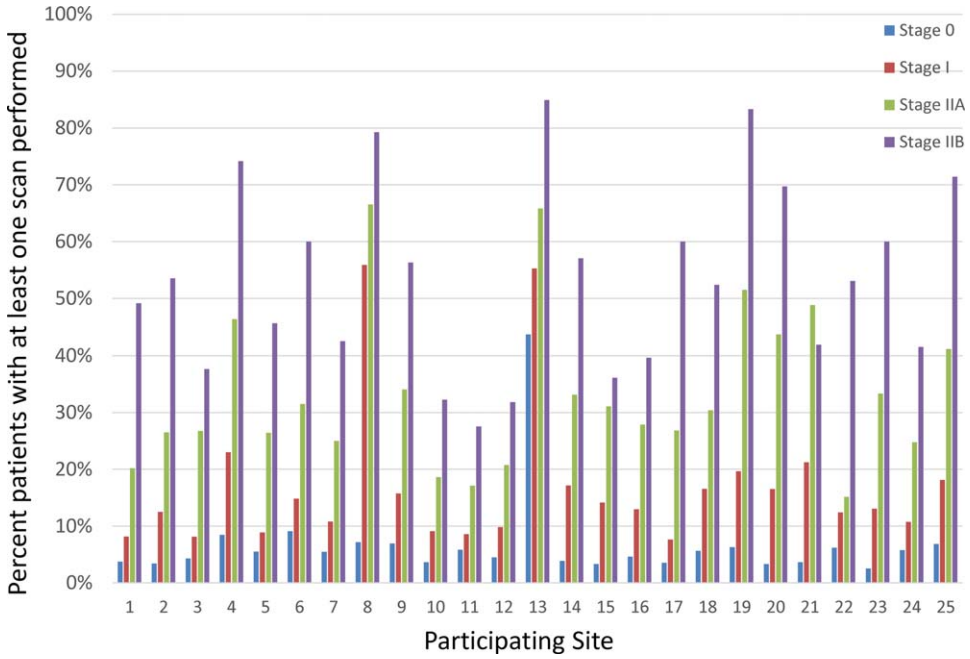

Figure 2. Percentage of patients who had at least 1 scan performed, by participating site. Sites are listed on the x axis from 1 to 25. Bars represent the different disease stages (blue = stage 0; red = stage I; green = stage IIA; purple = stage IIB).

the medians were 3.8% (0-47.0%), 10.7% (2.7-56.0%), and 27.8% (0-64.0%), respectively (Supporting Fig. 3B-D). For PET scans, the median for stage 0 was 0.4% (range, 0%-2.5%), for stage I was 1.8% (0.7%-8.2%), for stage IIA was 8.3% (1.0%-37.3%), and for stage IIB was 16.2% (2.8%-64.3%) (Supporting Fig. 3). The participating sites with the highest rates of testing with CT differed from those with the highest rates of testing with PET.

Associations Between Patient Characteristics and Advanced Imaging

Univariate and multivariate analyses were performed to assess associations between patient and pathologic characteristics and test ordering (Table 1). On univariate analysis, younger age, black race, lower socioeconomic status, higher comorbidity score, and higher clinical stage were associated with higher likelihood of advanced imaging. Pathologic characteristics associated with advanced imaging on univariate analysis included lack of ER expression, HER2 overexpression or amplification, higher tumor grade, larger tumor size, and greater number of involved lymph nodes. On multivariate analyses, all factors were statistically significant except for Charlson comorbidity index, mostly due to its correlation with several other patient factors.

Reasons for Testing

The medical records of patients from 2014 and 2015 were examined to determine reasons for testing (Table 2). Of the 1687 patients who had advanced imaging performed, 55.1% had imaging performed for reasons considered to be concordant with guidelines; the remaining 44.9% had tests performed for reasons considered nonconcordant or not documented in the medical record.

For patients with stage 0 disease, 4.4% had at least 1 advanced imaging test performed, 81% of which were considered to be concordant. Of those patients who underwent imaging, more than half did so to evaluate patient-reported symptoms, for a nonbreast cancer-related condition, or for follow-up of an abnormal test. Twenty percent of tests were ordered by outside providers for unknown reasons, and an additional 19% did not have a clearly documented reason.

