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The impact of radiotherapy costs on clinical outcomes in breast cancer

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Abstract

Background and Purpose—In cost-effective healthcare systems, the cost of services should parallel patient complexity or quality of care. The purpose of this study was to determine whether the cost of radiotherapy correlates with patient-related outcomes among a large cohort of breast cancer patients treated with adjuvant breast radiation.

Materials and Methods—23,127 women with non-metastatic breast cancer undergoing radiotherapy after breast conservation surgery were identified from the Surveillance, Epidemiology, and End Results database from 2000-2009. Medicare reimbursements were used as a proxy for cost of radiotherapy, and Medicare claims were examined to identify local toxicities, and breast cancer-related endpoints. The impact of cost on these outcomes was studied with multivariable Fine-Gray models to account for competing risks.

Results—The median cost (and interquartile range) of a course of breast radiation was $8,100 ($6,700-$9,700). Increased radiation costs were not associated with the occurrence of treatment-related toxicities (all p-values > 0.05), ipsilateral breast recurrence (p=0.55), or breast cancer-related mortality (p=0.55).

Conclusion—Higher costs for adjuvant radiation in breast cancer were not associated with a decreased risk of patient-related outcomes, suggesting inefficiency in Medicare reimbursements. Future efforts should focus on prospective evaluation of alternative payment models for radiotherapy.

Keywords

Breast cancer; radiation therapy; costs; outcomes

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Introduction

Radiation therapy is a standard component of treatment for women undergoing breast conservation treatment[1]. Breast radiation reduces the risk of local recurrence and improves survival after lumpectomy[2,3] However, despite the accepted clinical benefit of breast radiation, questions have been raised as to its costs particularly as new and more expensive technologies become available[4,5]. Breast cancer already accounts for the largest portion of expenditures in the United States (US) for cancer care[6], and evaluation of US healthcare payments has shown that relative increase in spending for radiation oncology far outpaces that of other medical specialties[7]. As a result, understanding the economic efficiency of radiation therapy for diseases such as breast cancer has become a topic of increasing interest.

In a cost-effective healthcare system, the cost of services should parallel patient complexity or quality of care. Previous research on Medicare beneficiaries demonstrates that the cost of breast radiation does not depend on patient-related factors, tumor characteristics, or other factors related to treatment[8]. However, research has yet to determine whether radiation cost within the US correlates with patient-related outcomes. Higher treatment costs correlating with improved outcomes would suggest that the reimbursement model in the US achieves the goal of reimbursing care based on value. Conversely, if the cost of radiation does not correlate with quality of care then this finding would suggest a degree of inefficiency in reimbursement for breast cancer. The purpose of this study was to evaluate the relationship of cost on patient-specific outcomes in a large cohort of Medicare beneficiaries with localized breast cancer treated with radiation therapy.

Methods

Data Source

We identified female breast cancer patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The National Cancer Institute manages the SEER program, which pools data from individual cancer registries from across the United States. SEER covers 28% of the population and provides a diverse cohort of patients that approximately represents the demographics of the US. Medicare is a federally funded health insurance program for individuals over the age of 65 and is the largest single payer of healthcare costs in the United States. Medicare reimburses according to a set schedule depending on the specific codes for services billed (claims) which is organized according to the coverage (Part A or B) selected by the patient. Part A coverage provides coverage for inpatient services excluding physician fees, home health services, and hospice. Part B reimburses physician fees, specifically identified in the Carrier Claims file, outpatient services including laboratory testing and imaging, and durable medical equipment. The SEER-Medicare linkage provides Part A and B Medicare claims for all beneficiaries within SEER. As a result, this population-based dataset provides researchers the opportunity to study longitudinal patterns of care, outcomes, and expenditures related to a patient's disease. The Institutional Review Board of the University of California San Diego deemed this study exempt from review.

