View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Carolina Digital Repository

A CLOSER LOOK: HEALTH SERVICES STRUCTURE AND ORGANIZATION, HEALTH DISPARITIES, AND RECEIPT OF HIGH QUALITY BREAST CANCER TREATMENT

Stephanie B. Wheeler

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Health Policy and Management in the Gillings School of Global Public Health

Chapel Hill
2010

Approved by

Andrea K. Biddle, PhD

William R. Carpenter, PhD

Jeffrey Peppercorn, MD

Anna P. Schenck, PhD

Morris Weinberger, PhD

© 2010
Stephanie B. Wheeler
ALL RIGHTS RESERVED

ABSTRACT

Stephanie B. Wheeler
A CLOSER LOOK: HEALTH SERVICES STRUCTURE AND ORGANIZATION, HEALTH DISPARITIES, AND RECEIPT OF HIGH QUALITY BREAST CANCER TREATMENT
(Under the direction of Andrea K. Biddle, PhD)

Racial/ethnic disparities in breast cancer outcomes have been well documented; however, the reasons why certain groups have widely different health experiences are not well understood. Recognizing that variation in quality of cancer care may correlate with socio-demographic and health system characteristics, the overall objectives of this dissertation were (1) to investigate the relationships between race/ethnicity and structural/organizational aspects of health services in terms of post-operative receipt and timing of initiation of radiation therapy and adjuvant chemotherapy, and (2) to determine whether timing of adjuvant therapy initiation affects mortality. This dissertation used population-based SEER-Medicare data to examine these issues in female Medicare beneficiaries ages 65 and older diagnosed with primary breast cancer in the years 1994 to 2002. Structural/organizational variables examined included characteristics of the surgical facility (i.e., type/ownership, teaching status, size, institutional affiliations, and presence of on-site radiation services), distance traveled to surgical facilities, distance to nearest radiation therapy provider, and distance to nearest chemotherapy provider. Racial/ethnic groups examined included non-Hispanic white, non-Hispanic black, and Hispanic patients. We found significant racial/ethnic disparities in terms of receipt and timing of initiation of radiation therapy, as well as all-cause and breast cancer specific mortality, whereas we found no evidence of racial/ethnic disparities in adjuvant chemotherapy. We also found evidence that certain health services characteristics, including type/ownership and size of

surgical facility, presence of on-site radiation at surgical facility, and distance from patient residence to adjuvant therapy providers, were associated with quality of care received, suggesting that health care systems or policies may be designed in such a way to improve outcomes for all breast cancer patients, and particularly, among minority women at risk for undertreatment. Finally, we found evidence that earlier initiation of radiation therapy and adjuvant chemotherapy may correspond to better health outcomes. This study documents the important role that health services characteristics may play in determining quality of care. Additionally, considering that black women are more likely to be diagnosed with aggressive, advanced stage cancers and more likely to die from breast cancer, this study suggests that earlier initiation of treatment may help minimize racial disparities in breast cancer mortality.

ACKNOWLEDGEMENTS

Although this dissertation bears my name on its title page, this work is actually a collaborative effort involving many people, without whom the final product would not have been possible. First and foremost, I thank my advisor and dissertation chair, Andrea Biddle, for her endless support of me throughout my four years at UNC and especially during the dissertation process. I knew when I began the PhD program in Health Policy and Management that a strong mentor-student relationship was important, but I never dreamed how truly essential it would be in order for me to finish in a timely manner. Andrea coached me through coursework selection and completion, served as my research assistant supervisor, sought out and encouraged me to apply for fellowship opportunities, served as a sounding board for all my dissertation ideas (and there were many!), helped me identify the ideal combination of committee members, pushed me to meet tight deadlines and to quicken my pace, provided amazingly quick turn-around on drafts no matter what else she might have had going on, and above all, gave me the boost of confidence I needed to ensure dissertation completion in the final stages of this process. I couldn't have done it without her. Or Morris Weinberger. As the director for the doctoral program in our department, before I even met Morris in person, we had spent hours on the phone as I deliberated upon which university to attend for my PhD training. Despite my compulsive and incessant inquiries and uncertainties about The Big Decision, Morris was incredibly patient, obliging, and in the end quite convincing—I only hope that the other 17 or so admitted students in my cohort didn't badger him too! Since that time, Morris has been an outstanding mentor to me and a thoughtful member of my dissertation committee, providing perspective as I developed and refined my professional goals and supplying the expertise in quality of care

and clinical medicine necessary for my dissertation. Perhaps most importantly, Morris' unwavering belief in my abilities and potential has opened many doors and enabled me to take advantage of opportunities I might not have otherwise had.

Speaking of opportunities, I would be remiss not to acknowledge the fortunate crossing of paths with Bill Carpenter early in my doctoral career. Interested in Bill's work, but having spent 3-4 years working in reproductive health and HIV/AIDS, I cornered Bill after a departmental seminar presentation and asked him how I might get involved in cancer outcomes research. Immediately, we were bouncing ideas back and forth, and I knew that I wanted to work with this intellectually engaging and incredibly personable researcher. As I developed my dissertation questions, over time, Bill connected me with most of the people I now know at UNC's Lineberger Cancer Center, Duke University, NCI, and the Carolinas Center for Medical Excellence (CCME), including my remaining two committee members, Jeff Peppercorn (of Duke) and Anna Schenck (of CCME and UNC). Bill also served on my committee, answering substantive questions about the dataset, helping me become more aware of SEER-Medicare strengths and limitations, and providing perspective on cancer outcomes research in general. Bill facilitated my use of the SEER-Medicare data, building upon an existing project that he and Bryan Weiner were pursuing; since that time, both Bill and Bryan have brought me into a number of projects, further providing experience and opportunity in cancer outcomes research at UNC. Without Bill, I don't know that I would have felt prepared to branch out beyond my "comfort zone" in reproductive/sexual health. In addition, without Bryan's financial assistance, I could not have afforded the programmer time needed to help manage the rather pesky Medicare claims data for my dissertation!

Both Jeff Peppercorn and Anna Schenck have been remarkable members of my dissertation "dream team". In fact, I often tell people that I had the perfect committee—responsive, supportive, available, and fully engaged, even when deadlines were extremely tight, as they were the last 2-3 months prior to my defense. Jeff was the insightful

oncologist, rapidly responding to my random and sometimes ridiculous clinical questions, while also providing thoughtful feedback in terms of the long-term clinical implications of this work. Anna was the claims-savvy cancer epidemiologist, who answered numerous questions about how to deal with these complex data, provided fantastic feedback about the logistical and data management decisions that needed to be made, and connected me with billing/coding specialists and programmers at CCME who helped with the rather arduous task of determining which ICD-9, HCPCS, and NDC codes applied and when to what... specifically, I extend many thanks to Sharon Peacock and Danielle Durham at CCME. As well, Tammie Hope at UNC assisted with this effort, and her time is much appreciated.

I must acknowledge several programmers at the Sheps Center for Health Services Research, without whom, I could have *never* finished my dissertation in 2010: John Bainbridge, Jane Darter, and Randy Randolph. John assisted with the initial SEER-Medicare sample definitions and helped me think through creation of the analytical dataset during the proposal writing stage. John also provided much of the data management assistance needed to process the analytic dataset, and anytime I had a question about the data and what they might (or might not) contain, I was always pretty certain John had the answers. Jane assisted with creation of the co-morbidity indices (thank goodness!), claims selection and dates processing, NCI hospital file matching, and distance-to-care calculations. Both Jane and John got occasional (okay, at times frequent) SAS programming questions from me and were quick to respond, sharing their expertise with this self-proclaimed Stata girl. Many, many thanks to you both! Randy's geospatial programming knowledge and programming skills were crucial in developing the distance traveled and distance-to-nearest adjuvant therapy provider measures. Importantly, I thank the Sheps Center, Tim Carey, and Roger Akers for lending John's, Jane's, and Randy's time to me and to this dissertation study.

This research was supported by a National Research Service Award (NRSA) Predoctoral Traineeship from the Agency for Healthcare Research and Quality sponsored by the Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Grant No. T32-HS-000032-20. This predoctoral award provided me with dedicated time, space, and mentoring to successfully complete the dissertation in a two-year period. The NRSA seminar group, consisting of fellows and mentoring faculty at the Sheps Center, contributed much-needed and much-appreciated feedback through works-in-progress sessions, which were instrumental in helping me define my research question and figuring out how to go about answering it. In particular, Mark Holmes and Tim Carey both read parts of my proposal, and I am much indebted to them for their thoughtful input.

I also want to acknowledge several others in the field of health services research, cancer outcomes research, and clinical medicine who were willing to sit down with me and "talk shop", providing in-the-field expertise to a student whose time had been most recently spent in-the-books. As I developed my proposal and analyzed the SEER-Medicare data, at different times in the process these folks were helpful and willing to answer my questions and/or read drafts of my work: Keith Amos, Michael O'Malley, Sally Stearns, Lisa Carey, Amy Abernethy, Hy Muss, and Kit Simpson. I also want to point out that it was Kit Simpson of the Medical University of South Carolina who, four and a half years ago after taking a decision sciences course with her to complete my MPH degree, convinced me that I needed to pursue my PhD. I had not given much thought to a PhD in public health and at the time was working as a trade analyst with a financial firm in Charleston. Talking with Kit opened my eyes to the possibilities of a career as an independent investigator and professor. At the time I was worried that I wouldn't get in to PhD programs, that I was too young, that I was ill-prepared, but it was Kit who asserted that I was wrong and that I was, in fact, ready. My path changed completely because she took me aside and took interest in my future. We

have continued to work together since then, and I am enormously indebted to Kit for her confidence in me as a student and increasingly, as a colleague.

In addition, I would like to acknowledge my many professors at the College of Charleston as an undergraduate student and at the University of Cape Town in South Africa as a Masters student who helped instill in me a thirst for continuing education and a desire to understand more fully the world in which we live. In particular, Dr. John Newell of the Honors College at the College of Charleston encouraged me in the early part of my undergraduate career to consider applying for a Rotary Ambassadorial/Academic Scholarship to pursue my Masters degree abroad. Thus planting the seed, being awarded the Rotary scholarship became an important part of my early professional goals. I know now that living and working in South Africa for that year and a half changed *everything* for me and helped me to understand the healthcare needs of underprivileged populations. I am so grateful to Rotary International and to the Rotarians in South Carolina and in South Africa for making those years possible. As well, Jill Conway and Maria Richardson of the Honors College at the College of Charleston acted as “mother hens” during my undergraduate experience and have continued to be great friends beyond, supporting me in all my academic and personal endeavors. Thank you so much for your encouragement!

Data purchase and programming time were further funded in part by a pilot grant (Grant No. 2KR50906) from the North Carolina Translational and Clinical Sciences (NC TraCS) Institute, Clinical and Translational Science Award (CTSA) Number UL1RR025747 from the National Center for Research Resources, National Institutes of Health and in part by NCI award No. 5RO1CA124402-03 (PI: Bryan Weiner). I am very grateful to the TraCS Institute and to Bryan Weiner for sharing these resources with graduate students in need of funding for data acquisition and management.

I wouldn’t be sane at this point in my trajectory without fabulously supportive and loyal friends. In particular, I acknowledge my roommate and member of my cohort, Laura

D'Arcy, who during this sometimes painful process was a constant source of econometrics and Stata programming advice, another sounding board for my dissertation ideas, and a necessary distraction from the seemingly endless pile of work (um, kickball anyone?) As well, Megan Parker spent hours and hours with me sitting in coffee shops around Chapel Hill and Durham, each of us working on our respective dissertations and sharing the occasional glass of wine at the end of the long workday. The girls of the Dissertation Dish dinner parties – Heather, Sarah, Michaela, and Laura – without you ladies, I wouldn't have been able to see that we *all* encounter dissertation challenges and hiccups and that eventually we can *all* break on through to the other side! To the rest of my friends in Charleston and in Chapel Hill, thank you for your unfailing friendship before, during, and after these difficult years.

To my parents, Jack and Sheila, mere words simply cannot express my vast appreciation for your unconditional love, tenacious encouragement to seek out and conquer new challenges, and emotional and financial support over the years. You have taught me how to be a good person, an ethical person, and a person who feels it is my life's purpose to help others who are more disadvantaged, vulnerable, and needy than me. You truly have been the best parents I could have had, and I hope that I have made you proud (even though I didn't go to medical school, ha!) As well, I am very lucky to be very close to all my grandparents, and they each have played an enormous role in my life. From Nannie's home cooked biscuits and hearty laugh, helping me realize that everything's going to be okay to Papa Jack's and my heated (and extremely educational!) political discussions, from Papa Brock's bad barber jokes and our chats about the economy to my late MeMa's enduring battle with diabetes that ultimately consumed this sweet lady's life, I have learned so much from you all over the years, and I love you and thank you for your positive influence.

To my life partner and best friend, Scotty: you were the bright spot in my days when things seemed pointless, you were the encourager and listener when I felt like I could not

succeed, you were the insistent boyfriend who made me go out on the boat or take a weekend off to decompress, you were the persistent believer in our long-distance relationship for four difficult years, you were and remain to this day the love of my life. After 4 years of college dating limbo, 1.5 years together in South Africa, 1.5 years spent obsessing over and trying to figure out my career plans, and 4 years of relentless doctoral stress, most men would have thrown in the towel long ago. You didn't, and I'm not entirely sure why you didn't, because I know I've been difficult… but I thank you. And I love you with all my heart.

Finally, to the women with breast cancer you shared their stories with me, in particular Kathy Cheek and Prinella Haygood, thank you for your time and honesty in helping me understand this devastating disease. I hope this dissertation helps, in one way or another, the hundreds of thousands of women like you who have had to endure a diagnosis of primary breast cancer.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACS	American Cancer Society
ACoSOG	American College of Surgeons Oncology Group
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
BCS	Breast Conserving Surgery
CCM	Chronic Care Model
CDC	Centers for Disease Control and Prevention
DCIS	Ductal Carcinoma in Situ
ER	Estrogen Receptor
HMO	Health Maintenance Organization
IOM	Institute of Medicine
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NICCQ	National Initiative for Cancer Care Quality
NIH	National Institutes of Health
NQF	National Quality Forum
PR	Progesterone Receptor
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance Epidemiology and End Results
SLNB	Sentinel Lymph Node Biopsy
TNM	Tumor Node Metastasis

CHAPTER 1: INTRODUCTION

Variation in cancer treatment and outcomes has been widely documented across providers and geographic regions within the United States, but until recently, there was weak consensus on quality metrics for cancer treatment. With increasing national pressure to improve health care quality in the cancer domain (Bowles et al., 2008), the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) released in July 2008 three revised quality metrics for breast cancer based on expert review of existing clinical guidelines (Desch et al., 2008). These metrics included (1) receipt of radiation therapy (RT) after breast conserving surgery (BCS) within one year of diagnosis for stage I-III tumors, (2) receipt of adjuvant chemotherapy within 120 days of diagnosis for hormone receptor negative, stage II-III tumors, and (3) receipt of tamoxifen or aromatase inhibitor within one year of diagnosis for hormone receptor positive, stage I-III tumors greater than 1 cm. Due to insufficient accumulation of clinical trial evidence about the effects of radiation and chemotherapy in older women, quality metrics for these two therapies were limited to women younger than 70. These measures were selected for their potential to improve disease-free and overall survival at the population level, as well as the feasibility of data collection and quality monitoring (Desch et al., 2008).

Although ensuring high quality cancer care in the general population is of critical importance, we should be especially concerned about disparities in quality within vulnerable sub-populations. If the quality of cancer care improves over time in the general population, but differences in quality across sub-populations persist or worsen over time, inequities in treatment that lead to disparate health outcomes may have been essentially ignored. A

bevy of previous research has shown that health disparities in breast cancer, particularly between white and black patients, persist in terms of timeliness of diagnosis, receipt of treatment, and long-term health outcomes (Bickell et al., 2005; Bickell et al., 2006; Bigby and Holmes, 2005; Bowen et al., 2006; Freedman et al., 2009; Gerend and Pai, 2008; Lund et al., 2008; Masi and Olopade, 2005; Shavers and Brown, 2002; Tammemagi, 2007). However, explanatory, rather than descriptive, cancer disparities research is limited. Possible explanations for enduring racial and ethnic disparities include differences in tumor behavior, patient-level psychosocial or behavioral factors, socioeconomic status, access to care, and treatment (Bickell, 2002; Blackman and Masi, 2006; Bowen et al., 2006; Chen et al., 1994; Demicheli et al., 2007; Gerend and Pai, 2008; Lund et al., 2009; Magai et al., 2008; Newman et al., 2003; Williams and Mohammed, 2009).

Organization and structure of health services are closely related to diffusion and implementation of high quality, evidence-based practices. Organizational theory and diffusion of innovations theory suggest that substantially different institutional cultures exist within different types of health organizations (Greenhalgh et al., 2004). Characteristics of local communities, including population density, local resource capacity, and neighborhood racial/ethnic composition, may affect the types of organizations that locate in particular settings. In addition, patient-level socio-demographic characteristics may be related to choice of residence, utilization of services with certain organizational characteristics, and access to well-trained health professionals (Birkmeyer et al., 2003; Coughlin et al, 2008). It is unclear exactly how structural/organizational features and functions of the health care system correlate with race/ethnicity and other patient-level characteristics. If differences in access to or availability of health services exist among vulnerable sub-populations, disparities in treatment or outcomes may result. Further, innovative treatments and care processes may diffuse more slowly within certain sub-populations over time.

The impetus for developing quality metrics for breast cancer was motivated by, and based upon, the existence of well-established clinical guidelines, such as those published by ASCO/NCCN. Accordingly, this dissertation examined the relationships between patient demographics (focusing on race/ethnicity) and structural/organizational aspects of health services in terms of receipt and diffusion of high quality care, as defined by two of the three breast cancer quality metrics developed by ASCO/NCCN (Desch et al., 2008). Specific aims included:

1. Examine receipt of radiation therapy after BCS within one year of diagnosis for stage I-III breast cancers:
    a. Characterize diffusion of RT after BCS using diffusion curves across sub-groups (e.g., by race/ethnicity, age group [< / ≥ 70 years])
    b. Examine the independent and interactive effects of race/ethnicity and structural/organizational factors on timing of receipt of RT after BCS
2. Examine receipt of adjuvant chemotherapy within four months of diagnosis for stage II and III, hormone receptor negative breast cancers:
    a. Characterize diffusion of adjuvant chemotherapy using diffusion curves across sub-groups (e.g., by race/ethnicity, age group [< / ≥ 70 years])
    b. Examine the independent and interactive effects of race/ethnicity and structural/organizational factors on timing of receipt of adjuvant chemotherapy
3. Examine the effect of timing of guideline-prescribed, clinically appropriate radiation therapy and/or chemotherapy on health outcomes, specifically all-cause and breast cancer-specific mortality, across diverse patient sub-groups:
    a. Examine mortality five years after diagnosis as a function of timing of radiation therapy after BCS among stage I-III breast cancers

b. Examine mortality five years after diagnosis as a function of timing of adjuvant chemotherapy among stage II-III, hormone receptor negative breast cancers

Information about women with breast cancer was obtained from registry data linked to claims data. Surveillance, Epidemiology and End Results (SEER) registry data from incident breast cancer cases, linked to Medicare claims data, were used to examine aims 1-3 among women ages 65 years and older.

We know little about diffusion of evidence-based guidelines across vulnerable sub-populations of breast cancer patients. To assess diffusion of high quality, evidence-based treatment over time within sub-populations, aims 1a and 2a were examined descriptively using SEER-Medicare data. Primary breast cancer cases diagnosed in 1994-2002, with claims data through 2003, were included. Diffusion curves based upon population-level proportions of eligible patients receiving RT after BCS within one year of diagnosis (aim 1a) and adjuvant chemotherapy within four months of diagnosis (aim 2a) were constructed for different sub-populations using Medicare claims data. Diffusion curves comparing proportions of patients receiving each therapy by race/ethnicity, age group, rural- versus urban-dwelling, SEER registry, and low income status, were contrasted using chi-squared tests, by year. To examine reliability between the registry and claims reporting sources, SEER data were compared to Medicare claims data for receipt of RT after BCS within the first four months post-diagnosis.

It is unclear whether structural and organizational differences in health services available to women can explain some of the racial/ethnic disparity in breast cancer treatment and outcomes. It is also unclear whether racial/ethnic differences in timing of treatment exist and whether timing of treatment is related to structural/organizational characteristics of health services. Using SEER-Medicare data, timing of initial receipt of radiation therapy (RT) (aim 1b) was examined as a binary variable indicating whether the

patient received a first course of RT within the specified time interval. Primary breast cancer cases diagnosed in 1994-2002, with claims through 2003, were included. Importantly, the ASCO/NCCN metric specifies that the patient must begin RT within one year of diagnosis; completion of a recommended course of RT is not included in the metric, however. Although adherence to or persistence in receiving the full treatment is clearly important, clinically appropriate variation across patients in dosage, timing of cycles, and administration makes assessment of therapy completion difficult. Additionally, the quality metric "deadline" of one year is considered by some clinicians and researchers to be lenient, in light of studies that have shown improved outcomes with earlier initiation of radiation therapy. The ASCO/NCCN panels relaxed the timing component of the denominator to allow for potential delays in administration and sequencing of multiple anticancer treatments (e.g., patients receiving surgery, chemotherapy, and RT) (Desch et al., 2008). Given the controversy over the optimal timing of initiation of RT, time intervals for receipt of RT at 1 to 6 months also were examined. As well, aim 3 helps to address the lack of consensus about the benefits of early initiation of radiation therapy by exploring the effects of timing of initiation of RT on health outcomes.

The SEER-Medicare linked data also were used to examine aim 2b in women ages 65 and older diagnosed with breast cancer in 1994-2002. Time to initiation of post-operative adjuvant chemotherapy was examined as a binary indicator of receipt during the specified time period. Notably, the ASCO/NCCN metric specifies that patients with stage II-III, hormone receptor negative breast cancer must begin adjuvant chemotherapy within four months of diagnosis, but completion of a full recommended course is not part of the metric. Although incomplete use of chemotherapy may have implications for treatment efficacy, chemotherapeutic regimens used may vary across patients, leading to clinically appropriate variation in dosage, timing of cycles, and administration. Until more detailed information is included in cancer registries, adherence to recommended chemotherapy schedules over

time cannot be assessed easily. The 120-day time allowance specified in the metric was intended to provide sufficient time for surgery and medical consultation, but may be overly lenient. As such, additional time intervals (1 to 3 months) were examined as binary dependent variables to detect differences in timing of receipt of clinically appropriate care. Finally, because the proliferation of hormone receptor testing and anticancer hormone therapies occurred during the time period of interest, thereby changing practice patterns and guidelines according to hormone receptor positivity, we also examined patterns in initiation of adjuvant chemotherapy over time in hormone receptor positive patients. Women who received preoperative or neoadjuvant chemotherapy were excluded.

The main independent variables for aims 1b and 2b included race/ethnicity (limited to non-Hispanic white, non-Hispanic black, and Hispanic) and structural/organizational characteristics of oncologic health services, including surgical facility type/ownership, bed size, teaching status, National Cancer Institute (NCI) Comprehensive Cancer Center designation, American College of Surgeons Oncology Group (ACoSOG) affiliation, NCI Radiation Therapy Oncology Group (RTOG) membership (aim 1b only), and presence of on-site radiation services (aim 1b only); and distance to oncology service providers. Control variables for aims 1b and 2b included age at diagnosis, rural/urban residence, zip code level income, education, and area racial composition; tumor stage, histologic grade, and ER/PR status (aim 1b only); receipt of chemotherapy prior to RT (aim 1b only); co-morbidity score; year of diagnosis; low income status (measured by State-Buy-In months); and marital status at diagnosis.

Aims 1b and 2b were analyzed using stratified multivariable logistic regression. Strata were constructed according to age-group (<70, 70 and older) and for aim 2b, hormone receptor positivity. Briefly, stratified models were used because of substantial differences in breast cancer guidelines and quality metrics (and presumably, practice patterns) based upon age and hormone receptor status. With respect to age, the lack of

inclusion of women older than 70 in clinical trials has translated to a lack of evidence for guideline and quality metric development within older age groups (Ballard-Barbash et al., 1996; Silliman et al., 1993; Wildiers and Brain, 2005). However, some studies have shown similar benefits of radiation therapy and chemotherapy in older women compared to younger women (<70 years old) (Owusu et al., 2007; Smith et al., 2006). As a result, conceivably, omission of older women from guidelines and denial of life-prolonging treatment could constitute age discrimination (Passage and McCarthy, 2007; Wildiers and Brain, 2005). As such, both younger (<70) and older (70 and older) women were studied in the current analysis; determining whether any differences in treatment exist by age group is an important and timely contribution to the literature.

Given the controversy over the significance of timing of treatment and whether timing is relevant in terms of clinical outcomes, aims 3a and 3b assessed the effect of timing of radiation therapy and chemotherapy on five-year mortality. Aims 3a and 3b were analyzed using SEER-Medicare from 1994-2002 diagnoses, to allow five-year follow-up of vital status for all patients through 2007. Fully adjusted logistic models were employed, stratified by age group (<70, 70 and older) and receipt of another anticancer therapeutic regimen, excluding hormone therapy for which information is not readily available in SEER-Medicare. All-cause mortality and disease-specific mortality at five years were outcomes of interest. The key independent variables, timing of radiation therapy and timing of chemotherapy, were specified as categorical variables using the time intervals described in aims 1b and 2b, primarily because timing of radiation therapy and chemotherapy are controversial issues in the literature, particularly among older women (>/= 70 years). Race/ethnicity also was a key independent variable of interest. Control variables for aims 3a and 3b were similar to aims 1b and 2b.

Structural/organizational and geographic characteristics of the health system may independently influence receipt of high quality care, and also may be correlated with

racial/ethnic group. To date, the breast cancer literature has not explicitly considered the role of multiple health services organization measures on racial/ethnic disparities in treatment and outcomes. The research presented in this dissertation reveals that differences in organizational health services characteristics can help to explain a portion of the racial and ethnic disparities in breast cancer, particularly in receipt of RT after BCS, but differences in treatment remain even after controlling for structural/organizational characteristics of health services. Vulnerable sub-populations (for example, poor, black, rural-dwelling women) who ultimately receive poorer quality care are likely to have worse health outcomes. Considering that elimination of health disparities was a key component of the United States Department of Health and Human Services' *Healthy People 2010* report (US DHHS, 2000) and the Institute of Medicine's (IOM) *Unequal Treatment* report (IOM, 2002), this dissertation suggests that pinpointing system-level factors that may contribute to persistent disparities can help policymakers focus efforts to equalize health care access and quality across diverse user populations.

Sections of the dissertation are organized as follows: Chapter 2 details the current literature on breast cancer disparities, quality of cancer care, and structural/organizational characteristics that may affect treatment, as well as the limitations of existing studies. Chapter 2 is intended to provide background and justification for the dissertation study and to provide the reader with an understanding of the complexity of breast cancer treatment and the array of patient-level and system-level factors that may affect quality of care received. Chapter 3 provides an overview of the methods used, including a discussion of the study design, data sources, study hypotheses, and analytical approach used. Chapters 4 through 6 are individual manuscripts corresponding to aims 1-3, respectively, and are intended for submission for peer-reviewed publication. Chapter 7 summarizes the strengths and limitations of this work, policy relevance, and future research plans. References are provided in a generalized bibliography at the end of the dissertation.

CHAPTER 2: LITERATURE REVIEW

Overview

The problem of health disparities in cancer care and outcomes is multifaceted and complex. Organizational, structural, economic, and sociopolitical dynamics of the American health system likely contribute to racial/ethnic, socioeconomic, age-related, and geographic health disparities and may not be amenable to rapid change. In the *Healthy People 2010* report, the United States Department of Health and Human Services (DHHS) made it clear that elimination of health disparities was one of its main priorities (DHHS, 2000). However, interim assessments of breast cancer epidemiological endpoints suggest that differences in outcomes by race/ethnicity persist. For example, although use of screening mammography is now nearly equivalent nationally among black and white women (Mayberry, Mili, and Ofili, 2002), mortality rates in the years 2000-2004 remained higher among black women, despite the fact that breast cancer is diagnosed more often in white women (American Cancer Society [ACS], 2008).

Differences by race/ethnicity in diagnosis, receipt of appropriate care, and mortality have been well-documented in the literature (Banerjee et al., 2007; Bickell, 2002; Bickell et al., 2006; Bigby and Holmes, 2005; Bowen et al., 2006; Chen et al., 2008; Freedman et al., 2009; Gerend and Pai, 2008; Haggstrom et al., 2005; Lund et al., 2008; Masi and Olopade, 2005; Shavers and Brown, 2002; Tammemagi, 2007). Possible explanations for enduring racial and ethnic disparities include biological differences in tumor behavior and morphology (Bowen et al., 2006; Carey et al., 2006; Chlebowski et al., 2005; Demicheli et al., 2007; Lund et al., 2009; Porter et al., 2004), pharmacogenetic differences in response to therapy (Flockhart, 2008; Goetz, 2005), patient-level psychosocial or behavioral factors

(Magai et al., 2008; O'Malley et al., 2004), socioeconomic status and access to care (Gerend and Pai, 2008; Maloney et al., 2006), and treatment differences (Blackman and Masi, 2006; Freedman et al., 2009; Lund et al., 2008). Clearly, race-specific genetic susceptibility to more aggressive cancers may not be affected by public health efforts; however, recognizing that there are racial differences in tumor biology may suggest the need for more focused screening or help identify environment-gene interactions that lead to strategies for cancer prevention. Additionally, societal-level correlates of race/ethnicity, such as access to insurance coverage and poor socioeconomic status may be slow to change over time. If, however, access to care and socioeconomic status are held constant, there is no good reason why an African American woman should be offered lower quality treatment than a white woman with the same clinical disease.

The decision to undergo certain treatment regimens is complex. Treatment decisions leading to differential quality of care may arise from patient-level, provider-level, or facility-level characteristics (Ballard-Barbash et al., 1996). Improving patient-level psychosocial or behavioral correlates of treatment disparities, such as health-seeking behavior and trust in the health care system, likely will require creative and sensitive interventions, given the complex historical experiences of American minority groups (Gerend and Pai, 2008; Shavers and Shavers, 2006). Provider-level and facility-level correlates of treatment decision-making, however, should be relatively similar across patients. For example, provider experience, access to specialists, and access to facilities capable of providing innovative procedures (such as sentinel lymph node biopsy [SLNB]) should be equally available to black, Hispanic, and non-Hispanic white patients, but this may not be true in reality. Of course, individuals can choose to forego guideline-recommended therapy, but as a rule, treatment options should be made equally available and accessible to all breast cancer patients with clinically similar tumors.

In epidemiologic terms, racial and ethnic differences in breast cancer-related morbidity and mortality can be thought of as being produced by multiple complementary causes (including patient-level psycho-social or behavioral factors, institutional racism, genetic predisposition to more aggressive tumors, etc. [Gerend and Pai, 2008; Tammemagi, 2007]), none of which is sufficiently explanatory alone. Although much research has been published in the areas of genetic/biological tumor variation and socioeconomic status as these relate to race/ethnicity-related breast cancer disparities, it remains largely unknown whether characteristics of the health system itself, including provider- and facility-level factors, are correlated with race/ethnicity or whether these factors mediate the effect of race/ethnicity on receipt of appropriate treatment for breast cancer. As such, the current study addresses this gap in the breast cancer literature by assessing the potential of structural/organizational health system characteristics to explain racial/ethnic variation in timely receipt of radiation therapy and adjuvant chemotherapy, when clinically indicated. Furthermore, this study examined trends in diffusion of high quality care over time, within vulnerable sub-populations, to determine whether guideline-recommended radiation therapy and chemotherapy have been uniformly received by all groups. Finally, this study contributes to the existing comparative effectiveness literature in cancer by examining treatment effects of radiation therapy and chemotherapy in different age groups at different times. In terms of policy relevance, results from this analysis can be used to (1) develop age-specific, place-specific, and culturally-specific interventions that target breast cancer patients who may be especially at risk for receiving poor quality care, (2) inform clinicians, policymakers, patient advocacy groups, and health care navigators about the current status and correlates of health disparities in breast cancer, and (3) provide additional evidence of radiation and chemotherapy treatment effectiveness and optimal timing of treatment for clinical guideline development.

Epidemiology of breast cancer and natural history of disease

With nearly 200,000 incident cases diagnosed annually in the United States, breast cancer is the most common non-skin cancer afflicting women (ACS, 2008; Ries et al., 2006). Based on data from 2001 to 2003, the American Cancer Society estimates the lifetime risk of developing breast cancer among women to be 12.7%, or 1 out of 8, if current trends continue (Ries et al., 2006). Although trend analyses of incidence rates show that incidence of breast cancer increased from 1980 to 2002 (Edwards et al., 2005), between 2001 and 2004, incidence rates decreased approximately 3.5% annually (ACS, 2008). This decrease may have resulted from more timely detection and treatment of early stage tumors, population saturation of screening mammography, or decreased used of hormone replacement therapy corresponding with release of the Women's Health Initiative (WHI) trial results in 2002 (ACS, 2008; Jemal et al., 2007). Worldwide, the greatest age-standardized incidence of breast cancer occurs in the United States and Northern Europe (Parkin et al., 2001).

Surpassed only by lung cancer mortality, breast cancer is the second most fatal cancer among women; an estimated 41,000 breast cancer deaths were anticipated in 2008 (ACS, 2008). Breast cancer survival is closely related to staging of disease. Staging is usually based on the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging system (Table 1) and may be determined clinically through the use of physical exam, biopsy, and imaging studies or pathologically after surgery. Pathologic staging is generally considered to be more accurate. Although prognosis is generally good for breast cancers diagnosed early (85-100% of stage I and II patients are alive after 5 years of follow-up), 5-year survival for patients with stage III and IV disease is only 58% and 19%, respectively (Gloeckler Ries et al., 2003). These statistics demonstrate the importance of early detection and treatment of invasive breast cancer. Recent

reductions in overall breast cancer mortality likely reflect development and uptake of more effective screening interventions and treatment options.

Table 1: American Joint Committee on Cancer (AJCC) Breast Cancer Staging Definitions modified with permission from Springer from Edge et al., (eds). Breast. In: *AJCC Cancer Staing Manual*, 7th edition. New York, NY, Springer, 345-376, 2010

In Situ Breast Cancer	
Stage 0	Non-invasive (e.g., Ductal Carcinoma in Situ [DCIS] and Lobular Carcinoma in Situ [LCIS]) and has not spread to lymph nodes
Early-stage Invasive Breast Cancer	
Stage IA	Tumor measures 2 cm or less and has not spread to lymph nodes
Stage IB	Small tumor; exclusively micrometastases in lymph nodes
Stage IIA	No evidence of a tumor but cancer has spread to lymph nodes under arm; *OR* Tumor is <=2 cm and has spread to lymph nodes under arm but no other nodes; *OR* Tumor is between 2-5 cm and has not spread to any lymph nodes
Stage IIB	Tumor measures between 2-5 cm and has spread to only lymph nodes under the arm on the same side as the cancer; *OR* Tumor is >5 cm but has not spread to any lymph nodes
Advanced-stage Invasive Breast Cancer	
Stage IIIA	Tumor is any size and cancer has spread to lymph nodes under arm and possibly other lymph nodes as well
Stage IIIB	Tumor is any size, has spread to breast skin or chest wall and possibly lymph nodes
Stage IIIC	Tumor is any size, may have spread to lymph nodes, but not elsewhere
Metastatic Breast Cancer	
Stage IV	Tumor is any size and has spread to other parts of body; *OR* Tumor has spread locally to skin and lymph nodes inside the neck, near collarbone

Risk of developing breast cancer is related to a number of factors, including age, gender, race/ethnicity, familial history of breast cancer, cumulative endogenous and exogenous hormone exposure, inherited mutations in the BRCA1 and BRCA2 and other genes, high breast density, radiation exposure, nutritional intake and alcohol use, exercise, and post-menopausal obesity (ACS, 2008; Colditz, Baer, and Tamimi, 2006; Vogel, 2008). Endogenous hormone exposure is particularly related to the cumulative effects of estrogen in breast epithelium. Reproductive factors, including age at menarche, parity, age at first full time pregnancy, lactation, and menopause, are closely related to circulating estrogen levels (Colditz, Baer, and Tamimi, 2006). With regard to exogenous hormone exposure, elevated risks of breast cancer have been observed with current and recent oral contraceptive use and peri- and post-menopausal use of hormone replacement therapy (Colditz, Baer, and Tamimi, 2006). Additionally, it is believed that post-menopausal obesity and weight gain are

associated with increased relative risk for breast cancer due to the role of fat tissues in storing estrogens (Eliassen et al., 2006). Interestingly, pre-menopausal excess weight may be a protective factor against breast cancer, due to irregular menstrual cycling and increased anovulatory infertility among heavier, reproductive-age women (Rich-Edwards et al., 1994).

Age and breast cancer are closely and meaningfully correlated (Vogel, 2008). The majority of breast cancer diagnoses occur in women older than 60, and the median age at breast cancer diagnosis is 62 years. Breast cancer incidence rises dramatically and non-linearly with age and levels off around the time of menopause (for most women, between 45 and 55 years of age) (Figure 1). This striking trend is biologically explained by the important role of reproductive factors and ovarian estrogens in breast cancer etiology (Colditz, Baer, and Tamimi, 2006). Further, behavioral and morphologic characteristics of the cancer itself differ by age. Younger women diagnosed with breast cancer tend to have more aggressive tumors and worse prognosis, whereas older women typically have more indolent disease (i.e., slower growing tumors) with better prognosis (Vogel, 2008; Wildiers and Brain, 2005). Younger women are more likely to have triple-negative breast cancers; that is, the tumor itself tests negative for estrogen receptors (ER), progesterone receptors (PR), and HER2/neu protein expression (Peppercorn et al., 2008). Certain targeted therapies, such as hormonal treatment with tamoxifen, are ineffective for triple negative and ER/PR-negative cancers. Understanding the characterization and clinical behavior of cancers with different biological characteristics has become increasingly important in recent years (Anders and Carey, 2008; Peppercorn et al., 2008). Indeed, many clinicians and researchers would argue that the various biological subtypes of breast cancer are so strikingly different from one another that they represent entirely different diseases and must be treated as such (Carey et al., 2006; Fejerman and Ziv, 2008; Kang, Martel, and Harris, 2008; Livasy et al., 2007; Millikan et al., 2008; Peppercorn et al., 2008).

Figure 1. Breast cancer incidence, by age at diagnosis and race/ethnicity, 1973-2005

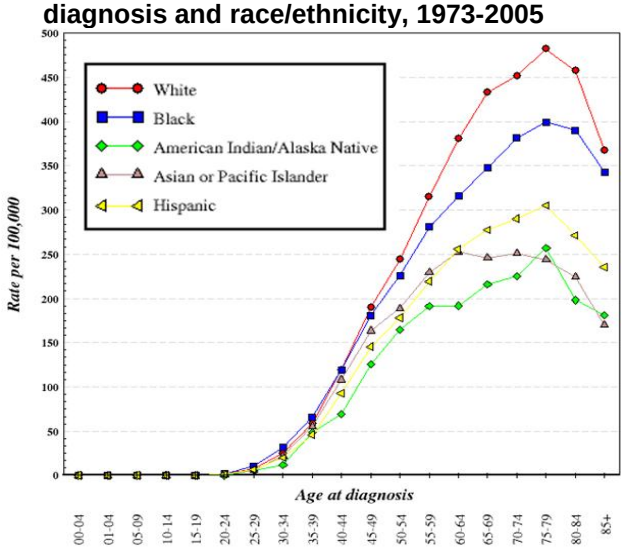
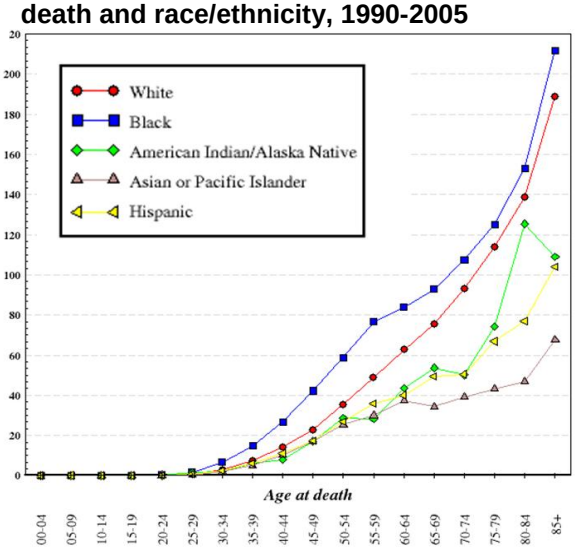


Figure 2. Breast cancer mortality, by age at death and race/ethnicity, 1990-2005



Notes: Includes invasive breast cancers only (stages I-IV) and represents all age groups; mortality source: US Mortality Files, National Center for Health Statistics (NCHS), CDC; incidence source: Surveillance Epidemiology and End Results (SEER)* Stat database; mortality and incidence graphs created using National Cancer Institute (NCI) interactive database (URL: http://www.seer.cancer.gov)

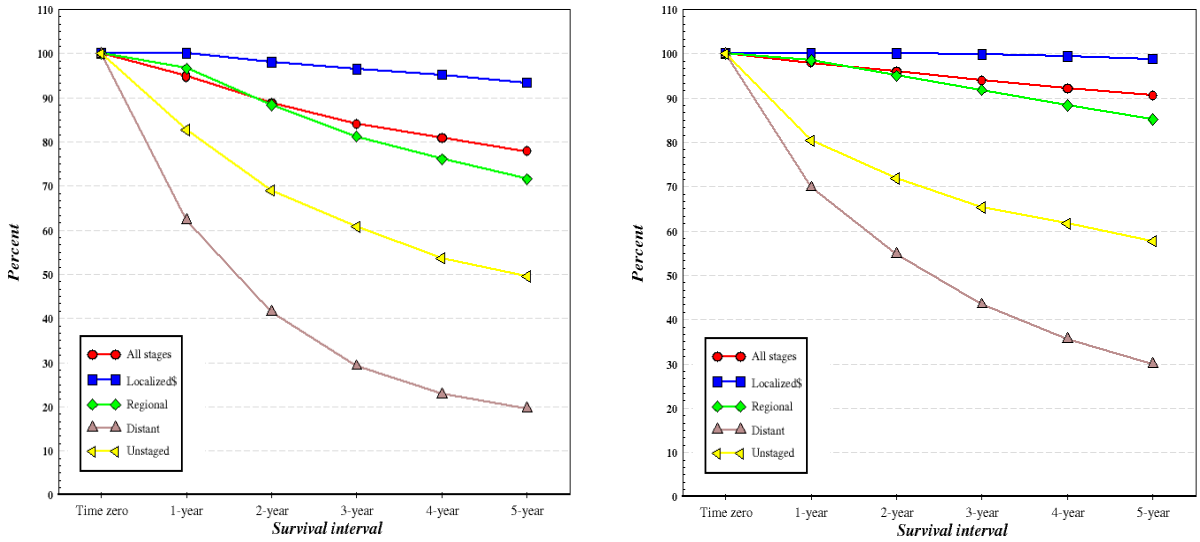
As previously noted, important differences in breast cancer exist between minority racial/ethnic groups and white groups. As can be seen in Figures 1 and 2, although breast cancer is diagnosed more often in white women, mortality from breast cancer is more pronounced in black women, suggesting that racial disparities may play an important role in health outcomes (Bach et al., 2002). As well, important age-specific racial/ethnic trends in breast cancer incidence and mortality are observed (graphs not shown) (Vogel, 2008). Specifically, young black women (<50 years old) have a higher incidence of breast cancer compared to young white women, but around the time of menopause, a crossover occurs and incidence rates among older white women surpass rates of older black women (Colditz, Baer, and Tamimi, 2006). Notably, mortality rates have been higher in black women, regardless of age, for years (NCI, 2005a).

Both biological and social factors are believed to contribute to racial/ethnic differences observed in breast cancer mortality. Biomarkers, histological features, and tumor behavior of breast cancers vary by race/ethnicity (Bowen, Stebbing, and Jones, 2006;

Demicheli et al., 2007; Morris and Mitchell, 2008; Porter et al., 2004). For example, African American women are more likely to be diagnosed with triple negative tumors (Lund et al., 2009). In another study, Chen and colleagues (1994) found that after adjusting for age, stage, socioeconomic status body mass index, reproductive history, insurance status, and location, black women with invasive breast cancer were more likely to have high grade nuclear atypia, high grade tumors, and more necrosis compared to white women (1994). Furthermore, black women were less likely to have ER-positive cancers (Chen et al., 1994). Bauer and colleagues (2007) have substantiated these findings in a California population. In a review of the literature on tumor aggressiveness in black women, Morris and Mitchell (2008) report that in addition to differences in pathologically-defined subtypes and BRCA mutations, African American women also are more likely to have over-expression of cell-cycle regulators, such as Cyclin E, p16, and p53, and polymorphisms in nucleotide excision repair genes. All of these results provide strong argument for biological differences between black and white women in breast cancer.

Despite the accumulating evidence for genetic and molecular biologic explanations for cancer aggressiveness, even after controlling for ER, PR, and HER2/neu status and BRCA1 and BRCA2 mutations, black women still have worse outcomes. Much of this difference historically was attributed to screening practices, specifically underuse of screening mammography or lack of diagnostic follow-up after an abnormal mammogram result, poor insurance coverage, or late stage at diagnosis (Bickell, 2002; Bowen, Stebbing, and Jones, 2006). However, use of screening mammography has been nearly equivalent among racial/ethnic groups for a decade (Bickell, 2002; Breen et al., 2001), and even when controlling for stage at diagnosis and insurance status, differences in mortality persist (Figure 3).

Figure 3: 5-year relative survival of female invasive breast cancer patients diagnosed 1973-2005 in SEER registries, all ages, by stage and race (Blacks on left; Whites on right)



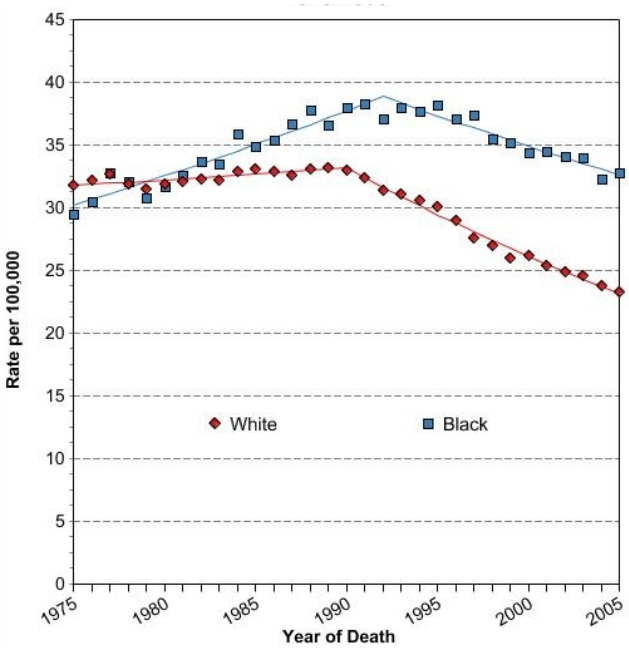
Notes: from National Cancer Institute (NCI) interactive database (URL: http://www.seer.cancer.gov)

Moreover, although secular trends in disease-specific mortality have shown improvements in the past 30 years, the relative difference between black women's mortality rate and non-Hispanic white women's mortality rate has not changed. Rather, the gap appears to be widening (Figure 4). It is clear from the literature that biological factors and access to care explain part of this racial/ethnic disparity in morbidity and mortality (Bickell et al., 2002; Bigby and Holmes, 2005; Carey et al., 2006). It is also clear that the African American sub-population is not the only group at risk for worse health outcomes. Elderly, rural-dwelling, less educated, poor, disabled, and Hispanic and/or non-English speaking women also experience significant disparities in breast cancer detection and survival after diagnosis (Bigby and Holmes, 2005; DeMichele et al., 2003; Freedman et al., 2009; Haggstrom et al., 2005). Interactions between these patient-level factors may have an additive or multiplicative negative effect on health outcomes, but little is known about whether and how these patient-level characteristics interrelate. Indeed, a poor, rural-dwelling, black woman may have more to worry about than triple-negative breast cancer;

she may also experience a triple burden in terms of health disparities in access to and receipt of high quality breast cancer care related to income/wealth, location, and race.

Mammography use and timely detection of early stage breast cancer have been widely studied, and both have been the target of many public health interventions and advocacy campaigns. Differences in treatment are now the focus of many studies examining health disparities in breast cancer (Bigby and Holmes, 2005). In the absence of confounding by socioeconomic status, insurance coverage, stage at diagnosis, and patient-level tumor characteristics, if certain sub-populations receive less-than-standard treatment (i.e., treatment appropriate for the genetic or molecular features of the cancer), we might expect to see continuing differences in outcomes. In other words, although we have come a long way in improving race/ethnic relations and equality in this country, persistent health disparities such as those seen in breast cancer, are an indicator that we still have a long way to go (Bradley, Given, and Roberts, 2001; Vainshtein, 2008).

Figure 4: Age-adjusted US female breast cancer-specific mortality rates, by race, 1975-2005



Citation: Fast Stats, 2010. Notes: Includes invasive breast cancers only (stages I-IV) and represents all age groups. Mortality source: US Mortality Files, National Center for Health Statistics (NCHS), CDC; rates are per 100,000 and age-adjusted to the 2000 US standard population; created using National Cancer Institute (NCI) interactive database (URL: http://www.seer.cancer.gov)

Economic burden of disease

Costs of breast cancer care can be quite high because surgery, radiation therapy, and chemotherapy often require considerable technical skill, resource capacity at the facility level, and patient follow-up. National estimates of expenditures in 1996 for breast cancer were on the order of $5.3 billion (Brown et al., 2002); in 2004, the national cost of treating breast cancer jumped to $8.1 billion. Using the Surveillance Epidemiology, and End Results (SEER)-Medicare linked dataset, Warren and colleagues (2008) estimated average Medicare fee-for-service payments for initial treatment to be $20,964 per breast cancer patient diagnosed in 2002. Long-term costs associated with cancer care can be staggering as well; in a systematic review published in *PharmacoEconomics* in 2009, lifetime costs of breast cancer care ranged from $20,000 to more than $100,000, depending on the perspective used, population studies, base-cost year (1984-2003), and duration of follow-up (Campbell and Ramsey, 2009). In another study of cumulative health care costs among fee-for-service Medicare beneficiaries diagnosed with early stage breast cancer, Warren and colleagues (2002a) estimated the average 25-year cost of health care to be nearly $73,000 in 1998 US dollars. Cancer-related treatments accounted for $27,697, or more than one-third, of that figure (Warren et al., 2002a). A one-year cost of trastuzumab alone, a key component of adjuvant therapy for approximately 25% of women with early breast cancer, costs approximately $50,000 (Kurian, 2007). For patients with metastatic breast cancer, use of the drug bevacizumab, approved as first line therapy with median duration of response of approximately one year, costs $55,000 in addition to other costs of chemotherapy and supportive care (Lee and Emanuel, 2008).

Uninsured or under-insured cancer patients are especially sensitive to high costs of care. Regardless of insurance status, hidden costs of cancer care, such as transportation to treatment centers; loss of income due to diminished productivity or loss of work days; and out-of-pocket premiums, deductibles, and co-payments can be especially burdensome to

the cancer patient (Wagner and Lacey, 2004). Indeed, in one national survey of cancer patients and families conducted by Kaiser Family Foundation, *USA Today*, and the Harvard School of Public Health (2006), nearly one in four privately insured patients said she exhausted all or most of her personal savings to pay for cancer-related care, and 13% of cancer patients reported being contacted by a collection agency demanding payment for cancer treatment. Costs of cancer care are not likely to decline substantially anytime soon. As treatment options become more sophisticated and prognosis continues to improve, survivorship and surveillance will become increasingly important issues to consider in estimating the financial burden of cancer. Nearly 2.5 million women alive on January 1, 2005, had a history of breast cancer (Ries et al., 2008). An increase in the surviving breast cancer patient population, coupled with a demographic shift in the US general population consistent with aging and fertility trends, may lead to significant demands for health resources both from the user/patient and system/provider perspectives.

