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First Do No Harm: Population-Based Study Shows Non-Evidence–Based Trastuzumab Prescription May Harm Elderly Women with Breast Cancer

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Abstract

Background—Trastuzumab, although cardiotoxic, is associated with improved survival in HER2-positive breast cancer. Non-compliance with HER2 testing guidelines before prescribing trastuzumab occurs in practice; however, the clinical consequences are unclear.

Methods—Using SEER–Medicare database (2000–2009), we assessed differences in baseline characteristics between women ≥65 with breast cancer who received and did not receive HER2 testing prior to trastuzumab prescription. We used propensity score matched-pair analysis to balance the confounders between these two groups. We assessed the differences in overall survival and 3-year rates of avoiding congestive heart failure (CHF) between women who received trastuzumab without HER2 testing (trastuzumab group) and women who had chemotherapy but did not receive trastuzumab (irrespective of testing) (chemo-only group). Based on the matched data, we used Cox regression in these assessments with double robust estimation or with stratification.

Results—Among women who received trastuzumab, 140 (4.7%) had no documentation of HER2 testing. Breast surgery, south residential region, and an earlier year of diagnosis were predictive of no HER2 testing in multivariate logistic regression. Women in the chemo-only group had similar overall survival (HR=1.28; P=0.108) over an 8-year follow-up and significantly higher likelihood

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of avoiding CHF over 3 years post-diagnosis (HR=1.66, P=0.036) compared to women in the trastuzumab group, using the propensity score matched data.

Conclusions—Non-evidence-based prescription of trastuzumab is associated with increased rates of CHF with no additional survival benefit among older women with breast cancer.

Impact—Inappropriate prescriptions of targeted therapies agent can lead to detrimental health and financial consequences.

Keywords

non-evidence-based prescription; trastuzumab; breast cancer; SEER-Medicare; propensity score

INTRODUCTION

Targeted therapies constitute a revolutionary advancement in medical oncology, markedly improving the survival time of individuals with cancer. However, such benefits are often limited to patients with certain molecular subtypes of disease.[1] Given the high cost of targeted therapy, its prescription should be limited to patients who are “correctly targeted” when an identified target exists. This practice, referred to as *evidence-based prescription* in our paper, not only ensures more efficient allocation of limited resources in the healthcare sector, but more importantly safeguards patients from exposure to potentially toxic treatments with low likelihood of benefit.

Trastuzumab is a monoclonal antibody that inhibits the human epidermal growth factor receptor 2 (HER2), and thus specifically targets breast tumors that overexpress that cell membrane receptor. HER2-positive (HER2+) tumors, which occur in 20%–25% of breast cancer, are usually more aggressive. Before the approval of trastuzumab, patients with HER2-positive breast cancer have lower overall and cancer-free survival rates and a higher likelihood of recurrence.[2, 3] Several clinical trials have demonstrated that trastuzumab, alone or in combination with other chemotherapy agents, is associated with significant improvement in tumor response rate, progression-free survival, and overall survival for patients with HER2+ breast cancer.[4–7] Trastuzumab was approved by the U.S. Food and Drug Administration for metastatic breast cancer in September 1998, and as adjuvant treatment for HER2+ early-stage breast cancer in November 2006.

Oncologists must exercise caution when prescribing trastuzumab because of its clinical and economic implications. Based on the average sale price (ASP), one study estimated costs up to \$100,000 for 52 weeks of adjuvant trastuzumab in a community setting.[8] More importantly, trastuzumab has been associated with an increased risk of cardiotoxicity.[9–14] The clinical benefit of trastuzumab depends critically on its use to treat breast cancer in only the appropriate subgroup that may truly benefit because HER2 negative patients derive no benefit but are at risk for associated side effects. This concern motivated the American Society of Clinical Oncology and the College of American Pathologists (ASCO-CAP) to jointly issue a guideline in 2007 recommending routine testing of HER2 tumor status for patients with newly diagnosed invasive breast cancer.[8] The same recommendation can also be found in the ASCO-CAP update guideline issued in 2013.[15]

Several studies have explored the adherence to the above ASCO-CAP guideline.[16–20] Overall, a higher rate of HER2 testing was reported in studies that considered only more recent data. While all studies agreed that prescribing trastuzumab without administering a HER2 test *a priori* represents highly inappropriate clinical practice, none evaluated its impact on health outcomes. Our objective is to use uninformed trastuzumab prescription (not based on HER2 test results) to exemplify the clinical consequences of non-evidence-based prescription of targeted therapy agents in oncology. Such information will assist decision-makers in projecting the potential benefit of evidence-based reimbursement policies.

