Prognostic Role of Detection Method and Its Relationship with Tumor Biomarkers in Breast Cancer: The University of Texas M. D. Anderson Cancer Center Experience

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Abstract

Purpose: **To assess the effect of tumor detection method (screening versus symptom-based diagnosis) in predicting breast cancer survival and investigate how biological features of breast cancer are related to the tumor detection method.**

Patients and Methods: **The study population consisted of 5,481 women diagnosed with primary invasive breast cancer between 1997 and 2005 and received their treatment at The University of Texas M. D. Anderson Cancer Center.**

Results: **Patients with symptom-detected tumors had an increased risk of recurrence or death [relative risk (RR), 1.34; $P = 0.006$] and breast cancer–specific death (RR, 1.31; $P = 0.117$) than patients with screen-detected tumors after adjusting for tumor characteristics and treatments received. This relationship was especially evident among estrogen receptor (ER)–negative tumors (RR, 1.60 for breast cancer recurrence for ER-negative tumors; RR, 1.18 for ER-positive tumors). ER status and Ki-67 expression were statistically significantly associated with symptom detection rate after adjusting for patients' age, tumor stage, tumor size, and nuclear grade [odds ratio (OR) of ER negative versus ER positive, 1.35; $P < 0.001$; OR of Ki-67 10-30% versus <10%, 1.40; $P = 0.005$; OR of Ki-67 >30% versus <10%, 2.11; $P < 0.001$].**

Conclusion: **The method of detection was a statistically significant independent predictor of breast cancer recurrence. Information on the method of tumor detection should be collected to improve the prediction of prognosis of breast cancer patients.** (Cancer Epidemiol Biomarkers Prev 2008;17(5):1096–103)

Introduction

The marked decrease in the U.S. breast cancer mortality rate since 1990 has been attributed to the use of early detection programs and improved adjuvant chemotherapy and endocrine therapy (1-6). Several studies have indicated that women with tumors detected by screening examinations have more favorable clinical prognoses than women whose tumors are detected symptomatically (7-11). The estimated hazards of death from breast cancer detected symptomatically range from 36% (7) to 90% (8), greater than that from screen-detected breast cancer, after accounting for characteristics of the disease. Part of this residual screening benefit is due to lead-time and length biases (12-17). Lead time is the period from detection of the disease by screening exam to the time of its usual clinical presentation in the absence of screening. Lead-time bias occurs because breast tumors detected through a screening exam tend to be at an earlier stage of development than those detected symptomatically. Length bias occurs because a screening exam is more likely to detect slower-growing tumors, which may be less deadly (15). Length bias may be explained by biological characteristics that determine the tumor growth rate.

In this study, we assessed the effect of the tumor detection method on breast cancer survival after adjusting for important risk factors at the time of diagnosis. We also investigated how the tumor detection method relates to tumor biologic features, including tumor expression of Ki-67, a protein associated with cell proliferation, and the tumor status of specific cell receptors: estrogen receptor (ER), progesterone receptor (PR), and HER-2/*neu*, an epidermal growth factor receptor.

Patients and Methods

Data Source. We used data on women diagnosed with primary breast cancer between 1997 and 2005 and treated at The University of Texas M. D. Anderson Cancer Center (MDACC). The data were abstracted from medical charts, reviewed, and entered into the Breast Cancer Management Systems, which is a prospective electronic database initiated since 1997. The data for this study included patient race, age at diagnosis, tumor detection method (screen-detected and symptom-detected), tumor characteristics at diagnosis, treatments received following diagnosis, and times to disease recurrence, death, and last patient follow-up. Tumor characteristics included tumor-node-metastasis stage, tumor size, axillary nodal status, nuclear grade,

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Table 1. Demographic and tumor characteristics by tumor detection method