Treatment guidelines

Treatment options for women with breast cancer vary by stage of disease, suitability of the patient to undergo treatment, insurance status, and patient and physician preferences. In short, women and their doctors choose among surgery, radiation therapy, chemotherapy, hormone therapy, and biological therapy, and generally, a combination of two or more of these are used to combat the cancer (NCI, 2005b). Local therapies include surgery and radiation therapy (RT) and are used for local control of the cancer. By contrast, systemic therapies are administered orally or intravenously and attack and destroy cancer cells throughout the body; these include chemotherapy, hormone therapy, and biologic therapy (NCI, 2005b). Surgical removal of the tumor involving removal of part (breast conserving surgery) or all (mastectomy) of the surrounding breast tissue is often the first line of defense against cancer, among women with operable cancers, though increasingly,

locally advanced tumors may be treated with pre-operative systemic therapy or "neoadjuvant" therapy. Generally, local and/or systemic therapies also are used to eliminate further spread of cancerous cells, but the combination, sequence, and duration of available radiation therapy, hormone therapy, biologic therapy, and chemotherapy depend primarily on stage and molecular or genetic features of the tumor (NCCN, 2008). A brief summary of historic clinical guidelines for breast cancer treatment is provided in Table 2.

As evidence has accumulated over time, clinical guidelines have evolved accordingly. Major advances in the past 15-20 years in breast cancer treatment approaches have included: (1) recommendation of breast conserving surgery plus RT over radical mastectomy, which preserves patient breast tissue and improves surgery-related side effect profiles; (2) widespread use of ER, PR, and HER2/neu testing to inform disease management and optimal use of hormonal, biologic, and chemotherapy treatment regimens; (3) proliferation of sentinel lymph node biopsy and use of immunohistochemistry for pathologic staging of disease; and (4) use of neoadjuvant chemotherapy to shrink tumors prior to surgical intervention (Andre and Pusztai, 2006; Cance et al., 2002; NCCN, 2008).

Table 2: Summary of changes in selected US breast cancer treatment guidelines over time

Organization	Year	Patient population	Treatment recommendation	Citation
National Institutes of Health (NIH)	1990	Patients with stage I-II breast cancer	Should receive breast conserving treatment (BCS plus RT) over mastectomy and axillary dissection because it provides survival equivalence and preserves tissue	NIH, 1990
National Institutes of Health (NIH)	1990	Patients with node-negative disease who received BCT or mastectomy	Are considered cured, but in light of evidence of the benefits of chemotherapy and tamoxifen in reducing recurrence, should consider adjuvant treatment	NIH, 1990
National Cancer Comprehensive Network (NCCN)	1996	Patients with DCIS, LCIS, stages I, or node-negative stage IIa tumors	Should receive BCS plus RT, or mastectomy without lymph node dissection (plus reconstruction), unless patient refuses	Carlson et al., 1996
National Cancer Comprehensive Network (NCCN)	1996	Patients with DCIS and negative margins, and all women with BCS or mastectomy with >/=T3 status	Should have radiation of standard fractionated doses totaling 40-60Gy, unless contraindicated or patient refuses	Carlson et al., 1996
National Cancer Comprehensive	1996	All patients with node positive disease and/or	Should receive multicycle adjuvant cytotoxic poly-chemotherapy,	Carlson et al.,

Organization	Year	Patient population	Treatment recommendation	Citation
Network (NCCN)		tumor >1cm, except for DCIS and LCIS	unless patient refuses	1996
National Cancer Comprehensive Network (NCCN)	1996	Patients with positive ER and/or PR status, regardless of diagnosis or stage	Should receive non-steroidal, anti-estrogen therapy, unless contraindicated or the patient refuses	Carlson et al., 1996
National Cancer Comprehensive Network (NCCN)	1996	Patients with stage IIIa, IIIb, or IV disease	Should receive modified radical mastectomy plus reconstruction, radiation, poly-chemotherapy, and tamoxifen if ER and/or PR-positive, unless the patient refuses	Carlson et al., 1996
American Society for Clinical Oncology (ASCO)	1996	Every primary breast cancer patient	Should have ER/PR status testing and upon determination of hormone receptor positivity, should be offered endocrine therapy	ASCO, 1996
American Society for Clinical Oncology (ASCO)	2000	Every primary breast cancer patient	Should be evaluated for over-expression of c-*erb*B-2 (HER2/neu) at time of diagnosis or recurrence, and status should inform disease management decisions (e.g., use of Herceptin)	Bast et al., 2001
National Institutes of Health (NIH)	2000	Patients <70 whose tumors express hormone receptor protein	Should receive adjuvant hormonal therapy, unless patient refuses	NIH, 2000
National Institutes of Health (NIH)	2000	Patients <70 with localized cancers >1cm, any nodal, menopausal, or ER/PR status	Should receive adjuvant poly-chemotherapy, unless patient refuses	NIH, 2000
National Institutes of Health (NIH)	2000	Patients who received mastectomy and have four or more positive lymph nodes or advanced primary cancer (>5cm)	Should receive postoperative radiation therapy within 6 months of mastectomy (but not concurrently with anthracycline chemotherapy), unless patient refuses	NIH, 2000
National Institutes of Health (NIH)	2000	Patients who received mastectomy and have 1-3 positive lymph nodes	Inconclusive evidence for post-operative RT	NIH, 2000
National Cancer Comprehensive Network (NCCN)	2008	Patients with stage I and II breast cancers receiving breast conserving surgery	Should receive whole breast irradiation. Evidence insufficient to support partial breast irradiation at this time	NCCN, 2008
National Cancer Comprehensive Network (NCCN)	2008	All patients with early breast cancer	Should receive sentinel lymph node biopsy as the preferred pathologic assessment method	NCCN, 2008
National Cancer Comprehensive Network (NCCN)	2008	All patients with primary breast cancer	Should be evaluated for hormone receptor and HER2-neu status, anatomic and pathologic tumor characteristics to determine the optimal systemic adjuvant therapy to reduce recurrence and improve survival	NCCN, 2008

More than anything, the nature of these improvements suggests that breast cancer is a highly complicated disease. Indeed, given the diversity in tumor characteristics (as determined by presence of biomarkers, pathologic features, and behavior), it could easily be argued that different types of breast cancers are actually different diseases (Andre and Pusztai, 2006; Munoz et al., 2008; Peppercorn et al., 2008).

Despite gains in our understanding of breast cancer, as evidenced by changes in treatment guidelines over time (Table 2), many nagging questions remain regarding optimal treatment strategies. Among these are questions about the utility of gene expression profiles in directing patient-centered care (Benowitz, 2008), appropriate management of elderly breast cancer patients (Passage and McCarthy, 2007; Wildiers and Brain, 2005), use of partial breast irradiation (Buchholz, Kuerer, and Strom, 2005); sequencing and compatibility of multiple systemic adjuvant therapies (Bartelink, 2007; Gradishar and O'Regan, 2003), use of *in vivo* intraoperative radiotherapy (IORT) (Stitzenberg et al., 2007a), and impact of delays in receipt of radiotherapy and chemotherapy on recurrence and survival (Hartsell et al., 1995; Hebert-Croteau et al., 2002; Lohrisch et al., 2006). As new treatment innovations emerge and new guidelines are developed, it will be increasingly important to monitor uptake and to ensure that vulnerable sub-populations have equal access to these evidence-based advances in care.

Quality improvement in cancer

Translating research findings into practice is not always as straightforward as it would seem (Davis et al., 2003; Gold and Taylor, 2007; Shiffman et al., 2004; Waitman and Miller, 2004). Indeed, there are many barriers to adoption of evidence-based guidelines, including poor dissemination systems, provider resistance or lack of awareness of new evidence, the fragmented nature of the health care financing system, lack of effective monitoring, and lack of incentives to change practices (Davis et al., 2003; Grol, 2001;

McGlynn et al., 2003). Older studies in diffusion of innovation from the 1970s and 1980s suggest that there is a considerable time delay, possibly as much as 10 or 15 years, between the production of technical evidence and full implementation (Dobbins et al., 2002). In recent years, the gap between research and practice has likely narrowed. After the Institute of Medicine (IOM) report in 2000, *To Err is Human*, concerns about quality and safety in medicine rose to fever pitch level. Physician adherence to clinical guidelines had perhaps been previously assumed and safety of medical care had been taken for granted; these assumptions were shattered with this report. Additionally, the proliferation of institutional and external quality monitoring programs, improved patient access to quality performance information, and electronic medical systems helped to spur providers to practice better medicine (Bowles et al., 2008; Neuss et al., 2005).

Cancer care has lagged somewhat in the national move towards quality improvement, but is quickly gaining ground. In 1999, the National Cancer Policy Board, part of the IOM, produced a report entitled *Ensuring Quality Cancer Care*, which summarized cancer treatment patterns in the US in one word: "inconsistent" (Hewitt and Simone, 1999). Since then, although everyone seems to agree that measurement of cancer care quality is important, there has been much debate about how to do it (Bickell, et al., 2005; Bowles et al., 2008; Cornfeld et al., 2001; Smith and Hillner, 2001; Zapka et al., 2003). Building upon the IOM report *Crossing the Quality Chasm*, which proposed that high quality care should be effective, safe, timely, efficient, equitable, and patient-centered, Bowles and colleagues (2008) interviewed professional experts in cancer care to describe barriers and facilitators to quality improvement in cancer. They concluded that the most important hindrances to high quality cancer care were: (1) unnecessary variation (lack of standardization and lack of adherence to guidelines), (2) inadequate coordination and communication among multidisciplinary care teams, (3) lack of patient awareness and empowerment, (4) delays during provider transitions, (5) inappropriate financial incentives within a fragmented

financing system, and (6) lack of interoperable electronic medical records (2008). Zapka and colleagues (2003) add that the complex nature of cancer care, which requires numerous transitions and handoffs among multiple providers and facilities, further complicates adherence to guidelines and quality monitoring. Despite these barriers, ensuring high quality practice in cancer care is possible, and diverse stakeholders are interested in this endeavor (Cornfeld et al., 2001; Hewitt and Simone, 1999; Schneider et al., 2004; Smith and Hillner, 2001). For instance, Medicare has demonstrated a strong commitment to quality improvement in cancer (Etheredge, 2009).

In response to the national demand for quality metrics, NCCN and ASCO nominated content and methodology experts in the cancer domain to develop national quality monitoring measures (Desch et al., 2008). This effort was coordinated with a similar process begun by the National Quality Forum in 2004. The criteria for evaluating whether an evidence-based guideline should become a metric included determining perceived impact on population survival, potential for improvement based on pilot data, and feasibility of data collection and reporting (Desch et al., 2008; Hassett et al., 2008). A metric is defined by a count numerator and an appropriate denominator indicating the eligible patient population that should receive the treatment or procedure (Hassett et al., 2008). Defining the denominator also requires specificity in timing; over what period should care be considered adherent if the treatment/procedure is received? Based upon these criteria and the potential for quality improvement in the breast cancer patient population, NCCN/ASCO released in July, 2008, three breast cancer quality metrics: (1) receipt of radiation therapy after breast conserving surgery within one year of diagnosis for stage I-III breast cancers, (2) receipt of post-operative adjuvant chemotherapy within 120 days of diagnosis for hormone receptor (ER and PR) negative, stage II-III cancers, and (3) receipt of tamoxifen or aromatase inhibitor within one year of diagnosis for hormone receptor positive tumors greater than 1 cm (Desch et al., 2008). These were refined from a much broader set of

metrics originally released by NCCN/ASCO in 2006 (Malin et al., 2006). Due to insufficient accumulation of clinical trial evidence about the effects of radiation and chemotherapy in older women, these metrics were limited to women younger than 70, but many experts agree that such an age-specification sets a low bar for quality, given observational evidence showing that older women benefit as much as younger women from these therapies (Wildiers and Brain, 2005). Moreover, a randomized trial published recently showed that women older than 70 treated less aggressively with chemotherapy fared worse (Muss, 2009).

Using data from five metropolitan areas, in 2006, a National Initiative for Cancer Care Quality (NICCQ) study reported high adherence to similar measures (96% for radiation therapy, 60-91% for chemotherapy, and 85-95% for hormonal therapy) (Malin et al., 2006). However, their results are likely unrepresentative of national norms because the study included only a small number of metropolitan districts and patients within institutions closely affiliated with a national quality monitoring organization (Desch et al., 2008; Malin et al., 2006). Patients from rural areas and hospitals unaffiliated with NICCQ may receive less adherent care. Other studies have shown substantial variation in guideline adherence. Using data from Philadelphia region oncology specialty practices, Bloom and colleagues (2004) reported that for stage I or IIA node-negative disease, 45-60% of women received adequate treatment according to NCCN guidelines, whereas for stage IIa or IIb node-positive disease, only 15% of women received guideline-recommended treatment. Among women with stages IIIa, IIIb, or IV disease, only 12% received guideline-appropriate care (Bloom et al., 2004). Eighty-two percent of women received hormone receptor testing (ER and PR status) as recommended by NCCN, but only 2% received HER2/neu oncogene testing. This finding could be explained by the fact that HER2/neu was a fairly new diagnostic test at the time of data collection. In a review article by Smith and Hillner (2001), participation in the development of quality monitoring programs had no demonstrable effects

on practice patterns. In another study in Virginia employing "report cards" based upon NIH guidelines, adherence to guidelines was generally low, but particularly disturbing were low rates of referral to medical oncologists to discuss adjuvant therapy after surgery (56%) and low rates of referral to plastic surgeons to discuss reconstructive options after mastectomy (27%) (Hillner et al., 1997).

Previous studies in health disparities and breast cancer treatment

Health disparities are profoundly apparent in post-diagnosis breast cancer treatment, particularly for black women, elderly women, and poor women. Whereas poor women mainly suffer problems of access to care due to lack of insurance, inability to afford out-of-pocket deductibles and co-payments, and/or lack of reliable or free transportation, the issues of race/ethnicity and age are more complex. Age-related disparities in cancer treatment are well-documented in the literature, but the implications of such disparities are muddied by poor representation of elderly breast cancer patients in clinical trials. These issues are discussed in detail elsewhere (Ballard-Barbash et al., 1996; Chagpar et al., 2007; DiMichele et al., 2003; Heflin et al., 2006; Hershman et al., 2008; Gorin et al., 2005; Kosiak, Sangl, and Correa-de-Araujo, 2006; Passage and McCarthy, 2007; Wildiers and Brain, 2005).

Previous studies have demonstrated that black women, more often than other women with the same stage disease, fail to receive mammography, timely diagnosis, and recommended treatment for breast cancer (Bradley, Given, and Roberts, 2001; O'Malley et al., 2001; Shavers and Brown, 2002). In abstracting inpatient and outpatient medical records from six New York City hospitals in 1999 and 2000, Bickell and colleagues (2006) found that 34% of black women and 23% of Hispanic women, compared to 16% of white women, failed to receive appropriate adjuvant therapy for early stage breast cancer. Non-optimal adjuvant treatment was defined as omissions of radiation therapy after BCS,

adjuvant chemotherapy after definitive surgery in hormone receptor negative tumors greater than or equal to 1cm in size, or hormonal therapy for hormone receptor positive tumors greater than or equal to 1cm in size (Bickell et al., 2006). Underuse was significantly associated with black or Hispanic racial/ethnic status, lack of medical oncologic referral, more co-morbid conditions, and lack of insurance. Black and Hispanic women were more than twice as likely to receive poorer care, after controlling for clinical tumor features, age, insurance status, and medical oncologist consultation. Consulting with a medical oncologist reduced the racial disparity somewhat, but not entirely; no other provider or health system factors were taken into account in this analysis (Bickell et al., 2006).

In a recent study by Freedman and colleagues (2009), SEER data from 1988 to 2004 were used to assess definitive local treatment (i.e., mastectomy or BCS with RT) for early stage cancers. Over time, rates of mastectomy decreased as BCS with RT diffused into practice; however, in adjusted models, rates of any definitive treatment remained lower for black and Hispanic women compared to white women, and no reduction of this disparity was observed over time (Freedman et al., 2009). Additionally, persistent age-related disparities in receipt of definitive treatment were observed for women younger than 60 years old and older than 70 years old. The lack of definitive treatment among women older than 70 years was consistent with findings from other studies and likely explained by the absence of sufficient clinical trial evidence on treatment for older women with breast cancer. The reasons for under-treatment of women younger than 60 were less clear, but may have been related to employment and insurance status. This analysis lacked information about employment, insurance status, and co-morbidities and did not control for possible organizational confounders. Control variables were limited to biologic features of the tumor, year of diagnosis, and region (Freedman et al., 2009).

Lund and colleagues examined first course of treatment among women diagnosed in 2000-2001 with invasive breast cancer in five Atlanta SEER counties (2008). They

described differences in treatment delay, cancer-directed surgery, and receipt of radiation, hormonal, and chemotherapy, focusing on racial differences between black and white women. In this analysis, black women were four to five times more likely to experience treatment delays longer than 60 days ($p<0.001$). Black women also were less likely to receive cancer-directed surgery, radiation therapy after BCS, and hormonal therapy, among women with hormone receptor positive tumors, controlling for age, tumor size, stage, lymph node involvement, and ER/PR status (Lund et al., 2008). This study was limited by the fact that the SEER registry collects treatment information only for the four-month time window after diagnosis, so later cancer-directed treatments may have been missed. Linking to Medicare data could have provided more detailed information about treatment for the portion of women covered by Medicare. This study also was limited by the inability to capture HER2/neu status, possible under-reporting of chemotherapy, lack of information about health status and co-morbidities, and lack of information about provider and system-level characteristics (Lund et al., 2008).

In a study employing SEER-Medicare data from 1992-1999, differences in processes of care were evaluated, focusing on BCS with RT, documentation of ER status, surveillance mammography during remission, and a combined measure of adequate care (Haggstrom, Quale, and Smith-Bindeman, 2005). In adjusted comparisons, Hispanic women were 33% less likely to receive adequate care, and black women were 23% less likely to receive adequate care, compared to white women. Black/white disparities actually worsened over time, as evidenced by a secondary analysis limited to 1997-1999 breast cancer diagnoses (adjusted odds ratio: 0.63; 95% CI: 0.50-0.79). Additionally, older women, and women from rural areas were significantly less likely to receive standard quality care. Interactions between race/ethnicity and age, and race/ethnicity and area income were tested, but not included in final models. Adjusted models controlled for median area income, year of diagnosis, SEER region, Charlson co-morbidity index, tumor size, and stage, but no

structural/organizational variables were assessed. This analysis was further limited by the exclusion of young women (i.e., younger than 65 years), women with stages III or IV cancer, women with larger tumors (>5cm), women with health maintenance organization (HMO) or private insurance coverage, and the lack of consideration of other therapies, including chemotherapy, biologic, and hormonal treatments (Haggstrom, Quale, and Smith-Bindeman, 2005).

Banerjee and colleagues (2007) assessed receipt of BCS, radiation, tamoxifen, and chemotherapy by conducting comprehensive medical record reviews of women diagnosed with breast cancer in 1990-1996 in Detroit at the Karmanos Cancer Institute and found that for local stage disease, white and black women received equivalent care across treatment paradigms, but for regional disease, black women were less likely to receive guideline-recommended hormonal therapy and chemotherapy. Interestingly, they also found that women enrolled in government insurance plans were less likely to receive BCS plus radiation; rather, government-insured patients tended to get the more invasive mastectomy procedure. Additionally, they found that married women with regional disease were more likely to receive guideline-recommended chemotherapy, compared to non-married women with regional disease, suggesting, as other authors have, that social support plays a role in treatment decision-making (Banerjee et al., 2007). Banerjee and colleagues (2007) also found that African American women had far more co-morbid conditions than white women, which implied a need to control for additional illnesses in future analyses to avoid potential confounding. Because this study was limited to one institution in the Detroit area, institutional, structural, and geographic factors were ignored in the analysis. Furthermore, the breast cancer patient population in the Detroit metropolitan region is mainly composed of older, insured, black women with low socioeconomic status; thus, variations in rural/urban residence, income and education, neighborhood racial composition, insurance status, and ethnic identity could not be easily assessed in the study.

We also know that black women enroll in clinical trials much less often than white women and thus may have poorer access to life prolonging treatment offered by many cancer trials (Advani et al., 2003; Movsas et al., 2007; Murthy, Krumholz, and Gross, 2004; Newman and Martin, 2007; Simon et al., 1999; Sateren et al., 2002; Tejeda et al., 1996). As a result, diffusion of research-related innovations may be disproportionately benefiting certain women as compared to others. As one example of an innovation that has perhaps diffused differently within sub-populations, some evidence suggests that black women are less likely to receive sentinel lymph node biopsy (SLNB) and that this disparity cannot be explained by differences in clinical factors, insurance status, type of hospital, teaching status of hospital, or age (Chen et al., 2008). Despite overall higher levels of uptake of SLNB between 1998 and 2005, racial/ethnic gaps in receipt of SLNB remained largely the same over time (Chen et al., 2008). In addition, Mitchell and colleagues (2009) found that few breast cancer randomized trials report or analyzed outcomes based on race/ethnicity, indicating a failure to report data that may help evaluate and overcome health disparities.

Additional review articles by Tammemagi (2007) and Shavers and Brown (2002) overwhelmingly echo the findings of specific empirical studies highlighted above. Shavers and Brown (2002) also reported on several other treatment disparities between racial/ethnic groups, including differences in receipt of biomarker testing, follow-up after diagnosis and initial treatment, and surveillance mammography. In their reviews of the literature, both Tammemagi (2007) and Blackman and Masi (2006) concluded that disparities in treatment were the result of patient/tumor-related, provider-related, and health system-related differences, but that these factors were rarely explicitly considered in empirical studies as acting in conjunction. Additionally, Tammemagi (2007) discussed the post-surgical experiences of black and Hispanic women and concluded, as previous authors have, that black and Hispanic women are more likely than white women to experience inadequate pain management and serious side effects of treatment (Bigby and Holmes, 2005; Payne,

Medina, and Hampton, 2003). Tammemagi also discussed the role of co-morbidities in explaining the survival disparity between white and black women; the co-morbidity issue is an important one and should not be overlooked (2007). Beyond the role of co-morbidities in survival, higher co-morbidity burden among blacks could lead to competing priorities in health care seeking-behavior. If, for example, a woman with uncontrolled diabetes and/or a serious disability has limited time and resources to attend health care appointments, she may prioritize certain health visits over others. Furthermore, if her functional status or mental health status is compromised by co-morbid condition(s), these may additionally inhibit, rather than promote, health-seeking behaviors for her cancer diagnosis, particularly if she feels she is at low risk for metastasis or death (i.e., she has early-stage cancer).

Beyond co-morbid conditions and biological tumor characteristics, both of which affect treatment options and health outcomes, several other patient-level factors may help explain why different patients receive different treatments, including health literacy and personal preferences (Polacek, Ramos, and Ferrer, 2007); insurance and socioeconomic status (Blackman and Masi, 2006; Bradley et al., 2005); cognitive and social network correlates (Magai et al., 2008); experience with/trust of the health care system; and fatalistic beliefs and health-seeking behavior (Blackman and Masi, 2006; Talcott et al., 2007). One example of an intervention that has successfully improved patient awareness, empowerment, and trust in the health care system is the introduction of patient navigation programs (Vargas et al., 2008).

Evidence suggests that when women across racial/ethnic groups receive equal treatment, equal outcomes follow (Dignam et al., 1997; Roach et al., 1997; Yood et al., 1999). Black patients are at no greater risk for chemotherapy-related hematologic toxicity than white patients (Smith et al., 2005), and clinical trial results suggest that patterns of response to local and systemic therapy are similar for black and white women with clinically equivalent disease (Newman et al., 2003). In light of this evidence, it is critically important

that the health system itself is designed in such a way that all women have access to life-prolonging cancer treatments, regardless of race, age, or socioeconomic status.

Organization of health services and cancer care

Organizational and structural factors affect diffusion of innovation and implementation of high quality, evidence-based practice (Greenhalgh et al., 2004). Generally, elements of the health care system are described in terms of physician-level factors (e.g., provider specialty, age, race/ethnicity, board certification), facility-level factors (e.g., type, size, profit status, procedural volume, teaching status), and system-level or structural factors (e.g., location, dispersion, and availability of health services, health care financing, technology investment, existence of quality monitoring systems). Several studies have investigated the effects of these factors on guideline-concordant practices in cancer care, but rarely are racial/ethnic (and other patient-level) variables considered in the context of the design and operation of the health system. Facility and physician characteristics of health services that have been associated with adherence (or lack thereof) to cancer clinical guidelines include:

- Geographic location (Chagpar et al., 2007 ; Engelman et al., 2004 ; Punglia et al., 2006a) ;
- Existence of cancer-directed programs or affiliation with cancer care organizations (Birkmeyer et al., 2005; Punglia et al., 2008; Stitzenberg, Thomas, and Ollila, 2007);
- Teaching status or academic affiliation of surgical hospital (Chagpar et al., 2007; Hebert-Croteau et al., 2005; Goldzweig et al., 2004; Gort et al., 2007; Jerome-D'Emilia and Begun, 2005; Lee-Feldstein, Anton-Culver, and Feldstein, 1994);

- Surgical, procedural, or cancer case volume (Allgood and Bachmann, 2006; Begg et al., 1998; Billingsley et al., 2007; Birkmeyer et al., 2003; Birkmeyer et al., 2006; Birkmeyer et al., 2007; Chagpar et al., 2007; Finlayson et al., 2003; Gilligan et al., 2007b; Gort et al., 2007; Hillner, Smith, and Desch, 2000; Jerome-D'Emilia and Begun, 2005; Neuner et al., 2004; Schrag et al., 2003; Wilt et al., 2008);
- Specialist consultation and primary physician training/specialization (Allgood and Bachmann, 2006; Hillner, Smith, and Desch, 2000; Stitzenberg, Thomas, and Ollila, 2007; Zork et al., 2008);
- On-site radiotherapy at surgical hospital (Hebert-Croteau et al., 2005);
- Research activity (Hebert-Croteau et al., 2005);
- Caseload severity (Hebert-Croteau et al., 2005; Schrag et al., 2006) ;
- Distance to care (Jones et al., 2008; Punglia et al., 2006; Shea et al., 2008; Stitzenberg et al., 2007b; Voti et al., 2006) ;
- Quality and procedural notification/reminder systems (Goins et al., 2003);
- Frequency of specialist/generalist collaboration (Goldzweig et al., 2004);
- Stated organizational commitment to quality improvement (Goldzweig et al., 2004);
- Incentive-based systems in place (Goins et al., 2003; Goldzweig et al., 2004);
- Gender, age, race/ethnicity, and education of physician/surgeon (Gilligan et al., 2007a; Hershman et al., 2008; Neuner et al., 2004; Waljee et al., 2006); and
- Facility type, practice setting, profit status, and size (Chaudhry, Goel, and Sawka, 2001; Gort et al., 2007; Himmelstein et al., 1999; Lee-Feldstein, Anton-Culver, and Feldstein, 1994; Stitzenberg, Thomas, and Ollila, 2007).

These physician- and facility-level factors have varying degrees of influence on quality of cancer care received. Several may be more or less problematic for particular patient sub-populations. For example, the issue of distance to care has been found to be more problematic for older women, perhaps not surprising, given the transportation and mobility difficulties some elderly women may face (Punglia et al., 2006). Bao and colleagues (2007) also have discussed the importance of distinguishing "within" physician differences from "between" physician differences, suggesting that the problem of one physician practicing poorly across all his/her patients is quite different from the problem of one physician providing worse quality care to certain patients, while providing better quality care to others.

In addition, health system-level factors play a role in high quality cancer care. Extent of interagency collaboration, local socioeconomic environment and resource capacity, supply of radiation oncologists, ratio of specialists to generalists, and investment in technology all may affect receipt of appropriate care (Jerome-D'Emilia and Begun, 2005).

Race/ethnicity and health services organization

Although many organizational and structural health services characteristics, such as facility location and profit status, are fixed over time, preference for and utilization of certain health services are not. Race, ethnicity, age, rural residence, and socioeconomic status may be correlated with health-seeking behavior and use of health services with certain structural/organizational characteristics. As an example, some ethnic groups may prefer hospitals which recognize and address language barriers by hiring translators; health facilities that can afford to do so are likely different in terms of organizational setup and size from those facilities that do not offer bilingual services.

In addition, membership in racial and ethnic groups may correlate with community residence, and type and location of health facilities may be related to socio-demographic

makeup of the local user population. As a result, access to medical innovations and new technology may be distributed unequally. If distribution and diffusion of evidence-based innovations are disproportionately benefiting certain women as compared to others, differential quality of care may be observed across socio-demographic groups.

Finally, patient socio-demographics could be associated with the types and quality of providers and health facilities that are available to the local user population. In terms of access to well-trained health professionals, one study showed that black cancer patients were more likely than white patients to be treated by physicians who lacked board certification, experience, and technical resources (Bach et al., 2004). Moreover, physicians treating black patients more often reported that they were unable to provide high quality care to their patients (Bach et al., 2004).

Despite strong evidence for racial/ethnic disparities in breast cancer outcomes, few empirical studies have explicitly considered the modifying or confounding potential of health services organization on race/ethnicity. Analyses that have included health system variables as covariates in addition to race/ethnicity have generally highlighted the importance of a few structural/organizational variables as confounders only, such as one publication by Jerome-D'Emilia and Begun (2005) using information from National Cancer Database (NCDB). In this study of diffusion of BCS, Jerome-D'Emilia and Begun highlighted the importance of hospital teaching status, regional supply of radiation oncologists, surgical volume, and ratio of specialists to generalists in predicting receipt of BCS over time; race/ethnicity was statistically non-significant. Other studies of screening mammography have found that black women more often than white women cite lack of physician referral or recommendation for mammography as the reason they failed to receive the test (Tropman-Hawley et al., 2000; Vernon et al., 1992).

The interactive effects of structural/organizational variables and race/ethnicity have been explored to a greater degree in literatures of other cancers. For example, in a two-

step analysis of rectal cancer patients, Morris and colleagues (2008) examined associations between race and specialist consultation and subsequent receipt of adjuvant therapy and found that blacks were equally likely to consult either a medical or radiation oncologist, but were less likely than whites to consult with both a medical and radiation oncologist (49.2% vs. 58.8%, p=0.03). Among patients who consulted with any oncologist, black patients remained less likely to receive chemotherapy and/or radiation therapy, suggesting that specialist consultation does not explain racial/ethnic disparities in receipt of adjuvant therapy in rectal cancers (Morris et al., 2008).

In another study of prostate cancer screening in North Carolina, researchers found that black men were at no greater distance to medical care, but that they had worse access to health facilities, less continuity in medical care (lack of a "medical home"), and poorer insurance coverage overall (Talcott et al., 2007). In examining racial disparities in survival after rectal cancer treatment, Morris et al. (2006) demonstrated that African Americans more often were treated by low-volume physicians and were less likely to receive adjuvant therapy. Importantly, after adjusting for provider variables, the effect of race became statistically non-significant, suggesting that provider-level differences in treatment explain a portion of racial disparities in health outcomes (Morris et al., 2006). In another study by Gooden and colleagues, black men with prostate cancer were more likely to receive surgery at high volume hospitals and at NCI-designated Cancer Centers, but were more likely to be treated by low volume surgeons, regardless of hospital surgical volume (2008). In spite of these differences in volume by race, the authors found that racial differences in prostate cancer recurrence-free survival persisted, even after stratifying by hospital and surgical volume. Finally, in a study by Earle and colleagues (2002) of advanced lung cancer patients, African Americans, particularly of lower socioeconomic statuses, were less likely to see an oncology specialist and subsequently, less likely to receive clinically-recommended

chemotherapy, after controlling for age, sex, year of diagnosis, region, hospital teaching status, and co-morbidities.

Significance and contribution

Cancer outcomes are a function of not only innate biological factors, but also modifiable characteristics of individual behavior and decision-making, characteristics of the patient-health system interaction, and characteristics of the health system itself. Disparities in cancer care have been well documented; however, the reasons why certain groups have widely different health experiences are not well understood. Attempts to explain persistent racial/ethnic disparities have mostly been limited to discussion of differences in insurance coverage, socioeconomic status, stage at diagnosis, co-morbidity, and molecular subtype of the tumor. In the current study, access to insurance coverage was effectively controlled by limiting the study to Medicare beneficiaries. Socioeconomic status and resource availability, as measured by State-Buy-In months (a proxy for low income status) and census-tract median income and education level, also were included in analytic models. Finally, stage at diagnosis and ER and PR status of the primary tumor were included as covariates. This study adds to the evidence by examining racial/ethnic disparities in treatment in light of structural/organizational characteristics of health services, controlling for each of the other important "complementary" causes of disparities that have been discussed in the literature. Because breast cancer care requires a high degree of multidisciplinary team collaboration, structural/organizational features of care are important. Exploring the interaction between race/ethnicity and health services organization in terms of receipt of high quality breast cancer care is therefore an important contribution to the health services literature.

Recognizing that variation in quality of cancer care received may be correlated with socio-demographic and health system characteristics may assist policymakers in identifying strategies to distribute more equally clinical expertise and health infrastructure across

multiple user populations. Rather than simply describing health disparities in cancer, this study goes one step further towards pinpointing policy levers in health services organization that may be modified to improve health outcomes for underserved breast cancer patients.

CHAPTER 3: STUDY DESIGN AND METHODS

Overview and study design

This study was a secondary analysis of data collected for ongoing cancer surveillance and control efforts and administrative insurance billing (from government-based insurance claims). The study employed a retrospective design using linked SEER-Medicare data to identify women diagnosed with clinically-defined primary breast cancers. The binary dependent variables of interest were timing of receipt of radiation therapy, timing of receipt of adjuvant chemotherapy, and all-cause and breast cancer-specific mortality. Independent variables of interest included race/ethnicity, and structural/organizational characteristics of oncologic services, including surgical hospital type, size, teaching status, NCI Cancer Center designation, ACoSOG affiliation, RTOG affiliation, availability of on-site radiation services; and distance to providers.

Conceptual framework: the Chronic Care Model and Diffusion Theory

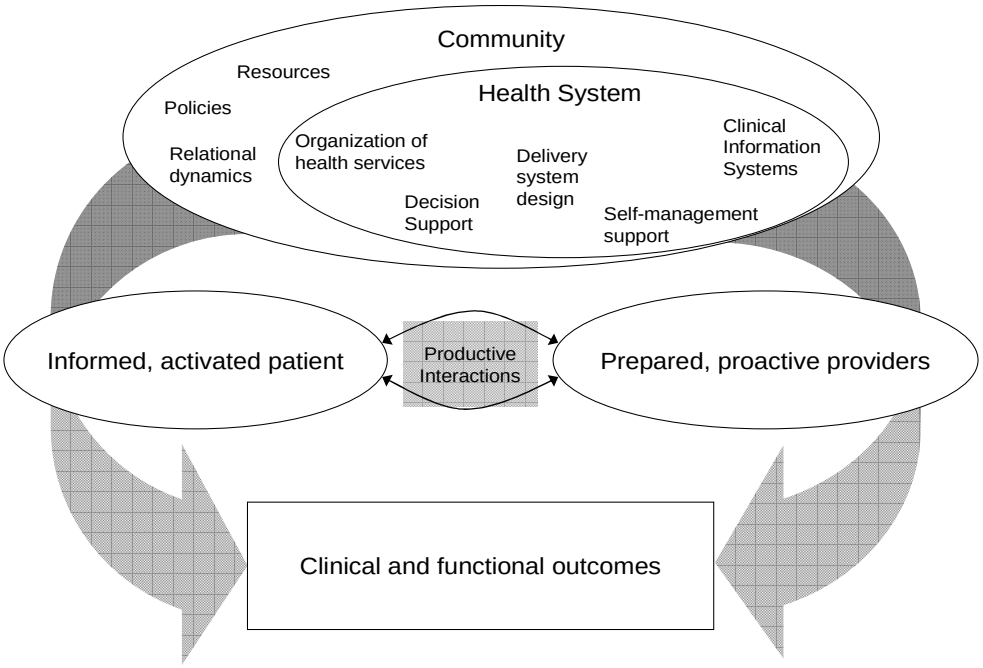
The conceptual framework for this study was informed by two models or theories of patient interactions with health systems. The first is the Chronic Care Model (CCM), initially conceived by Wagner, Austin, and Von Korff (1996a) and revised in 2002 (Bodenheimer, Wagner, and Grumbach, 2002a; Bodenheimer, Wagner, and Grumbach, 2002b). These authors recognized that adequate management of long-term illnesses required coordinated efforts on the parts of patients, providers, the health system, and the environment that extended beyond traditional self-management. These authors argued that focusing only on patient self-management would be an insufficient and potentially overtly passive approach to controlling serious diseases - arguably, a hands-off approach. With ever-increasing costs of

health care, aging of the American population, and national emphasis on improving and monitoring quality of care in the 1990s, “disease management” became a popular catch phrase in American health care, but it was Wagner and colleagues who, drawing upon disease management activities across the nation, most clearly delineated critical interacting components of high-quality chronic illness care. Their model for effective chronic illness care posits that high quality care requires a coordinated and appropriately organized health care system existing within and cognizant of the context of local community resources and policies (Wagner et al., 2002). Appropriately organized health care systems are composed of six essential elements: community resources and policies, health services organization, decision support, self-management support, delivery system design, and clinical information systems (Bodenheimer, Wagner, and Grumbach, 2002a; Bodenheimer, Wagner, and Grumbach, 2002b). According to the authors, a well-designed system should lead to more productive interactions between informed, activated patients and prepared, proactive professional health care providers (Figure 5).

Positive clinical outcomes, then, are a product of a coordinated care experience, involving: (1) an expert, informed, easily accessible, health system with continuing provider education, decision support, prevention programs, and patient self-management support; (2) community resources and policies to ensure equity in access to health services; (3) informed, activated patients; and (4) proactive, well-trained providers. Although the CCM traditionally has been discussed in the management of diseases such as diabetes, congestive heart failure, and chronic obstructive pulmonary disease, cancer care also fits nicely within this framework for several reasons (Goins et al., 2003; Zapka et al., 2003). First, medical management of the condition requires harmonization of many moving clinical parts. Multiple medications, specialists, visits, and procedures must be coordinated to ensure optimal effectiveness of treatment regimens. Second, self-management is required in juggling multiple health visits, making treatment decisions, and dealing with side-effects

and toxicities of treatment. Changes in lifestyle and quality of life frequently accompany cancer treatments, and patients must adjust their lives accordingly. Moreover, continued self-surveillance through screening is critically important as survivors are generally at a greater risk for recurrent cancers. Third, from the perspective of the health system, monitoring and following patients closely can improve performance/quality measures, ensure a more efficient system, and eliminate costly redundancies (Zapka et al., 2003).

Figure 5: A model for effective chronic illness care, adapted with permission from Elsevier from Wagner et al., Journal of Nursing Care Quality, 16(2):67-80, 2002.



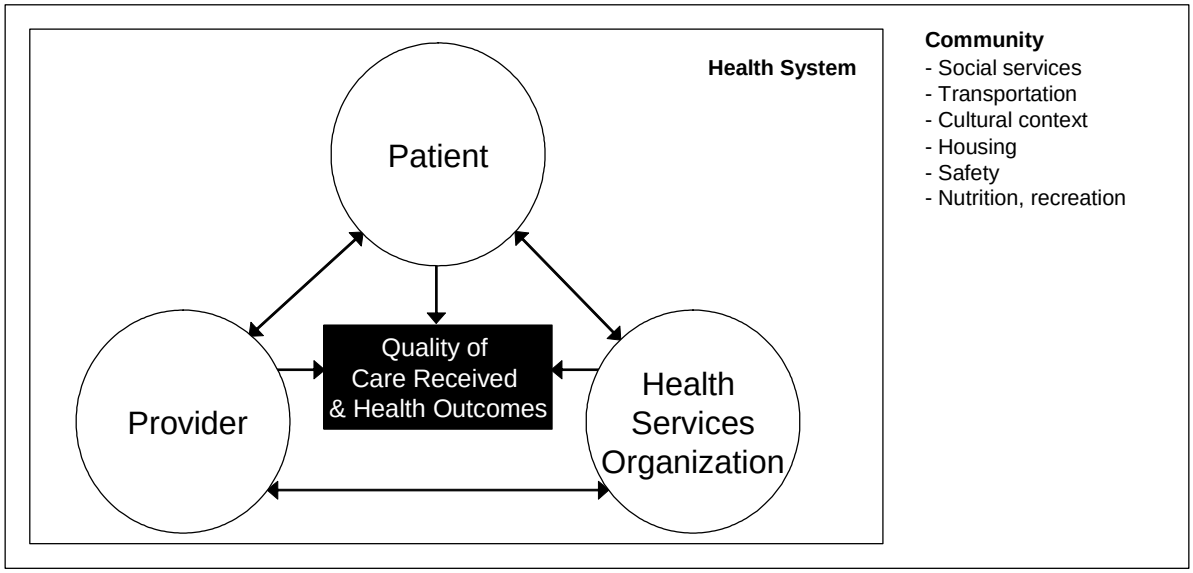
In addition to the CCM, Rogers' theory of Diffusion of Innovations provides insight to the process by which health care innovations and technologies are adopted over time. First introduced in 1962, Rogers theorized that innovations moved through communities following an "S" curve until reaching a saturation point. In 1995, Rogers further adapted this model to demonstrate how health decision-making occurred in the context of a new innovation being introduced. In other words, Rogers described the research-to-practice paradigm. Specifically, knowledge and information lead to persuasion, based upon perceived

characteristics of the innovation, such as relative or competitive advantage, compatibility, complexity, trialability, and observability (1995a). Through persuasion of key stakeholders and decision-makers about the merits of the innovation, a decision is made to either adopt or reject the innovation. After this decision, implementation or scale-up occurs, during which time, continued evaluation of the effectiveness and value of the innovation may either confirm its usefulness in practice or lead to its discontinuation (Dobbins et al., 2002). Factors in decision-making are the usefulness or value of the innovation, the influence of key individuals who are stakeholders in the decision, and the influence and readiness of the system itself (Bowen and Zwi, 2005). This decision-making process is negotiated through communication channels existing between patients, providers, health plans, researchers, and policymakers. Diffusion of innovations theory fits nicely with the coordinated nature of the CCM, but provides a more linear or chronologic perspective to adoption of evidence-based, high quality care over time.

The conceptual framework guiding the current study is depicted in Figure 6 (adapted from Bickell et al., 2005). Here, quality of care received and subsequent clinical outcomes are shown as a product of interacting patient-level, provider-level, and health system-level factors. Previous analyses too often have assumed that these factors affect health care via direct pathways only. That is, patient-level factors such as race and socioeconomic status are independently related to health care received, but indirect and/or mediating pathways are often ignored. Given that race/ethnicity and socioeconomic status are historically-embedded, socially-rooted constructs, it is plausible that provider and health system characteristics may differ across patients and that these differences could lead to differential care experiences. On the one hand, race/ethnicity may affect community residence, which may be correlated with types, availability, and quality of local health services. On the other hand, organizational theory suggests that characteristics of the local community, including population density, local resource capacity, and neighborhood racial/ethnic composition,

may affect the types of organizations that locate in a particular setting. Organizational and structural characteristics of the health system independently may influence receipt of high quality care, but also may be correlated with racial/ethnic group, age, and/or socioeconomic status, potentially explaining a portion of perceived disparities. The conceptual framework depicted here encompasses the interconnectedness of various units within the health system, which exists within the context of the larger community and society.

Figure 6: Conceptual framework, adapted with permission from Elsevier from Bickell et al., Surgical Oncology Clinics of North America, 14(1), page 106, vi, 2005.



Provider
- Race, age, sex, SES, language
- Training and competency
- Knowledge, attitudes, beliefs
- Communication skills
- Payment incentives
- Practice culture

Patient
- Race, age, sex, SES
- Health status, clinical factors
- Health insurance
- Competing demands
- Knowledge, attitudes, beliefs
- Communication and trust

Health Services Organization
- Service availability and location
- Size/capacity of facilities
- Technical resources and training
- Academic/organizational affiliation
- Racism, ageism, discrimination
- Electronic medical records

Research questions and hypotheses

Research question 1a: Are diffusion curves similar across sub-populations for evidence-based practices in breast cancer care, specifically receipt of RT after BCS within one year of diagnosis for stage I-III cancers?

H1a: Diffusion curves over time for receipt of RT after BCS will be significantly different across sub-populations of interest and specifically, diffusion will be slower within black, Hispanic, and older sub-populations.

Research question 1b: What effects do race/ethnicity and structural/organizational factors have on timing of receipt of radiation therapy (RT) after breast conserving surgery (BCS) for stage I-III breast cancers, controlling for known covariates?

H1b: Structural/organizational factors (including surgical hospital type, size, teaching status, NCI Cancer Center designation, American College of Surgeons Oncology Group (ACoSOG) affiliation, and presence of on-site radiation services; distance traveled to surgery; and distance to nearest radiation providers) will predict timing of initiation of RT after BCS, and structural/organizational factors will confound the effect of race/ethnicity.

Research question 2a: Are diffusion curves similar across sub-populations for evidence-based practices in breast cancer care, specifically receipt of adjuvant chemotherapy within four months of diagnosis for stage II and III, hormone receptor negative cancers?

H2a: Diffusion curves over time for receipt of adjuvant chemotherapy will be significantly different across sub-populations of interest and specifically, diffusion will be slower within black, Hispanic, and older sub-populations.

Research question 2b: What effects do race/ethnicity and structural/organizational factors have on timing of receipt of adjuvant chemotherapy for stage II and III, hormone receptor negative breast cancers, controlling for known covariates?

H2b: Structural/organizational factors (including surgical hospital type, size, teaching status, NCI Cancer Center designation, and ACoSOG affiliation; distance traveled to surgery; and distance to nearest chemotherapy providers) will independently predict timing of initiation of adjuvant chemotherapy and will confound the effect of race/ethnicity.

Research question 3a: What is the effect of timing of radiation therapy on health outcomes, specifically five-year, all-cause and disease-specific mortality across sub-populations?

H3a: Late timing of RT after BCS, relative to the shortest time period between diagnosis and receipt of initial RT treatment, will be positively associated with mortality, and black patients will experience greater all-cause and disease-specific mortality.

Research question 3b: What is the effect of timing of adjuvant chemotherapy on health outcomes, specifically five-year all-cause and disease-specific mortality across sub-populations?

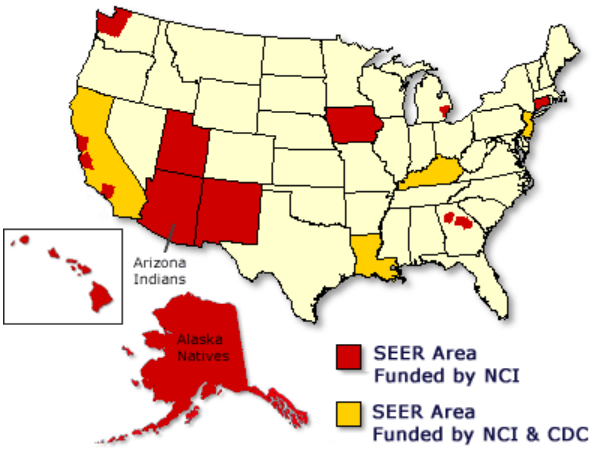
H3b: Late timing of adjuvant chemotherapy, relative to the shortest time period between diagnosis and receipt of initial adjuvant chemotherapy, will be positively associated with mortality, and black patients will experience greater all-cause and disease-specific mortality.

Data

Specific aims 1-3 employed linked SEER-Medicare data from 1994-2003, with vital status follow-up through 2007. SEER-13 registries, excluding the Alaska Native Tumor Registry since it is limited to Native Americans, were used for construction of the descriptive diffusion curves (aims 1a and 2a), due to the fact that the SEER registry system expanded over time, and diffusion curves needed to reflect patterns of care within registries that existed during the entire time period; registries with insufficient numbers of minority breast cancer patients were excluded. SEER-17 registries, excluding the Alaska Native Tumor Registry, were used for multivariate analyses (aims 1b, 2b, 3a, and 3b). Due to low numbers of minority breast cancer patients in some registries by year, additional sensitivity analyses explored the effect of excluding registries with low minority representation. The SEER program was originally designed by NCI to be an epidemiologic surveillance system

for incident cancers (Warren et al., 2002c). The SEER program publishes data from population-based registries across the country, representing approximately 26% of the US population. Registrars in SEER areas report information about each newly diagnosed cancer, including patient demographic characteristics; date of diagnosis; tumor histology; stage, grade, and size; type of surgical treatment; radiation therapy and chemotherapy provided in the first four months after diagnosis; vital status; and cause of death, when applicable (Warren et al., 2002c). The SEER program has existed since 1973 and has grown to encompass diverse geographic areas across the country (Figure 7) and is considered to be largely representative of the US general population. SEER registry data have been linked to Medicare claims data by social security number, name, sex, and age for the population of individuals eligible for and enrolled in Medicare (Warren et al., 2002c). Eligibility for Medicare is based on age (65 and older), disability, and/or disease (end stage renal disease). Medicare is the primary insurance provider for the vast majority of the older US population, covering 97% of Americans ages 65 years and older. Part A (inpatient care, skilled nursing facilities, home health, and hospice care) and Part B (outpatient care, durable medical equipment, and physician services) claims have been linked to individuals with cancer picked up by the SEER system. Medicare Part D pharmacy claims are not yet linked to the SEER data.

Figure 7: SEER regions and funding



NCI, 2009; http://seer.cancer.gov/registries/

Within the SEER-Medicare linked data, there are several types of files. The Patient entitlement and diagnosis summary file (PEDSF) contains all of the SEER registry data, Medicare HMO and entitlement information, initial treatment information up to four months post-diagnosis, and area socioeconomic information, derived from linked census data. The

Medicare analysis and procedure file (MEDPAR) contains claims and billing data from any inpatient hospitalizations (Part A services). The Medicare outpatient file contains claims and billing data from outpatient services rendered (Part B services). The carrier claims (physician/supplier) file contains all bills from physicians and other health professionals, which can occur in hospital or office settings. The durable medical equipment file contains claims processed by the Durable Medical Equipment Regional Carriers (DMERCs) and may include claims for some cancer-related therapies, such as oral equivalents of IV chemotherapies (NCI, 2009). Limited information about providers and facilities may be obtained from the NCI hospital file, which collects facility-level data from the Center for Medicare and Medicaid Services (CMS) Healthcare Cost Report (HCRIS) and the Provider of Service (POS) survey. Additional hospital and physician data may be obtained by linking the SEER-Medicare data to the American Medical Association (AMA) provider database or to American Hospital Association (AHA) database (Warren et al., 2002c). Table 3 provides a summary of the data files which were used in this study.

Table 3: SEER-Medicare data files used

Requested cancer site	**PEDSF Site recode number**
Breast cancer (female only)	46 (female only)
Requested data file name	**Years**
Patient Entitlement and Diagnosis Summary File (PEDSF)	1994-2007
Medicare Provider Analysis and Review (MEDPAR) file	1994-2003
Carrier Claims file (NCH)	1994-2003
Outpatient Claims file	1994-2003
Durable Medical Equipment (DME) file	1994-2003
NCI Hospital file	All possible

Study population and inclusion/exclusion criteria

The population of interest was female, Medicare beneficiaries aged 65 and older who lived in SEER regions and who had been diagnosed with primary cancer of the breast. Due to the lack of claims information in Medicare from beneficiaries enrolled in HMOs, only continuously enrolled, fee-for-service enrollees were included in this analysis. Continuous

enrollment was defined as continuous enrollment during the one year period prior to diagnosis and at least one year post-diagnosis, or until death, whichever occurred first. Approximately 15-20% of Medicare beneficiaries are enrolled in HMOs. Men with breast cancer were excluded, as were women younger than 65 and women whose eligibility for Medicare was due to end stage renal disease (ESRD). Table 4 provides a summary of inclusion and exclusion criteria for the study.

