Delays in Initiation of Radiation Therapy after Breast Conserving Surgery May Explain Disparities in Breast Cancer Mortality among Older Women

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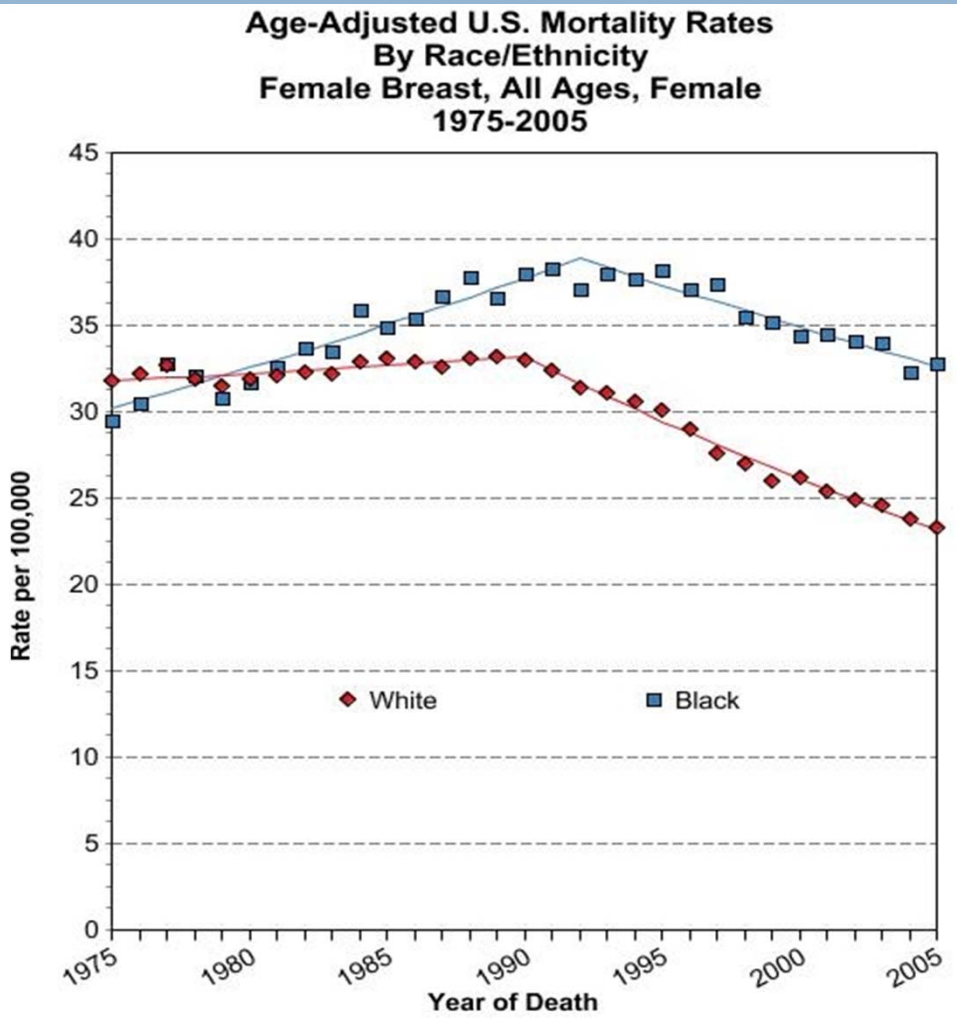
Background and Rationale

Racial Disparities in Breast Cancer

- Black/white disparities in breast cancer outcomes well-documented
- Modest improvements in overall mortality over time, but the gap between races widening
  - Mammography receipt (Swan et al, 2003)
  - Stage at diagnosis (NCI, 2008)



Citation: US Mortality Files, National Center for Health Statistics (NCHS), CDC; created using National Cancer Institute (NCI) interactive database (URL: http:/www.seer.cancer.gov)

Does Treatment Timing Matter?

