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Population-based Estimate of the Prevalence of HER-2 Positive Breast Cancer Tumors for Early Stage Patients in the US

Kathleen A. Cronin[1,*], **Linda C. Harlan**[2], **Kevin W. Dodd**[1], **Jeffrey S. Abrams**[3], and **Rachel Ballard-Barbash**[2]

[1]Surveillance Research Program, National Cancer Institute, Bethesda, Maryland, USA

[2]Applied Research Program, National Cancer Institute, Bethesda, Maryland, USA

[3]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland, USA

Abstract

The goal of this study was to estimate prevalence of HER-2 positive tumors in a population-based sample of 1026 women diagnosed in 2005 with early stage breast cancer. We modeled the relationship between patient and tumor characteristics and HER-2. HER-2 positive estimates were 19% for women aged ≤49 years and 15% aged ≥50 years. HER-2 varied by tumor grade and size in women aged ≤49 years but was not significant in multivariate analysis. Tumor grade and race were associated with HER-2 for women aged ≥50 years after controlling for other variables. HER-2 varies by age and by race and tumor in older women.

Keywords

Breast carcinoma; HER-2/neu; Population-based study; SEER program

INTRODUCTION

Recent reports showed that the use of the recombinant monoclonal antibody trastuzumab, in addition to adjuvant chemotherapy, for breast cancer with overexpression of the HER-2 protein or amplification of the *HER-2/neu* gene reduced the risk of recurrence by 50% in women irrespective of nodal status (1, 2). HER-2 positive tumors are associated with an increased tumor aggressiveness, recurrence, and poorer survival (3). How the use of trastuzumab will translate into a benefit for the overall population depends on the prevalence of HER-2 positive tumors among breast cancer patients. This analysis uses population-based data from the Surveillance, Epidemiology, and End-Results Program (SEER) cancer registries to obtain an estimate of HER-2 positive tumors in early stage disease representative of the US population. This study includes the largest sample of women with HER-2 tumors reported to date and is the first to report national prevalence estimates.

Correspondence to: Kathleen Cronin, PhD, MPH, 6116 Executive Blvd, Suite 503, Statistical Research and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD 20892-7344, USA, cronink@mail.nih.gov.

DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

An initial analysis reported in the literature (4, 5) on 189 primary breast cancers (103 in one sample and 86 in a second sample) estimated the prevalence of HER-2 positive tumors to be in the range of 20–25%. Subsequent analyses estimated the prevalence of HER-2 positive tumors to be in the range of 11–30%, depending on the characteristics of the population studied and the definition of HER-2 positive (6–12). A study using population-based data from the Carolina Breast Cancer Study found 22% of the sample to be HER-2 positive (12). Prevalence estimates in these studies were related to tumor characteristics such as stage, grade, and hormone receptor status. More recently, tissue microarrays of 354 breast cancer patients diagnosed in 1995 prepared from discarded tissue blocks within the catchment area of the Hawaii tumor registries were analyzed (13). This study found 12% of patients examined were HER-2 positive [8% of which were ER (estrogen receptor) negative and 4% ER positive].

In 2005 National Cancer Institute (NCI) conducted one of its annual Patterns of Care (POC) studies in a population-based sample of early stage breast cancer patients registered in SEER. Using these data we provide a population-based estimate of the prevalence of HER-2 positive tumors in the US and investigated correlation with other prognostic factors.

METHODS

NCI's SEER program is a population-based cancer registry system that routinely collects data from medical records within hospitals, outpatient surgical centers, pathology centers, and free-standing radiology centers. The SEER registries collect data on all cancer patients residing within their defined geographic region. The data collected include detailed information on demographics, diagnosis, and tumor characteristics. Treatment information also is collected. However, data on adjuvant therapy often are incomplete, because much of this therapy is given in the outpatient setting. Therefore, NCI supplements routine SEER data by conducting annually POC studies that reabstract data and ask each patient's treating physician to verify the therapy provided.