Study Population

An initial query of the SEER database identified 56,128 patients at least 66 years old who were diagnosed between July 2000 and December 2009 with histologically confirmed, non-metastatic breast cancer with known tumor laterality treated with breast conserving surgery and radiation therapy. Due to changes in outpatient Medicare billing, patients diagnosed prior to July 2000 were not included in the initial study cohort in order to have a uniform reimbursement system for radiation therapy[9]. Patients were required to have continuous Medicare Part A and B coverage from one year before diagnosis until death or the end of the study period (December 2010) to allow for the ascertainment of comorbidities before diagnosis, the cost of radiation therapy, and health outcomes after radiation. Patients enrolled in Medicare Part C, which allows private managed care plans to provide Part A and B coverage, were excluded from the study as these managed care organizations do not routinely submit claims to Medicare resulting in incomplete claims data. Additional patient selection criteria are described below, and the final study cohort included 23,127 patients. The complete patient selection schema is shown in Figure 1.

Study covariates

SEER data was used to identify patient characteristics such as age at diagnosis, race, marital status, year of diagnosis, tumor stage (local or regional), primary tumor size and grade, number of positive lymph nodes, laterality, regional lymph node surgery, and median income determined from 2000 US Census tract data. Inpatient and outpatient Medicare claims from the year before diagnosis were used to asses pre-existing comorbidity using the Deyo adaptation of the Charlson comorbidity index[10]. The administration of chemotherapy was ascertained using previously described methods[11]. Specific chemotherapeutic drugs with known cardiovascular toxicities[12] were identified using Healthcare Common Procedure Coding System (HCPCS) J codes (Supplemental Table 1). Care at a teaching hospital was defined as any indirect medical education payment noted during a hospitalization after the patient's diagnosis of cancer. The use of breast MRI after diagnosis was identified using HCPCS codes. Patient characteristics, including radiation-related variables, are presented in Table 1.

Radiation therapy

Radiation therapy was identified from the Carrier Claims and outpatient files using relevant HCPCS codes for each step in the delivery of treatment[13]. The individual components of a course of radiation included the radiation simulation, radiation treatment planning, daily radiation treatments, and weekly management activities. A course of radiation therapy was defined as a cluster of claims within a month of each other; a break of 30 days or more between subsequent radiation codes was assumed to be indicative of an additional course of radiation. Only patients who received one course of radiation were included in this study to ensure that the impact of the first course of radiation was not confounded by later radiation treatments. Patients who received brachytherapy as part of their treatment plan were excluded. Intensity modulated radiation therapy (IMRT), known to be associated with increased treatment costs[5], was defined by the presence of any IMRT planning or treatment code during the course of radiation. To reduce the likelihood of including patients

with incomplete records or recurrent or metastatic disease, we included only patients treated within one year of diagnosis who received between 15 to 40 days of radiation treatment, which includes hypofractionated and standard treatment regimens[14].

Toxicities

Known radiation side effects were identified from current literature[15-17]. Outcomes evaluated included cardiac toxicities (myocardial infarction, coronary artery disease, congestive heart failure, electrical abnormalities, pericarditis, valvular disease, cardiomyopathy), skin toxicities (breast deformity, fat necrosis, mastodynia, capsular contracture), radiation pneumonitis, closed rib fracture, and brachial plexopathy. ICD-9 diagnosis codes were used to identify radiation toxicities in the inpatient, outpatient, and Carrier Claims files (Supplementary Table 1). As many of the toxicities we studied are not exclusively caused by radiation therapy, we accounted for the presence of these events prior to radiation by assessing by ICD-9 diagnosis codes in the year prior to diagnosis through the start of radiation. Only the year before diagnosis was evaluated to ensure that patients were assessed equivalently for pre-existing conditions regardless of diagnosis date. If patients had a malignancy other than breast cancer or radiation pneumonitis noted prior to the delivery of radiation, they were excluded from further evaluation in order to ensure breast cancer was the primary cancer.

Breast cancer-related outcomes

Local breast tumor recurrence is not explicitly recorded in either SEER or Medicare; therefore we used a proxy measure for ipsilateral breast tumor recurrence as previously described[18]. Briefly, ipsilateral breast tumor recurrence was defined as either the presence of Medicare claims for a secondary surgery on the same breast after radiation (Supplemental Table 1) or the development of a second primary breast cancer in the ipsilateral breast as noted in SEER. Breast cancer-related death was ascertained from SEER.