- Many potential explanations for racial disparities
- Differences in timing of radiation therapy (RT) after breast conserving surgery may account for some variation in outcomes
- Previous research on importance of RT timing conflicting (Gold et al., 2008; Hebert-Croteau et al., 2004; Hershman et al., 2006; Hickey et al., 2006; Hartsell et al., 1995; Tsoutsou et al., 2009) and limited by:
  - Incomplete assessment of all relevant time intervals
  - Focus on younger women
  - Failure to account for racial/ethnic variation
  - Failure to consider the role of other adjuvant therapy (e.g. chemo)
- Current quality metrics in breast cancer specify RT must be initiated within 1 year of diagnosis (ASCO/NCCN, 2008)

Research Objective

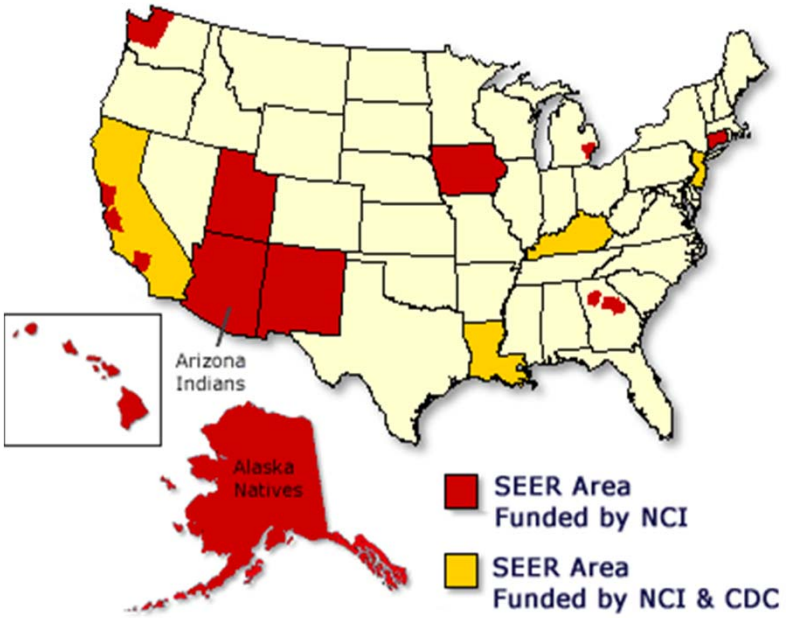
To examine racial/ethnic variation in timing of initiation of guideline-recommended radiation therapy (RT)* and its effect on all-cause and breast cancer-specific mortality

* Among Medicare-enrolled patients with stage I-III cancer who received breast conserving surgery (BCS)

Study Design

Data and Population

- Linked Surveillance Epidemiology and End Results (SEER) – Medicare dataset
- Female, community-dwelling, Medicare beneficiaries ages 65+ who were diagnosed with primary breast cancer in SEER regions during 1994-2002



Exclusion Criteria

- Not enrolled in Parts A/B fee-for-service for the duration of the study period
- In situ or stage IV cancers
- ESRD
- Diagnosed at autopsy or death
- Other racial/ethnic groups (beyond non-Hispanic white, non-Hispanic black, and Hispanic)
- Did not receive BCS
- Additional cancer diagnosis within 1 year
- **Starting sample = 254,803; final sample = 38,574**

Analytic Methods

- **Outcomes:** All-cause and breast cancer-specific mortality
- **Exposures:** Race and timing of initiation of RT
  - RT timing: measured in months elapsed from diagnosis month to first indication of RT, determined by service dates in inpatient, outpatient, physician claims)
- **Analysis:** Multivariate logistic regression
  - Stratified by age and receipt of chemotherapy
  - Limited to women who received RT after BCS
- **Covariates:** Distance to nearest RT facility, distance traveled to surgery, timing of surgery, age at diagnosis, stage, grade, hormone receptor status, lymph node involvement, co-morbidity burden, marital status, low income status (proxied using State-Buy-In), year of diagnosis, regional (zip code level) socioeconomic status

Results

Descriptive Statistics, by Race

Patient-level variables	% or mean (SD) WHITE (N=34,965)	% or mean (SD) BLACK (N=2,273)	% or mean (SD) HISPANIC (N=1,336)
Age at diagnosis	75.7 (6.64)	75.2 (6.79)	74.4 (6.37)
Stage at diagnosis			
Stage I	64.47	52.35	56.44
Stage II	32.3	41.53	38.47
Stage III	3.23	6.12	5.09
Hormone receptor status			
ER positive	71.8	56.8	66.24
PR positive	59.02	45.18	54.27
Node positive	18.51	23.8	22.83
Co-morbidity	0.25 (0.46)	0.41 (0.61)	0.33 (0.53)
Chemo	19.91	24.34	23.16
Married	44.97	24.33	39.3
Low income	13.47	44.57	49.4