Women diagnosed in 2005 with early stage breast cancer, defined in this analysis as stages I through IIIA (American Joint Committee on Cancer), were stratified by age at diagnosis (age 49 years or younger, age 50 years or older), stage, race/ethnicity, and registry, and a random sample was selected. Women aged 50 years or younger, nonHispanic black women and Hispanic women, were oversampled to obtain stable estimates for these groups. Women with a previous diagnosis of cancer other than nonmelanoma skin cancers, a simultaneous cancer diagnosis, or who were younger than 20 years were ineligible for the study.

The 12 participating SEER registries (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Utah, Seattle, Atlanta, San Jose/Monterey, Los Angeles, and Alaska) reabstracted the hospital record of the selected patients to verify tumor characteristics, treatment provision, and demographic information. SEER did not routinely collect information on HER-2 status in 2005, but HER-2 status was ascertained for the selected patients.

Abstractors noted from the medical record whether HER-2 status was determined and whether fluorescence in situ hybridization (FISH) and/or immunohistochemical (IHC) test were performed and the results of those tests. FISH results were classified as negative if less then 1.8, equivocal if between 1.8 and 2.2, and positive if greater than 2.2. IHC was classified as positive if 3+, equivocal if 2+, and negative if 1+ or 0. For patients where both IHC and FISH were performed, results for FISH were used to determine HER-2 status. In some cases the test values were not included in the record, but a note indicated that the results were positive, equivocal, or negative and which test was perform or that the type of test was not known. These patients were included in the analysis.

Descriptive information was based on observed patients in the POC study. Owing to the oversampling of younger women and by race/ethnicity, descriptive results do not directly represent the population of SEER patients. To obtain population estimates of the HER-2 positive patients by covariates, we weighted the sample of patients to the total SEER population of early stage breast cancer and incorporated the sampling design with Proc Surveymeans and Proc Surveyfreq in SAS (14). HER-2 prevalence was estimated for unknown covariate values (such as unknown ER status or unknown grade), but unknown values were excluded when performing univariate chi-square test for association. We used multiple logistic regression to further define the relationship between prognostic variables and HER-2 status with Proc Surveylogistic in SAS (14). Cases with unknown covariate values were excluded from the logistic regression analysis.

RESULTS

Table 1 describes the number of cases in the analysis, the number with known HER-2 status, and the testing method used for all cases that were considered HER-2 positive. The sample consisted of 1026 women diagnosed with stage I, II, and IIIA breast cancer in the year 2005. Of those 872 (85%) had a known HER-2 status. A total of 154 (15%) had unknown HER-2 status, either because both tests were not done (75 women) or the status was listed as unknown (79 women). Table 2 shows the percentage of women with known HER-2 status by several covariates. Women with missing HER-2 status were more likely to also have missing ER and PR (progesterone receptor) status and unknown grade than women with known HER-2 status. Although there was evidence suggesting that HER-2 status may not be missing at random, we did not adjust for this possibility because of the tendency for those patients to also have other missing covariates.

Of the 883 known HER-2 status, 171 or 16% (95% CI, 12%, 21%) were HER-2 positive. Tables 3a and 3b provide HER-2 status stratified by age (age 49 years or younger, age 50 years or older), race/ethnicity, and prognostic factors. The univariate analysis showed HER-2 status is significantly correlated with tumor size and grade for women aged 49 years or younger and correlated with race/ethnicity, ER status, tumor size, and grade for women aged 50 years and older.

Table 4 gives results from the logistic regression models using excluding women with unknown tumor size, nodal status, grade, or ER status (excluding 41 women aged 49 years or younger and 58 women aged 50 years or older). Equivocal patients were reclassified as

negative for the regression analysis. Regressions excluding patients with equivocal tests gave similar results (results not shown). Although larger tumor size and higher grade appeared to be associated with higher rates of HER-2 positivity for women aged 49 years or younger, it did not reach the level of statistically significance. Race/ethnicity and tumor grade were associated with HER-2 status in women aged 50 years and older.

In our data set we estimate that 15% of white women and 31% of African-American women aged 50 years and younger and 12% of white women and 28% of African-American women over age 50 had triple negative tumors.