Table 4: Inclusion and exclusion criteria for study

	Inclusion Criteria	Exclusion Criteria
Sex	Women	Men
Cancer diagnosis	Incident in situ, Stage I (T1N0), II (T1N1, T2N0, T2N1, and T3N0), and III (T1N2, T2N2, T3N1, T3N2, T4N0, T4N1, T4N2, T1N3, T2N3, T3N3, and T4N3), primary breast cancers (site code 46)	Unclassified or unknown tumor or node status
		Secondary breast cancers (metastasized to breast)
		Prior breast cancer diagnosis
		Cancers diagnosed at autopsy
Insurance	Continuously enrolled in Medicare Parts A and B, Fee-For-Service	Enrolled in Medicare Advantage (HMO) at any time during study period
		Non-continuously enrolled
Surgical Treatment	Primary surgery received as 1st definitive treatment, defined as: Breast conserving surgery (BCS) includes segmental mastectomy, lumpectomy, quadrantectomy, tylectomy, wedge resection, nipple resection, excisional biopsy, or partial mastectomy; Non-BCS includes total simple, modified radical, radical, extended radical, or subcutaneous mastectomy	First definitive treatment is not surgery, i.e., received neoadjuvant chemotherapy prior to surgery or did not receive tumor removal surgery first

Notes: BCS: Breast conserving Surgery; HMO: Health Maintenance Organization; T: tumor, N: node, of the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging

For analytic models, only invasive, non-metastasized breast cancers were examined; therefore, in situ and metastatic (stage IV) cases were excluded. Secondary breast cancers (metastases from other sites) were excluded. Additionally, only women who received primary surgery as the first definitive treatment were included; as such, patients receiving neoadjuvant chemotherapy prior to surgery were excluded from analytic models. Because care-seeking behavior may be different among people previously diagnosed with breast cancer, women with prior histories of breast cancer were excluded. Finally, in cases of multiple primary tumors, to eliminate any confusion about which cancer-directed treatments

were targeted to which cancer, women with additional cancer diagnoses within one year of the index breast cancer diagnosis were excluded.

Sample size

SEER-Medicare data were used to examine receipt of radiation therapy and chemotherapy descriptively and analytically. SEER-Medicare data from breast cancer patients diagnosed in 1994-2002 with claims through 2003 and vital status follow-up through 2007 were used. From previous studies employing SEER-Medicare data, we knew that approximately 2,500-3,500 female Medicare beneficiaries living in SEER regions were diagnosed annually with stages I and II breast cancer (Haggstrom et al., 2005; Hershman et al., 2008). From 1992-1999, 22,701 new diagnoses of early stage breast cancer occurred among women in the SEER-Medicare dataset (ages 66-79) (Haggstrom et al., 2005). Another study of women with stage I or II breast cancer using SEER-Medicare data reported that 29,760 women were newly diagnosed in the years 1991-2002 (Hershman et al., 2008). Examining all invasive breast cancers (i.e., excluding only in situ cancers) diagnosed in the SEER-Medicare dataset from 1993-1999, Keating and colleagues (2005) found that approximately 5,700 to 6,100 incident breast cancer diagnoses occurred each year. Based on these figures, we estimated that approximately 4,000-5,000 incident stage I, II, or III breast cancer diagnoses per year would be included in the sample; over a 9-year period (i.e., 1994-2002), we expected 36,000-45,000 women would have been newly diagnosed with stages I-III, primary breast cancer.

Of these cases, we estimated that 3-5% would be missing data for race/ethnicity or date of diagnosis (i.e., month and year) (Gilligan et al., 2007b). Another 10-15% would likely be excluded because they were not eligible for Medicare Parts A and/or B or because they were enrolled in a Medicare HMO (Gilligan et al., 2007b). We estimated that another 2-5% would not receive surgery (i.e., either BCS or mastectomy) as the first definitive treatment

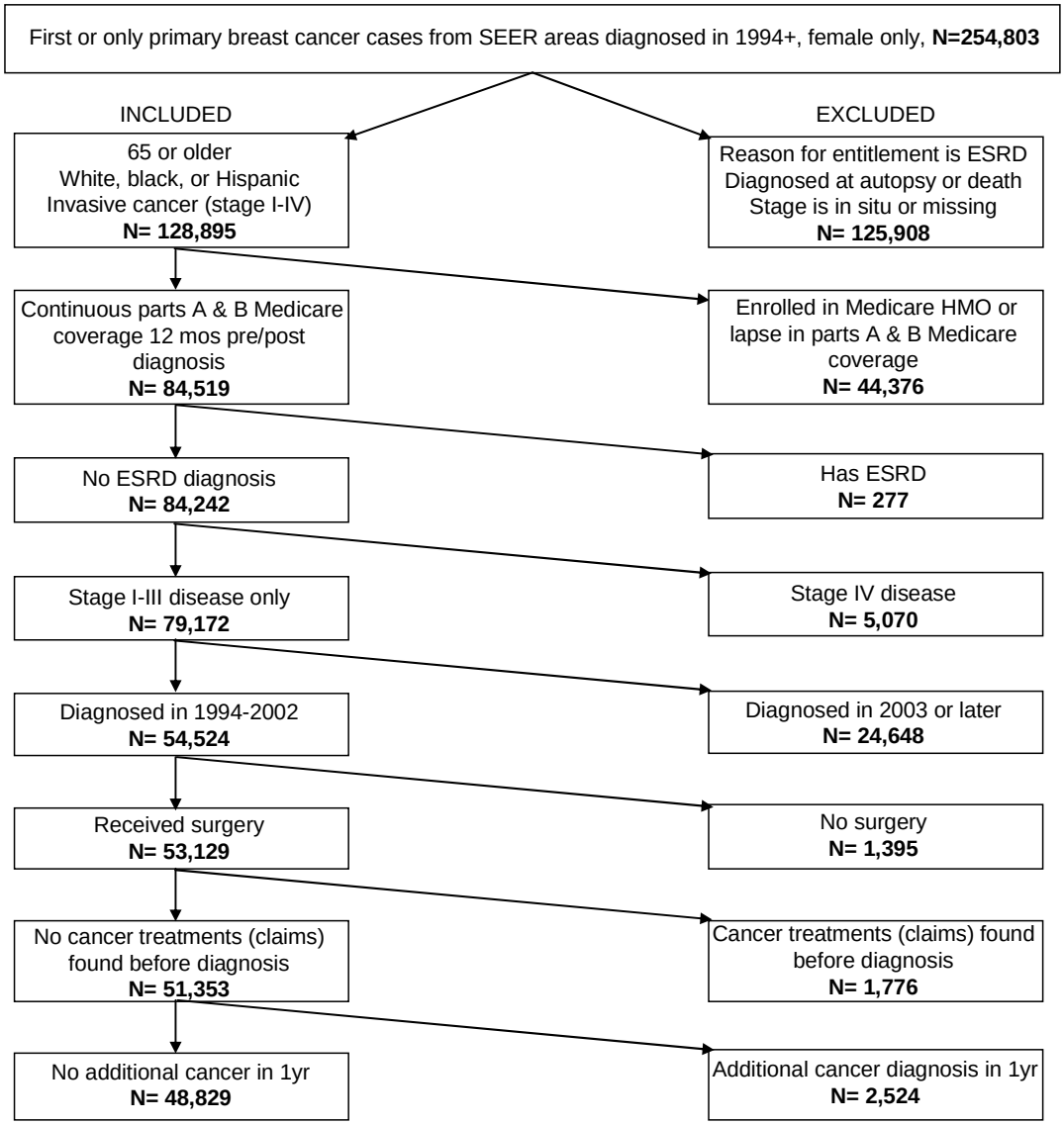
post-diagnosis. Based upon these numbers, approximately 15-25% of the total sample diagnosed between 1994 and 2002 would be expected to be excluded from analyses. As such, the analytic SEER-Medicare sample was expected to include approximately 27,000-38,250 women with non-metastatic, primary breast cancer. Given that the earlier analyses using SEER-Medicare data upon which these estimations were based included fewer registries, it was believed that this expected sample size was a conservative estimate.

For aims related to receipt of radiation therapy after BCS (1a, 1b, and 3a), we know that approximately 40-60% of women with stage I and II breast cancer received breast conserving surgery in 1994-1996 (Gilligan et al., 2007b; Jerome-D-Emilia and Begun, 2005; Neuner et al., 2004). This proportion likely has increased over time, as it may have taken several years for BCS plus RT, which has been the preferred standard of care since 1990, to diffuse into practice (Jerome-D'Emilia and Begun, 2005). Assuming that 70% of women diagnosed with breast cancer in 1996-2002 received BCS over mastectomy, the expected analytic sample size for aim 1b was approximately 18,900-26,775.

For aims related to receipt of adjuvant chemotherapy (2a, 2b, and 3b), the NCCN/ASCO metric is specific to stage II and III, hormone receptor negative cancers. Desch and colleagues (2008) estimated the annual denominator for this metric (i.e., number of eligible patients) in the entire United States to be 38,000; however, this number reflects only women younger than 70 years old. As a very rough calculation of the sub-sample of women with hormone receptor negative status in SEER-Medicare, we used this number and assumed that 40% of breast cancer diagnoses (or about 25,300 diagnoses) occur in women older than age 65 (Vogel, 2008; NCI, 2009), 97% of the US population older than 65 years is enrolled in Medicare (Warren et al., 2002c), SEER registries capture cancer diagnoses in approximately 26% of the US population (NCI, 2009), and ER/PR-negativity is distributed equally across age groups, leaving about 6,300 women per year in the SEER-Medicare dataset who should be eligible to receive adjuvant chemotherapy (Warren et al., 2002c).

This number seems high, given the number of incident cases estimated annually. In a study of women with stage I or II breast cancer using SEER-Medicare data from 1991-2002, approximately 10% of women had both ER-negative and PR-negative tumors (Hershman et al., 2008). This proportion applied to the number of women who met inclusion criteria and were stage II-III was expected to reflect a more realistic picture of sample size for aims 2a, 2b, and 3b. A schematic showing inclusion and exclusion criteria for the SEER-Medicare analytic sample is provided below (Figure 8).

Figure 8: Sample size schematic based upon inclusion/exclusion criteria



Notes: ESRD: End Stage Renal Disease; HMO: Health Maintenance Organization; SEER: Surveillance, Epidemiology and End Results

Variables and measurement

Variable constructs, dimensions, and measures of interest in this study and the SEER-Medicare data sources from which they were obtained are summarized in Table 5. In brief, receipt and timing of initiation of breast cancer treatments and long-term health outcomes were the dependent variable constructs of interest, and race/ethnicity and health system organization and navigability were key independent variable constructs of interest. Based upon review of the literature, control variable constructs that were included were: socioeconomic status, social support, community resources and socio-cultural context, biological features of the tumor, competing health risks, and environmental factors. Appendix A contains more detailed information about variable definitions and sources.

Dependent variables

For aims 1 and 2, primary outcomes of interest were timing of receipt of radiation therapy after BCS for stage I-III cancers and timing of receipt of adjuvant chemotherapy after definitive surgery among hormone receptor negative stage II-III breast cancers. Time to treatment for diffusion curves in aims 1a and 2a was considered categorically as receipt or non-receipt of RT after BCS within one year of diagnosis and receipt or non-receipt of adjuvant chemotherapy within four months, according to the ASCO/NCCN quality metrics, respectively. For aims 1b and 2b, time to treatment between diagnosis and therapy was considered as receipt of therapy within the ASCO/NCCN specified time periods, as well as additional time intervals shown to be potentially clinically meaningful in the literature. The primary outcomes of interest for aims 3a and 3b were all-cause and breast cancer-specific mortality at five years. Mortality was used instead of survival in light of inherent problems with measurement, including possible lead-time bias, length-time bias, and analytic difficulties in teasing out competing risks of death, discussed at length by other authors (Earle et al., 2002; Boyle et al., 2005; Ries et al., 2006; Sant et al., 2006; Shwartz, 1980).

Table 5: Variable measures and data sources

Construct	*Dimension*	*Measure/Variable*	*Source*
Dependent Variables			
Quality of breast cancer treatment	Timing of receipt of radiation therapy (RT)	Time in months between diagnosis and RT for stage I-III breast cancers	Claims; PEDSF
	Timing of receipt of adjuvant chemotherapy	Time in months between diagnosis and chemotherapy for stage II-III, ER/PR-negative breast cancers	Claims; PEDSF
Long-term health outcomes	Mortality	Breast cancer-specific mortality at 5 yrs	PEDSF
		All-cause mortality at 5 yrs	PEDSF
Key Independent Variables			
Patient-level characteristics	Race/ethnicity	Non-Hispanic white	PEDSF
		Non-Hispanic black	PEDSF
		Hispanic	PEDSF
Health system organization and navigability	Facility-level factors (institutional experience at surgical hospital)	Bed size of surgical facility	NCI file
		ACoSOG and RTOG affiliation	NCI file
		Teaching status	NCI file
		On-site radiation at surgical facility	NCI file
		Type/ownership	NCI file
		NCI Cancer Center designation	NCI file
	Relational factors	Distance to nearest radiation facility	Claims; PEDSF
		Distance to nearest chemotherapy facility	Claims; PEDSF
		Distance traveled for surgery	Claims; PEDSF
Control Variables			
Patient-level characteristics	Age	Age at diagnosis	PEDSF
	Residential area	Rural/urban residence	PEDSF
	Low income status	State-buy-in months	PEDSF
	Social support	Marital status	PEDSF
Community resources and cultural context	Area/aggregate socioeconomic status	% of census tract (2000) with less than high school education	PEDSF
		Median census tract (2000) income	PEDSF
	Area racial/ethnic profile	% Caucasian within census tract	PEDSF
		% black within census tract	PEDSF
		% Hispanic within census tract	PEDSF
Tumor/biological characteristics	Extent of disease	Stage	PEDSF
	Cell differentiation	Histologic grade	PEDSF
	Hormone receptor status	Estrogen receptor (ER) status	PEDSF
		Progesterone receptor (PR) status	PEDSF
Competing health risks	Co-morbid conditions	Constructed NCI-combined co-morbidity index (using claims data)	Claims
Temporal factors	Time	Year of diagnosis	PEDSF

Notes: ACoSOG: American College of Surgeons Oncology Group; NCI: National Cancer Institute; PEDSF: Patient Entitlement and Diagnosis Summary file; RTOG: Radiation Therapy Oncology Group; SEER: Surveillance Epidemiology and End Results

Because women received surgery, radiation and chemotherapy from various types of facilities, multiple claims files were examined in order to fully capture the therapeutic

experiences of women, including the MEDPAR (inpatient), carrier claims, outpatient, and durable medical equipment (DME) files (Virnig et al., 2002). Identification of breast cancer-related therapy has been discussed at length elsewhere (Cooper et al., 2002; Lamont et al., 2002; Virnig et al., 2002; Warren et al., 2002b); however, to ensure that all relevant codes for surgery, radiation therapy and chemotherapy were captured, billing and coding specialists and clinicians were consulted. Relevant codes for this analysis primarily came from the Healthcare Common Procedure Classification System (HCPCS) and International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification (ICD-9-CM) (Table 6). However, some chemotherapy claims may be identified by National Drug Codes (NDC) in the DME files; as such, a HCPCS/NDC crosswalk was created for chemotherapy drugs relevant for this analysis (available upon request).

Table 6: Identification of breast cancer treatments in Medicare claims

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
Chemotherapy	ICD9CM procedure: 99.25, 285.3, 999.81 CPT/HCPCS: 51720, **96400-96549**, 99555, **Q0083-Q0085 (oral),** C9127, C9415, C9420, C9421, C9431, C8953-C8955, S9329-S9331, G0355, G0357-G0363, G9021-G9032, **J8510, J8520, J8521, J8530-J8999 (oral), J9000-J9999 (IV)** Revenue Center Code: **0331; 0332; 0335** Betos: O1D DRG: 410; 492 Other: V58.1, V58.11, V66.2, V67.2, V87.41, NDC codes

Notes: Bold type indicates commonly used codes; CPT: Current Procedural Terminology; DRG: Diagnostic Related Group HCPCS: Healthcare Common Procedure Classification System; ICD-9-CM: International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification; NDC: National Drug Codes

Key independent variables

Key independent variables included race/ethnicity and structural/organizational characteristics of health services. Race/ethnicity was taken from the PEDSF file, using

SEER-reported data instead of Medicare-reported race/ethnicity data, due to well-known measurement problems and inconsistencies over time in the Social Security Administration's definition of racial and ethnic groups (Bach et al., 2002a). It is believed that the SEER data, which uses a Spanish-surname algorithm in addition to self-reported race information, is the superior source for this measure (Bach et al., 2002a). For the purposes of this analysis, racial/ethnic classification was limited to non-Hispanic white, non-Hispanic black, and Hispanic.

Key structural/organizational variables of interest included facility-level factors (surgical facility bed size, NCI Cancer Center designation, ACoSOG affiliation, RTOG affiliation, teaching status, type/ownership, as well as presence of an on-site radiologic facility at the surgical hospital), and relational factors (distance to nearest radiation and chemotherapy facilities and distance traveled for definitive surgery). These variables were obtained from the NCI hospital file, Medicare claims, and PEDSF file. Please refer to Table 5, Appendix A, and individual manuscripts (chapters 4, 5, and 6) for more detail about measurement and coding of these variables.

In terms of relational factors (i.e., distance to care), distances were calculated by assigning spatial coordinates (latitudes and longitudes) to 5 digit ZIP codes and using spherical geometry to calculate distances between points. Nearest neighbor analysis was performed by executing a Cartesian product of all patients and providers, calculating, all distances by the above method, and selecting the minimum distance for each patient. Data files from various companies with geographic information for ZIP codes have been purchased over the past 15 years (Healthcare Solution Series database for ZIP codes, Nielsen Claritas Inc., Ithaca, NY: 1998-2000; Trendline database for ZIP codes, Nielsen Claritas Inc., Ithaca, NY: 1995-1996; Pop-Facts database for ZIP codes, Nielsen Claritas Inc., Ithaca, NY: 2003-2009) and combined into an aggregate file where every ZIP code found in any of these files has been assigned geographic coordinates for every year. The

ZIP code coordinates provided in data files are internal points to ZIP code polygons, but companies do not claim these points to be centers of gravity or population nor do they document their methods. Some changes are just movement of borders, but ZIP codes are created and eliminated every year. For the aggregate location file, if a ZIP code does not have data for a given year information from the last year preceding was used, when available. If no information for preceding years was available, information for the soonest following year was used. was used for calculating distances in miles between two sets of geographic coordinates. This formula is necessary (as opposed to simple Pythagorean equation) because lines of longitude converge while traveling north, so the distance between varies with latitude. The Great Circle formula has been shown to be imprecise at distances of less than a tenth of a mile, but is reliable for distance to care calculations.

Control variables

Review of the breast cancer literature reveals that there are several potentially confounding variables that must be considered in any analysis of patient treatment and outcomes. These include age and tumor biology, both of which affect physician prescribing patterns and suitability of the patient to withstand invasive therapeutic treatment. Age is found within the PEDSF file and was considered categorically (i.e., in five-year age groups) and continuously in model specification. Features of tumor biology, including stage of disease, ER status, PR status, and histologic grade are reported by SEER registrars and were considered categorically in analytic models. Given evidence of regional variation in cancer treatment, rural/urban residence was included as a covariate when possible (too little variation in some cases precluded inclusion of this measure). Rural/urban residence was measured categorically, with rurality/urbanicity defined as: metropolitan (250,000 - >1 million), urban (2,500-250,000), and (<2500 per county) from the source geographic cancer registry (Gorin et al., 2005).

Socioeconomic status was considered by including a variable for any evidence of State-Buy-In months (a proxy for low income status) and by including zip code-level socioeconomic measures (i.e., median income and proportion of residents with less than a high school education). Neighborhood racial and ethnic diversity was measured by assessing proportions of white, black, and Hispanic residents within the zip code. Social/familial support has been shown to be a predictor for receipt of and adherence to anti-cancer therapeutic regimens (Banerjee et al., 2007). Due to limitations in using registry-based claims data, social/familial support could be obtained only by examining marital status, so a categorical indicator for marriage status was included in analytic models. Co-morbidities were assessed by developing an analytic index of co-morbid conditions using the NCI combined index (NCICI) method described by Klabunde and colleagues (2007). This co-morbidity index was developed for use with the SEER-Medicare data, with risk adjustment weights specific to each cancer site of interest (Klabunde et al., 2007). Compared with other co-morbidity indices, the NCICI performed better in predicting non-cancer mortality for the population of survivors of cancer (Klabunde et al., 2007). Models for receipt of radiation therapy further were adjusted by receipt of adjuvant chemotherapy (yes/no), to allow for possible time delays associated with treatment sequencing. Finally, year of diagnosis dummy variables were included as covariates to adjust for cohort effects and secular changes in healthcare policies and practices over time.

Statistical analyses by aim

Descriptive statistics were run prior to running analytic models to examine proportions and means of patient demographics and clinical features of the cancers across the sample. Descriptive statistics were stratified according to age group (i.e., younger than 70 years versus 70 years and older) and by race/ethnicity. Chi-square tests and t-tests were used, as appropriate, to determine whether differences between groups were statistically

significant at the 5% level of significance (Chernoff and Lehmann, 1954; Pagano and Gauvreau, 2000).

Aims 1a and 2a were examined using SEER-Medicare data from years 1994-2003 in SEER-13 regions, excluding the Alaska Native Tumor Registry which is limited to Native Americans. Diffusion curves (Rogers, 1995a) based upon proportions of the sample receiving clinically recommended RT within one year and receipt of chemotherapy within four months were constructed for different sub-populations (e.g., by race/ethnicity, age group). Groups were compared using chi-square tests by year (Chernoff and Lehmann, 1954; Pagano and Gauvreau, 2000).

Aims 1b and 2b were examined using SEER-Medicare breast cancer cases diagnosed in 1994-2002 with claims through 2003 from SEER-17 regions, excluding the Alaska Native Tumor Registry. Multivariate logistic regression (Berkson, 1944; Hosmer and Lemeshow, 2000; Rothman et al., 2008) was employed for each binary dependent variable, specifically, receipt of radiation within the specified time frame (aim 1b) and receipt of chemotherapy within the specified time frame (aim 2b). Multivariate analyses were conducted employing a backwards model building strategy that included race/ethnicity, all structural/organizational variables, covariates, interactions of race/ethnicity and structural/organizational variables, and interactions of race/ethnicity and year of diagnosis in "full" or "saturated" versions of the logit models (Kleinbaum et al., 1998; Mickey and Greenland, 1989; Rothman et al., 2008). Each variable and interaction, in turn, was assessed for modification or confounding potential, by removing terms one-by-one from the model, starting with interaction terms (i.e., to assess modification potential). Modification and confounding were evaluated by examining changes in the magnitude or significance of the main effect of race/ethnicity (using the hazard ratio/odds ratio), changes in the likelihood ratio (LR) test statistic, and Wald test statistics for individual terms and interactions (Mickey and Greenland, 1989). The 5% level of significance was to assess predictive power of each

individual term, and a change threshold of 10% was used to assess confounding and modification potential of covariates (Hosmer and Lemeshow, 2000; Mickey and Greenland, 1989). Wald tests were used to test significance of variable constructs (e.g., the group of dummy variables for year of diagnosis) (Wooldridge, 2006). All logistic models were stratified by age-group (<70, 70 and above) (Rothman et al., 2008; Wooldridge, 2006). Final estimations were adjusted for heteroskedasticity using Huber-White robust standard errors.

Aims 3a and 3b (which focus on the effects of timing of radiation therapy and chemotherapy on five-year mortality) were examined using data from patients diagnosed with breast cancer in 1994-2002 with vital statistics through 2007, living in SEER-17 regions excluding the Alaska Native Tumor Registry (which is limited to Native Americans only). Multivariate logistic regression was used to determine likelihood of mortality at five years as a function of timing of first RT and/or chemotherapy, controlling for known covariates (Berkson, 1944; Hosmer and Lemeshow, 2000; Rothman et al., 2008). Specification of the explanatory variables, timing of RT and timing of adjuvant chemotherapy, was informed by results from aims 1b and 2b and by consulting the clinical literature.

Analyses were performed using Stata version 10.0 (Stata Corporation, College Station, Texas) and SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

CHAPTER 4: EFFECT OF STRUCTURAL/ORGANIZATIONAL CHARACTERISTICS OF HEALTH SERVICES ON THE RELATIONSHIP BETWEEN RACE/ETHNICITY AND TIMELY RECEIPT OF RADIATION THERAPY IN BREAST CANCER PATIENTS

Abstract

Purpose

Racial/ethnic health disparities in breast cancer outcomes are well documented but the factors contributing to disparities remain poorly understood. Characteristics of the health system may affect whether and when women receive high quality breast cancer care and may explain in part racial/ethnic and age-related disparities in outcomes. Given that current quality metrics in breast cancer were based upon well-established breast cancer treatment guidelines (Desch et al., 2008), this study retrospectively examined the relationships between race/ethnicity and health services characteristics in terms of receipt, timing of initiation, and diffusion of high quality cancer care, specifically radiation therapy (RT) after breast conserving surgery (BCS) for stage I-III cancers.

Methods

We used the linked Surveillance Epidemiology and End Results (SEER) – Medicare longitudinal dataset to isolate registry information and claims for women ages 65 and older whose first or only cancer diagnosis was primary breast cancer in 1994-2002. To be included, women had to be continuously enrolled in Medicare parts A and B fee-for-service one year prior to and one year post-diagnosis. Overall receipt and timing of initiation of RT, the primary outcomes of interest, were measured as binary variables indicating whether the patient ever initiated RT and whether the patient initiated RT within several time intervals varying from one to twelve months. Diffusion curves were used to describe trends in

guideline adoption across sub-populations over time; multivariate logistic regression was employed to examine the confounding potential of facility-level characteristics, including profit status, teaching status, institutional affiliations, and distance-to-care, on the effect of race/ethnicity. Covariates in multivariate analyses included age at diagnosis, marital status, socioeconomic status, tumor characteristics, co-morbid conditions, and year of diagnosis.

Results

Among the 38,574 women who met inclusion/exclusion criteria, 6% were non-Hispanic black and 4% were Hispanic. Overall, two-thirds received RT after breast conserving surgery, with significant variation by race/ethnicity and age. Specifically, receipt of RT was significantly higher among non-Hispanic white women ($p<0.001$) and women younger than 70 years old ($p<0.001$). Trends in timing of receipt of RT also varied significantly over time by race/ethnicity, age, and surgical provider characteristics. Multivariate models demonstrated that although structural/organizational variables have predictive power and vary by race/ethnicity, they do not eliminate disparities in treatment. For example, black women 70 years and older had significantly lower odds of receiving clinically-appropriate RT within one year of diagnosis (ORblack: 0.77; $p<0.05$) compared to white women, controlling for all covariates. As well, black women of all ages had significantly lower odds of receiving RT across all time intervals examined, whereas the Hispanic disparity in treatment disappeared in older age groups.

Conclusion

Despite guidelines calling for RT after BCS within 1 year, a substantial minority of older women with breast cancer fail to receive this important therapy. Significant disparities persist in receipt of RT for breast cancer after adjusting for structural/organizational characteristics of health services that may affect the type of care offered to vulnerable

groups. Recognizing that structural/organizational characteristics of health services may be correlated with race/ethnicity may enable us to identify strategies targeting health interventions to especially vulnerable breast cancer patients; however, more creative approaches to improve quality in vulnerable sub-populations must be identified.

Introduction

Variation in breast cancer treatment quality and outcomes has been documented widely across providers and geographic regions within the United States (Ballard-Barbash et al., 1996; Bickell et al., 2006; Bloom et al., 2004; Chaudry et al., 2001; Gilligan et al., 2007a; Gilligan et al., 2007b; Haggstrom et al., 2005; Hebert-Croteau et al., 2005; Hershman et al., 2008; Jerome-D'Emilia and Begun, 2005; Keating et al., 2003; Keating et al., 2009; Laliberte et al., 2005; Onega et al., 2009). Particularly at risk for poor quality breast cancer care are minority and elderly women (Edwards et al., 2005; Freedman et al., 2009; Haggstrom et al., 2005). Breast cancer trends during the past 25-30 years have shown general improvements in guideline adherence and mortality (Edwards et al., 2005); however, if the quality of cancer care improves over time in the general population but differences in quality across sub-populations persist or worsen over time, inequities in treatment that lead to disparate health outcomes may not have been adequately recognized or addressed.

Often cited reasons for racial/ethnic disparities in breast cancer are differences in socioeconomic status, co-morbid conditions, and biological characteristics of the tumor (Carey et al., 2006; Du et al., 2008; Gross et al., 2005; Lund et al., 2009; Schootman et al., 2009). The most commonly cited reasons for age-related differences in breast cancer management are differences in health status or co-morbidities and lack of guidelines for elder age groups (Ballard-Barbash et al., 1996; Desch et al., 2008; Passage and McCarthy, 2007). However, other explanations may be possible. Specifically, organizational and structural characteristics of the health system, such as distance between patient residence and health services, may independently influence receipt of high quality care, and also may be correlated with racial/ethnic group and/or age, potentially explaining a portion of observed disparities. As an example, in a study by Punglia and colleagues (2006a), among elderly women, increasing distance to the nearest radiation treatment facility significantly

lowered the likelihood of receiving guideline-recommended radiation therapy (RT), and the effect of distance was more pronounced with increasing patient age.

Previous studies have explored the role of organizational/structural factors in determining quality of breast cancer care and health outcomes without examining whether these characteristics vary by patient demographics. For example, studies have examined the effects of facility caseload or volume (Gilligan et al., 2007b; Hebert-Croteau et al., 2005), teaching facility status (Chaudry et al., 2001; Hebert-Croteau et al., 2005; Jerome-D'Emilia and Begun, 2005), surgeon characteristics (Gilligan et al., 2007a), and NCI Comprehensive Cancer Center designation (Birkmeyer et al., 2005; Laliberte et al., 2005; Onega et al., 2009) on treatment and outcomes. Institutional theory and diffusion of innovations theory suggest that substantially different institutional cultures exist within different types of organizations, such as institutions that engage in cancer-directed research compared to those that do not (DiMaggio and Powell, 1983; Hebert-Croteau et al., 2005; Laliberte et al., 2005; Scott et al., 2000). Characteristics of the local community, including population density, local resource capacity, and neighborhood racial/ethnic composition, may affect the types of health organizations that locate in a particular setting. Conversely, racial/ethnic identification and/or age may influence health-seeking behavior, utilization of certain types of providers, and choice of residence. It is unclear exactly how multiple characteristics of the health care system correlate with patient demographics such as race/ethnicity and whether they act in conjunction to determine receipt of high quality breast cancer care. Because structure and organization of health services are closely related to diffusion and implementation of evidence-based practices, if differences in access to or availability of certain types of health services exist among vulnerable sub-populations, disparities in treatment or outcomes may result. Furthermore, innovative treatments and evidence-based guidelines may diffuse more slowly within certain sub-populations over time.

Accordingly, we examined the relationships between race/ethnicity and structural/organizational aspects of health services in terms of diffusion of guideline-recommended care, specifically, initiation of RT within 1 year of diagnosis among women who received breast conserving surgery (BCS). We also examined initiation of RT within additional time intervals. BCS with subsequent RT is considered a standard option for women with early stage breast cancer, which may be preferable to mastectomy due to a similar survival benefit and improved quality of life outcomes for some patients (NIH, 1990). Considering the importance of age in determining receipt of RT, as demonstrated by Punglia and colleagues (2006a) among others, all analyses were stratified by age group (<70 versus 70 years and older). Although a substantial body of evidence has documented racial/ethnic and age-related disparities in overall receipt of RT after BCS (Bickell et al., 2006; Freedman et al., 2009; Haggstrom et al., 2005; Keating et al., 2009), we sought to add to this literature by exploring possible explanations for persistent disparities, by examining the effects of structural/organizational factors, including distance to care and surgical facility characteristics, on racial/ethnic variation in receipt of RT after BCS for stage I-III cancers. We also examined uptake of this guideline over time across vulnerable sub-populations and racial/ethnic variation in timing of initiation of RT.

Methods

Data Source and Patient Population

Surveillance, Epidemiology, and End Results (SEER) registry data from 1994-2002 linked to Medicare claims through 2003 were used for this study. SEER registries represent approximately 26% of the US population, and Medicare is the primary insurer for 97% of the American population ages 65 and older (Warren et al., 2002c). Patient records from SEER-13 regions (excluding the registry consisting of Native Americans from Alaska) were used for construction of the descriptive diffusion curves, due to the fact that the SEER registry

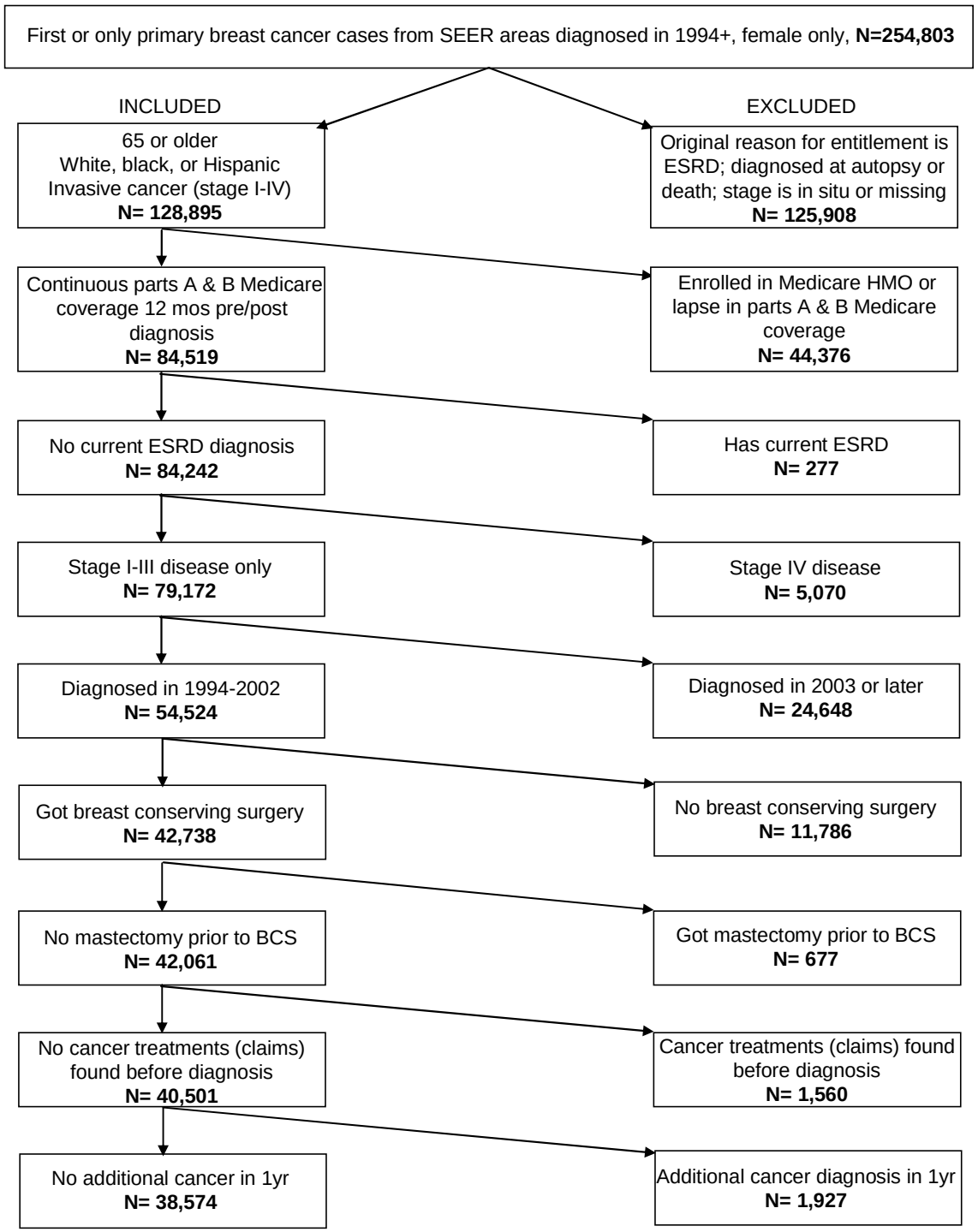
system expanded over time, and diffusion curves needed to reflect patterns of care within registries that existed during the entire time period. Patient records from SEER-17 registries were used for all multivariate analyses.

The Patient Entitlement and Diagnosis Summary File (PEDSF) was used to assess clinical, demographic, geographic, and census-derived aggregate socioeconomic information about breast cancer patients. The Medicare analysis and procedure (MEDPAR) file, carrier claims file, outpatient claims file, and Durable Medical Equipment (DME) file were used to ascertain details about surgery and RT services provided to breast cancer patients, as well as distance to healthcare providers. The National Cancer Institute (NCI) hospital file was used to explore organizational characteristics related to the surgical provider, including type/ownership; size; NCI Comprehensive Cancer Center designation; NCI Radiation Therapy Oncology Group (RTOG) membership; American College of Surgeons Oncology Group (ACoSOG) affiliation; teaching status; and presence of on-site radiation services.

The population examined was female, Medicare beneficiaries living in SEER regions who were diagnosed with stage I-III primary cancer of the breast in 1994-2002 and who received BCS. Due to the lack of claims information in Medicare from beneficiaries enrolled in managed care, only continuously enrolled (from one year prior to one year post-diagnosis) in parts A and B fee-for-service beneficiaries were included in the analysis. Men with breast cancer were excluded, as were women of racial/ethnic background other than non-Hispanic white, non-Hispanic black, and Hispanic, due to insufficient numbers of women from other racial/ethnic groups for analyses. Hispanic ethnicity was determined by SEER and is considered to be more accurate than Medicare's or the Social Security Administration's classification, in part because of a Spanish surname algorithm employed by SEER to supplement ethnicity information (Bach et al., 2002). Individuals with end-stage renal disease and those women who had an additional cancer diagnosis within one year of

the index diagnosis also were excluded. Inclusion and exclusion criteria for this study and the corresponding effects on sample size are illustrated in Figure 9.

Figure 9: Sample size diagram based on inclusion/exclusion criteria



Notes: ESRD: End Stage Renal Disease; HMO: Health Maintenance Organization

Dependent Variable

Timing of initial receipt of radiation therapy (RT) was examined as a binary variable indicating whether the patient received a first course of RT within a specified time interval. Importantly, the ASCO/NCCN quality metric specifies that the patient must begin RT within one year of diagnosis; completion of a recommended course of RT is not included in the metric (Desch et al., 2008). Although adherence to or persistence in receiving the full treatment is clearly important, clinically appropriate variation across patients in dosage, timing of cycles, and administration makes assessment of therapy completion difficult. Different time intervals for initiation of RT at one to twelve months post-diagnosis were also examined in the current study because we were interested in variation in initiation of RT.

Identification of breast cancer-related therapy has been discussed at length elsewhere (Cooper et al., 2002; Virnig et al., 2002). Relevant codes used in this analysis from the Healthcare Common Procedure Classification System (HCPCS) and the International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification (ICD-9-CM) are summarized in Table 7.

Table 7: Identification of breast conserving surgery and radiation therapy in Medicare claims

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
Breast conserving surgery	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

Notes: CPT: Current Procedural Terminology; DRG: Diagnostic Related Group; HCPCS: Healthcare Common Procedure Classification System; ICD-9-CM: International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification

Independent Variables of Interest

The main independent variables were race/ethnicity (defined as non-Hispanic white, non-Hispanic black, and Hispanic) and characteristics of the health system and providers,

including characteristics of the facility where women received surgery (i.e., type/ownership; size; NCI Comprehensive Cancer Center designation; NCI Radiation Therapy Oncology Group (RTOG) membership; American College of Surgeons Oncology Group (ACoSOG) affiliation; teaching status; and presence of on-site radiation) and distance to care (i.e., distance traveled for surgery and distance to nearest RT facility).

Surgical facility characteristics have been shown by other researchers to be important predictors of subsequent breast cancer care (Keating et al., 2009), survival (Hebert-Croteau et al., 2005), and mortality (Birkmeyer et al., 2005). Previous studies have mostly examined the effect of a single variable, such as hospital teaching status; in the current study, a number of surgical facility characteristics were considered in conjunction. The NCI Hospital File, a data resource combining provider information from the Healthcare Cost Report (HCRIS) and Provider of Service (POS) survey, was used in our study to provide information about structural and organizational features of the hospital-affiliated facilities where women received primary surgery, as identified in the medical claims data (NCI, 2009). Data in this file were collected somewhat irregularly in 1996, 1998, and 2000-2006; as such, we used the closest date to the claims date to determine surgical provider characteristics.

Distance traveled for surgery was determined by identifying the unique provider ID and zip code associated with first reported incidence of a surgical claim for BCS in the MEDPAR, carrier claims, and/or outpatient claims files and identifying patient zip code at diagnosis. Distances from patient zip code centroid and surgical provider zip code centroid were then calculated by assigning spatial coordinates (latitudes and longitudes) to zip codes and using spherical geometry and the Great Circle Distance Formula to calculate distance in miles between two sets of geographic coordinates. This method has been shown to be more precise than simple Pythagorean equations because lines of longitude converge while traveling north. We used this approach to proxy the distance in miles that patients traveled

for surgery; previous analyses have used a similar approach (Shea et al., 2008; Nattinger et al., 2001; Meden et al., 2002; Schroen et al., 2005). To calculate distance to the nearest radiation facility (as a measure of patient access to radiation providers), we identified all Medicare beneficiaries treated for breast cancer in SEER regions from 1994-2003 and all providers/facilities for which radiation therapy claims were filed. From this information, we created a master file of all radiation therapy providers who had treated Medicare patients over the study period and their associated zip codes. Using a minimum distance algorithm based on Cartesian products of all latitude and longitude of zip code centroids, we determined shortest distance to the nearest radiation facility for each woman in the study sample (Phibbs and Luft, 1995). Data files from various companies with geographic information for ZIP code analysis were consulted, matching the year of patient diagnosis to the closest year for which updated ZIP code information was available. If a ZIP code did not have data for a given year, information from the last year preceding was used. If no information for preceding years was available, information for the soonest following year was used. Previous authors have demonstrated that straight-line distances are a reasonable proxy for travel time and geographic access to care in the absence of patient-level data on actual time spent traveling to health care providers (Phibbs and Luft, 1995).

Control Variables

Control variables were age at diagnosis, rural/urban residence, zip code-level income, education, and racial/ethnic composition, tumor characteristics (stage, grade, estrogen receptor [ER] status, and progesterone receptor [PR] status), receipt of chemotherapy prior to RT, year of diagnosis, low income status (in this case, defined as whether the patient had any indication of State-Buy-In during the study period) (Bach et al., 2002a), and marital status at diagnosis. Additionally, a measure of co-morbidity was included as a covariate, assessed by developing an analytic index of co-morbid conditions

using the NCI combined index (NCICI) method described by Klabunde and colleagues (2007). This co-morbidity index was developed with risk adjustment weights specific to each cancer site of interest (Klabunde et al., 2007). Compared with other co-morbidity indices, the NCICI is the best predictor of non-cancer mortality among cancer survivors, including survivors of breast cancer (Klabunde et al., 2007).

Statistical Analysis

To assess dissemination and uptake of high quality, evidence-based treatment over time, an overall diffusion curve was constructed based upon population-level proportions of eligible patients receiving RT after BCS within one year of diagnosis (Rogers, 1962; Rogers, 1995a). Then, diffusion curves within sub-populations comparing patients by racial/ethnic group, age groups, rural versus urban residence, and health services characteristics were constructed and contrasted using chi-squared tests (Pagano and Gauvreau, 2000; Chernoff and Lehmann, 1954), by year.

Unadjusted odds ratios were first examined showing the effect of race/ethnicity on receipt of RT by each time endpoint (i.e., one to twelve months post-diagnosis), stratified by age group (under 70 versus 70 years and older) and excluding women who received a subsequent mastectomy during each time period of interest. The exclusion of these women is critical, because many breast cancer patients undergo mastectomy following an initial breast conserving surgery due to positive margins or another clinically meaningful reason; as such, adherence to the RT guideline is no longer relevant. Confounding potential of structural/organizational variables on race/ethnicity was assessed in bivariate analyses by constructing 2x*r* tables; chi-squared tests or t-tests then were used to examine differences by group, as appropriate (Mickey and Greenland, 1989; Pagano and Gauvreau, 2000). Modification potential of health services characteristics on race/ethnicity was assessed by running unadjusted models of race/ethnicity on receipt of RT, stratified by

structural/organizational variables and comparing the odds ratios (and 95% confidence intervals and confidence limit ratios) among strata (Mickey and Greenland, 1989; Rothman et al., 2008).

Multivariate logistic regressions were specified, excluding women who received mastectomy subsequent to BCS within each time interval of interest and stratifying on age (younger than 70 versus 70 years and older). Each variable and interaction, in turn, was assessed as a modifier or confounder by examining changes in the magnitude or significance of the main effect of race/ethnicity, changes in the likelihood ratio test (LRT) statistic, and Wald test statistics for individual terms and interactions (Mickey and Greenland, 1989; Rothman et al., 2008). The 5% level of significance was used to assess predictive power of each individual term, and a change threshold of 10% was used to assess confounding and modification potential of covariates (Mickey and Greenland, 1989; Hosmer and Lemeshow, 2000). Wald tests were used to test the joint significance of variable constructs (e.g., the group of dummy variables for year of diagnosis) (Wooldridge, 2006). Due to lack of evidence for modification of the main effect of race/ethnicity, interactions with structural/organizational health services characteristics were ultimately omitted in final model estimations.

Additional tests were employed to determine the most appropriate variable specification for final analytic models. Specifically, the functional forms of continuous variables, such as age, distance to care, and co-morbidity score, were tested to determine whether continuous or multiple categorical forms of these variables should be used. As well, multicollinearity among variables was tested (Wooldridge, 2006). Finally, Huber-White robust standard errors were used to correct standard errors in all final model estimations, due to inherent heteroskedasticity in the general equation. Analyses were performed using Stata version 10.0 (Stata Corporation, College Station, Texas) and SAS version 9.2 (SAS

Institute, Inc., Cary, North Carolina). The primary logistic regression model takes the following general form:

$$\Pr(RT_i) = f(\beta_0 + \beta_1 \text{Race/Ethnicity}_i + \beta_2 \text{Struct}_i + \beta_3 \text{Time}_i + \gamma Z_i + \varepsilon_i)$$

where "RT" is receipt of radiation therapy during the time interval of interest, "Race/Ethnicity" is non-Hispanic white, non-Hispanic black, or Hispanic, "Struct" is a vector of health services structural/organizational variables, "Time" is year of diagnosis, "Z" is a vector of all other patient and community control variables, and "ε" is the error term.

Results

Of all women in the SEER-Medicare dataset diagnosed with primary breast cancer during the period 1994-2002, 38,574 who underwent BCS met inclusion criteria and were included in the current study. Descriptive characteristics of the full sample are summarized in Table 8. Average age at diagnosis was 75.6 years, and the majority (90%; n=34,965) was non-Hispanic white, whereas approximately 6% of women (n=2,273) were non-Hispanic black and 4% of women (n=1,336) were Hispanic. In total, about 60% of all women received RT at some time after BCS. Importantly one-third of the total sample received mastectomy subsequent to BCS in the one-year period following diagnosis. When subsequent mastectomy within one year is taken into account, the proportion of women who received RT in the absence of a subsequent mastectomy is elevated to 78%, whereas only 18% of women with a subsequent mastectomy also received radiation therapy. The majority of women received first definitive surgery in the same month as diagnosis, with little variation by race/ethnicity or age. In general, older women were significantly less likely to receive RT or chemotherapy. In terms of clinical differences in cancers by race/ethnicity, black women were more likely to be diagnosed with advanced stage disease (i.e., stage III), less likely to

Table 8: Descriptive statistics of full SEER-Medicare patient sample who received BCS

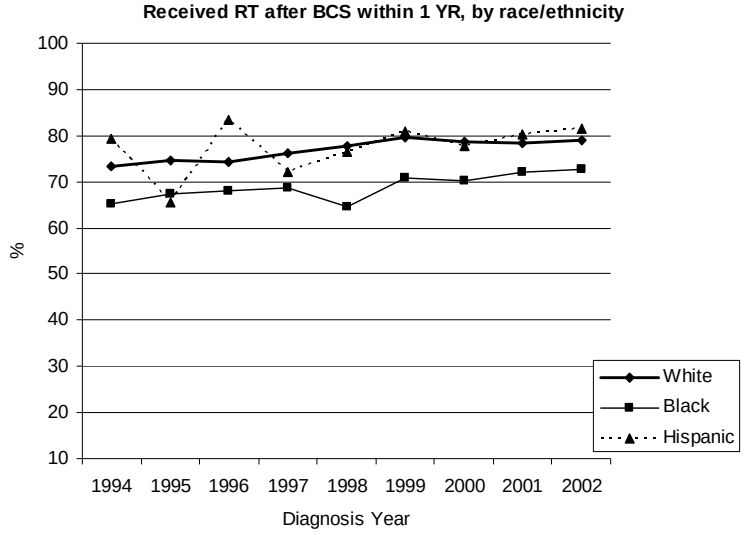
Characteristic	% or mean (N=38,574) *OVERALL*	% or mean (N=7082) *< 70 years, White*	% or mean (N=526) *< 70 years, Black*	% or mean (N=349) *< 70 years, Hispanic*	% or mean (N=27,883) *>/= 70 years, White*	% or mean (N=1747) *>/= 70 years, Black*	% or mean (N=987) *>/= 70 years, Hispanic*
Patient/demographic characteristics							
Age (years)	75.6	67.5	67.3	67.4	77.8	77.7	76.8
Married	43.5%	61.3%	31.7%	52.4%	40.8%	22.1%	34.7%
Low income	16.5%	10.5%	39.9%	45.8%	14.2%	46.0%	50.7%
Residence							
Metro	85.1%	83.2%	94.1%	88.3%	84.6%	95.0%	89.8%
Urban	13.3%	14.9%	5.9%	11.5%	13.7%	4.8%	9.8%
Rural	1.6%	1.9%	0.0%	0.3%	1.8%	0.2%	0.4%
Year of diagnosis							
1994	8.6%	9.7%	8.9%	6.6%	8.3%	8.6%	6.9%
1995	8.8%	9.0%	9.9%	10.0%	8.7%	8.6%	8.7%
1996	8.5%	8.9%	8.7%	9.5%	8.4%	8.6%	8.0%
1997	8.8%	8.6%	7.6%	8.3%	8.8%	8.5%	9.4%
1998	8.5%	8.1%	8.6%	7.2%	8.6%	8.8%	7.9%
1999	8.9%	8.2%	8.2%	8.0%	9.1%	7.8%	9.3%
2000	15.9%	15.6%	16.7%	18.6%	15.9%	18.0%	16.1%
2001	16.2%	15.7%	15.2%	14.3%	16.4%	15.8%	17.4%
2002	15.8%	16.3%	16.2%	17.5%	15.7%	15.3%	16.2%
Clinical characteristics							
Stage I	63.5%	63.8%	55.5%	56.2%	64.6%	51.4%	56.5%
Stage II	33.0%	33.5%	38.4%	40.1%	32.0%	42.5%	37.9%
Stage III	3.5%	2.7%	6.1%	3.7%	3.4%	6.1%	5.6%
Hormone receptors							
ER+	70.7%	72.1%	52.3%	67.0%	71.7%	58.2%	66.0%
PR+	58.0%	59.8%	39.5%	56.4%	58.8%	46.9%	53.5%
Co-morbidity score	0.26	0.17	0.33	0.26	0.27	0.43	0.36
Node status							
Positive	19.0%	22.6%	27.9%	25.2%	17.5%	22.6%	22.0%
Missing	24.2%	10.2%	14.8%	9.2%	27.7%	30.5%	25.6%
Treatment							
RT after BCS in 4 months	48.3%	54.0%	48.4%	47.6%	47.9%	36.1%	46.6%
RT after BCS in 1 year	56.7%	68.2%	57.6%	63.3%	54.3%	47.4%	54.8%
Ever received RT after BCS	57.8%	69.2%	59.2%	65.3%	55.4%	49.0%	55.9%
Received surgery in same month as diagnosis	70.6%	71.1%	65.0%	67.3%	70.9%	67.0%	68.9%
Ever received chemotherapy	20.3%	32.7%	37.3%	33.8%	16.7%	20.4%	19.4%

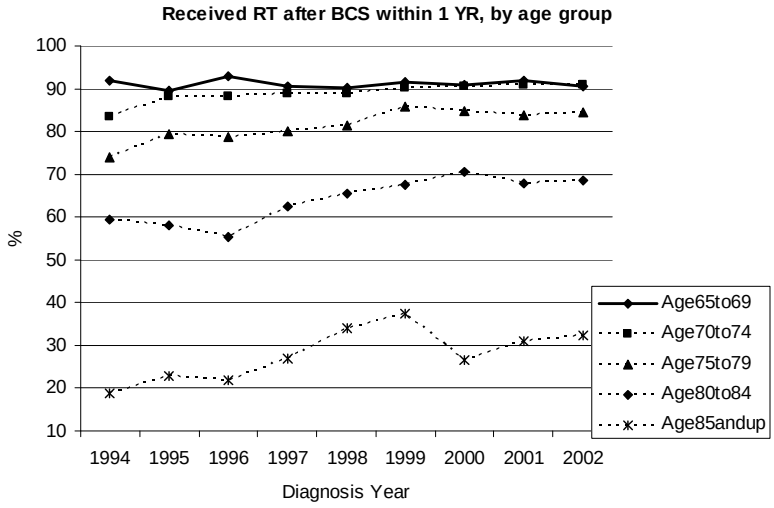
Notes: Full sample included in descriptive statistics – no exclusions for subsequent mastectomy during the time interval of interest; BCS: breast conserving surgery; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; SEER: Surveillance Epidemiology and End Results

have hormone receptor positive tumors, and more likely to have lymph node status missing (Table 8). Missing lymph node status was significantly correlated with registry ($p<0.001$), so this black/white difference potentially could be explained by differences in reporting by registry. Black women also suffered greater co-morbidity. In general, Hispanic women tracked between white and black women with respect to tumor characteristics and co-morbid conditions (Table 8). In terms of socio-demographic differences by race/ethnicity, black and Hispanic women were more likely to be low income (according to the State-Buy-In variable) and less likely to live in a rural area (Table 8). Black women also were much less likely to be married.