Variable	Screen detected (n = 2,387), n (%)	Symptom detected (n = 3,094), n (%)	Total (n = 5,481), n (%)	P
Age at diagnosis (y)				
40-49	572 (24.0)	1,129 (36.5)	1,701 (31.0)	
50-59	834 (34.9)	1,067 (34.5)	1,901 (34.7)	
≥60	981 (41.1)	898 (29.0)	1,879 (34.3)	<0.001
Race				
White	1,903 (79.7)	2,206 (71.3)	4,109 (75.0)	
African American	199 (8.3)	342 (11.1)	541 (9.9)	
Other	285 (12.0)	546 (17.6)	831 (15.1)	<0.001
Tumor stage				
I	1,432 (60.0)	779 (25.2)	2,211 (40.3)	
II	813 (34.1)	1,541 (49.8)	2,354 (43.0)	
III	125 (5.2)	660 (21.3)	785 (14.3)	
IV	17 (0.7)	114 (3.7)	131 (2.4)	<0.001
Tumor size				
T_0	16 (0.7)	38 (1.3)	54 (1.0)	
T_1	1,817 (76.3)	1,221 (39.7)	3,038 (55.7)	
T_2	444 (18.7)	1,192 (38.8)	1,636 (30.0)	
T_3-T_4	103 (4.3)	622 (20.2)	725 (13.3)	
Unknown	7	21	28	<0.001
Nodal status				
Negative	1,684 (70.6)	1,594 (51.7)	3,278 (59.9)	
Positive	700 (29.4)	1,492 (48.3)	2,192 (40.1)	
Unknown	3	8	11	<0.001
Nuclear grade				
Well/moderately differentiated	1,453 (62.1)	1,329 (44.3)	2,782 (52.1)	
Poorly differentiated	885 (37.9)	1,669 (55.7)	2,554 (47.9)	
Unknown	49	96	145	<0.001
Lymphatic/vascular invasion				
No	1,995 (84.3)	2,261 (74.9)	4,256 (79.0)	
Yes	372 (15.7)	758 (25.1)	1,130 (21.0)	
Unknown	20	75	95	<0.001
ER status				
Negative	432 (19.0)	975 (32.7)	1,407 (26.8)	
Positive	1,839 (81.0)	2,004 (67.3)	3,843 (73.2)	
Unknown	116	115	231	<0.001
PR status				
Negative	768 (34.0)	1,267 (42.8)	2,035 (39.0)	
Positive	1,492 (66.0)	1,692 (57.2)	3,184 (61.0)	
Unknown	127	135	262	<0.001
HER-2/*neu* immunohistochemistry score				
0 or 1+	1,280 (75.6)	1,433 (66.9)	2,713 (70.7)	
2+	201 (11.9)	319 (14.9)	520 (13.6)	
3+	212 (12.5)	390 (18.2)	602 (15.7)	
Unknown	694	952	1,646	<0.001
Ki-67 proliferation				
<10%	307 (30.1)	216 (17.2)	523 (23.0)	
10-30%	518 (50.7)	574 (45.7)	1,092 (48.0)	
>30%	196 (19.2)	465 (37.1)	661 (29.0)	
Unknown	1,366	1,839	3,205	<0.001
Surgery and radiation				
Breast-conserving surgery alone	111 (4.7)	134 (4.3)	245 (4.5)	
Breast-conserving surgery + radiation	1,208 (50.6)	1,114 (36.0)	2,322 (42.4)	
Mastectomy alone	827 (34.6)	935 (30.2)	1,762 (32.1)	
Mastectomy + radiation	226 (9.5)	841 (27.2)	1,067 (19.5)	
None	15 (0.6)	70 (2.3)	85 (1.5)	<0.001
Adjuvant chemotherapy				
No	1,515 (63.5)	1,659 (53.6)	3,174 (57.9)	
Yes	872 (36.5)	1,435 (46.4)	2,307 (42.1)	<0.001
Adjuvant endocrine therapy				
No	765 (32.0)	1,260 (40.7)	2,025 (36.9)	
Yes	1,622 (68.0)	1,834 (59.3)	3,456 (63.1)	<0.001
Neoadjuvant chemotherapy				
No	2,102 (88.1)	1,896 (61.3)	3,998 (72.9)	
Yes	285 (11.9)	1,198 (38.7)	1,483 (27.1)	<0.001
Total	2,387 (43.5)	3,094 (56.5)	5,481 (100.0)	

lymphatic/vascular invasion, ER status, PR status, HER-2/*neu* immunohistochemistry score, and tumor expression of Ki-67. All the information had been prospectively collected in the Breast Cancer Management Systems database by trained personnel. The study was approved by the Institutional Review Board of the MDACC. Tumor staging and size determination were based on pathologic staging and measurement of the tumor size. For patients

receiving neoadjuvant therapy, the clinical stage and tumor size measurements before the initiation of therapy were used. Tumor HER-2/*neu* score was determined by testing HER-2/*neu* protein expression using immunohistochemistry.

Patient Inclusion Criteria. We used data from all breast cancer patients (7,451) who had been consecutively registered in the MDACC Breast Cancer Management Systems database from 1997 to 2005. Then, we excluded patients who were either diagnosed to have ductal carcinoma *in situ* and lobular carcinoma *in situ*, ages <40 years at diagnosis, had unknown information on method of detection, or had unknown surgery/treatment information. The resulting study cohort consisted of 5,481 patients.

Tumor Detection Method. Physicians in the MDACC Breast Center interviewed patients and documented the information of the tumor detection method in the medical charts. Screen-detected breast cancers were defined as those initially detected through an abnormal mammography finding or an abnormal clinical breast exam. Symptom-detected breast cancers were those initially detected through the patient's discovery of disease-related symptoms.