DISCUSSION

This analysis estimated the prevalence of HER-2 positive breast cancers in 12 population-based SEER registries at 19% (13%, 25%) of women aged 49 years or younger and 15% (9%, 21%) of women aged 50 years or older with early stage breast cancer. The overall prevalence estimate for the SEER population was 16% (12%, 21%) for stage I, II, and IIIa breast cancer. These results were consistent with previously reported estimates for early stage disease and provide the first national prevalence estimates for HER-2 positive breast cancer for the US.

The data reported were generally consistent with other findings on the relationship between HER-2 positive tumors and other prognostic factors. Konecny *et al.* found HER-2 inversely related to ER and PR levels (11). In a single cohort of women with primary breast cancer analyzed by Huang ER, PR, and tumor grade were independent predictors of HER-2 status, with ER and PR being negatively and grade being positively related to HER-2 overexpression (8). Further analysis of the cohort by age found that the relationship between HER-2 and ER/PR varied by age, and hormone receptors were not independent predictors of HER-2 overexpression in women 45 years of age or younger (9). We found ER status to be significantly inversely related to HER-2 overexpression in the univariate analysis of women aged 50 years and older. However, this relationship between hormone status and HER-2 positivity did not remain after controlling for other variables. No relationship between hormonal status and HER-2 status was seen in younger women.

Stark *et al.* and Carey *et al.* found no significant difference in the prevalence of HER-2 tumors between African-American and white women (7, 12). However, Stark found grade and stage were associated with HER-2 status in whites but not in African-Americans (7). We did find a significant relationship between race/ethnicity in older women with black women at a lower risk than white nonHispanic women, and Hispanic women and Asian women at a higher risk. Note that the lower risk of HER-2 positive disease in black women was after controlling for ER and PR status and does not imply lower rates of HER-2 disease in black women, because they also have higher rates of ER and PR negative disease. Table 3b showed 12.5% of nonHispanic white women and 17% of black women had HER-2 positive disease.

There were several limitations to this study. Nearly 15% of the patients did not have their HER-2 status recorded, either because it was not done or was missing from the record. Table 2 shows that missing HER-2 status often occurred along with other unknown variables such

as unknown ER and PR status and unknown grade. This tendency for a patient to have multiple missing variables makes it difficult to model or impute missing HER-2 values.

The tests reported here were not performed at a central laboratory and 113 out of 171 positive results were based on IHC. Paik *et al.* reported that a central laboratory found 18% of IHC assays reported as positive from community laboratories were not confirmed as either strongly positive by the HercepTest™ or positive for gene amplification by central review (15). Similarly Perez *et al.* found a high degree of discordance between local and central test for IHC and FISH (16). Although we required that IHC be 3+ to be positive, this would still tend to increase the percentage of patients with HER-2 positive tumors in our sample. In addition, 43 out of 171 positive results were recorded as positive without the specific test values available. Of those 43, 15 also did not specify the type of test performed.

The strength of the study is that it used a geographically diverse population-based sample of women and reflects diagnosis, testing, and treatment in the community. In addition, it is the largest study to date and provides the first national prevalence estimates for the US. However, despite this strength, it is clear from the wide confidence intervals for estimates in some subgroups that larger studies are needed to determine if the prevalence of HER-2 varies by patient or tumor characteristics. Starting in 2010 SEER will begin routine collection of HER-2 status for breast cancer patients. In addition, larger samples and directed studies would be needed to determine if the benefit of treatment by trastuzumab varies as detailed data on chemotherapy is not yet routinely available in cancer registries. The American Cancer Society estimates that 184,450 cases of female breast cancer were diagnosed in 2008 (17). Based on previous stage distributions observed in SEER, we would expect that approximately 90% of patients overall would be stage I, II, and IIIa. Assuming 16% prevalence of HER-2 positive cases among these patients, this would suggest just over 29,000 women might benefit from trastuzumab a year. If the reduction in recurrence reported from the clinical trial extends to the US population, use of trastuzumab may have the potential to have a major impact on the number of recurrences in the next several years.

