COMPARATIVE EFFECTIVENESS AND COST OF PREOPERATIVE
BREAST MRI IN ELDERLY BREAST CANCER PATIENTS

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ABSTRACT

ALICE K. FORTUNE-GREELEY: Comparative effectiveness and cost of preoperative breast MRI in elderly breast cancer patients
(Under the direction of William R. Carpenter, PhD)

Preoperative breast magnetic resonance imaging (MRI) has been used increasingly in the preoperative evaluation of women with newly diagnosed breast cancer. Despite its rapid adoption, limited evidence exists to support the routine use of breast MRI, creating controversy in breast cancer management. Existing evidence suggests that breast MRI may change treatment patterns, leading to surgical treatment delay and more extensive surgeries but may not improve patient outcomes. This study is one of the first to examine the association between preoperative breast MRI and surgical planning (i.e., time to complete surgery and type of initial surgery), short-term outcomes (i.e., re-excision and second breast cancer event rates), and cost in the elderly women using a large, population-based dataset.

In this observational, retrospective analysis, we identified women diagnosed with early-stage (I-IIB), operable breast cancer from 2004-2007 in the Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset. Medicare claims were used to define the initial treatment phase, to identify breast cancer treatments, and to categorize Medicare payments. Second breast cancer events (i.e., recurrence or a second primary breast cancer) were identified through an algorithm validated in breast cancer patients. To control for measured confounders, we used propensity score methods.

Twelve percent of our sample had a preoperative breast MRI. Compared to women who did not undergo breast MRI, we found that receipt of breast MRI was associated with a median 15-day delay in complete surgery and an increased likelihood of a mastectomy as the initial surgery. Breast MRI was not significantly associated with re-excision rates, but

was associated with an increased hazard of a second breast cancer event. Women who received a breast MRI had higher total all-cause and breast cancer-attributable costs during the initial treatment phase than those women who did not undergo a breast MRI.

Since findings from this dissertation indicate that breast MRI was associated with a slight surgical delay and an increased likelihood of a mastectomy in the absence of evidence for improved short-term outcomes, healthcare providers and elderly breast cancer patients should consider these factors when making informed decisions about whether the use of breast MRI is appropriate.

DEDICATION

This dissertation is dedicated to my parents. Mom, thank you for the encouragement to

pursue whatever my heart desires and, Dad, thank you for inspiring the passion and work

ethic to see these dreams come to fruition. I am profoundly grateful for your support as I

strive to define my career and am deeply appreciative to both of you for demonstrating the

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Finally, I would like to thank my friends and family whose presence, love, and support have brightened my way and lightened my load. Specifically, I would like to thank

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LIST OF ABBREVIATIONS

ACOSOG   American College of Surgeons Oncology Group

ACS   American Cancer Society

ACRIN   American College of Radiology Imaging Network

AHA   American Heart Association

AJCC   American Joint Committee on Cancer

ASCO   American Society of Clinical Oncology

ARF   Area Resource File

BCT   Breast Conserving Therapy

BCS   Breast Conserving Surgery

CER   Comparative Effectiveness Research

COMICE   Comparative Effectiveness of Magnetic Resonance Imaging in Breast Cancer

CMS   Centers for Medicare & Medicaid Services

CI   Confidence interval

CALGB   Cancer and Leukemia Group B

CPT   Current Procedural Terminology

DCIS   Ductal carcinoma in situ

ECOG   Eastern Cooperative Oncology Group

EDB   Enrollment Data Base

ER   Estrogen Receptor

EUSOMA   European Society of Breast Cancer Specialists

GLM   Generalized linear models

HCPCS   Healthcare Common Procedure Coding System

HER2   Human Epidermal Growth Factor Receptor 2

HMO   Health Maintenance Organization

HR	Hazard ratio
ICD-9-CM	International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification
ILC	Invasive lobular carcinoma
IOM	Institute of Medicine
MEDPAR	Medicare Provider Analysis and Review
MONET	Mammography of non-palpable breast tumors trial
MRI	Magnetic Resonance Imaging
MSA	Metropolitan Statistical Area
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	Odds ratio
PEDSF	Patient Entitlement and Diagnosis Summary File
PR	Progesterone Receptor
RCT	Randomized Control Trial
SEER	Surveillance, Epidemiology and End Results
SWOG	Southwest Oncology Group
TNM	Tumor, Node, Metastasis System
US	United States

Advanced imaging modalities in cancer care are being adopted rapidly, but scientific evidence about their impact in real world settings lags behind.[1-4] As new and advanced imaging modalities that assist with diagnosing, staging, and treating cancer are introduced into clinical practice, it is important to examine their impact on treatment planning and to develop evidence about their influence on short- and long-term outcomes. This evidence can be used, in turn, to determine their appropriateness and to inform dissemination into clinical practice. Breast magnetic resonance imaging (MRI) is one type of advanced imaging that is being used to a greater extent in practice with limited evidence demonstrating its benefit.

During the past ten years, breast MRI has been used increasingly as part of preoperative planning for patients with early stage invasive breast cancer.[1,2,5-16] The percentage of elderly breast cancer patients with preoperative breast MRI increased from 1.2% in 2002 to 18.8% in 2007.[13] Breast MRI has been used in addition to conventional assessment, which includes clinical examination of the breasts, mammography and ultrasound, and pathological assessment of suspicious lesions, to measure the extent of disease and provide enhanced cancer detection. Preoperative breast MRI is highly sensitive and capable of detecting suspicious lesions not visible with mammography or ultrasound, but is limited in its specificity.[17-19] Despite routine use, evidence suggests that breast MRI may not provide as much benefit as expected, resulting in more extensive surgeries[17,18,20-22] and treatment delay[5,15,23] without any measurable differences in re-excision[17,18,20-22] or breast cancer recurrence rates.[10,20,24-27] Furthermore, the effect that breast MRI has on initial surgical planning and clinical outcomes remains unknown in the elderly United States (US)

population. Additional research is needed to examine the influence of breast MRI on outcomes in the real world setting to inform its appropriate use.

Existing evidence examining the association between breast MRI and surgical planning, short-term outcomes, and healthcare costs is limited in several aspects. First, much of the evidence is based on multiple studies from single institutions and two randomized controlled trials (RCT). To our knowledge, few studies examine the effect of MRI on surgical planning, outcomes, and cost in a population comparable to the US elderly population. Patients and medical groups participating in the RCTs and single institution studies were highly selective and the study populations were not comparable to the US elderly population. For example, the median and mean ages for the RCTs were 57[20] and 55.5 years,[21] two decades younger than the average age of breast cancer patients enrolled in Medicare[28] and the average patient in our study (76.1 years). Second, to our knowledge, only one study[29] has examined the impact of breast MRI on surgical planning or short-term outcomes in older women, a population that is least likely to benefit from breast MRIs because older patients are more likely to have less dense breasts and, therefore, fewer occult tumors with conventional assessment.[30-35] Third, the two randomized controlled trials were conducted in the Netherlands[21] and the United Kingdom[20,36] where physician practice patterns, payment and referral structures, health insurance coverage, fiscal considerations, and patient preferences for mastectomy over breast conserving surgery (BCS) differ significantly from the US.[37-39] Fourth, no study, to our knowledge, has examined the association between breast MRI and the cost of initial treatment in the US. The only study to examine the cost of breast MRI was a randomized controlled trial conducted in the United Kingdom.[36]

This dissertation addressed this gap in the literature by examining preoperative breast MRI used in addition to conventional assessment to measure the extent of disease as part of the preoperative work-up. We examine breast MRI's impact on surgical planning,

short-term outcomes, and Medicare costs in older, newly-diagnosed breast cancer patients using a large, population-based dataset. It is worth noting that, although breast MRI is used for other, non-preoperative indications such as screening high-risk women[12,40-47] or monitoring the response to neoadjuvant therapy,[48-54] these indications for breast MRI are not the focus of this study.

Our central hypothesis was that preoperative breast MRI would be associated with a surgical treatment delay and an increased likelihood of a mastectomy as the initial surgery without evidence for improved short-term outcomes. Additionally, we hypothesized that breast MRI would be associated with increased costs to treat the incident breast cancer.

Specific aims include:

1. Examine the association between preoperative breast MRIs and surgical planning:

    a. Examine the association between preoperative breast MRI and the **time elapsed** from the date of the first claim for a suspected breast disorder to the date of complete surgical treatment; and

    b. Examine the association between of preoperative breast MRI and initial **type** of breast surgery (i.e., mastectomy vs. breast conserving surgery).

2. Examine the association between preoperative breast MRIs and short-term outcomes:

    a. Examine the association between preoperative breast MRI and whether a patient had a **re-excision**; and

    b. Examine the association between preoperative breast MRI and whether a patient had a **second breast cancer event.**

3. Examine the costs associated with breast MRI during the initial treatment phase from the perspective of Medicare.

Aim 1a examined the time elapsed from the date of the first claim for a suspected breast disorder (e.g., lump or mass in breast or abnormal mammogram) until the date of complete surgical treatment for women with and without breast MRI. Examining the time to complete surgical treatment is important because a surgical delay of 3 - 8 months may have detrimental effects on breast cancer outcomes.[55,56] Moreover, any delay in treatment may be anxiety-provoking for patients, lead to uncertainties related to the interpretation and management of additional findings, and delay the start of adjuvant therapy.[57] Previous single institution studies have found that breast MRI was associated with a 22- to 41-day delay.[5,15,23]

Aim 1b examined the association between breast MRI and initial type of breast surgery (i.e., BCS vs. mastectomy). Recent studies have reported that mastectomy rates for early-stage breast cancer patients have increased, and more patients with early-stage breast cancer are undergoing aggressive surgical treatment.[11,58-62] Although evidence has shown that breast conserving therapy (BCT), or BCS followed by radiation, and mastectomy yield equivalent survival outcomes[63-65] and the decision regarding the type of initial surgery has been considered a "preference-sensitive decision,"[66,67] it is important to examine what other factors, such as breast MRI, may influence the likelihood of a mastectomy over BCT. In multiple recent single institutional studies,[10,23,26,68-77] meta-analyses,[17,18,22] and two European RCTs,[20,21] breast MRI was found to be associated with an increased likelihood of mastectomy compared to breast conserving surgery due to additional lesions detected by MRI that were occult with conventional assessment. However, there is a dearth of literature examining the association between breast MRI and surgical planning on a sample comparable to the US elderly population.

In the observational, retrospective analyses for Aim 1, we identified women diagnosed with early stage (I-IIB), operable breast cancer from 2004-2007 whose data comprise a subset of the Surveillance, Epidemiology, and End Results (SEER) registry and

was linked to Medicare claims. Cancer treatment and breast MRI receipt were identified from the Medicare claims. Time from the first claim for a suspected breast disorder to complete surgical treatment was defined as the number of days from the first claim for a suspected breast disorder diagnosis to the last surgical procedure in the initial treatment phase. The first surgical procedure was defined as the first surgery that was either a BCS (partial mastectomy or a breast excision) or a full mastectomy. To control for measured confounders, we used propensity score methods.[78,79] Based on previous findings,[13,17-22] we hypothesized that women who received preoperative breast MRI would be associated with: (a) a longer time to complete surgery; and (b) more extensive initial surgeries (i.e., mastectomy) than those women who did not receive a breast MRI.

In Aims 1a and 1b, we used multivariate logistic regression to determine each patient's propensity for receipt of preoperative breast MRI on the basis of observed patient and surgical facility characteristics.[80] We selected variables based on their hypothesized relationship with breast MRI receipt and the outcome (either time to surgery or type of first surgery). Patient-level covariates included year of diagnosis (2004-2007), age group at diagnosis (in five-year intervals), marital status, Medicare state buy-in coverage status, race, and co-morbidities using the National Cancer Institute (NCI) combined index.[81] We included person-level tumor characteristics such as stage, grade, histology, and tumor size as well as hormone receptor status. Surgical provider variables were included, such as whether or not the surgical facility was affiliated with NCI Cooperative Groups with breast cancer research portfolios, a designated NCI Cancer Center, a teaching hospital, or had high breast cancer surgical volume. We also included indicators for SEER region and education level as the percentage of high school graduates in the patient's zip code of residence.