Statistical Analysis. We used the χ^2 test to compare the distributions of tumor characteristics by the detection method. Logistic regression was used to determine whether the probability of a tumor being screen-detected was associated with the observed biologic features, including ER, PR, HER-2/*neu*, and Ki-67 status, after controlling for patient age, race, disease stage, tumor size, nodal status, nuclear grade, and lymphatic/vascular invasion. The primary clinical outcomes were recurrence-free survival (RFS) and breast cancer–specific survival (BCSS). We measured RFS from the time of diagnosis to disease progression (including local recurrence, distant metastasis, or contralateral breast tumor) or death, whichever occurred first. Death was used as the endpoint for any patient who had distant tumor metastasis at diagnosis. We measured BCSS from the time of diagnosis to death due to breast cancer. We estimated Kaplan-Meier curves by tumor detection method and used multivariable Cox models to determine the effect of tumor detection method on survival distributions after adjusting for the potential risk factors (patient age, race, tumor size, nodal status, nuclear grade, lymphatic/vascular invasion, ER status, PR status, HER-2/*neu* immunohistochemistry score, and Ki-67 expression) and treatments received (surgery, radiation, adjuvant chemotherapy, adjuvant endocrine therapy, and neoadjuvant chemotherapy). We obtained the final multivariable model using a backward selection approach, removing the least significant covariate from the full model one at a time, and $P < 0.05$ was used as the limit for inclusion. All P values are two sided. We used SAS 9.1.3 and S-PLUS 7.0 for the analyses.

Results

Tumor Characteristics at Diagnosis by Detection Method. In Table 1, we list patient demographics and tumor characteristics by tumor detection method. Among 5,481 patients, 2,387 (43.5%) were diagnosed by screening examinations and 3,094 (56.5%) were diagnosed as a result of symptoms, which included a breast lump (80.2%), breast pain and discomfort (6.0%), axillary mass (3.5%), breast swelling (2.6%), nipple discharge (2.0%), inverted nipple (2.4%), and other or unknown symptoms (3.3%). In this study cohort, screen-detected tumors were more common in women ages ≥60 years (41.1%, ages ≥60 years; 34.9%, ages 50-59 years; 24.0%, ages <50 years). Symptom-detected tumors were more common in African American and other minority women than in Whites.

As expected, screen-detected tumors tended to be at an earlier stage compared with symptom-detected tumors. Screen-detected tumors were of significantly smaller size and lower nuclear grade, had fewer

Table 2. OR (95% CI) for symptom-detected versus screen-detected invasive breast cancers for the following biomarkers

Biomarker	Univariate models (for single biomarker)		Multivariable models* (for single biomarker)		Multivariable model † (for all biomarkers)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
ER status						
Positive	1.00		1.00		1.00	
Negative	2.07 (1.82-2.36)	<0.001	1.35 (1.15-1.59)	<0.001	1.28 (0.93-1.77)	1.131
PR status						
Positive	1.00		1.00		1.00	
Negative	1.45 (1.30-1.63)	<0.001	1.08 (0.94-1.23)	0.274	0.85 (0.66-1.09)	0.207
HER-2/*neu* immunohistochemistry score						
0 or 1+	1.00		1.00		1.00	
2+	1.42 (1.17-1.72)	<0.001	1.28 (1.04-1.58)	0.022	1.13 (0.83-1.54)	0.433
3+	1.64 (1.37-1.97)	<0.001	1.07 (0.87-1.32)	0.527	0.88 (0.64-1.22)	0.446
Ki-67						
<10%	1.00		1.00		1.00	
10-30%	1.57 (1.28-1.94)	<0.001	1.40 (1.11-1.77)	0.005	1.46 (1.12-1.91)	0.005
>30%	3.37 (2.65-4.29)	<0.001	2.11 (1.57-2.85)	<0.001	2.24 (1.58-3.19)	<0.001

* Risk factors–age, stage, tumor size, and nuclear grade, were included in the multivariable logistic models for each single biomarker.
† The multivariable logistic model for all four biomarkers included ER status, PR status, HER-2/*neu* immunohistochemistry score, Ki-67, and age, stage, tumor size, and nuclear grade.

