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THE IMPACT OF EMERGING SAFETY AND EFFECTIVENESS EVIDENCE ON THE USE OF PHYSICIAN-ADMINISTERED DRUGS: THE CASE OF BEVACIZUMAB FOR BREAST CANCER

Rena M. Conti, PhD[1], **Stacie B. Dusetzina, PhD**[2],[3], **Ann C. Herbert, MPP**[4], **Ernst R. Berndt, PhD**[5],[6], **Haiden A. Huskamp, PhD**[7], and **Nancy L. Keating, MD, MPH**[7],[8]

[2]Division of General Medicine and Clinical Epidemiology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina [3]Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina [4]Department of Population Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [5]Massachusetts Institute of Technology, Sloan School of Management, Cambridge, MA [6]The National Bureau of Economic Research, Cambridge, MA [7]Department of Health Care Policy, Harvard Medical School, Boston, MA [8]Division of General Internal Medicine, Brigham and Women's Hospital, Boston, MA

Abstract

Background—Spending on physician-administered drugs is high and uses not approved by the U.S. Food and Drug Administration (FDA) are frequent. While these drugs may be targets of future policy efforts to rationalize use, little is known regarding how physicians respond to emerging safety and effectiveness evidence.

Study objective—We analyzed changes in bevacizumab (Avastin™) use for breast cancer in response to its market launch (Feb-2008), two FDA meetings reviewing data suggesting that its risks exceed its benefits (July-2010, June-2011), and the FDA's withdrawal of approval (Nov-2011).

Data—Data from a population-based audit of oncologists' prescribing (IntrinsiQ Intellidose) were used to measure the monthly number of breast cancer patients treated with bevacizumab January, 2008-April,2012.

Methods—The number of bevacizumab patients following each regulatory action was estimated using negative binomial regression, compared with patients before the first FDA meeting, adjusting for cancer stage, treatment line, patient age and outpatient office affiliation.

Results—Bevacizumab use for breast cancer increased significantly after FDA approval. Following all regulatory actions, there was a 65% decline (95%CI=64%-65%) in use compared with the period before the first meeting. The largest decline was in the six-month period following

[1]Corresponding author: Assistant Professor of Health Policy and Economics, Department of Pediatrics, Section of Hematology/ Oncology, The University of Chicago, Chicago, Illinois, rconti@uchicago.edu, tel: 773-834-4343.

the first meeting (37%, 95%CI=28%-47%). The rate of decline did not differ by patient or cancer characteristics and differed minimally by office affiliation.

Discussion—Bevacizumab use for breast cancer declined dramatically after FDA meetings and regulatory actions, a period without changes in guideline recommendations or insurance coverage. Physicians appear responsive to emerging evidence concerning physician-administered drug safety and effectiveness.

Introduction

Physician-administered prescription drugs are an increasingly important component of total United States (U.S.) drug expenditures.[1] Medicare is the dominant payer for many physician-administered drugs.[2] Recent evidence suggests thirty percent of these drugs' use in 2010 was for clinical indications not approved by the Food and Drug Administration (FDA).[3] Thus, these drugs may be targets of future policy initiatives intending to rationalize their use.

The impact of initiatives to improve drug prescribing is dependent upon the degree to which physicians respond to emerging evidence. Prior empirical evidence has largely evaluated regulatory communications impact on oral drug utilization,[4-9] with most studies identifying declines in drug use after safety or effectiveness concerns emerge.[4,5,7,9] These studies have primarily focused on drugs prescribed in primary care settings.[4,7,9] Yet, physicians' responses to emerging drug safety and effectiveness evidence are likely related to the institutional setting where they are administered,[4,6,10,11] since the income for some specialty physicians, such as oncologists, may be closely tied to drugs administered in outpatient offices.[2,3,12-14] Oncologists treating patients in private practice outpatient settings thus face direct financial incentives to closely follow the emerging evidence regarding physician-administered drugs.[1,2,12-15] Only one study we are aware of examines trends in the use of a physician-administered drug following changes in evidence supporting its clinical use.[5] In that study, use of anthracycline-based chemotherapy declined sharply and taxane-based chemotherapy increased among ambulatory breast cancer patients immediately following scientific presentations of two well-publicized clinical trials in 2005.