Aim 2a examined the association between breast MRI and the likelihood of re-excision after a patient's initial surgery. Re-excision rates after initial breast conserving surgery are an important clinical issue. Re-excisions have been found to occur after 17% to

60% of breast conserving surgeries.[82-86] Re-excisions have multiple negative consequences, including a worsened cosmetic outcome, delay in adjuvant therapy, and higher cost associated with additional treatment.[84,85,87-89] Reoperation rates are also an important clinical issue in the elderly population. Operations and re-excisions are more problematic for elderly women who are more likely to have co-morbidities and for whom it is riskier to undergo anesthesia. Furthermore, recovery from surgery is much more difficult for these women. Because of its sensitivity and enhanced imaging, researchers and clinicians have begun to investigate whether or not breast MRI can increase the likelihood of identifying clear margins after the initial surgery and reduce the need for re-excisions. Multiple single institution studies, meta-analyses, and two RCTs found no difference in re-excision rates between patients with and without preoperative breast MRI.[10,17,18,20-23,26,27,68]

Aim 2b examined the likelihood of whether the women had a second breast cancer event, either a recurrence or a second cancer in the contralateral breast. Studies have shown that recurrence rates after the completion of adjuvant therapy are 6–13%,[90-92] and the likelihood of recurrence has been reported to peak within the first five years after primary treatment.[93-95] A second breast cancer event is an important short-term outcome due to its effect on overall survival[96] as well as the physiological and physical distress of additional cancer treatments. Additionally, anxiety from fear of recurrence or a second breast cancer is one of the most prevalent long-term psychological consequences of breast cancer.[97-99] Because of breast MRI sensitivity and enhanced imaging, researchers and clinicians have examined whether or not breast MRI can reduce the likelihood of a second breast cancer event. One RCT from United Kingdom[20] found no significant difference in one-year, local recurrence-free interval rates, which is consistent with other retrospective, single institution studies reporting that preoperative breast MRI was not associated with reduced local recurrence rates.[10,24-27] Despite existing evidence examining the effectiveness of preoperative breast MRI, there is a dearth of evidence examining the association between

breast MRI and the likelihood of a re-excision or second breast cancer event in a sample comparable to the US elderly population.

Aims 2a and 2b used a similar cohort of elderly women described in Aim 1. However, for Aim 2a, we limited our sample to women eligible for re-excision by including only women with BCS as their initial surgery. Cancer treatment and breast MRI receipt were again identified from the Medicare claims. A re-excision was defined as a claim for a breast surgical procedure (a breast excision, partial mastectomy, or conversion to mastectomy) after the initial surgery but during the initial treatment phase, which ended on the last day of treatment before a treatment gap of 90 days. Second breast cancer events were identified through an algorithm validated in breast cancer patients using information regarding secondary cancers and surgical procedures from claims data and SEER registries.[100] To control for measured confounders, we used propensity score methods[78,79] to estimate the association of breast MRI on the likelihood of a re-excision and the hazard of a second breast cancer event. Based on previous findings,[10,17,20-22,24-27] we hypothesized that the group of women who received a preoperative breast MRI would have a similar likelihood of a re-excision (Aim 2a) and a second breast cancer event (Aim 2b) as the group of women who did not have a preoperative breast MRI.

As with Aim 1, we used multivariate logistic regression in the analyses for Aim 2 to determine each patient's propensity for receipt of preoperative breast MRI on the basis of observed patient and surgical facility characteristics.[80] Again, we selected from the previously mentioned variables based on their hypothesized relationship with breast MRI receipt and outcome (re-excision or second breast cancer event).

The third study aim focused on the costs associated with breast MRI for elderly breast cancer patients in the US from the perspective of Medicare. Funds spent on breast cancer, the most expensive cancer diagnosis, are estimated at $16.5 billion, which comprise 13.3% of total healthcare spending. Based on US population changes alone, it has been

estimated that national expenditures for breast cancer will increase by 24.2% and reach

$20.5 billion by 2020.[101] Spending on breast cancer is not only growing due to increased

prevalence, but also due to escalating treatment costs per patient.[102-104] Studies also have

estimated that the inflation-adjusted cost of initial care for each breast cancer patient

increased by 25% from $16,775 in 1991 to $20,964 in 2002.[105] Stakeholders view the

increasing cost of cancer care as a major societal issue that may impact the health of the

US population and exacerbate disparities in care and outcomes.[106] Rising costs have

prompted the American Society of Clinical Oncology (ASCO) to create a task force on the

cost of cancer care to examine the drivers of increasing cancer costs, their impact, and

strategies to modulate them in order to sustain progress against cancer and universal

access to high-quality care.[106,107]

The rising cost of breast cancer treatment has been attributed to changes in

treatment patterns and the increased use of targeted therapies and supportive medicine.[102-104] Additionally, it has been estimated that the growing use of advanced imaging contributes

to the accelerating cost of breast cancer care, with the costs of advanced imaging

increasing at a greater rate than total costs among Medicare beneficiaries with cancer.[2,3]

Preoperative breast MRI is an example of an advanced imaging modality that is being

rapidly adopted, and research has shown that breast MRI may change treatment patterns in

ways that may affect the cost of the initial treatment phase through additional diagnostic

work-up[21,108,109] and lead to extensive surgical treatment without reducing the likelihood and

cost of re-excision surgeries.[17,18,20-22] Because of breast MRI's influence on treatment

patterns and limited evidence for improved outcomes, it is important to examine the effect

this imaging has on the overall cost to care for women with breast cancer. No study, to our

knowledge, has examined the association between breast MRI and the cost of initial

treatment in the US. The only study to examine the cost of breast MRI was a RCT

conducted in the United Kingdom.[36]

For the third study aim, we used the same patient sample from Aim 1, or women diagnosed with early stage (I-IIB), operable breast cancer from 2004-2007 in the SEER registries. Using claims from 2004 through 2009, we identified Medicare payments during the initial treatment phase, which we defined to include the diagnostic, preoperative, surgical, and adjuvant therapy stages of care. For women with and without a preoperative breast MRI, we examined unadjusted all-cause and breast cancer-attributed Medicare payments during the initial treatment phase. Further, we used multivariate generalized linear models, controlling for the same independent variables as in Aims 1 and 2, to generate the adjusted multiplicative and marginal effects of preoperative breast MRI on all-cause or breast cancer-attributed Medicare payments. We hypothesized that the overall cost of care for older women with breast cancer would be higher for those women who received a preoperative breast MRI than for women who did not.[20]

The subsequent chapters are organized as follows: (a) Chapter 2 provides an overview of the breast cancer burden and a review of the current standards for diagnosis, staging, and treatment, including conventional and breast MRI evaluation of breast cancer; (b) Chapter 3 describes the methods used in this dissertation, detailing the conceptual framework, research questions and hypotheses, data sources, study population, variables and measurement, and statistical analyses employed; (c) Chapters 4, 5, and 6 comprise Aims 1, 2, and 3, respectively, and each of these chapters is written as a self-contained journal manuscript and, hence, includes an overview, introduction, methods, results, and discussion (because they are to be submitted for publication, there are some redundancies across papers); and (d) Chapter 7 summarizes this dissertation's strengths and limitations, policy relevance, and future research plans.

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CHAPTER 2: LITERATURE REVIEW

Breast cancer burden in the United States

Cancer is a major public health problem in the United States (US), both in terms of the number of life-years lost and the cost of treatment. Presently, one in four deaths in the US are attributable to cancer, which is the leading cause of death in adults aged 40 to 79.[110] In 2013, it has been estimated that more than 1.6 million Americans will be newly diagnosed with cancer and more than half a million people will die from the disease.[110] Additionally, cancer prevalence is predicted to increase over the next decade with the number of estimated cancer survivors in the US increasing from 13.8 million in 2010 to 18.1 million in 2020.[101]

Over the past twenty years, the medical costs of cancer have nearly doubled.[111] The overall costs of cancer in 2010 have been estimated at $263.8 billion, with direct medical costs, indirect morbidity costs, and interect mortality costs comprising $102.8, $20.9, and $140.1 billion, respectively.[112] Elements contributing to the rising cost of cancer care include increasing cancer incidence rates as the population ages, increasing prices for novel techniques and chemotherapy agents, and increasing intensity of cancer care.[102,103,105,111,113-115] Stakeholders view the increasing cost of cancer care as a major societal issue that may impact the health of the population and exacerbate disparities in care and outcomes.[106] Rising costs have prompted the American Society of Clinical Oncology to create a task force on the cost of cancer care to examine drivers of increasing cancer costs, their impact, and strategies to modulate them in order to sustain progress against cancer and universal access to high quality care.[106,107]

Breast cancer is the most common cancer among women, with an estimated 3.5 million breast cancer survivors in the US in 2010,[101] and is the second most fatal cancer site.[110] In 2013, an estimated 234,580 women have been diagnosed with breast cancer and an estimated 39,620 are expected to die from the disease.[110] Elderly women are most at risk for developing breast cancer. The incidence among women age 65 or older is approximately five times greater than the incidence among women younger than 65, and risk increases at all ages until age 80.[116] Breast cancer has a high treatment burden and, as a result of the disease and its treatments, health-related quality of life in breast cancer patients is significantly diminished through compromised physical, psychological, and social functioning.[117] In addition, breast cancer presents a significant cost burden in national expenditures, which were estimated at $16.5 billion in 2010. This figure constitutes 13.3% of total healthcare spending on cancer, more than any other cancer site.[112,118] Based on US population changes alone, it has been estimated that national expenditures for breast cancer will increase by 24.2% and reach $20.5 billion by 2020.[101] Spending on breast cancer is not only growing due to increased prevalence, but also to escalating treatment costs per patient.[102-104] It has been estimated that the inflation-adjusted cost of initial care for each breast cancer patient increased 25% from 1991 ($16,775) to 2002 ($20,964).[105] Thus, the significant morbidity, mortality, and cost of treating breast cancer patients result in a considerable breast cancer burden in the US.

Overview of breast cancer diagnosis, staging, and treatment

After breast cancer is detected, patients have the best chance of a successful outcome if the extent of the cancer is accurately identified, diagnosed, staged, and treated accordingly. The cancer stage at diagnosis determines the type and extent of disease in the body and the type of surgical and/or systemic treatment the patient will receive.[119,120] The American Joint Committee on Cancer (AJCC) staging system is used by patients and

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providers to determine prognosis and treatment options.[121] The AJCC system (Table 2.1),

also referred to as the Tumor, Node, Metastasis (TNM) system, is used to ascertain whether

a cancer is invasive or non-invasive, the size of the tumor (T), how many lymph nodes are

involved (N), and if the cancer has spread to other parts of the body (M). Patients have a

better prognosis if cancer is diagnosed at an early stage. Five-year survival rates for women

diagnosed between 2000-2007 with localized (i.e., confined to primary site), regional (i.e.,

spread to regional lymph nodes), and distant (i.e., metastasized) tumors were 98.6%,

83.8%, 23.3%, respectively.[122] In addition to staging, other tumor factors can influence

treatment decisions and patient outcomes. Hormone receptor tests determine whether or

not the tumor is estrogen receptor (ER) or progesterone receptor (PR) positive. ER/PR

positive tumors are dependent on estrogen and progesterone to grow and, thus, hormone

therapy is often recommended to block the cancer cell from using these hormones. Testing

is available to determine the amount of Human Epidermal Growth Factor Receptor 2, also

known as HER2/neu, which is a protein that stimulates the growth of breast cancer cells in

cancerous tissue. If cancerous tissue has excessive amounts of the protein, the patient

might be eligible for a targeted therapy that blocks growth of HER2/neu.[47] Additionally, the

nature of the tumor, such as whether or not it is multifocal (i.e., smaller cancer spots

occurring in the same quadrant of the breast as the main tumor) or multicentric (i.e., smaller

cancer spots in other quadrants than the one containing the main tumor), can influence

treatment decisions.

     Multiple treatment guidelines and practice standards exist for the management of

patients with breast cancer, each with different treatment risks, costs, and outcomes. For

most women with operable breast cancer, treatment involves local therapy, such as surgery

and radiation, to remove or destroy the breast cancer, and/or systemic therapy, such as

hormone therapy, chemotherapy, and targeted therapy.[47] Women with early-stage, invasive

breast cancer may receive a combination of treatments (Figure 2.1). Most women will either

undergo BCS or a mastectomy and may possibly have the lymph nodes under an arm removed. After the initial surgery, a pathologist examines the excised tumor to see if cancerous tissue remains at the margins. If the margins are positive, the patient may need a re-excision to obtain negative tumor margins.

After surgery, many women receive adjuvant therapy to lower the chance of breast cancer recurrence. The National Comprehensive Cancer Network (NCCN) recommends that women who undergo BCS also receive adjuvant radiation therapy, or the combination of the two, which is known as breast conserving therapy (BCT).[47] Women may also receive hormone therapy, chemotherapy, targeted therapy, or a combination of these therapies to eliminate any remaining cancer and reduce the risk of recurrence.

Treatment decision-making by a woman diagnosed with early-stage breast cancer is complex. Treatment decisions are based on a wide range of biological, physical, emotional, economic, and social factors.[123-129] These factors include stage of disease, genetic indicators, age, family history, and risk of local recurrence. They also include personal experiences, concern about radiation exposure, the inconvenience of adding daily radiation to a complicated treatment regimen, social factors, educational status, insurance coverage, patient preferences regarding physical appearance, and patient fears of recurrence. Geographic location and type of clinical care provider also play a role in treatment decisions.[122]

Since the early 1990s, evidence has shown that BCT and mastectomy are equally effective,[130] and trials reporting long-term survival have found equivalent outcomes for both surgeries.[63,131-135] Additional research reported improved quality of life with BCT, which is often associated with improved psychosocial health in terms of body image, sexuality, and short-term physical functioning.[64,65,135-140] In 1990, NCI reported that BCS "is preferable

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because it provides survival equivalent to total mastectomy while preserving the breast," and professional consensus began to favor the less-invasive surgery.[64,132,140]

After NCI's 1990 publication, mastectomy rates for early-stage breast cancer patients markedly decreased in the United States.[141-144] However, recent studies have reported that this trend is changing and more patients with early-stage breast cancer are undergoing more aggressive surgical treatment. Single institution studies indicate that mastectomy rates for early-stage breast cancer patients increased from 35% in 2004 to 60% in 2007 at Moffitt Cancer Center,[58] from 35% of in 2004 to 60% at the Magee-Women's' Hospital at the University of Pittsburgh,[59] and from 31% in 2003 to 43% in 2006 at the Mayo Clinic.[11] Additional studies using SEER registry data (Figure 2.2) showed that mastectomies for elderly women decreased from 2000-2005, but then increased in 2006-2008.[38,61] Research using SEER registries and single institution data[145-147] has also documented a trend toward more aggressive surgical treatment, which was exhibited by contralateral prophylactic mastectomy rate in the US that more than doubled from 1998 to 2003.