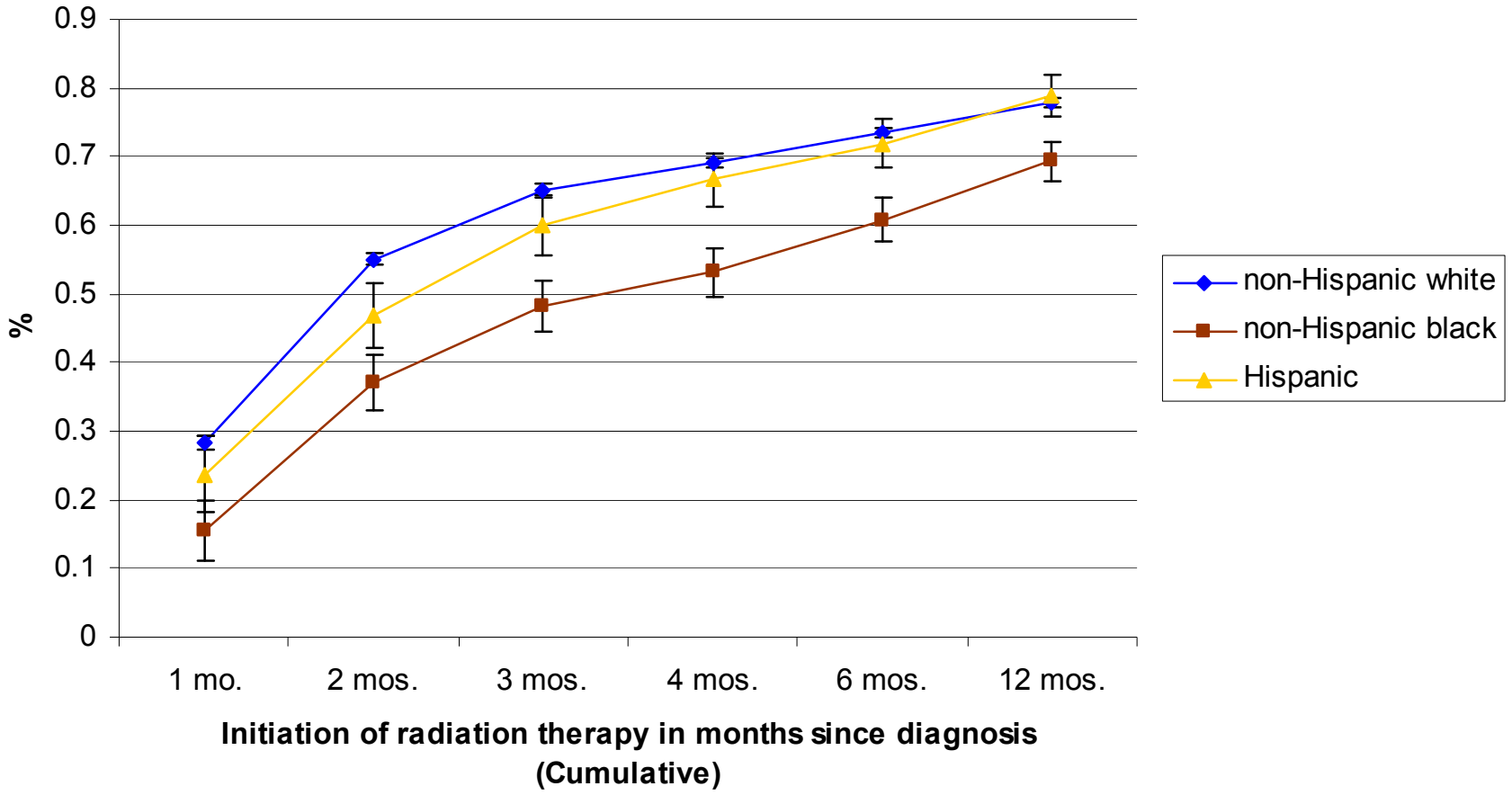
Notes: All racial differences were statistically significant at the $p<0.05$ level, as derived from chi-squared tests or t-tests; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; SD: standard deviation