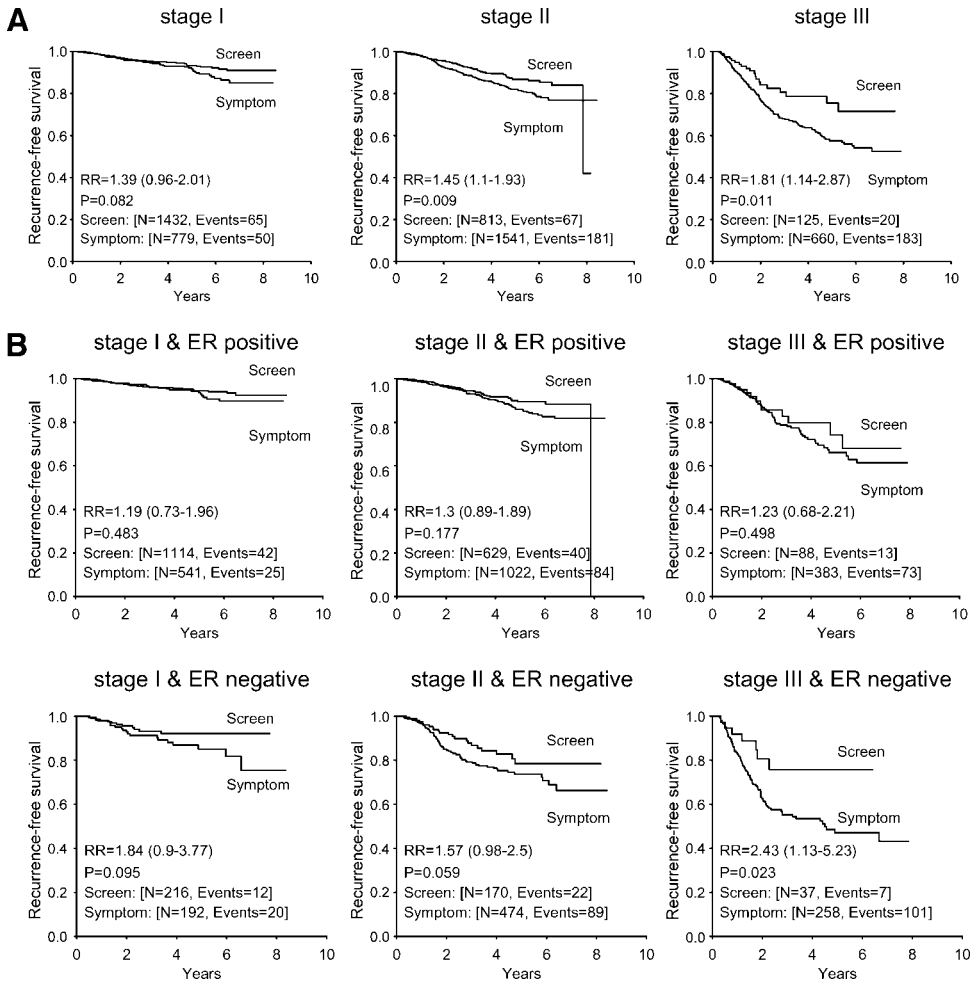

Figure 1. A. RFS curves for patients with symptom-detected breast cancer compared with those of patients with screen-detected breast cancer adjusting for the tumor stage at diagnosis. **B.** RFS curves for patients with symptom-detected breast cancer compared with those of patients with screen-detected breast cancer after controlling for tumor stage and ER status. RR (95% CI).

axillary lymph nodes involved, and were less likely to have invaded intramammary lymphatic or vascular tissue compared with symptom-detected tumors (all P values < 0.001).

The screen-detected tumors showed favorable biologic features; 81.0% of screen-detected tumors were ER positive compared with 67.3% of symptom-detected tumors ($P < 0.001$). We observed the same trend within each age group (75.4% screen-detected versus 64.0% symptom-detected ER positive for ages <50 years, $P < 0.001$; 82.7% versus 69.2% for ages ≥50 years, $P < 0.001$). The proportion of low Ki-67 expression (Ki-67 < 10%) was significantly higher among screen-detected tumors compared with that for symptom-detected tumors (30.1% versus 17.2%, $P < 0.001$).

The odds of patients diagnosed with symptoms were statistically higher for ER-negative tumors than for ER-positive tumors [odds ratio (OR), 1.35; 95% confidence interval (95% CI), 1.15-1.59] even adjusting for patients' age, tumor stage, tumor size, and nuclear grade (Table 2). Ki-67 expression was also significantly associated with detection method after adjusting for the above risk factors. Tumors with a high Ki-67 expression (compared with a low expression: Ki-67 < 10%) were more likely to be symptomatically detected (OR for Ki-67 10-30%, 1.40; 95% CI, 1.11-1.77; OR for Ki-67 >30%, 2.11; 95% CI, 1.57-2.85). Compared with HER-2/*neu* score 0 or 1+ tumors, tumors with HER-2/*neu* score 2+ were more likely to be symptomatically detected (OR for HER-2/*neu* score 2+, 1.28; 95% CI, 1.04-1.58). PR status was not statistically significantly associated with detection method after adjusting for these risk factors.

When including all four biomarkers (ER, PR, HER-2/*neu*, and Ki-67) in a multivariable model, we found only Ki-67 to be a statistically significant predictor of the tumor detection method (OR for Ki-67 10-30% versus <10%, 1.46; 95% CI, 1.12-1.91; OR for Ki-67 >30% versus <10%, 2.24; 95% CI, 1.58-3.19), whereas ER, PR, and HER-2/*neu* were not statistically significant in the model.