Cost

Cost of radiotherapy represented the primary variable of interest. We used Medicare reimbursement for radiation as a proxy for cost as is commonly used in health economics research [19]. All references to cost in this manuscript refer to Medicare reimbursement for radiation therapy delivery. Medicare reimbursement for radiation is based on a fee-for-service billing structure in which each individual claim receives a pre-defined payment from Medicare, a supplemental insurance, or the beneficiary. Our estimation of cost only considered Medicare payments as described previously [20,21] and did not include the fraction of cost from supplemental insurance or beneficiary. The cost of an individual course of radiation was determined by summing all radiation-related claims from the Carrier Claims and outpatient files. Additionally, Medicare varies its reimbursement based on geography to account for regional differences in the cost of delivering care. We removed this geographic variation through adjustment of cost with the Geographic Cost Pricing Index [22]. Finally, all reported costs were inflation-adjusted to December 2010 dollars with the Medicare Economic Index [23].

Statistical analysis

The association between radiation cost and clinical outcomes was evaluated using cumulative incidence analyses and multivariable Fine-Gray regression models to account for the competing risk of death[24]. Radiation therapy costs were evaluated as a continuous predictor; outcomes were binary. The effect of radiation therapy cost on ipsilateral breast cancer and cancer-specific survival was demonstrated graphically using cumulative incidence analyses and Gray's test of equality was used to compare the incidence of outcomes across quartiles of radiation therapy costs.

For all multivariable Fine-Gray analyses, covariates controlled for were defined *a priori* and included age at diagnosis, marital status, race, metropolitan area, SEER region, treatment at a teaching hospital, median income, Charlson comorbidity index, year of diagnosis, tumor size, stage, and grade, node status, secondary surgeries, chemotherapy, length of radiation treatment, and breast MRI prior to radiation. All covariates noted above were categorical with groupings presented in Table 1. For cardiac outcomes, covariates were included to control for the receipt of cardiotoxic chemotherapeutic drugs or if any cardiac diagnosis had been noted in the year prior to breast cancer diagnosis until the start of radiation. A similar pre-existing condition variable was included in the regression models for skin-related toxicities, brachial plexopathy, and closed rib fracture. Patients were allowed to experience multiple distinct events; however, only the first event for each outcome was considered for analysis. All statistical tests performed were two sided with a p-value < 0.05 considered significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

For the final study cohort of 23,127 patients, the median cost of radiation therapy was $8,100 with an interquartile range of $6,700-$9,700. When stratifying patient characteristics by quartile of Medicare payments (Table 1), women in the highest quartile of radiation therapy costs were more likely to have been diagnosed between 2007-2009, to be located in the South or Midwest, to have left sided disease, and to have received chemotherapy or a breast MRI. Over 90% of patients who received IMRT were in the highest quartile cost group. Patients in the lowest quartile group for cost were more likely to be over 80 and treated at a teaching hospital. Although patients in the highest cost group were more likely to have received IMRT and to have left sided tumors, the number of patients with pre-existing cardiac conditions was similar between each cost quartile.

Cardiac events, namely coronary artery disease and conduction abnormalities or dysrhythmias, were the most frequently noted outcomes after initiation of radiation therapy. Skin toxicities were the most common non-cardiac claims. In evaluating the unadjusted five-year cumulative incidence of outcomes by quartile of radiation therapy costs (Table 2), increased cost was associated with decreased rates of coronary artery disease, conduction abnormalities or dysrhythmias, congestive heart failure, skin toxicities, and cellulitis or abscess of the breast (all $p < 0.05$). However, multivariable analysis, in which the effect of cost was adjusted by patient, tumor, and treatment-related factors, revealed no association between Medicare payments and any radiation-related toxicity (Figure 2, all p-values > 0.05).

For breast cancer related outcomes, the unadjusted cumulative incidence of ipsilateral breast cancer reoccurrence did not vary by radiation cost (Figure 3, p=0.30). Likewise, the unadjusted cumulative incidence of breast cancer mortality did not correlate with radiation cost (Figure 3, p = 0.41). Multivariable analysis confirmed these findings, with no association between radiation cost and ipsilateral breast cancer reoccurrence (SDHR 0.988, p=0.55) or breast cancer mortality (SDHR 1.006, p=0.55).