The objective of this study is to examine trends in the use of a physician-administered chemotherapy, bevacizumab (Avastin™, Genentech Inc.) for breast cancer, between its provisional FDA approval and subsequent regulatory actions (Figure 1).

Bevacizumab was the first anti-angiogenic drug approved by FDA for treatment of metastatic colorectal cancer (2004) and for unresectable, locally-advanced, recurrent or metastatic non-squamous non-small cell lung cancer (2006).[16-18] In February 2008, the FDA granted accelerated provisional approval for bevacizumab as first-line therapy for metastatic human epidermal growth factor receptor-2 (HER-2) negative breast cancer.[18-21]

The FDA's provisional approval of bevacizumab for this indication was based on early results from the Eastern Cooperative Oncology Group (ECOG) E2100 trial indicating an improvement in progression-free survival (PFS).[19] The FDA required Genentech to provide subsequent data to confirm the clinical benefits for PFS and overall survival (OS).[20] Longer

term follow-up of the E2100 trial, the Avastin and Docetaxel (AVADO) trial[22] and the Regimens in Bevacizumab for Breast Oncology (RIBBON-1) trial,[23] showed modest improvements in PFS but failed to demonstrate an improvement in OS with the addition of bevacizumab to standard chemotherapy among breast cancer patients with metastatic disease. Upon reviewing the trial data in July 2010, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted to remove the indication for breast cancer from bevacizumab's label, and in December 2010 the FDA announced its plans to withdraw approval for breast cancer.[20,24] This announcement was followed by a June 2011 hearing where ODAC voted again to rescind bevacizumab's breast cancer indication.[20] FDA revoked bevacizumab's indication for breast cancer on November 18, 2011 (Figure 1).[25]

METHODS

Data

We employed data from the Intellidose software system (AmerisourceBergen Specialty Group) for the analysis.[3,26,27] During the study period, Intellidose was used as the exclusive computerized method of outpatient chemotherapy order entry and billing for 122 medical oncology practices, comprising 570 oncologists across 35 states. These outpatient offices were largely physician-owned or affiliated with community hospitals/clinics. The number of practices remained stable and the system did not employ clinical decision aids during the study period. For each patient initiating chemotherapy, practice staff recorded date of birth, sex, cancer type, cancer stage,[28] diagnosis date and chemotherapy date.

Sample Selection

Women with a primary diagnosis of breast cancer who were treated with bevacizumab between February 2008 and April 2012 were identified. Patients with missing cancer stage, stage 0 cancers and those participating in a clinical trial (<1% in each month) were excluded from analysis.

Variables

The monthly number of patients treated with bevacizumab was identified; if a patient received more than two doses in a month, it was counted only once. Each patient's cancer stage (stage IV (metastatic) vs. stages I-III (non-metastatic)) and treatment line (first vs. second or later) were characterized. We examined patterns of bevacizumab use by outpatient office affiliation (academic, community hospital/clinic, and private), since oncologist revenues in private practice have been most closely tied to chemotherapy use.[14,29] We also investigated use by patient age (≥sixty-five vs. <sixty-five), because changes in use among those over sixty-five years of age could be related to Medicare's coverage policies.[12,14,29]

Study Periods

Five distinct time segments were created based on the FDA regulatory actions regarding bevacizumab and breast cancer: (1) Post-provisional approval but pre-ODAC period: February 2008-May 2010; (2) First ODAC meeting: June 2010-November 2010; (3) FDA announcement of plans to withdraw approval: December 2010-May 2011; (4) Second

ODAC meeting: June 2011-October 2011; and (5) FDA withdrawal of approval: November 2011-April 2012 (Figure 1).