Trends in receipt of radiation therapy over time varied significantly by race/ethnicity and age group, as evidenced in Figure 10. Receipt of guideline-recommended RT after BCS within 1 year (in the absence of a subsequent mastectomy) was significantly more common among non-Hispanic white women (78%) and Hispanic women (79%) compared to non-Hispanic black women (69%) ($p<0.001$); as well, women younger than 70 years were more likely to receive RT after BCS within 1 year (91% compared to 74%, $p<0.001$). In examining race/ethnicity and age simultaneously, black women 70 years and older were least likely to receive RT within 1 year of BCS (in the absence of a subsequent mastectomy) compared with other groups (proportions over time ranging from 59-73% in older black women compared to a steady 90-92% in white women younger than 70; $p<0.01$) (Figure 10). The Hispanic trend line shows greater volatility, due to lower numbers of Hispanic women in the dataset, leading to a higher degree of random noise. Figures 11 and 12 demonstrate differences in receipt of RT after BCS among all women (including those who may have received a subsequent mastectomy), according to structural/organizational characteristics of health care providers. In general, receipt of RT increased over time. Women who received primary surgery at a facility that also provided radiation therapy services were more likely to eventually get radiation therapy, as were women who received

Figure 10: Receipt of radiation therapy (RT) within 1 year, among women who received breast conserving surgery and no subsequent mastectomy – trends by race/ethnicity and age group





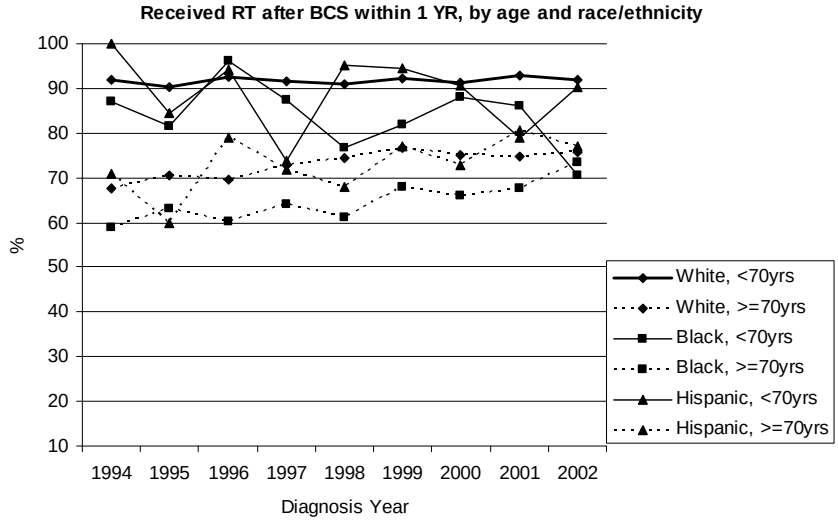


Figure 11: Receipt of radiation therapy (RT) at any time after breast conserving surgery, among all women with stage I-III cancers – trends by selected surgical provider characteristics

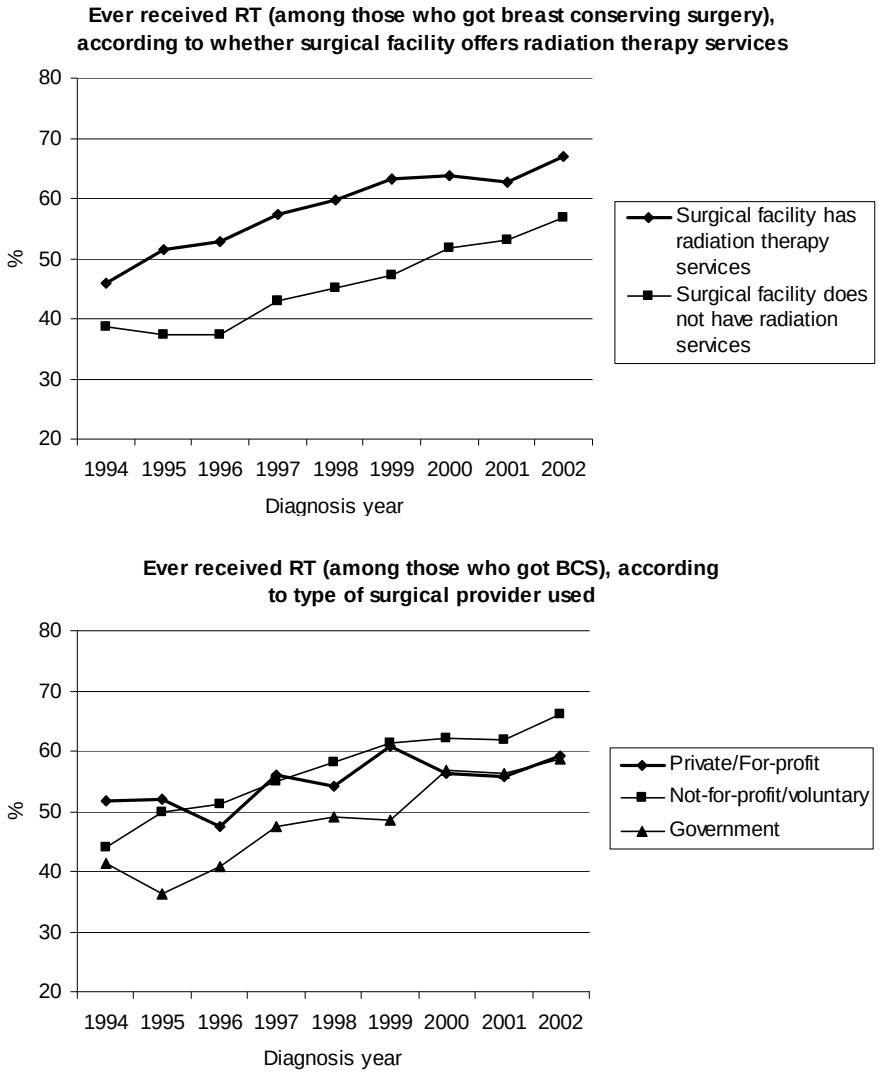
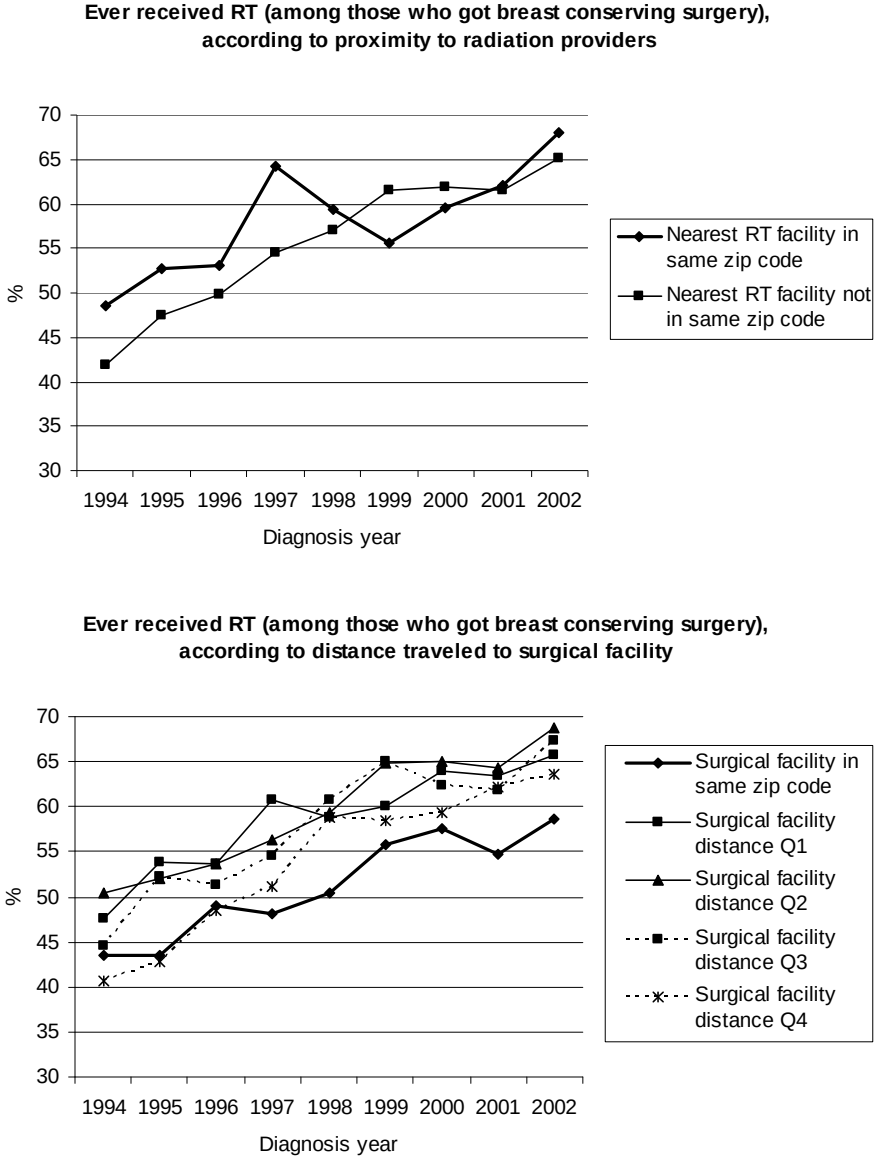


Figure 12: Receipt of radiation therapy (RT) at any time after breast conserving surgery, among all women with state I-III breast cancers - trends by proximity to health services



Notes: Q1: Closest to RT facility – Q4: Furthest from RT facility

primary surgery at a facility that was a member of the NCI-affiliated Radiation Therapy Oncology Group (RTOG) (Figure 11). Women receiving surgery at government facilities, compared to private/for-profit and non-governmental/non-profit facilities, were less likely to eventually receive RT, a trend that largely dissipated over time (Figure 11). Trends in

overall receipt of RT according to geographic access to health care providers, specifically distance to nearest radiation therapy and to surgery, varied over time (Figure 12).

Comparing health services characteristics by racial/ethnic group, it is clear from bivariate analyses that significant differences exist in the types of surgical facilities used by racial/ethnic groups as well as geographical access to surgery and RT providers (Table 9). For example, 11% of black women received surgery at an NCI-designated Comprehensive Cancer Center, compared with 2% of white women and 3% of Hispanic women ($p<0.001$), and black women more often received surgery an American College of Surgeons Oncology Group (ACoSOG)-affiliated facility (35% compared with 24% of white women and 16% of Hispanic women, $p<0.001$), a teaching/academic health center (63% compared with 47% of white women and 37% of Hispanic women, $p<0.001$), or a facility where radiation services were offered (85% compared with 77% of white women and 73% of Hispanic women, $p<0.001$). Hispanic women, on the other hand, were more likely to attend for-profit/private health care facilities (15% compared with 7% of white women and 8% of black women, $p<0.001$) and least likely to receive care from a teaching/academic health center (38% compared with 47% of white women and 63% of white women, $p<0.001$) (Table 9). Among women who received surgery and radiation therapy, white women traveled the furthest on average to surgical facilities and radiation therapy facilities, respectively (Table 9).

Comparison of race/ethnicity-specific plots for timing of initiation of RT after BCS (Figure 13) reveals that black women were significantly less likely than white women to receive guideline-appropriate care and that when appropriate care was received it was initiated later in time. Similar relationships were observed for Hispanic women, although by 4 months follow-up, the differences were no longer statistically significant.

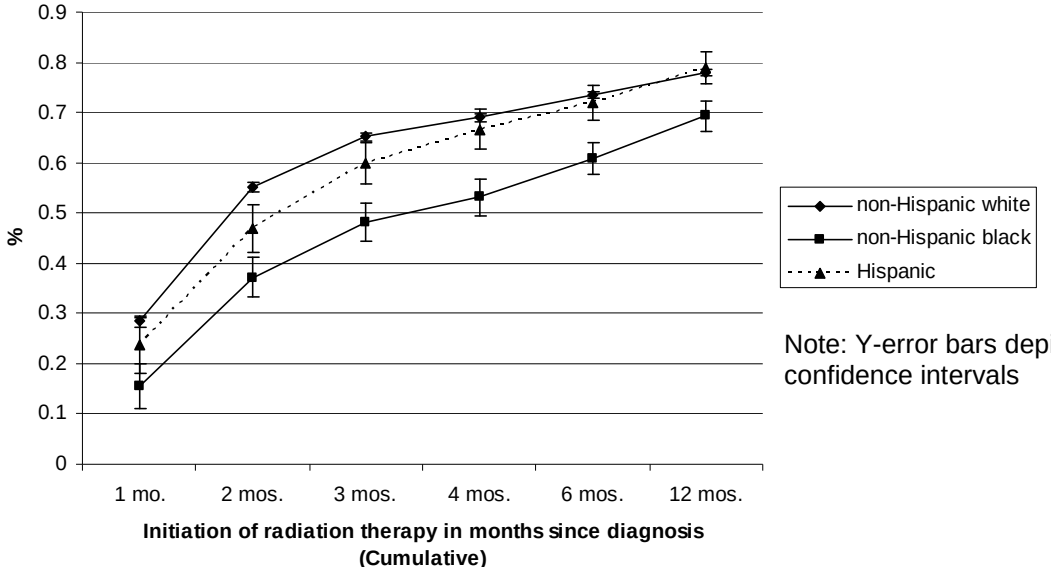
In multivariate models including all women in the sample (i.e., unstratified), black women had significantly lower odds of initiating RT at every time interval examined, and Hispanic women had significantly lower odds of initiation RT up to 2 months post-diagnosis

Table 9: Bivariate comparisons of health system organizational factors by race/ethnicity

Organizational Covariate	% or mean *White*	% or mean *Black*	% or mean *Hispanic*	p-value (from chi-square test or t-test)
Surgical facility characteristics				
Type/ownership				
For-profit/private	6.7%	7.9%	15.3%	<0.001
Non-profit/voluntary	78.9%	79.9%	70.9%	<0.001
Government Bed size	14.4%	12.2%	13.9%	0.019
NCI Comprehensive Cancer Center	2.4%	10.7%	3.1%	<0.001
ACoSOG-affiliated	23.8%	34.8%	16.2%	<0.001
RTOG-affiliated	26.6%	28.8%	22.2%	<0.001
Teaching/academic facility	47.1%	63.3%	37.6%	<0.001
Rural location	13.2%	3.2%	9.6%	<0.001
On-site RT services offered	77.1%	84.6%	73.1%	<0.001
Number of beds	358.4	486.2	300.3	<0.001~ <0.001#
Relational factors/access to care				
Nearest radiation facility (miles)	2.81	1.84	2.80	<0.001~ 0.969#
Nearest radiation facility is located in same zip code as patient residence	21.1%	22.7%	17.9%	0.003
Facility where patient received primary surgery is located in same zip code as patient residence	17.3%	13.4%	17.5%	<0.001
Average distance traveled for primary surgery (miles)	14.9	10.5	12.9	0.001~ 0.249#
Average distance traveled to radiation facility, among those who received RT (first incidence of use) (miles)	17.3	12.3	15.3	0.041~ 0.490#

Notes: ACoSOG: American College of Surgeons Oncology Group; NCI: National Cancer Institute; RT: radiation therapy; RTOG: Radiation Therapy Oncology Group member; ~ indicates two-sample t-tests between white and black groups; # indicates two-sample t-tests between white and Hispanic groups

Figure 13: Timing of initiation of RT among women who received BCS, by race/ethnic group (excluding women who received subsequent mastectomy during each time interval of interest)



Note: Y-error bars depict 95% confidence intervals

Table 10: Multivariate logit regressions for breast cancer patients (unstratified)

Variables	Odds Ratios for receipt of radiation therapy after BCS, all ages (robust standard errors used)						
	@ 1mo.	*@ 2 mos.*	*@ 3 mos.*	*@ 4 mos.*	*@ 6 mos.*	*@ 1 yr.*	*Ever*
Crude ORs for the effect of race/ethnicity							
Non-Hispanic white				*(reference)*			
Non-Hispanic black	0.44**	0.48**	0.50**	0.52**	0.57**	0.64**	0.78**
Hispanic	0.78**	0.72**	0.79**	0.89	0.94	1.10	1.00
Fully adjusted ORs							
Non-Hispanic white				*(reference)*			
Non-Hispanic black	0.54**	0.61**	0.59**	0.62**	0.67**	0.75**	0.93
Hispanic	0.87	0.79*	0.85	0.99	0.99	1.21	1.08
Structural/organizational variables							
Surgical facility characteristics (Non-profit is reference)							
Private/for-profit	1.39**	1.33**	1.24**	1.20*	1.23*	1.19+	1.10+
Governmental	0.94	0.89*	0.84**	0.85**	0.86*	0.86*	0.90**
Teaching facility	1.03	0.99	1.01	1.03	1.04	1.05	0.98
On site radiation	1.45**	1.37**	1.32**	1.34**	1.34**	1.34**	1.28**
Fewer beds (<median)	1.09*	1.09*	1.15**	1.19**	1.18**	1.16**	0.98
NCI Comprehensive Cancer Center	0.79*	0.68**	0.84+	0.98	1.06	0.96	1.15+
ACoSOG-affiliated	1.03	1.08+	1.02	1	1.01	1.08	1.11**
RTOG member	1.05	1.05	1.06	1.07	1.08	1.10+	1.20**
Distance traveled to surgery (in quartiles; same zip code/zero distance is reference)							
Surgery distance Q1	1.11+	1.06	1.09	1.06	1.08	1.1	1.09*
Surgery distance Q2	1.08	1.02	1.07	1.08	1.1	1.09	1.10*
Surgery distance Q3	0.96	0.97	1	1.01	1.06	1.01	1.02
Surgery distance Q4	0.97	0.89+	0.88+	0.9	0.88+	0.9	1.01
Distance to nearest radiation facility provider (in quartiles; same zip code/zero distance is reference)							
Radiation provider Q1	1.02	1	0.9	0.9	0.88+	0.84*	0.91*
Radiation provider Q2	1.06	1.01	0.91	0.91	0.91	0.84*	0.92+
Radiation provider Q3	0.95	0.93	0.85*	0.86*	0.82**	0.74**	0.87**
Radiation provider Q4	1.22**	1.1	0.95	0.92	0.9	0.83*	0.81**
Clinical and patient characteristics							
NCI Combined Index Co-morbidity score (Score = 0 is reference)							
Score=.01to1	0.92*	0.85**	0.88**	0.88**	0.92+	0.89*	0.84**
Score=1.01to2	0.72**	0.70**	0.64**	0.61**	0.61**	0.57**	0.67**
Score : Greater than 2	0.75+	0.60**	0.53**	0.49**	0.46**	0.41**	0.51**
Age group (70-74 years is reference)							
70-74 years	1.11*	1.13**	1.09	0.99	1.02	0.86+	0.92*
75-79 years	1	0.99	0.87*	0.75**	0.73**	0.54**	0.76**
80-84 years	0.87*	0.77**	0.56**	0.45**	0.41**	0.29**	0.50**
85 years and older	0.40**	0.28**	0.19**	0.14**	0.13**	0.09**	0.20**
Surgery in same month as diagnosis	4.50**	2.22**	1.46**	1.24**	1.11*	0.95	0.53**
Received chemo during time interval of interest	0.43**	0.14**	0.08**	0.09**	0.23**	1.91**	1.54**
ER-status (negative, borderline, or unknown is reference							
ER-positive	1.23**	1.35**	1.35**	1.36**	1.34**	1.41**	1.24**
PR-status (negative, borderline, or unknown is reference)							
PR-positive	1.08+	1.10*	1.12*	1.12*	1.13*	1.11+	1.06
Stage at diagnosis (stage 1 is reference)							
Stage2	0.78**	0.74**	0.66**	0.64**	0.66**	0.67**	0.62**
Stage3	0.59**	0.48**	0.48**	0.52**	0.52**	0.42**	0.99
Lymph node status (negative is reference)							

Variables	Odds Ratios for receipt of radiation therapy after BCS, all ages (robust standard errors used)						
	@ 1mo.	*@ 2 mos.*	*@ 3 mos.*	*@ 4 mos.*	*@ 6 mos.*	*@ 1 yr.*	*Ever*
Node-positive	0.65**	0.62**	0.68**	0.71**	0.68**	1.06	1.23**
Node status missing	0.78**	0.34**	0.22**	0.18**	0.17**	0.17**	0.91**
Grade (well differentiated is reference)							
Moderate	0.99	1.06	1.07	1.13*	1.16**	1.22**	0.97
Poor	0.90*	0.95	1.03	1.13*	1.20**	1.29**	0.98
Anaplastic	0.9	0.89	0.81	0.91	0.94	0.87	0.87
Grade missing	0.83**	0.85**	0.86*	0.87*	0.92	0.97	0.75**
Medicaid enrolled	0.77**	0.71**	0.66**	0.64**	0.63**	0.58**	0.66**
Married	1.20**	1.21**	1.22**	1.19**	1.22**	1.32**	1.13**
Metropolitan residence (metro is reference)							
Urban residence	1	1.02	1	0.9	0.89	0.86+	0.86**
Rural residence	1.01	1.04	0.81	0.68*	0.67*	0.73+	0.73**
Year of diagnosis (1994 is reference)							
1995	1.02	1.05	1.09	1.07	1.12	1.11	1.18**
1996	0.99	0.96	1.05	1.09	1.13	1.11	1.21**
1997	0.89	0.96	1.1	1.13	1.22+	1.27*	1.49**
1998	0.83*	0.9	1.01	1.05	1.27*	1.27*	1.62**
1999	0.69**	0.76**	0.95	1.05	1.28*	1.52**	1.90**
2000	0.60**	0.68**	0.88	0.95	1.12	1.46**	2.08**
2001	0.49**	0.59**	0.78**	0.88	1.08	1.27*	1.97**
2002	0.48**	0.59**	0.75**	0.81*	1.01	1.14	2.18**
Neighborhood characteristics (by zip code)							
Hi%Black (>median)	1.12**	1.04	1.03	1	1.02	1.04	1.04
Hi%Hisp (>median)	1.16**	1.08+	1.04	1.05	1.04	0.97	1.17**
Hi%White (>median)	1.01	1.02	1.02	1.04	1.05	1.06	0.94+
More high school grads (>median)	1.28**	1.18**	1.09+	1.09+	1.01	0.99	1.10**
Lowest quartile of neighborhood median income (zpmedQ1 is reference)							
zpmedQ2	1.06	0.99	0.95	0.96	0.96	1	1.02
zpmedQ3	0.90+	0.92	1	1.02	1.04	1.06	1.21**
zpmedQ4	0.80**	0.84**	0.95	0.95	0.99	1.05	1.28**
Observations	23020	21411	21078	20933	20814	20699	32691

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; each logit model excludes women who received mastectomy subsequent to breast conserving surgery during the time interval of interest, with the exception of "Ever" models, which examine receipt of radiation therapy at any point during follow-up of the patient; ACoSOG: American College of Surgeons Oncology Group; BCS: breast conserving surgery; ER: estrogen receptor; NCI: National Cancer Institute; PR: progesterone receptor; RTOG: Radiation Therapy Oncology Group

(Table 10). Comparison of the multivariate odds ratios with the crude/unadjusted odds ratios in this table reveals that racial/ethnic disparities in receipt of RT at each time point were somewhat attenuated with inclusion of structural/organizational and other covariates.

In models stratified by age 70 (reflecting the lack of clinical trial evidence and quality metrics for women 70 years and older), some important differences by age group emerge

(Tables 11 and 12). In the younger group (65-69 years), the adjusted odds ratio for black women receiving RT within 1 year was statistically non-significant (Table 11), whereas the adjusted odds ratio for black women receiving RT within 1 year was 0.75 in the unstratified model ($p<0.01$, Table 10) and 0.77 in the model limited to women 70 years and older ($p<0.05$, Table 12). With respect to the odds ratios for the effect of Hispanic ethnicity, none were significant in multivariate models of women 70 years and older (Table 12), whereas in multivariate models of women ages 65-69 years old, Hispanic ethnicity corresponded to lower odds of initiation of RT at each time interval up to 6 months (Table 11).

In general, omission of structural/organizational variables, especially surgical facility characteristics, yielded changes in effect size and significance of other variables, notably race/ethnicity variables. Younger women who attended a surgical facility with on-site radiation services had 1.23 greater odds of ever receiving RT ($p<0.01$) (Table 11), and women who received surgery at a smaller facility with fewer beds were about 1.3 times more likely to receive RT 3, and 4 months ($p<0.05$), controlling for all other factors (Table 11). Among younger women, distance traveled to surgery and distance to the nearest radiation therapy provider played little role in predicting timing of RT, with the exception of the model examining whether women *ever* received RT, in which case, increasing distance to the nearest RT provider was associated with significantly lower odds of receiving RT (as compared to the nearest RT facility being located in the same zip code as patient residence). In women 70 years and older, black/white disparities persisted despite inclusion of structural/organizational variables and covariates (Table 12). Importantly, structural and organizational variables and distance to care were much more informative in this older age group. Specifically, attending a private/for-profit surgical facility was associated with higher odds of initiation of RT at each time interval (ORs ranging from 1.13 to 1.39), attending a surgical facility with on-site radiation was associated with higher odds of initiation of RT at each time interval (ORs ranging from 1.30 to 1.49), and attending a smaller surgical facility

with fewer beds was associated with higher odds of initiating RT at each time interval (ORs ranging from 1.08 to 1.19). With respect to distance, increasing distance to nearest radiation therapy provider (relative to a RT provider being located in the same zip code as patient residence) was associated with lower odds of initiating RT by one year (ORs for RT provider distance quartiles: 0.86, 0.82, 0.72, 0.84) (Table 12); this trend was largely true across models, although not always statistically significant.

Table 11: Logit regressions for breast cancer patients <70 years old

Variables	**Odds Ratios for receipt of radiation therapy after BCS, among women < 70 years old (robust standard errors used)**						
	@ 1mo.	*@ 2 mos.*	*@ 3 mos.*	*@ 4 mos.*	*@ 6 mos.*	*@ 1 yr.*	*Ever*
Crude ORs for the effect of race/ethnicity							
Non-Hispanic white							
Non-Hispanic black	0.41**	0.46**	0.42**	0.42**	0.42**	0.37**	0.66**
Hispanic	0.59**	0.52**	0.51**	0.58**	0.50**	0.54*	0.80+
Fully adjusted ORs							
Non-Hispanic white				*(reference)*			
Non-Hispanic black	0.56**	0.70*	0.50**	0.49**	0.60**	0.65+	0.86
Hispanic	0.68+	0.58**	0.52**	0.66+	0.59*	1.02	0.98
Structural/organizational variables							
Surgical facility characteristics (non-profit is reference)							
Private/for-profit	1.40*	1.29	1.11	0.98	0.92	1.02	1.02
Governmental	0.89	0.77*	0.86	0.89	0.87	0.91	0.89
Teaching facility	1.04	0.88	0.97	1.00	1.01	1.12	0.99
On site radiation	1.32**	1.48**	1.27+	1.28+	1.33*	1.19	1.23**
Fewer beds (<median)	1.13	1.18+	1.26*	1.27*	1.16	1.26	0.97
NCI Comprehensive Cancer Center	0.82	0.68*	0.92	1.24	1.42	1.21	1.07
ACoSOG-affiliated	1.07	1.16	1.13	1.12	0.98	1.34	1.07
RTOG member	1.07	1.09	0.99	0.96	0.97	1.18	1.10
Distance traveled to surgery (in quartiles; same zip code/zero distance is reference)							
Surgery Q1	1.02	0.85	0.90	0.85	0.87	0.84	1.10
Surgery Q2	0.90	0.88	0.96	0.98	1.04	1.00	1.16
Surgery Q3	0.91	0.82	1.02	1.04	1.18	1.17	1.17
Surgery Q4	0.90	0.74*	0.81	0.82	0.86	0.83	1.09
Distance to nearest radiation facility provider (in quartiles; same zip code/zero distance is reference)							
RT provider Q1	1.04	0.88	0.78	0.82	0.79	0.71	0.70**
RT provider Q2	1.14	0.97	0.85	0.94	1.04	0.94	0.80*
RT provider Q3	1.07	1.03	0.93	0.97	0.93	0.88	0.74**
RT provider Q4	1.23	0.98	0.82	0.88	0.83	0.75	0.67**
Clinical and patient characteristics							
NCI Combined Index Co-morbidity score (Score = 0 is reference)							
Score=.01to1	0.90	0.89	0.96	0.87	1.01	1.00	0.88*
Score=1.01to2	0.93	0.82	0.65+	0.48**	0.61+	0.60+	0.66**
Score>2.0	0.51	0.16**	0.37	0.30+	0.25**	0.28**	0.47*
Surgery in same month as diagnosis	4.52**	2.71**	1.85**	1.62**	1.33**	0.82	0.47**

Variables	Odds Ratios for receipt of radiation therapy after BCS, among women < 70 years old (robust standard errors used)						
	@ 1mo.	*@ 2 mos.*	*@ 3 mos.*	*@ 4 mos.*	*@ 6 mos.*	*@ 1 yr.*	*Ever*
Received chemo during time interval	0.40**	0.12**	0.07**	0.08**	0.21**	3.29**	1.36**
ER-status (negative, borderline, or unknown is reference)							
ER-positive	1.40**	1.56**	1.42**	1.33*	1.36*	1.50*	1.17+
PR-status (negative, borderline, or unknown is reference)							
PR-positive	0.97	1.05	1.10	1.07	1.04	1.13	1.13
Stage at diagnosis (stage 1 is reference)							
Stage2	0.63**	0.59**	0.55**	0.49**	0.53**	0.39**	0.58**
Stage3	0.65	0.49*	0.62	0.59+	0.45*	0.30*	1.23
Lymph node status (negative is reference							
Node-positive	0.53**	0.50**	0.60**	0.67**	0.56**	1.28	1.20*
Node status missing	0.86	0.43**	0.27**	0.23**	0.19**	0.19**	1.10
Grade (well-differentiated is reference)							
Moderate	0.93	0.93	0.92	1.08	0.98	1.16	0.82**
Poor	0.83+	0.77*	0.78+	1.00	0.97	1.05	0.82*
Anaplastic	0.72	0.69	0.49*	0.54	0.54	0.37*	0.56**
Grade missing	0.79+	0.69**	0.78	0.73+	0.71+	0.95	0.65**
Medicaid enrolled	0.72**	0.79*	0.67**	0.61**	0.57**	0.46**	0.77**
Married	1.13+	1.32**	1.28**	1.12	1.10	1.23	1.09
Metropolitan residence (metro is reference)							
Urban residence	1.26+	1.18	1.10	0.82	0.88	0.80	0.92
Rural residence	1.40	1.47	0.90	0.79	1.30	0.76	0.88
Year of diagnosis (1994 is reference)							
1995	0.86	0.98	0.76	0.71	0.79	0.64	0.99
1996	1.04	1.03	0.88	1.04	1.00	0.82	1.07
1997	0.65*	0.79	0.62+	0.67	0.77	0.63	1.46**
1998	0.64**	0.60**	0.49**	0.54*	0.78	0.55+	1.38*
1999	0.50**	0.48**	0.51*	0.54*	0.69	0.64	1.67**
2000	0.49**	0.46**	0.43**	0.45**	0.56*	0.76	2.17**
2001	0.37**	0.36**	0.37**	0.46**	0.58*	0.77	2.27**
2002	0.39**	0.40**	0.33**	0.41**	0.61+	0.74	2.28**
Neighborhood characteristics (by zip code)							
Hi%Black (>median)	1.05	1.03	0.95	0.93	0.87	0.85	1.01
Hi%Hisp (>median)	1.06	1.02	0.93	0.99	1.05	0.86	1.13+
Hi%White (>median)	0.93	1.07	1.03	1.12	1.18	1.36	0.94
More high school grads (>median)	1.28**	1.19+	0.98	0.98	0.89	0.90	1.25**
Lowest quartile of neighborhood median income (zpmedQ1 is reference)							
zpmedQ2	1.20	1.16	0.99	0.96	0.98	0.97	1.02
zpmedQ3	1.02	1.15	1.12	1.10	1.18	1.05	1.34**
zpmedQ4	0.86	0.99	0.95	0.91	0.99	1.07	1.30*
Observations	4811	4476	4406	4366	4335	4304	6822

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; each logit model excludes women who received mastectomy subsequent to breast conserving surgery during the time interval of interest, with the exception of "Ever" models, which examine receipt of radiation therapy at any point during follow-up of the patient; ACoSOG: American College of Surgeons Oncology Group; BCS: breast conserving surgery; ER: estrogen receptor; NCI: National Cancer Institute; PR: progesterone receptor; RT: radiation therapy; RTOG: Radiation Therapy Oncology Group

Table 12: Logit regressions for breast cancer patients 70 years and older

Variables	Odds Ratios for receipt of radiation therapy after BCS, among women >/= 70 years old (robust standard errors used)						
	@ 1mo.	*@ 2 mos.*	*@ 3 mos.*	*@ 4 mos.*	*@ 6 mos.*	*@ 1 yr.*	*Ever*
Crude ORs for the effect of race/ethnicity							
Non-Hispanic white				*(reference)*			
Non-Hispanic black	0.45**	0.49**	0.52**	0.54**	0.59**	0.66**	0.79**
Hispanic	0.85+	0.80*	0.90	0.99	1.06	1.13	1.03
Fully adjusted ORs							
Non-Hispanic white				*(reference)*			
Non-Hispanic black	0.53**	0.58**	0.61**	0.65**	0.68**	0.77*	0.95
Hispanic	0.96	0.88	1.00	1.13	1.17	1.29+	1.14
Structural/organizational variables							
Surgical facility characteristics (Non-profit is reference)							
Private/for-profit	1.39**	1.33**	1.26**	1.24*	1.30**	1.22+	1.13*
Governmental	0.95	0.92	0.84**	0.84**	0.87*	0.85*	0.91*
Teaching facility	1.02	1.01	1.01	1.04	1.03	1.04	0.97
On site radiation	1.49**	1.35**	1.34**	1.37**	1.36**	1.36**	1.30**
Fewer beds (<median)	1.08+	1.08+	1.14**	1.18**	1.19**	1.16**	0.98
NCI Comprehensive Cancer Center	0.79*	0.68**	0.83	0.93	0.99	0.92	1.18+
ACoSOG-affiliated	1.02	1.06	1.00	0.97	1.01	1.05	1.12**
RTOG member	1.04	1.05	1.07	1.09+	1.10+	1.10	1.23**
Distance traveled to surgery (in quartiles; same zip code/zero distance is reference)							
Surgery Q1	1.13*	1.11+	1.13+	1.10	1.12+	1.13	1.08+
Surgery Q2	1.13+	1.06	1.10	1.10	1.12	1.10	1.09+
Surgery Q3	0.96	1.00	1.00	1.01	1.04	0.99	0.99
Surgery Q4	0.99	0.94	0.91	0.92	0.89	0.90	0.99
Distance to nearest radiation facility provider (in quartiles; same zip code/zero distance is reference)							
RT provider Q1	1.00	1.02	0.91	0.91	0.89	0.86+	0.96
RT provider Q2	1.04	1.01	0.91	0.89	0.88	0.82*	0.95
RT provider Q3	0.91	0.90+	0.82**	0.83*	0.79**	0.72**	0.90*
RT provider Q4	1.21**	1.12	0.97	0.92	0.91	0.84+	0.85**
Clinical and patient characteristics							
NCI Combined Index Co-morbidity score (Score = 0 is reference)							
Score=.01to1	0.92+	0.85**	0.86**	0.89*	0.90*	0.89*	0.83**
Score=1.01to2	0.69**	0.68**	0.64**	0.62**	0.61**	0.57**	0.66**
Score>2.0	0.78	0.66**	0.55**	0.51**	0.49**	0.43**	0.51**
Age group (70-74 years is reference)							
75-79 years	0.91*	0.89**	0.81**	0.78**	0.73**	0.63**	0.83**
80-84 years	0.79**	0.70**	0.53**	0.48**	0.42**	0.33**	0.55**
85 years and older	0.36**	0.26**	0.18**	0.15**	0.13**	0.11**	0.22**
Surgery in same month as diagnosis	4.50**	2.12**	1.39**	1.18**	1.06	0.96	0.54**
Received chemo during time interval	0.47**	0.16**	0.10**	0.11**	0.27**	1.80**	1.64**
ER-status (negative, borderline, or unknown is reference							
ER-positive	1.19**	1.31**	1.34**	1.37**	1.35**	1.40**	1.25**
PR-status (negative, borderline, or unknown is reference)							
PR-positive	1.12*	1.11*	1.13*	1.14*	1.16*	1.12+	1.04
Stage at diagnosis (stage 1 is reference)							
Stage2	0.82**	0.78**	0.69**	0.67**	0.69**	0.71**	0.63**
Stage3	0.57**	0.46**	0.43**	0.48**	0.50**	0.43**	0.94
Lymph node status (negative is reference)							

Variables	Odds Ratios for receipt of radiation therapy after BCS, among women >/= 70 years old (robust standard errors used)						
	@ 1mo.	*@ 2 mos.*	*@ 3 mos.*	*@ 4 mos.*	*@ 6 mos.*	*@ 1 yr.*	*Ever*
Node-positive	0.71**	0.66**	0.70**	0.74**	0.74**	1.03	1.24**
Node status missing	0.78**	0.34**	0.22**	0.18**	0.17**	0.16**	0.90**
Grade (well differentiated is reference)							
Moderate	1.01	1.09+	1.11*	1.13*	1.19**	1.23**	1.01
Poor	0.92	1.00	1.10	1.16*	1.25**	1.32**	1.02
Anaplastic	0.96	0.94	0.91	1.02	1.09	1.05	0.98
Grade missing	0.84**	0.88+	0.87*	0.89	0.95	0.97	0.77**
Medicaid enrolled	0.78**	0.69**	0.66**	0.65**	0.63**	0.60**	0.64**
Married	1.21**	1.18**	1.20**	1.19**	1.24**	1.33**	1.15**
Metropolitan residence (metro is reference)							
Urban residence	0.93	0.98	0.97	0.92	0.89	0.85+	0.84**
Rural residence	0.89	0.93	0.77	0.65*	0.58**	0.71	0.69**
Year of diagnosis (1994 is reference)							
1995	1.08	1.09	1.17	1.16	1.20+	1.18	1.24**
1996	0.99	0.97	1.11	1.13	1.17	1.17	1.26**
1997	0.98	1.03	1.24*	1.26*	1.33*	1.39**	1.51**
1998	0.89	1.00	1.17	1.19+	1.38**	1.40**	1.70**
1999	0.76**	0.86	1.09	1.20	1.44**	1.67**	1.98**
2000	0.64**	0.75**	1.02	1.10	1.28*	1.58**	2.07**
2001	0.53**	0.67**	0.91	1.00	1.21+	1.35**	1.94**
2002	0.52**	0.66**	0.89	0.93	1.11	1.20	2.18**
Neighborhood characteristics (by zip code)							
Hi%Black (>median)	1.14**	1.05	1.05	1.01	1.06	1.07	1.05
Hi%Hisp (>median)	1.19**	1.09+	1.06	1.06	1.03	0.97	1.18**
Hi%White (>median)	1.03	1.00	1.01	1.02	1.02	1.03	0.94
More high school grads (>median)	1.28**	1.19**	1.12*	1.13*	1.04	1.01	1.07+
Lowest quartile of neighborhood median income (zpmedQ1 is reference)							
zpmedQ2	1.03	0.95	0.95	0.96	0.96	1.00	1.02
zpmedQ3	0.87*	0.86*	0.97	0.99	1.02	1.06	1.18**
zpmedQ4	0.79**	0.80**	0.95	0.96	0.99	1.05	1.27**
Observations	18209	16935	16672	16567	16479	16395	25869

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; each logit model excludes women who received mastectomy subsequent to breast conserving surgery during the time interval of interest, with the exception of "Ever" models, which examine receipt of radiation therapy at any point during follow-up of the patient; ACoSOG: American College of Surgeons Oncology Group; BCS: breast conserving surgery; ER: estrogen receptor; NCI: National Cancer Institute; PR: progesterone receptor; RT: radiation therapy RTOG: Radiation Therapy Oncology Group

Other covariates behaved in expected ways; for example, in younger women (Table 11), greater co-morbidity burden was associated with lower odds of RT, receiving chemotherapy during the time interval of interest was associated with lower odds of concurrent RT, married women had higher odds of receiving RT, low income status was associated with lower odds of RT, and living in a zip code with a more highly educated

population was associated with higher odds of initiating RT earlier. Notably, women younger than 70 who received surgery in the same month as diagnosis had higher odds of rapid progression to radiation therapy, and women with more advanced stage disease, ER-positive tumors, and/or node-positive tumors were less likely to initiate RT within each time period, presumably due to receipt of chemotherapy in these intervals. Interestingly, the odds of receiving guideline-appropriate RT after BCS in the absence of subsequent mastectomy at each time interval decreased slightly with increasing year of diagnosis starting in 1997, whereas overall receipt of RT in the full sample (indicated by the "Ever" model, column 7) increased over time. Co-morbidities in the older sub-population (Table 12) played a larger role in determining receipt of RT; the odds of initiating RT at each time interval decreased significantly with each increasing level of co-morbidity burden. Notably, the effect of rural residence was more potent in this older population, decreasing the likelihood of receiving RT in general, although the effect did not always attain statistical significance. Behavior of other covariates was similar to that in models of younger women.

Discussion

This study examined 38,000 women with breast cancer in SEER-Medicare data to understand health care structural and organizational characteristics and their association with racial/ethnic differences in receipt of high quality cancer treatment. Previous, mostly cross-sectional, studies on age- and race/ethnicity-related disparities in breast cancer provide interesting descriptive data, but are limited in their ability to provide insights into how the health care system or health policies may improve quality of care for breast cancer patients. By focusing only on Medicare beneficiaries in the current study, access to insurance coverage was effectively controlled. Accordingly, we were able to explore whether characteristics of the health system itself potentially could be used to narrow differences in quality of care, and since all patients in our study had insurance provided by

the same payer, the role of this important factor in determining treatment was limited. In this study, structural/organizational characteristics of health services, specifically surgical facility type/ownership, size, presence of on-site radiation, and distance to RT providers, were associated with variation in receipt of RT and timing of initiation of RT. To some extent, these factors also played a role in racial/ethnic variation in treatment, but they did not fully account for racial/ethnic disparities in receipt of high quality care. In this study, disparities in treatment by race/ethnicity, especially among black women, persisted even when controlling for biological features of the tumor, socioeconomic status, co-morbidity, marital status, rural/urban residence, year of diagnosis, and insurance status, in addition to structural/organizational health services characteristics. As well, receipt of RT varied significantly by age group, and distance to care and surgical facility characteristics played a greater role in determining overall receipt of RT and timing of initiation of RT among women ages 70 and older. Disparities between Hispanic women and non-Hispanic white women disappeared with older age, whereas disparities in treatment between non-Hispanic black and non-Hispanic white women were apparent in both older and younger age groups.

With respect to the effects of structural and organizational variables, it is clear from these data that several characteristics of surgical providers, including type/ownership, presence of on-site radiation services, and size of the surgical facility, are informative in predicting receipt and timing of initiation of RT after BCS. ACoSOG affiliation, NCI Comprehensive Cancer designation, and teaching status of the surgical facility, on the other hand, were not as informative, in contrast to studies that have found institutional affiliations and teaching status to be predictive of treatment quality and health outcomes in the absence of other structural and organizational variables (Jerome-D'Emila and Begun, 2005; Laliberte et al., 2005; Onega et al., 2009; Chaudry et al., 2001). Structural/organizational factors did not appear to modify the effects of race/ethnicity, a finding that may be explained by SEER sampling. Specifically, although the SEER-Medicare data were designed to reflect diverse

geographic communities and racial/ethnic groups (Warren et al., 2002c) they do not necessarily reflect racial/ethnic diversity across different types of geographic communities. For example, the majority of black women in the SEER-Medicare dataset live in metropolitan areas (e.g., Detroit and Atlanta), whereas the majority of Hispanic women in SEER-Medicare live in certain states (e.g., New Mexico and California). As such, the bivariate findings by race/ethnicity and heath system characteristics in Table 9 (e.g., black women are more likely to receive surgery at a teaching/academic health center and/or a NCI Comprehensive Cancer Center) may be explained by the fact that black women in SEER-Medicare are more likely to live in urban areas, where larger hospitals exist. It is therefore difficult to extend findings from SEER-Medicare to the experiences of rural-dwelling black and Hispanic women.

To a lesser extent, increasing distance to radiation providers was associated with lower overall receipt of RT and lower odds of initiation of RT within 1 year, although this effect was not consistently statistically significant. This lack of consistent statistical significance may be due to the fact that the majority of people in this study lived within 3 miles of a radiation therapy provider (mean: 2.75; median: 0.16), again perhaps reflective of the more urban sampling scheme. Straight-line distance to care using zip-to-zip centroids, although not the absolute best proxy for geographic access, has been shown to be a highly correlated with travel time and by extension transportation burden (Phibbs and Luft, 1995), and in this study was found to be more important among older women 70 years and older (Table 12). Transportation burden and geographic access to care have been shown to be problematic for elderly women seeking health care in other studies (Punglia et al., 2006a; Mobley et al., 2006; Mobley et al., 2009). On the other hand, the trend line depicting receipt of RT over time by distance traveled to surgery (Figure 12) suggested that women who received surgery within their own zip codes fared less well, a finding that may be logical if

women bypass local providers to seek a surgeon at a higher quality health facility, but this effect generally was shown to be non-statistically significant in multivariate models.

Our overall finding that receipt of RT remains sub-optimal is in line with much of the literature in this area (Smith et al., 2010; Hershman et al., 2008; Haggstrom et al., 2005; Gross et al., 2008; Edwards et al., 2005). Indeed, consistent with our findings, Freedman and colleagues (2009) have shown that although mastectomy rates have decreased over time, presumably in favor of BCS, overall definitive therapy (receipt of BCS plus RT or mastectomy) has decreased as well. We observed that the time horizon of follow-up and consideration of subsequent mastectomy are important parameters in examination of treatment quality. Many women delay initiation of RT for clinically meaningful reasons, such as receiving another anti-cancer regimen like adjuvant chemotherapy; as well, many women who received BCS initially subsequently get mastectomy due to positive margins, recurrence, or other clinically valid reasons, thereby obviating the necessity of RT. Assessment of adherence to RT guidelines for breast cancer may be underestimated if timing of receipt of RT and the possibility of subsequent mastectomy after BCS are not taken into account. It is largely unclear whether previous analyses have considered this possibility, with the exception of one study using North Carolina cancer registry and Medicare data, which found significant changes in results related to adherence to radiation therapy guidelines depending on the time period examined and whether follow-up mastectomy was taken into account (Weiner et. al., 2009).

One of the strengths of our study is the examination of initiation of RT at different time intervals. The time interval of one year specified in the ASCO/NCCN quality metric may be somewhat lenient, in light of studies that have shown improved outcomes with earlier initiation of RT (Gold et al., 2008; Hershman et al., 2006b; Hebert-Croteau et al., 2004). The ASCO/NCCN panels relaxed the timing component of the denominator to allow for administration and sequencing of multiple anticancer treatments. However, given the

controversy over the optimal timing of initiation of RT, and considering that we have shown significant racial/ethnic differences in timing of initiation of RT, it may be that earlier initiation of RT is particularly important for vulnerable breast cancer patients (e.g., black women with hormone receptor negative, advanced stage disease).

The relationships between age, adjuvant therapy, and clinical guideline development are complex and somewhat controversial. An important study published in 2004 in the *New England Journal of Medicine* showed that among women 70 years and older with stage I, estrogen-receptor positive breast cancer, RT could be safely omitted after lumpectomy when women were receiving tamoxifen (Hughes et al., 2004). The only significant difference between groups in which women received RT plus tamoxifen or tamoxifen only was an increased risk of local or regional recurrence at 5 years in the group that did not receive RT; no differences were found in survival, distant metastases, or rates of mastectomy for local recurrence (Hughes et al., 2004). Although these findings were published after the time interval examined in our study and as such, did not affect clinical guidelines we examined, preliminary results from this trial were likely presented prior to publication, and providers who knew about or participated in the much-anticipated trial may have changed their approaches to treating older women with early, ER-positive breast cancer. It is difficult to determine what the impact of this study might have been, how far-reaching its influence was, and whether responses to this study, if they existed at the time, varied by institutions and racial/ethnic groups across institutions; nevertheless, it is important to consider that practice patterns may have begun to change in light of new evidence seemingly in conflict with clinical guidelines.