These results have generated significant discussion in the lay press and medical literature about how to explain these trends.[39,148-151] Some authors have suggested that recent changes in preoperative management may explain the changing trend, such as genetic testing for BRCA1 and BRCA2 mutations, increased education regarding surgical treatment options, concern over the long-term side effects of radiation, and the introduction of new or improved imaging modalities (e.g., MRI or digital mammography).[11,152-157] Increased mastectomy rates could also be due to improvements in mastectomy techniques and reconstruction options,[125,151,158,159] however, this explanation may be more likely in younger populations. The findings also suggest a possible global shift in breast surgical treatment preferences toward mastectomy, and may reflect a growing patient choice for a preventive surgical approach against local recurrence and new primary breast cancers.[11]

Conventional evaluation of breast cancer

Breast cancer can be discovered through screening mammograms, routine clinical breast exams, breast self-exams, breast symptoms, or routine screening of high-risk individuals with breast MRI.[47] If a screening mammogram shows an abnormal area of the breast or the patient experiences unusual breast changes, such as a lump, pain, tissue thickening, nipple discharge, or a change in breast size or shape, it is recommended that the patient undergo a diagnostic mammogram. NCCN recommends that all women diagnosed with breast cancer be evaluated using standard breast imaging with mammography and, when indicated, diagnostic breast ultrasound.[47] Suspicious lesions should then be biopsied and the presence of malignant cells confirmed by a pathologist.

Once the patient has a confirmed diagnosis, the cancer is then staged. According to NCCN guidelines, clinical staging includes a physical examination of the skin of the breast, mammary glands, and lymph nodes, as well as imaging and pathologic examination of the breast or other tissues.[47] Based on the physical examination and imaging results, the cancer is then staged based on the size of primary tumor, chest wall invasion, and presence or absence of regional or distant metastasis according to the AJCC staging system described earlier.

Breast MRI evaluation of breast cancer

Although the diagnostic mammogram has been the imaging gold standard to determine the extent of disease, MRI has been used increasingly in the preoperative evaluation of women with newly diagnosed breast cancer to provide enhanced cancer detection during the past ten years.[1,2,5-16] There is strong evidence demonstrating that breast MRI has improved sensitivity over mammography to detect additional cancerous disease;[17,19,160] however, it has not been shown that breast MRI improves patient outcomes, such as re-excision rates[17,18,20-22] or local recurrence.[10,20,24-27] Thus, the use of preoperative

breast MRI to detect additional disease in the absence of evidence for improved patient outcomes has become a controversial issue in breast cancer management.[12,17-19,24,160-174]

Several consensus-based guidelines state that the use of preoperative breast MRI to evaluate the extent of disease for surgical planning is optional and may be used in addition to conventional assessment.[47,49,175,176] For example, NCCN does not advocate for or against the use of routine preoperative breast MRI for the assessment of ipsilateral breast cancer, but instead, recommends that decisions to use MRI are made in concert with the multidisciplinary treatment team and any alteration in surgical management should be considered after the MRI-detected lesion is biopsied due to the high rate of false positive findings.[47] NCCN also recommends that breast MRI should "generally be considered" in the staging of breast cancer for patients whose breasts were inadequately imaged with mammography and ultrasound (e.g., women with dense breast tissue or positive axillary nodal status and occult primary tumor presumed to originate in the breast). Further, the guidelines state that breast MRI may be useful for detecting additional disease in women with mammographically dense breasts, but the evidence does not show differential detection rates for any subset by breast pattern (breast density) or disease type (e.g., ductal carcinoma in situ (DCIS), invasive ductal cancer, or invasive lobular cancer). The European Society of Breast Cancer Specialists (EUSOMA) working group provides additional selection criteria for preoperative MRI, including women with lobular cancer, patients under 60 years of age with a tumor size discrepancy greater than one centimeter between mammography and ultrasound, and patients at high risk for breast cancer.[49] The EUSOMA group also recommends that women newly diagnosed with breast cancer should always be informed of the potential risks and benefits of preoperative MRI before undergoing the test.

It is worth noting that evidence exists for the use of breast MRI in a limited number of other clinical settings. For example, breast MRI has been recommended to *screen* high-risk women,[12,40-47] to investigate an occult primary breast cancer in patients presenting with

metastatic cancer in axillary nodes,[12,47] to examine patients considering partial breast irradiation,[12,49] and to evaluate tumor response to neoadjuvant chemotherapy.[48-54] These indications are beyond the scope of this study, which focuses on the use of breast MRI to preoperatively evaluate the extent of disease for surgical planning.

Strong evidence demonstrates that breast MRI is highly sensitive and has the ability to detect suspicious lesions not visible with mammography or ultrasound. Numerous articles have been published summarizing the sensitivity and specificity of breast MRI,[17,31,69,162,163,166-169,177,178] including three meta-analyses.[17-19] One meta-analysis of 19 published studies, including 2,610 breast cancer patients undergoing preoperative MRI, reported that MRI detected additional disease in 16% of women.[18] However, the authors found that breast MRI had limited specificity with a summary positive predictive value of 66%. An additional meta-analysis of women with newly diagnosed breast cancer showed that MRI detected abnormal contralateral lesions not seen on conventional imaging in 9.3% of women.[19] However, more than half of these lesions were false positives, and the authors found a true-positive to false-positive ratio of 0.92, indicating that MRI does not reliably distinguish benign from malignant findings.[19] Consistent with previous data, a third meta-analysis, including 50 articles and 10,881 women, found that MRI detected additional disease in 20% of women, but had limited specificity with a summary positive predictive value of 67%.[17]

Because of its increased sensitivity, research has shown that the use of breast MRI may influence surgical planning and treatment patterns for newly diagnosed breast cancer patients. Numerous studies have shown that patients with a preoperative breast MRI have an increased likelihood of more extensive surgery compared to those patients without preoperative breast MRI. A recent meta-analysis of newly diagnosed breast cancer patients,[22] including two randomized controlled trials[20,21] and four comparative cohort studies[10,23,26,68] that included a total of 3,112 subjects, demonstrated consistent evidence

that preoperative MRI significantly increased the odds of having mastectomy, either as initial

surgery [OR, 2.22 (P < 0.001); adjusted OR, 3.06 (P < 0.001)] or as a complete surgery

[OR, 1.54 (P < 0.001); adjusted OR, 1.51 (P < 0.001)]. These findings are consistent with

previous meta-analyses[17,18] and recently published single institution studies,[69-77] which found

that preoperative breast MRI leads to more extensive surgeries based on additional findings

from the MRI. Some findings suggest that the changes in surgical management were not

always beneficial and some modifications toward more extensive surgery were based on

false-positive results.[17,18,33,179,180] In their meta-analysis, Houssami and colleagues found

that, based on true-positive MRI findings, 8.1% of women were converted from wide local

excision to mastectomy and 11.3% from wide local excision to more extensive surgery, such

as wider/additional excision or mastectomy.[18] Based on false-positive MRI results, 1% of

patients converted to mastectomy and 5.5% converted from wide local excision to more

extensive surgery. Authors of an additional meta-analysis reported similar results with true-

positive MRI findings, prompting conversion to more extensive surgery in 12.8% of women,

however, this conversion was based on false-positive findings in 6.3% of these women.[17]

Although one randomized, prospective clinical trial examining the impact of breast MRI

(MONET) found that the BCS rate did not significantly differ between groups with and

without breast MRI,[21] another randomized, prospective clinical trial (COMICE) observed that

7% of the breast MRI group underwent a mastectomy at the initial operation compared to

1% of the no MRI group, and 2% of all MRI patients had a pathologically avoidable

mastectomy.[20,36]

Existing evidence also suggests that the receipt of breast MRI may delay initial

treatment. This delay could be due to additional diagnostic work-up needed for a breast

MRI, including managing breast MRI findings that may require MR-guided needle

biopsy.[21,108,109] One study by Bleicher and colleagues found that women who underwent

breast MRI experienced a 22-day increase in the time period from diagnosis to initial surgery

when compared to women who did not receive a breast MRI.[23] Another study by Krishnan and colleagues reported a delay for patients receiving a breast MRI of 27-41 days.[5] A third study found that patients with breast MRI had a longer median time to treatment (43 days) than those who did not (32 days).[15] The authors suggest that these delays were possibly related to the fact that imaging and biopsy prompted by MRIs were sometimes performed outside their breast center. Though these results are worthy of note, they were single institution studies and do not reflect nationwide treatment patterns.

Because breast MRI is a sensitive imaging technology that may be associated with more extensive surgeries and treatment delay, it is important to examine whether MR breast imaging offers clinical benefit. One assumption related to breast MRI is that its use results in improved surgical precision by helping to plan resection of the tumor, thus, reducing re-excision rates for incomplete excisions, local recurrences, or distant metastases. However, based on current literature, documentation of the benefits of breast MRI for improved outcomes is limited. Research has shown that the routine rate of positive margins after BCS is high, ranging from 17% to 60%.[72,82-86] However, evidence suggests that breast MRI does not reduce the need for re-excision compared to routine standard of care (Table 2.2).[10,20,21,23,26,27,68] For example, in the COMICE trial, the authors found that there were no differences in secondary outcomes between. the groups who did and did not receive breast MRIs.[20] Nineteen percent of the patients in both the MRI group and the non-MRI group needed re-excision. In the MONET randomized trial, the number of re-excisions after initial breast conserving surgery was greater in the MRI group compared to the control group (34% versus 12%).[21] Furthermore, a meta-analysis including 3,112 newly diagnosed breast cancer patients reported no differences in the odds of having positive margins or re-excision surgery for women with and without preoperative breast MRI.[22]

Studies have also shown that recurrence rates are similar for patients with and without breast MRI (Table 2.3).[10,20,24-27] For example, in the COMICE trial, the local

recurrence-free interval rate at one year was 99.87% for patients randomized to the MRI group when compared with 99.73% for patients randomized to the non-MRI group.[20,36] Four additional, single institution studies[10,24-27] showed that recurrence rates did not differ significantly between groups. Only one study[25] reported that patients with preoperative breast MRI had fewer local recurrences than patients without breast MRI (1.2% vs. 6.8%, respectively; p-value <0.001), but it is worth noting that this study did not control for differences between the groups.

The juxtaposition of breast MRI's superior sensitivity to detect additional breast cancer tumors over conventional imaging and the lack of evidence for improved clinical outcomes has led some researchers to suggest that the majority of additional cancer detected by breast MRI may not be of clinical relevance.[12,20,23,85,164,171,172] Rather, these additional cancer tumors may be adequately managed by radiotherapy or systemic therapy[12,23,39,171,172,181] and, therefore, the increased rate of mastectomy, possible treatment delay, and additional work-up procedures following MRI may not always be justified.