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Table 1

Description of Cases and Tests Used for HER-2 Positive

	Number of Cases
Cases in study	1026
HER-2 status known	872
Total number with positive HER-2 results *Test used to determine positive HER-2 status*	171
Fluorescence *in situ* hybridization (FISH)	
Known FISH value	33
Positive FISH value unknown	10
Immunohistochemical (IHC)	
Known IHC value	95
Positive IHC value unknown	18
Positive result type of test unknown	15

Table 2

POC 2005 – Distribution of Patients With Known vs. Unknown HER-2 Status by Non-clinical and Clinical Factors

	HER-2 Status Known		HER-2 Status Unknown or Not Tested	
	%	Count	%	Count
Overall	85.0	872	15.0	154
Age				
<50	86.5	385	13.5	60
≥50	83.8	487	16.2	94
Race/Ethnicity				
White nonHispanic	83.5	223	16.5	44
Black nonHispanic	86.2	218	13.8	35
Hispanic	83.4	206	16.6	41
Asian/PI	87.7	178	12.3	25
AI/AN	83.9	47	16.1	9
Nodes[a]				
Positive	88.0	409	12.0	56
Negative	82.9	437	17.1	90
Unknown/None examined	76.5	26	23.5	8
ER expression[a]				
Positive	85.7	608	14.3	101
Negative	88.5	230	11.5	30
Unknown	59.6	34	40.4	23
PR expression[a]				
Positive	85.0	516	15.0	91
Negative	89.4	319	10.6	38
Unknown/None examined	59.7	37	40.3	25
Tumor size				
< 2 cm	83.3	424	16.7	85
2–4 cm	86.3	340	13.7	54
> 4 cm	87.7	107	12.3	15
Unknown	100.0	1		
Grade				
Well/Moderate (I, II)	84.7	461	15.3	83
Poorly/Undifferentiated (III, IV)	86.7	364	13.3	56
Unknown	75.8	47	24.2	15
Stage				
Stage I	82.0	324	18.0	71
Stage II	86.5	402	13.6	63
Stage IIIa	87.9	146	12.1	20

[a] *p*-value <.05 for chi-square test for association.

Asian/PI - Asian/Pacific Islander, AI/AN - American Indian/Alaska Native.

Table 3

a. POC 2005 – Distribution of Nonclinical and Clinical Factors by Age Group and HER-2 Status

	Age 49 Years or Younger (*n* = 385)					
	HER-2 Negative		HER-2 Equivocal		HER-2 Positive	
	% (CI)[a]	Count	% (CI)[a]	Count	% (CI)[a]	Count
Overall	77.4(71.4, 83.4)	288	3.4(1.0, 5.7)	18	19.2(13.5, 24.9)	79
Race/Ethnicity						
White nonHispanic	76.6(67.7, 85.7)	74	2.4(0.0, 5.2)	3	20.9(12.2, 29.6)	19
Black nonHispanic	86.0(79.0, 93.1)	76	1.7(0.0, 3.7)	5	12.3(5.4, 19.2)	16
Hispanic	73.2(59.6, 86.9)	65	7.3(0.0, 16.0)	4	19.5(8.0, 31.0)	20
Asian/PI	78.5(69.0, 88.1)	57	4.5(0.0, 9.5)	6	16.9(8.0, 25.8)	20
AI/AN	79.8(64.2, 95.5)	16		0	20.2(4.5, 35.8)	4
Nodes						
Positive	70.0(60.5, 79.9)	130	4.6(2.4, 8.9)	10	25.4(16.2, 34.3)	49
Negative	82.4(74.7, 90.0)	152	2.7(0.0, 5.5)	8	14.9(7.6, 22.2)	27
Unknown/None examined	83.7(58.7, 100)	6		0	16.6(0.0, 41.3)	3
ER expression						
Positive	78.7(71.1, 86.2)	203	2.7(0.1, 5.2)	9	18.6(11.5, 25.7)	57
Negative	78.4(67.6, 89.2)	74	2.2(0.0, 5.0)	6	19.5(8.8, 30.1)	19
Unknown	50.4(24.6, 76.1)	11	23.1(0.0, 49.3)	3	26.6(10.4, 42.7)	3
PR expression						
Positive	81.6(74.3, 88.9)	187	3.0(0.1, 5.9)	9	15.4(8.5, 22.3)	47
Negative	71.9(60.0, 83.9)	88	1.7(0.0, 4.0)	6	26.4(14.4, 38.2)	29
Unknown	62.1(37.1, 87.3)	13	17.6(0.0, 39.6)	3	20.3(6.6, 34.0)	3
Tumor size[b]						
<2 cm	85.7(78.8, 92.7)	142	3.3(0.4, 6.3)	10	10.9(4.5, 17.3)	20
2–4 cm	71.7(60.3, 83.0)	114	4.4(0.0, 9.3)	7	23.9(13.1, 34.7)	41
>4 cm	53.4(32.7, 74.1)	31	0.1(0.0, 0.4)	1	46.4(25.7, 67.1)	18
Unknown	100	1		0		0
Grade[b]						
Well/Moderate (I, II)	84.9(78.3, 91.4)	154	2.3(0.2, 4.3)	11	12.8(6.6, 19.1)	28