This study is accompanied by several limitations in addition to the generalizability issues associated with use of the SEER-Medicare dataset highlighted previously. Namely, these data do not contain information about hormonal therapy, an important anti-cancer therapeutic option which may affect treatment planning (Warren et al., 2002c). These data

also are limited to patients ages 65 and older who are not enrolled in Medicare managed care plans; we would expect younger women and those enrolled in managed care plans to be healthier, and thus, treatment experiences may be different. The risks of possible misclassification of claims and/or errors in reporting and billing are certainly existent, although such misclassification if it exists should be random and therefore should not affect study findings. Another issue related to measurement is the lack of month/day/year date of diagnosis; SEER provides only month and year of diagnosis, leading to potential imprecision in date classifications. For example a woman diagnosed on the last day of the month and receiving first primary surgery on the first day of the next month is classified as having received surgery one month after diagnosis. Possible omitted variables include more precise measures of individual socioeconomic status, and supplemental private health insurance. We have tried to account for these factors in the absence of good data about individual wealth, income, education, and unmeasured access to additional health care financing by including measures for State-Buy-In (a proxy for low income status and Medicaid dual enrollment) and neighborhood (zip-code level) education, income, and racial/ethnic composition as a measure of local social support (Mobley et al., 2009). Other possible unmeasured factors at work are patient health seeking behavior, trust in the health care system, and provider intent; we cannot determine from these data whether women were referred to radiation oncologists and did not attend appointments or were never referred at all. As an example, in adjusted models of women under the age of 70, the disparity between black and white women in timing of initiation of RT was significant at each time interval up to 6 months and non-significant at 1 year and for overall receipt. One possible explanation for this difference in early initiation is that black women delay initiation of RT because they more often seek second opinions or because health care providers are not initially convinced that an unmarried, older black woman has the social support to successfully complete treatment (on the contrary, many would argue that black women have

very rich social support networks extending beyond that of a married partner). Unfortunately, we cannot measure intentions of or intermediary discussions with health providers, only the outcome of interest – did women receive RT or not? Future studies could employ the use of chart reviews or qualitative interviews to better understand the nuances of the decision making process around treatment.

We have shown that racial/ethnic minority groups and elderly women who received BCS initiated radiation therapy later than other women and that structural and organizational health services factors explained part but not all differences observed in adjuvant treatment. Characteristics of the surgical facility where women receive breast conserving surgery (including presence of on-site radiation services, type/ownership, and size) were informative in predicting timing of subsequent initiation of RT, and for women older than 70 years, distance to radiation providers may present an additional burden to seeking care. In terms of implications of this work, interventions that target facilities performing less well as a group may be warranted. On the other hand, since we have shown that distance to RT providers may influence overall receipt of RT and initiation of RT within 1 year, interventions that offer transportation options for older women may lead to better uptake of RT, among women healthy enough to undergo treatment. Recognizing the importance of such health system level variables in the context of significant sub-population variation in breast cancer treatment quality may help policymakers, clinicians, and other stakeholders better identify women at risk for poor quality care and may inspire more creative inclusion strategies for community-based programs and clinical trial investigations.

CHAPTER 5: EFFECT OF STRUCTURAL/ORGANIZATIONAL CHARACTERISTICS OF HEALTH SERVICES ON RACIAL/ETHNIC AND AGE-RELATED DISPARITIES IN THE TIMELY RECEIPT OF CHEMOTHERAPY IN BREAST CANCER PATIENTS

Abstract

Purpose

To explore whether factors related to the health care system help explain a portion of extant disparities in breast cancer care quality, we retrospectively examined the relationships between race/ethnicity, age, and structural/organizational characteristics of oncology providers in terms of (1) use of adjuvant chemotherapy over time and (2) differences in timing of initiation of adjuvant chemotherapy. The primary outcome of interest was postoperative receipt of adjuvant chemotherapy for stage II and III breast cancers.

Methods

This study was a retrospective analysis of secondary data collected for ongoing surveillance and billing/administrative reasons. Female Medicare beneficiaries ages 65 and older living in Surveillance Epidemiology and End Results (SEER) registry regions were the focus of this study. Women whose first or only cancer diagnosis was primary breast cancer in 1994-2002, with Medicare claims through 2003, who had received surgery (lumpectomy or mastectomy) were included. Women with in situ and metastatic (stage IV) cancers were excluded, as were women receiving neoadjuvant chemotherapy and women with end stage renal disease. This study was limited to non-Hispanic white, non-Hispanic black, and Hispanic patients. Timing of initiation of chemotherapy was measured as a binary variable indicating whether the patient initiated chemotherapy within several time intervals post-diagnosis. Diffusion curves were used to describe trends in receipt of adjuvant

chemotherapy across sub-populations over time, and multivariate logistic regression, stratified by hormone receptor status and age group, was employed to examine the potential role of structural/organizational characteristics of health services, including size, ownership, teaching status, National Cancer Institute (NCI) Cancer Center designation, and American College of Surgeons Oncology Group (ACoSOG) affiliations of the surgical providers, and distance to care, in explaining differences in treatment, controlling for known covariates.

Results

The study included 20,898 women who met inclusion/exclusion criteria, of whom 8% were non-Hispanic black and approximately 4% were Hispanic. In total, 68% of women (14,220) were hormone receptor positive, of whom 98% were estrogen receptor (ER) positive and 79% were progesterone receptor (PR) positive, leaving 6,678 women who were neither ER nor PR positive. Receipt of adjuvant chemotherapy increased significantly from 1994-2002, with approximately 24% of all women diagnosed in 1994 receiving adjuvant chemotherapy compared with 45% of all women diagnosed in 2002. Receipt of adjuvant chemotherapy and timing of initiation differed by age group, hormone receptor status, and to a lesser extent by race/ethnicity. In bivariate analyses, black women were more likely to receive surgery at an NCI-designated Comprehensive Cancer Center ($p<0.001$), an academic or teaching facility ($p<0.001$), an ACoSOG-affiliated facility ($p<0.001$), or larger hospitals ($p<0.001$), and black women lived closest to chemotherapy providers ($p<0.001$); Hispanic women were more likely to be treated at for-profit health care facilities and resided furthest away from a chemotherapy provider ($p<0.001$). Inclusion of health services-related structural/organizational variables in multivariate models offered little explanatory insight for differences in receipt or timing of initiation of adjuvant chemotherapy.

Conclusions

Although use of adjuvant chemotherapy generally has increased over time, substantial variation in uptake exists, and overall use remains low in stage II and III, hormone receptor negative patients despite the existence of clinical guidelines encouraging its use. Given the complexity of decision making processes around systemic therapy and recognizing the long-term benefit of chemotherapy in hormone receptor negative patients, public health interventions should seek to identify women potentially at risk for under-treatment, including the healthy elderly, the poor, and vulnerable minority groups, and to increase access to information about the risks and benefits of adjuvant chemotherapy among both patients and clinicians.

Introduction

Poorer outcomes in breast cancer among vulnerable sub-populations, including elderly women and racial/ethnic minorities, are well documented (Edwards et al., 2005; Lund et al., 2008) and may be due to variation in quality of breast cancer treatment and differential adoption of treatment guidelines across sub-populations. As evidence has accumulated over time, clinical guidelines in breast cancer have evolved accordingly. Since 1990, National Institutes of Health (NIH) consensus statements have encouraged the use of adjuvant chemotherapy to prevent breast cancer recurrence. In 1996, the National Comprehensive Cancer Network (NCCN) modified guidelines to read that all invasive breast cancer patients with node positive disease and/or tumor sizes larger than 1cm should receive multicycle adjuvant cytotoxic poly-chemotherapy (Carlson et al., 1996). In 2000, NIH revised its guidelines to read that all patients younger than 70 with invasive cancers larger than 1cm (any lymph nodal status or hormone receptor status) should receive adjuvant poly-chemotherapy, unless the patient refuses. In more recent years, a combination of increased use of hormone receptor testing, development of new adjuvant endocrine therapy options, and improved understanding of the role of adjuvant chemotherapy in hormone receptor positive patients has led to a more refined view, with clear guidelines for use of adjuvant chemotherapy in hormone receptor negative patients and case-by-case consideration of adjuvant chemotherapy in hormone receptor positive patients. For stage II-III, hormone receptor negative tumors, however, adjuvant chemotherapy essentially has been advised since the early 1990s, and as such, the American Society for Clinical Oncology (ASCO) and NCCN recently created a quality metric to help monitor and to further encourage its use (Desch et al., 2008).

Translating evidence into practice is not always as straightforward as it would seem (Davis et al., 2003; Gold and Taylor, 2007; Shiffman et al., 2004; Waitman and Miller, 2004). Indeed, there are many barriers to adoption of evidence-based guidelines, including poor

dissemination systems, provider resistance or lack of awareness of new evidence, the fragmented nature of the health care financing system, lack of effective monitoring, and lack of incentives to change practices (Davis et al., 2003; Grol, 2001; McGlynn et al., 2003). Previous studies have demonstrated that black women, more often than other women with the same stage disease, fail to receive adjuvant treatment for breast cancer (Bradley, Given, and Roberts, 2001; O'Malley et al., 2001; Shavers and Brown, 2002). Several descriptive studies have examined receipt of adjuvant chemotherapy by race/ethnicity among breast cancer patients and found that black and Hispanic women are substantially less likely to receive appropriate care, even after controlling for insurance status, socioeconomic status, age, and co-morbidities (Banerjee et al., 2007; Bhargava and Du, 2009; Bickell et al., 2006). Most evidence suggests that when women across racial/ethnic groups receive equal treatment, equal outcomes follow (Dignam et al., 1997; Roach et al., 1997; Yood et al., 1999). However, one clinical trial limited to patients with metastatic breast cancer showed that even with identical treatment and controlling for clinicopathologic features (including estrogen receptor status), health disparities between black and white women in terms of survival persisted (Polite et al., 2008). This trial also demonstrated, as other studies have, that black patients were at no greater risk for chemotherapy-related hematologic toxicity than white patients and that patterns of tumor response were similar for black and white women with clinically equivalent disease (Polite et al., 2008; Newman et al., 2003; Smith et al., 2005). The authors therefore concluded that differences in co-morbidity and/or receipt of subsequent adjuvant treatment may have explained the difference in survival between blacks and whites (Polite et al., 2008).

Age and breast cancer are closely and meaningfully related (Vogel, 2008). The majority of breast cancer diagnoses occur in women older than 60; breast cancer incidence rises dramatically and non-linearly with age, a striking trend which is explained biologically by the important role of reproductive factors and ovarian estrogens in breast cancer etiology

(Colditz, Baer, and Tamimi, 2006). In the past, clinical trials exploring use of adjuvant chemotherapy often failed to recruit enough women older than 70 years to have sufficient power to report benefits and risks of chemotherapy in older women; as a result, many clinical guidelines and the ASCO/NCCN quality metrics were limited to women younger than 70 (Desch et al., 2008). However, many experts agree that such an age-specification sets a low bar for quality, given observational evidence showing that women older than 70 benefit as much as younger women from chemotherapy (Wildiers and Brain, 2005). Moreover, a randomized trial published recently showed that women older than 70 treated less aggressively with chemotherapy fared worse (Muss, 2009).

In light of this evidence, it is critically important that the health system itself is designed in such a way that all women have access to life-prolonging cancer treatments, regardless of race/ethnicity, age, or socioeconomic status. Certain types of health services, such as National Cancer Institute (NCI)-designated Cancer Centers, may be distributed unevenly across racial/ethnic and elderly sub-populations, and access to care, including distance to healthcare, also may vary across sub-populations. However, it is unclear whether such factors affect timely receipt of high quality breast cancer care and subsequent outcomes. Additionally, it is unclear whether evidence-based treatment practices diffuse more slowly within certain sub-populations over time (Groeneveld et al., 2005). The interactive effects of structural/organizational characteristics of health services and high quality care have been explored in literatures of other diseases (Bach et al., 2004; Birkmeyer et al., 2005; Gooden et al., 2008; Groeneveld et al., 2005; Morris et al., 2008; Talcott et al., 2007). The relationships between health system variables, race/ethnicity, and age have been explored much less systematically and comprehensively in the breast cancer treatment literature. One study conducted in North Carolina among Medicaid beneficiaries showed that poor quality breast cancer care was related to older age, living in a low-population density county, receiving surgery at a smaller hospital, and living in a low-

specialist density county (Anderson et al., 2008). In a different study examining receipt of radiation therapy, after controlling for health system characteristics (hospital teaching status, regional specialist supply, and surgical volume), race/ethnicity was no longer significantly predictive of treatment quality (Jerome-D'Emilia and Begun, 2005). We therefore aimed to expand upon existing work in this area by examining trends in receipt and timing of initiation of adjuvant chemotherapy over a ten-year period and by determining whether differences in structural/organizational characteristics of health services, including distance to care and institutional affiliations, explained a portion of existing disparities in treatment.

Methods

Data Source and Patient Population

The linked Surveillance, Epidemiology and End Results (SEER)-Medicare dataset was used in the current study and included breast cancer cases diagnosed in 1994-2002. The SEER program was designed by the NCI to be an epidemiologic surveillance system for incident cancers and covers 26% of the US population (Warren et al., 2002c). Part A (inpatient care, skilled nursing facilities, home health, and hospice care) and Part B (outpatient care, durable medical equipment, and physician services) claims were linked to individuals with first or only primary breast cancers identified by SEER registrars among patients enrolled in Medicare (Warren et al., 2002). Clinical and socio-demographic information for the study was taken from the Patient Entitlement and Diagnosis Summary File (PEDSF), whereas cancer treatment information, co-morbidities, and structural/organizational variables for health service providers were provided in the Medicare claims (Warren et al., 2002c).

To be included in this study, women must have been continuously enrolled in Medicare parts A and B fee-for-service during the one-year period prior to diagnosis and at least one year post-diagnosis, or until death, whichever occurred first. Our study was limited

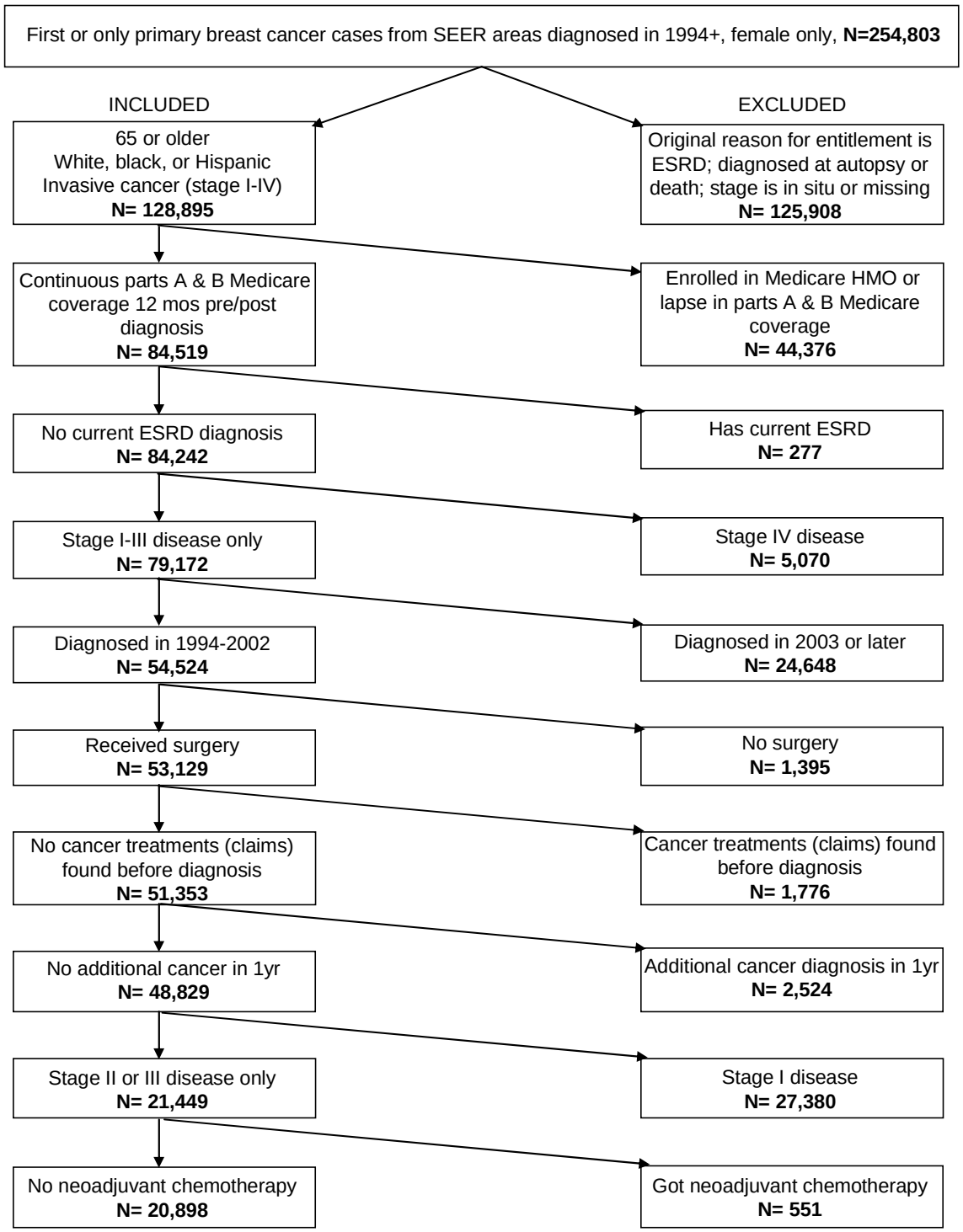
in scope to non-Hispanic white, non-Hispanic black, and Hispanic patients, due to concerns about insufficient numbers of other racial/ethnic groups for sub-group analyses. Men were excluded, as were women younger than 65 and women who had end stage renal disease (ESRD). In situ and metastatic (stage IV) cases were excluded, as were cases diagnosed at death or autopsy. Only women who received primary surgery (defined as breast conserving surgery or aggressive surgery/mastectomy) as the first anti-cancer treatment were included; as such, patients receiving neoadjuvant chemotherapy prior to surgery were excluded. Because care-seeking behavior may be different among individuals previously diagnosed with breast cancer, women with prior histories of breast cancer were excluded. Finally, in cases of multiple primary tumors, to eliminate any confusion about which cancer-directed treatments were targeted to which cancer, women with additional cancer diagnoses within one year of the index breast cancer diagnosis were excluded. The effects of these inclusion/exclusion criteria on overall sample size are summarized in Figure 14.

Dependent Variable

Initiation of post-operative adjuvant chemotherapy was examined as a binary indicator of any chemotherapy use and initiation of chemotherapy during several specified time periods. The ASCO/NCCN quality metric specifies that patients with stage II-III, hormone receptor negative breast cancer must begin adjuvant chemotherapy within four months of diagnosis, but completion of a full recommended course is not part of the metric (Desch et al., 2008). Although incomplete use of chemotherapy may have implications for treatment efficacy, chemotherapeutic regimens used may vary across patients, leading to clinically appropriate variation in dosage, timing of cycles, and administration. Adherence to recommended chemotherapy schedules over time therefore cannot be assessed easily. The four month time allowance specified in the metric was intended to provide sufficient time for surgery and medical consultation, but may be overly lenient. As such, additional time

intervals (1-3 months) were examined to detect differences in timing of initiation of adjuvant chemotherapy.

Figure 14: Sample size diagram based on inclusion/exclusion criteria



Notes: SEER: Surveillance, Epidemiology and End Results; ESRD: End Stage Renal Disease; HMO: Health Maintenance Organization

As well, although the ASCO/NCCN quality metric is limited to hormone receptor negative patients, reflecting more recent evidence about the limitations of chemotherapy in hormone receptor positive patients (Desch et al., 2008), clinical guidelines in the early 1990s encouraged the use of chemotherapy based on size of the tumor regardless of hormone receptor status (and indeed before the proliferation of hormone receptor testing). Therefore, for exploratory purposes, we also examined trends in use of chemotherapy among hormone receptor positive patients during a time period when guidelines were changing with respect to hormone receptor status.

Because women receive chemotherapy from various types of facilities, multiple files were examined in order to fully capture the therapeutic experiences of women, including the MEDPAR (inpatient), carrier claims, outpatient, and durable medical equipment (DME) files (i.e., some oral chemotherapy agents may be found in the DME file) (Virnig et al., 2002). Identification of breast cancer-related therapy has been discussed at length elsewhere (Cooper et al., 2002; Lamont et al., 2002; Virnig et al., 2002; Warren et al., 2002b). Based upon previous analyses and consultation with clinical and billing specialists, we identified relevant codes for this analysis from the Healthcare Common Procedure Classification System (HCPCS), the International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification (ICD-9-CM), and National Drug Codes (NDC), the latter of which have been used in DME files to classify chemotherapy drugs. Diagnostic, procedural, and drug codes used in this analysis are summarized in Table 13, excepting the numerous drug-specific NDC codes that were included in searches of the DME claims (codes available upon request).

Table 13: Identification of surgery and chemotherapy in Medicare claims

Treatment	Primary means of identification
Diagnostic codes	ICD-9-CM diagnosis codes: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9 Other: V10.3
Aggressive surgery	ICD-9-CM 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
Breast conserving surgery	ICD-9-CM procedure: 85.20, 85.21, 85.22, 85.23, 85.24, 85.25 CPT/HCPCS: 19120, 19125, 19126, 19160, 19162, 19301, 19302
Chemotherapy	ICD-9-CM procedure: 99.25, 285.3, 999.81 CPT/HCPCS: 51720, 96400-96549, 99555, Q0083-Q0085 (oral), C9127, C9415, C9420, C9421, C9431, C8953-C8955, S9329-S9331, G0355, G0357-G0363, G9021-G9032, J8510, J8520, J8521, J8530-J8999 (oral), J9000-J9999 (IV) Revenue Center Code: 0331, 0332, 0335 DRG: 410, 492 Other: V58.1, V58.11, V66.2, V67.2, V87.41, NDC codes

Notes: CPT: Current Procedural Terminology; DRG: Diagnostic Related Group HCPCS: Healthcare Common Procedure Classification System; ICD-9-CM: International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification; NDC: National Drug Code

Independent Variables of Interest

Structural/organizational characteristics of oncologic health services included characteristics of the surgical facility women attended and distance to providers. Specifically, surgical facility type/ownership, bed size, teaching status, NCI Cancer Center designation and American College of Surgeons Oncology Group (ACoSOG) affiliation were available in the SEER-Medicare data. ACoSOG membership is believed to be a proxy for organizational clinical expertise in the absence of information about Commission on Cancer (CoC) accreditation, which is not available in the SEER-Medicare data; in general, most ACoSOG hospitals are CoC accredited. Distance to providers (distance traveled for surgery and distance to nearest chemotherapy provider) was calculated using zip code centroid to zip code centroid minimum distance algorithms (Meden et al., 2002; Nattinger et al., 2001; Schroen et al., 2005; Shea et al., 2008). Specifically, distances were determined by assigning spatial coordinates (latitudes and longitudes) to 5 digit ZIP codes and using spherical geometry to calculate distances between points. Nearest facility analysis was performed by executing a Cartesian product of all patients and providers, calculating, all distances by the above method, and selecting the minimum distance for each patient.

Race/ethnicity was defined as non-Hispanic white, non-Hispanic black, and Hispanic, according to SEER registry definitions which are believed to be more accurate than Medicare assessment of race/ethnicity (Bach et al., 2002). Age was also an important patient-level attribute of interest. Due to major differences in age-specific guidelines and practicing patterns reflecting aforementioned lack of information about the effects of adjuvant chemotherapy in women 70 years and older, we stratified analyses by age group (65-69 years old versus 70 years and older) and included age as a categorical independent variable in the models of women 70 years and older.

Control Variables

Extensive review of the breast cancer literature revealed that several potentially confounding variables must be considered in any analysis of patient treatment and outcomes. Tumor biology, for example, influences clinician decision making and suitability of the patient for therapeutic treatment (Andre and Puztai, 2006; NCCN, 2008). As such, features of tumor biology, including stage of disease and histologic grade, as reported by SEER registrars were included categorically in analytic models.

Social support has been shown to influence receipt of and adherence to anti-cancer therapeutic regimens (Banerjee et al., 2007). Due to limitations in using registry-based claims data, social/familial support could be obtained only by examining marital status, so a categorical indicator for marriage status was included in analytic models. Additionally, we included a measure of neighborhood racial and ethnic cohesion, measured by assessing proportions of white, black, and Hispanic residents within the zip code of residence (Haas et al., 2008; Schootman et al., 2009).

Socioeconomic status, which is related to race/ethnicity and access to healthcare (Bao et al., 2007; Bharghava and Du, 2009), was considered by including a variable for indication of any State-Buy-In months within a one-year period (an indicator for Medicaid

enrollment, but more accurately, low-income status) (Bach et al., 2002). We also included measures of neighborhood socioeconomic context by including in analytic models zip code area median income and proportion of residents with less than a high school education.

Presence of a serious co-morbidity may affect cancer care planning (Du et al., 2008; Tammemagi et al., 2005), and co-morbidity burden generally increases with age. As well, black women may be at greater risk for co-morbid disease than white women (Banerjee et al., 2007). As such, co-morbidities were assessed using the NCI combined index method described by Klabunde and colleagues (2007), which uses breast cancer specific weighted co-morbidity scores for conditions identified by Charlson as important predictors of mortality. Based upon diagnostic codes identified in either the inpatient or physician claims during the 12 month period prior to cancer diagnosis, the NCI combined index has been shown to be a better predictor of non-cancer mortality among breast cancer survivors than other commonly used co-morbidity measures (Klabunde et al., 2007).

Finally, year of diagnosis dummy variables were included as covariates to adjust for cohort effects and secular changes in healthcare policies and practices over time.

Statistical Analysis

Receipt of adjuvant chemotherapy within several specified time frames was examined descriptively and modeled analytically using multivariate logistic regression. Diffusion curves (Rogers, 1995a) comparing proportions of sub-populations (by age group, race/ethnicity, and patients using health services with certain structural/organizational health services characteristics) receiving adjuvant chemotherapy by year were constructed and evaluated using chi-squared tests (Chernoff and Lehmann, 1954; Pagano and Gauvreau, 2000). The overall timing of initiation of chemotherapy by month among racial/ethnic groups was determined, and bivariate analyses compared receipt of chemotherapy and distribution

of structural/organizational factors by racial/ethnic group and age group, using chi-squared tests (Chernoff and Lehmann, 1954; Pagano and Gauvreau, 2000).

As anticipated, major differences in chemotherapy use were observed according to hormone receptor status and age; as such, all multivariate logit models were stratified according to age-group (<70 years versus 70 years and older) and hormone receptor status (ER and/or PR positive versus not) to reflect distinct treatment patterns in these different groups. In building analytic multivariate logit models, modifying or confounding power of key structural and organizational variables was explored (Hosmer and Lemeshow, 2000; Mickey and Greenland, 1989; Rothman et al., 2008). A 10%-change in the effect of race/ethnicity on receipt of adjuvant chemotherapy was used as a threshold for modification and confounding, and Wald tests with a p-value threshold of 0.05 were examined for predictive potential of structural and organizational variables (Mickey and Greenland, 1989). Interactions of race/ethnicity and time and race/ethnicity and age were of interest, allowing us to examine whether trends in chemotherapy varied by race/ethnicity over time or with age (Groeneveld et al., 2005). However, exploratory analyses showed that interactions terms were jointly non-significant and did not modify the main effect of race/ethnicity; therefore, these terms were omitted from final models.

Given evidence of regional variation in breast cancer treatment and outcomes (Bettencourt et al., 2007; Canto et al., 2001), we also tested the confounding potential of rural/urban residence and SEER registry region. These variables were measured categorically, with rurality/urbanicity defined as: metropolitan (250,000+ per county), urban (2,500-250,000 per county), and rural areas (<2500 per county) from the source geographic cancer registry (Gorin et al., 2005). Due to the lack of predictive and confounding power of these regional/geographic variables across models, final models omitted rural/urban residence and SEER region as covariates.

Additional tests were employed to determine the most appropriate variable specification for the final analytic models (e.g., use of the continuous versus categorical forms of co-morbidity index score) (Rothman et al., 2008; Wooldridge, 2006). Corrected Huber-White standard errors were reported for all regressions, and tests for multicollinearity among variables were conducted (Wooldridge, 2006). The general form for the logit model used in this analysis is:

$$\Pr(Chemo_i) = f(\beta_0 + \beta_1 \text{Race/Ethnicity}_i + \beta_2 \text{Struct}_i + \beta_3 \text{Time}_i + \gamma Z_i + \varepsilon_i)$$

where "Chemo" is chemotherapy, "Race/Ethnicity" is non-Hispanic white, non-Hispanic black, or Hispanic, "Struct" is a vector of health services structural/organizational variables, "Time" is year of diagnosis, "Z" is a vector of all other patient and community control variables, and "ε" is the error term.

Results

After applying inclusion/exclusion criteria to the population of women in SEER-Medicare diagnosed with incident breast cancer in 1994-2002, 20,898 women were included in the current study. Descriptive characteristics of the sample are summarized in Table 14 by age group and race/ethnicity. Approximately 8% of women were identified as non-Hispanic black, and 4% were identified as Hispanic; the rest were non-Hispanic white. The median age at diagnosis was 76.6 years. In total, 68% of women (14,220) were endocrine receptor positive, of whom 98% (13,915) were estrogen receptor (ER) positive and 79% (11,215) were progesterone receptor (PR) positive leaving 6,678 women who were neither ER nor PR positive. Black women less often had hormone receptor positive tumors, were more likely to have been diagnosed with stage III disease, and had greater co-morbidity burden. In addition, black women were least likely to be married, and black and Hispanic women were more likely to be identified as low income (Table 14).

Table 14: Descriptive statistics of full patient sample meeting inclusion criteria

Characteristic	% or mean (N=20,898) *OVERALL*	% or mean (N=3360) *< 70 years, White*	% or mean (N=336) *< 70 years, Black*	% or mean (N=193) *< 70 years, Hispanic*	% or mean (N=15102) *>/= 70 years, White*	% or mean (N=1260) *>/= 70 years, Black*	% or mean (N=647) *>/= 70 years, Hispanic*
Patient/demographic characteristics							
Age at diagnosis	76.6	67.46	67.33	67.44	78.72	78.54	78.01
Married	38.5%	58.6%	30.1%	50.8%	35.9%	21.5%	29.2%
Low income	21.6%	14.0%	47.0%	53.9%	18.5%	50.3%	53.8%
Patient residence							
Metro	83.8%	81.9%	89.9%	88.1%	83.1%	93.5%	88.4%
Urban	14.3%	16.1%	9.5%	11.9%	14.9%	5.9%	10.7%
Rural	1.9%	2.0%	0.6%	0.0%	2.0%	0.6%	0.9%
Year of diagnosis							
1994	9.1%	9.6%	8.9%	9.3%	9.0%	8.6%	8.3%
1995	8.7%	8.8%	9.2%	9.3%	8.6%	8.6%	9.1%
1996	8.1%	8.3%	6.8%	8.3%	8.1%	8.2%	7.4%
1997	8.1%	7.6%	7.1%	7.8%	8.2%	7.9%	9.3%
1998	8.1%	7.5%	7.7%	5.2%	8.3%	8.1%	8.8%
1999	8.2%	8.6%	7.7%	7.8%	8.1%	8.7%	9.3%
2000	16.3%	16.2%	19.0%	19.7%	16.2%	18.0%	15.3%
2001	16.9%	17.5%	14.9%	17.1%	17.0%	15.3%	17.3%
2002	16.4%	16.0%	18.5%	15.5%	16.5%	16.7%	15.1%
Clinical characteristics							
Stage							
Stage II	86.8%	90.0%	83.0%	88.6%	86.7%	81.8%	84.1%
Stage III	13.2%	10.0%	17.0%	11.4%	13.3%	18.2%	15.9%
ER/PR status							
ER+	66.6%	69.6%	49.7%	59.6%	67.5%	54.4%	63.5%
ER-	16.3%	17.3%	27.7%	17.6%	15.4%	21.4%	15.6%
ER unk/bord	17.1%	13.1%	22.6%	22.8%	17.0%	24.2%	20.9%
PR+	53.7%	57.4%	37.8%	52.3%	54.2%	42.5%	52.1%
PR-	27.7%	27.2%	32.1%	25.0%	27.8%	37.8%	25.4%
PR unk/bord	18.6%	18.6%	25.3%	22.9%	14.8%	24.4%	22.3%
NCICI score	0.30	0.17	0.38	0.27	0.31	0.43	0.37
Lymph nodes							
Node positive	53.9%	62.9%	65.2%	59.1%	51.9%	50.4%	53.9%
Status missing	15.3%	5.1%	8.6%	4.1%	17.4%	20.0%	17.2%
Treatment							
Received chemo within 1 month of diagnosis	10.7%	21.8%	16.1%	14.5%	8.4%	7.5%	10.2%
Received chemo within 4 months of diagnosis	29.4%	58.2%	52.1%	52.8%	22.8%	24.2%	25.1%
Ever received post-operative chemotherapy	35.0%	62.5%	59.5%	59.4%	28.5%	30.8%	30.2%
Received surgery in same month as diagnosis	65.8%	67.2%	61.6%	60.6%	65.8%	63.5%	65.8%

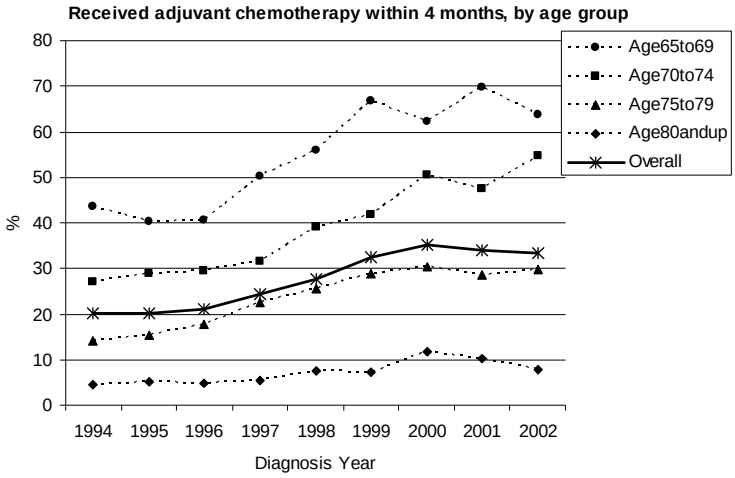
Notes: ER: Estrogen Receptor; NCICI: National Cancer Institute Combined Co-morbidity Index; PR: Progesterone Receptor; SEER: Surveillance, Epidemiology, and End Results

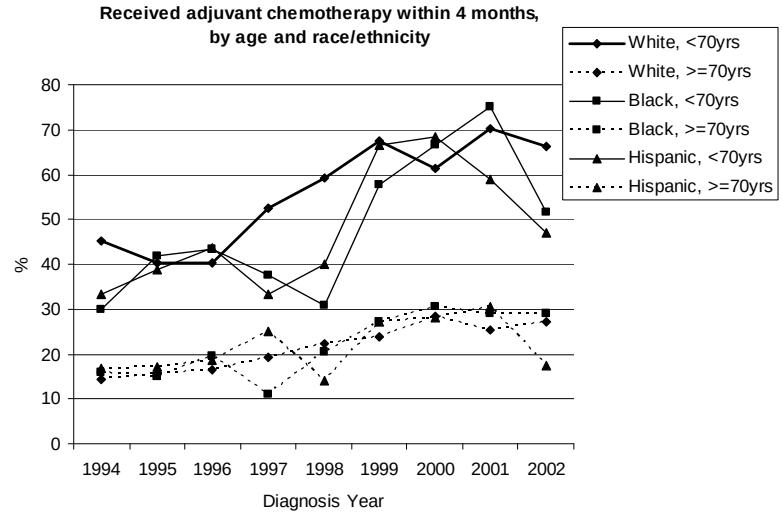
Bivariate Analyses: Adjuvant Chemotherapy and Patient Characteristics

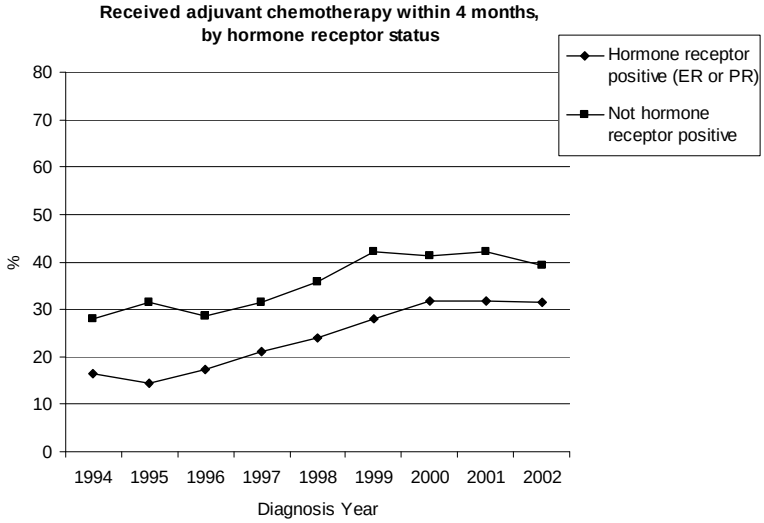
In exploratory analyses, significant differences existed in overall receipt and timing of initiation of adjuvant chemotherapy by patient-level characteristics of interest, including age and hormone receptor status and to a lesser extent by race/ethnicity (Table 14 and Figure 15). Overall use of adjuvant chemotherapy increased significantly from 1994 to 2002 across age groups and racial/ethnic groups, but remained quite low overall (45%) even in 2002. Among women ages 65-69 years old, 60% ever received adjuvant chemotherapy, compared to only 30% of women older than 70 (Table 14). Among younger women (65-69 years old), significant differences were observed by race/ethnicity in timing of initiation of chemotherapy within 1 month of diagnosis (22% in white women compared to 16% and 15% in black and Hispanic women, respectively; p=0.004) and 4 months of diagnosis (58% in white women compared to 52% and 53% in black and Hispanic women, respectively; p=0.04). In terms of trends over time in timing of initiation of adjuvant chemotherapy, initiation within 4 months of diagnosis was more common among younger women, and initiation within this time interval generally increased from 1994-2002, as evidenced by Figure 15.

In exploratory analyses, hormone receptor status played an important role in determination of overall receipt and timing of initiation of adjuvant chemotherapy (Figure 15). Women with hormone receptor positive tumors (ER and/or PR-positive) were significantly less likely to receive chemotherapy (results not shown) and to initiate chemotherapy within four months of diagnosis (Figure 15). Overall use of adjuvant chemotherapy and earlier initiation of adjuvant chemotherapy increased from 1994-2002 regardless of hormone receptor status. In 1994, 28% of women whose tumors were not ER/PR-positive and 17% of women with hormone receptor positive tumors initiated chemotherapy within 4 months of diagnosis; by 2002, approximately 40% of women whose tumors were not ER/PR-positive and 31% of women with hormone receptor positive tumors initiated chemotherapy by 4 months post-diagnosis.

Figure 15: Trends in receipt of adjuvant chemotherapy within 4 months of diagnosis, by patient characteristics, among women with sate II-III breast cancers who received surgery



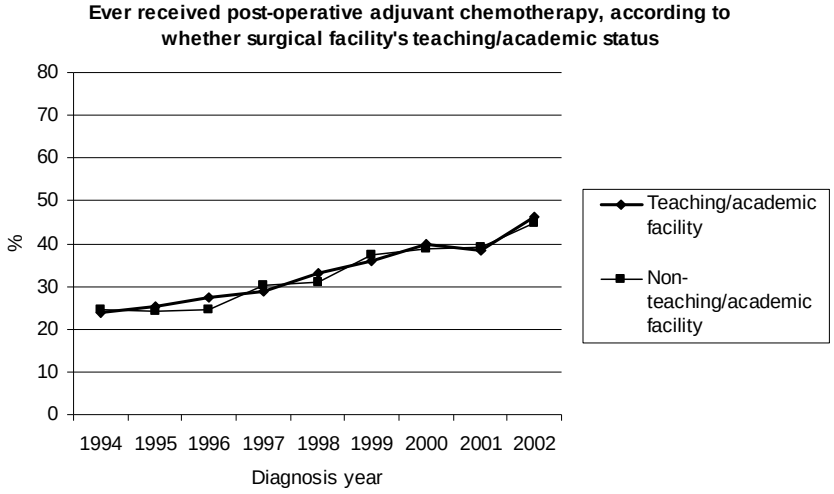


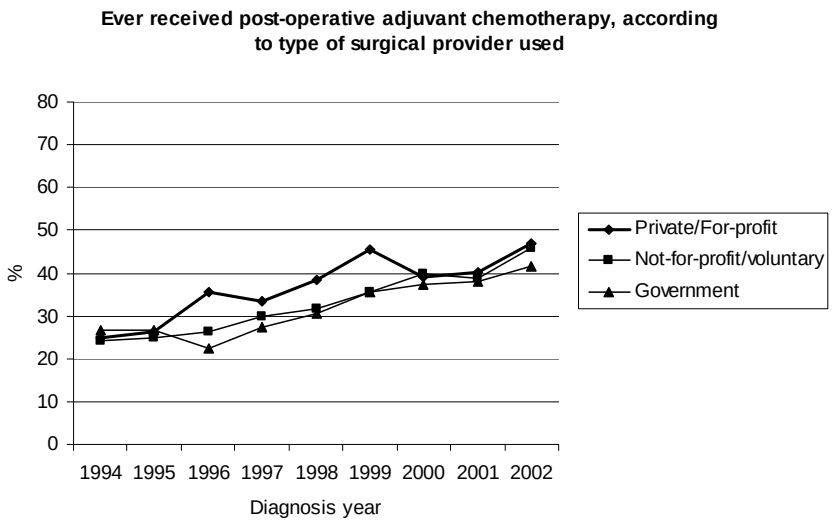


Bivariate Analyses: Adjuvant Chemotherapy and Health Services Characteristics

Figures 16 and 17 depict trends in any use of adjuvant chemotherapy over time according to select structural and organizational characteristics of health services, including teaching status, type/ownership, NCI Comprehensive Cancer Center designation, and distance to care. From these graphs, it is evident that overall receipt of adjuvant chemotherapy was low, and few differences existed according to structural and organizational factors. During certain years, women receiving surgery at for-profit facilities and NCI Comprehensive Cancer Centers appeared to be more likely to receive subsequent chemotherapy, but these relationships were not consistently statistically significant (Figure 16). In general, living in a zip code where the nearest chemotherapy facility was in the same zip code was not associated with receipt of adjuvant chemotherapy, but in 1997, 1999, and 2001, living nearer to a chemotherapy facility was associated with greater rates of adjuvant chemotherapy use (Figure 17). According to Table 15, structural/organizational characteristics of health services were distributed unequally across racial/ethnic sub-populations. Hispanic women were treated more often at for-profit surgical facilities (16% compared to 7% in whites and 8% in blacks; $p<0.001$), and black women received surgery more often at NCI Comprehensive Cancer Centers (9% compared to 2% in white women and 3% in Hispanic women; $p<0.001$), ACoSOG-affiliated facilities (32% compared to 22% in white women and 15% in Hispanic women; $p<0.001$), and teaching/academic health centers (62% compared to 48% in white women and 41% in Hispanic women; $p<0.001$) (Table 15). Hispanic women lived the furthest away from a chemotherapy provider (4.2 miles on average; $p<0.001$), and non-Hispanic white women traveled the furthest for surgery (16 miles on average; $p<0.001$) (Table 15).

Figure 16: Receipt of adjuvant chemotherapy at any time after surgery, among women with stage II-III breast cancers - trends by surgical provider characteristics





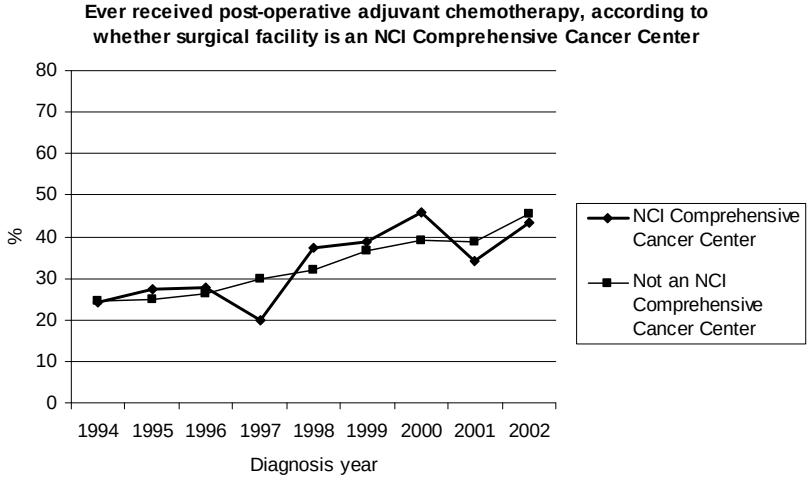
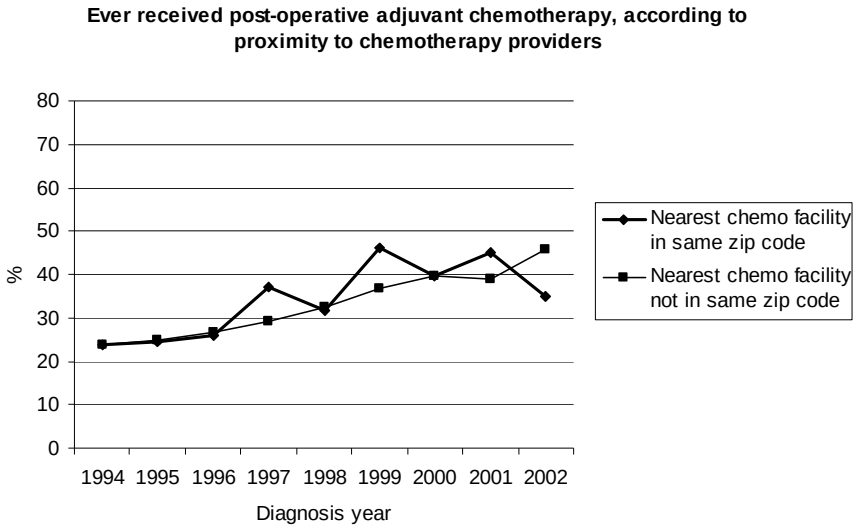


Figure 17: Receipt of adjuvant chemotherapy at any time after surgery, among women with stage II-III breast cancers - trends by proximity to health services



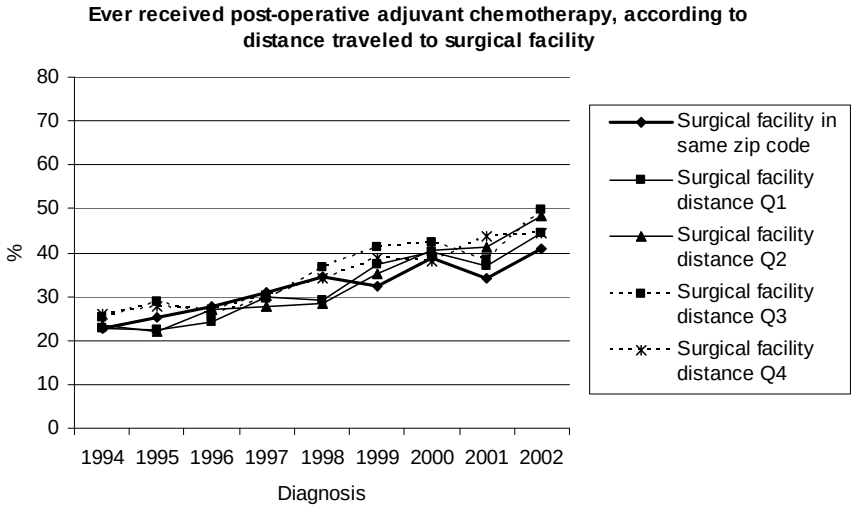


Table 15: Bivariate comparisons of health system organizational factors by race/ethnicity

Organizational Covariate	% or mean (SD) *White*	% or mean (SD) *Black*	% or mean (SD) *Hispanic*	p-value (from chi-square test or t-test)
Surgical facility characteristics				
Type/ownership				
For-profit/private	6.9%	8.4%	15.7%	<0.001
Non-profit/voluntary	78.5%	77.9%	69.7%	<0.001
Government	14.5%	13.7%	14.6%	0.682
NCI Comprehensive Cancer Center	2.3%	9.5%	3.0%	<0.001
ACoSOG-affiliated	22.3%	32.4%	14.9%	<0.001
Teaching/academic facility	48.5%	61.6%	41.1%	<0.001
Rural location	14.0%	4.9%	9.9%	<0.001
Number of beds	353 (226.2)	465 (259)	302 (219)	<0.001~ <0.001#
Relational factors/access to care				
Nearest chemotherapy facility (miles)	3.2 (6.2)	1.9 (3.9)	4.2 (10.0)	<0.001~ <0.001#
Nearest chemotherapy facility is located in same zip code as patient residence	84.9%	80.2%	87.4%	<0.001
Facility where patient received primary surgery is located in same zip code as patient residence	17.5%	14.9%	16.3%	0.027
Average distance traveled for primary surgery (miles)	15.6 (61.6)	11.5 (50.9)	11.5 (31.8)	0.011~ 0.061#
Average distance traveled to chemotherapy provider, among those who received chemotherapy (first incidence of use) (miles)	17.5 (55.4)	11.5 (31.4)	13.3 (23.5)	0.029~ 0.53#

Notes: ACoSOG: American College of Surgeons Oncology Group; NCI: National Cancer Institute; ~ indicates two-sample t-tests between white and black groups; # indicates two-sample t-tests between white and Hispanic groups

Multivariate Analyses

In stratified multivariate models (Tables 16-19), the effects of race/ethnicity were not statistically significant, and adding structural/organizational factors to the models did not appear to confound or modify the main relationships between race/ethnicity and receipt or timing of initiation of adjuvant chemotherapy. Across models, characteristics of the surgical facility where women were treated were not predictive of receipt or timing of initiation of adjuvant chemotherapy at the 5% level of significance. Distance to care as a predictor of receipt and timing of initiation of adjuvant chemotherapy did not attain statistical significance in most multivariate models; however, among women 70 and older (Tables 17 and 19),

increasing distance to a chemotherapy facility was consistently associated with lower odds of initiation of adjuvant chemotherapy, although the effect was often statistically non-significant (ORs ranging from 0.74 to 0.99).

In models of women whose tumors were not hormone receptor positive (i.e., those women for whom clinical guidelines clearly recommended adjuvant chemotherapy during the entire time period examined) (Tables 16 and 17), women with ER-borderline or ER-unknown tumors had significantly lower odds of initiating chemotherapy within 4 months (OR: 0.27 among women 65-69 years old, $p<0.05$; OR: 0.35 among women 70 years and older, $p<0.01$) and lower odds of ever receiving chemotherapy (OR: 0.36 among women 65-69 years old, $p<0.10$; OR: 0.37 among women 70 years and older, $p<0.01$), compared to women whose tumors were known to be ER-negative. In terms of other covariates in models of women with non-positive hormone receptor statuses, having positive lymph nodes and being diagnosed as stage III (relative to stage II) were associated with significantly higher odds of initiation of chemotherapy within 4 months and overall (Tables 16 and 17). Among women 70 and older with non-positive hormone receptor status (Table 17), poorer histologic grade was associated with significantly higher odds of initiation of chemotherapy (ORs ranging from 1.62 to 3.09, $p<0.05$), and greater co-morbidity was associated with significantly lower odds of initiation of chemotherapy (ORs ranging from 0.59 to 0.69 in third and fourth co-morbidity quartiles, $p<0.01$). Finally, regardless of age or hormone receptor stratification, increasing year of diagnosis was significantly associated with greater odds of initiating adjuvant chemotherapy at each time period examined and overall (Tables 16-19), indicating that use of adjuvant chemotherapy increased over time, particularly since 1997, after which point, odds ratios on year of diagnosis were statistically significant across models.