METHODS

Database

We used the 2000–2009 Surveillance, Epidemiology, and End Results (SEER)–Medicare data, which included SEER data up to 2009 and Medicare claims through 2010. The SEER Program is an epidemiological surveillance system of population-based tumor registries that collects data from 17 geographic areas in the United States. The SEER–Medicare database links cancer patients in the SEER Program with Medicare enrollment and claims files for Medicare beneficiaries identified from the SEER. The database provides clinical (e.g., primary tumor site, grade and stage at diagnosis) and economic (e.g., resource utilization, Medicare payment) information on Medicare-eligible cancer patients.[21]

Ascertainment of Study Cohort and Identification of HER2 Test

We first selected women aged 65 and over whose breast cancer was diagnosed between January 1, 2000 and December 31, 2009. We used primary tumor site to identify breast cancer, and excluded women younger than 65 years at diagnosis and those who had *in situ* or unknown stage breast cancer or had had other previous cancer. We restricted the study cohort to those who were alive at diagnosis, had continuous Medicare Parts A & B enrollment, and did not have any HMO enrollment within one year before and after the breast cancer diagnosis to ensure completeness of claims for calculating comorbidity and identifying treatment related to breast cancer. We defined users of trastuzumab as women with at least two different claims for trastuzumab more than 30 days apart within one year of their breast cancer diagnosis via the Health Common Procedure Coding System code J9355 from outpatient, carriers, durable medical equipment (DME), home health agency and hospice files, as well as National Drug Codes 50242013460, 50242013468, 50242005656, and 63552047001 from the DME and Part D files.

Using the first claim date for trastuzumab as the reference date, we traced back to the date of breast cancer diagnosis to determine whether each woman had received a HER2 test. We considered a woman as having had HER2 testing prior to trastuzumab prescription if she had a claim with the following Current Procedural Terminology codes during the above period of observation: 83950, 88182, 88342, 88360, 88361, 88365, 88367, and 88368.[20, 22, 23]

Outcome Measures and Covariates

We measured health outcomes according to the overall survival time after breast cancer diagnosis and the occurrence of congestive heart failure (CHF) within 3 years of first

administration of chemotherapy or trastuzumab. To identify CHF events, we used all Medicare claims files with the ICD-9 diagnosis codes 425, 428, and 787.51. We considered a woman to have CHF if she had at least one claim indicating a CHF event in the inpatient file or at least two such claims more than 30 days apart in the outpatient files after first date of chemotherapy or trastuzumab. Covariates explored in the multivariate analysis included patient demographics (age at diagnosis, race, and marital status), census region of residence, and clinical information (tumor stage, grade, ER/PR status, year of diagnosis, receipt of anthracycline-based chemotherapy, radiation therapy, and breast surgery, and history of CHF). We calculated the severity of comorbid conditions for each woman based on a modified Charlson comorbidity score validated in prior claims-based studies.[24, 25]

Statistical Analysis

We calculated the percentage of women prescribed trastuzumab without a HER2 test and explored that trend by calendar year of the diagnosis, using the Cochran-Armitage test.[26] Among the women who received trastuzumab, we examined differences in the distribution of baseline characteristics by HER2 testing status (yes vs. no) using the chi-squared test for categorical variables. Next, we applied the backward selection method to yield the parsimonious multivariate logistic regression model that predicts HER2 testing status in this cohort.

To determine whether non-evidence-based trastuzumab prescription has beneficial or detrimental effects on clinical outcomes, we compared the overall survival and 3-year CHF-free distributions between women with breast cancer who received trastuzumab, either alone or in conjunction with chemotherapy, without HER2 testing (the trastuzumab group) and those who received chemotherapy but did not receive trastuzumab (the chemo-only group). To minimize the selection bias associated with the nonrandom assignment of trastuzumab treatment in the above cohort, we used a matched-pair analysis based on a propensity score to balance the observed confounders between the two groups. Specifically, we estimated the propensity score for receiving trastuzumab without HER2 testing using a non-parsimonious logistic model that included the following potential confounders: age, comorbidity score, history of CHF, ER/PR status, tumor grade, receipt of anthracycline-based chemotherapy, stage at diagnosis (late stage versus I, II and III), receipt of breast surgery, and year of diagnosis, irrespective of the clinical outcomes. Using the propensity score predicted from the above logistic model, we then matched each woman in the trastuzumab group with two women in the chemo-only group, using an 8-to-1 greedy matching algorithm without replacement.[27] These procedures ensured that the 9 distribution of each observed confounder was similar between the trastuzumab and chemo-only groups in the above 1-to-2 matched cohort.