a. POC 2005 – Distribution of Nonclinical and Clinical Factors by Age Group and HER-2 Status

	Age 49 Years or Younger (*n* = 385)					
	HER-2 Negative		HER-2 Equivocal		HER-2 Positive	
	% (CI)[a]	Count	% (CI)[a]	Count	% (CI)[a]	Count
Poorly/Undifferentiated (III, IV)	69.8(59.1, 79.4)	121	3.6(0.0, 7.6)	6	27.1(17.5, 36.7)	48
Unknown	71.7(41.7, 100)	13	12.2(0.0, 35.1)	1	16.0(0.0, 37.4)	3
Stage						
Stage I	83.9(76.5, 91.4)	109	3.2(0.0, 6.6)	6	12.8(6.1, 19.6)	17
Stage II	71.6(61.1, 82.1)	131	4.8(0.5, 9.3)	11	23.6(13.7, 33.4)	37
Stage IIIa	73.0(56.2, 89.8)	48	0.1(0.0, 0.3)	1	26.9(10.1, 43.7)	25

b. POC 2005 – Distribution of Nonclinical and Clinical Factors by Age Group and HER-2 Status

	Age 50 Years or Older (*n* = 486)					
	HER-2 Negative		HER-2 Equivocal		HER-2 Positive	
	% (CI)[a]	Count	% (CI)[a]	Count	% (CI)[a]	Count
Overall	79.2(72.9, 85.4)	359	5.8(2.8, 8.7)	36	15.1(9.3, 20.8)	92
Race/Ethnicity[b]						
White nonHispanic	82.3(74.4, 90.1)	102	5.3(1.6, 8.9)	8	12.5(5.2, 19.7)	17
Black nonHispanic	75.3(66.1, 84.5)	88	7.8(2.1, 13.5)	11	16.9(8.9, 25.0)	22
Hispanic	59.4(43.4, 75.4)	85	10.3(1.2, 19.3)	9	30.3(15.2, 45.5)	23
Asian/PI	72.8(61.8, 83.9)	64	3.9(0.3, 7.6)	7	23.3(12.3, 34.2)	24
AI/AN	73.8(62.8, 84.9)	20	1.7(0.0, 5.3)	1	24.4(13.3, 35.4)	6
Nodes						
Positive	75.7(68.5, 83.0)	155	9.0(3.2, 14.7)	20	15.3(8.8, 21.8)	45
Negative	80.4(71.8, 88.9)	192	4.4(0.9, 7.9)	12	15.2(7.4, 23.1)	46
Unknown/None examined	86.0(65.1, 100)	12	7.1(0.0, 18.2)	4	6.9(0.0, 21.8)	1
ER expression[b]						
Positive	82.7(75.2, 90.3)	276	5.7(2.1, 9.4)	24	11.5(4.6, 18.4)	39
Negative	62.9(47.1, 78.7)	69	7.0(0.0, 15.6)	12	30.0(16.5, 43.5)	50
Unknown	98.6(96.3, 100)	14	0	0	1.4(0.0, 3.7)	3
PR expression						

b. POC 2005 – Distribution of Nonclinical and Clinical Factors by Age Group and HER-2 Status