For patients with stage I disease, 10.3% had at least 1 advanced imaging test performed, of which 69% were considered to be concordant. Of those who were tested, 23% of patients underwent imaging to evaluate patient-reported symptoms, 21% for follow-up of an abnormal test, and 4% because of clinicopathologic features that do not clearly indicate the need for imaging, such as abnormal-appearing lymph nodes, large tumor size based on imaging, young age, and triple negative disease. Nine

TABLE 1. Patient and Pathologic Characteristics Associated With Use of Advanced Imaging

Characteristic	Scan (n = 6853)	No Scan (n = 27,225)	*P*	
			Univariate	Multivariate
Age, y				
<50	1740 (25)	5188 (75)	<.001	.020
50-69	3503 (19)	14660 (81)		
70+	1610 (18)	7377 (82)		
Race/Ethnicity				
White	5190 (19)	22243 (81)	<.001	<.001
Black	1163 (27)	3190 (73)		
Other	108 (26)	308 (74)		
Hispanic	392 (21)	1484 (79)		
Socioeconomic status (tertiles)				
High	1866 (17)	9296 (83)	<.001	<.001
Medium	2326 (21)	8818 (79)		
Low	2563 (23)	8696 (77)		
Missing	98 (19)	415 (81)		
Clinical tumor stage				
0	476 (7)	6528 (93)	<.001	<.001
I	2734 (17)	13211 (83)		
II	2906 (40)	4365 (60)		
III	99 (77)	29 (23)		
IV	7 (88)	1 (12)		
Missing	631 (17)	3091 (83)		
Pathologic tumor stage				
pT1	3085 (17)	14640 (83)	<.001	<.001
pT2	1810 (30)	4169 (70)		
pT3	116 (46)	135 (54)		
pT4	3 (50)	3 (50)		
Other	543 (7)	7536 (93)		
Missing	1296 (64)	742 (36)		
Nodal involvement				
pN0	3473 (15)	19416 (85)	<.001	<.001
pN1mi	245 (25)	747 (75)		
pN1	1425 (39)	2191 (61)		
pN2	5 (100)	0		
Missing	1705 (26)	4871 (74)		
Grade				
1	1213 (17)	6111 (83)	<.001	<.001
2	2610 (23)	8927 (77)		
3	2412 (34)	4735 (66)		
Missing	618 (8)	7452 (92)		
ER-positive	5156 (75)	23122 (85)	<.001	<.001
HER2-positive	1148 (18)	2220 (11)	<.001	<.001
Charlson comorbidity index				
0	5309 (20)	21661 (80)	.001	>.99
1	745 (21)	2733 (79)		
2	508 (21)	1862 (79)		
≥3	291 (23)	969 (77)		

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
Data are presented as n (%).

percent of tests were ordered by outside providers for unknown reasons, and an additional 26% did not have a clear reason documented in the medical record.

For patients with stage IIA and IIB disease, 33.8% had at least 1 advanced imaging test performed. For those with stage IIA disease, 52% were considered to be concordant, as opposed to 47% of with stage IIB disease. Of those patients who were tested, fewer underwent imaging because of patient-reported symptoms or follow-up of an abnormal test compared with patients with stage I disease. Approximately one-fifth of patients underwent testing before initiation of neoadjuvant chemotherapy. Compared with stage I disease, a higher percentage of patients underwent evaluation with advanced imaging because of node-positive disease that did not meet the criteria for clinical stage III disease (14%-26%). Approximately one-quarter of tests were performed for reasons not clearly documented in the medical record.

TABLE 2. Reasons for Testing, According to Medical Record Documentation, 2014-2015

Reason	Stage			
	Stage 0 (n = 54)	Stage I (n = 423)	Stage IIA (n = 569)	Stage IIB (n = 641)
Concordant	44 (81)	291 (69)	295 (52)	299 (47)
Patient-reported symptom	12 (22)	96 (23)	55 (10)	29 (5)
Evaluation of abnormal imaging study	5 (9)	55 (13)	32 (6)	29 (5)
Evaluation of abnormal laboratory test	1 (2)	33 (8)	18 (3)	14 (2)
Clinical stage III or IV	0	0	13 (2)	29 (5)
Pathologic stage III (but clinically lower stage at diagnosis)	0	6 (1)	0	1 (0.2)
Neoadjuvant chemotherapy	0	13 (3)	104 (18)	149 (23)
In anticipation of reconstruction	4 (7)	14 (3)	8 (1)	2 (0.3)
Testing required by clinical trial	0	0	1 (0.1)	1 (0.2)
Outside provider	11 (20)	40 (9)	46 (8)	36 (6)
Unrelated condition	9 (17)	27 (6)	15 (3)	6 (0.9)
Lung cancer screening	2 (4)	3 (0.7)	3 (0.5)	3 (0.5)
Uncertain recurrence vs new primary	0	4 (0.9)	0	0
Nonconcordant	10 (19)	132 (31)	274 (48)	342 (53)
Recommended by tumor board	0	2 (0.5)	6 (1)	1 (0.2)
Not documented	10 (19)	110 (26)	169 (30)	134 (21)
Factors that do not meet guideline criteria for imaging				
Node-positive disease/abnormal appearing lymph nodes	0	8 (2)	81 (14)	166 (26)
ER/PR/HER2-negative	0	2 (0.5)	6 (1)	6 (0.9)
Large tumor size	0	3 (0.7)	6 (1)	21 (4)
Bilateral disease	0	4 (0.9)	6 (1)	4
Young age	0	1 (0.2)	0	5 (0.8)
Patient requested	0	2 (0.5)	0	5 (0.8)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
Data are presented as n (%). Percentages given are percent of the total number of patients with that stage of disease who had imaging performed.