Current breast MRI utilization

Despite uncertainty surrounding the clinical benefits of routine use of breast MRI in women with a new cancer diagnosis, breast MRI has been increasingly adopted in practice. One recent study found that the percentage of early-stage breast cancer patients undergoing a breast MRI from 2003 to 2006 by stage were: a) ductal carcinoma in situ, 7%; b) stage I, 15%; and c) stage II, 22%. The percentage of all patients receiving a breast MRI increased from 10% in 2003 to 23% in 2006.[11] Additionally, the proportion of older patients with newly diagnosed, invasive breast cancer receiving breast MRI increased from 1.2% in 2002 to 18.8% in 2007 (Figure 2.3).[13]

Recent publications have suggested ways to optimize the benefits of breast MRI as a preoperative tool.[47,166,182] Patients with the potential for greater benefit include women: a)

with mammographically dense breasts; b) with a unilateral multifocal/ multicentric cancer; c) with synchronous bilateral cancer already diagnosed at mammography and ultrasound; d) with invasive lobular carcinoma; e) at high-risk for breast cancer based on a BRCA mutation or family history; f) with a cancer that shows a discrepancy in size of >1 cm between mammography and ultrasound; or g) who are under consideration for partial breast irradiation.[47,166,182]

Despite these recommendations, evidence suggests that breast MRI is being differentially adopted and the variation is unlikely to be related to differing patient clinical characteristics alone. One study of radiologists found that academic practices were more likely to perform screening breast MRI than nonacademic practices (83.2% vs. 58.5%).[8] This finding is consistent with previous results showing that the adoption of medical technologies is associated with teaching status, academic affiliation, case volume, research activity, medical/training culture, institutional characteristics, specific attributes of the technology, and the political and economic climate.[183,184] Sommer and colleagues found that women were more likely to receive an MRI if they were recently diagnosed, younger, white, or Hispanic.[1] This unequal adoption is consistent with studies documenting racial disparities in treatment patterns in women with breast cancer.[185-187] Additionally, these authors found that diagnostic breast MRI use was associated with geographic variation. Women living in more urban areas, areas of higher income, and areas with a greater proportion of high school graduates were most likely to receive breast MRI. Significant differences also were found in the overall utilization rate of MRI between SEER regions. The percentage of women receiving MRI ranged from 0.85% in the Hawaii SEER region to 18.0% in New Mexico. These findings are consistent with previous literature documenting regional variations in care among the Medicare population.[64,188] The variability in the adoption of breast MRI is also consistent with research showing that test or treatments with uncertain evidence to support their utility are more likely to be inconsistently adopted into practice.[189]

Medicare covers diagnostic breast MRI scans that are considered reasonable and necessary if they are performed with FDA-approved MRI equipment. Local Medicare contractors have the ability to determine the circumstances under which an MRI scan is covered. Some contractors have selective coverage for MRI breast imaging, depending on the patient's diagnosis. The amount paid for MRI scans ranges from $800 to $2,000 compared to $85 to $150 for mammograms. The amount that a patient may pay for these screenings can vary considerably across the United States.[190]

Limitations of current breast MRI research

The current breast MRI literature is limited in several aspects. First, much of the evidence is based on multiple studies from single institutions and two randomized controlled trials. There is a dearth of evidence examining the effect of MRI on surgical planning, outcomes, and cost in a population comparable to the US elderly population. The patients and medical groups participating in the RCTs and single institution studies were highly selective and the study populations were not comparable to the US elderly population. For example, the median and mean ages for the RCTs were 57[20] and 55.5,[21] two decades younger than the average age of breast cancer patients enrolled in Medicare[28] and the average patient in our study (76.1 years).

Second, to our knowledge, there is a dearth of evidence examining the impact of breast MRI on surgical planning or short-term outcomes in *older women*. Elderly women are least likely to benefit from breast MRIs because they are more likely to have less dense breasts and fewer occult tumors with conventional assessment.[30-33] Despite the perceived lack of benefit, as much as 20% of elderly women with newly diagnosed breast cancer may be receiving breast MRI.[13] Thus, examining the risks and benefits of preoperative breast MRI in this subset of the population is warranted.

Third, the two randomized controlled trials mentioned previously were conducted in the Netherlands[21] and the United Kingdom[20,36] where physician practice patterns and patient preferences for mastectomy over BCT differ significantly from those in the US.[37-39] Thus, the effect of preoperative breast MRI on surgical planning and outcomes in the US may be different than results from European studies.

Fourth, to our knowledge, no study has examined the association between breast MRI and the cost of initial treatment in the US. The only study to examine the cost of breast MRI was a randomized controlled trial conducted in the United Kingdom[36] where payment, referral structures, health insurance coverage, and fiscal considerations are different than those in the US.

Table 2.1. American Joint Committee on Cancer breast cancer staging definitions

In Situ Breast Cancer	
Stage 0	Ductal carcinoma in situ and lobular carcinoma in situ and has not spread to lymph nodes
Early-stage Invasive Breast Cancer	
Stage I	Tumor measures 2 cm or less and has not spread to lymph nodes
Stage IIA	No evidence of a tumor but cancer has spread to lymph nodes under arm on the same side as the cancer; *OR* Tumor is 2 cm or less and has spread to lymph nodes under arm but no other lymph node involvement; *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 on the same side as the cancer and possibly other lymph nodes as well
Stage IIIB	Tumor is any size and has spread to breast skin or chest wall and possibly lymph nodes
Stage IIIC	Tumor is any size and may have spread to lymph nodes near the sternum or collarbone, but not other parts of body
Metastatic Breast Cancer	
Stage IV	Tumor is any size and has spread to other parts of body

Note: Created using information from American Joint Committee on Cancer (AJCC) with permission. Breast. In: *AJCC on Cancer: AJCC Cancer Staging Manual*, 6th edition. New York, NY: Springer, 2002, pp. 227-228.

Figure 2.1. Initial tests and treatment pathways for early-stage, invasive breast cancer

Diagnostic work-up
- Medical history and physical exam to assess general health and symptoms
- Complete blood count and chemical tests
- Diagnostic bilateral (both breasts) mammogram, ultrasound as needed
- Pathology review of biopsy sample
- Determination of tumor estrogen/progesterone receptor status and HER2 status
- Genetic counseling if patient is high risk for hereditary breast cancer

Other studies for breast imaging:
- **Breast MRI**

Primary surgical treatment options
for Stages I-IIB*

Breast conserving surgery (BCS)**

Mastectomy**

Positive margin?

Negative margin?

Re-excision
(either BCS or mastectomy)

Depending on lymph node involvement, possible **chemotherapy**, and/or **radiation therapy** to the chest wall, supraclavicular area and/or the lymph nodes next to the breast bone and **endocrine therapy** for hormone receptor positive women

Radiation therapy to the entire breast with or without added boost to tumor site and clavicle area

Chemotherapy if needed based on stage, hormone receptor status and HER2 status

Endocrine therapy for hormone receptor positive women

Follow-up care,
including monitoring for a second breast cancer event

HER2, Human Epidermal Growth Factor Receptor 2.
*Excluding women with large tumors eligible for neoadjuvant chemotherapy
** With possible lymph node procedure
Created using information from NCCN Guidelines National Comprehensive Cancer Network. (2009). "NCCN Clinical Practice Guidelines in Oncology." nccn.org,
 from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp and with the input of oncologists (Muss, Reeder-Hayes) and breast surgeon (Amos)

Figure 2.2. Mastectomy rates by age at diagnosis, 2000–2008
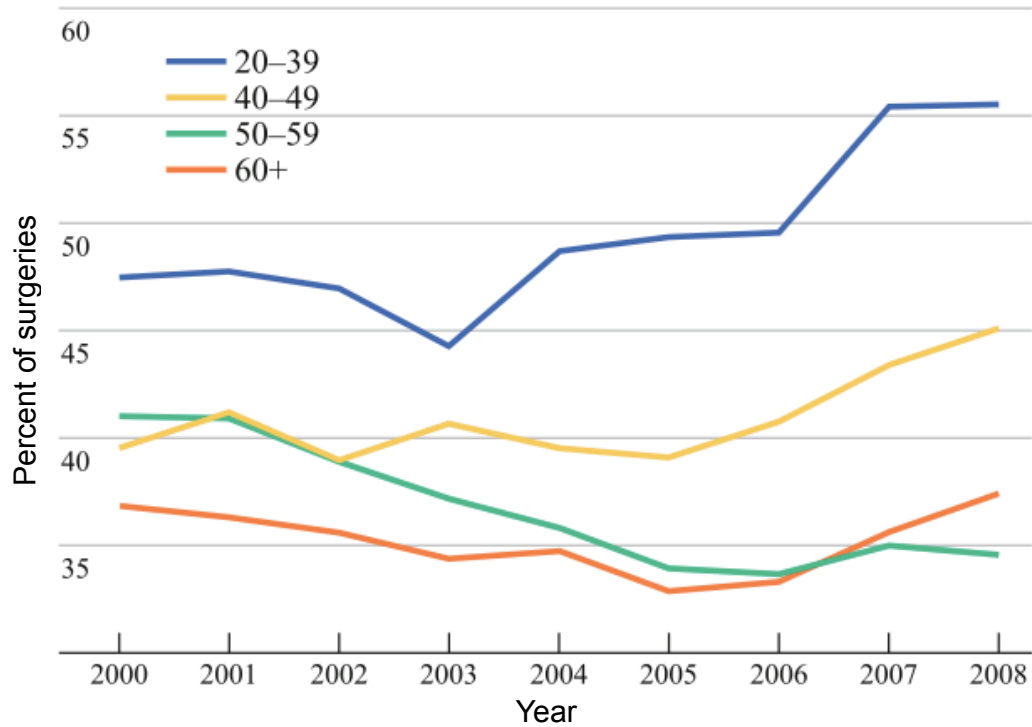
Reprinted with permission from Mahmood U et al. Ann Surg Oncol 2012 Nov 8. [Epub ahead of print]

Table 2.2. Association between preoperative breast MRI and re-excision rates, a review of studies using a controlled design

First author, year	Number of subjects eligible for re-excision	Re-excision rates			Type of breast cancers included	Study design
		no-MRI	MRI	p-value		
Turnbull et al[20] (COMICE), 2010	1,623	19%	19%	0.8	DCIS and invasive	RCT
Peters et al (MONET), 2011[21]	103	12%	34%	<0.01	DCIS and invasive	RCT
Miller et al, 2012[26]	265	18%	14%	0.3	DCIS and invasive	Comparative cohort
Hwang et al, 2009[10]	472	13%	12%	0.5	Invasive	Comparative cohort
Bleicher et al, 2009*[23]	290	14%	22%	0.2	DCIS and invasive	Comparative cohort
Pengel et al, 2009**[68]	339	19%	14%	0.2	Invasive	Comparative cohort
Shin et al, 2012[27]	794	13%	18%	0.1	DCIS and invasive	Comparative cohort

* Tumor involved margins rather than re-excision rate reported
** Incomplete tumor excision rate
MRI, Magnetic resonance imaging; RCT, Randomized control trial; DCIS, ductal carcinoma in situ.

Table 2.3. Association between preoperative breast MRI and recurrence rates, a review of studies using a controlled design

First author, year	Number of subjects	Median follow-up time, years	Ipsilateral breast recurrence rate			Type of breast cancers included	Study design
			no-MRI	MRI	p-value		
Turnbull et al[36] (COMICE), 2010*	1,623	2.1	3.5%	6.1%	NS	DCIS and invasive	RCT
Miller et al, 2012[26]	414	4.1, no MRI; 2.1, MRI	5.0%	1.6%	0.13	DCIS and invasive	Comparative cohort
Hwang et al, 2009[10]	463	4.5	2.5%	1.8%	0.67	Invasive	Comparative cohort
Fischer et al, 2004[25]	346	3.4 (mean)	6.8%	1.2%	<0.001	Invasive	Comparative cohort
Solin et al, 2008**[24]	756	4.6	4%	3%	0.51	DCIS and invasive	Comparative cohort
Shin et al, 2012[27]	1,558	5.9	1.2%	2.3%	0.33	DCIS and invasive	Comparative cohort

* This reflects local recurrence-free interval at 3 years of 96.5% (no MRI group) and 93.9% (MRI group)
** Eight-year rate of local failure (i.e., ipsilateral recurrence)
MRI, Magnetic resonance imaging; RCT, Randomized control trial; DCIS, ductal carcinoma in situ; NS, not significant

Figure 2.3. Percent MRI use among elderly women diagnosed with ductal carcinoma in situ or locally invasive breast cancer from SEER-Medicare, 2002–2007

	2002	2003	2004	2005	2006	2007
——DCIS	0.5%	1.7%	3.2%	5.7%	8.2%	15.8%
——Invasive	1.2%	2.3%	4.7%	7.7%	11.6%	18.8%
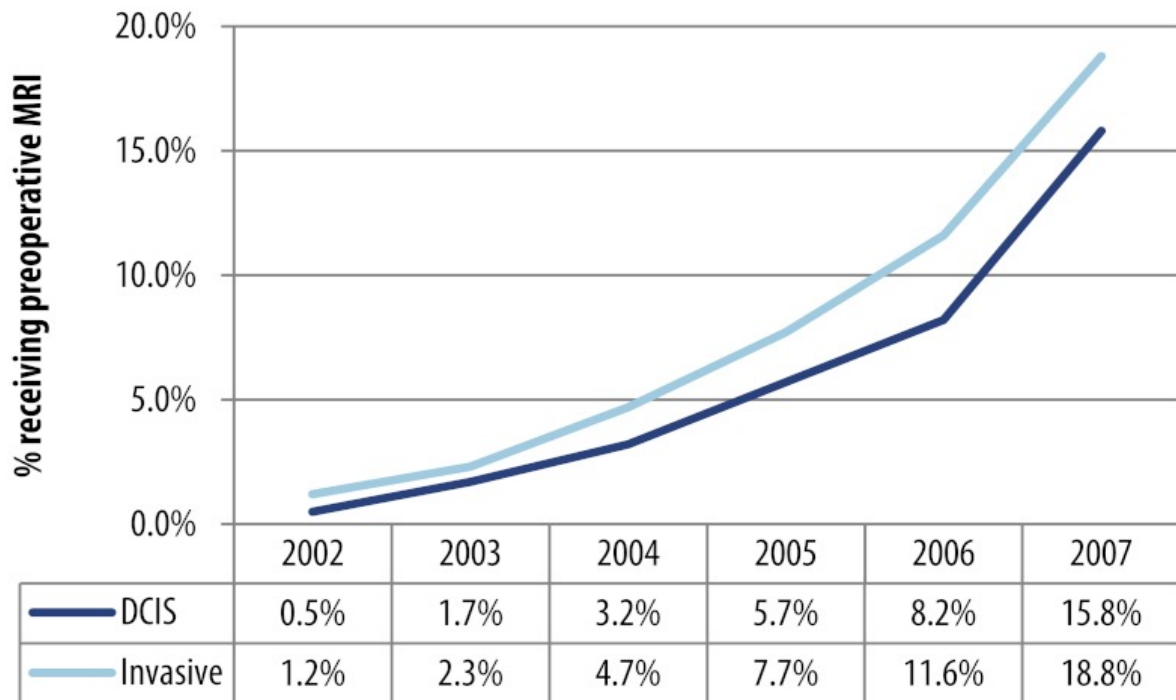
Reprinted from Tuttle, T. M., S. Jarosek, et al. Use of Preoperative MRI Among Older Women with Ductal Carcinoma in Situ (DCIS) and Early Invasive Breast Cancer: Use of Preoperative Breast MRI (2012), AHRQ public domain publication No. 12-EHC086-EF.