Using the matched cohort consisting of 420 observations, we estimated Kaplan-Meier curves and their medians for the women in the trastuzumab and chemo-only groups. We then used Cox regression to estimate the hazard ratios (HRs), while adjusting the covariates for remaining sample differences between the two groups with the double robust estimation.[28, 29] Double robust estimation combines propensity score matching with direct regression on the outcomes has been shown to lead to more robust and efficient estimation.

[30] In a sensitivity analysis, we also estimated the HRs in the Cox regression with treatment indicator only by stratifying on the matched pair to adjust the standard errors.[31]

We reported the HRs and corresponding 95% confidence intervals (CIs) for the overall survival outcome since breast cancer diagnosis and time to the first CHF event within 3 years of first administration of chemotherapy or trastuzumab. We used SAS 9.3 software (Cary, NC) and S-PLUS 8.0 (Palo Alto, CA) to conduct all analyses; we reported statistical significance as $P < 0.05$.

The University of Chicago's Institutional Review Board exempted this study for approval because all patients in the database had been de-identified.

RESULTS

Factors associated with non-evidence–based trastuzumab prescription

Of 100,555 women ages 65 and older who were newly diagnosed with invasive breast cancer between 2000 and 2009, 2,984 received trastuzumab within 12 months of their diagnosis. Among those, 140 (4.7%) had no claim indicating they received HER2 testing prior to initiating trastuzumab treatment (Table 1).

Table 2 lists the characteristics of the women who were treated with trastuzumab. A significantly higher proportion of women in the “no HER2 test” group had late-stage breast cancer (22.1% vs. 12.2%, $P=0.002$), negative ER/PR status (57.9% vs. 48.1%, $P=0.024$), did not receive radiation therapy (50.7 vs. 40.8%, $P=0.02$), and did not have surgery (22.9% vs. 7.2%, $P<<0.001$); the latter probably reflecting late-stage disease at diagnosis for a higher proportion of women in the “no HER2 test” group. Evidence-based trastuzumab prescription substantially improved over time; the proportion of women who received trastuzumab without HER2 testing decreased from over 20% in 2000 to less than 3% in 2009. Results from multivariate logistic regression with backward selection (Table 3) identified three predictors of non-evidenced–based trastuzumab prescription: surgery (yes/no), region of residence (South vs. other census regions), and year of diagnosis (2004 and earlier vs. 2005 and after).

Comparison of Health Outcomes

Propensity score analysis showed that with the exception of tumor grade the absolute standardized difference for each covariate between women in the trastuzumab group and those in the chemo-only group was less than 10% in the matched cohort. The matched cohort had a negligible imbalance on the measurable characteristics, as demonstrated in Table 4.

Survival analyses showed no significant benefit in overall survival among the trastuzumab group compared to the chemo-only group ($HR=1.28$; $P=0.108$). The proportions of women who survived up to 2, 4, 6, and 8 years after their breast cancer diagnosis were 83%, 64%, 55%, and 52%, respectively, for the chemo-only group and 81%, 63%, 46%, and 34%, respectively, for the trastuzumab group. The analysis of the time to a CHF event within 3 years of breast cancer diagnosis showed a higher likelihood of having CHF event during this

period for the trastuzumab group ($HR=1.66$, $P=0.036$). At 6 months and 1, 2, and 3 years after breast cancer diagnosis, the proportions of women who had not experienced a CHF event were 93%, 90%, 86%, and 83%, respectively, for the chemo-only group and 89%, 83%, 79%, and 77%, respectively, for the trastuzumab group.

In sensitivity analyses, we fitted a univariate Cox model stratified on matched sets to account for matched cohort designs for OS and CHF events, respectively. Similar results were obtained for OS ($HR=1.24$, $P=0.234$) and CHF ($HR=1.60$, $P=0.067$). As expected, the stratified analyses based on paired data are less efficient than the double robust estimation, causing large P-values in these analyses.