Discussion

The key finding in these analyses is the lack of correlation between Medicare payments for radiation and patient-specific quality of care endpoints among for elderly women with early stage breast cancer. Although our study differs from conventional cost-effectiveness research, which focuses on comparing incremental costs to incremental health utility or quality of life of different treatment modalities, our work directly compares Medicare reimbursement with patient-specific outcomes. This research also broadly assesses whether the current US-based reimbursement system for radiation therapy provides value-based care in a large cohort of women with breast cancer.

Reimbursement for radiation therapy is based on a fee-for-service model in the US Medicare system; payments for a course of radiation directly depend on the number of daily radiation fractions delivered and the technology used to deliver treatment [25]. Therefore, longer courses of radiation and the use more advanced technology such as IMRT further increases payments relative to simpler or shorter techniques of radiation delivery [5,26,27]. Multiple randomized trials in breast cancer have demonstrated no clinical difference between shorter courses (hypofractionated) and longer courses of radiation in terms of toxicity or tumor control[28,29]. Similarly, randomized trials comparing IMRT to standard radiation in breast cancer have shown that although IMRT reduces skin toxicities and improved cosmesis [30,31], there is no difference in overall survival or ipsilateral recurrence [32]. These results indirectly add support to our finding that there is no correlation between more expensive Medicare payments for radiation and outcomes after treatment.

Both the cost and quality of healthcare delivery represent two critical health policy aspects in the 21st century, and yet we lack substantial research defining the direct association between these two metrics[33]. Recent research by Paravati et al. found that less than 3% of the variation in Medicare cost of radiation in breast cancer depends on the patient, the patient's tumor, or treatment[8], which suggests that radiation cost does not correlate with patient complexity. This current research builds upon this prior study, demonstrating that cost does not correlate with quality of care. These results together suggest that a high degree of inefficiency is built into reimbursement for radiation therapy for breast cancer in the Medicare program.

Because of increasing radiation therapy costs and the field's outlying excess expenditures compared to other specialties [7], there has been an increasing realization that restructuring of the complex fee-for-service payment model is needed within the US Medicare system [25]. This reform is particularly pertinent for reimbursement for treatments related to breast cancer given the large proportion of healthcare costs attributable to this disease [6].

Reducing inefficiency in payments for radiation therapy could aid in reducing fiscal burden of this treatment in the United States and ensure that patients receive care based on maximizing quality, not quantity. These changes could include bundled payment adjusted for patient complexities or models which incentivize greater adherence to evidence-based recommendations. In a pilot program, the Blue Cross Blue Shield of Massachusetts and the Massachusetts Radiation Oncology Physicians Advisory Council issued guidelines pertaining to IMRT and decreased the usage of the technology by 17% [34]. Any of these reimbursement options would ideally undergo prospective evaluation to determine the impact on patient care, patient satisfaction, healthcare costs, as well as the effect on the provider and healthcare system behavior.

This study has limitations that must be acknowledged. This research focused on patients over the age of 65, and therefore our conclusions may not generalize to a younger population. For example, younger patients benefit more from longer courses of radiation with an additional boost[35] and may live longer to experience late radiation effects such as cardiac-related toxicity[2,36], which could translate to improved outcomes for those who received more costly treatment. Similarly, follow-up was limited particularly for patients diagnosed more recently and further long term data might justify higher cost radiation treatments. Another important consideration relates to the fact that other countries employ dramatically different reimbursement systems, and therefore our findings are limited to the United States. Additionally, toxicities for which a patient did not seek medical care or that lack a diagnosis code cannot be analyzed. Therefore, we cannot comment on minor lower grade toxicities. While our analysis controlled for some factors that reflect patient complexity, we cannot account for factors such as body habitus or anatomy. Therefore, it could be argued that higher cost radiation was appropriately used in patients inherently at higher risk of toxicity due to factors not captured by SEER or Medicare. Similar to other research we used Medicare reimbursement as a proxy for cost, and therefore cannot comment on the true cost of delivering radiation therapy. Furthermore, this study only included breast cancer, and additional research is required to assess the correlation between cost and quality in other cancer subtypes. This research also does not take into account patient perspective or quality of life, all of which are critical to evaluating the efficiency of a healthcare system.