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Overview and study design

The goal of this dissertation was to examine the effects of preoperative breast MRI on secondary outcomes and costs for elderly women with breast cancer. This retrospective analysis included women aged 66 or older with early-stage (I-IIB), operable breast cancer diagnosed between January 1, 2004 and December 31, 2007 from SEER-Medicare data. The independent variable of interest for all three study aims was whether or not the patient received a preoperative breast MRI. In Aim 1, the dependent variables of interest were: (a) the time elapsed from the date of the first claim for a suspected breast disorder to the date of complete surgical treatment; and (b) whether or not the initial type of surgery was a mastectomy or breast conserving surgery (BCS). In Aim 2, the dependent variables of interest were: (a) whether or not the patient had a re-excision after her initial breast cancer surgery; and (b) whether or not the patient experienced a second breast cancer event. In Aim 3, the dependent variables of interest were total all-cause and total breast cancer-attributable Medicare payments per patient during the initial treatment phase. We controlled for tumor, demographic, and provider characteristics in our multivariate analyses and, for Aims 1 & 2, used propensity score methods to control for measured confounders associated with the initial receipt of breast MRI based and our outcomes of interest.

Conceptual framework: Cancer Care Continuum

We examined our three aims using a framework adapted from Zapka and colleagues' cancer care continuum.[119,120] This framework (Figure 3.1) provided us with a systematic approach for assessing factors that influence cancer outcomes across the span

of care, including risk assessment, primary prevention, screening, detection, diagnosis, treatment, recurrence surveillance, and end-of-life care. Potential failures during the process of care are manifested in two ways: (a) first, as breakdowns in specific types of care delivered to individuals at different points in the history of their cancer (short vertical arrows); and (b) second, as breakdowns during the transitions between these types of care (long vertical arrows). Specifically, this study focused on the diagnosis, treatment, recurrence, and surveillance phases of care (Figure 3.1a).

For the present study, our main independent variable of interest was whether or not the patient received a breast MRI in the diagnosis phase. The outcomes of interest were the timing and type of initial surgery (Aims 1a & b), re-excisions in the treatment stage (Aim 2a), and a second breast cancer event in the surveillance stage (Aim 2b). Procedures and treatments in the diagnosis and treatment stage influence the cost of care during the initial treatment phase (Aim 3 outcome of interest). As Figure 3.1 illustrates, characteristics of the patient and the cancer itself contribute to the various outcomes. Thus, it was important to control for cancer characteristics such as tumor size, nodal involvement, tumor histology, hormone receptor status, and patient characteristics, including age, in our models.

Factors at many levels affect the process of cancer (Figure 3.2). These factors influence: (a) the receipt of breast MRI; (b) the delivery of high quality cancer care; and (c) short- and long-term outcomes and costs.[119] Elements in the immediate practice setting that can affect cancer care include clinician/team characteristics, such as professional group affiliation or medical training, as well as patient characteristics, such as their social support system. Clinician/team level factors could include whether or not the medical group is affiliated with an academic medical center or the group's culture of routine preoperative breast MRI utilization. At the community level, factors may consist of the availability of radiation facilities and healthcare, or MRI utilization practices in a given metropolitan statistical area (MSA). Given that these factors may influence both the receipt of

preoperative breast MRI and short-term outcomes as well as cost, it was important to control for them in our analyses. Because our study focused on the association between preoperative breast MRI, surgical planning, and outcomes, we considered the surgical provider as the provider of interest.

Research questions and hypotheses

Aim 1: To examine the association between preoperative breast MRIs and surgical planning. Specifically, to determine: (a) the time elapsed from the date of the first suspected breast disorder to the date of complete surgical treatment; and (b) the initial type of breast cancer surgery.

H1a: Older women with breast cancer who received a preoperative breast MRI will be more likely to experience a delay in surgical treatment surgery than those women who did not have a breast MRI.

H1b: Older women with breast cancer who received a preoperative breast MRI will be more likely to have a mastectomy as their initial surgery than those women who did not have a breast MRI.

Aim 2: To examine the effect of preoperative MRI on the likelihood of a re-excision (2a) and a second breast cancer event (2b).

H2: Elderly women with breast cancer who received a preoperative breast will have the same likelihood of a re-excision (Aim 2a) and a second breast cancer event (Aim 2b) as those women who did not have a breast MRI.

Aim 3: To examine the effect of preoperative MRI on the costs to Medicare during the initial treatment phase.

H3: The total all-cause and total breast cancer-attributable Medicare payments per patient during the initial treatment phase will be higher for those patients who received breast MRI than for those patients who did not.

Data

This retrospective study used data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset.[191] The SEER-Medicare dataset comes from a consortium of population-based cancer registries across the United States linked to Medicare administrative data and healthcare claims. The SEER-Medicare data have been used to examine various factors across the cancer care continuum, including sociodemographics, physician and hospital characteristics, surgery, chemotherapy, radiation, comorbidities, complications, screening, relapse, and costs (See Medical Care 2002 Medicare Supplement;40 (8S):IV).

The SEER data comprise 17 registries nationwide and cover approximately 25% of the incident US cancer population. The data contain demographic and incident cancer characteristics, including histology, grade, and stage, as well as treatment information and vital statistics for people living in Connecticut, Detroit, Hawaii, Iowa, New Mexico, Utah, Alaska, California, Kentucky, Louisiana, New Jersey, metropolitan areas of Atlanta, San Francisco-Oakland, Los Angeles, San Jose-Monterey, Seattle-Puget Sound, and rural Georgia. The SEER data also contain ecological measures of income, education, and other characteristics at each patient's census tract and zip code of residence. The population covered by the program is comparable with the US general population with regard to measures of poverty and education.[191]

Medicare covers hospital services, physician services, some drug therapy, and other medical services for more than 97% of Americans aged 65 and older. Medicare data include information about the use and cost of health care services and co-morbid health conditions. The National Cancer Institute (NCI) hospital file contains hospital-level information, including staffing, structure, research network affiliation, and information on accreditation.[192]

Study population and inclusion/exclusion criteria

The present study included women with a primary diagnosis of unilateral, pathologically confirmed breast cancer identified from SEER-Medicare data (American Joint Committee on Cancer [AJCC] sixth edition, International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification [ICD-9-CM] code 147) (Table 3.1). Women were included if they were diagnosed with their first primary, unilateral breast cancer between January 1, 2004 and December 31, 2007, and had no previous cancers. Focusing on elderly breast cancer patients, we excluded women who were younger than 66 at diagnosis and women enrolled in Medicare for renal disease or disability. We excluded women who were diagnosed at autopsy or death. We also excluded women who were not continuously enrolled in Medicare Part A and Part B, and women who were enrolled in a health maintenance organization (HMO) during the study period because these beneficiaries had incomplete claims in the SEER-Medicare dataset. As a result, we were unable to examine their healthcare utilization in its entirety. The NCI comorbidity index was calculated based on 12 months of claims. Thus, women not enrolled 12 months prior to diagnosis were excluded.

Additional exclusion criterion (Figure 3.3) included limiting our analysis to women with stage I-IIB operable breast cancer whose first definitive treatment was surgery, thus excluding women who received neoadjuvant chemotherapy prior to surgery (n=435). These women were eliminated because breast MRI can also be used to measure tumor response to neoadjuvant chemotherapy,[50-54] which is not the focus of the present study. We also excluded patients who had conflicting claims for mastectomy and partial mastectomy on the same day in the Medicare outpatient setting, inpatient setting, and physician files (n=647). We excluded these women because we were unable to determine the type of initial surgery. Data from this sample of women (n=25,038) was utilized for analyzing the time to surgery (Aim 1a).

Aim 1b & 2b. In the analyses examining the initial type of surgery (Aim 1b) and second breast cancer event (Aim 2b), we excluded women who had their first biopsy or breast surgical procedure more than four months before or after the SEER diagnosis month (n=599) because we were concerned that those surgical claims did not correspond to the first primary breast cancer identified from the SEER registry.

Aim 2a. For the analysis examining re-excision (Aim 2a), we excluded those women who had a mastectomy as their first surgical procedure (n=4,631) because re-excisions after mastectomies are rare and unlikely.[83] In our sample of women who had a mastectomy as their first surgery, only 2.0% had a re-excision. We excluded women who died within a year of diagnosis in order to have enough time to observe if the women underwent a re-excision. We also excluded women who were diagnosed with a second primary cancer identified in SEER within 12 months of diagnosis because we would not have been able to determine whether the surgery was a re-excision or a surgical treatment for the second primary tumor.

Aim 3. In the analysis examining costs to Medicare (Aim 3), the sample of women was identical to those included in the assessments for Aims 1b and 2b, however, we excluded those women who did not have a breast surgical procedure within a year of the first suspected breast disorder (n=846) in order to ensure we were capturing the correct initial treatment period. We also excluded women died within a year of diagnosis or while in active treatment (n=629). We eliminated these women and because research has shown that healthcare utilization and cost is significantly different in the terminal phase of care than in the initial phase of care,[192-198] which is the focus of this study. The final analytic sample for Aim 3 was 22,947 women.

Variables and measures

Initial treatment phase. We examined all claims during the initial treatment phase (Table 3.2) from 2004 through 2009. We defined the initial treatment phase to capture the

diagnostic, preoperative, and initial treatment stages and to include healthcare utilization

from when the patient was first suspected of having breast cancer up through the end of

each patient's initial treatment. The start of the initial treatment phase began on the date of

the first claim for a suspected breast disorder (e.g., lump or mass in breast, or an abnormal

mammogram) one year prior to the SEER diagnosis month. We defined the end of the initial

treatment phase as the last day of breast cancer treatment before a treatment gap of more

than 90 days,[93,95,199] the patient's death, or the end of the study period, which was

December 31, 2009. We identified healthcare utilization, breast cancer events, and

Medicare payments during the initial treatment phase by reviewing the Medicare outpatient,

carrier, and Medicare Provider Analysis And Review (MEDPAR) files using the following

coding systems: (a) American Medical Association Current Procedural Terminology (CPT);

(b) Healthcare Common Procedure Classification System (HCPCS); and (c) ICD-9-CM

codes.

For each aim, our independent variable of interest was a binary indicator for whether

or not the patient received a preoperative breast MRI. Patients were classified as having a

preoperative breast MRI if they had a claim for a breast MRI (CPT: 76093-94, 77058-59,

HCPCS: C8903-C8908) on or after the first day of suspected breast disorder but before the

date of their first surgical procedure. Though this approach may capture breast MRIs that

were ordered for screening purposes, we are not concerned about including these breast

MRIs as "preoperative" because breast images taken during the initial treatment phase,

even for screening purposes, would most likely be used as a part of the surgical planning

process (Dr. Keith Amos. Personal communication. May 23, 2012).

Outcome variables. The outcome variables in our study are defined in Table 3.4. We

examined the association between breast MRI and surgical planning (Aim 1) with the time to

complete surgery (Aim 1a) and whether or not the initial surgery was a mastectomy (Aim

1b). We examined whether or not the patient had a re-excision (Aim 2a) and the time to a

second breast cancer event (Aim 2b) when assessing short-term outcomes (Aim 2). We also examined the association between breast MRI and all-cause and breast cancer attributable payments during the initial treatment phase (Aim 3).

Control Variables and Measures. Based on the cancer care continuum (Figure 3.1) and factors that impact the processes of care, we included patient (Table 3.5), medical group, and community-level factors (Table 3.6) to control for these variables' association with whether or not the patient received an MRI and their impact on health outcomes. Patient-level covariates (Table 3.5) included year of diagnosis (2004-2007) and age at diagnosis. Because social support has been associated with improved outcomes, we controlled for marital status.[200,201] As an indicator of the patient's financial resources, we controlled for Medicare state buy-in coverage status. We controlled for race because research has shown that race may be associated with treatment selection and outcomes. We also controlled for co-morbidities using the NCI Combined Index[81] to address competing health demands and risks of complications that may affect treatment selection. Person-level tumor characteristics included stage, grade, histology, and tumor size as well as hormone receptor status identified from SEER data. These tumor and biological characteristics are important measures of cancer severity.