Table 16: Multivariate logit regressions for breast cancer patients <70 years old with non-positive (i.e. negative, borderline, or unknown) hormone receptor status

Variables	Odds Ratios for receipt of adjuvant chemotherapy, among women < 70 years old (robust standard errors used)	
	@ 4 mos.	*Ever*
Non-Hispanic white	*(reference)*	
Non-Hispanic black	0.84	0.76
Hispanic	1.58	1.63
Structural/organizational variables		
Surgical facility characteristics		
Non-profit	*(reference)*	
Private/for-profit	1.07	1.05
Governmental	1.04	0.94
Teaching facility	0.86	0.73+
Fewer beds (<median)	1.02	0.91
NCI Comprehensive Cancer Center	0.60	0.98
ACoSOG-affiliated	1.04	0.91
Distance traveled to surgery (in quartiles)		
Same zip code	*(reference)*	
Surgery distance Q1	1.27	1.65+
Surgery distance Q2	0.88	1.22
Surgery distance Q3	0.93	1.24
Surgery distance Q4	1.37	1.73+
Distance to nearest chemotherapy provider (in quartiles)		
Same zip code	*(reference)*	
Chemotherapy distance Q1	1.24	1.30
Chemotherapy distance Q2	1.08	0.95
Chemotherapy distance Q3	1.14	1.00
Chemotherapy distance Q4	1.16	0.91
Clinical and patient characteristics		
NCI Combined Index Co-morbidity score (in quartiles)		
None (score=0)	*(reference)*	
Co-morbidity Q1	0.95	0.98
Co-morbidity Q2	1.27	1.33
Co-morbidity Q3	0.78	0.76
Co-morbidity Q4	0.32**	0.40**
Surgery received in same month as diagnosis	1.30	1.28
ER-negative	*(reference)*	
ER-borderline or unknown	0.27*	0.36+
PR-negative	*(reference)*	
PR-borderline or unknown	1.14	0.72
Stage2	*(reference)*	
Stage3	1.93*	1.64+
Node-negative	*(reference)*	
Node-positive	4.33**	4.45**
Node status missing	1.05	0.96
Grade		
Well differentiated	*(reference)*	
Moderately differentiated	1.17	1.10
Poorly differentiated	1.51	1.36
Anaplastic	1.02	0.86
Grade missing	0.80	0.70
Low income proxy (State-Buy-In)	0.49**	0.53**

Variables	Odds Ratios for receipt of adjuvant chemotherapy, among women < 70 years old (robust standard errors used)	
	@ 4 mos.	*Ever*
Married	1.54**	1.74**
Year of diagnosis		
1994	*(reference)*	
1995	1.46	1.45
1996	0.72	0.80
1997	1.16	1.41
1998	1.85+	2.09*
1999	3.26**	3.11**
2000	2.41**	2.58**
2001	2.87**	3.44**
2002	2.00*	2.91**
Observations	1082	1086

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; Models also control for neighborhood characteristics by zip code (odds ratios not reported here); RT: radiation therapy; ER: estrogen receptor; PR: progesterone receptor; Hisp: Hispanic

Table 17: Multivariate logit regressions for breast caner patients 70 years and older with non-positive (i.e., negative borderline, or unknown) hormone receptor statuses

Variables	Odds Ratios for receipt of adjuvant chemotherapy, among women 70 years and older (robust standard errors used)	
	@ 4 mos.	*Ever*
Non-Hispanic white	*(reference)*	
Non-Hispanic black	1.04	1.15
Hispanic	1.49+	1.36
Structural/organizational variables		
Surgical facility characteristics		
Non-profit	*(reference)*	
Private/for-profit	1.17	1.2
Governmental	0.83	0.87
Teaching facility	0.94	1.01
Fewer beds (<median)	1.03	1.09
NCI Comprehensive Cancer Center	0.84	0.85
ACoSOG-affiliated	1.07	1.00
Distance traveled to surgery (in quartiles)		
Same zip code	*(reference)*	
Surgery distance Q1	0.88	0.93
Surgery distance Q2	0.85	0.9
Surgery distance Q3	0.86	0.97
Surgery distance Q4	0.79+	0.89
Distance to nearest chemotherapy provider (in quartiles)		
Same zip code	*(reference)*	
Chemotherapy distance Q1	0.86	0.92
Chemotherapy distance Q2	0.74*	0.91
Chemotherapy distance Q3	0.8	0.86
Chemotherapy distance Q4	0.92	0.99
Clinical and patient characteristics		
NCI Combined Index Co-morbidity score		
None (score=0)	*(reference)*	
Co-morbidity Q1	0.92	0.94
Co-morbidity Q2	0.79	0.76*
Co-morbidity Q3	0.64**	0.69**
Co-morbidity Q4	0.59**	0.62**
Age 70-74years	*(reference)*	
Age 75-79years	0.45**	0.48**
Age 80-84years	0.18**	0.21**
Age 85years and up	0.04**	0.07**
Surgery received in same month as diagnosis	1.20*	1.02
ER-negative	*(reference)*	
ER-borderline or unknown	0.35**	0.37**
PR-negative	*(reference)*	
PR-borderline or unknown	0.84	0.96
Stage2	*(reference)*	
Stage3	1.50**	1.48**
Node-negative	*(reference)*	
Node-positive	4.00**	3.52**
Node status missing	1.03	0.98
Grade		
Well differentiated	*(reference)*	
Moderately differentiated	2.00**	1.75**

Variables	**Odds Ratios for receipt of adjuvant chemotherapy, among women 70 years and older (robust standard errors used)**	
	@ 4 mos.	*Ever*
Poorly differentiated	3.02**	2.81**
Anaplastic	3.09**	2.64**
Grade missing	1.79**	1.62*
Low income proxy (State-Buy-In)	0.59**	0.59**
Married	1.14+	1.22**
Year of diagnosis		
1994	*(reference)*	
1995	1.08	0.95
1996	1.11	1.21
1997	1.53*	1.38+
1998	1.81**	1.45*
1999	2.15**	1.74**
2000	2.66**	2.21**
2001	2.52**	1.94**
2002	2.56**	3.04**
Observations	4823	4827

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; Models also control for neighborhood characteristics by zip code (odds ratios not reported here); RT: radiation therapy; ER: estrogen receptor; PR: progesterone receptor

Table 18: Multivariate logit regressions for breast cancer patients < 70 years old with positive hormone receptor (ER+ or PR+) status

Variables	Odds Ratios for receipt of adjuvant chemotherapy, among women < 70 years old (robust standard errors used)	
	@ 4 mos.	*Ever*
Non-Hispanic white	*(reference)*	
Non-Hispanic black	0.7	0.93
Hispanic	1.11	1.1
Structural/organizational variables		
Surgical facility characteristics		
Non-profit	*(reference)*	
Private/for-profit	1.16	1.00
Governmental	0.92	0.85
Teaching facility	0.95	0.91
Fewer beds (<median)	0.92	0.94
NCI Comprehensive Cancer Center	0.66	0.8
ACoSOG-affiliated	0.97	1.00
Distance traveled to surgery (in quartiles)		
Same zip code	*(reference)*	
Surgery distance Q1	0.91	0.88
Surgery distance Q2	0.83	0.74+
Surgery distance Q3	0.85	0.78
Surgery distance Q4	0.86	0.77
Distance to nearest chemotherapy provider (in quartiles)		
Same zip code	*(reference)*	
Chemotherapy distance Q1	0.91	0.96
Chemotherapy distance Q2	0.88	0.82
Chemotherapy distance Q3	1.11	1.15
Chemotherapy distance Q4	0.97	1.03
Clinical and patient characteristics		
NCI Combined Index Co-morbidity score (in quartiles)		
None (score=0)	*(reference)*	
Co-morbidity Q1	0.84	0.86
Co-morbidity Q2	0.75+	0.85
Co-morbidity Q3	0.63*	0.77
Co-morbidity Q4	0.31**	0.36**
Surgery received in same month as diagnosis	1.31**	1.31**
Stage2	*(reference)*	
Stage3	1.67**	1.65**
Node-negative	*(reference)*	
Node-positive	4.81**	4.36**
Node status missing	0.92	1.02
Grade		
Well differentiated	*(reference)*	
Moderately differentiated	1.28+	1.2
Poorly differentiated	2.34**	2.27**
Anaplastic	1.58	1.33
Grade missing	1.41+	1.37+
Low income proxy (State-Buy-In)	0.66**	0.64**
Married	0.97	1.00
Year of diagnosis		
1994	*(reference)*	

Variables	**Odds Ratios for receipt of adjuvant chemotherapy, among women < 70 years old (robust standard errors used)**	
	@ 4 mos.	*Ever*
1995	0.86	0.97
1996	1.26	1.34
1997	2.10**	2.29**
1998	3.08**	3.20**
1999	3.31**	3.84**
2000	4.24**	4.45**
2001	5.01**	5.23**
2002	5.05**	6.86**
Observations	2398	2398

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; Models also control for neighborhood characteristics by zip code (odds ratios not reported here); RT: radiation therapy; ER: estrogen receptor; PR: progesterone receptor

Table 19: Multivariate logit regressions for breast cancer patients 70 years and older, with positive hormone receptor (ER+ or PR+) status

Variables	Odds Ratios for receipt of adjuvant chemotherapy, among women 70 years and older (robust standard errors used)	
	@ 4 mos.	*Ever*
Non-Hispanic white	*(reference)*	
Non-Hispanic black	1.16	1.14
Hispanic	0.92	0.9
Structural/organizational variables		
Surgical facility characteristics		
Non-profit	*(reference)*	
Private/for-profit	1.16	1.11
Governmental	1.04	1.03
Teaching facility	0.91	0.96
Fewer beds (<median)	1.12	1.04
NCI Comprehensive Cancer Center	0.77	0.88
ACoSOG-affiliated	1.05	1.07
Distance traveled to surgery (in quartiles)		
Same zip code	*(reference)*	
Surgery distance Q1	1.08	0.95
Surgery distance Q2	1.07	0.94
Surgery distance Q3	1.04	0.94
Surgery distance Q4	0.91	0.84+
Distance to nearest chemotherapy provider (in quartiles)		
Same zip code	*(reference)*	
Chemotherapy distance Q1	0.85	0.92
Chemotherapy distance Q2	0.77*	0.83+
Chemotherapy distance Q3	0.85	0.91
Chemotherapy distance Q4	0.87	0.94
Clinical and patient characteristics		
NCI Combined Index Co-morbidity score		
None (score=0)	*(reference)*	
Co-morbidity Q1	1.01	1.08
Co-morbidity Q2	0.72**	0.79*
Co-morbidity Q3	0.84	0.89
Co-morbidity Q4	0.55**	0.70**
Age 70-74years	*(reference)*	
Age 75-79years	0.49**	0.54**
Age 80-84years	0.17**	0.23**
Age 85years and up	0.04**	0.10**
Surgery received in same month as diagnosis	1.32**	1.17**
Stage2	*(reference)*	
Stage3	1.74**	1.68**
Node-negative	*(reference)*	
Node-positive	4.23**	3.20**
Node status missing	0.95	1.03
Grade		
Well differentiated	*(reference)*	
Moderately differentiated	1.31**	1.22*
Poorly differentiated	1.99**	1.88**
Anaplastic	1.77*	1.57*
Grade missing	1.44**	1.40**
Low income proxy (State-Buy-	0.63**	0.66**

Variables	Odds Ratios for receipt of adjuvant chemotherapy, among women 70 years and older (robust standard errors used)	
	@ 4 mos.	*Ever*
In)		
Married	1.25**	1.21**
Year of diagnosis		
1994	*(reference)*	
1995	1.14	1.29+
1996	1.40*	1.32*
1997	1.82**	1.74**
1998	2.54**	2.26**
1999	3.00**	2.54**
2000	4.18**	3.31**
2001	4.07**	2.94**
2002	4.03**	4.98**
Observations	10188	10189

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; Models also control for neighborhood characteristics by zip code (odds ratios not reported here); RT: radiation therapy; ER: estrogen receptor; PR: progesterone receptor

Discussion

With a goal of examining structural/organizational reasons for disparities in receipt of adjuvant therapy, our study explored treatment patterns in adjuvant chemotherapy among women diagnosed with breast cancer between 1994 and 2002. Given the lack of quality metrics for women older than 70 years juxtaposed against recent demonstrable benefits of adjuvant chemotherapy in older women (Elkin et al., 2006; Giordano et al., 2006; Owusu et al., 2007) both younger (65-70 years) and older (70 and older) Medicare beneficiaries were studied in the current analysis, providing additional timely and important evidence with respect to age.

Contrary to expectations, we found no evidence of a racial/ethnic disparity in receipt and timing of receipt of adjuvant chemotherapy in multivariate models. The lack of racial/ethnic differences in receipt of chemotherapy after consideration of other potential confounders is in contrast with evidence from Giordano and colleagues (2006), but is consistent with evidence from Lund and colleagues (2008), Du and Goodwin (2001), and recent findings from Bhargava and Du (2009) showing that racial disparities in receipt of adjuvant chemotherapy among women ages 65-69 years old were largely explained by

area-level poverty (which we accounted for by using zip code-level median income). Studies of timing of chemotherapy use in other cancers, including lung cancer, have shown that black patients tend to experience more delays in initiation of chemotherapy (Shugarman et al., 2009), but that finding was not corroborated in this study of breast cancer patients.

Structural and organizational characteristics of health services played a very minor role in determining receipt and timing of receipt of adjuvant chemotherapy. Among women ages 70 and older, increasing distance to chemotherapy providers was associated with lower odds of receiving adjuvant chemotherapy at one year and overall, but this effect was not always statistically significant (Tables 17 and 19). If distance to care does play a role in determining receipt of adjuvant treatment, this finding may have implications for workforce planning, amidst concerns about oncology provider supply, particularly in rural areas, and the aging oncology workforce. Further, if distance to care presents an obstacle to elderly women, public health programs focused of providing reliable transportation options may benefit women. Given the limitations of using straight-line distances between patient zip code centroid and provider zip code centroid in determining geographic to care, it is possible that our measures were too imprecise to detect the true effect of distance and what role it may have played in terms of health care seeking burden. After all, health care markets transcend zip codes. As such, future research should attempt to explore the issues around geographic access to care as it relates to treatment planning and perceived burden of seeking oncology services (specifically adjuvant therapy) among elderly women.

The absence of a statistically significant effect of other types of structural or organizational health services characteristics on timing of receipt of chemotherapy may suggest that factors like NCI Cancer Center designation and teaching status of the surgical facility have no impact on timing of initiation or overall receipt of adjuvant chemotherapy. On the other hand, features of SEER-Medicare sampling, problems with measurement of structural/organizational variables, and/or omission of unobservable variables could explain

this finding. For instance, although SEER is one of the largest national cancer registry programs in the world, SEER largely samples black and Hispanic cancer patients from specific areas which may not be representative of the experiences of all black and Hispanic persons in the United States (Warren et al., 2002c). Black patients tend to be oversampled from urban areas like Detroit and Atlanta, limiting the ability of SEER-Medicare to reflect on the experiences of rural blacks, whereas Hispanic patients tend to be oversampled from New Mexico and California, limiting the ability of SEER-Medicare to reflect on the experiences of rural Hispanic patients living in the southeastern United States, for example. The bivariate analyses comparing health system organizational/structural factors by race/ethnicity (Table 15) support such a statement, as black women in this study were more likely to be treated at larger hospitals, NCI Comprehensive Cancer Centers, academic facilities, etc., all of which have been associated with improved treatment quality and/or health outcomes (Chaudhry et al., 2001; Hebert-Croteau et al., 2005; Laliberte et al., 2005; Onega et al., 2009) and which are reflective of more urban health facilities. Tables 14 and 15 further suggest that rural-dwelling Hispanic women may be under-represented in the current study. If organizational features of health services are associated with geographic location of health facilities as we might expect then this study's inability to sample rural-dwelling black and Hispanic women may have limited its power to detect meaningful relationships between race/ethnicity and health system factors. Another limitation may be related to the types of structural and organizational measures used; specifically, only information from hospital-affiliated surgical facilities was available. Thus, we could not explore how structural/organizational characteristics of non-hospital affiliated facilities affected treatment planning. We also could not say anything about the providers and facilities patients consulted after initial surgery; clearly, although the surgical facility plays a role in subsequent care, other providers outside of the surgical facility are important. The lack of such information indicates a critical need for better data and improved access to data

resources about the health systems providing care to cancer patients, including structural and organizational characteristics of non-hospital-affiliated facilities and providers in the community.

We found that receipt of adjuvant chemotherapy in stage II and III, hormone receptor negative breast cancers was somewhat low, at approximately 51% for women diagnosed in 2002, despite the fact that evidence supporting its use has existed since the 1980s. The decision making process around chemotherapy use is complex, given the serious side effects and logistical burdens patients face when considering whether or not to undergo chemotherapy. As such, reasons for underuse of adjuvant chemotherapy are multifaceted and cannot be completely understood in a retrospective observational study of this nature. In this study, underuse among women with non-positive hormone receptor statuses was highly associated with increasing age, earlier year of diagnosis, being unmarried, lower socioeconomic status, and certain tumor characteristics, controlling for all other factors. Despite the high predictive power of these variables, we were unable to directly measure intent, treatment choice, or other behavioral factors that may have affected receipt of care. Additional reasons for underuse may not be observable in this dataset; for example, it is unclear whether women who did not receive chemotherapy were actually offered chemotherapy and refused it, or were never offered chemotherapy at all.

As expected, age played an enormous role in determining receipt of adjuvant chemotherapy consistent with many prior studies (Bhargava and Du, 2009; Du et al., 2003; Du and Goodwin, 2001; Goodwin et al., 2006). This relationship persisted over time despite increasing controversy during the time period examined about omission of potentially life-prolonging therapy in older women (Wildiers and Brain, 2005). Due to insufficient accumulation of clinical trial evidence about the effects of adjuvant chemotherapy in older women, the ASCO/NCCN quality metrics for use of chemotherapy for breast cancer were limited to women younger than 70 years old (Desch et al., 2008). However, many experts

have argued that the lack of inclusion of older women in clinical trials should not preclude older women from receiving life-prolonging breast cancer treatments (Ballard-Barbash et al., 1996; Passage and McCarthy, 2007; Wildiers and Brain, 2005). Several studies now have shown substantial benefits of chemotherapy in older women (Elkin et al., 2006; Giordano et al., 2006; Owusu et al., 2007), and at least one randomized trial has shown that omission of aggressive chemotherapy among women older than 70 leads to poorer outcomes (Muss, 2009). Rather than focusing on age as a sole criterion for treatment, many authors have argued that co-morbidity burden and/or functional status are more appropriate considerations for treatment planning among elderly cancer patients (Barni et al., 2010; Bouchardy et al., 2007). Our study echoed previous findings that women with more co-morbidities were less likely to receive adjuvant chemotherapy, controlling for all other factors (Du and Goodwin, 2001) and that black women tended to have greater co-morbidity burden (Tammemagi et al., 2005).

This study has several strengths, including its use of a large, population-based cancer registry linked with Medicare claims data and longitudinal examination of trends in breast cancer care. We have also addressed a potential source of omitted variable bias that some previous studies failed to consider or measured inadequately – insurance status – by limiting our study to insured Medicare beneficiaries enrolled in parts A and B fee-for-service. Our study contributes to the existing literature in use of adjuvant chemotherapy for breast cancer by documenting low utilization of adjuvant chemotherapy over time by important patient sub-populations, illustrating differences in timing of initiation of chemotherapy (which may be related to subsequent health outcomes [see Hershman et al., 2006a, for example]), and by showing that potential age-related disparities in treatment may exist among healthy elderly women with good functional status. If use of chemotherapy is indeed inappropriately low in hormone receptor negative patients, then combined with recent data on the likely benefit of adjuvant chemotherapy in the older breast cancer population, it may be that

outcomes could be improved for a substantial number of older patients. Based on these findings, future studies should seek to explore the more nuanced reasons why older women do not receive chemotherapy and the appropriateness (or inappropriateness) of chemotherapy omission, to examine the effects of timing of chemotherapy initiation on health outcomes, and to sample more representatively minority sub-populations from diverse geographic regions in the United States.

CHAPTER 6: TIMING OF RECEIPT OF BREAST CANCER TREATMENT, RACE/ETHNICITY, AND LONG-TERM HEALTH OUTCOMES

Abstract

Purpose

Optimal timing of anticancer therapy, including radiation therapy and adjuvant chemotherapy, is an unresolved issue in breast cancer care. Treatment delays may be predictive of long-term health outcomes and are more common in racial/ethnic minority groups. Accordingly, we examined racial/ethnic variation in (1) all-cause and breast cancer-specific mortality five years after diagnosis as a function of timing of radiation therapy after breast conserving surgery among stage I-III breast cancers and (2) all-cause and breast cancer-specific mortality five years after diagnosis as a function of timing of adjuvant chemotherapy among stage II-III breast cancers.

Methods

We conducted a retrospective analysis of secondary data using Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare claims for women ages 65 and older diagnosed with primary breast cancer in 1994-2002, with vital status follow-up through 2007. We examined the effect of therapeutic timing on five-year all-cause mortality and breast cancer-specific mortality in multivariate logistic regressions. Timing of initiation of adjuvant radiation therapy (RT) and adjuvant chemotherapy, both measured in months since diagnosis, were independent variables of interest in separate regressions. Race/ethnicity, defined by SEER as non-Hispanic white, non-Hispanic black, or Hispanic, was an important independent variable of interest. Control variables included stage;

histologic grade; hormone receptor status; axillary lymph node involvement; co-morbidity score; marital status at diagnosis; State-Buy-In months (a proxy for low income status) (Bach et al., 2002); year of diagnosis; and zip code level income, education, and neighborhood racial composition.

Results

In total, 38,574 women met criteria for models examining timing of initiation of RT, of whom 6% (2,273) were black and 4% (1,336) were Hispanic; within this sample, 58% of white women, 51% of black women, and 58% of Hispanic women ever received RT ($p<0.001$). In total, 20,989 women met criteria for models examining timing of initiation of chemotherapy, of whom 8% (1,596) were black and 4% (840) were Hispanic; within this sample, 35% of white women, 37% of black women, and 37% of Hispanic women ever received chemotherapy ($p=0.111$). In bivariate analyses, compared to white women, black women had higher 5-year breast cancer specific mortality ($p<0.001$) and higher all-cause mortality ($p<0.001$). Timing of initiation of RT varied significantly by race/ethnicity; among women who did not receive chemotherapy, 54% of non-Hispanic white women initiated RT within 6 months of diagnosis, compared to 44% of black women and 55% of Hispanic women ($p<0.001$). Among women who received chemotherapy, 48% of non-Hispanic white women initiated RT within 6 months, compared to 37% of black women and 39% of Hispanic women ($p<0.001$). In multivariate models stratified by age group and receipt of another adjuvant treatment, receipt of RT more than 1 year post-diagnosis was associated with higher odds of all-cause and breast cancer specific mortality (ORs ranging from 3.88 to 13.04, $p<0.01$). Initiation of chemotherapy beyond four months post-diagnosis was associated with higher odds of all-cause mortality (ORs ranging from 1.67 to 2.79, $p<0.05$) and breast cancer-specific mortality (ORs ranging from 1.69 to 3.89). The effect of timing of chemotherapy was more important among younger women ages 65-69 years old. After

controlling for other covariates, race/ethnicity was only predictive of mortality in models assessing the effect of timing of chemotherapy among women who also received RT.

Conclusions

In this study, black and Hispanic women experienced more treatment delays and were less likely to receive guideline-recommended care compared to white women. Black and Hispanic women also were more likely to have clinical characteristics associated with poorer prognosis. Delays in initiation of RT beyond 6 months and delays in initiation of chemotherapy beyond 4 months generally were associated with worse health outcomes, as did certain clinical characteristics including advanced stage, having positive lymph nodes, and negative hormone receptor status. It is therefore critically important that elderly minority women at risk for under-treatment and delayed treatment be informed of the potential benefits and risks of adjuvant therapy and initiate treatment as soon as possible after diagnosis.

Introduction

Surpassed only by lung cancer mortality, breast cancer is the second most fatal cancer among women, with an estimated 41,000 deaths attributable to breast cancer in 2008 (American Cancer Society [ACS], 2008). Although prognosis is generally good for breast cancers diagnosed early (i.e., 85-100% of stage I and II patients are alive after five years of follow-up), 5-year survival rates for patients with stage III and IV disease are only 58% and 19%, respectively (Gloeckler Ries et al., 2003). Recent reductions in overall breast cancer mortality likely reflect the development and uptake of screening interventions and innovative treatment options (Berry et al., 2005). However, breast cancer-specific mortality remains disproportionately higher among black women, even after controlling for differences in stage of disease, tumor biology (e.g., estrogen receptor [ER] and progesterone receptor [PR] status), and insurance access (ACS, 2008; Bach et al., 2002a).

Racial/ethnic variation in mammography use and timely detection of early stage breast cancer has been widely studied, and both have been the target of many public health interventions and advocacy campaigns (Campbell, 2002; Hahn et al., 2007). Differences in treatment are now the focus of many studies examining health disparities in breast cancer (Banerjee et al., 2007; Bigby and Holmes, 2005; Curtis et al., 2008; Du and Simon, 2005; Gorin et al., 2006; Lund et al., 2008). In general, black women are more likely to experience treatment delays after diagnosis and less likely to receive cancer-directed surgery, radiation therapy (RT) after breast conserving surgery (BCS), and hormonal therapy, even after controlling for age, tumor size, stage, ER/PR status, and nodal status (Lund et al., 2008).

Many nagging questions remain with respect to optimal breast cancer treatment strategies, including questions about sequencing and compatibility of multiple systemic adjuvant therapies (Bartelink, 2007; Gradishar and O'Regan, 2003) as well as impact of delays in initiation of radiotherapy and chemotherapy on recurrence and survival (Hartsell et al., 1995; Hebert-Croteau et al., 2002; Lohrisch et al., 2006). Appropriate timing of breast

cancer care is an important unresolved issue in the literature. Some studies have demonstrated that 2-3 month delays in initiation of RT are associated with higher mortality and/or local recurrence (Gold et al., 2008; Hebert-Croteau et al., 2004; Hershman et al., 2006b; Wyatt et al., 2008). Similarly, other studies have found that delays of 2-3 months in initiation of adjuvant chemotherapy after surgery correspond to higher mortality (Hershman et al., 2006a) and/or inferior survival (Lohrisch et al., 2006). On the other hand, some studies report that timing of initiation of RT and chemotherapy does not significantly affect long-term survival (Hartsell et al., 1995; Hebert-Croteau et al., 2004; Hershman et al., 2006a; Shannon et al., 2003), and a recently published Cochrane review article by Hickey and colleagues (2006) on the topic concludes that different approaches to sequencing and timing of chemotherapy and RT do not significantly alter survival or recurrence as long as RT is initiated within 7 months of surgery. At least two studies have shown that delays in breast cancer diagnosis and treatment are more common among black women (Gorin et al., 2006; Lund et al., 2008); as such, if timing of initiation of RT or chemotherapy is important, differential timing of receipt of these by race/ethnicity may explain in part disparities in health outcomes.

The impetus for developing quality metrics for breast cancer was motivated by, and based upon, the existence of well-established clinical guidelines (Desch et al., 2008). Quality metrics published by the American Society for Clinical Oncology (ASCO)/National Comprehensive Cancer Network (NCCN) not only specify appropriate type of therapy and clinical indications for use in breast cancer patients, but also time frames within which such therapy should commence (Desch et al., 2008). Specifically, a quality metric is defined by a count numerator and an appropriate denominator indicating the eligible patient population that should receive the treatment or procedure (Hassett et al., 2008). Defining the denominator requires specificity in timing; over what period should care be considered adherent if the treatment/procedure is received? (Hassett et al., 2008) Current breast

cancer quality metrics published by ASCO/NCCN specify that RT after BCS should be received within 1 year of diagnosis for stage I-III cancers and that postoperative, adjuvant chemotherapy should be received within 4 months of diagnosis for stage II-III, hormone receptor negative cancers (Desch et al., 2008). Given the controversy over the clinical significance of timing of treatment and concurrent existence of quality metrics based upon time-sensitive endpoints, we assessed the effect of timing of initiation of RT and chemotherapy on 5-year, all-cause and disease-specific mortality. Recognizing that each type of therapy is clinically indicated for different patient populations, this study examined timing of radiation therapy among women with stage I-III breast cancers who first received BCS, and timing of postoperative, adjuvant chemotherapy was examined among women with stage II-III breast cancers who received any surgery (either mastectomy or BCS) in separate regressions (Carlson et al., 1996; Desch et al., 2008; NIH, 1990; NIH, 2000).

Methods

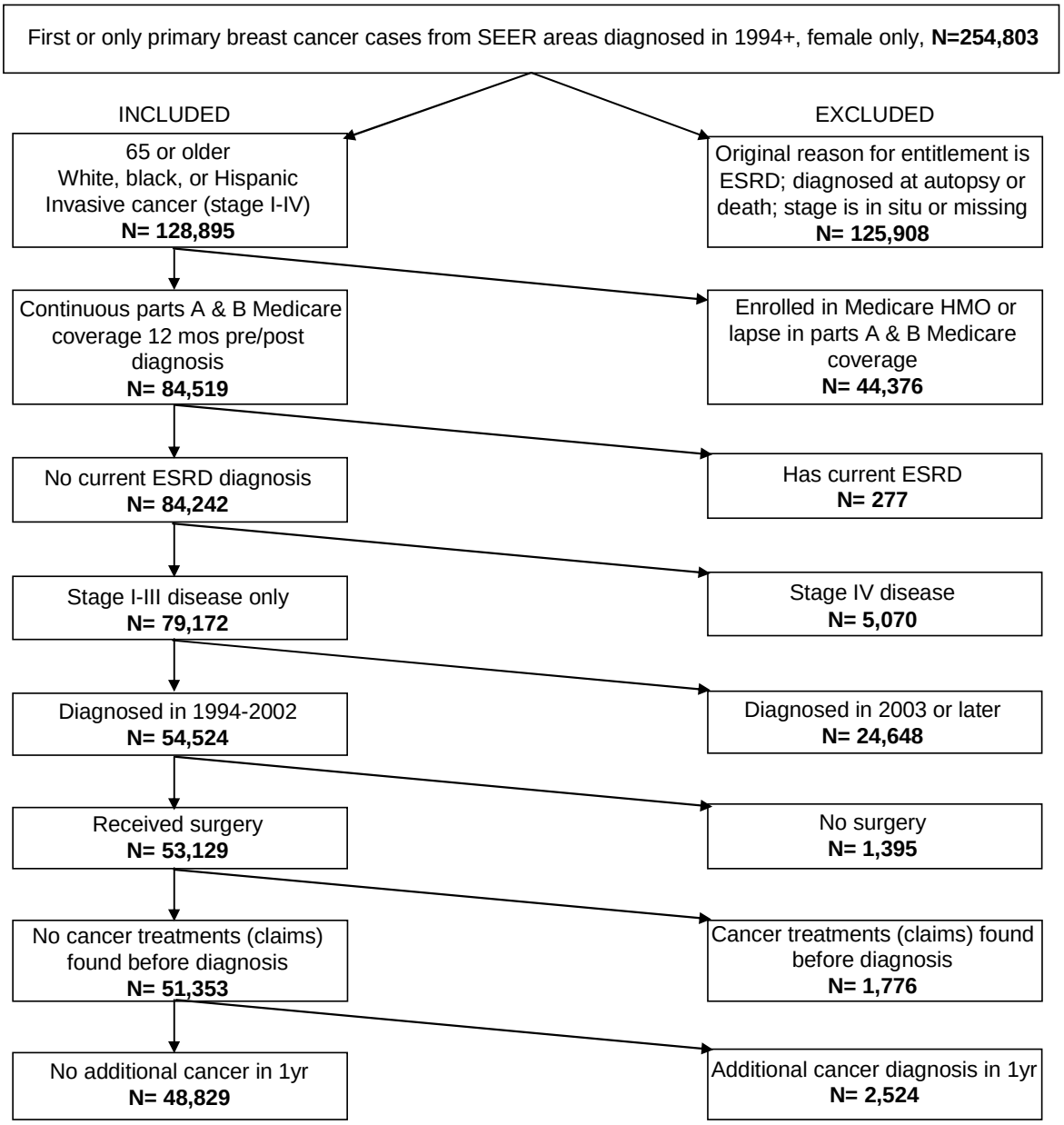
Data Source and Patient Population

Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare claims data were used to examine the effect of therapeutic timing on long-term health outcomes for the population of women ages 65 and older diagnosed with primary breast cancer in 1994-2002, with vital status follow-up through 2007. SEER data contain information about basic demographics, diagnosis, staging, tumor characteristics, and initial mode of treatment and have been linked to claims data for the population of older women insured by Medicare in order to provide more detailed information about cancer treatment, healthcare cost and utilization patterns, co-morbid conditions, and timing of treatment (Warren et al., 2002c).

Inclusion/exclusion criteria for the current study required that subjects be females with a new diagnosis of American Joint Committee on Cancer (AJCC) stage I-III primary

breast cancer first reported during the study period. Women with a prior breast cancer diagnosis, unknown or unclassified stage of disease, in situ disease, or stage IV disease were excluded. In addition, women of racial/ethnic background other than non-Hispanic white, non-Hispanic black, and Hispanic were excluded, due to concerns about insufficient power to conduct sub-analyses, given the low number of these individuals in SEER registry areas. Additionally, to ensure that we captured complete medical claims and treatment information, we included only women who were enrolled in parts A and B Medicare fee-for-service in the 12 months prior to diagnosis and post-diagnosis, or until death, whichever occurred first. We further excluded women with end stage renal disease (ESRD) and women younger than 65. In addition, women with additional cancer diagnoses within 12 months of the index breast cancer diagnosis were excluded to avoid confusion in distinguishing adjuvant therapies targeting multiple cancers. Finally, only cancer patients who had received primary surgery were eligible for inclusion. Primary surgery was defined as receipt of breast-conserving surgery (including segmental mastectomy, lumpectomy, quadrantectomy, tylectomy, wedge resection, nipple resection, excisional biopsy, or partial mastectomy) or mastectomy (including total simple, modified radical, radical, extended radical, or subcutaneous mastectomy) as the first definitive cancer treatment. Figure 18 summarizes these general inclusion/exclusion criteria and resulting effects on sample size. For regression models of the effect of timing of RT, analyses were further limited to women who first received breast conserving surgery. For regression models of the effect of timing of adjuvant chemotherapy, analyses were limited to women with stage II-III disease who had not received neoadjuvant chemotherapy.

Figure 18: General inclusion/exclusion criteria and corresponding effects on sample size



Notes: SEER: Surveillance, Epidemiology and End Results; ESRD: End Stage Renal Disease; HMO: Health Maintenance Organization

Dependent Variable

The primary outcomes of interest for this study were all-cause and breast cancer-specific mortality at five years post-diagnosis. Overall survival time was not examined in light of inherent problems with measurement, including possible lead-time bias, length-time

bias, and analytic difficulties in teasing out competing risks of death in hazard models, which have been discussed at length by other authors (Boyle et al., 2005; Earle et al., 2002; Ries et al., 2006; Sant et al., 2006; Schwartz, 1980). Recurrence also was not the focus of the current study, given that nearly all previous analyses have demonstrated that delayed therapy leads to significantly greater risk of recurrence (Gold et al., 2008; Hartsell et al., 1995; Hebert-Croteau et al., 2004; Wyatt et al., 2008); more importantly, breast cancer recurrence or relapse is not easily measured using SEER-Medicare data. Five years post-diagnosis was considered an appropriate time period of follow-up to observe long-term benefits (and risks) of cancer treatment and is consistent with follow-up time employed in the literature.

Independent Variables of Interest

Timing of initiation of radiation therapy after breast conserving surgery and initiation of adjuvant chemotherapy in months since diagnosis were independent variables of interest in separate regressions. Follow-up time for receipt of radiation therapy and adjuvant chemotherapy in the Medicare claims was extended to 24 months post-diagnosis in an attempt to capture all relevant RT and chemotherapy claims. The first claim on record for each of the treatments of interest was retained as the initial date of service and from it we subtracted the date of diagnosis to determine time in months between diagnosis and initiation of therapy. Some imprecision in time elapsed may exist because SEER reports only month and year of diagnosis, not month/day/year; as such, a woman diagnosed and receiving surgery on the last day of one month and receiving RT on the first day of the next month is classified as having received RT one month post-diagnosis. Specification of timing variables was considered continuously and categorically based upon cutoff times previously shown in the clinical literature to be meaningful (Gold et al., 2008; Hartsell et al., 1995; Hebert-Croteau et al., 2004; Hershman et al., 2006a; Hershman et al., 2006b; Hickey et al.,

2006; Lohrisch et al., 2006; Tsoutsou et al., 2009); based upon individual Wald test statistics and comparisons of the overall log likelihoods, categorical versions of timing variables were retained in final models.

Race/ethnicity was also an important independent variable of interest. Race/ethnicity was taken from SEER-reported data instead of Medicare-reported race/ethnicity data, because of well-known measurement problems and inconsistencies over time in the Social Security Administration's definition of racial and ethnic groups and the fact that SEER uses a Spanish-surname algorithm in addition to self-reported race information to ensure greater accuracy in reporting Hispanic ethnicity (Bach et al., 2002a). For the purposes of this analysis, racial/ethnic classification was limited to non-Hispanic white, non-Hispanic black, and Hispanic.

Control Variables

Control variables included age; stage; histologic grade; hormone receptor (estrogen and progesterone receptor) status; axillary lymph node involvement; co-morbidity score; State-Buy-In months (a proxy for eligibility for state assistance and low income status); marital status at diagnosis; year of diagnosis; census-tract level income, education, and neighborhood racial composition; and distances to nearest radiation therapy and chemotherapy providers and distance traveled for surgery. With the exception of the co-morbidity score and distance to providers, all control variables were obtained directly from the SEER-Medicare data files. Co-morbidity score was calculated using a breast cancer-specific method described by Klabunde and colleagues (2007), which expands upon the Charlson co-morbidity index by adding breast cancer-specific weights to the overall score for co-morbid conditions identified in inpatient and/or physician claims during the 12 month period prior to cancer diagnosis. The NCI combined index has been shown to be a better predictor of non-cancer mortality in the breast cancer population compared to other

commonly used co-morbidity indices (Klabunde et al., 2007). Distance traveled for surgery was calculated by obtaining the geographic longitudinal/latitudinal distance between patient residence zip code centroid and provider zip code centroid for the facility where women received breast conserving surgery or mastectomy, in an approach similar to that used by other authors (Meden et al., 2002; Nattinger et al., 2001; Schroen et al., 2005; Shea et al., 2008). Distance to nearest radiation and chemotherapy providers was determined similarly by calculating the minimum possible distance between patient residence zip code centroid and the zip code centroid for the nearest radiation and chemotherapy providers (based upon Medicare-certified providers who filed any radiation therapy or chemotherapy claim for any breast cancer patient during the time since 1994). Straight-line distance to care has been shown to be a reasonable proxy for relative travel time and geographic access to care (Phibbs and Luft, 1995). Distance variables were measured in miles and specified in analytic models using indicators for non-zero distances and zero distances (i.e., when provider and patient zip code were identical).

Statistical Analysis

Bivariate descriptive statistics first assessed overall and breast cancer-specific mortality 5 years post-diagnosis by racial/ethnic group (Pagano and Gauvreau, 2000; Rothman et al., 2008). Survival time and timing of receipt of RT and/or chemotherapy also were examined by race/ethnicity. Bivariate analyses employed chi-squared and t-tests as appropriate to test differences by group (Chernoff and Lehmann, 1954; Pagano and Gauvreau, 2000).

Among those women who met inclusion criteria and received BCS followed by RT, multivariate logistic regression was used to determine likelihood of all-cause and breast cancer-specific mortality five years post-diagnosis as a function of timing of initiation of RT and race/ethnicity, controlling for covariates (Berkson, 1944; Hosmer and Lemeshow, 2000;

Rothman et al., 2008). Among those women who met inclusion criteria and received post-operative adjuvant chemotherapy, multivariate logistic regression was used to determine the likelihood of 5-year all-cause and breast cancer specific mortality as a function of timing of initiation of chemotherapy and race/ethnicity, controlling for covariates. All models of timing of therapy were limited to only those women who actually received the treatment of interest; as such, women who did not receive RT at all were not included in timing of RT models, and women who did not receive chemotherapy at all were not included in timing of chemotherapy models. Interactions of race/ethnicity and timing of therapy were examined to determine whether the effect of timing varied by racial/ethnic group (i.e., to test sub-population variations in treatment effect) (Rothman et al., 2008; Wooldridge, 2006); lack of evidence for effect modification in multiple models led us to exclude these interaction terms from final model specification.

We theorized that model behavior would vary substantially by age group and receipt of another anticancer therapeutic regimen, leading to a need to stratify by age group (younger than 70 years versus 70 years and older) and by receipt of another anticancer treatment (Rothman et al., 2008). Clinical trials and subsequent guidelines for many years omitted women 70 years and older, likely affecting physician practicing patterns and health outcomes. In addition, the effect of timing of one anticancer treatment on mortality may be modified by receipt of another anticancer therapy (e.g., chemotherapy when timing of RT is of primary interest in the model) due to the nature of sequencing and treatment planning. We tested the need for stratum-specific models empirically by first interacting each variable in the models with binary indicators for age group, receipt of chemotherapy (in RT timing models), and receipt of RT (in models of chemotherapy timing). We then ran unrestricted (with interactions) and restricted models and comparing likelihood ratio test statistics (Rothman et al., 2008). We also examined Wald test statistics for the joint significance of

the age-specific, chemotherapy-specific, and RT-specific interaction terms, in a Chow-like test fashion for the nonlinear model (Rothman et al., 2008).

Missing data were examined closely. In general, missing data were rare in the SEER-Medicare dataset; however, we included dummy indicators for important clinical variables that were missing in higher numbers (such as grade and lymph node status) and used complete case analysis (CCA) for remaining missing variables.

Wald tests were used to test significance of variable constructs (e.g., the group of dummy variables for year of diagnosis) (Wooldridge, 2006). Huber-White robust standard errors were reported for all final regressions, and the 5% level of significance was to assess predictive power of each independent variable (Hosmer and Lemeshow, 2000; Wooldridge, 2006). The general form for the adjusted logistic regression model examining the effect of timing of radiation therapy is:

$$\Pr(Death_i) = f(\beta_0 + \beta_1 \text{TimingRT}_i + \beta_2 \text{Race/Ethnicity}_i + \beta_3 \text{Chemo}_i + \gamma Z_i + \varepsilon_i)$$

Where "TimingRT" is timing of receipt of radiation therapy, "Race/Ethnicity" is non-Hispanic white, non-Hispanic black, or Hispanic, "Chemo" is chemotherapy, "Z" is a vector of all other patient and community control variables, and "ε" is the error term.

The general form of the adjusted logistic regression examining the effect of timing of adjuvant chemotherapy is:

$$\Pr(Death_i) = f(\beta_0 + \beta_1 \text{TimingC}_i + \beta_2 \text{Race/Ethnicity}_i + \beta_3 \text{RT}_i + \gamma Z_i + \varepsilon_i)$$

Where "TimingC" is timing of receipt of chemotherapy, "Race/Ethnicity" is non-Hispanic white, non-Hispanic black, or Hispanic, "RT" is radiation therapy, "Z" is a vector of all other patient and community control variables, and "ε" is the error term.

Results

Of the 48,829 women who met general inclusion/exclusion criteria, 38,574 women received breast conserving surgery as the first anticancer treatment post-diagnosis and were eligible for the sub-sample of women for whom timing of RT was assessed. 20,898 women with stage II-III disease received surgery, had no claims for neoadjuvant chemotherapy, and thus were included in the sub-sample for women for whom timing of chemotherapy was assessed. In bivariate analyses, across both RT and chemotherapy sub-samples (Tables 20 and 21), non-Hispanic black women died more often from breast cancer within 5 years (11% versus 5% in non-Hispanic white women and 7% in Hipanic women; $p<0.001$) and had higher all-cause mortality at 5 years (31% versus 22% in non-Hispanic white women and 23% in Hispanic women; $p<0.001$). Black women were also least likely to ever receive RT (51% versus 58% in white women and 58% in Hispanic women; $p<0.001$) (Table 20). No statistically significant differences were observed in overall receipt of adjuvant chemotherapy by race/ethnicity ($p=0.111$). Median time to initiation of RT was 2 months post-diagnosis, conditioned on not having received chemotherapy, whereas median time to initiation of RT was 5 months post-diagnosis, among women who received chemotherapy. Timing of initiation of RT varied significantly by race/ethnicity; overall, approximately 40% of white women receiving RT within two months of diagnosis, compared to 26% of black women and 34% of Hispanic women ($p<0.001$), but black women and Hispanic women who received RT also were more likely to have received adjuvant chemotherapy (24% and 23% respectively, compared to 20% in white women, $p<0.001$) (Table 20). Median time to initiation of adjuvant chemotherapy was 2 months post-diagnosis; timing of initiation of chemotherapy also varied across racial/ethnic group, but to a lesser extent, with non-Hispanic black women being slightly more likely to commence chemotherapy beyond 2 months post-diagnosis (Table 21).

Table 20: Descriptive statistics of SEER-Medicare patient sample for timing of radiation therapy models (women with stage I-III cancer who received breast conserving surgery)

Characteristic	% or mean(SD) *White (N=34,965)*	% or mean(SD) *Black (N=2,273)*	% or mean(SD) *Hispanic (N=1,336)*	p-value
Dependent variable				
Died within 5 yrs of diagnosis	22.22	30.53	22.75	<0.001
Died of breast cancer in 5 yrs	5.33	10.07	6.89	<0.001
Mean survival time (months)	59.9 (36.9)	53.4 (36.2)	56.7 (36.4)	<0.001~ 0.053#
Key independent variable				
Ever received RT	58.18	51.37	58.35	<0.001
Timing of initiation of RT, conditioned on having received RT (mean in months)	2.73 (2.93)	3.79 (3.51)	3.12 (3.00)	<0.001~ <0.001#
<=6 mos.	90.90	82.23	87.48	
>6 and <=12 mos.	7.43	14.85	10.71	<0.001
>12 mos.	1.67	2.92	1.81	
Patient-level variables				
Age at diagnosis	75.7 (6.64)	75.2 (6.79)	74.4 (6.37)	0.0013~ <0.001#
Stage at diagnosis				
Stage I	64.47	52.35	56.44	
Stage II	32.3	41.53	38.47	<0.001
Stage III	3.23	6.12	5.09	
Grade				
Well-differentiated	22.71	15.05	21.78	
Moderately-differentiated	40.58	34.49	36.75	
Poorly-differentiated	22.76	31.54	26.57	<0.001
Anaplastic	1.54	1.63	1.27	
Grade missing	12.41	17.29	13.62	
Hormone receptor status				
ER positive	71.8	56.8	66.24	
ER unknown	16.51	24.55	21.11	<0.001
PR positive	59.02	45.18	54.27	
PR unknown	17.81	25.60	22.16	
Node positive	18.51	23.8	22.83	<0.001
Node status missing	24.14	26.88	21.33	
Co-morbidity index score	0.25 (0.46)	0.41 (0.61)	0.33 (0.53)	<0.001~ <0.001#
Received chemotherapy	19.91	24.34	23.16	<0.001
Married	44.97	24.33	39.3	<0.001
Low income (State-Buy-In)	13.47	44.57	49.4	<0.001
Year of diagnosis				
1994	8.62	8.67	6.81	
1995	8.76	8.93	9.06	
1996	8.54	8.62	8.38	
1997	8.78	8.32	9.13	
1998	8.49	8.71	7.71	0.444
1999	8.93	7.88	8.98	
2000	15.81	17.69	16.77	
2001	16.26	15.66	16.62	
2002	15.82	15.53	16.54	

Notes: p-values derived from chi-squared tests or t-tests as appropriate; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; SD: standard deviation; ~ indicates two-sample t-tests between white and black groups; # indicates two-sample t-tests between white and Hispanic groups

Table 21: Descriptive statistics of SEER-Medicare patient sample for timing of adjuvant chemotherapy models (women with stage II-III cancers who received primary surgery)

Characteristic	% or mean(SD) *White (N=18,462)*	% or mean(SD) *Black (N=1,596)*	% or mean(SD) *Hispanic (N=840)*	p-value
Dependent variable				
Died within 5 yrs of diagnosis	35.14	44.55	34.68	<0.001
Died of breast cancer in 5 yrs	13.05	19.92	14.66	<0.001
Mean survival time (months)	51.1 (34.9)	44.8 (32.6)	50.3 (34.5)	<0.001~ 0.69#
Key independent variable				
Ever received chemotherapy	34.7	36.85	36.87	0.111
Timing of chemotherapy initiation, conditioned on receiving chemotherapy (mean in months)	3.78 (5.22)	4.09 (5.16)	3.31 (4.25)	0.117~ 0.168#
<=4 mos.	84.53	81.77	85.71	0.169
>4 mos.	15.47	18.23	14.29	
Patient-level variables				
Age at diagnosis	76.7 (7.1)	76.2 (7.17)	75.6 (7.13)	0.009~ <0.001#
Stage at diagnosis				
Stage II	87.33	82.08	85.12	<0.001
Stage III	12.67	17.92	14.88	
Grade				
Well-differentiated	12.1	7.96	9.29	
Moderately-differentiated	38.75	30.2	37.14	
Poorly-differentiated	34.84	45.55	39.52	<0.001
Anaplastic	2.28	1.69	1.9	
Grade missing	12.02	14.6	12.14	
Hormone receptor status				
ER positive	67.91	53.38	62.62	
ER unknown	16.1	23.5	21.07	<0.001
PR positive	54.78	41.54	52.14	
PR unknown	17.2	24.19	22.14	
Axillary lymph nodes				
Node positive	53.92	53.51	55.12	0.066
Node status missing	15.15	17.61	14.17	
Co-morbidity index score	0.29 (0.51)	0.41 (0.62)	0.35 (0.55)	<0.001~ 0.001#
Married	40.01	23.31	34.17	<0.001
Low income (State-Buy-In)	17.69	49.62	53.81	<0.001
Year of diagnosis				
1994	9.14	8.65	8.57	
1995	8.64	8.71	9.17	
1996	8.15	7.89	7.62	
1997	8.06	7.71	8.93	
1998	8.15	8.02	7.98	0.807
1999	8.16	8.52	8.93	
2000	16.18	18.23	16.31	
2001	17.08	15.23	17.26	
2002	16.45	17.04	15.24	

Notes: p-values derived from chi-squared tests or t-tests as appropriate; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; SD: standard deviation; ~ indicates two-sample t-tests between white and black groups; # indicates two-sample t-tests between white and Hispanic groups

In terms of the distribution of covariates across racial/ethnic group, black and Hispanic women were more likely to be diagnosed with more advanced stage disease ($p<0.001$) in both sub-samples (Tables 20 and 21). Black women more often were classified as having poor histologic grade and less often had hormone receptor positive tumors (Tables 20 and 21). Black women also suffered the highest burden of co-morbidities, followed by Hispanic women (Tables 20 and 21). As well, black women and Hispanic women were less likely than white women to be married and more likely to be classified as low-income according to the State-Buy-In variable (Tables 20 and 21).

Mortality: Effect of Timing of RT

Results of multivariate analyses of the effects of timing of RT on all-cause and breast cancer-specific mortality are summarized in Tables 22 and 23, stratified by age group (65-69 years versus 70 years and older) and receipt of chemotherapy. Across all models, regardless of age group and receipt of chemotherapy, receiving RT more than 1 year after diagnosis corresponded to significantly higher odds of all-cause and breast-cancer specific mortality (ORs ranging from 3.88 to 13.04, $p<0.01$) (Tables 22 and 23). Among women ages 65-69 who did not receive chemotherapy (Table 23), initiating RT between 4 and 5 months corresponded to 2.95 higher odds of all-cause mortality ($p<0.05$), and initiation RT between 5 and 6 months corresponded to 4.85 higher odds of all-cause mortality ($p<0.05$), as compared with women initiating RT within 1 month of diagnosis. Among women ages 70 and older who did not receive adjuvant chemotherapy (Table 23), initiating RT more than 6 months after diagnosis resulted in significantly higher odds of both all-cause mortality (Odds Ratio ([OR] 6-12mos: 2.80, $p<0.01$; OR1year+: 3.88, $p<0.01$) and breast cancer-specific mortality (OR6-12mos: 7.35, $p<0.01$; OR1year+: 6.31, $p<0.01$).