Despite these limitations, this research represents the first direct comparison between radiation therapy reimbursement in the United States and patient-related outcomes in a large cohort of elderly breast cancer patients. The increasing cost of radiation therapy has led to a heightened interest in evaluating the overall health economics of the field. Future research should focus on addressing the inefficiency of the current Medicare fee-for-service structure and prospectively developing novel payment models aimed at creating a value-based reimbursement system in the United States for radiation oncology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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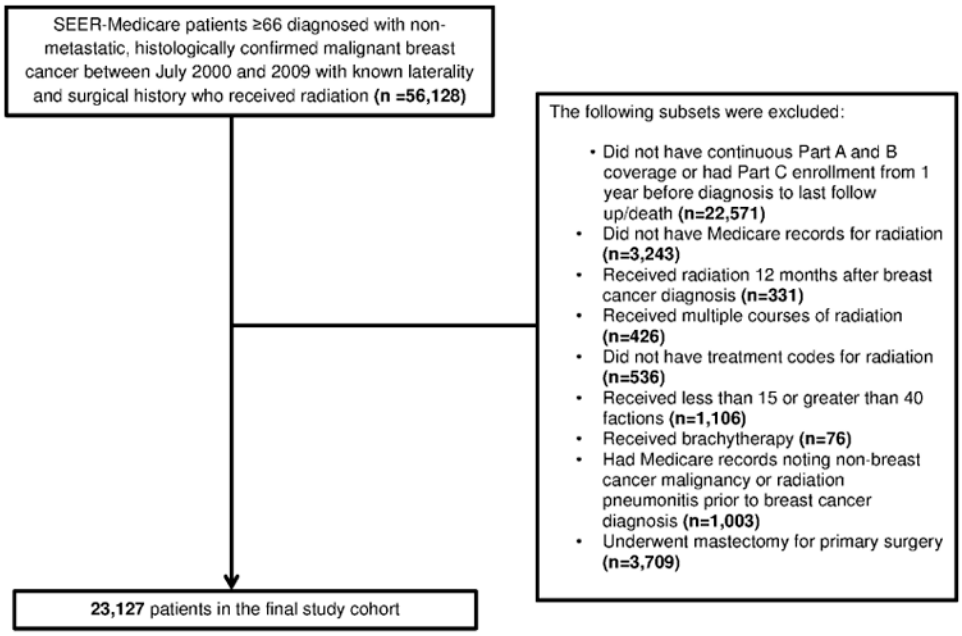

Figure 1.
Patient selection criteria. The final study cohort included 23,127 patients.

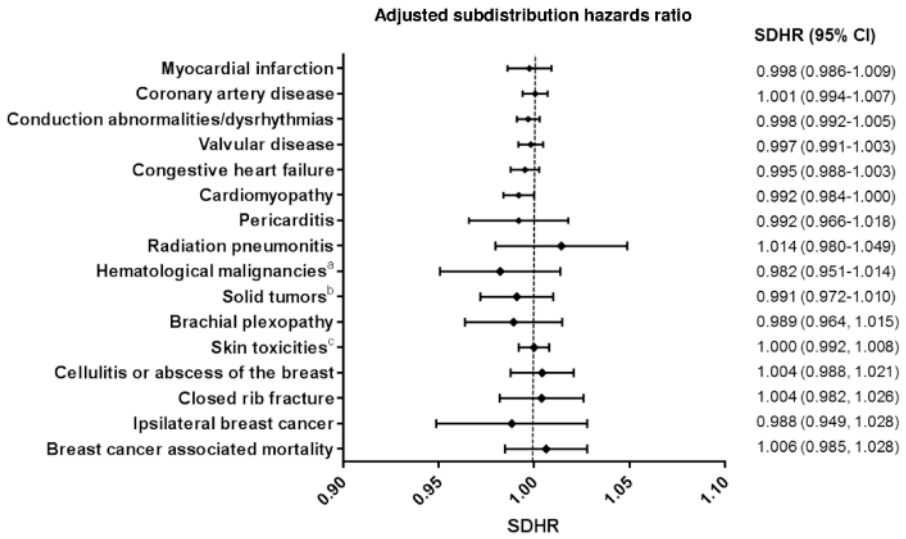

Figure 2.