We controlled for several surgical facility characteristics (Table 3.6) that could be associated with breast MRI receipt and affect breast cancer outcomes. We identified the facility where the first surgical procedure took place and linked it to the NCI Hospital file, which includes measures for whether or not the facility was a teaching hospital, a designated NCI Cancer Center, and had on-site radiation facilities. We also examined facility ownership type (i.e., for-profit vs. not-for-profit) and constructed a variable for whether or not the facility was affiliated with NCI Cooperative Groups having breast cancer research portfolios, including the American College of Surgeons Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, Southwest Oncology Group,

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and the National Surgical Adjuvant Breast and Bowel Project.[183] We also included a variable measuring breast cancer surgical volume (low volume vs. high volume). To construct this variable, we used the number of breast cancer surgeries (partial/full mastectomy) for each surgery site from 2004-2009.

To measure resource availability within the community, we used ecological variables, including median income and percentage of high school graduates at the zip code level, unique to each patient for their zip code of residence at diagnosis. Since geographic region and health services area may influence breast MRI practices and availability, we also included SEER registry region as a variable.

Analyses

Aims 1 & 2. For each aim, we compared unadjusted baseline characteristics between the groups of women with and without a preoperative breast MRI using Pearson chi-squared tests for categorical variables and Student's t-tests for continuous variables. To estimate the association of each covariate on the likelihood of receiving breast MRI, we used multivariate logistic regression. We calculated odds ratios, 95% confidence intervals (CI), and two-sided p values for each predictor.

Because baseline characteristics for elderly women who receive a preoperative breast MRI may systematically differ from women who do not, in Aims 1 and 2 we used propensity score methods[80] to balance the groups of women with and without breast MRI on measured covariates and to control for potential confounders. Propensity score methods have been previously used when examining SEER-Medicare data.[202-206]

First, we developed propensity scores to estimate the probability, on the basis of observed patient and surgical facility characteristics described above, that patients would have a breast MRI using multivariate logistic regression.[80] We selected covariates to include

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in the logistic regression based on their hypothesized relationship with breast MRI receipt and the outcome of interest (either time to complete surgery or initial type of surgery).[207]

Second, we adjusted for differences between the groups that did and did not receive a breast MRI using inverse probability weighting.[78,79] To create balance, each patient with a breast MRI was weighted by the inverse of the probability that she would be selected for a breast MRI based on her covariates, and each patient without a breast MRI was weighted by the inverse of the probability that she would not have a breast MRI. We then stabilized these weights by multiplying the inverse probability weights by the marginal prevalence of the breast MRI receipt.[208,209]

To assess balance and the performance of the propensity model, we examined the distribution of propensity scores and covariates between the two groups (MRI vs. no MRI), examining balance by decile of propensity score.[210] We also used standardized differences to compare the distribution of baseline covariates between the two groups before and after inverse probability weighting.[211] We examined excluding women with non-overlapping propensity score distributions (i.e., women without a preoperative breast MRI who had a propensity score higher than the maximum or lower than the minimum propensity score of women with preoperative breast MRI).[210] To reduce bias due to unmeasured confounders, we also assessed asymmetrically trimming patients who were treated most contrary to prediction.[208] We examined trimming patients at three different cut points corresponding to the 1st and 99th percentiles, the 2.5th and 97.5[th] percentiles, and the 5th and 95th percentiles at the tails of the propensity score distribution in the treated (i.e., breast MRI) and untreated (i.e., no breast MRI) patients, respectively.

In the analyses examining the time until complete surgery (Aim 1a) and the time to a second breast cancer event (Aim 2b), we generated unadjusted survival curves using the Kaplan-Meier method.[56] We estimated adjusted survival curves using inverse-probability weighting approach from Cole and Hernan.[212] The adjusted curves represent the expected

rate of the event (i.e., surgery or a second breast cancer event): (1) if all study patients had a MRI; and (2) if all study patients did not have an MRI. We estimated the median time to the event for both groups after adjusting for the inverse-probability weights and used bootstrap methods to obtain 95% confidence intervals. We estimated hazard ratios using the Cox proportional-hazards model,[213] generating unadjusted estimates and estimates (a) adjusted for covariates and (b) adjusted using inverse-probability weighting. We evaluated the proportional hazards assumption by graphical methods using Schoenfeld residuals.[214]

In the analyses estimating the likelihood of a mastectomy as the first surgical procedure (Aim 1b) and the likelihood of a re-excision (Aim 2a), we used multivariate logistic regression weighted with the inverse probability weights and robust standard errors.[78,215] Z-test statistics and 95% confidence intervals were used to examine the difference in the likelihood of a re-excision between those women with and without a breast MRI.

Aims 3. Descriptive statistics were calculated for patients with and without a preoperative breast MRI. We tested for differences in the clinical, demographic, and treatment characteristics across patients with and without breast MRI using the Pearson chi-squared test for categorical variables and the Student's t-test for continuous variables. We also used t-tests in our bivariate analyses of breast MRI receipt and different measures of healthcare utilization and cost.

In our multivariate analyses examining the association between breast MRI and cost, we fitted a generalized linear model with a log-link and gamma distribution variance function with robust standard errors.[216,217] We used a log transformation to normalize the cost distribution, which is typically highly skewed.[44] Because all of the women in our sample had surgery within our study's timeframe, almost all women had Medicare payments during the initial treatment phase and two-part models were not required.[218,219]

Diagnostic and procedure codes were identified and verified using medical literature, coding experts, EpiCoder (Yost Engineering Inc., Ohio) and the Integrated Cancer

Information and Surveillance System coding references.[220] Analyses were performed using Stata version 12.0 (Stata Corporation, College Station, Texas). All tests were conducted using a minimum significance level of 0.05.

Figure 3.1. The cancer care continuum

Figure 3.1a

TYPES of CARE

| Risk Assessment | Primary Prevention | Detection | Diagnosis | Treatment | Recurrence Surveillance | End-of-Life Care |

OUTCOMES

Risk status
Clinical status
Functional Status
Quality of Life
Satisfaction
Mortality
Cost of Care

POTENTIAL FAILURES DURING the PROCESS of CARE

Figure 3.1a

Independent variable of interest (all aims)

DIAGNOSIS
- Physical exam
- **Imaging (MRI)**
- Biopsy
- Repeat exams
- Laboratory Tests

Aim IA, IB & IIA dependent variables

TREATMENT
- **Initial surgery (IA&B)**
- **Re-excision (IIA)**
- Radiation
- Adjuvant Chemo
- Palliation

Aim IIB dependent variable

RECURRENCE SURVEILLANCE
-Testing
-Follow-up care
-**Recurrence (IIB)**
-Palliation
-Survivorship care

Aim III dependent variable

END-OF-LIFE CARE

OUTCOME
Risk status
Clinical status
Functional Status
Quality of Life
Satisfaction
Mortality
Cost of Care (III)

Adapted with permission from Zapka et al. Cancer Epidemiol Biomarkers Prev 2003;12:4-13 and Taplin and Rogers JNCI Monographs 2010: 40.

Figure 3.2. Levels and factors that impact the cancer care continuum

Community Level Resources
Medical resources
Population SES
Local Hospital Market/Local
Cancer Services Market
Market Structure
Level of Competition
Pay for Performance
Initiatives
HMO/Managed Care
penetration
Third party payors/insurance
Percent Non-profit
Local Professional Norms
MD practice organizations
Use of Guidelines
Practice Patterns
Perceived Consensus on
practice norms

Knowledge, communication
skills
Perceived barriers, norms,
test efficacy
Turnover
Staffing mix
Role definition
Teamwork

Sociodemographics
Risk status
Comorbidities
Appraisal and control
Psychological
reaction/coping
Knowledge and attitudes

Medicare reimbursement
rates
Federal efforts to reform
health care
National cancer initiatives
Accreditation (JCAHO,
Commission on Cancer,
NCCN, etc.)

State Medicaid
reimbursement rates
Hospital performance data
policies (dissemination,
visibility, etc.)
State cancer plans/programs
Regulations/limitations on
reimbursement of clinical
trials
Visibility of statewide
advocacy groups

Leadership
Organizational structure,
policies and incentives
Delivery system design
Clinical decision support
Clinical information systems
Patient education and
navigation

Family dynamics
Friends, network support

National Health Policy
Environment

State Health Policy
Environment

Local Community
Environment

Organization and/or
Practice Setting

Provider/Team

Family & Social
Supports

Individual
Patient

Proactive
Provider Team

Productive
Encounters

Activated
Patients

Encounters occurring across the continuum of cancer care

Reprinted with permission from Taplin and Rogers JNCI Monographs 2010; 40.

Table 3.1. SEER-Medicare inclusion/ exclusion criteria

Inclusion Criteria	Included	Excluded
Breast cancer diagnosis in SEER	260,079	
Diagnosed between 2003 and 2007 (inclusive)	143,757	116,322
First or primary cancer	131,974	11,783
Age 66 or older at diagnosis	86,127	45,847
Female	85,367	760
Reporting source not autopsy or death certificate	84,466	901
Laterality is not bilateral or unknown	83,659	807
Original reason for Medicare entitlement not disability or ESRD	79,355	4,304
Has valid month of diagnosis	79,114	241
Has no HMO enrollment during study period*	56,652	22,462
Has continuous enrollment in Part A&B during the study period*	52,038	4,614
Has comorbidity score and was able to be matched to claims during the study period*	48,283	3,755
Diagnosed between 2004 and 2007**	39,652	8,631

*Study period is 12 months prior to diagnosis month until the end of data or death

ESRD, end stage renal disease; HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology and End Results

** We excluded patients diagnosed in 2003 because few patients (n=148) had a breast MRI, and were unable to be balanced using propensity scores.

Figure 3.3. Inclusion/exclusion criteria schematic, all study aims

Women diagnosed with their first primary breast cancer in SEER in 2004-2007*
n= 39,652

INCLUDED

Known Stage I-IIIA disease, tumor size <5cm, histology codes indicating malignant breast cancer
N=26,751

EXCLUDED

Stage 0 or IV disease, stage unknown; tumor size greater than 5cm; histology codes indicating in situ/ non-malignant disease or non-breast primary tumors
n=12,901

Able to determine the first definitive surgical treatment and have no prior cancer treatments before surgery
n= 25,669

Medicare claims identified conflicting surgical procedures on the same day; receipt of cancer treatments prior to surgery
n=1,082

Patients with a breast surgical procedure Linkable to their surgical provider
n= 25,038

Unable to link patient to her surgical provider
n= 631

Sample for the analysis examining time to surgery (Aim 1a)
n= 25,038

INCLUDED

Had a first biopsy or breast surgical procedure† Within 4 months of SEER diagnosis month
n= 24,439

EXCLUDED

First breast breast biopsy or surgical procedure† claim more than 4 months from SEER diagnosis month
n= 599

Sample for the analysis examining the likelihood of a mastectomy as the initial surgery (Aim 1b), the hazard of a second breast cancer event (Aim 2b), and cost (Aim 3)**
n= 24,439

INCLUDED

Did not have a second primary cancer identified in SEER
n= 22,348

EXCLUDED

Had a second primary cancer identified in SEER within 12 months of diagnosis
n= 2,091

Alive 12 months after diagnosis
n= 21,830

Died within 12 months of diagnosis
n= 518

Had breast conserving surgery‡ as the first surgical procedure
n= 17,199

Had mastectomy as the first surgical procedure
n= 4,631

Sample for the analysis examining the likelihood of a re-excision (Aim 2a)
n= 17,199

SEER, Surveillance, Epidemiology and End Results
* Meeting SEER-Medicare inclusion requirements of aged 66 or older at diagnosis, reporting source not autopsy or death certificate, laterality not bilateral or unknown, original reason for Medicare entitlement not disability or end stage renal disease, valid month of diagnosis, no health maintenance organization enrollment during study period, continuous enrollment in Parts A & B during the study period, comorbidity score and was able to be matched to claims during the study period. Study period is defined here as the 12 months prior to diagnosis month till the end of data or death
** The sample for Aim 3 also excluded those women who did not have a breast surgical procedure within a year of the first suspected breast disorder (n=846) or died within a year of diagnosis or while in active treatment (n=629) for a sample of 22,947 women
† Breast surgical procedure includes breast excision, partial/subtotal mastectomy and mastectomy
‡ Breast conserving surgery is defined as breast excision or partial/ subtotal mastectomy

Table 3.2 Definition of study timeframe

Construct	Definition
Suspected breast disorder diagnosis codes	174.* Malignant neoplasm of female breast 217. Benign neoplasm of breast 233.0 Carcinoma in situ of breast 238.3 Neoplasm of uncertain behavior of breast 239.3 Neoplasms of unspecified nature breast 610.0 Solitary cyst of breast 610.1 Diffuse cystic mastopathy 610.2 Fibroadenosis of breast 610.3 Fibrosclerosis of breast 610.9 Benign mammary dysplasia, unspecified 611.0 Inflammatory disease of breast 611.1 Hypertrophy of breast 611.3 Fat necrosis of breast 611.8 Other specified disorders of breast 611.9 Unspecified breast disorder 611.71 Signs and symptoms in breast 611.72 Lump or mass in breast 611.79 Signs and symptoms in breast 793.80 Abnormal mammogram, unspecified 793.81 Mammographic microcalcification 793.89 Other (abnormal) findings on radiological examination of breast V711 Observation for suspected malignant neoplasm
First suspected breast disorder date	The day of the first breast diagnosis code listed above within one year prior to the SEER diagnosis month
Initial treatment phase	All claims from the first claim with a breast diagnosis code to the end of the initial treatment as defined as the last day of treatment before a gap in treatment of 90 days or more or the end of the study period (December 31, 2009) or patient's death.