Table 22: Odds ratios for the effect of timing of RT on mortality, among breast cancer patients who received breast conserving surgery and 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**

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; robust standard errors used; BrCa: breast cancer; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; regressions also control for distance traveled to surgery, distance to nearest RT provider, and zip code-level socioeconomic variables;

Table 23: Odds ratios for the effect of timing of RT on mortality, in breast cancer patients who received breast conserving surgery with no adjuvant 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**

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; # this variable perfectly predicted the outcome, as a result, 17 observations were dropped; BrCa: breast cancer; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; regressions also control for distance traveled to surgery, distance to nearest RT provider, and zip code-level socioeconomic variables

In models omitting timing of RT variables (not shown), race/ethnicity as a construct was a significant predictor of all-cause and breast cancer-specific mortality; however, when timing of therapy was considered, the effects of black race and Hispanic ethnicity were no longer statistically significant. The exception to this finding was the model examining breast cancer-specific mortality among women ages 65-69 years old conditioned on receiving chemotherapy (Table 21), in which black race was associated with nearly twice the odds of breast cancer-specific mortality, controlling for all other variables ($p<0.05$).

Other covariates behaved in expected ways; specifically, increasing age, more advanced stage of disease, worse histologic grade, lymph node positivity and missing lymph node status, and higher co-morbidity all were generally associated with higher odds of both all-cause and breast cancer-specific mortality (Tables 22 and 23). Odds of all-cause and breast-cancer specific mortality generally were generally lower with hormone receptor positivity and more recent year of diagnosis (Tables 22 and 23). Low income status and distance to care (results not shown) were not predictive of mortality in this sub-sample (Tables 22 and 23). Among younger women ages 65-69 who received chemotherapy in addition to RT (Table 22), receiving surgery in the same month as diagnosis corresponded to a higher likelihood of all-cause (OR: 1.45, $p<0.05$) and breast cancer-specific (OR: 2.40, $p<0.01$) mortality. Among women ages 70 years and older who did not receive chemotherapy (Table 23), being married was associated with significantly lower odds of all-cause (OR: 0.87, $p<0.05$) and breast cancer-specific (OR: 0.76, $p<0.05$) mortality.

Mortality: Effect of Timing of Chemotherapy

Results of multivariate analyses of the effects of timing of adjuvant chemotherapy on all-cause and breast cancer-specific mortality are summarized in Tables 24 and 25, stratified by age group and receipt of RT. In models conditioned on having received RT (Table 24), regardless of age group examined, initiating chemotherapy more than 4 months post-

diagnosis was highly associated with increased odds of both all-cause and disease-specific mortality; however, in these models, initiation of chemotherapy from prior to 4 months post-diagnosis was not significantly different from initiating chemotherapy within 1 month of diagnosis (the reference group). Among women who did not receive RT in addition to chemotherapy (Table 25), commencing adjuvant chemotherapy more than 4 months post-diagnosis generally was associated with higher mortality, regardless of age group, but in women ages 65-69, the odds of all-cause mortality increased substantially with increasing time to initiation of RT (OR2-3mos: 1.69; $p<0.10$; OR3-4mos: 2.91; $p<0.05$; OR4mos+: 2.34; $p<0.05$). In terms of race/ethnicity, chemotherapy timing models conditioned on having received RT (Table 24) indicated that black race among younger women was highly associated with increased odds of all-cause mortality (ORblack: 1.97, $p<0.01$) and breast cancer-specific mortality (ORblack: 2.40, $p<0.01$), whereas Hispanic ethnicity was associated with higher odds of breast cancer-specific mortality among women 70 years and older. In contrast, in multivariate chemotherapy models conditioned on not having received RT, race/ethnicity was not predictive of mortality (Table 25).

In terms of covariates in these models, increasing age, more advanced stage, and poorly differentiated cell grade were highly correlated with increased odds of all-cause and breast cancer-specific mortality across models, regardless of age or RT receipt, whereas hormone receptor positivity and increasing year of diagnosis generally were associated with lower odds of mortality (Tables 24 and 25). Important differences existed across strata and across the dependent variable specified. For example, lymph node positivity and missing lymph node status were more important (and highly significant) predictors of all-cause and breast cancer specific mortality among women 70 years and older (Tables 24 and 25). As well, the effect of low income status only appeared to matter among women younger than 70 who did not receive RT (OR for all-cause mortality: 2.03, $p<0.01$; OR for breast cancer-specific mortality: 2.01, $p<0.01$) (Table 25). Finally, depending on the dependent variable

examined (all-cause mortality versus breast cancer-specific mortality), the effects of covariates varied; for example co-morbidity burden played a greater role in predicting all-cause mortality than it did in predicting breast cancer-specific mortality (Tables 24 and 25).

Table 24: Odds ratios for the effect of timing of adjuvant chemotherapy on mortality, among stage II-III breast cancer patients who received surgery and RT, stratified by age group

Independent Variable	*65-69 years old (N=1481)*		*70 years and older (N=2713)*	
	All-cause mortality	*BrCa mortality*	*All-cause mortality*	*BrCa mortality*
Timing of initiation of chemotherapy (<=1 month post-diagnosis is reference)				
>1 and <=2 mos.	0.87	0.98	1.07	1.12
>2 and <=3 mos.	1.02	0.75	1.18	1.14
>3 and <=4 mos	0.51	0.46	1.12	1.04
>4 mos.	2.79**	3.89**	2.77**	2.64**
Race/ethnicity (white is reference)				
Black	1.97**	2.40**	1.14	1.22
Hispanic	1.33	1.4	1.53	1.79*
Covariates				
Age (grouped in 5-year categories; 70-74 years is reference)				
75-79 years	-	-	1.64**	1.55**
80-84 years	-	-	1.95**	1.48*
85 years and older	-	-	2.59**	2.08**
Received surgery in diagnosis month	1.52*	1.77**	1.09	1.02
Stage at diagnosis (stage II is reference)				
Stage III	2.49**	2.74**	2.54**	2.62**
Grade (well/moderately differentiated is reference)				
Poorly differentiated/anaplastic	2.00**	2.51**	1.74**	2.21**
Grade missing	1.36	1.69	1.1	1.29
Hormone receptor status (negative, borderline, or unknown is reference)				
ER positive	0.53**	0.47**	0.73*	0.63**
PR positive	0.91	0.73	0.65**	0.62**
Node status (node negative is reference)				
Node positive	1.21	1.33	1.26+	1.45*
Node status missing	1.90+	1.9	1.53*	1.2
Co-morbidity index (score of 0 is reference)				
0.01-1	1.52*	0.98	1.39**	0.96
> 1	1.92	1.0	2.59**	1.14
Married	0.74*	0.87	0.84+	0.84
Low income proxy (State-Buy-In)	0.97	1.05	1.08	1.03
Year of diagnosis (1994 is reference)				
1995	0.71	0.63	0.64+	0.59+
1996	0.91	1.14	0.58*	0.61+
1997	1.37	1.22	0.53*	0.48*
1998	0.82	1.01	0.35**	0.29**
1999	1.0	0.87	0.42**	0.35**
2000	0.56+	0.62	0.45**	0.31**
2001	0.63	0.50+	0.42**	0.29**
2002	0.53+	0.38*	0.29**	0.17**

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; robust standard errors used; BrCa: breast cancer; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; regressions also control for distance traveled to surgery, distance to nearest RT provider, and zip code-level socioeconomic variables

Table 25: Odds ratios for the effect of timing of adjuvant chemotherapy on mortality, in stage II-III breast cancer patients who received surgery and no RT, stratified by age group

Independent Variable	*65-69 years old (N=811)*		*70 years and older (N=1792)*	
	All-cause mortality	*BrCa mortality*	*All-cause mortality*	*BrCa mortality*
Timing of initiation of chemotherapy (<=1 month post-diagnosis is reference)				
>1 and <=2 mos.	0.77	0.82	1.15	0.79
>2 and <=3 mos.	1.69+	1.04	1.05	1.03
>3 and <=4 mos	2.91*	1.08	1.42	1.30
>4 mos.	2.34*	2.10	1.67**	1.69*
Race/ethnicity (white is reference)				
Black	0.77	0.64	1.25	0.99
Hispanic	1.35	0.52	0.68	0.82
Covariates				
Age (grouped in 5-year categories; 70-74 years is reference)				
75-79 years	-	-	1.38*	1.05
80-84 years	-	-	2.21**	1.25
85 years and older	-	-	3.19**	1.12
Received surgery in diagnosis month	1.59+	1.48	1.11	0.95
Stage at diagnosis (stage II is reference)				
Stage III	1.81+	1.64	3.14**	4.96**
Grade (well/moderately differentiated is reference)				
Poorly differentiated/anaplastic	3.28**	3.85**	1.60**	2.32**
Grade missing	1.90+	1.64	1.38+	1.38
Hormone receptor status (negative, borderline, or unknown is reference)				
ER positive	0.64	0.56	0.95	0.79
PR positive	0.86	0.69	0.69*	0.54**
Node status (node negative is reference)				
Node positive	1.00	1.78+	1.52**	1.78**
Node status missing	1.17	2.01	2.06**	2.44**
Co-morbidity index (score of 0 is reference)				
0.01-1	1.44	0.72	1.36*	0.93
> 1	5.06**	1.43	3.74**	1.75*
Married	0.50**	0.91	0.75*	0.70*
Low income proxy (State-Buy-In)	2.03**	2.01*	1.08	0.74
Year of diagnosis (1994 is reference)				
1995	0.81	1.02	1.11	0.97
1996	0.88	1.58	1.12	0.96
1997	1.72	1.86	1.12	0.90
1998	0.59	0.85	1.10	0.81
1999	0.86	0.46	0.97	0.65
2000	1.79	1.85	1.10	0.76
2001	0.72	0.59	0.96	0.67
2002	0.71	0.61	1.26	0.53*

Notes: + significant at 10%; * significant at 5%; ** significant at 1%; robust standard errors used; BrCa: breast cancer; ER: estrogen receptor; PR: progesterone receptor; RT: radiation therapy; OR: odds ratio; regressions also control for distance traveled to surgery, distance to nearest RT provider, and zip code-level socioeconomic variables

Discussion

This study examined early versus late receipt of RT and chemotherapy and variation in treatment effects, in terms of the long-term effects of RT and chemotherapy in different

racial/ethnic and age groups over time. Consistent with prior studies (Gorin et al., 2006; Lund et al., 2008; Shugarman et al., 2009), we have shown that significant differences exist by racial/ethnic group in timing of initiation of radiation therapy and to a lesser extent in timing of initiation of chemotherapy. We also have demonstrated that differences in timing of therapy correlate with health outcomes, specifically, all-cause and breast cancer-specific mortality. Our analyses indicate that initiation of RT beyond 1 year post-diagnosis, regardless of age and receipt of adjuvant chemotherapy, is associated with a greater likelihood of both all-cause and disease specific mortality. Additionally, among women 70 years and older who received RT in the absence of chemotherapy, initiation of RT more than 6 months post-diagnosis was associated with about three times the odds of all-cause mortality and seven times the odds of breast cancer-specific mortality. As well, we observed that among women ages 65-69 who did not receive chemotherapy, initiating RT later than 4-5 months post-diagnosis, relative to initiation within one month of diagnosis, was associated with significantly higher odds of all-cause mortality (Table 23). These data imply that risk of local recurrence in this population may contribute to mortality and that RT generally should be initiated within six months of diagnosis, particularly if adjuvant chemotherapy is not part of the treatment plan. This finding is similar to the conclusions reached by Tsoutsou and colleagues (2009) and Hickey and colleagues (2006) that RT should be initiated within 7 months of surgery, but different studies have suggested that RT should be initiated within 3-4 months to reduce the likelihood of poor health outcomes (Gold et al., 2008; Hartsell et al., 1995; Hebert-Croteau et al., 2004; Hershman et al., 2006b).

In terms of timing of adjuvant chemotherapy, initiation of chemotherapy more than 4 months post-diagnosis was associated with significantly worse outcomes in terms of both all-cause and breast-cancer specific mortality. This finding is somewhat similar to findings from Lohrisch and colleagues (2006) and Hershman and colleagues (2006a) whose studies suggested that adjuvant chemotherapy should be commenced within 12 weeks of surgery.

Particularly among younger women (65-69 years) who did not receive RT, early initiation of chemotherapy (within 2 months of diagnosis) appeared important, at least in terms of all-cause mortality (Table 25). Receipt of adjuvant chemotherapy earlier than 3 months post-diagnosis was not significantly different from initiation of chemotherapy within one month of diagnosis across models, as seen in other observational studies cited above. In models of women ages 65-69 who received RT in addition to chemotherapy, black race was associated with increased odds of all-cause and breast cancer specific mortality, controlling for all other variables; similarly, Hispanic ethnicity was associated with higher odds of breast cancer-specific mortality among women ages 70 and older who received RT (Table 24). The effects of race/ethnicity mattered less in models of women who received chemotherapy in the absence of RT, after controlling for covariates (Table 25).

Delays in care occur for a number of reasons and may be related to poor provider-patient communication, delays in referral, inadequate social support, lack of transportation, distance to oncology providers, opportunity costs involved in seeking care (e.g., missed work days or loss of employment), and/or ambiguity about the value of adjuvant therapy, given the side effect profile of many anticancer treatments (Carpenter and Peppercorn, 2009; Gold et al., 2008; Hershman et al., 2006a, Hershman et al., 2006b). The decision to undergo potentially difficult treatment regimens like chemotherapy is complex given the risks and benefits of adjuvant therapy and requires a more nuanced view of clinical decision making, including an understanding of the structural and organizational characteristics of health services that may impact decisions (Wheeler et al., unpublished data). It is therefore important to further evaluate the potential for delays in receipt of RT among black women and Hispanic women with early stage breast cancer to contribute to disparities in breast cancer outcomes and if validated, to develop educational and structural interventions to address this issue.

This study has several strengths and limitations worth mention. This study reflects the experiences of tens of thousands of women in the US diagnosed with breast cancer over a nine-year period and thus provides important information about the longitudinal effects of timing of radiation therapy and timing of chemotherapy on long term health outcomes. These data are a unique resource for examining patterns of care in cancer among Medicare beneficiaries, who represent 97% of the US population ages 65 and older, and can provide more treatment detail than registry-based data or claims data alone (Warren et al., 2002c). Additionally, we have attempted to control for endogeneity in treatment selection by limiting our analyses to women who received surgery plus the adjuvant treatment of interest and by stratifying on additional adjuvant treatments (excluding hormone therapy); thus, we were able to isolate the effect of timing and effects of race/ethnicity from potentially selection-biased decisions about whether to undergo treatment at all. Previous authors have demonstrated that black women with breast cancer may be less likely to receive certain anticancer treatments compared to white women (see, for example, Bhargava and Du, 2009), and treatment selection may play a substantial role in determining heterogeneity in outcomes (Basu et al., 2007; Hadley et al., 2003). We have further attempted to limit possible endogeneity in the form of reverse causality (specifically in this case, higher likelihood of mortality and poor health status affecting timing of treatment) by including measures for co-morbidity and cancer severity. Nevertheless, some bias may remain; unobservable variables such as physician practicing patterns and intent, health-seeking behavior, social support beyond marital status, and patient trust in the health care system may affect timing of care and long-term health outcomes. Omission of such variables, if important, could have led to an incomplete picture of the effect of timing of therapy on mortality.

We used complete case analysis (CCA) to deal with missing data and to avoid systematic bias potentially introduced by imputation (Rothman et al., 2008; Wooldridge,

2006). CCA involves dropping observations for which data are incomplete and running the analyses only on observations with complete information. The advantage to this approach is that it avoids the biases involved in using multiple imputation approaches, when data are missing at random (Rothman et al., 2008; Wooldridge, 2006). When data are not missing at random, however, using CCA can compound problems because it essentially excludes whole groups of the sample that may be important (i.e., introducing selection bias) (Rothman et al., 2008; Wooldridge, 2006). Alternatives to using CCA are imputing values for missing data and dropping variables for which there are significant missing numbers (Rothman et al., 2008; Wooldridge, 2006). The latter would mean that we would no longer have effect estimates for the covariates missing data and moreover, there may be a confounding problem if the covariate is no longer in the model (Rothman et al., 2008). The former may not make sense particularly with clinical data because treatment decisions are made based upon available clinical information, and imputation often involves random replacement, which is of course not clinically meaningful. Based upon these considerations and after noting that missing data were rare in the SEER-Medicare dataset, we opted against imputation and rather checked for patterns/predictors of missing data (Rothman et al., 2008) and used dummy variables for missing data where appropriate (e.g., lymph node positivity and histological grade).

Noting that racial/ethnic minority groups in this study were more likely to have clinically poorer prognosis based upon tumor features and clinical measures such as stage, histologic grade, hormone receptor status, and lymph node positivity and further noting that these factors were highly predictive of all-cause and breast cancer-specific mortality, it is critical that at-risk minority patients receive guideline-appropriate care as early as possible. Based on our findings and supported by prior studies as noted above, RT should be initiated within six months of diagnosis and adjuvant chemotherapy should be initiated within four months of diagnosis in appropriate patients. Understandably, co-morbidity burden and

ability to withstand potentially invasive adjuvant treatments play a role in treatment planning, and evidence suggests that they vary with race/ethnicity and age (Barni et al., 2010; Bouchardy et al., 2007; Du and Goodwin, 2001; Tammemagi et al., 2005). However, among healthy women, there is very little evidence to suggest that increasing age or ethnic/racial identification reduces the effectiveness of RT or chemotherapy (Barni et al., 2010; Smith et al., 2005). Given that delay in initiation of adjuvant therapy may contribute to poor breast cancer outcomes among minority patients, research is needed to address the causes of delay, address barriers to care, and explore public health interventions that might address health disparities through improved and timely utilization of adjuvant therapies.

CHAPTER 7: POLICY IMPLICATIONS, LIMITATIONS, AND CONCLUSIONS

Summary of findings, policy implications and limitations

This study used population-based SEER-Medicare data to examine receipt of high quality care across vulnerable sub-population groups, focusing on structural/organizational features of health services and dispersion of these characteristics across diverse groups of people. This study represents one of the first attempts to examine these issues interactively and comprehensively in breast cancer research. Previous studies that have explored the relationships between race/ethnicity and health system factors primarily have focused upon different types of structural/organizational variables, such as surgical volume or hospital teaching status (Jerome D'Emilia and Begun, 2005).

In chapter 4, we explored variation in receipt of RT after BCS over time and found that a substantial minority of breast cancer patients 65 years and older failed to receive guideline-recommended RT after BCS and that timing of initiation of RT varied significantly by age group and race/ethnicity. We found evidence that characteristics of the health system play a role in determining receipt of RT and timing of initiation of RT and that these factors, when omitted, likely confound the effect of race/ethnicity. For example, presence of on-site radiation services at the facility where women received surgery resulted in higher odds of RT at nearly every time period examined. Among women 70 years and older, other structural and organizational characteristics, including surgical facility type/ownership, ACoSOG and Radiation Therapy Oncology Group (RTOG) affiliation, played significant roles in determining overall receipt of RT. We also showed that increasing distance to the nearest radiation facility generally was associated with lower odds of ever receiving RT among women ages 65-69 and women ages 70 and older. Finally, we demonstrated that delayed

initiation of RT after BCS is more common among non-Hispanic black women and Hispanic women younger than 70 years old, even after controlling for health services structural/organizational characteristics and multiple covariates, and racial/ethnic differences in ever receiving RT disappear after controlling for health system factors and other potential confounders.

In chapter 5, we examined variation in receipt and timing of initiation of adjuvant chemotherapy among women diagnosed with breast cancer in 1994-2002 and found that although overall use of chemotherapy increased over time, less than half of women diagnosed with stage II or III breast cancer received chemotherapy at the last time period examined (i.e., 2002 diagnoses). Not surprisingly, overall receipt of adjuvant chemotherapy and timing of initiation of adjuvant chemotherapy were closely related to age and hormone receptor status. Generally, women with hormone receptor positive tumors were less likely to receive adjuvant chemotherapy, likely reflecting increased use of hormone therapy, consistent with changing evidence-based guidelines during the time period of interest. In multivariate analyses, race/ethnicity was not significantly predictive of receipt of adjuvant chemotherapy at 4 months post-diagnosis, nor was it predictive of ever receiving adjuvant chemotherapy. Contrary to expectations, structural and organizational characteristics of the surgical facility played a minor role in determining receipt and timing of initiation of chemotherapy; this finding could reflect the disconnect between structural/organizational characteristics measured at the surgical facility and care provided in the community post-surgery. Unfortunately, better institutional and provider data are not readily available at this time, and the need for better structural/organizational measures at oncology care facilities beyond the hospital is critical. Distance to care was not predictive of chemotherapy use in women ages 65-69 years, but among women 70 years and older, increasing distance to the nearest chemotherapy provider generally was associated with lower odds of chemotherapy use at 4 months and ever, although this effect was not always statistically significant.

In chapter 6, we asked whether timing of initiation of RT and adjuvant chemotherapy affected health outcomes, specifically, 5-year all-cause and breast cancer specific mortality. In bivariate analyses, black women died more often from breast cancer and experienced greater overall mortality compared with white women; as well, significant differences in timing of initiation of RT, and to a lesser extent in timing of initiation of adjuvant chemotherapy, were observed by race/ethnicity. In multivariate models examining timing of RT (stratified by age group and conditioned on receipt of chemotherapy), receipt of RT more than 1 year post-diagnosis was associated with significantly higher odds of all-cause and breast cancer specific mortality. In RT timing models conditioned on *not* having received chemotherapy, among women 70 years and older receipt of RT more than 6 months after diagnosis corresponded to 6 to 8 times the odds of breast cancer specific mortality and 3 to 4 times the odds of all-cause mortality. Additionally, in RT timing models conditioned on not having received chemotherapy, among younger women ages 65-69 years, receipt of RT more than 4 months after diagnosis was associated with significantly higher odds of all-cause mortality, relative to women who received RT within one month of diagnosis. In multivariate models examining timing of chemotherapy (stratified by age group and conditioned on receipt of RT), receipt of chemotherapy more than 4 months post-diagnosis was associated with higher odds of both all-cause and breast cancer specific mortality, with odds ratios ranging from 1.7 to 3.9, regardless of receipt of RT; the odds ratios, however, were larger in magnitude generally among women who also received RT. The last point could reflect greater importance of earlier initiation of chemotherapy among women treated with both RT and chemotherapy or it could simply be related to differences in treatment selection (i.e., sicker women are treated more aggressively). We have tried to account for the possibility of bias resulting from treatment selection by including multiple measures of cancer severity and co-morbidity, but use of another technique such as instrumental variables methods may be an important approach to use in future work, as discussed in the

next section. With respect to racial/ethnic disparities in this third paper, among black women ages 65-69 who received both chemotherapy and RT, inclusion of multiple controls in addition to therapeutic timing variables did not eliminate the disparity in mortality between black women and white women; however, the racial/ethnic disparity in mortality in other models disappeared after inclusion of treatment timing variables and other covariates.

This dissertation makes several important contributions to the literature. Few previous analyses have examined racial/ethnic variation in receipt of RT and chemotherapy using specific time-sensitive endpoints. Given the conflicting evidence about the effect of timing of therapy on health outcomes, particularly in older women (Gold et al., 2008; Hartsell et al., 1995; Hebert Croteau et al., 2004; Hershman et al., 2006a; Hershman et al., 2006b; Lorhisch et al., 2006), this study provides additional evidence on optimal timing of radiation therapy and chemotherapy. Further, considering that black women are more likely to be diagnosed with aggressive, advanced stage cancers and that they are more likely to die from breast cancer, as we have shown, earlier initiation of treatment may help minimize racial disparities in breast cancer mortality.

This study also documents the important role that health services characteristics may play in determining quality of care, in particular, receipt of guideline-recommended RT after BCS. To our knowledge, no studies to date have examined how distance to care may affect timing of initiation of breast cancer treatment in elderly women. Distance to care is often examined in terms of overall receipt of radiation therapy or chemotherapy, but timing of treatment as a function of distance to care is not well understood. Among elderly women, distance to care may be especially problematic when transportation and/or family members are not available to help ensure patients make that first critical RT or chemotherapy appointment. Disparities in the quality of care related to age and race/ethnicity have been well-documented in many diseases, including breast cancer. Most previous studies have been cross-sectional in nature and only provide a descriptive picture of disparities; as such,

they are limited in their ability to provide insights as to how the design and functions of the health care system can narrow these differences. In this study, we have shown that health care systems or policies can be designed in such a way to improve the quality of care for breast cancer patients. The possibilities are numerous. For example, interventions that may be inspired by this study include community-level programs designed to provide transportation to RT or chemotherapy treatments for the elderly and for racial/ethnic minorities without regular access to transportation; use of telemedicine collaboration between facilities that are RTOG or ACoSOG affiliated centers often treating complicated breast cancer cases and smaller community hospitals whose advanced breast cancer patients may benefit from inter-institutional tumor board meetings; and greater emphasis on the training and use of nurse navigators to encourage early initiation of adjuvant therapy and to limit underuse of adjuvant therapy in racial/ethnic minorities and elderly patients

Furthermore, despite increased interest in innovation diffusion in health care, diffusion trends across sub-populations have not been examined in breast cancer with the exception of Freedman and colleagues (2009) and Jerome-D'Emilia and Begun (2005). Regional variation in health care cost, utilization, and quality of care has been well documented, but studies examining diffusion trends across racial/ethnic groups, age groups, socioeconomic classes, and organizations are limited in number. This study thus fills an important gap in the diffusion of innovations and health disparities literature.

In addition to the above contributions to the literature, this study has several additional strengths in its design. First, the SEER-Medicare dataset itself allowed us to estimate population-level receipt of appropriate and timely breast cancer treatment across racial/ethnic groups and other sub-populations over time. Medicare claims provide richer detail to treatments received by breast cancer patients than cancer registries alone and allow historic assessment of co-morbid conditions that may affect health care seeking behavior and overall health status. Second, by controlling for a number of potential

confounders determined to be important in the literature, including marital status, neighborhood socioeconomic status, biological features of the tumor, and co-morbidities, this study was able to isolate the effect of structural/organizational variables on the relationships between race/ethnicity and receipt of guideline concordant care. Finally, because this study was limited to Medicare beneficiaries and included State-Buy-In months as a covariate (a proxy for Medicaid enrollment and low income status), the important effect of insurance status on receipt of health care was effectively controlled. Thus, we were able to examine quality of care among fully insured breast cancer patients.

Several limitations exist in this dissertation. First, this study may not be generalizable to the US general population. Our data were limited to Medicare-eligible women ages 65 and older enrolled in parts A and B fee-for-service and living in SEER regions. SEER regions were purposefully chosen to adequately represent minority sub-populations, and studies have shown that the SEER population is very similar to the general population in terms of sex, race, and age distribution (Warren et al., 2002c). Despite this fact, SEER-Medicare data generally represent more urban, affluent, and well-educated people (Warren et al., 2002c); in particular, the lack of information about the cancer experiences of racial/ethnic minorities living in rural areas is unfortunate.

SEER-Medicare data are several years old before they can be used to ensure complete reporting, and late claims may still be a concern (Clegg et al., 2002). More recent data cannot be obtained from NCI, so it is difficult to know whether quality of care has improved or declined in recent years. Additionally, quality of reporting procedures, especially non-hospital-based outpatient chemotherapy and radiotherapy, may be variable or underreported (Clegg et al., 2002; Lamont et al., 2002; Virnig et al., 2002; Warren et al., 2002c). However, because claims are linked to payment, we believe the incidence of underreporting is low. It is also unclear how validly or reliably ER and PR status are recorded in practice and whether variation in ER/PR testing exists by facility type. An

additional limitation of the structural/organizational measures we used was that only information from hospital-affiliated surgical facilities was available. Thus, we could not explore how structural/organizational characteristics of non-hospital affiliated facilities affected treatment planning. We also could not say anything about the providers and facilities patients consulted after initial surgery; clearly, although the surgical facility plays a role in subsequent care, other providers outside of the surgical facility may be important. The lack of information about such facilities indicates a critical need for better data about the health systems providing care to cancer patients, including structural and organizational characteristics of individual facilities and providers. Such information on a national scale is difficult, arguably impossible, for researchers to obtain currently.

The patient information we have from the SEER-Medicare data is somewhat limited in that we did not have access to individual-level income, wealth, or education information (Bach et al., 2002a). We also had no reliable information about supplemental private insurance coverage. Medicaid dual coverage (proxied in this study by State-Buy-In months) is related to socioeconomic status and access to health care resources at the individual level. Including aggregate measures of zip code median income and educational attainment also provided some insight into local resources and socioeconomic environment. Other patient-level factors about which we know nothing include BMI, diet, parity/reproductive history, access to transportation, and burden of seeking care/traveling for appointments, all of which could affect receipt of therapy and/or health outcomes. We also do not have access to the complete medical record, which would provide more detail about care administered and reasons why certain clinical decisions were made (or not made). It may be unclear from the analysis conducted exactly why patients do not get high quality care or why initiation of therapy was delayed. For example, if a woman with stage I disease who has had BCS does not receive RT, is it because the handoff/transition was poorly handled between providers, because the radiation therapist saw the patient but did not

recommend/administer radiation, or because the patient declined radiation? If a woman receives BCS within the same month as diagnosis, but receipt of initial RT occurs 8 months afterwards, is it because the woman was too sick to withstand radiation, because she moved to another state and switched health care providers, or because chemotherapy administration delayed initiation of RT? Such questions are not easily answered in a retrospective study of this nature; however, future studies involving qualitative methods or medical chart reviews may provide additional insight into understanding treatment decision making.

Health care utilization is a complicated measure, in that unobserved variables, such as risk aversion, trust in the health care system, and having a primary "medical home" may affect whether or not a woman receives RT or chemotherapy in a timely manner. Including known confounders from prior studies is one way we have attempted to reduce bias from omitted variables. However, despite our best efforts, unobservable factors may have biased our estimates; most noteworthy is perhaps the absence of information about other breast cancer treatments beyond surgery, radiation therapy, and chemotherapy, such as hormone therapy use. At this time, SEER-Medicare data do not include Part D claims; thus, we have no information about prescription drugs, including hormonal therapy (e.g., tamoxifen).

Finally, this study was observational in nature, which precludes us making statements about causality. However, an experimental study examining these issues, particularly in aim 3, would be ethically infeasible because we could not deny life-prolonging, systemic, breast cancer treatment to women in a control group. Additionally, randomizing women to health facilities with certain structural/organizational characteristics would likely be difficult, and enrollment tricky.

Despite these limitations, this study is a policy-relevant and timely contribution to research about breast cancer and health disparities. From this study, it is clear that structural/organizational characteristics of the health system may independently influence

receipt of high quality care, and also may be correlated with racial/ethnic group. It is further evident that racial/ethnic and age-related disparities in treatment may be minimized by the introduction of creative interventions targeted at the health system itself.

Future research agenda

Considering the possible issues with generalizability associated with using a Medicare fee-for-service population, it would be a natural extension of this work to examine specific aims 1, 2, and 3 in a younger population and in a Medicare managed care population. Information about breast cancer treatment in younger women (i.e., those younger than 65 years old) could be obtained from employer-based, private insurance plan databases. One possible source is private insurance claims data from the National Rural Electric Cooperative Association (NRECA). The NRECA provides employer-based, private insurance to employees and dependents of national electric/utility cooperatives (NRECA, 2009). The NRECA has expressed an interest in improving quality of care among its beneficiaries and has a particular interest in cancer care quality. These data contain personal health information from the medical record, as well as medical claims from inpatient and outpatient medical visits and services rendered (personal communication, Dr. Jeffrey Peppercorn, April 2009). Health care information within this dataset has been relatively underutilized and is unique, in that it may allow targeted exploration of the cancer experiences of rural-dwelling women, who are overrepresented in NRECA membership. Information about breast cancer treatment within Medicare managed care plans could be obtained from private insurance providers who contract with Medicare to provide managed care and from the Medicare-linked Health Outcomes Survey.

This study may benefit from use of instrumental variables (IV) estimation to further address the possibility of bias from treatment selection in aim 3 (Wooldridge, 2006). As described above, despite our best efforts to control for factors that may have affected

treatment planning and timing – in particular, health status and prognosis, using the NCI combined co-morbidity index and tumor characteristics – endogeneity in the form of treatment selection may not have been adequately addressed. We collected data on distance to oncology providers, which did not have an effect on the outcome of interest in aim 3, mortality, but which did to varying extents have an effect on RT and chemotherapy initiation. Distance to care measures may be ideal and appropriate instruments in this case. According to Wooldridge (2006), the two criteria for a good instrument are (1) that it has no effect on the primary outcome of interest (i.e., all-cause and breast cancer specific mortality), and (2) that it is significantly predictive of the endogenous independent variable (in this case, timing of receipt of RT and chemotherapy). These criteria can be tested empirically, and provided that distance measures are found to be appropriate instruments, another paper emerging from this dissertation could be to compare our current results against results from IV estimations.

Additional innovations of interest for future diffusion and health disparities studies in breast cancer care include use of neoadjuvant chemotherapy, decision aids such as the Oncotype Dx® test, breast magnetic resonance imaging (MRI), and sentinel lymph node biopsy (Chen et al., 2008; Katipamula et al., 2009; Mamounas, 2006; Schegerin et al., 2009). These innovations would be excellent candidates for comparative effectiveness studies. Furthermore, given rising health care costs, especially in cancer care, there is a need to evaluate the economic feasibility of using such innovations; as such, cost-effectiveness models for these new detection and treatment modalities need to be developed and validated.

Future studies of breast cancer treatment quality and disparities should include examinations of structural and organizational factors and race/ethnicity in receipt of post-mastectomy RT for tumors greater than 5 centimeters or with four or more positive nodes and patterns of care in stage IV breast cancer. Punglia and colleagues (2006a) and Smith

and colleagues (2008) examined receipt of radiation therapy after mastectomy in elderly women during the 1990s and found that adoption trends differed across practice settings, but more recent practice trends and more detailed structural/organizational factors have not been examined. With respect to stage IV or advanced breast cancer, many treatment options exist (NCCN, 2008), and treatment options have rapidly changed over the years; as such, future studies should examine racial/ethnic, socioeconomic, geographic, and structural/organizational variation in treatment of advanced disease.

Another interesting question related to health disparities in breast cancer is whether and to what degree the introduction of Federally Qualified Health Centers (FQHCs) increased access to and quality of breast cancer care within vulnerable populations. Low-income women with poor access to health care providers and limited financial resources to pay for cancer care may have benefited considerably from the introduction and expansion of this federal initiative, but to our knowledge, no study has explicitly examined the role of FQHCs on improving breast cancer care for at-risk women and eliminating disparities.

Finally, systems thinking could be used to build, parameterize, and validate models to help coordinate breast cancer care across providers and facilities. Recognizing that supply of oncologists and other cancer specialists is limited and that cancer prevalence may be increasing given the aging American population, optimal use of cancer resources is important. For example, earlier stage, uncomplicated breast cancer patients may be treated sufficiently well at lower volume, community-based facilities, whereas advanced stage patients with significant clinical complications may benefit from being treated at higher volume medical facilities with ACoSOG or RTOG affiliations. Because there are fewer of the latter, we should seek to optimize patient allocation in such a way that clinical expertise, technical resource capacity, transportation/travel, and case complexity can be taken into account to ensure the best outcomes for all patients, regardless of stage of disease, socioeconomic status, or race/ethnicity. Use of telemedicine to conduct inter-institutional

tumor board meetings is one way to disseminate expertise across health facilities. However, creative optimization models drawing upon the methods used in industrial engineering and operations research could be used to suggest ways to improve patient care at the health system level.

Conclusions

This dissertation revealed that differences in structure and organization of health services help explain a portion of the racial and ethnic disparities in breast cancer treatment patterns and that timing of adjuvant treatment is important in determining long term health outcomes, including breast cancer specific and all-cause mortality. Further, given that non-Hispanic black women are more often than non-Hispanic white women diagnosed with advanced stage disease with clinical characteristics commonly associated with poorer prognosis, it may be vitally important that they initiate adjuvant treatment earlier to improve chances of survival. This study is a truly unique contribution to the health services and breast cancer literatures in that it helps identify system-level factors that may contribute to persistent disparities in breast cancer. Findings should help policymakers and stakeholders better target efforts to equalize health care access and quality across diverse user populations and to ensure that patients and their health care providers have access to the most comprehensive clinical information possible to make informed health care decisions.

APPENDIX A. VARIABLE CODING SCHEMES AND DEFINITIONS

Variable Name	*Source*	*Description*	*Coding*
Identification variables (for purposes of identifying the sample within the SEER-Medicare dataset)			
regcase	PEDSF-Master file	Patient unique ID number	Numeric string (10 characters)
cssch1-cssch10	PEDSF-SEER	Collaborative Stage (CS) schema grouping based on primary site and histology	Numeric string (2 characters) Breast: 58
siter1-siter10	PEDSF-SEER	Site group in which the primary tumor originated, based on International Classification of Disease (ICD) codes	Numeric string (2 characters) Breast:46
med_dod	PEDSF-EDB	Medicare date of death, reported by Social Security Administration	Numeric: MMDDYYYY
dod_flg	PEDSF-IMS	Level of agreement between SEER and Medicare on patient's death and date of death	Categorical 0-not dead 1-dead, files agree 2-dead, off by 1-3 months 3-dead, off by 4-6 months 4-dead Medicare only 5-dead SEER only 6-dead, months missing
codpub	PEDSF-SEER	Cause of death recode (accounts for newly valid International Classification of Disease codes and includes cancer and non-cancer causes of death)	Numeric string (4 characters) Breast cancer-specific death: 046
m_sex	PEDSF-EDB	Patient's sex according to Medicare	Categorical 1-male 2-female
rsncd1	PEDSF-EDB	Original reason for entitlement for Medicare (age, disability, or end stage renal disease [ESRD])	Categorical 0-age 1-disability 2-ESRD 3-disability/ESRD
cur_ent	PEDSF-EDB	Current reason for entitlement for Medicare (age, disability, or end stage renal disease [ESRD])	Categorical 0-age 1-disability 2-ESRD 3-disability/ESRD
chr_esrd	PEDSF-EDB	End stage renal disease (ESRD) status	Categorical 0-no ESRD Y-has ESRD
MDCRSTAT	MEDPAR	Beneficiary Medicare status code; reason for beneficiary's entitlement as of the reference date (age, disability, or end stage renal disease [ESRD])	Categorical 10-aged without ESRD 11-aged with ESRD 20-disabled without ESRD 21-disabled with ESRD

Variable Name	*Source*	*Description*	*Coding*
			31-ESRD only
ptacnt1986-ptacnt2007	PEDSF-EDB	Number of months covered for Part A in each year from 1986-2007	Categorical 0-not covered 01-12-months covered
ptbcnt1986-ptbcnt2007	PEDSF-EDB	Number of months covered for Part B in each year from 1986-2007	Categorical 0-not covered 01-12-months
hmocnt1986-hmocnt2007	PEDSF-EDB	Number of months as a health maintenance organization (HMO) member in each year from 1986-2007	Categorical 0-not covered 01-12-months covered
numprims	PEDSF-SEER	Number of primary tumors ever recorded for the patient	Continuous
seq1-seq10	PEDSF-SEER	Number and sequence of all reportable malignant, in situ, benign, and borderline primary tumors over patient's lifetime	Numeric string (2 characters)
lat1-lat10	PEDSF-SEER	Laterality: side of a paired organ of side of the body on which the reportable tumor emerged	Categorical 0-not paired site 1-right; origin of primary 2-left; origin of primary 3-only one side, but unspecified 4-bilateral involvement 9-paired site, no info on laterality
src1-src10	PEDSF-EDB	Type of reporting source	Categorical 1-hospital/outpatient 3-lab only 4-physician's office 5-nursing home or hospice 6-autopsy 7-death certificate
Patient-level socio-demographic variables			
rac_recb	PEDSF-SEER	Recoded race/ethnicity from SEER (more accurate than Medicare)	Categorical 1-non-Hispanic white 2-black 3-8,12-other 9-unknown 11-Hispanic
birthm	PEDSF-EDB	Medicare month of birth	Numeric string (2 characters)
birthyr	PEDSF-EDB	Medicare year of birth	Numeric string (4 characters)
modx1-modx10	PEDSF-SEER	Month of diagnosis by a recognized medical practitioner	Categorical 01-12-valid month 13,99-unknown
yrdx1-yrdx10	PEDSF-SEER	Year of diagnosis by a recognized medical practitioner	Categorical 1973-2005-valid

Variable Name	***Source***	***Description***	***Coding***
			year
age1dx	PEDSF-SEER	Age at first ever cancer diagnosis	Continuous
age_dx	PEDSF-SEER	Age at diagnosis	Continuous
ager1-ager10	PEDSF-SEER	Age at diagnosis recode to 5-year intervals	Categorical
dx65m, dx65y	PEDSF-SEER	Diagnosis date at age 65 or older	Numeric: MMDDYYYY
seq1ov65	PEDSF-SEER	Shows whether patient was 65 or older at first cancer diagnosis	Categorical Y=yes N=no
stbuy1986-stbuy2007	PEDSF-EDB	Medicaid dual enrollment; number of months with state buy-in (Medicaid) coverage in each year from 1986-2007	Categorical 0-not covered 01-12-months
zip1986-zip2007	PEDSF-EDB	Patient zip code; assigned as last zip code of patient residence in that year	Numeric string (9 characters)
county	PEDSF-SEER	Patient county	See FIPS county codes
state	PEDSF-SEER	Patient state	See FIPS state codes
hsa	PEDSF-ARF	Health Service Area, taken from Area Resource File (ARF)	Numeric string (3 characters)
reg1-reg10	PEDSF-SEER	SEER registry code at diagnosis	Categorical 01-San Francisco 02-Connecticut 20-Detroit 21-Hawaii 22-Iowa 23-New Mexico 25-Seattle 26-Utah 27-Atlanta 31-San Jose 35-Los Angeles 37-rural Georgia 41-greater California 42-Kentucky 43-Louisiana 44-New Jersey
marst1-marst10	PEDSF-SEER	Patient's marital status at the time of diagnosis of the reportable tumor	Categorical 1-single 2-married 3-separated 4-divorced 5-widowed 9-unknown
urbrur	PEDSF-ARF	Urban/rural recode for patient residence	Categorical 1-large metro 2-metro 3-urban 4-less urban 5-rural 9-unknown

Variable Name	*Source*	*Description*	*Coding*
Area/aggregate socio-demographic variables			
ctmed00 and ctmed90	PEDSF-Census	Median household income for census tract	Continuous
medag00 and medag90	PEDSF-Census	Median household income by age for census tract	Continuous
medrc00 and medrc90	PEDSF-Census	Median household income by race for census tract	Continuous
zpmed00 and zpmed90	PEDSF-Census	Median household income for zip code	Continuous
ctnon00 and ctnon90	PEDSF-Census	Percent of persons aged 25+ with < high school education within the census tract	Continuous (0-1)
zpnon00 and zpnon90	PEDSF-Census	Percent of persons aged 25+ with < high school education within the zip code	Continuous (0-1)
ctblk00 and ctblk90	PEDSF-Census	Ratio of black population to total population within the census tract	Continuous (0-1)
ctwht00 and ctwht90	PEDSF-Census	Ratio of white population to total population within the census tract	Continuous (0-1)
cthsp00 and cthsp90	PEDSF-Census	Ratio of Hispanic population to total population within the census tract	Continuous (0-1)
zpblk00 and zpblk90	PEDSF-Census	Ratio of black population to total population within the zip code	Continuous (0-1)
zpwht00 and zpwht90	PEDSF-Census	Ratio of white population to total population within the zip code	Continuous (0-1)
zphsp00 and zphsp90	PEDSF-Census	Ratio of Hispanic population to total population within the zip code	Continuous (0-1)
Clinical variables			
numprims	PEDSF-IMS	Total number of primaries based on the number of tumors ever recorded in SEER	Continuous (1-10)
multprim1-multprim10	PEDSF-SEER	Multiple primary indicator based on all tumors in SEER	Categorical 0-first in situ, no malignant cancers 1-first malignant 9-second or subsequent
tumor1_1-tumor1_10 (1990-2003) OR cs1st1-cs1st10 (2004+)	PEDSF-SEER	Prognostic indicator for estrogen receptor status for breast cases (ERA for 1990-2003 and CS Site-specific factor for 2004+)	Categorical 0-no test performed 1-positive 2-negative 3-borderline 8-ordered, but unavailable 9-unknown
tumor2_1-tumor2_10 (1990-2003) OR cs2st1-cs2st10 (2004+)	PEDSF-SEER	Prognostic indicator for progesterone receptor status for breast cases (ERA for 1990-2003 and CS Site-specific factor for 2004+)	Categorical 0-no test performed 1-positive 2-negative 3-borderline 8-ordered, but unavailable 9-unknown
grade1-grade10	PEDSF-	Histologic grading and differentiation,	Categorical

Variable Name	*Source*	*Description*	*Coding*
	SEER	based on International Classification of Disease codes	1-well differentiated 2-moderately differentiated 3-poorly differentiated 4-undifferentiated, anaplastic 5-T-cell/precursor 6-B-cell/B-precursor 7-null ; non T, non B 8-natural killer cell 9-unknown
aj3sr1-aj3sr10	PEDSF-SEER	Modified American Joint Committee on Cancer (AJCC) stage (for diagnosis years 1988-2003)	Categorical
dajccstg1-dajccstg10	PEDSF-SEER	Derived American Joint Committee on Cancer (AJCC) stage group, 6th edition (for diagnosis years 2004+)	Categorical
ajccstg1-ajccstg10	PEDSF-SEER	Derived American Joint Committee on Cancer (AJCC) stage 3rd edition, 1988+	Categorical
e10sz1-e10sz10 (1988-2003) OR cstum1-cstum10 (2004+)	PEDSF-SEER	Primary tumor size in mm (1988-2003), from 10-digit extent of disease; diameter of primary tumor in mm (2004+)	Continuous 999-unknown size
e10pn1-e10pn10	PEDSF-SEER	Number of positive nodes; exact number of regional lymph nodes examined by pathologist that were found to contain metastasis	Categorical 00-all nodes negative 01-89-#positive nodes 97-positive nodes, number unspecified 98-nodes unexamined 99-unknown
survt1-survt10	PEDSF-SEER	Total survival time count in months of patient survival from time of diagnosis	Continuous
survy1-survy10	PEDSF-SEER	Survival time recode in years, calculated from date of diagnosis to one of the following: date of death, date last known alive, or follow-up cutoff (censor) date	Continuous YY-#full years survived 99-unknown
survm1-survm10	PEDSF-SEER	Survival time recode in months, calculated from date of diagnosis to one of the following: date of death, date last known alive, or censor date	Continuous MM-#full months survived 99-unknown
Treatment variables in SEER			
sssurg1-sssurg10	PEDSF-SEER	Site specific surgery performed (1983-1997)	Categorical (see PEDSF)
nosrg1-nosrg10	PEDSF-SEER	Was cancer-directed surgery performed?	Categorical 0-surgery performed 1-not recommended 2-contraindicated; not

Variable Name	*Source*	*Description*	*Coding*
			recommended 5-not performed; patient died 6-recommended; not performed, unknown reason 7-recommended; not received, patient refused 8-recommended; unknown if performed 9-unknown
sxprif1-sxprif10	PEDFSF-SEER	Surgery of primary site (1998+); describes surgical procedure that removes or destroys tissue as part of initial work-up or first course of therapy	Categorical (see PEDSF)
recstr1-recstr10	PEDSF-SEER	First course of reconstruction surgery (1998-2002)	Categorical (see PEDSF)
rad1-rad10	PEDSF-SEER	Receipt of radiation therapy and type received	Categorical 0-none 1-beam 2-radioactive implants 3-radioisotopes 4-combination (beam with implants or isotopes) 5-radiation received, unspecified 7-refused 8-recommended, receipt unknown 9-unknown
other_tx1-other_tx10	PEDSF-SEER	Other cancer-directed therapy received	Categorical (see PEDSF)
radsurg1-radsurg10	PEDSF-SEER	Radiation sequence with surgery	Categorical (see PEDSF)
Health system structure and organization (provider- and facility-level variables)			
prov3230 and prov2700 and F71	NCI Hospital file	State code	Character string (see NCI Hospital file)
prov2885	NCI Hospital file	Indicates the nature (profit status/type) of the organization that operates as the provider of services	Categorical 01-voluntary non-profit, church 02-voluntary non-profit, private 03-voluntary non-profit, other 04-proprietary/private 05-government, federal 06-government,

Variable Name	*Source*	*Description*	*Coding*
			stage 07-government, local 08-government, hospital dist. or authority
F25	NCI Hospital file	Type of control (nonprofit, proprietary, government, etc.)	Categorical (see NCI hospital file)
F26	NCI Hospital file	Type of facility	Categorical (see NCI hospital file; 3=cancer facility)
prov0740 OR F85	NCI Hospital file	Total number of beds in hospital facility	Continuous
prov2445	NCI Hospital file	Indicates how/whether therapeutic radiology services are offered by the hospital	Categorical 0-not provided 1-provided by staff 2-provided under arrangement 3-provided by staff and arrangement
F47	NCI Hospital file	Does hospital qualify as a rural primary hospital?	Categorical Y-yes
F29	NCI Hospital file	Urban/rural location of hospital	Categorical 1-urban 2-rural
F38	NCI Hospital file	Teaching hospital or affiliated with teaching hospital	Categorical Y-yes
prov0645	NCI Hospital file	Type of affiliation the hospital may have with a medical school	Categorical 1-major 2-limited 3-graduate 4-no affiliation
seer_area	NCI Hospital file	Indicates if the provider is in a SEER area or not	Categorical 0-not a SEER area 1-SEER area
nci_cen_02 and nci_cen_05	NCI Hospital file	NCI-designated center as of 2002 and as of 2005	Categorical 0-no 1-clinical 2-comprehensive
ACOSOG_02 and ACOSOG_05	NCI Hospital file	American College of Surgeons (ACoS) Oncology group affiliation as of 2002 and as of 2005	Categorical 0-not a member 1-member
CTSU_02 and CTSU_05	NCI Hospital file	Cancer trials support unit (NCI)	Categorical 0-not a member 1-member
NSABP_02 and NSABP_05	NCI Hospital file	National Surgical Adjuvant Breast and Bowel Project	Categorical 0-not a member 1-member
RTOG_02 and RTOG_05	NCI Hospital file	Radiation Therapy Oncology Group	Categorical 0-not a member 1-member

Variable Name	***Source***	***Description***	***Coding***
Zip	NCI Hospital file	Hospital zip code	Numeric string (5 characters)
Other (Related to procedures, services, dates of claims, and charges/payments found in Medicare claims data			
ONCLGIND	MEDPAR	Indicates whether the beneficiary received radiation oncology services during the stay (linked to revenue code 028x)	Categorical 0-No rad/oncology 1-Yes rad/oncology
RADTHIND	MEDPAR	Indicates whether the beneficiary received therapeutic radiology services during the stay (linked to revenue code 033x)	Categorical 0-No rad/therapeutic 1-Yes rad/therapeutic
ADM_M, ADM_D, ADM_Y and DIS_M, DIS_D, DIS_Y, LOS	MEDPAR	Admission date and discharge date and length of stay	Numeric: MMDDYYYY and continuous days count
PROVNUMB	MEDPAR	Provider number	Numeric string (6 characters)
DIAGCD1-DIAGCD10	MEDPAR	Diagnosis code: the ICD-9-CM code identifying the primary condition or other existing conditions shown in medical records as affecting services provided	Numeric string (5 characters)
SRGCDE1-SRGCDE6	MEDPAR	Surgical Procedure Code: the ICD-9-CM surgical procedure that was performed	Numeric string (4 characters)
SG1_M, SG1_D, SG1_Y	MEDPAR	Surgical procedure date performed	Numeric: MMDDYYYY
DRGCODE	MEDPAR	Code indicating the diagnostic related group (DRG) to which the claims that comprise the stay belong	Numeric string (3 characters)
ADMDXCDE	MEDPAR	Primary diagnosis code at time of admission	Categorical (see MEDPAR)
hcpcs	Carrier claims	Health Care Financing Administration Common Procedure Coding System (HCPCS) code for procedure, supplies, products, or services	Numeric string (5 characters)
linediag	Carrier claims	ICD-9-CM code indicating diagnosis supporting this procedure or service	Numeric string (5 characters)
pdgns_cd	Carrier claims	Beneficiary's principle diagnosis code	Numeric string (5 characters)
dgn_cd1-dgn_cd8	Carrier claims	Up to 8 ICD-9-CM diagnosis codes allowed per claim	Numeric string (5 characters)
Betos	Carrier claims	Berenson-Eggers type of service procedure code	See Carrier claims appendix
hcfaspec	Carrier claims	Provider's specialty code for service (HCFA)	See Carrier claims appendix
hcfatype	Carrier claims	Carrier's type of service code (HCFA)	See carrier claims appendix
frexpenm, frexpend, frexpeny	Carrier claims	Beginning date of service	Numeric: MMDDYYYY
lsexpenm, lsexpend,	Carrier claims	Ending date of service	Numeric: MMDDYYYY

Variable Name	*Source*	*Description*	*Coding*
lsdexpeny			
from_dtm, from_dtd, from_dty	Carrier claims	Claim from date (first day of provider's/physician's billing statement)	Numeric: MMDDYYYY
thru_dtm, thru_dtd, thru_dty	Carrier claims	Claim thru date (last day of provider's/physician's billing statement	Numeric: MMDDYYYY
prv_type	Carrier claims	Code identifying type of provider furnishing the services for the line item on Part B claim	Categorical (see Carrier claims)
prozip	Carrier claims	Zip code of physician/supplier who performed the Part B service for this line item	Numeric string (9 characters)
plcsrvc	Carrier claims	Carrier's place of service for this procedure code	Numeric string (2 characters)
perupin	Carrier claims	Unique carrier line performing UPIN number for procedure specified by HCPCS code (encrypted)	Numeric string (6 characters)
fac_type	Outpatient claims	Claim facility type code of the facility providing care	Categorical 1-hospital 2-skilled nursing facility 3-Home Health Association 4-Religious hospital 5-religious extended care 6-intermediate care 7-clinic 8-special facility 9-reserved
typesrvc	Outpatient claims	Classification of type of claims service provided to the beneficiary	Categorical (see Outpatient claims)
from_dtm, from_dtd, from_dty	Outpatient claims	Claim from date (first day of provider's/physician's billing statement)	Numeric: MMDDYYYY
thru_dtm, thru_dtd, thru_dty	Outpatient claims	Claim thru date (last day of provider's/physician's billing statement	Numeric: MMDDYYYY
hcpcs	Outpatient claims	Health Care Financing Administration Common Procedure Coding System (HCPCS) code; procedures, supplies, products, or services provided to Medicare beneficiaries	Numeric string (5 characters)
dgn_cd1-dgn_cd10	Outpatient claims	ICD-9-CM diagnosis codes; coexisting conditions that affect services provided	Numeric string (5 characters)
pr_cd1-pr_cd6	Outpatient claims	ICD-9-CM code that indicates primary or other procedure performed during the period covered by the institutional claim	Numeric string (5 characters)
prdtm1-prdtm6, prdtd1-prdtd6, prdty1-prdty6	Outpatient claims	Procedure performed dates; on an institutional claim, the date on which the principle or other procedure was performed	Numeric: MMDDYYYY
provider	Outpatient claims	Medicare certified provider number	Numeric string (6 characters)
hcpcs	DME claims	Health Care Financing Administration Common Procedure Coding System	Numeric string (5 characters)

Variable Name	*Source*	*Description*	*Coding*
		(HCPCS) code; procedures, supplies, products, or services provided	
hcfatype	DME claims	HCFA carrier's type of service code used for pricing services	Categorical (see DME claims)
plcsrvc	DME claims	Place of service for procedure code	Categorical (see DME claims)
frexpenm, frexpend, frexpeny	DME claims	Beginning date of service	Numeric: MMDDYYYY
linediag	DME claims	ICD-9-CM code indicating diagnosis supporting this procedure/service	Numeric string (5 characters)
betos	DME claims	Berenson-Eggers type of service for the procedure code based on clinically meaningful groupings of procedures and services	Numeric string (3 characters)
ndc_cd	DME claims	National Drug Code identifies oral anti-cancer drugs	Numeric string (11 characters)
dgnscd1-dgnscd8	DME claims	ICD-9-CM diagnosis codes	Numeric string (5 characters)

Notes: AJCC: American Joint Committee on Cancer; ARF: area resource file; ASC: ambulatory surgical center; DME: durable medical equipment file; EDB: Medicare Entitlement Database; HCFA: Health Care Financing Administration; ICD-9-CM: International Classification of Diseases, Modification 9; MEDPAR: Medical Provider Analysis and Review file; NCI: National Cancer Institute; PEDSF: Patient Entitlement and Diagnosis Summary file; RT: radiation therapy; SEER: Surveillance Epidemiology and End Results; SNF: skilled nursing facility; UPIN: unique provider identification number

REFERENCES

Advani, A. S., B. Atkeson, C. L. Brown, et al. Barriers to the participation of African American patients with cancer in clinical trials. Cancer 97:1499-1506, 2003.