	Age 50 Years or Older (*n* = 486)					
	HER-2 Negative		HER-2 Equivocal		HER-2 Positive	
	% (CI)[a]	Count	% (CI)[a]	Count	% (CI)[a]	Count
Positive	83.9(75.1, 92.7)	227	5.9(1.7, 10.1)	19	10.2(2.3, 18.1)	27
Negative	68.2(57.1, 79.3)	118	6.3(0.4, 12.1)	17	25.5(15.6, 35.3)	61
Unknown	96.7(93.6, 99.9)	14	0	0	3.2(0.1, 6.4)	4
Tumor size[b]						
<2 cm	81.4(71.9, 90.8)	195	3.6(0.1, 7.1)	15	15.1(6.2, 24.0)	42
2–4 cm	81.4(73.6, 89.1)	129	5.5(1.3, 9.8)	14	13.1(6.1, 20.0)	35
>4 cm	48.0(26.4, 69.7)	35	26.1(1.6, 50.7)	7	25.8(8.2, 43.5)	15
Grade[b]						
Well/Moderate (I, II)	86.7(78.2, 95.2)	226	5.5(1.4, 9.5)	21	7.8(0.2, 15.4)	21
Poorly/Undifferentiated (III, IV)	66.6(55.4, 77.7)	114	6.2(0.1, 12.3)	11	27.2(17.2, 37.1)	64
Unknown	65.1(39.3, 91.0)	19	6.5(0.0, 14.7)	4	28.3(2.7, 54.0)	7
Stage						
Stage I	82.3(71.8, 92.9)	150	2.6(0.0, 6.2)	11	15.0(5.1, 25.0)	31
Stage II	77.8(69.7, 86.0)	160	8.6(2.6, 14.6)	19	13.6(7.2, 20.0)	44
Stage IIIa	66.9(51.0, 82.8)	49	11.4(0.0, 24.4)	6	21.6(7.5, 35.8)	17

[a] Percentages are weight to represent the SEER population sampled.

[b] *p*-value <.05 for chi-square test for association, unknown categories are excluded when performing chi-squared test.

Asian/PI - Asian/Pacific Islander, AI/AN - American Indian/Alaska Native.

Table 4

Odds of HER-2 Positive Tumor in Women Diagnosed in 2005 With Early Stage Breast Cancer Stratified by Age at Diagnosis and *p*-value for Covariate Effect

	Age 49 Years or Younger *N* = 344	**Age 50 Years or Older *N* = 428**
Race/Ethnicity[b]	*p*-value = .49	*p*-value = .05
White non-Hispanic	1	1
Black non-Hispanic	0.46 (0.18, 1.18)	0.72 (0.28, 1.89)
Hispanic	0.49 (0.14, 1.67)	2.52 (0.93, 6.81)
Asian/PI	0.74 (0.29, 1.88)	2.52 (0.86, 7.39)
AI/AN	0.98 (0.30, 3.26)	1.56 (0.64, 3.85)
ER/PR	*p*-value = .55	*p*-value = .41
ER or PR positive	1	1
Both Negative	0.71 (0.24, 2.16)	1.67 (0.49,5.74)
Nodal status	*p*-value = .71	*p*-value = .82
No nodes positive	1	1
Positive nodes	1.20 (0.44, 3.35)	0.91 (0.40, 2.06)
Tumor size	*p*-value = .21	*p*-value = .70
<2 cm	1	1
2–4 cm	1.66 (0.50, 5.59)	0.67 (0.24, 1.86)
>4 cm	3.85 (0.84, 17.72)	1.02 (0.30, 3.58)
Grade	*p*-value = .07	*p*-value = .03
I or II	1	1
III or IV	2.59 (0.92, 7.34)	3.82 (1.15, 12.66)

Asian/PI - Asian/Pacific Islander, AI/AN - American Indian/Alaska Native.