Bivariate Findings, by Race

Outcomes	***White (N=34,965)***	***Black (N=2,273)***	***Hispanic (N=1,336)***	***p-value***
% died within 5 yrs of diagnosis	22.2	30.5	22.7	<0.001
% died of breast cancer in 5 yrs	5.3	10.1	6.9	<0.001
Mean survival time (months)	60.0 (37.0)	53.4 (36.2)	56.7 (36.4)	<0.001~ 0.053#
Timing of RT initiation				
% ever received RT	58.2	51.4	58.3	<0.001
Mean RT initiation (months)	2.7 (2.9)	3.8 (3.5)	3.1 (3.0)	<0.001~ <0.001#
% received in ≤6 mos.	90.9	82.2	87.5	
% received in >6 and ≤12 mos	7.4	14.8	10.7	<0.001
% received in >12 mos	1.7	2.9	1.8	

- By chemotherapy: median time to RT initiation was 2 months post-diagnosis among those who did not receive chemotherapy, whereas median time to RT initiation was 5 months post-diagnosis, among those who received chemotherapy.
- P-values from chi-squared and t-tests, as appropriate

Timing of initiation of RT among women who received BCS, by race/ethnicity (excluding women who received subsequent mastectomy during each time interval of interest)



Note: Y-error bars depict 95% confidence intervals

Odds ratios for effect of RT timing on mortality, conditioned *on receiving chemotherapy*

Independent Variable	*65-69 yrs (N=1,762)*		*70 yrs+ (N=3,253)*	
	All mortality	*BrCa*	*All mortality*	*BrCa*
Timing of initiation of RT (≤1 month post-diagnosis is reference)				
>1 and ≤2 mos.	1.73+	1.56	1.21	0.97
>2 and ≤3 mos.	0.66	0.68	1.05	0.74
>3 and ≤4 mos.	0.53*	0.57	0.69+	0.97
>4 and ≤5 mos.	0.61	0.70	0.73	0.95
>5 and ≤6 mos.	0.49**	0.64	0.95	1.07
>6 and ≤12 mos.	0.74	0.92	0.85	0.99
>12 mos.	5.79**	6.58**	4.14**	5.04**
Race/ethnicity (white is reference)				
Black	1.54	1.97*	1.24	1.38
Hispanic	1.21	0.85	1.28	1.58

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; ORs for control variables not shown

- More advanced stage disease associated with greater all-cause and BrCa mortality
- Being ER or PR positive associated with lower all cause and BrCa mortality
- Higher co-morbidity associated with greater all-cause mortality

Odds ratios for effect of RT timing on mortality, conditioned *on not receiving chemotherapy*

Independent Variable	*65-69 yrs (N=3,320)*		*70 yrs +(N=12,184)*	
	All mortality	*BrCa*	*All mortality*	*BrCa*
Timing of initiation of RT (≤1 month post-diagnosis is reference)				
>1 and ≤2 mos.	1.19	1.36	0.99	0.98
>2 and ≤3 mos.	1.10	0.66	0.93	0.91
>3 and ≤4 mos.	0.64	1.18	1.28+	1.51
>4 and ≤5 mos.	2.95*	1.05	0.94	1.33
>5 and ≤6 mos.	4.85*	1.00	1.22	1.52
>6 and ≤12 mos.	1.85	2.16	2.80**	7.35**
>12 mos.	6.54**	13.04**	3.88**	6.31**
Race/ethnicity (white is reference)				
Black	0.68	1.78	1.01	0.86
Hispanic	0.63	2.39	0.87	1.09

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; ORs for control variables not shown

- More advanced stage disease associated with greater all-cause and BrCa mortality
- Higher co-morbidity associated with greater all-cause mortality
- Marital status associated with protective effect against mortality for 70+ population

Limitations

- Limited generalizability
- Difficult to determine where “things went wrong”…
- Possible endogeneity/unmeasured confounding
  - Propensity to initiate RT early may be related to unmeasurable functional/health status
  - No info on endocrine therapy (no Part D)
  - Burden of seeking care/traveling for appointments