Disease Prognosis by Tumor Detection Method. Among 5,481 patients with invasive tumors, 174 (3.2%) experienced local recurrences, 528 (9.6%) had distant metastases, 78 (1.4%) developed contralateral breast cancers, and 296 (5.4%) died of breast cancer during a median follow-up of 3.2 years (a patient may have experienced more than one of these events). Without adjusting for the risk factors, patients with symptom-detected tumors had a significantly increased risk of recurrence [relative risk (RR), 2.40; 95% CI,

2.00-2.87; $P < 0.001$] and breast cancer–specific death (RR, 3.09; 95% CI, 2.33-4.10; $P < 0.001$) compared with patients with screen-detected tumors. The lead-time bias and length bias can contribute to this screening benefit. To minimize the lead-time bias and length bias, we first compared survival distributions by tumor detection method among patients with tumors of the same stage and ER status.

Table 3. Cox proportional hazards regression models of RFS among patients with invasive cancer

Variable	Model 1	Model 2	Model 3	Model 4
	All patients, RR (95% CI)	Patients with ER-positive tumors, RR (95% CI)	Patients with ER-negative tumors, RR (95% CI)	Adjusted for all biomarkers, RR (95% CI)
Unadjusted				
Method of detection				
Screen detected	1.00	1.00	1.00	—
Symptom detected	2.40 (2.00-2.87)*	2.03 (1.60-2.59)*	2.42 (1.77-3.31)*	—
P	<0.001	<0.001	<0.001	—
No. recurrences or deaths/total (%)	626/5,481 (11.4)	304/3,843 (7.9)	281/1,407 (20.0)	—
Adjusted				
Method of detection				
Screen detected	1.00	1.00	1.00	1.00
Symptom detected	1.34 (1.09-1.66)†	1.18 (0.90-1.56)	1.60 (1.14-2.25)†	1.29 (0.89-1.87)
P	0.006	0.233	0.007	0.181
Age (per 10-y increase)	‡	‡	‡	‡
Race				
Non-African American	‡	‡	‡	1.00
African American	‡	‡	‡	1.56 (1.02-2.39)†
Tumor size				
T_1	1.00	1.00	1.00	1.00
T_2	1.68 (1.34-2.10)*	1.61 (1.19-2.19)†	1.78 (1.27-2.50)*	1.76 (1.18-2.63)†
T_3	2.76 (2.02-3.78)*	2.79 (1.81-4.29)*	2.77 (1.72-4.46)*	2.87 (1.72-4.78)*
T_4	3.42 (2.54-4.61)*	3.43 (2.23-5.28)*	3.69 (2.41-5.67)*	3.68 (2.24-6.06)*
Nodal status				
Negative	1.00	1.00	1.00	1.00
Positive	1.89 (1.53-2.32)*	1.75 (1.31-2.33)*	2.00 (1.49-2.69)*	1.90 (1.33-2.72)*
Nuclear grade				
Well/moderately differentiated	‡	‡	‡	‡
Poorly differentiated	‡	‡	‡	‡
Lymphatic/vascular invasion				
No	1.00	1.00	1.00	1.00
Yes	1.60 (1.33-1.94)*	1.42 (1.08-1.86)†	1.90 (1.46-2.48)†	1.55 (1.10-2.18)†
Surgery and radiation				
Breast-conserving surgery alone	2.37 (1.65-3.42)*	1.95 (1.20-3.17)†	3.40 (1.95-5.94)*	‡
Breast-conserving surgery + radiation	0.81 (0.64-1.03)	0.76 (0.55-1.06)	0.85 (0.60-1.21)	‡
Mastectomy alone	1.00	1.00	1.00	‡
Mastectomy + radiation	1.08 (0.84-1.38)	1.06 (0.76-1.48)	1.03 (0.71-1.49)	‡
Adjuvant chemotherapy				
No	1.00	‡	1.00	‡
Yes	0.75 (0.63-0.91)†	‡	0.68 (0.52-0.88)†	‡
Adjuvant endocrine therapy				
No	1.00	1.00	1.00	1.00
Yes	0.47 (0.37-0.59)*	0.44 (0.33-0.58)*	0.48 (0.32-0.73)*	0.37 (0.24-0.55)*
ER status				
ER positive	1.00	‡	‡	1.00
ER negative	1.60 (1.27-2.02)*	‡	‡	1.20 (0.75-1.91)
PR status				
PR positive	‡	1.00	‡	1.00
PR negative	‡	1.37 (1.06-1.77)†	‡	0.95 (0.64-1.39)
HER-2/*neu* immunohistochemistry score				
0 or 1+	‡	‡	‡	1.00
2+	‡	‡	‡	0.58 (0.33-1.01)
3+	‡	‡	‡	0.94 (0.64-1.38)
Ki-67 expression				
<10%	§	§	§	1.00
10-30%	§	§	§	1.29 (0.78-2.14)
>30%	§	§	§	1.86 (1.09-3.18)†
No. recurrences or deaths/total (%)	536/5,110 (10.5)	280/3,752 (7.5)	254/1,340 (19.0)	166/1,810 (9.2)

* $P < 0.001$.