Analyses

The outcome for all analyses was the number of patients treated monthly with bevacizumab during the study period. A generalized negative binomial model was used to estimate changes in average monthly bevacizumab use compared with the pre-ODAC period, adjusting for time since approval, quarter, patient and cancer characteristics and office affiliation.[30-32] The predicted number of patients treated monthly with bevacizumab was calculated based on model results. We present average predicted patient counts per period and percent declines per period compared with pre-ODAC meeting patient counts with 95% confidence intervals (95% CI). Tests of statistical significance in average percent declines compared with pre-ODAC levels were based on two-sided Student t-tests with unequal variances assumed derived from model estimates; p-values <0.05 were considered statistically significant.

Sensitivity analysis

We re-estimated percent declines per period compared with pre-ODAC meeting patient counts stratified by covariates to detect policy relevant differences in bevacizumab use trends by patient and cancer characteristics and office affiliation, and we tested for statistical significance of interactions using two-sided Student T-tests. We re-estimated models using counts of administrations (instead of patients) as the main outcome variable, since this is the typical billing unit for insurer reimbursement.

RESULTS

During the study period, most patients treated with bevacizumab had metastatic disease, received bevacizumab as second or later line therapy, were younger than sixty-five years, and were treated in a private practice or community hospital/clinic (Table 1).

Upon FDA approval through the quarter preceding the first ODAC meeting, there was a 54 percent increase in the average number of breast cancer patients who were treated with bevacizumab in a given month, from 16,280 to over 24,000 patients (Figure 2.a). These increases are concentrated among patients with metastatic disease (Figure 2.a), second or later line of therapy (Figure 2.b), under sixty-five years of age (Figure 2.c) and those treated in private practice (Figure 2.d). Declines were observed in the number of breast cancer patients using bevacizumab coincident with the first ODAC meeting, continuing through 2012 (Figures 1.a-d).

Table 2 reports the average predicted number of patients and estimated percent declines in patients treated with bevacizumab in each period compared with that predicted in the pre-ODAC period based on model results. In the pre-ODAC period a monthly average of 23,682 patients used bevacizumab. From the pre-ODAC period to the period following FDA withdrawal of breast cancer approval in December 2011, there was a 65 percent decline (95%CI=64%-65%) in the monthly number of patients treated with bevacizumab. The largest declines observed were during the six-month period following the initial ODAC

meeting (July 2010), during which average monthly bevacizumab use declined by 37 percent from the pre-advisory period (95%CI=28%-47%).

Results of the sensitivity analyses were similar to those estimated in the main models. Associations were non-significantly different between all patient and cancer subgroups at traditional levels (P>0.05 for interactions of period with patient age, cancer stage, treatment line). The magnitude of the percentage decline in patients treated with bevacizumab in academic medical centers following all regulatory actions was greater than that estimated for patients treated in other settings (P-value<0.001). However, the absolute difference between these groups was small (67% decline in academic medical centers vs. 64% in community hospitals/clinics and 65% in private practices).

4. DISCUSSION

This study is among the first to examine trends in prescribing of physician-administered drugs following changes in supportive evidence and subsequent regulatory actions. In a population-based audit of oncologists, bevacizumab use declined 65 percent after regulatory actions. The largest decline (37 percent) occurred following the FDA's initial evidence review in July 2010.

While changes in bevacizumab use in response to emerging safety and effectiveness evidence could be related to changes in guideline recommendations and/or insurers' coverage policies, we did not find evidence to suggest these changes occurred. There was no change in the guideline recommendation by the National Comprehensive Care Network (NCCN), and Medicare did not alter reimbursement policy during the study period.[3,21] Communications with the medical directors of two large commercial insurers, (Wellpoint (34 million members)[33] and Aetna (18 million members))[34] also reported no changes were made to their coverage of bevacizumab for breast cancer.