Cost Impact of Decreased Testing Over Time

The cost of advanced imaging tests performed in patients diagnosed in 2010 and 2011, before the publication of the Choosing Wisely recommendations, were compared with the cost of those performed in patients diagnosed in 2015. As shown in Table 3, using the average cost for the scans based on the Centers for Medicare & Medicaid Services fee schedule from 2011 there was a 33% decrease over time in the total cost of scans for patients with stage 0-II breast cancer. When divided by stage, there was a trend toward a greater savings for those with stage I disease (36%) compared with stage 0 or II (16% and 23%, respectively). Similar trends were identified when each individual imaging modality was examined.

DISCUSSION

In this large statewide registry, use of advanced imaging within 90 days of diagnosis of stage 0-IIA breast cancer decreased between 2008 and 2014. As expected, higher rates of imaging were seen in patients who were at higher risk of disease recurrence. There was considerable variability in use of imaging across the 25 participating hospital systems, which varied by both disease stage and imaging modality. Symptoms, abnormalities identified on other testing, or other disease conditions were identified as the reasons for testing for about half of patients with stage 0 or I disease. In contrast, factors associated with more aggressive disease were more commonly cited as reasons for testing in those with stage II disease. These findings support and extend those reported in the literature.[9-13]

The Choosing Wisely recommendations were developed to reduce the use of advanced imaging in asymptomatic patients with newly diagnosed stage 0-II breast cancer because of the minimal benefits and potential harms of testing. The likelihood of having metastatic disease in this setting has been demonstrated to be less than 2% in multiple studies.[14,15] Harm from performing unnecessary imaging can include the cost of testing to patients and society, radiation exposure from the imaging tests, and anxiety related to testing.

Another potential form of harm that can arise is the need to expose patients to additional radiation and/or invasive procedures to evaluate abnormal findings.[8] However, in the MiBOQI registry we did not collect

TABLE 3. Cost Savings Analysis Comparing the Cost of Advanced Imaging Scans Performed Within 90 Days of Diagnosis per 1000 Patients in 2010-2011 and 2015 Using Estimated Costs From the 2011 Medicare Fee Schedule

Stage	Total Cost 2010-2011 per 1000 Patients	Total Cost 2015 per 1000 Patients	Percentage Reduction in Cost
All imaging modalities			
All stages	$202,400	$135,754	33%
0	$40,133	$33,536	16%
I	$141,543	$90,643	36%
II	$433,007	$333,249	23%
CT scan			
All stages	$113,494	$75,245	34%
0	$33,500	$25,051	25%
I	$83,112	$47,741	43%
II	$227,826	$152,981	33%
Bone scan			
All stages	$33,485	$17,473	48%
0	$3056	$1465	52%
I	$25,972	$9254	64%
II	$70,104	$41,373	41%
PET scan			
All stages	$55,421	$43,035	22%
0	$3577	$5429	-52%
I	$32,459	$16,929	48%
II	$135,076	$110,164	18%

downstream effects of imaging, including frequency of abnormal scan results or use of additional imaging or biopsies. Both of these can increase risk to patients as well as increase the cost of care. As recently reported in a study of patients with stage II and III breast cancer, more than 80% of patients had an abnormality noted on advanced imaging, and 43% underwent additional evaluation.[14]

Use of testing for patients with stage IIB disease remained high throughout the study period. Although asymptomatic patients with stage IIB disease were included in the Choosing Wisely recommendations, it is unclear whether these patients should be excluded from routine extent of disease evaluation. These patients are at increased risk of having metastatic disease compared with those with lower-stage breast cancer. In addition, many patients with stage IIB disease undergo treatment with primary systemic therapy, and therefore their actual extent of disease is unknown at the time of imaging, assuming imaging is performed before treatment initiation. Routine use of imaging in this population may therefore need to be subjected to further study.