Subdistribution hazard ratios (SDHR) of cost for all radiation associated toxicities and ipsilateral breast cancer reoccurrence are reported with 95% confidence intervals (CI) below. SDHR was reported per thousand dollars of Medicare payments.

[a] Leukemia and myelodysplastic syndrome

[b] Lung, esophageal, and sarcoma

[c] Breast deformation, capsular contracture, mastodynia, and fat necrosis

* All models controlled for age, marital status, race, metropolitan area, SEER region, treatment at a teaching hospital, median income, Charlson comorbidity index, year of diagnosis, tumor size, stage, and grade, node status, secondary surgeries, chemotherapy, length of radiation treatment, and breast MRI prior to radiation. Cardiac models also included parameters for a previous history of cardiac events prior to diagnosis and the receipt of cardiotoxic chemotherapeutic drugs (anthracycline, trastuzumab, taxanes, cyclophosphamide, and fluorouracil). Terms to control for outcomes noted prior to breast cancer diagnosis were also included in the models for skin toxicity, brachial plexopathy, cellulitis/abscess, and rib fracture.

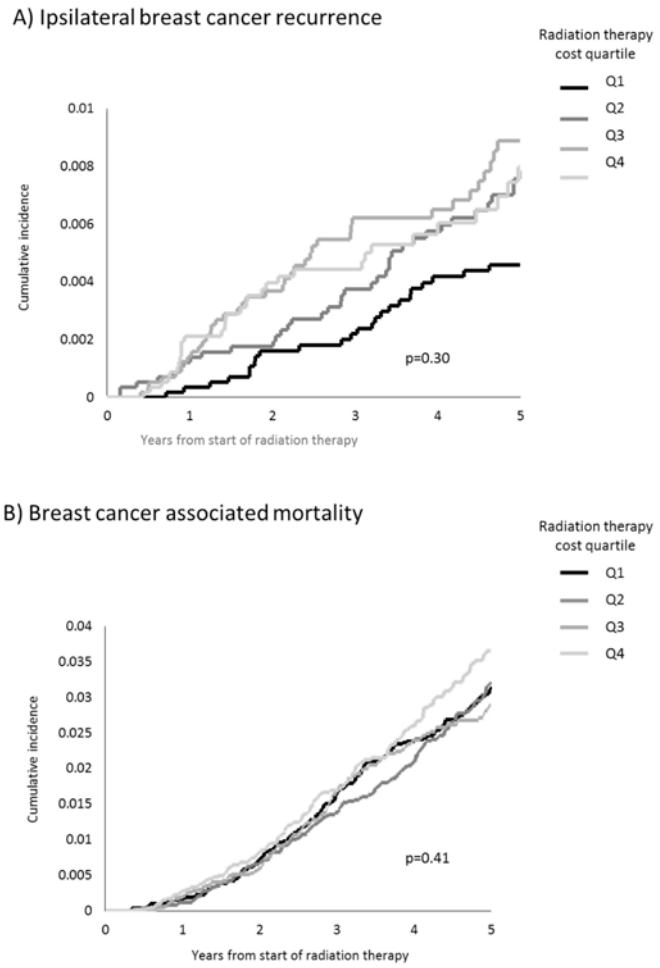

Figure 3.

The five year cumulative incidence of breast cancer related outcomes (A, ipsilateral recurrence; B, breast cancer related mortality) stratified by quartile of radiation therapy cost. Gray's test of equality was used to compare the incidence of ipsilateral recurrence between quartiles.

Table 1

Descriptive characteristics of the study patients with stratification by quartile of radiation therapy costs. Chi-square tests were used to evaluate significant differences in the distribution of covariates across cost quartiles.