DISCUSSION

At a recent workshop of the Institute of Medicine, entitled “Delivering Affordable Cancer Care in the 21st Century,” major concerns were expressed regarding the potentially inhibiting effect of exorbitant treatment costs on the healthcare system’s ability to deliver high-quality cancer care for patients in the United States.[32] Workshop participants urged clinicians to reduce waste and inefficiency in the healthcare delivery system by minimizing practices that provide little or no benefit to patients. Prescribing trastuzumab without performing a HER2 test exemplifies such practice. In our analysis of SEER–Medicare data, we found that close to 5% of older women with newly diagnosed breast cancer who received trastuzumab had no claim indicating the administration of a HER2 test. While the percentage appeared modest, given the large number of women with breast cancer, the overall impact can be substantial.

In our exploration of whether non-evidence–based trastuzumab prescription is harmful, we compared older women with breast cancer who were treated with trastuzumab without evidence of HER2 testing (the trastuzumab group) with a matched cohort who had chemotherapy but did not receive trastuzumab regardless of their HER2 testing status (the chemo-only group). We found that on average the overall survival for women in the trastuzumab group was no better than that of women in the chemo-only group. Furthermore, the hazard ratio associated with CHF-free survival within three years of first administration of chemotherapy or trastuzumab was significantly higher for women in the chemo-only group than for those in the trastuzumab group. The 3-year duration was chosen because cardiotoxicity caused by trastuzumab appears to be reversible; it has been shown that patients recover their cardiac function within months of discontinuing trastuzumab.[33, 34] These findings suggest that the practice of non-evidence–based trastuzumab prescription was harmful to elderly women with breast cancer. Strictly speaking a highly inappropriate, non-evidence–based practice constitutes prescribing trastuzumab to treat breast cancer that is known to be HER2-negative. We used the lack of a HER2 test in the duration between breast cancer diagnosis and first trastuzumab administration to signal the behavior of non-evidence–based prescribing because we could not ascertain the HER2 status of the patients since this information was not collected in SEER data nor Medicare claims. It is possible that some women in the trastuzumab group may have had HER2+ tumor status and would have benefited from trastuzumab. However, considering that only about 20%–25% of women with breast cancer have HER2+ tumor status, it is reasonable to expect that the

majority of women given non-evidence-based trastuzumab prescriptions did not have HER2+ tumor status and therefore would not benefit from this targeted therapy.

The practice of non-evidence-based trastuzumab prescribing could have several explanations. First, the high cost of trastuzumab may be a create financial incentives for oncologists to prescribe this drug as it has been shown that the current Medicare reimbursement for infused drugs under Medicare Part B (ASP plus 6% mark-up) appears to have created a perverse financial incentive to prescribe more expensive drugs.[35] Second, oncologists may be responding to patients' requests for the newest therapy available on the market. Studies have found that a large proportion of patients with advanced-stage, incurable cancers have unrealistically optimistic expectations of cancer therapies.[36, 37] Such expectations could prompt patients with breast cancer, especially those with advanced-stage disease, to demand trastuzumab treatments regardless of their HER2 status. The above observation is in line with our finding that a disproportionately higher percentage of women prescribed trastuzumab without HER2 testing had stage IV breast cancer (Table 2). Lastly, non-evidence-based trastuzumab prescribing could reflect the learning curve associated with the release of a new agent or technology. It takes time for professional societies to develop and disseminate practice guidelines regarding the application of new technology; therefore, it is not unusual to observe a higher rate of non-evidence-based prescribing at the early phase of new technology diffusion. In a single institution study, Stark et al. (2004) showed that the proportion of women diagnosed with primary invasive breast cancers who were tested for HER2 status increased by two-fold from 1999 to 2000.[18] Using 2005 Medicare claims, Tong et al. (2007) reported that 32% of patients with breast cancer who received trastuzumab had not received HER2 testing.[20] In our study, the rate of non-evidence-based prescription of this agent decreased from 20% in 2000 to less than 3% in 2009.