† $P \geq 0.001$ and $P < 0.05$.

‡ The variable was included in the original full model but it was not statistically significant ($P \geq 0.05$). Thus, it was not included in the reduced model. A variable representing whether a patient received neoadjuvant chemotherapy was excluded for the same reason. The original full model included method of detection, age, race, tumor size, nodal status, nuclear grade, lymphatic/vascular invasion, surgery and radiation, adjuvant chemotherapy, neoadjuvant chemotherapy, adjuvant endocrine therapy, ER status, PR status, and HER-2/*neu* immunohistochemistry score.

§ The variable was not included in the full model.

Table 4. Cox proportional hazards regression models of BCSS among patients with invasive breast cancer

Variable	Model 1	Model 2	Model 3	Model 4
	All patients, RR (95% CI)	Patients with ER-positive tumors, RR (95% CI)	Patients with ER-negative tumors, RR (95% CI)	Adjusted for all biomarkers, RR (95% CI)
Unadjusted				
Method of detection				
Screen detected	1.00	1.00	1.00	—
Symptom detected	3.09 (2.33-4.10)*	2.21 (1.48-3.30)*	2.65 (1.73-4.06)*	—
P	<0.001	<0.001	<0.001	—
No. deaths/total (%)	296/5,481 (5.4)	115/3,843 (3.0)	168/1,407 (11.9)	—
Adjusted				
Method of detection				
Screen detected	1.00	1.00	1.00	1.00
Symptom detected	1.31 (0.93-1.84)	1.13 (0.68-1.86)	1.46 (0.91-2.35)	1.19 (0.66-2.15)
P	0.117	0.638	0.117	0.562
Age (per 10-y increase)	‡	1.46 (1.22-1.76)*	‡	‡
Race			‡	
Non-African American	1.00	1.00	‡	1.00
African American	1.87 (1.36-2.58)*	2.84 (1.73-4.68)*		2.21 (1.25-3.89) †
Tumor size				
T_1	1.00	1.00	1.00	1.00
T_2	3.06 (2.08-4.51)*	1.89 (1.07-3.35) †	4.86 (2.77-8.55)*	3.18 (1.58-6.41) †
T_3	4.47 (2.71-7.39)*	2.28 (1.05-4.99) †	8.50 (4.19-17.22)*	4.21 (1.83-9.67)*
T_4	6.47 (4.06-10.32)*	3.61 (1.78-7.31)*	11.96 (6.20-23.08)*	7.19 (3.27-15.81)*
Nodal status				
Negative	1.00	1.00	1.00	1.00
Positive	2.22 (1.61-3.07)*	2.26 (1.31-3.89) †	2.50 (1.72-3.65)*	2.50 (1.40-4.46)*
Nuclear grade			‡	‡
Well/moderately differentiated	1.00	1.00	‡	‡
Poorly differentiated	1.62 (1.13-2.33) †	1.85 (1.20-2.86) †		
Lymphatic/vascular invasion			‡	
No	1.00	1.00	‡	1.00
Yes	1.52 (1.15-2.01) †	2.02 (1.29-3.18) †		2.06 (1.25-3.39) †
Surgery and radiation				‡
Breast-conserving surgery alone	2.95 (1.73-5.01)*	2.79 (1.23-6.33) †	3.92 (2.00-7.70)*	‡
Breast-conserving surgery + radiation	1.04 (0.70-1.53)	1.41 (0.74-2.66)	0.78 (0.48-1.26)	‡
Mastectomy alone	1.00	1.00	1.00	‡
Mastectomy + radiation	1.13 (0.78-1.65)	1.91 (1.06-3.45) †	0.83 (0.52-1.32)	
Adjuvant chemotherapy		‡		
No	1.00	‡	1.00	1.00
Yes	0.49 (0.37-0.65)*		0.46 (0.32-0.65)*	0.42 (0.26-0.69)*
Adjuvant endocrine therapy			‡	‡
No	1.00	1.00	‡	‡
Yes	0.48 (0.34-0.69)*	0.34 (0.21-0.53)*		
ER status		‡	‡	
ER positive	1.00	‡	‡	1.00
ER negative	2.14 (1.49-3.07)*			3.74 (2.08-6.72)*
PR status	‡		‡	
PR positive	‡	1.00	‡	1.00
PR negative		1.86 (1.23-2.83) †		1.41 (0.83-2.38)
HER-2/*neu* immunohistochemistry score	‡	‡	‡	
0 or 1+	‡	‡	‡	1.00
2+	‡	‡	‡	0.69 (0.32-1.46)
3+				0.60 (0.33-1.09)
Ki-67 expression	§	§	§	
<10%	§	§	§	1.00
10-30%	§	§	§	1.77 (0.72-4.36)
>30%				2.52 (1.01-6.35) †
No. deaths/total (%)	237/5,024 (4.7)	95/3,693 (2.6)	146/1,355 (10.7)	76/1,810 (4.2)