The reduction in testing within the first 90 days after diagnosis that occurred between 2010-2011 and 2015 resulted in substantial cost savings overall based on the Medicare fee schedule, especially in patients with stage I breast cancer. Because of limitations in the registry, we were unable to account for downstream imaging or biopsies that resulted from initial extent of disease evaluation. Therefore, because of this limitation and the use of Medicare reimbursement rates rather than private payer rates, the cost savings is likely greater than was identified in this analysis.

Rates of testing decreased at the 25 participating sites across Michigan during the period in which the Choosing Wisely recommendations were published. However, it is unknown what led to this reduction. One possibility is the Choosing Wisely campaign itself and the associated media coverage, although rates of testing in Michigan appeared to start decreasing before the publication. In addition, others have demonstrated minimal difference in use of testing before and after the publication.[11] Furthermore, numerous studies have demonstrated a significant lag in the uptake of new guidelines or findings by physicians following their initial publication or presentation.[16] Therefore, it is possible that practice patterns changed in Michigan because of increased awareness of MiBOQI participating physicians related to regular discussions of the topic at MiBOQI's triannual meetings, and subsequent dissemination of the information to colleagues at tumor board conferences. A formal collaborative quality initiative was launched in May 2013, although the topic was discussed at meetings during the previous year. A final possibility is the requirement for prior authorization of advanced imaging tests by insurance companies, which may have resulted in fewer imaging tests being performed but may not have altered the actual ordering of scans by providers.

In 2014 and 2015, 20%-30% of imaging tests ordered for patients with stage 0-II disease did not have a clearly documented reason in the medical record. It is possible that almost all of the testing performed in these more recent years was guideline-concordant, but it is difficult to tell because of incomplete documentation. Using strategies such as multidisciplinary tumor conference case reviews and decision making tools incorporated into the electronic health record could potentially help reduce unnecessary test ordering; the latter has been used for prevention of venous thromboembolic disease and reducing overuse of antibiotics.[17-19]

The variability of testing across participating hospital systems was also notable, and similar to what has been reported in the literature.[9,13,20] Those sites with the highest percentage of nonconcordant testing of patients with stage II disease treated fewer patients compared with those with lower rates of testing, although numerous other sites that treated smaller numbers of patients also had low rates of testing. The reasons for the variation are unknown but could be related to differences in local practice patterns, patient mix across practice sites, lack of a multidisciplinary tumor board, concerns about litigation, or financial pressures.

Overall, these findings represent changes in frequency of imaging at the time of breast cancer diagnosis that have occurred across a single state during the time frame that spanned publication of the Choosing Wisely guidelines. Our results are based on a large registry of patients treated in a variety of practice settings. Although we used a predefined list when assessing reasons for testing, the data are limited because they were collected retrospectively by data abstractors with physician involvement as needed, and not prospectively at the time of ordering.

In conclusion, within MiBOQI the rate of imaging within 90 days of diagnosis of stage 0-IIA breast cancer decreased significantly between 2008 and 2015, although imaging in stage IIB disease remained relatively stable. This decrease likely reduced exposure to different types of harm, including radiation exposure, unnecessary invasive procedures, and financial toxicity. Although great strides have been made to date, additional interventions are required to reduce the rates of unnecessary testing even further, thereby improving the quality of care for patients with breast cancer.

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CONFLICTS OF INTEREST DISCLOSURES

Samuel M. Silver has received grants from Michigan Blue Cross Blue Shield and personal fees from Amgen, 3M, and BlueCare Network of Michigan.

AUTHOR CONTRIBUTIONS

Conceptualization: **N. Lynn Henry**, **Samuel M. Silver**, **Jennifer J. Griggs**. Software: **Thomas M. Braun**. Formal analysis: **Thomas M. Braun**. Investigation: **N. Lynn Henry**, **Thomas M. Braun**. Data curation: **Thomas M. Braun**. Writing (original draft): **N. Lynn Henry**. Writing (review and editing): **N. Lynn Henry**, **Thomas M. Braun**, **Samuel M. Silver**, **David H. Gorski**, **Tara M. Breslin**, **Jennifer J. Griggs**. Visualization: **N. Lynn Henry**, **Thomas M. Braun**. Funding acquisition: **N. Lynn Henry**, **Samuel M. Silver**.

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