SEER, Surveillance, Epidemiology and End Results

Table 3.3. Identification of breast magnetic resonance imaging

Treatment	Primary means of identification	Years Effective
Unilateral		
without and/or with contrast material(s);	CPT Code: 76093	1/1/2007-Present
without and/or with contrast material(s);	CPT Code: 77058	1/1/1995-12/31/2006
with contrast	HCPCS Code: C8903	10/1/2001-Present
without contrast	HCPCS Code: C8904	10/1/2001-Present
without contrast followed by with contrast	HCPCS Code: C8905	10/1/2001-Present
Bilateral		
without and/or with contrast material(s);	CPT Code:76094	1/1/2007-Present
without and/or with contrast material(s);	CPT Code: 77059	1/1/1995-12/31/2006
with contrast	HCPCS Code: C8906	10/1/2001-Present
without contrast	HCPCS Code: C8907	10/1/2001-Present
without contrast followed by with contrast	HCPCS Code: C8908	10/1/2001-Present

Notes: HCPCS: Healthcare Common Procedure Classification System; CPT: Current Procedural Terminology.

Table 3.4. Outcome by aim

Aim	Outcome	Definition
Aim 1a	Time to complete surgery	Time in days from the date of the first claim for a suspected breast disorder until the date of last surgical procedure (i.e. partial or full mastectomy) in the initial treatment phase
Aim 1b	Initial surgery a mastectomy	First surgical procedure a mastectomy as compared to breast conserving surgery (i.e. breast excision or partial mastectomy)
Aim 2a	Re-excision	Additional breast surgical procedure (i.e. breast excision, partial mastectomy, or full mastectomy) after the initial surgery during the initial treatment phase
Aim 2b	Time to 2nd breast cancer event	Time in days from the date of the first claim for a suspected breast disorder until the date of the second breast cancer event identified through a validated algorithm (Chubak et al. 2012)
Aim 3	All-cause Medicare payments	The sum of Medicare payments from all claims during the initial treatment phase from the outpatient, carrier, and MEDPAR files (including claims for ED, long and short-term inpatient, and skilled nursing facility stays)
Aim 3	Breast cancer-attributable payments	The sum of Medicare payments from claims with breast biopsy, breast surgery, chemotherapy, radiation, mammogram, ultrasound, breast MRI or from a claim with a breast diagnosis code within the claim's first four diagnosis codes during the initial treatment phase. Claims from the outpatient, carrier, and MEDPAR files were included.

MRI, Magnetic resonance imaging; ED, emergency department; MEDPAR, Medicare Provider Analysis And Review

Table 3.5. Patient characteristics

Construct	Dimension	Measure/Variable	Data Source
Patient characteristics	Age	Age at diagnosis	PEDSF-SEER
	Residential area	Rural/urban residence	PEDSF-ARF
	Medicaid enrollment	Any indication of dual Medicaid coverage	PEDSF-EDB
	Social/familial support	Marital status	PEDSF-SEER
	Race/ethnicity	White	PEDSF-SEER
		Non-white	PEDSF-SEER
Tumor/biological characteristics	Extent of disease	Stage	PEDSF-SEER
	Cellular differentiation	Histologic grade	PEDSF-SEER
	Molecular subtypes	Estrogen receptor status	PEDSF-SEER
		Progesterone receptor status	PEDSF-SEER
	Tumor size	Tumor size in cm	PEDSF-SEER
Heath status/ healthcare utilization	Co-morbid conditions	NCI- co-morbidity index	MEDPAR; carrier claims; outpatient claims
Time	Time	Year of diagnosis	SEER – PEDSF

Notes: AHA, American Heart Association; ARF, Area Resource File; EDB, Enrollment Data Base; MEDPAR, Medicare Provider Analysis and Review; PEDSF, Patient Entitlement and Diagnosis Summary File; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute

Table 3.6. Surgical facility and community characteristics

Dimension	Measure/Variable	Data Source
Surgical facility-level factors	High routine preoperative breast MRI utilization	PEDSF-SEER
	Bed size of surgical facility	NCI Hospital file
	ACOSOG group affiliation of surgical facility	NCI Hospital file
	Teaching status of surgical facility	NCI Hospital file
	On-site radiation at surgical facility	NCI Hospital file
	Surgical facility type/ownership	NCI Hospital file
	NCI affiliation of surgical facility	NCI Hospital file
	Surgical hospital location (rural/urban)	NCI Hospital file
Area/ aggregate socioeconomic status	Percent of census tract (2000) with less than high school education	PEDSF-Census
	Median census tract (2000) income	PEDSF-Census
Geographic region	SEER registry	PEDSF-SEER

Notes: ACOSOG, American College of Surgeons Oncology Group; ARF, Area Resource File; PEDSF, Patient Entitlement and Diagnosis Summary File; MRI, Magnetic Resonance Imaging; MSA, Metropolitan Statistical Area; NCI, National Cancer Institute; SEER, Surveillance, Epidemiology and End Results.

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CHAPTER 4: THE ASSOCIATION BETWEEN PREOPERATIVE BREAST MRI, SURGICAL DELAY, AND TYPE OF INITIAL SURGERY IN ELDERLY BREAST CANCER PATIENTS

Overview

Magnetic Resonance Imaging (MRI) has been used increasingly in the preoperative evaluation of women with newly diagnosed breast cancer in addition to conventional assessment. Despite its increasing utilization, some research suggests that using MRI for preoperative planning leads to more extensive surgeries and treatment delay with limited evidence of clinical benefit. This study examines the relationship between preoperative breast MRI and: (a) time from the first date of suspected breast disorder to complete surgical treatment; and (b) the type of first surgical procedure in a large, population-based cohort of older women with early-stage breast cancer.

In this observational, retrospective analysis, we identified women diagnosed with early-stage (I-IIB), operable breast cancer from 2004-2007 in the Surveillance, Epidemiology, and End Results registry data linked to Medicare claims. Cancer treatment and breast MRI receipt were identified from the Medicare claims. Time from the first the suspected breast disorder (e.g., lump or mass in breast or abnormal mammogram) to complete surgical treatment was defined as the number of days from the first breast-related diagnosis code claim to the last surgical procedure before a gap in treatment claims of at least 90 days. The first surgical procedure was defined as the first surgery that was either a breast conserving surgery (partial mastectomy or a breast excision) or a full mastectomy. To control for measured confounders, we used propensity score methods.

We identified 25,038 women who meet our inclusion criteria for the time to surgery analysis and 24,439 women who meet our inclusion criteria for the type of initial breast

surgery analysis. Twelve percent of women in both samples received a preoperative breast MRI. The unadjusted median time to complete surgery was 53 days for patients without a breast MRI and 63 days for patients with a breast MRI (p<0.001). Using inverse probability weighting, having a preoperative breast MRI was associated with a median 15-day delay in the time to complete surgery (95% CI: [11, 19]; HR: 0.90, 95% CI: [0.85, 0.95]). More than one-fifth (22.3%) of women in our sample had a mastectomy as their first surgical procedure (22.0% of no MRI group; 24.1% MRI group). After adjustment using inverse probability weighting, having a breast MRI was associated with a significant increase in the odds of having a mastectomy (OR: 1.30, 95% CI [1.12, 1.50]).

Given that preoperative breast MRI was associated with a slight delay in the time to complete surgery and an increased likelihood of mastectomy, healthcare providers and their patients should consider these factors when making informed decisions about the use of breast MRI for elderly women with breast cancer. Further research should examine the impact of preoperative MRI on outcomes such as reoperation rates, recurrence, and survival.

Introduction

During the past ten years, breast magnetic resonance imaging (MRI) has been used increasingly in the preoperative evaluation of women with newly diagnosed breast cancer, providing enhanced cancer detection and supplementing conventional assessment, which includes clinical examination of the breasts, mammography and ultrasound, and pathological assessment of suspicious lesions.[1-8] Breast MRIs used as a part of preoperative surgical planning to measure the extent of disease are reported to be highly sensitive and capable of detecting suspicious lesions not visible with mammography or ultrasound, but are limited in their specificity.[9-19] Two European randomized controlled trials (RCT) and multiple retrospective single institution studies have suggested that breast MRI

may not provide as much benefit as expected, resulting in treatment delay and more extensive surgeries without clear evidence of clinical benefit.[12,18-21] However, despite use, the effect that breast MRI has on initial surgical planning and surgical delay remain unknown in the elderly US population.

Research has shown that the use of preoperative breast MRI may influence treatment patterns for newly diagnosed breast cancer patients. First, the receipt of breast MRI has been associated with a delay in surgical treatment. Single institution studies report a 22- to 41-day increase in the time period from diagnosis to surgery for women with breast MRI when compared to those women without breast MRI.[22-24] Second, breast MRI has been associated with an increased likelihood of mastectomy compared to breast conserving surgery (BCS).[12,18,25-30] In two meta-analyses, true-positive MRI findings prompted conversion to more extensive surgery in 11-13% of women, however, changes in surgical management were not always beneficial as 5-6% of women converted from wide local excision to more extensive surgery based on false positive results.[12,18] Two European randomized, prospective clinical trials have examined the efficacy of breast MRI.[20,21,31] One trial from the Netherlands (n=149) found that the type of initial surgery did not significantly differ (p = 0.776) between the groups with (32% received mastectomy) and without breast MRI (34% received a mastectomy).[21] Conversely, the other randomized trial from the United Kingdom (n=1,623) found that significantly more patients underwent a mastectomy at the initial operation in the MRI group (7%) compared to the patients in the group without an MRI (1%).[20,31]

Existing evidence examining the association between breast MRI with treatment delay and the type of initial surgery is limited in several aspects. First, much of the evidence is based on studies from single institutions rather than nationally representative populations. The patients and medical groups in the RCTs and single institution studies were highly selective and not generalizable to US elderly population. For example, the median and

mean ages for the RCTs were 57[20] and 55.5 years,[32] two decades younger than the average age of breast cancer patients enrolled in Medicare[33] and the average patient in our study (76.1 years). Second, to our knowledge, there is a dearth of evidence examining the impact of breast MRI on surgical planning in older women, a population that is least likely to benefit from breast MRIs because older patients are more likely to have less dense breasts and, therefore, fewer occult tumors with conventional assessment.[27,34-36] Third, the two randomized controlled trials were conducted in the Netherlands[21] and the United Kingdom[20,31] where physician practice patterns, payment and referral structures, fiscal considerations, and patient preferences for mastectomy over BCT differ significantly from the United States (US).[37-39]

The present study examined the association between preoperative MRI with time from the date of first suspected breast disorder (e.g., lump or mass in breast, or abnormal mammogram) to complete surgery and the likelihood of a mastectomy as the first surgical procedure in a population-based sample of newly diagnosed, elderly breast cancer patients in the US. Since evidence suggests that elderly women who receive breast MRI differ from women who do not receive breast MRI on baseline characteristics such as age, race, and health service area resources,[2] we attempted to balance the groups of women with and without breast MRI on measured covariates and to control for potential confounders using propensity score methods. Thus, this observational analysis generates estimates about the association of breast MRI with breast cancer treatment patterns that may reflect real world practice in the US elderly population. The evidence generated by this study is intended to inform the decision-making process regarding the benefits and drawbacks of breast MRI and help determine its appropriateness for routine utilization.

Methods

Data

We conducted a retrospective study using data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset. The SEER-Medicare dataset comes from a consortium of population-based cancer registries across the United States linked to Medicare administrative data and healthcare claims.[40] The SEER dataset comprises 17 registries nationwide and cover approximately 25% of the incident US cancer population, and the population covered by the program is comparable to the overall US population with regard to measures of poverty and education.[40] The data contain demographic and incident cancer characteristics, including histology, grade, and stage as well as treatment information and vital statistics. The SEER data also contain ecological measures of income, education, and other characteristics at each patient's census tract and zip code of residence.