Our findings suggest oncologists responded quickly to emerging evidence about the limited benefit to risk trade-off of bevacizumab for breast cancer even before the FDA withdrew approval for this indication *and* without concomitant changes to clinical guidelines or insurers' coverage policies. Moreover, these changes likely represent a lower bound on bevacizumab use in response to regulatory actions, since the monthly patient counts included both those initiating and continuing bevacizumab treatment. Sample characteristics were consistent with other published reports regarding use of bevacizumab-based breast cancer treatment over this period, providing some additional assurance of the data's external validity.[18,35,36] Interestingly, after additional evidence emerged we observed slightly larger declines in use by physicians practicing in academic medical centers vs. other settings, but not by other patient or cancer characteristics.

The magnitude of the decline in bevacizumab use we document is larger than that reported in primary care contexts,[4,8,9] but similar to declines estimated for anthracycline based chemotherapy for breast cancer[5] and for hormone replacement therapy use after the publication of the Women's Health Initiative.[37] The magnitude of the estimated decline might be related to the larger number of regulatory actions targeting bevacizumab.[4] Future

work is needed to document whether these responses generalize to the release of new evidence in the treatment of other cancers or the use of other physician-administered drugs.

Important questions remain regarding the clinical implications of the substantial declines in bevacizumab use following regulatory actions we observed.The continued recommendation of bevacizumab for breast cancer in the NCCN guidelines suggests that experts still believe bevacizumab has value in treating metastatic breast cancer despite the FDA's actions.[21] Future observational studies might leverage area-level differences in the changes in use of bevacizumab to assess whether changes in use of bevacizumab led to better outcomes for patients.

The analyses have several limitations. While breast cancer incidence overall and by stage was stable between 2005 and 2009,[40] the declines we estimate may be partially attributable to changes in the mix of cancer types amenable to bevacizumab treatment. Also, although IntrinsiQ represents a large number of practices located throughout the U.S., practices using Intellidose may be more technologically savvy and/or guideline adherent compared to average practices.[3,13,26] Unfortunately, we were unable to assess changes in patient or physician preferences or changes in bevacizumab promotion, nor did we have data to examine trends in prescribing variations by individual physicians or outpatient office practices. Some patients under the age of sixty-five may have received insurance coverage by Medicare during the study period.

In sum, bevacizumab use for breast cancer treatment declined dramatically following FDA regulatory actions in July 2010 and thereafter. Unlike previous work in primary care settings, declines in use appear unrelated to changes in guideline recommendations or insurance coverage. Declines in bevacizumab use suggest oncologists are responsive to emerging evidence regarding physician-administered drug safety and effectiveness.