Escalating costs have motivated several payors and oncology practice groups to pilot-test novel payment methods or care delivery models to provide high-quality, affordable cancer care.[32] A value-based insurance design that aligns reimbursement to evidence-based practice has been commonly discussed. While pilot studies of evidence-based reimbursement showed promising results,[38, 39] the impact of large-scale implementation of such payment methods to the Medicare program remains unknown. Findings from our population-based study support the development, refinement, and dissemination of evidence-based payment methods to dissuade practice patterns that not only lead to inefficient resource allocation, but which are potentially harmful to patients.

Our study has several limitations. First, we ascertained HER2 testing based on the billing codes in Medicare claims for immunohistochemistry or fluorescence in situ hybridization tests. Although both tests are recommended in the guidelines, they could have been administered for other medical indications, which is something we cannot determine because there is no unique billing code that distinguishes the medical indications for these tests.[23, 40] However, this issue should not have a large effect on our study because the absence of a claim for either test would indicate that no effort had been made to determine the patient's HER2 status. Second, it is possible that a patient received a HER2 test but that her provider either submitted the HER2 test claim under a pathology billing code that allows for bundled claims or the provider did not bill Medicare for the test. A validation study that

compared administrative claims and medical records in a commercial insurance plan concluded that HER2 testing as identified from claims was under-reported.[23] To what extent this conclusion is applicable to the Medicare population should be verified in future studies. However, given that Medicare is the primary payor for the vast majority of Medicare-eligible beneficiaries and we restricted our study cohort to those under Medicare fee-for-service payment (by excluding HMO enrollees), which has not yet considered bundled payments for HER2 tests, the magnitude of any reporting bias should be lower than that in commercial claims. Lastly, the propensity score analysis may not remove a hidden bias induced by unmeasurable or unobserved prognostic variables, unless unmeasured variables are correlated to the measured variables used to compute the propensity score.[41] Despite this limitation, which is commonly found in studies using observational data, the analytical method we employed is a viable approach to address the topic we examined, given that it is unlikely to be explored in a randomized clinical trial.

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Figure 1.
Overall survival based on trastuzumab treatment (1:2 match, trastuzumab: chemo-only)

Figure 2.
3-year CHF-free survival based on trastuzumab treatment (1:2 match, trastuzumab:chemo-only)

Table 1

Study Cohort Determination

Step	Criteria	# of pts/ observations	# excluded
0	First, stage I–IV breast cancer diagnosed during 2000 – 2009 in SEER–Medicare data	283,339	
1	Female only	280,747	2,592
2	Age 65+ at diagnosis	185,132	95,615
4	Alive at diagnosis	185,078	54
5	Enrolled with Medicare Parts A & B, but no HMO for 12 months post diagnosis	117,691	67,387
6	Enrolled with Medicare Parts A & B, but not enrolled with HMO during 12 months before the diagnosis	110,555	7,136
7	Received any chemotherapy	25,975	84,580
8	Received trastuzumab treatment within 12 months of the breast cancer diagnosis	2,984	22,991
9	Without HER2 testing prior to trastuzumab treatment	140	2,844

Table 2

Cohort of Women Given Trastuzumab Treatment (N=2,984)

Factor	HER2 Testing		P value
	No (N=140)	Yes(N=2844)	
Age			
65–74	94 (67.14%)	1835 (64.52%)	0.5871
>=75	46 (32.86%)	1009 (35.48%)	
Race			
White	116 (82.86%)	2493 (87.66%)	0.1154
Others	24 (17.14%)	351 (12.34%)	
Marital status			
married	597 (42.14%)	1392 (48.95%)	0.1198
Others	81 (57.86%)	1452 (51.05%)	
Region (based on where the patient lived at the diagnosis)			
Northeast	31 (22.14%)	594 (20.89%)	0.2712
South	43 (30.71%)	688 (24.19%)	
Midwest	12 (8.57%)	275 (9.67%)	
West	54 (38.57%)	1287 (45.25%)	
Tumor Grade			
Well/moderately differentiated	45 (32.14%)	870 (30.59%)	0.3288
Poorly/undifferentiated	82 (58.57%)	1792 (63.01%)	
Unknown	13 (9.29%)	182 (6.40%)	
Tumor stage at the diagnosis			0.0016
I, II & III	109 (77.86%)	2496 (87.76%)	
IV	31 (22.14%)	348 (12.24%)	
Comorbidity Score 0			1.000
>=1	43 (30.71%)	886 (31.15%)	
ER/PR status			0.0244
Negative	81 (57.86%)	1367 (48.07%)	
Positive	59 (42.14%)	1477 (51.93%)	0.4544
Anthracycline regimen			
No	101 (72.14%)	1957 (68.81%)	0.0222
Yes	39 (27.86%)	887 (31.19%)	
Radiation therapy			
No	71 (50.71%)	1161 (40.82%)	0.0222
Yes	69 (49.29%)	1683 (59.18%)	
Surgery (Mastectomy/Lumpectomy)			
No	32 (22.86%)	205 (7.21%)	<0.0001
Yes	108 (77.14%)	2639 (92.79%)	
Year of diagnosis			
2000 – 2004*	38 (27.14%)	324 (11.39%)	<0.0001†