Conclusions

- Black women experience greater mortality and live about 6 months less than white women
- Black and Hispanic women experience more treatment delays
- In multivariate models controlling for timing of RT and other covariates, the effect of race is no longer significant
- Across all models, receipt of RT more than 1 year post-diagnosis was strongly associated with higher odds of all-cause and breast cancer-specific mortality
  - Among women ages 65-69 who did not receive chemotherapy, initiating RT more than 4 months post-diagnosis associated with higher odds of all-cause mortality
  - Among women ages 70 and older who did not receive chemotherapy, initiating RT more than 6 months post-diagnosis associated with higher odds of all-cause and breast cancer-specific mortality
- **Black women are diagnosed later and have clinically poorer prognosis based upon biological tumor features**
  - **Therefore, if timing does matter, it is precisely this group of women who should receive care as early as possible**

Thank you!

Odds ratios for the effect of timing of RT on mortality, conditioned on receiving adjuvant chemotherapy, stratified by age group

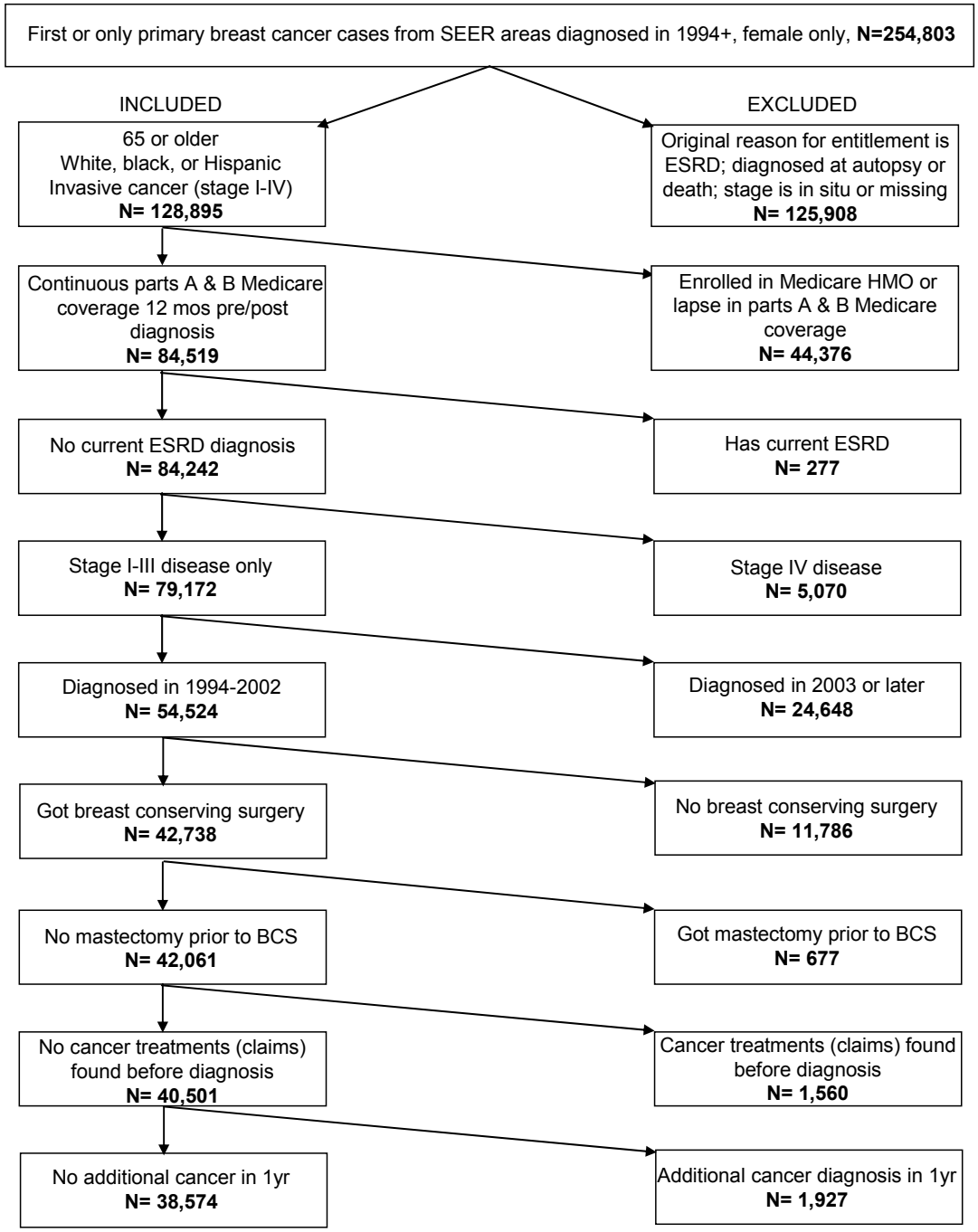
Independent Variable	*65-69 years old (N=1762)*		*70 years and older (N=3253)*	
	All-cause mortality	*BrCa mortality*	*All-cause mortality*	*BrCa mortality*
Timing of initiation of RT (<=1 month post-diagnosis is reference)				
>1 and <=2 mos.	1.73+	1.56	1.21	0.97
>2 and <=3 mos.	0.66	0.68	1.05	0.74
>3 and <=4 mos.	0.53*	0.57	0.69+	0.97
>4 and <=5 mos.	0.61	0.70	0.73	0.95
>5 and <=6 mos.	0.49**	0.64	0.95	1.07