NOTE: The original full model included method of detection, age, race, tumor size, nodal status, nuclear grade, lymphatic/vascular invasion, surgery and radiation, adjuvant chemotherapy, neoadjuvant chemotherapy, adjuvant endocrine therapy, ER status, PR status, and HER-2/*neu* immunohistochemistry score.

* $P \leq 0.001$.

† $P \geq 0.001$ and $P \leq 0.05$.

‡ The variable was included in the original full model but it was not statistically significant ($P \geq 0.05$). Thus, it was not included in the reduced model. A variable representing whether a patient received neoadjuvant chemotherapy was excluded for the same reason.

§ The variable was not included in the full model.

Univariate Analyses. The graphs of Fig. 1A show a greater RFS for patients with screen-detected tumors compared with those with symptom-detected tumors within each stage (RR, 1.39, $P = 0.082$ for stage I; RR, 1.45, $P = 0.009$ for stage II; RR, 1.81, $P = 0.011$ for stage III).

Figure 1B shows a comparison of the RFS distributions by tumor detection method after fixing disease stage and

ER status and indicates that the benefit in RFS due to detection through screening remains. The differences were statistically or marginally significant among patients with ER-negative tumors of stages I to III. The differences were more evident among ER-negative tumors than those among ER-positive tumors.

Multivariable Analyses

Recurrence-Free Survival. In Table 3, we show the results of our multivariable analyses of Cox proportional hazards models for RFS. Race was not a statistically significant predictive factor for RFS in the multivariable models (model 1). RFS was significantly associated with patient tumor size, nodal status, lymphatic/vascular invasion, and ER status. Patients with symptom-detected tumors had a greater risk of relapse with RR increase of 1.34 (95% CI, 1.09-1.66; $P = 0.006$) compared with patients with screen-detected tumors after adjusting for the other factors (model 1).

We did similar multivariable analyses among subsets of patients categorized by tumor ER status. Among patients with ER-positive tumors, the adjusted RR of recurrence was 1.18 for patients with symptom-detected tumors (95% CI, 0.90-1.56; $P = 0.233$) compared with those with screen-detected tumors (model 2). Among patients with ER-negative tumors, the RR was 1.60 (95% CI, 1.14-2.25; $P = 0.007$; model 3).

Breast Cancer–Specific Survival. Similar to the results for RFS, we found that the patients with symptom-detected tumors had an increased risk of breast cancer death (RR, 1.31; 95% CI, 0.93-1.84; $P = 0.117$) compared with the patients with screen-detected tumors, although the differences were not statistically significant because there were few deaths (Table 4). African American race was associated with a significantly elevated risk of death from breast cancer compared with women of other races (RR, 1.87; 95% CI, 1.36-2.58; $P < 0.001$).

In subset analyses, the adjusted RR of breast cancer death was 1.13 (95% CI, 0.68-1.86; $P = 0.638$) among subgroup with ER-positive tumors and 1.46 (95% CI, 0.91-2.35; $P = 0.117$) among subgroup with ER-negative tumors.

The survival model (model 4) included tumor characteristics, treatments, and HER-2/*neu* and Ki-67. Among 1,810 patients with all biomarkers data available, the adjusted RR of tumor method of detection was 1.29 for RFS (95% CI, 0.89-1.87) and 1.19 for BCSS (95% CI, 0.66-2.15), which were similar to the results in model 1. Because of the smaller number of event, the method of detection was not a statistically significant predictor for RFS and BCSS.

Discussion

In summary, we compared the clinical outcomes of patients whose tumors were detected by screening examinations with those whose tumors were detected symptomatically. After adjusting for the known prognostic factors and major treatments received, we found the tumor detection method to be an independent predictor of disease recurrence. Specifically, patients with symptom-detected breast tumors had a greater risk of recurrence and death (RR for RFS, 1.34; 95% CI, 1.09-1.66; $P = 0.006$; RR for BCSS, 1.31; 95% CI, 0.93-1.84; $P = 0.117$) than patients with screen-detected tumors.