Factor	HER2 Testing		P value
	No (N=140)	Yes(N=2844)	
2005	23 (16.43%)	384 (13.50%)	
2006	21 (15.00%)	495 (17.41%)	
2007	23 (16.43%)	523 (18.39%)	
2008	20 (14.29%)	529 (18.60%)	
2009	15 (10.71%)	589 (20.71%)	

NOTE:

* We combined years 2000 to 2004 in the table because the number of cases in the “No HER2 test” group was smaller than 11 in some of these years.

† We used the Cochran-Armitage trend test.

Table 3

Factors Associated with Non-Evidence–Based Prescription of Trastuzumab

Factor	Odds Ratio (95% CI)	P value
Breast surgery (yes vs. no)	0.298 (0.193 – 0.458)	<0.0001
Census region (South vs. others)	1.551 (1.064 – 2.259)	0.0223
Year of diagnosis (2005 or later vs. 2004 or earlier)	0.389 (0.260 – 0.4)	<0.0001

Table 4

1-to-2 (Trastuzumab: Chemo-Only) Propensity Score Matched Sample

Factor	Before matching (N=23,131)			After matching (N=420)		
	Chemo-Only (N=22,991)	Trastuzumab without HER2 testing (N=140)	Standard difference	Chemo-Only (N=280)	Trastuzumab without HER2 testing (N=140)	Standard difference
Age at diagnosis						
Mean	72.6	72.6	0.0076	72.5	72.6	0.0292
Std.	5.4	5.6		5.4	5.6	
Comorbidity score 0						
0	15961 69.422%	97 69.29%	0.0030	190 67.86%	97 69.29%	0.0308
>=1	7030 30.58%	43 30.71%		90 32.14%	43 30.71%	
ER/PR status						
Negative	8108 35.27%	81 57.86%	0.4650	150 53.57%	81 57.86%	0.0864
Positive	14883 64.73%	59 42.14%		130 46.43%	59 42.14%	
History of CHF						
No	21924 95.36%	*	0.0940	*	*	0.000
Yes	1067 4.64%	*		*	*	
Anthracycline chemotherapy						
No	11584 50.38%	101 72.14%	0.4582	206 73.57%	101 72.14%	0.0321
Yes	11407 49.62%	39 27.86%		74 26.43%	39 27.86%	
Breast surgery						
No	1215 5.28%	32 22.86%	0.5223	66 23.57%	32 22.86%	0.0169
Yes	21776 94.72%	108 77.14%		214 76.43%	108 77.14%	
Tumor Grade		0.3629				0.1175

Factor	Before matching (N=23,131)		After matching (N=420)	
	Chemo-Only (N=22,991)	Trastuzumab without HER2 testing (N=140)	Chemo-Only (N=280)	Trastuzumab without HER2 testing (N=140)
	Standard difference	Standard difference	Standard difference	Standard difference
Well or moderate differentiated	11367 49.44%	45 32.14%	90 32.14%	45 32.14%
Poorly or undifferentiated	9704 42.21%	82 58.57%	154 55.00%	82 58.57%
Unknown	1920 8.35%	13 9.29%	36 12.86%	13 9.29%
Tumor stage				
I, II, & III	21508 93.55%	109 77.86%	207 73.93%	109 77.86%
IV	1483 6.45%	31 22.14%	73 26.07%	31 22.14%
Year of diagnosis				
< 2005	12487 54.31%	38 27.14%	72 25.71%	38 27.14%
>=2005	10504 45.69%	102 72.86%	208 74.29%	102 72.86%
				0.0324

NOTE:

* We did not show the counts and percentages in these cells because the confidentiality policies for users of SEER-Medicare data require that data cells with less than 11 observations to be suppressed in any data reporting.