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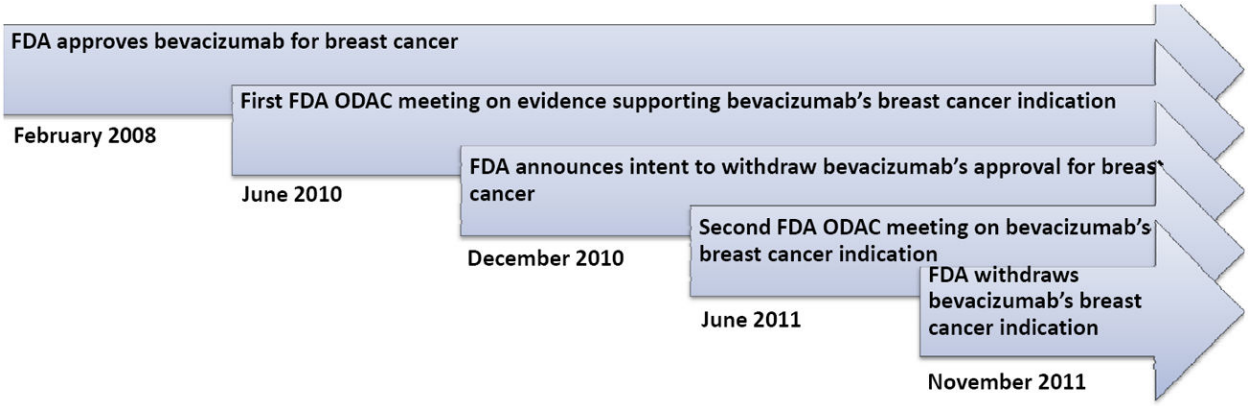