The only tumor characteristic significantly associated with method of detection was Ki-67, when including all four biomarkers in the regression model (the last column in Table 2). Our observation that screen-detected tumors tended to have lower Ki-67 expression and ER-positive status is consistent with earlier observations that screening examinations preferentially identify cancers with these prognostic features (18-20). Because of missing Ki-67 and HER-2/*neu* score in the data, we did exploratory analyses to examine the missing patterns of Ki-67 expression and HER-2/*neu* score by patient age, race, and other tumor characteristics. The results indicated that the subgroup of patients who had Ki-67 information was sufficiently representative of the general cohort of patients with breast cancer at the MDACC, because the missing Ki-67 data were evenly distributed among each of the above factors. The analysis results using Ki-67 data should be representative enough in Tables 2 to 4. In contrast, the missing pattern of HER-2/*neu* immunohistochemistry score was dependent on the year of diagnosis. Patients diagnosed between 1997 and 1998 were less likely to have HER-2/*neu* data, as expected.

Similar to the findings in many other studies (21-23), we found that African American women had an elevated risk of death from breast cancer (RR, 1.87; 95% CI, 1.36-2.58) compared with women of other races after adjusting for method of detection, tumor characteristics, and treatments. Although it is critical to promote targeting education and screening services to minority populations, a parallel effort is to better understand biological difference in tumors among different ethnic groups to improve disease prognosis among minorities.

Our results are also consistent with conclusions from randomized screening trials, including a study of the Health Insurance Plan and the Canadian National Breast Screening Studies (7) and an observational study based on the Finnish Cancer Registry (8). In the former study, patients in the control groups had an increased risk of breast cancer–specific death (RR, 1.36; 95% CI, 1.10-1.68) than patients in the screening groups after accounting for tumor size, lymph node status, and disease stage. In the latter study, patients in the nonscreened group had 1.90 times greater risk of distant recurrence (RR, 1.90; 95% CI, 1.15-3.11) and 2.11 times greater risk of breast cancer–specific death (RR, 2.11; 95% CI, 1.16-3.85) after controlling for the number of positive lymph nodes, tumor size, PR status, histologic grade, HER-2/*neu* amplification, and patient age. The differences separating the current study from the earlier studies with similar conclusions include the following: (*a*) this study uses the largest sample size from one of the largest multidisciplinary breast cancer centers in the United States; (*b*) this study focuses on recently diagnosed patients (1997-2005) who have received adjuvant chemotherapy and hormonal therapies in the modern era; and (*c*) patient information in this study includes biomarker data, such as Ki-67 expression and HER-2/*neu* immunohistochemistry score that has become available only recently.

There are several limitations of our study. First, it is observational. Unlike randomized controlled screening trials, women who chose to have screening examinations may have very different characteristics from those who did not. However, despite the possibility of such a bias, our conclusions from this observational study are

consistent with those of our earlier study of the Health Insurance Plan and Canadian National Breast Screening Studies randomized trials (7). Second, conclusions from this study were based on the data from a single hospital, which may be subject to some selection bias. Compared with the Surveillance, Epidemiology, and End Results data collected from 17 geographic areas of the United States for women ages ≥40 years and diagnosed with primary invasive breast cancer between 1997 and 2003, we found that more patients represented in the breast cancer database at the MDACC tended to have later-stage breast cancer (16.7% stage III/IV tumors compared with 10.4% stage III/IV tumors from Surveillance, Epidemiology, and End Results) and to be of a racial/ethnic minority (9.9% African American and 15.1% Hispanic and other minority women compared with 8.3% African American and 7.2% other minority women from Surveillance, Epidemiology, and End Results). Patients represented in the database at the MDACC were also younger than those from the Surveillance, Epidemiology, and End Results database: 31.0% compared with 18.4% of patients, respectively, were younger than 50 years. Finally, the information on breast density at diagnosis is not available in our database.

Part of the observed residual survival benefit associated with tumor screening may not be completely due to screening itself but is partially due to lead-time bias and length bias. As indicated in our results, women diagnosed by screening examinations often had better tumor characteristics at diagnosis than those otherwise diagnosed, which explained the lead-time bias. The amount of time by which the diagnosis is advanced as a result of early detection by screening is the lead time. Length-bias is revealed from the fact that tumors detected by screening examination may have biological profiles (e.g., slower growing or less aggressive) that are different from tumors otherwise diagnosed (7). The finding that patients with screen-detected tumors still have better prognosis than those with symptomatically detected tumors after adjusting for tumor characteristics, such as ER/PR status, Ki-67 expression, and HER-2/*neu* score in the models indicates that the improved prognosis of screen-detected patients is due to some combination of length bias and actual screening benefit. But it is impossible to separate length bias and the actual screening benefit.

Breast tumors are heterogeneous. It is still impossible now to obtain a complete profile to describe the heterogeneity of the tumors. Including method of detection in the model better enables predicting patients' prognoses. Method of detection is not a prognostic factor in the conventional sense (such as tumor size and nodal status), but it gives important information and partially adjusts for length bias.

This study suggests that the information of the detection method should be routinely collected in the breast cancer database to help clinical trialists and health-care providers improve prognosis prediction for patients with breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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