>6 and <=12 mos.	0.74	0.92	0.85	0.99
>12 mos.	5.79**	6.58**	4.14**	5.04**
Race/ethnicity (white is reference)				
Black	1.54	1.97*	1.24	1.38
Hispanic	1.21	0.85	1.28	1.58
Covariates				
Age (grouped in 5-year categories; 70-74 years is reference)				
75-79 years	-	-	1.49**	1.38*
80-84 years	-	-	2.01**	1.54*
85 years and older	-	-	2.43**	1.36
Received surgery in diagnosis month	1.45*	2.40**	1.09	1.2
Stage at diagnosis (stage I is reference)				
Stage II	1.83**	2.29**	1.73**	2.20**
Stage III	5.32**	6.55**	4.35**	5.84**
Grade (well-differentiated is reference)				
Moderately-differentiated	1.89*	3.04*	1.06	1.49
Poorly-differentiated	3.02**	6.45**	1.51**	2.59**
Anaplastic	2.63	5.73*	1.4	2.29*
Grade missing	2.27*	5.72**	1.05	1.61
Hormone receptor status (negative, borderline, or unknown is reference)				
ER positive	0.68+	0.66	0.81+	0.69*
PR positive	0.75	0.58+	0.77*	0.63**
Node status (node negative is reference)				
Node positive	1.15	1.01	1.06	1.31
Node status missing	1.86*	1.34	1.87**	1.16
Co-morbidity index (score of 0 is reference)				
0.01-1	1.39+	0.81	1.53**	1.16
1.01-2	3.06**	2.50*	2.84**	1.35
> 2	2.24	1.28	3.43**	0.63
Married	0.8	1.02	0.91	0.87
Low income proxy (State-Buy-In)	1.19	1.53	0.91	0.88
Year of diagnosis (1994 is reference)				
1995	0.84	0.87	0.53*	0.54*
1996	1.02	1.36	0.46**	0.49*
1997	1.29	1.33	0.52*	0.53*
1998	0.75	0.90	0.40**	0.30**
1999	0.88	1.08	0.49**	0.37**
2000	0.49+	0.62	0.44**	0.31**
2001	0.71	0.66	0.41**	0.24**
2002	0.56	0.47	0.27**	0.19**

Odds ratios for the effect of timing of RT on mortality, conditioned on not receiving chemotherapy, stratified by age group