		Medicare Payment Quartile			
Variables	**N (%)**	**Q1**	**Q2**	**Q3**	**Q4**
Total	23,127	5,781	5,782	5,782	5,782
Age at diagnosis[φ]					
66-74	11,665 (50.4)	2,739	2,863	2996	3,070
75-79	6,161 (26.7)	1,600	1,580	1503	1,479
≥80	5,300 (22.9)	1,445	1,339	1283	1,233
Marital status[φ]					
Married	11,871 (51.3)	2,895	2,926	3,072	2,978
Divorced	1,659 (7.2)	410	423	377	449
Single	1,373 (5.9)	347	372	329	325
Other	8,224 (35.6)	2,129	2,061	2,004	2,030
Race[φ]					
White	21,013 (90.9)	5,189	5,222	5,320	5,282
Black	1,014 (4.4)	212	263	228	311
Other	1,100 (4.7)	380	297	234	189
Charlson comorbidity score					
0	16,156 (69.8)	4,097	4,024	4022	4,012
1	4,915 (21.3)	1,198	1,222	1242	1,253
2	1,393 (6.0)	337	354	64	338
≥3	663 (2.9)	149	182	154	178
Conditions noted prior to breast cancer diagnosis					
Cardiac[a]	11,319 (48.9)	2,757	2,888	2,871	2,803
Brachial plexopathy	178 (0.8)	43	51	45	39
Skin (breast)[b]	2572 (11.2)	667	641	617	647
Cellulitis or abscess (breast)[φ]	230 (1.0)	39	75	52	64
Closed rib fracture	117 (0.5)	25	30	25	37

Variables	N (%)	Medicare Payment Quartile Q1	Q2	Q3	Q4
Year of diagnosis$^{\varphi}$					
2000-2003	8,411 (36.4)	3,589	2,058	1,470	1,294
2004-2006	2,066 (35.5)	1372	2,306	1,946	1,442
2007-2009	7,650 (33.1)	820	1,418	2,366	3,046
Region$^{\varphi}$					
East	5,669 (24.5)	1,720	1,740	1,443	766
Midwest	3,049 (13.2)	431	624	842	1,152
South	3,533 (15.3)	554	684	983	1,312
West	10,876 (47.0)	3,076	2,734	2,514	2,552
Metropolitan area$^{\varphi}$	20,244 (87.5)	5,229	5,186	4,900	4,929
Teaching hospital$^{\varphi}$	7,921 (34.2)	2,354	2,131	1,764	1,672
Primary tumor size$^{\varphi}$					
b0-2 cm	18,470 (79.9)	4,696	4,664	4,592	4,538
2-5 cm	4,10 (17.7)	921	987	1,064	1131
>5 cm	231 (1.0)	56	58	68	49
Unknown	323 (1.4)	108	93	58	64
Positive nodes$^{\varphi}$					
None	17,277 (74.7)	4,300	4,414	4,308	4,255
1-5	3,412 (14.7)	731	792	929	960
6+	362 (1.6)	52	61	103	146
Unknown	2,076 (9.0)	698	515	442	421
Laterality$^{\varphi}$					
Right	11,641 (50.3)	2,982	2,863	2,957	2,684
Left	11,486 (49.7)	2,799	2,919	2,825	3,098
Stage$^{\varphi}$					
Localized	18,939 (81.9)	4,890	4,829	4,645	4,564
Regional	4,189 (18.1)	891	943	1,137	1,218
Grade$^{\varphi}$					
Well or moderately	16,832 (72.8)	4,159	4,230	4,211	4,232