Ai, Chunrong, and Edward C. Norton. Interaction terms in logit and probit models. Economic Letters 80(1):123-129, 2003.

Allgood, P. C. and M. O. Bachmann. Effects of specialisation on treatment and outcomes in screen-detected breast cancers in Wales: cohort study. British Journal of Cancer 94(1):36-42, 2006.

American Cancer Society (ACS): Cancer Facts and Figures 2008. Atlanta, Georgia, American Cancer Society, 2008.

American Society of Clinical Oncology (ASCO). Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. Journal of Clinical Oncology 14(10):2843-2877, 1996.

Anders, C. and L. A. Carey. Understanding and treating triple-negative breast cancer. Oncology (Williston Park) 22(11):1233-1239; discussion 1239-40, 1243, 2008.

Andre, F. and L. Pusztai. Molecular classification of breast cancer: implications for selection of adjuvant chemotherapy. Nature Clinical Practice Oncology 3(11):621-632, 2006.

Bach, P. B., E. Guadagnoli, D. Schrag, et al. Patient demographic and socioeconomic characteristics in the SEER-Medicare database applications and limitations. Medical Care 40:IV-19-25, 2002a (suppl 8).

Bach, P. B., D. Schrag, O. W. Brawley, et al. Survival of blacks and whites after a cancer diagnosis. Journal of the American Medical Association 287(16):2106-2113, 2002b.

Bach, P. B., H. H. Pham, D. Shrag, et al. Primary care physicians who treat blacks and whites. New England Journal of Medicine 351:575-584, 2004.

Ballard-Barbash, R., A. L. Potosky, L. C. Harlan, et al. Factors associated with surgical and radiation therapy for early stage breast cancer in older women. Journal of the National Cancer Institute 88(11):716-726, 1996.

Banerjee, M., J. George, C. Yee, et al. Disentangling the effects of race on breast cancer treatment. Cancer 110(10):2169-2177, 2007.

Bao, Y., S. A. Fox, and J. J. Escarce. Socioeconomic and racial/ethnic differences in the discussion of cancer screening: "between-" versus "within-" physician differences. Health Services Research 42(3 Pt 1):950-970, 2007.

Barni, S., M. Cabbidu, and F. Petrelli. Benefit of adjuvant chemotherapy in elderly ER-negative breast cancer patients: benefits and pitfalls. Expert Rev Anticancer Ther 10(2):185-198, 2010.

Bartelink, H. Systemic adjuvant therapies and radiotherapy to the conserved breast: strategies revisited. The Breast 16:84-88, 2007.

Bast et al. 2000 Update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the ASCO. Journal of Clinical Oncology 19(6):1865-1878, 2001.

Basu, A., J. J. Heckman, et al. Use of instrumental variables in the presence of heterogeneity and self-selection: an application to treatments of breast cancer patients. Health Economics 16(11):1133-1157, 2007

Bauer, K. R., M. Brown, R. D. Cress, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. Cancer 109(9):1721-1728, 2007.

Begg, C. B., L. D. Cramer, W. J. Hoskins, et al. Impact of hospital volume on operative mortality for major cancer surgery. Journal of the American Medical Association 280(20):1747-1751, 1998.

Benowitz, S. Revised guidelines signal that gene expression profiles are coming of age. Journal of the National Cancer Institute 100(13):916-917, 2008.

Berkson J. Application of the logistic function to bio-assay. Journal of the American Statistical Association 39: 357-365, 1944.

Berry, D. A., K. A. Cronin, S. K. Plevritis, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. New England Journal of Medicine 353(17):1784-1792, 2005.

Bhargava, A., and X. L. Du. Racial and socioeconomic disparities in adjuvant chemotherapy for older women with lymph node-positive, operable breast cancer. Cancer 115:2999-3008, 2009.

Bickell, N. A. Race, ethnicity, and disparities in breast cancer: victories and challenges. Womens Health Issues 12(5):238-251, 2002.

Bickell, N. A., J. Mendez, and A. A. Guth. The quality of early-stage breast cancer treatment: what can we do to improve? Surg Oncol Clin N Am 14(1):103-117, vi, 2005.

Bickell, N. A., J. J. Wang, S. Oluwole, et al. Missed opportunities: racial disparities in adjuvant breast cancer treatment. Journal of Clinical Oncology 24(9):1357-1362, 2006.

Bigby, J. and M. D. Holmes. Disparities across the breast cancer continuum. Cancer Causes Control 16(1):35-44, 2005.

Billingsley, K. G., A. M. Morris, J. A. Dominitz, et al. Surgeon and hospital characteristics as predictors of major adverse outcomes following colon cancer surgery: understanding the volume-outcome relationship. Archives of Surgery 142(1):23-31; discussion 32, 2007.

Birkmeyer, N. J., P. P. Goodney, T. A. Stukel, et al. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? Cancer 103(3):435-441, 2005.

Birkmeyer, J. D., A. E. Siewers, N. J. Marth, et al. Regionalization of high-risk surgery and implications for patient travel times. Journal of the American Medical Association 290(20):2703-2708, 2003.

Birkmeyer, J. D., Y. Sun, S. L. Wong, et al. Hospital volume and late survival after cancer surgery. Annals of Surgery 245(5):777-783, 2007.

Birkmeyer, J. D., Y. Sun, A. Goldfaden, et al. Volume and process of care in high-risk cancer surgery. Cancer 106(11):2476-2481, 2006.

Blackman, J. and C. M. Masi. Racial and ethnic disparities in breast cancer mortality: are we doing enough to address the root causes? Journal of Clinical Oncology 24(14):2170-2178, 2006.

Bloom, B. S., N. de Pouvourville, S. Chhatre, et al. Breast cancer treatment in clinical practice compared to best evidence and practice guidelines. British Journal of Cancer 90:26-30, 2004.

Bodenheimer, T., E. H. Wagner, and K. Grumbach. Improving primary care for patients with chronic illness. Journal of the American Medical Association 288(14):1775-1779, 2002a.

Bodenheimer, T., E. H. Wagner, and K. Grumbach. Improving primary care for patients with chronic illness: The Chronic Care Model, Part 2. Journal of the American Medical Association 288(15):1909-1914, 2002b.

Bouchardy, C., E. Rapiti, S. Blagojevic, et al. Older female cancer patients : Importance, causes, and consequences of undertreatment. Journal of Clinical Oncology 25(14):1858-1869, 2007.

Bowen, R. L., J. Stebbing, and L. J. Jones. A review of the ethnic differences in breast cancer. Pharmacogenomics 7(6):935-942, 2006.

Bowen, S, and A. B. Zwi. Pathways to “evidence-informed” policy and practice: a framework for action. PLoS Medicine 2(7):0600-0605, 2005.

Bowles, E. A., L. Tuzzio, C. J. Wiese, et al. Understanding high quality cancer care: A summary of expert perspectives. Cancer 112:934-942, 2008.

Boyle, P. and J. Ferlay. Mortality and survival in breast and colorectal cancer. Nature Clinical Practice Oncology 2:424-425, 2005.

Bradley, C. J., J. Gardiner, C. W. Given, et al. Cancer, Medicaid enrollment, and survival disparities. Cancer 103(8):1712-1718, 2005.

Bradley, C. J., C. W. Given, and C. Roberts. Disparities in cancer diagnosis and survival. Cancer 91(1):178-188, 2001.

Breen, N., D. K. Wagener, M. L. Brown, et al Progress in cancer screening over a decade: results of screening from the 1987, 1992, and 1998 National Health Interview Surveys. Journal of the National Cancer Institute 93:1704-1713, 2001.

Brown, M. L., G. F. Riley, N. Schussler, et al. Estimating health care costs related to cancer treatment from SEER-Medicare data. Medical Care 40:IV-104-117, 2002 (suppl 8).

Buchholz, T. A., H. M. Kuerer, and E. A. Strom. Is partial breast irradiation a step forward or backward? Semin Radiat Oncol 15(2):69-75, 2005.

Campbell, J. B. Breast cancer – race, ethnicity, and survival: A literature review. Breast Cancer Research and Treatment 74(2):187-192, 2002.

Campbell, J. D., and S. D. Ramsey. The costs of treating breast cancer in the US: a synthesis of published evidence. Pharmacoeconomics 27(3):199-209, 2009.

Cance, W. G., L. A. Carey, B. F. Calvo, et al. Long-term outcome of neoadjuvant therapy for locally advanced breast carcinoma: effective clinical downstaging allows breast preservation and predicts outstanding local control and survival. Annals of Surgery 236(3):295-302; discussion 302-303, 2002.

Carey L. A., C. M. Perou, C. A. Livasy, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. Journal of the American Medical Association 295(21):2492-2502, 2006.

Carlson, R. W., L. J. Goldstein, W. J. Gradishar, et al. NCCN breast cancer practice guidelines. The National Comprehensive Cancer Network. Oncology (Williston Park) 10:S47-S75, 1996 (suppl 11).

Carpenter, W. R., and J. Peppercorn. Beyond toxicity: The challenge and importance of understanding the full impact of treatment decisions. Cancer 115(12):2598-2601, 2009.

Chagpar, A. B., C. R. Scoggins, R. C. Martin, et al. Factors determining adequacy of axillary node dissection in breast cancer patients. Breast J 13(3):233-237, 2007.

Chaudhry, R., V. Goel, and C. Sawka. Breast cancer survival by teaching status of the initial treating hospital. Canadian Medical Journal 164(2):183-188, 2001.

Chen, A. Y., M. T. Halpern, N. M. Schrag, et al. Disparities and trends in sentinel lymph node biopsy among early-stage breast cancer patients (1998-2005). Journal of the National Cancer Institute 100(7):462-474, 2008.

Chen, V. W., P. Correa, R. J. Kurman, et al. Histological characteristics of breast carcinoma in blacks and whites. Cancer Epidemiol Biomarkers Prev 3(2):127-135, 1994.

Chernoff H, and E. L. Lehmann. The use of maximum likelihood estimates in χ^2 tests for goodness-of-fit. The Annals of Mathematical Statistics 25:579-586, 1954.

Chlebowski R. T., Z. Chen, G. L. Anderson, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. Journal of the National Cancer Institute 97:439-448, 2005.

Clegg, L. X., E. J. Feuer, D. N. Midthune, et al. Impact of reporting delay and reporting error on cancer incidence rates and trends. Journal of the National Cancer Institute 94(20):1537-1545, 2002.

Colditz, G. A., H. J. Baer, and R. M. Tamimi: Chapter 51: Breast cancer, in D Schottenfeld and JF Fraumeni Jr (ed): Cancer Epidemiology and Prevention (ed 3). New York, NY, Oxford University Press, Inc., 2006, pp 995-1012.

Cooper, G. S., B. Virnig, C. N. Klabunde, et al. Use of SEER-Medicare data for measuring cancer surgery. Med Care 40:IV-43-48, 2002 (suppl 8).

Cornfeld, M. J., A. Jadwin, P. O'Grady, et al. Feasibility of assessing quality in medical oncology practices. Cancer Practice 9(5): 231-235, 2001.

Coughlin, S. S., S. A. Sabatino, and K. M. Shaw. What factors are associated with where women undergo clinical breast examination? Results from the 2005 National Health Interview Survey. Open Clin Cancer J 2:32-43, 2008.

Curtis, E., C. Quale, et al. Racial and ethnic differences in breast cancer survival : how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics? Cancer 112(1):171-180, 2008.

Davis, D., M. Evans, A. Jadad, et al. The case for knowledge translation: shortening the journey from evidence to effect. British Medical Journal 327:33-35, 2003.

Demicheli, R., M. W. Retsky, W. J. Hrushesky, et al. Racial disparities in breast cancer outcome: insights into host-tumor interactions. Cancer 110(9):1880-1888, 2007.

DeMichele, A., M. Putt, Y. Zhang, et al. Older age predicts a decline in adjuvant chemotherapy recommendations for patients with breast carcinoma. Cancer 97(9):2150-2159, 2003.

Desch, C. E., K. K. McNiff, E. C. Schneider, et al. American Society of Clinical Oncology/National Comprehensive Cancer Network Quality Measures. Journal of Clinical Oncology 26(21):3631-3637, 2008.

Dignam, J. J., C. K. Redmond, B. Fisher, et al. Prognosis among African-American women and white women with lymph node negative breast carcinoma: findings from 2 randomized clinical trials of the National Surgical Adjuvant Breast and Bowel Project (NSABP). Cancer 80:80-90, 1997.

DiMaggio, P. and W. Powell. The Iron Cage Revisited: Institutional Isomorphism and Collective Rationality in Organizational Fields. American Sociological Review 48:147-60, 1983.

Dobbins, M., D. Ciliska, R. Cockerill, et al. A framework for the dissemination and utilization of research for health care policy and practice. The Online Journal for Knowledge Synthesis for Nursing 9(7), 2002.

Du, X. and J. S. Goodwin. Increase of chemotherapy use in older women with breast carcinoma from 1991 to 1996. Cancer 92(4):730-737, 2001.

Du, X. L., C. R. Key, et al. Discrepancy between consensus recommendations and actual community use of adjuvant chemotherapy in women with breast cancer. Annals of Internal Medicine 138(2):90-97, 2003.

Du, W., and M. S. Simon. Racial disparities in treatment and survival of women with stage I-III breast cancer at a large academic medical center in metropolitan Detroit. Breast Cancer Research and Treatment 91(3):243-248, 2005.

Du, X. L., S. Fang, et al. Impact of treatment and socioeconomic status on racial disparities among older women with breast cancer. American Journal of Clinical Oncology 31(2):125-132, 2008.

Earle, C. C., P. J. Neumann, R. D. Gelber, et al. Impact of referral patterns on the use of chemotherapy for lung cancer. Journal of Clinical Oncology 20(7): 1786-1792, 2002.

Edge, S. B., D. R. Byrd, C. C. Compton, et al. (eds): Breast. In: *AJCC Cancer Staging Manual* (ed 2). New York, NY, Springer, 347-376, 2010.

Edwards, B. K., M. L. Brown, P. A. Wingo, HL, et al. Annual Report to the Nation on the Status of Cancer, 1975-2002, Featuring Population-Based Trends in Cancer Treatment. Journal of the National Cancer Institute 97(19):1407-1427, 2005.

Eliassen, A. H., G. A. Colditz, B. Rosner, et al Adult weight change and risk of postmenopausal breast cancer. Journal of the American Medical Association 296(2):193-201, 2006.

Engelman, K. K., E. F. Ellerbeck, M. S. Mayo, et al. Mammography facility characteristics and repeat mammography use among Medicare beneficiaries. Prev Med 39(3):491-497, 2004.

Etheredge, L. M. Medicare's future: cancer care. Health Affairs (Millwood) 28(1): 148-159, 2009.

Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats. Last accessed on 3-19-2010.

Fejerman, L. and E. Ziv Population differences in breast cancer severity. Pharmacogenomics 9(3):323-333, 2008.

Flockhart D. CYP2D6 genotyping and the pharmacogenetics of tamoxifen. Clin Adv Hematol Oncol 6:493-494, 2008

Finlayson, E. V. and J. D. Birkmeyer. Effects of hospital volume on life expectancy after selected cancer operations in older adults: a decision analysis. Journal of the American College of Surgeons 196(3):410-417, 2003.

Freedman, R. A., Y. He, E. P. Winer, et al. Trends in racial and age disparities in definitive local therapy of early-stage breast cancer. Journal of Clinical Oncology 27(5):713-719, 2009.

Frome, E. L. The analysis for rates using Poisson regression models. Biometrics 39: 665-674, 1983.

Gerend, M. A. and M. Pai. Social determinants of Black-White disparities in breast cancer mortality: a review. Cancer Epidemiol Biomarkers Prev 17(11):2913-2923, 2008.

Gloeckler Ries, L. A., M. E. Reichman, D. R. Lewis, et al. Cancer survival and incidence from the Surveillance, Epidemioloy, and End Results (SEER) program. The Oncologist 8(6):541-552, 2003.

Gilligan, M.A., J. Neuner, R. Sparapani, et al. Surgeon characteristics and variations in treatment for early-stage breast cancer. Archives of Surgery 142:17-22, 2007a.

Gilligan, M. A., J. Neuner, X. Zhang, et al. Relationship between number of breast cancer operations performed and 5-year survival after treatment for early-stage breast cancer. American Journal of Public Health 97(3):539-544, 2007b.

Goetz M. P., J. M. Rae, V. J. Suman, et al: Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. Journal of Clinical Oncology 23:9312-9318, 2005

Goins, K. V., J. G. Zapka, A. M. Geiger, et al. Implementation of systems strategies for breast and cervical cancer screening services in health maintenance organizations. American Journal of Managed Care 9(11):745-755, 2003.

Gold, H. T., H. T. Do, et al. Correlates and effect of suboptimal radiotherapy in women with carcinoma in situ or early invasive breast cancer. Cancer 113(11):3108-3115, 2008.

Gold, M., and E. F. Taylor. Moving research into practice: lessons learned from the US Agency for Healthcare Research and Quality's IDSRN program. Implementation Science 2(9), 2007.

Goldzweig, C. L., P. H. Parkerton, D. L. Washington, et al. Primary care practice and facility quality orientation: influence on breast and cervical cancer screening rates. American Journal of Managed Care 10(4):265-272, 2004.

Gooden, K. M., D. L. Howard, W. R. Carpenter, et al. The effect of hospital and surgeon volume on racial differences in recurrence-free survival after radical prostatectomy. Medical Care 46(11):1170-1176, 2008.

Gorin, S. S., J. E. Heck, S. Albert, et al. Treatment for breast cancer in patients with Alzheimer's disease. J Am Geriatr Soc 53(11):1897-1904, 2005.

Gorin, S. S., J. E. Heck, et al. Delays in breast cancer diagnosis and treatment by racial/ethnic group. Archives of Internal Medicine 166(20):2244-2252, 2006.

Gort, M., M. Broekhuis, R. Otter, et al. Improvement of best practice in early breast cancer: actionable surgeon and hospital factors. Breast Cancer Res Treat 102(2): 219-226, 2007.

Gradishar, W. J. and R. M. O'Regan. Progress in systemic adjuvant therapy of early-stage breast cancer. International Journal of Clinical Oncology 8(4):239-247, 2003.

Greenhalgh, T., G. Robert, F. MacFarlane, et al. Diffusion of innovations in service organizations: systematic review and recommendations. Milbank Quarterly 82(4):581-629, 2004.

Grol, R. Successes and failures in the implementation of evidence-based guidelines for clinical practice. Medical Care 39(8):S1146-S1154, 2001 (suppl 2).

Gross, C. P., G. Filardo, et al. The impact of socioeconomic status and race on trial participation for older women with breast cancer. Cancer 103(3):483-491, 2005.

Gross, C. P., B. D. Smith, et al. Racial disparities in cancer therapy: did the gap narrow between 1992 and 2002? Cancer 112(4):900-908, 2008.

Hadley, J., D. Polsky, et al. An exploratory instrumental variable analysis of the outcomes of localized breast cancer treatments in a Medicare population. Health Economics 12(3):171-186, 2003.

Haggstrom, D. A., C. Quale, and R. Smith-Bindman. Differences in the quality of breast cancer care among vulnerable populations. Cancer 104(11):2347-2358, 2005.

Hahn, K. M., M. L. Bondy, et al. Factors associated with advanced disease stage at diagnosis in a population-based study of patients with newly diagnosed breast cancer. American Journal of Epidemiology 166(9):1035-1044, 2007.

Hartsell, W. R., D. C. Recine, K. L. Griem, et al. Delaying the initiation of intact breast irradiation for patients with lymph node positive breast cancer increases the risk of local recurrence. Cancer 76(12):2497-2503, 1995.

Hassett, M. J., M. E. Hughes, J. C. Niland, et al. Selecting high priority quality measures for breast cancer quality improvement. Medical Care 46:762-770, 2008.

Hebert-Croteau, N., J. Brisson, J. Lemaire, et al. Investigating the correlation between hospital of primary treatment and the survival of women with breast cancer. Cancer 104(7):1343-1348, 2005.

Hebert-Croteau, N., C. R. Freeman, J. Latreille, et al. Delay in adjuvant radiation treatment and outcomes of breast cancer--a review. Breast Cancer Res Treat 74(1):77-94, 2002.

Hebert-Croteau, N., C. R. Freeman, J. Latreille, et al. A population-based study of the impact of delaying radiotherapy after conservative surgery for breast cancer. Breast Cancer Research and Treatment 88:187-196, 2004.

Heflin, M. T., K. I. Pollak, M. N. Kuchibhatla, et al. The impact of health status on physicians' intentions to offer cancer screening to older women. J Gerontol A Biol Sci Med Sci 61(8):844-850, 2006.

Hershman, D. L.., D. Buono, R. B. McBride, et al. Surgeon characteristics and receipt of adjuvant radiotherapy in women with breast cancer. Journal of the National Cancer Institute 100(3):199-206, 2008.

Hershman, D. L.., X. Wang, R. McBride, et al. Delay of adjuvant chemotherapy initiation following breast cancer surgery among elderly women. Breast Cancer Research and Treatment 99(3):313-321, 2006a.

Hershman, D. L.., X. Wang, R. McBride, et al. Delay in initiating adjuvant radiotherapy following breast conservation and its impact on survival. Int J Radiat Oncol Biol Phys 65(5):1353-1360, 2006b.

Hewitt, M. and J. Simone: Ensuring quality cancer care. Washington, DC, National Academy Press, 1999.

Hickey, B. E., D. P. Francis, and M. Lehman. Sequencing of chemotherapy and radiation therapy for early breast cancer. Cochrane Database of Systematic Reviews 4. Art. No.: CD005212, 2006.

Hillner, B. E., M. K. McDonald, L. Penberthy, et al. Measuring standards of care for early breast cancer in an insured population. Journal of Clinical Oncology 15(4):1401-1408, 1997.

Hillner, B. E., T. J. Smith, and C. E. Desch. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. Journal of Clinical Oncology 18(11):2327-2340, 2000.

Himmelstein, D. U., S. Woolhandler, I. Hellander, et al. Quality of care in investor-owned versus not-for-profit HMOs. Journal of the American Medical Association 282(2):159-163, 1999.

Hosmer, D. W. and S. Lemeshow: Applied Logistic Regression (ed 2). New York, NY, John Wiley & Sons, Inc., 2000.

Hughes, K. S., L. A. Schnaper, D. Berry, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. New England Journal of Medicine 351(10):971-977, 2004.

Institute of Medicine (IOM): To Err is Human: Building a Safer Health System. Edited by LT Kohn, JM Corrigan, and MS Donaldson. Washington, DC, National Academy Press, 2000.

Institute of Medicine (IOM): Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC, National Academy of Sciences, 2002.

Jemal, A., E. Ward, and M. J. Thun. Recent Trends in Breast Cancer Incidence Rates by Age and Tumor Characteristics among US Women. Breast Cancer Research 9: R28, 2007.

Jerome-D'Emilia, B. and J. W. Begun. Diffusion of breast conserving surgery in medical communities. Social Science and Medicine 60(1):143-151, 2005.

Jones, A. P., R. Haynes, V. Sauerzapf, et al. Travel time to hospital and treatment for breast, colon, rectum, lung, ovary, and prostate cancer. European Journal of Cancer 44:992-999, 2008.

Kang, S. P., M. Martel, and L. N. Harris. Triple negative breast cancer: current understanding of biology and treatment options. Current Opinions in Obstetrics and Gynecology 20(1):40-46, 2008.

Kaiser Family Foundation (KFF): National Survey of Households Affected by Cancer: Summary and Chartpack. Publication #7591, Washington, DC, Kaiser Family Foundation, 2006. http://www.kff.org.

Katipamula, R., A. C. Degnim, T. Hoskin, et al. Trends in mastectomy rates at the Mayo clinic Rochester : Effect of surgical year and preoperative magnetic resonance imaging. Journal of Clinical Oncology 27(25):4082-4088, 2009.

Keating, N. L., M. B. Landrum, et al. Consultation with a medical oncologist before surgery and type of surgery among elderly women with early-stage breast cancer. Journal of Clinical Oncology 21(24):4532-4539, 2003.

Keating, N. L., M. B. Landrum, E. Meara, et al. Do increases in the market share of managed care influence quality of cancer care in the fee-for-service sector? Journal National Cancer Institute 97(4):257-264, 2005.

Keating. N.L., E. Kouri, et al. Racial differences in definitive breast cancer therapy in older women: are they explained by the hospitals where patients undergo surgery? Medical Care 47(7):765-773, 2009.

Klabunde, C. N., J. M. Legler, J. L. Warren, et al. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Annals of Epidemiology 17:584-590, 2007.

Kleinbaum, D. G., L. L. Kupper, K. E. Muller, et al.: Applied regression analysis and other multivariable methods (ed 3). Pacific Grove, CA, Duxbury Press, 1998.

Kosiak, B., J. Sangl, and R. Correa-de-Araujo. Quality of health care for older women: what do we know? Women's Health Issues 16:89-99, 2006.

Kurian A. W., Thompson R. N., Gaw A. F., et al. A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer. Journal of Clinical Oncology 25:634-641, 2007.

Laliberte, L., M. L. Fennell, et al. The relationship of membership in research networks to compliance with treatment guidelines for early-stage breast cancer. Medical Care 43(5):471-479, 2005.

Lamont, E. B., D. S. Lauderdale, R. L. Schilsky, et al. Construct validity of medicare chemotherapy claims: the case of 5FU. Medical Care 40(3):201-211, 2002.

Lee T. H., and E. J. Emanuel. Tier 4 drugs and the fraying of the social compact. New England Journal of Medicine 359:333-335, 2008.

Lee-Feldstein, A., H. Anton-Culver, and P. J. Feldstein. Treatment differences and other prognostic factors related to breast cancer survival. Delivery systems and medical outcomes. Journal of the American Medical Association 271(15):1163-1168, 1994.

Livasy, C. A., C. M. Perou, G. Karaca, et al. Identifcation of a basal-like subtype of breast ductal carcinoma in situ. Human Pathology 38(2):197-204, 2007.

Lohrisch, C., C. Paltiel, K. Gelmon, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. Journal of Clinical Oncology 24(30):4888-4894, 2006.

Lund, M. J., O. P. Brawley, K. C. Ward, et al. Parity and disparity in first course treatment of invasive breast cancer. Breast Cancer Res Treat 109(3):545-557, 2008.

Lund, M. J., K. F. Trivers, P. L. Porter, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat 113(2):357-370, 2009.

Magai, C., N. S. Consedine, B. A. Adjei, et al. Psychosocial influences on suboptimal adjuvant breast cancer treatment adherence among African American women: implications for education and intervention. Health Educ Behav 35(6):835-854, 2008.

Malin, J. L., A. Epstein, J. Adams, et al. Results for the national Initiative for Cancer Care Quality; How can we improve the quality of cancer care in the United States? Journal of Clinical Oncology 24:626-634, 2006.

Maloney, N., M. Koch, D. Erb, et al. Impact of race on breast cancer in lower socioeconomic status women. Breast J 12(1):58-62, 2006.

Mamounas, E. P. Neoadjuvant chemotherapy in operable breast cancer: the pros. Breast Care 1:348-351, 2006.

Masi, C. M. and O. I. Olopade. Racial and ethnic disparities in breast cancer: a multilevel perspective. Med Clin North Am 89(4):753-70, 2005.

Mayberry, R. M., F. Mili, and E. Ofili: Chapter 10: Racial and ethnic differences in access to medical care, in LaVeist, TA (ed): Race, Ethnicity, and Health: A Public Health Reader. San Francisco, CA, John Wiley and Sons, Jossey-Bass, 2002, pp 173-174.

McGlynn, E. A., S. M. Asch, J. Adams, et al. The quality of care delivered to adults in the United States. New England Journal of Medicine 348:2635-2645, 2003.

Meden, T., C. St. John-Larkin, D Hermes, et al. Relationship between travel distance and utilization of breast cancer treatment in rural northern Michigan. JAMA 287(1):111, 2002.

Mickey, R. M., and S. Greenland, S. The impact of confounder selection criteria on effect estimation. American Journal of Epidemiology, 129(1), 125–137, 1989.

Millikan, R. C., B. Newman, C. K. Tse, et al. Epidemiology of basal-like breast cancer. Breast Cancer Research and Treatment 109:123-139, 2008.

Mitchell K. W., L. A. Carey, J. Peppercorn: Reporting of race and ethnicity in breast cancer research: room for improvement. Breast Cancer Research and Treatment 118(3):511-517, 2009.

Mobley, L. R., E. Root, L. Anselin, et al. Spatial analysis of elderly access to primary care services. International Journal of Health Geographics 5:19, 2006.

Mobley, L. R., T. Kuo, L. J. Clayton, et al. Mammography facilities are accessible, so why is utilization so low ? Cancer Causes Control 20:1017-1028, 2009.

Morris, A. M., K. G. Billingsley, A. J. Hayanga, et al. Residual treatment disparities after oncology referral for rectal cancer. Journal of the National Cancer Institute 100(10):738-744, 2008.

Morris, A. M., Y. Wei, N. J. Birkmeyer, et al. Racial disparities in late survival after rectal cancer surgery. Journal of the American College of Surgeons 203(6):787-94, 2006.

Morris, G. J. and E. P. Mitchell. Higher incidence of aggressive breast cancers in African-American women: a review. Journal of the National Medical Association 100(6):698-702, 2008.

Movsas, B., J. Moughan, J. Owen, et al. Who enrolls onto clinical oncology trials? A radiation patterns of care study analysis. International Journal of Radiation Oncology Biology Physics 68(4):1145-50, 2007.

Munoz, M., L. G. Estevez, I. Alvarez, et al. Evaluation of international treatment guidelines and prognostic tests for the treatment of early breast cancer. Cancer Treat Rev 34(8):701-9, 2008.

Murthy, V. H., H. M. Krumholz, and C. P. Gross. Participation in cancer clinical trials: race-, sex-, and age-based disparities. Journal of the American Medical Association 291(22):2720-2726, 2004.

Muss H. B., D. A. Berry, C. T. Cirrincione, et al: Adjuvant chemotherapy in older women with early-stage breast cancer. New England Journal of Medicine 360:2055-65, 2009

National Cancer Institute (NCI): Cancer Trends Progress Report. Bethesda, MD, National Cancer Institute, National Institutes of Health, 2005a.

National Cancer Institute (NCI): What you need to know about breast cancer. Rockville, MD, National Cancer Institute, NIH Publication No. 05-1556, pp 2-75, 2005b.

National Cancer Institute (NCI): SEER-Medicare Linked Database. Bethesda, MD, National Cancer Institute, National Institutes of Health, 2009. http://healthservices.cancer.gov/seermedicare. Last accessed on August 13, 2009.

National Comprehensive Cancer Network (NCCN): Clinical practice guidelines in oncology: Breast cancer - version 1.2009. National Comprehensive Cancer Network, Inc., 2008. http://www.nccn.org. Last accessed on April 15, 2009.

National Institutes of Health (NIH): Treatment of early stage breast cancer. NIH Consensus Statement 8(6):1-19, Jun 18-21, 1990.

National Institutes of Health (NIH): Adjuvant therapy for breast cancer. NIH Consensus Statement 17(4):1-35. Nov 1-3, 2000.

National Rural Electric Cooperative Association (NRECA): Careers Overview, 2009. http://www.nreca.org. Last accessed on November 15, 2009.

Nattinger, A. B., R. T. Kneusel, R. G. Hoffman, et al. Relationship of distance from a radiotherapy facility and initial breast cancer treatment. Journal of the National Cancer Institute 93(17):1344-1346, 2001

Neuner, J. M., M. A. Gilligan, R. Sparapani, et al. Decentralization of breast cancer surgery in the United States. Cancer 101(6):1323-9, 2004.

Newman, L. A., R. Therialt, N. Clendinnin, et al. Treatment choices and response rates in African American women with breast carcinoma. Cancer 97:S246-252, 2003 (suppl 1).

Newman, L. and I. Martin. Disparities in breast cancer. Current Problems in Cancer 31(3):134-156, 2007.

O'Malley, A. S., V. B. Sheppard, M. Schwartz, and J. Mandelblatt. The role of trust in use of preventative services among low-income African-American women. Preventive Medicine 38:777-785, 2004.

O'Malley, M. S., J. A. Earp, S. T. Hawley, et al. The association of race/ethnicity, socioeconomic status, and physician recommendation for mammography: who gets the message about breast cancer screening? American Journal of Public Health 91(1):49-54, 2001.

Onega, T., E. J. Duell, et al. Influence of NCI-Cancer Center attendance on mortality in lung, breast, colorectal, and prostate cancer patients. Medical Care Research and Review 66(5):542-560, 2009.

Owusu, C., T. L. Lash, and R. A. Silliman. Effect of undertreatment on the disparity in age-related breast cancer-specific survival among older women. Breast Cancer Res Treat 102(2):227-236, 2007.

Pagano, M., and K. Gauvreau : Principles of biostatistics (ed 2). Pacific Grove, CA, Duxbury Press, 2000.

Parkin, D. M. Global cancer statistics in the year 2000. Lancet Oncology 2(9): 533-543, 2001.

Passage, K. J. and N. J. McCarthy. Critical review of the management of early-stage breast cancer in elderly women. Intern Med J 37(3):181-189, 2007.

Payne, R., E. Medina, and J. W. Hampton. Quality of life concerns in patients with breast cancer: evidence for disparity of outcomes and experiences in pain management and palliative care among African-American women. Cancer 97:S311-S117, 2003 (suppl 1).

Peppercorn, J., C. M. Perou, and L. A. Carey. Molecular subtypes in breast cancer evaluation and management: divide and conquer. Cancer Invest 26(1):1-10, 2008.

Phibbs, C. S., and H. S. Luft. Correlation of travel time on roads versus straight line distance. Medical Care Research and Review 52(4):532-542, 1995.

Polacek, G. N., M. C. Ramos, and R. L. Ferrer. Breast cancer disparities and decision-making among U.S. women. Patient Educ Couns 65(2):158-165, 2007.

Polite, B. N., C. Cirrincione, G. F. Fleming, et al. Racial differences in clinical outcomes from metastatic breast cancer : A pooled analysis of CALGB 9342 and 9840 – Cancer and Leukemia Group B. Journal of Clinical Oncology 26(16):2659-2665, 2008.

Porter, P. L., M. J. Lund, M. G. Lin, et al. Racial differences in the expression of cell cycle-regulatory proteins in breast carcinoma. Cancer 100(12):2533-42, 2004.

Punglia, R. S., M. E. Hughes, S. B. Edge, et al. Factors associated with guideline-concordant use of radiotherapy after mastectomy in the National Comprehensive Cancer Network. International Journal of Radiation Oncology Biology Physics 72(5):1434-1440, 2008.

Punglia, R. S., J. C. Weeks, B. A. Neville, et al. Effect of distance to radiation treatment facility on use of radiation therapy after mastectomy in elderly women. International Journal of Radiation Oncology Biology Physics 66(1):56-63, 2006a.

Punglia, R. S., J. C. Weeks, B. A. Neville, et al. Radiation therapy after mastectomy between 1991 and 1999 in elderly women: response to clinical trial information. Journal of Clinical Oncology 24(21):3474-3482, 2006b.

Rich-Edwards, J. W., M. B. Goldman, W. C. Willett, et al. Adolescent body mass index and ovulatory infertility. American Journal of Obstetrics and Gynecology 171:171-177, 1994.

Ries L. A. G., D. Harkins, M. Krapcho, et al (eds): SEER Cancer Statistics Review, 1975-2003. Bethesda, MD, National Cancer Institute. http://seer.cancer.gov/csr/1975_2003/, 2006.

Ries L. A. G., D. Melbert, M. Krapcho, et al (eds): SEER Cancer Statistics Review, 1975-2005. Bethesda, MD, National Cancer Institute. http://seer.cancer.gov/csr/1975_2005/, 2008.

Roach, M., C. Cirrincione, D. Budman, et al. Race and survival from breast cancer: based on Cancer and Leukemia Group B trial 8541. Cancer Journal of Scientific America 3:107-112, 1997.

Rogers, E. M.: Diffusion of innovations (ed 4). New York, NY, the Free Press: A Division of Simon and Schuster, 1995a.

Rogers, E. M. Lessons for guidelines from the diffusion of innovations. Jt Comm J Qual Improv 21:324-328, 1995b.

Rogers, E.M.: Diffusion of innovations. New York, NY, the Free Press, 1962.

Rothman, K. J., S. Greenland, T. L. Lash (eds): Modern Epidemiology (ed 3). Philadelphia, PA, Lippincott Williams & Wilkins, 2008.

Sant, M., S. Francisci, R. Capocaccia, et al. Should we use incidence, survival, or mortality to assess breast cancer trends in European women? Nature Clinical Practice Oncology 3(5):228-229, 2006.

Sateren, W. B., E. L. Trimble, J. Abrams, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. Journal of Clinical Oncology 20(8):2109-2117, 2002.

Schegerin, M., A. N. A. Tosteson, P. A. Kaufman, et al. Prognostic imaging in neoadjuvant chemotherapy of locally-advanced breast cancer should be cost-effective. Breast Cancer Research and Treatment 114:537-547, 2009.

Schootman, M., D. B., Jeffe, et al. Racial disparities in the development of breast cancer metastases among older women: a multilevel study. Cancer 115(4):731-740, 2009.

Schneider, E. C. A. M. Epstein, J. L. Malin, et al. Developing a system to assess the quality of cancer care: ASCO's national initiative on cancer care quality. Journal of Clinical Oncology 22(15):2985-2991, 2004.

Schrag, D., C. Earle, F. Xu, et al. Associations between hospital and surgeon procedure volumes and patient outcomes after ovarian cancer resection. Journal of the National Cancer Institute 98(3):163-171, 2006.

Schrag, D., K. S. Panageas, E. Riedel, et al. Surgeon volume compared to hospital volume as a predictor of outcome following primary colon cancer resection. J Surg Oncol 83(2):68-78; discussion 78-79, 2003.

Schroen, A. T., D. R. Brenin, M. D. Kelly, et al. Impact of patient distance to radiation therapy on mastectomy use in early-stage breast cancer patients. Journal of Clinical Oncology 23(28):7074-7080, 2005.

Schwartz, M. Estimates of lead time and length time bias in a breast cancer screening program. Cancer 46:844-851, 1980.

Scott, W., et al., in Institutional Change and Healthcare Organizations: From Professional Dominance to Managed Care. Chicago, IL, University of Chicago Press, 2000.

Shannon, C., S. Ashley, and I. E. Smith. Does timing of adjuvant chemotherapy for early breast cancer influence survival? Journal of Clinical Oncology 21(20):3792-3797, 2003.

Shavers, V. L. and M. L. Brown. Racial and ethnic disparities in the receipt of cancer treatment. Journal of the National Cancer Institute 94(5):334-357, 2002.

Shavers, V. L. and B. S. Shavers. Racism and health inequity among Americans. Journal of the National Medical Association 98(3):386-396, 2006.

Shea, A. M., L. H. Curtis, B. G. Hammill, et al. Association between the Medicare Modernization Act of 2003 and patient wait times and travel distance for chemotherapy. Journal of the American Medical Association 300(2):189-196, 2008.

Shiffman, R. N., G. Michel, A. Essaihi, et al. Bridging the guideline information gap: a systematic, document-centered approach to guideline implementation. Journal of the American Medical Association 11:418-426, 2004.

Shugarman, L. R., K. Mack, M. E. S. Sorbero, et al. Race and sex differences in the receipt of timely and appropriate lung cancer treatment. Medical Care 47(7):774-781, 2009.

Silliman, R. A., E. Guadagnoli, et al. Adjuvant tamoxifen prescription in women 65 years and older with primary breast cancer. Journal of Clinical Oncology 20(11):2680-2688, 2002.

Simon, M. S., D. R. Brown, Wei Du, et al. Acrrual to breast cancer clinical trials at a university-affiliated hospital in metropolitan Detroit. American Journal of Clinical Oncology 22(1):42-46, 1999.

Smith, B. D., C. P. Gross, G. L. Smith, et al. Effectiveness of radiation therapy for older women with early breast cancer. Journal of the National Cancer Institute 98(10):681-690, 2006.

Smith, G. L., Y. T. Shih, Y. Xu, et al. Racial disparities in the use of radiotherapy after breast conserving surgery. Cancer 116:734-741, 2010.

Smith, T. J., and B. E. Hillner. Ensuring quality cancer care by the use of clinical practice guidelines and critical pathways. Journal of Clinical Oncology 19(11):2886-2897, 2001.

Smith, K., L. Wray, M. Klein-Cabral, et al. Ethnic disparities in adjuvant chemotherapy for breast cancer are not caused by excess toxicity in black patients. Clin Breast Cancer 6(3):260-266, 2005.

Smith, B. D., B. G. Haffty, G. L. Smith, et al. Use of postmastectomy radiotherapy in older women. International Journal of Radiation Oncology Biology Physics 71(1):98-106, 2008.

Stitzenberg, K. B., N. Klauber-Demore, X. S. Chang, et al. In vivo intraoperative radiotherapy: a novel approach to radiotherapy for early stage breast cancer. Ann Surg Oncol 14(4):1515-1516, 2007a.

Stitzenberg, K. B., N. E. Thomas, K. Dalton, et al. Distance to diagnosing provider as a measure of access for patients with melanoma. Arch Dermatol 143(8):991-998, 2007b.

Stitzenberg, K. B., N. E. Thomas, and D. W. Ollila. Influence of provider and practice characteristics on melanoma care. Am J Surg 193(2):206-212, 2007.

Talcott, J. A., P. Spain, J. A. Clark, et al. Hidden barriers between knowledge and behavior: the North Carolina prostate cancer screening and treatment experience. Cancer 109(8):1599-1606, 2007.

Tammemagi, C. M. Racial/ethnic disparities in breast and gynecologic cancer treatment and outcomes. Curr Opin Obstet Gynecol 19(1):31-36, 2007.

Tammemagi, C. M., D. Nerenz, C Neslund-Dudas, et al. Comorbidity and survival disparities among black and white patients with breast cancer. Journal of the American Medical Association 294(14):1765-1772, 2005.

Tejeda, H. A., S. B. Green, E. L. Trimble, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. Journal of the National Cancer Institute 88(12):812-816, 1996.

Tropman-Hawley, S., J. Earp, M. O'Malley, et al. The role of physician recommendation in women's mammography use: Is it a 2-stage process? Medical Care 38:392-403, 2000.

Tsoutsou, P. G., M. I. Koukourakis, D. Azria, et al. Optimal timing for adjuvant radiation therapy in breast cancer: a comprehensive review and perspectives. Critical Reviews in Oncology/Hematology 71:102-116, 2009.

U.S. Department of Health and Human Services: Healthy People 2010: Understanding and Improving Health (ed 2). Washington, DC, U.S. Government Printing Office, 2000.

Vainshtein, J. Disparities in breast cancer incidence across racial/ethnic strata and socioeconomic status: A systematic review. Journal of the National Medical Association 100(7):833-839, 2008.

Vargas, R. B., G. W. Ryan, C. A. Jackson, et al. Characteristics of the original patient navigation programs to reduce disparities in the diagnosis and treatment of breast cancer. Cancer 113(2):426-433, 2008.

Vernon, S. W., V. G. Vogel, S. Halabi, et al. Breast cancer screening behaviors and attitudes in three racial/ethnic groups. Cancer 69:165-174, 1992.

Virnig, B. A., J. L. Warren, G. S. Cooper, et al. Studying radiation therapy using SEER-Medicare-linked data. Medical Care 40:IV-49-54, 2002 (suppl 8).

Vogel, V. G. Epidemiology, genetics, and risk evaluation of postmenopausal women at risk of breast cancer. Menopause 15:S782-S789, 2008 (suppl 4).

Voti, L., L. C. Richardson, I. Reis, et al. The effect of race/ethnicity and insurance in the administration of standard therapy for local breast cancer in Florida. Breast Cancer Res Treat 95(1):89-95, 2006.

Wagner, E. H., B. T. Austin, and M. Von Korff. Improving outcomes in chronic illness. Managed Care Quarterly 4(2):12-25, 1996a.

Wagner, E. H., B. T. Austin, and M. Von Korff. Organizing care for patients with chronic illness. The Milbank Quarterly 74(4):511-544, 1996b.

Wagner, E. H., C. Davis, J. Schaefer, et al. A survey of leading chronic disease management programs: are they consistent with the literature? Journal of Nursing Care Quality 16(2):67-80, 2002.

Wagner, L. and M. D. Lacey. The hidden costs of cancer care: an overview with implications and referral resources for oncology nurses. Clin J Oncol Nurs 8(3):279-287, 2004.

Waitman, L. R. and R. A. Miller. Pragmatics of implementing guidelines on the front lines. Journal of the American Medical Association 11:436-438, 2004.

Waljee, J. F., L. J. Greenfield, J. B. Dimick, et al. Surgeon age and operative mortality in the United States. Annals of Surgery 244(3):353-362, 2006.

Warren, J. L., M. L. Brown, M. P. Fay, et al. Costs of treatment for elderly women with early-stage breast cancer in fee-for-service settings. Journal of Clinical Oncology 20(1):307-316, 2002a.

Warren, J. L., L. C. Harlan, A. Fahey, et al. Utility of the SEER-Medicare data to identify chemotherapy use. Medical Care 40:IV-55-61, 2002b (suppl 8).

Warren, J. L., C. N. Klabunde, D. Schrag, et al. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Medical Care 40:IV-3-18, 2002c (suppl 8).

Warren, J. L., K. R. Yabroff, A. Meekins, et al. Evaluation of trends in the cost of initial cancer treatment. Journal of the National Cancer Institute 100(12):888-897, 2008.

Weiner, B., W. R. Carpenter, L. Richardson, et al. Beyond Claims Data: Assessing the Problem of Access to Radiation Therapy for Low-Income Women with Breast Cancer. Presented at the American Public Health Association (APHA) 137th Annual Meeting, Philadelphia, PA, November 9, 2009.

Wildiers, H. and E. G. Brain. Adjuvant chemotherapy in elderly patients with breast cancer: where are we? Curr Opin Oncol 17(6):566-572, 2005.

Williams, D. R. and S. A. Mohammed. Discrimination and racial disparities in health: evidence and needed research. J Behav Med 32(1):20-47, 2009.

Wilt, T. J., T. A. Shamliyan, B. C. Taylor, et al. Association between hospital and surgeon radical prostatectomy volume and patient outcomes: A systematic review. J Urol 180(3):820-828; discussion 828-829, 2008.

Wooldridge, Jeffrey M.: Introductory Economics: A Modern Approach (ed 3). Mason, OH, Thomson-Southwestern Publishing, 2006.

Wyatt, R. M., B. J. Jones, and R. G. Dale. Radiotherapy treatment delays and their influence on tumour control achieved by various fractionation schedules. The British Journal of Radiology 81:549-563, 2008.

Yood, M. U., C. C. Johnson, A. Blount et al. Race and differences in breast cancer survival in a managed care population. Journal of the National Cancer Institute 91:1487-1491, 1999.

Zapka, J. G., S. H. Taplin, L. I. Solberg, et al. A framework for improving the quality of cancer care: the case of breast and cervical cancer screening. Cancer Epidemiology, Biomarkers, and Prevention 12:4-13, 2003.

Zork, N. M., I. K. Komenaka, R. E. Pennington, et al. The effect of dedicated breast surgeons on the short-term outcomes in breast cancer. Annals of Surgery 248(2):280-285, 2008.