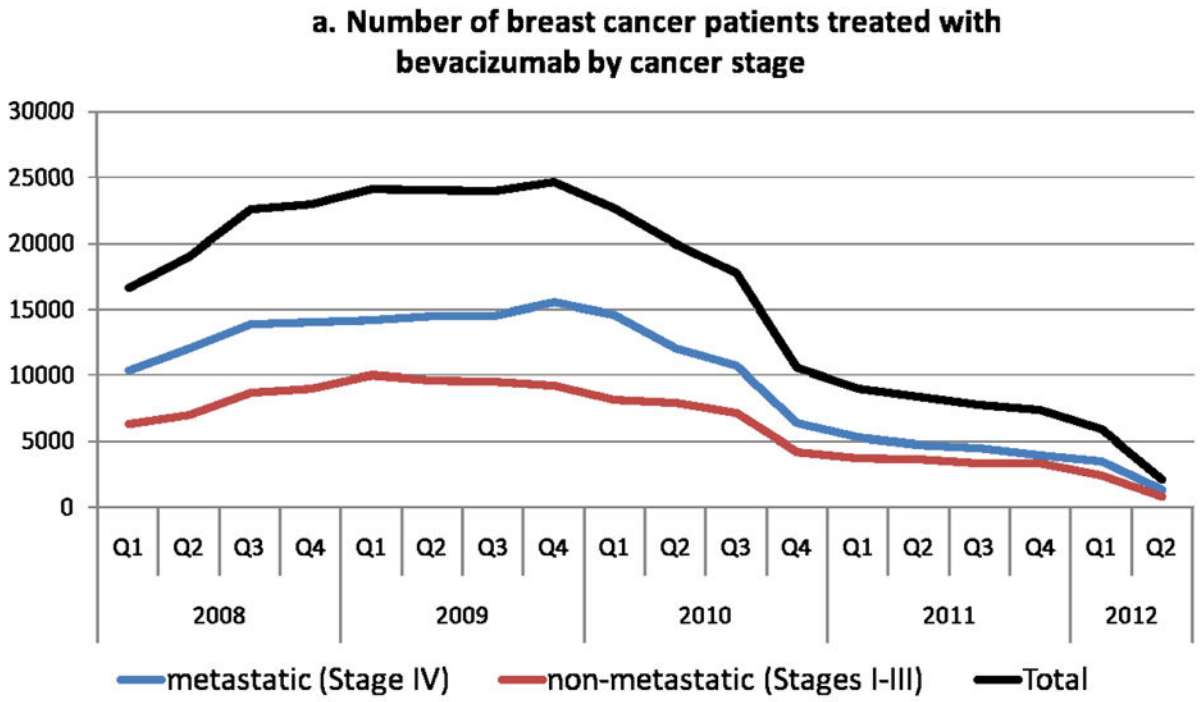
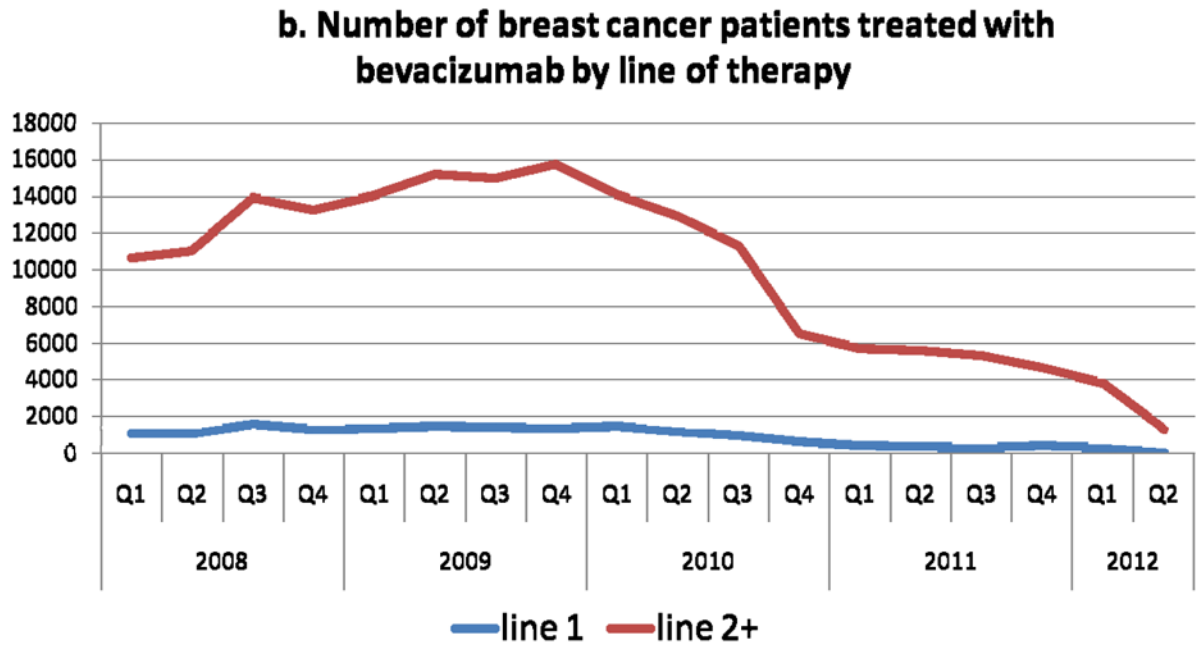