Independent Variable	*65-69 years old (N=3320)*		*70 years and older (N=12184)*	
	All-cause mortality	*BrCa mortality*	*All-cause mortality*	*BrCa mortality*
Timing of initiation of RT (<=1 month post-diagnosis is reference)				
>1 and <=2 mos.	1.19	1.36	0.99	0.98
>2 and <=3 mos.	1.10	0.66	0.93	0.91
>3 and <=4 mos	0.64	1.18	1.28+	1.51
>4 and <=5 mos.	2.95*	1.05	0.94	1.33
>5 and <=6 mos.	4.85*	#	1.22	1.52
>6 and <=12 mos.	1.85	2.16	2.80**	7.35**
>12 mos.	6.54**	13.04**	3.88**	6.31**
Race/ethnicity (white is reference)				
Black	0.68	1.78	1.01	0.86
Hispanic	0.63	2.39	0.87	1.09
Covariates				
Age (grouped in 5-year categories; 70-74 years is reference)				
75-79 years	-	-	1.27**	1.05
80-84 years	-	-	1.99**	1.41*
85 years and older	-	-	3.35**	1.3
Received surgery in diagnosis month	1.17	0.96	0.93	0.9
Stage at diagnosis (stage I is reference)				
Stage II	1.67*	2.37*	1.50**	2.98**
Stage III	3.89*	2.77	3.29**	6.32**
Grade (well-differentiated is reference)				
Moderately-differentiated	1.14	2.15	1.26**	2.27**
Poorly-differentiated	1.52+	3.67**	1.66**	4.75**
Anaplastic	4.02**	7.19*	1.25	5.10**
Grade missing	0.9	0.84	1.25*	2.52**
Hormone receptor status (negative, borderline, or unknown is reference)				
ER positive	0.99	0.67	0.88	0.61**
PR positive	1.04	1.27	0.95	1.03
Node status (node negative is reference)				
Node positive	1.60+	1.83	1.27*	1.62**
Node status missing	1.62*	0.95	1.58**	2.14**
Co-morbidity index (score of 0 is reference)				
0.01-1	2.43**	1.44	2.02**	1.05
1.01-2	5.94**	2.00	3.38**	1.36
> 2	11.39**	4.70	10.06**	3.14**
Married	0.97	0.88	0.87*	0.76*
Low income proxy (State-Buy-In)	1.29	0.7	1.06	0.8
Year of diagnosis (1994 is reference)				
1995	0.65	0.81	0.82	0.72
1996	0.47*	0.39	0.70**	0.63*
1997	0.71	1.05	0.76*	0.60*
1998	1.0	0.79	0.81	0.81
1999	0.64	0.95	0.74*	0.76
2000	0.81	1.0	0.76*	0.78
2001	0.61	1.01	0.81+	0.59*
2002	0.73	0.10+	0.72*	0.50**

Measurement: health care services

Treatment	Primary means of identification
Diagnostic codes	174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9 Other: V10.3
Aggressive surgery	ICD9CM procedure: 85.41, 85.42, 85.43, 85.44, 85.45, 85.46, 85.47, 85.48 CPT/HCPCS: **19180, 19182**, **19200, 19220, 19240**, 19260-19272, **19303-19307**
BCS	ICD9CM procedure: 85.20, 85.21, 85.22, 85.23, 85.24, 85.25 CPT/HCPCS: 19120, 19125, 19126, **19160, 19162, 19301, 19302**
Radiation therapy	ICD9CM procedure: 92.21-92.29 CPT/HCPCS: **77261-77499**, 77520, 77522, 77523, 77525, 77750-77799, G0256, G0261 Revenue Center Code: 0330, **0333**, 0339 DRG: 409 Other: V58.0, V66.1, V67.1


First or only primary breast cancer cases from SEER areas diagnosed in 1994+, female only, N=254,803
INCLUDED
EXCLUDED
65 or older
White, black, or Hispanic
Invasive cancer (stage I-IV)
N= 128,895
Original reason for entitlement is ESRD; diagnosed at autopsy or death; stage is in situ or missing
N= 125,908
Continuous parts A & B Medicare coverage 12 mos pre/post diagnosis
N= 84,519
Enrolled in Medicare HMO or lapse in parts A & B Medicare coverage
N= 44,376
No current ESRD diagnosis
N= 84,242
Has current ESRD
N= 277
Stage I-III disease only
N= 79,172
Stage IV disease
N= 5,070
Diagnosed in 1994-2002
N= 54,524
Diagnosed in 2003 or later
N= 24,648
Got breast conserving surgery
N= 42,738
No breast conserving surgery
N= 11,786
No mastectomy prior to BCS
N= 42,061
Got mastectomy prior to BCS
N= 677
No cancer treatments (claims) found before diagnosis
N= 40,501
Cancer treatments (claims) found before diagnosis
N= 1,560
No additional cancer in 1yr
N= 38,574
Additional cancer diagnosis in 1yr
N= 1,927