Variables	N (%)	Medicare Payment Quartile Q1	Q2	Q3	Q4
differentiated					
Poorly or undifferentiated	5,010 (21.7)	1,220	1,216	1,281	1,293
Unknown	1,285 (5.5)	402	336	290	257
Breast MRI$^{\varphi}$	2,721 (11.8)	357	596	784	984
Lymph node surgery*					
None	2,061 (8.9)	711	519	429	402
Sentinel	10,761 (44.5)	2,196	2,587	2,682	2,822
Regional	10,761 (46.5)	2,868	2,671	2,666	2,556
Number of fractions delivered$^{\varphi}$					
15-20	867 (3.8)	598	129	62	78
21-25	832 (3.6)	530	170	61	71
26-30	4,245 (18.4)	1,681	1,117	801	646
31-35	15,620 (67.5)	2,784	3,932	4,447	4,457
36-40	1,563 (6.7)	188	434	411	530
IMRT$^{\varphi}$	2,556 (11.1)	100	67	77	2,312
Chemotherapy$^{\varphi}$	4,738 (20.5)	1,096	1,096	1,268	1,345
Specific chemotherapeutics					
Anthracyclines$^{\varphi}$	2,006 (8.7)	453	453	562	565
Cyclophosphamide$^{\varphi}$	3,034 (13.2)	679	679	848	920
Trastuzumab$^{\varphi}$	582 (2.5)	73	122	176	211
Taxanes$^{\varphi}$	1,197 (5.2)	216	232	351	398
Flurouracil	975 (4.22)	277	234	229	235

[a] Cardiac events were defined as myocardial infarction, coronary artery disease, valvular disease, electrical abnormalities or dysrhythmia, congestive heart failure, or pericarditis

[b] Skin related conditions were defined as breast deformation, capsular contracture, fat necrosis, and mastodynia

$^{\varphi}$ $p < 0.05$ for a Chi-Squared test evaluating the distribution of demographic characteristics across cost quartile

Table 2

The five year cumulative incidence of specific outcomes after radiation therapy with stratification by quartile of radiotherapy costs. Gray' test for equality were used to evaluate significant differences in the cumulative incidence of outcomes across cost quartiles.

	5-Year Cumulative Incidence, % (95% CI)	5-Year Cumulative Incidence by Quartile of Radiotherapy Cost, %			
		Q1	Q2	Q3	Q4
Cardiac Related Toxicities					
Myocardial infarction	10.1 (9.6, 10.5)	10.8	10.1	9.6	9.4
Coronary artery disease$^{\varphi}$	41.7 (41.0, 42.4)	42.5	43.2	41.3	39.2
Valvular disease	33.9 (33.2, 34.5)	33.4	35.1	34.1	32.9
Conduction abnormalities/dysrhythmias$^{\varphi}$	45.3 (44.6, 46.1)	46.2	46.2	45.5	43.4
Congestive heart failure$^{\varphi}$	24.3 (23.7, 24.9)	24.9	24.6	24.8	22.4
Cardiomyopathy	24.6 (23.9, 25.2)	25.5	25.0	24.3	22.9
Pericarditis	2.4 (2.2, 2.7)	2.2	2.7	2.6	2.3
Non-Cardiac Related Toxicities					
Radiation pneumonitis	0.9 (0.8, 1.0)	1.0	0.9	0.8	0.9
Hematological malignancies^{a}	1.5 (1.3, 1.7)	1.2	1.5	1.8	1.5
Solid tumors^{b}	4.8 (4.5, 5.1)	5.3	5.1	4.4	4.4
Brachial plexopathy	2.4 (2.2, 2.6)	2.6	2.4	2.1	2.5
Skin toxicities$^{c\varphi}$	19.0 (18.4, 19.6)	17.4	19.6	19.0	20.3
Cellulitis or abscess of the breast$^{\varphi}$	3.0 (2.8, 3.2)	2.7	2.7	3.3	3.4
Closed rib fracture	2.7 (2.5, 2.9)	2.8	3.0	2.3	2.8
Breast Cancer Related Outcomes					
Ipsilateral breast cancer	0.7 (0.6, 0.8)	0.5	0.7	0.9	0.9
Breast cancer-associated mortality	3.2 (2.9, 3.5)	3.1	3.2	2.9	3.7

^{a}Leukemia and myelodysplastic syndrome

^{b}Lung, esophageal, and sarcoma cancers

^{c}Breast deformation, capsular contracture, mastodynia, and fat necrosis

$^{\varphi}$p-value < 0.05 for Gray's test of equality for overall differences in the cumulative incidence of events per cost quartile