Figure 1.

Timeline of events affecting bevacizumab's United States Food and Drug Administration (FDA) approval for the treatment of breast cancer, January 2008-December 2011





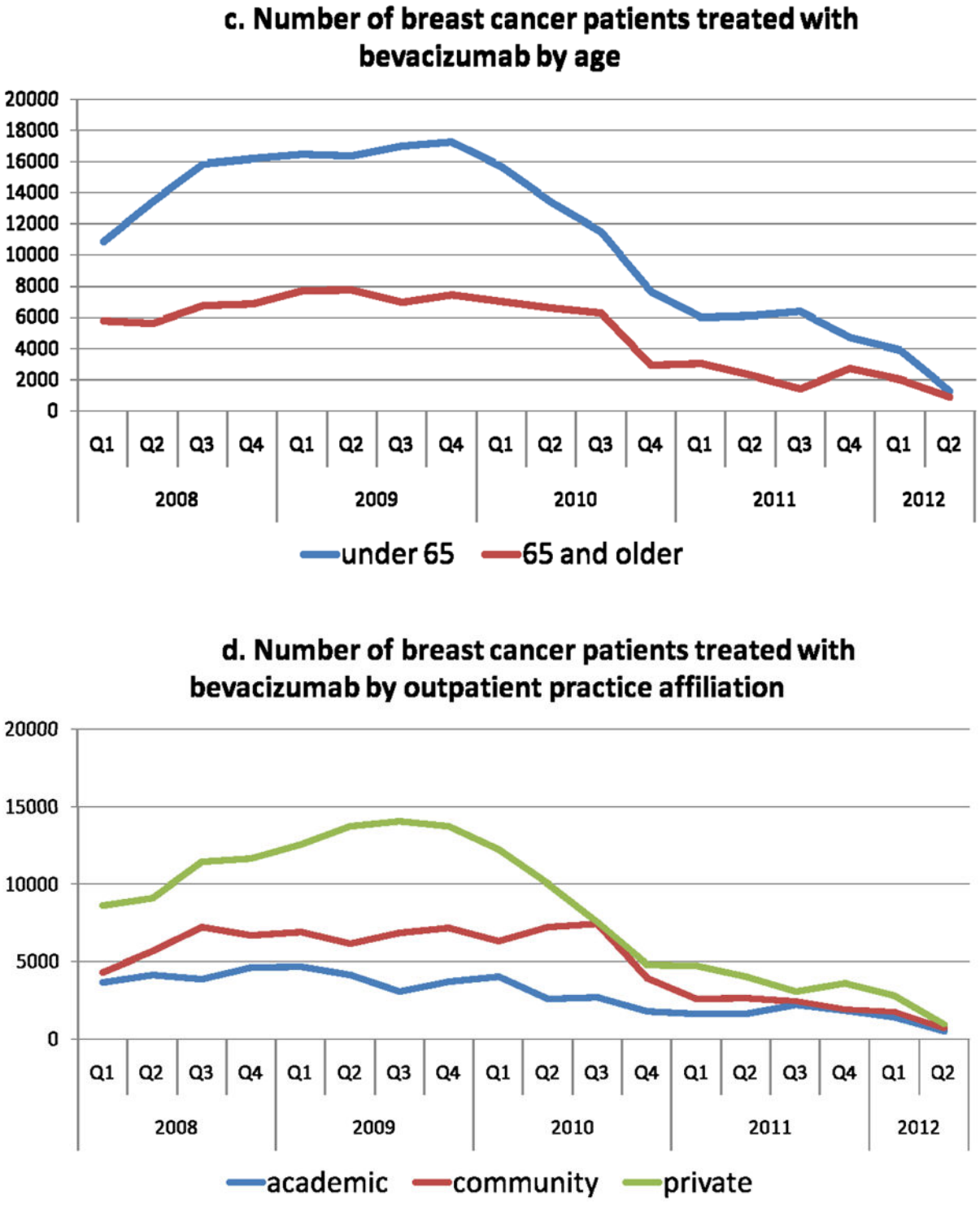


Figure 2.

a-d. Trends in the number of breast cancer patients treated with bevacizumab, February 2008-April 2012.

a. Trends in breast cancer patients treated with bevacizumab overall and by cancer stage

b. Trends in breast cancer patients treated with bevacizumab by line of therapy

c. Trends in breast cancer patients by age

d. Trends in breast cancer patients treated with bevacizumab by outpatient office affiliation

Table 1

Descriptive statistics of breast cancer patient sample treated with bevacizumab, February 2008 - April 2012

	Average number of patients (month)	Standard deviation	Min	Max
Overall patients	15954	7668	2213	26187
Patients by cancer stage				
metastatic disease (Stage IV)	12414	6102	1949	20320
non-metastatic disease (Stage I-III)	3540	1616	264	6218
Patients by line of therapy				
first line	952	511	142	1710
second or later line	10128	4813	1380	16833
Patients by age				
65 years of age or older	5229	2179	1551	8075
younger than 65 years of age	11824	5176	3584	19406
Patients by outpatient practice affiliation				
treated in academic medical center	2918	1353	240	5681
treated in community hospital/clinic	4731	2322	629	8900
treated in private practice	3256	4410	1218	16352

Data on monthly number of breast cancer patients treated with bevacizumab drawn from IntrinsiQ Intellidose data system, February 2008-April 2012.

Table 2

Predicted average number of breast cancer patients treated with bevacizumab and estimated percent decline following regulatory actions

	Patient number	95% CI	Percent decline	95% CI
FDA approval (February 2008) – May 2010	23682	22689-24675	REF	
Following first FDA ODAC meeting reviewing evidence (June 2010) – November 2010	14879	12010-17749	**37%**	28-47%
Following FDA's announcement of intent to withdraw approval (December 2010) – May 2011	12107	11223-12991	**49%**	47-51%
Following second FDA ODAC meeting reviewing evidence (June 2011) – October 2011	8678	7831-9524	**63%**	61-65%
Following FDA withdrawal of approval (November 2011) – April 2012	8357	8197-8517	**65%**	64-65%

Data on monthly number of breast cancer patients treated with bevacizumab drawn from IntrinsiQ Intellidose data system, February 2008-April 2012.

°Estimates based on multivariable negative binomial model, adjusting for time, site of care, age of patient, cancer stage and line of therapy.

Bolded changes compared to pre-ODAC levels are statistically significantly different than zero at p-value<0.05 level based on Student's t-test with assumed unequal variances.