Medicare covers payment for hospital services, physician services, some drug therapy, and other medical services for more than 97% of Americans aged 65 and older.[41] The Medicare claims provide information about the use and cost of health care services and co-morbid health conditions. The National Cancer Institute (NCI) hospital file contains hospital-level information, including staffing, structure, research network affiliation, and information on accreditation.[41]

Study Population

This study included women aged 66 or older with an initial diagnosis of unilateral, pathologically confirmed, stages I-IIB operable breast cancer (American Joint Committee on Cancer [AJCC] sixth edition, International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification [ICD-9-CM]) code 147). Our sample included women diagnosed between January 1, 2004 and December 31, 2007. Since this study focused on the effect of breast MRI in elderly patients, we excluded women enrolled in

Medicare due to end-stage renal disease or disability since they might differ from those women eligible for Medicare on the basis of age. We also excluded women with previous cancers, women who were not continuously enrolled in Medicare Part A and Part B, and women who were enrolled in a health maintenance organization (HMO) during the study period. We were concerned that these beneficiaries would have incomplete claims in the SEER-Medicare dataset, and we would be unable to examine their healthcare utilization in its entirety. A comorbidity index was calculated based on 12 months of claims, thus, women not enrolled 12 months prior to diagnosis were excluded (SEER-Medicare inclusion/exclusion table can be found in Appendix Table A.1).

We limited this analysis to women with operable tumors whose first definitive treatment was surgery (Figure 4.1). Thus, we excluded patients with operable breast cancer who had large tumors (T3, tumor > 5cm across) (n=2,114) because BCS is generally not recommended for these women in the absence of neoadjuvant therapy.[42] We also excluded women who received neoadjuvant chemotherapy prior to surgery (n=435). We eliminated these women because breast MRI also can be used to measure tumor response to neoadjuvant chemotherapy,[43-47] and our research focuses on the use of preoperative breast MRI to measure the extent of disease in the breast as a part of preoperative surgical planning. We also excluded patients who had conflicting claims for mastectomy and partial mastectomy on the same day in the Medicare outpatient setting, inpatient setting, and physician files because we were unable to determine the type of initial surgery (n=647). For the analysis examining the initial type of surgery, we excluded women who had their first biopsy or breast surgical procedure more than four months from the SEER-diagnosis month (n=599) because we were concerned that the claims did not correspond to the correct SEER registry tumor sequence. Our SEER-Medicare inclusion/exclusion criteria are displayed in Figure 4.1.

Type of first surgical procedure (main analysis and sub-samples). When examining

the type of first surgical procedure, we conducted a main and sub-analysis using two

different definitions of breast conserving surgery (Figure 4.2). In our main analysis, we

liberally defined BCS as a breast excision or partial mastectomy (for procedure codes, see

Appendix Table A.2). In our sub-analysis, we conservatively defined BCS as a partial

mastectomy alone and excluded women whose first surgery was a breast excision

(n=6,497). We conducted both analyses because our study focuses on the use of

preoperative breast MRI on therapeutic surgical planning, and previous research has

classified claims for breast excisions as both a diagnostic procedure[48,49] and as breast

conserving surgical treatment.[50-52] Since it is not possible to differentiate between breast

excisions that were intended to be curative (i.e., BCS) rather than diagnostic (i.e., open

biopsy) using claims data, we limited our sample to women definitive therapeutic surgeries

(i.e., partial or full mastectomy) in our sub-analysis.

Variables and Measures

We examined all claims in Medicare outpatient, inpatient, and physician claims files

during each patient's initial treatment phase from 2004 through 2009. The initial treatment

phase was defined to capture the diagnostic, preoperative, and initial treatment stages. The

start of the initial treatment phase began on the date of the first claim for a suspected breast

disorder[53] (e.g., lump or mass in breast, or abnormal mammogram; see Appendix Table A.2

for codes) 12 or fewer months prior to the SEER diagnosis month. We defined the end of

the initial treatment phase as the last day of breast cancer treatment (i.e., partial

mastectomy, mastectomy, radiation, or chemotherapy; for codes, see Appendix Table A.2)

before a treatment gap of more than 90 days,[62-64] the patient's death, or the end of the study

period, which was December 31, 2009. We identified breast cancer treatments and surgical

procedures during the initial treatment phase using the American Medical Association

Current Procedural Terminology (CPT) and the Healthcare Common Procedure

Classification System (HCPCS) codes (See Appendix Table A.2).

The main independent variable of interest was a binary indicator for whether or not

the patient received a preoperative breast MRI. Patients were classified as having a

preoperative breast MRI if they had a claim for a breast MRI (CPT: 76093-94, 77058-59,

HCPCS: C8903-C8908) on or after the first day of suspected breast disorder but before the

date of their first surgical procedure. Though this approach may capture breast MRIs that

were ordered for screening purposes, we are not concerned about including these breast

MRIs as "preoperative" because breast images taken during the initial treatment phase,

even for screening purposes, would most likely be used as a part of the surgical planning

process (Dr. Keith Amos. Personal communication. May 23, 2012). For women in our time to

surgery analysis without complete surgical treatment, we defined "preoperative" MRI as a

breast MRI claim after the first day of suspected breast disorder but before their first breast

excision (n=167) or four months after their SEER diagnosis (n=23) .

Time to surgery. We measured time to complete surgery as time from the first

suspected breast disorder date to the last surgical treatment (either a partial or full

mastectomy) in the initial treatment phase. For several reasons, we used suspected breast

disorder date, identified by the first claim with a breast-related diagnosis code within one

year prior to the patient's SEER diagnosis, rather than diagnosis date. First, SEER registry

data only include the month and year, thus, the day of diagnosis was not available. Second,

women can receive preoperative breast MRIs before (as a screening procedure) or after (as

a diagnostic or preoperative procedure) their date of diagnosis; thus, we were concerned

with underrepresenting exposure time by using date of diagnosis. Third, we wanted to

ensure that the start of follow-up did not differ by our exposure of interest (i.e., breast MRI).

To examine the appropriateness of using the first claim with breast-related diagnosis code

as the start of follow-up, we examined the distributions and time to breast events for each of

the breast-related diagnosis codes (see Appendix Table A.3) and determined it was a suitable start date. We used the date of complete surgery as our endpoint to include the initial surgery and re-excision to obtain clear margins.

Type of initial surgery. Using Medicare claims, we constructed a binary variable to indicate that a patient had a mastectomy compared to BCS as her first surgical procedure. In the main analysis, as previously mentioned (Figure 4.2, Appendix Table A.2 for codes), BCS was liberally defined as either a breast excision or partial mastectomy. In the sub-analysis, BCS was more conservatively defined as a partial mastectomy and women with breast excisions as their first surgery were excluded.

Additional covariates. We examined numerous variables that could potentially be associated with breast MRI receipt and/or our outcomes of interest to include in our propensity score and multivariate models. We included a variable for tumor histology (ductal, lobular, mixed ductal lobular, and other; see Appendix Table A.2 for codes) because research has shown that lobular tumors are more likely to be mammographically occult and, thus, patients have the potential for greater benefit from breast MRI.[17] Other tumor characteristics examined included grade (well, moderately, poorly undifferentiated, and undetermined), tumor size (<2cm vs. ≥ 2cm & < 5cm), any node positivity (yes vs. no), and hormone receptor status identified from SEER data [positive (ER+/PR+, ER+/PR-, ER+/no PR data, ER-/PR+, or no ER data/PR+), negative (ER-/PR-), unknown]. We used the NCI Comorbidity Index method to address competing health demands and risks of complications that may affect treatment selection (0, 0-1, >1).[57] Demographic characteristics examined included age group (in 5-year intervals) at diagnosis, marital status (married vs. unmarried), race (white vs. nonwhite), Hispanic ethnicity (yes vs. no), SEER region (grouping together [1] the four California registries, [2] the two Northeast registries, and [3] Atlanta and rural Georgia) and urban or rural location (urban vs. rural county). We included quartiles of the percentage of high school graduates in a given zip code of residence, and we included a

95

person-level indicator for Medicare state buy-in coverage (yes vs. no) which identified women who had their Medicare premiums and deductibles subsidized by the state during the study period owing to their financial status.

We examined surgical facility characteristics that could be associated with breast MRI receipt and affect surgical treatment patterns. We identified the facility where the first surgical procedure took place and linked it to the NCI Hospital file, which includes measures for whether or not the facility was a teaching hospital (yes vs. no), a designated NCI Cancer Center (yes vs. no), and had on-site radiation facilities (yes vs. no). We also examined facility ownership type (for-profit vs. not-for-profit) and constructed a variable for whether or not the facility was affiliated (yes vs. no) with NCI Cooperative Groups having breast cancer research portfolios, including the American College of Surgeons Oncology Group (ACOSOG), Eastern Cooperative Oncology Group (ECOG), Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), and the National Surgical Adjuvant Breast and Bowel Project (NSABP).[58] We also included a variable measuring breast cancer surgical volume (low volume vs. high volume). To construct this variable, we used the number of breast cancer surgeries (partial/ full mastectomy) for each surgery site from 2004-2009.

Statistical Analysis

We compared unadjusted baseline characteristics between the groups of women with and without a preoperative breast MRI using Pearson chi-squared tests for categorical variables and Student's t-tests for continuous variables. To estimate the association of each covariate on the crude likelihood of receiving breast MRI, we used multivariate logistic regression. We calculated odds ratios, 95% confidence intervals (CI), and two-sided p values for each predictor.

Propensity score methods. Because baseline characteristics for elderly women who receive a preoperative breast MRI may systematically differ from women who do not, we

used propensity score methods[59] to balance the groups of women with and without breast MRI on measured covariates and to control for potential confounders. Propensity score methods have been previously used when examining SEER-Medicare data.[60-64]

First, propensity scores to estimate the probability, on the basis of observed patient and surgical facility characteristics described above, that patients would have a breast MRI were developed using multivariate logistic regression.[59] We selected covariates to include in the logistic regression based on their hypothesized relationship with breast MRI receipt and the outcome (either time to complete surgery or initial type of surgery).[65]

Second, we adjusted for measured baseline differences between the group that received a breast MRI and the group that did not using inverse probability weighting.[66,67] Each patient with a breast MRI was weighted by the inverse of the probability that she would be selected for a breast MRI based on her covariates, and each patient without a breast MRI was weighted by the inverse of the probability that she would not have a breast MRI. We then stabilized these weights by multiplying the inverse probability weights by the marginal prevalence of the breast MRI receipt.[68,69]

To assess balance and the performance of the propensity model, we examined the distribution of propensity scores and covariates between the two groups (MRI vs. no MRI), examining balance by decile of propensity score.[70] Additionally, we calculated the change in standardized difference for each variable before and after inverse probability weighting.[71] We examined excluding patients with non-overlapping propensity score distributions (i.e., women without a preoperative breast MRI who had a propensity score higher than the maximum or lower than the minimum propensity score of women with preoperative breast MRI).[70,66] To reduce bias due to unmeasured confounders, we also assessed asymmetrically trimming patients who were treated most contrary to prediction.[68] We examined trimming patients at three different cut points corresponding to the 1st and 99th percentiles, the 2.5th and 97.5th percentiles, and the 5th and 95th percentiles at the tails of the

propensity score distribution in the treated (i.e., breast MRI) and untreated (i.e., no breast MRI) patients, respectively.

Analytic Approach. In our first analysis examining the time until complete surgery, we generated unadjusted survival curves using the Kaplan-Meier method.[56] We estimated adjusted survival curves using the inverse-probability weighting approach from Cole and Hernan.[72] We estimated the median time to surgery for both groups after adjusting for the inverse-probability weights and used bootstrap methods to obtain 95% confidence intervals. We estimated hazard ratios using the Cox proportional-hazards model,[73] generating unadjusted estimates and estimates (a) adjusted for covariates and (b) adjusted using inverse-probability weighting. We evaluated the proportional hazards assumption by graphical methods using Schoenfeld residuals[74] and did not find any clear violations of the proportional hazard assumption.

In our second analysis estimating the likelihood of a mastectomy as the first surgical procedure, we used multivariate logistic regression weighted with the inverse probability weights and robust standard errors.[66,75] Z-test statistics and 95% confidence intervals were used to examine the difference in the likelihood of a re-excision between those women with and without a breast MRI.

Diagnostic and procedure codes were identified and verified using medical literature, coding experts, EpiCoder (Yost Engineering Inc., Ohio), and the Integrated Cancer Information and Surveillance System coding references.[76] Analyses were performed using Stata version 12.0 (Stata Corporation, College Station, Texas). All tests were conducted using a minimum significance level of 0.05.

Results

Characteristics of the study population. Of the 26,751 women diagnosed during 2004-2007 in SEER-Medicare with stages I-IIB breast cancer, 25,038 were included in our

analysis examining time to surgery (Figure 4.1). After excluding women who had their first

breast biopsy or surgical procedure claim more than four months before or after their SEER

diagnosis, 24,439 women were included in our main analysis examining the likelihood of a

mastectomy. Over the five-year study period, the percentage of women receiving

preoperative breast MRI increased dramatically from 5.7% in 2004 to 20.5% in 2007.

Baseline characteristics for the sample examining time to surgery and the sample examining

the likelihood of a mastectomy were similar (Tables 4.1 and 4.2) with 12% of women

receiving a preoperative breast MRI. In the bivariate analysis before adjustment with the use

of inverse probability weighting, women who received breast MRI differed significantly from

women who did not for all baseline characteristics except lymph node involvement.

In our multivariate logistic regression modeling, significant predictors of MRI receipt

included the likelihood of preoperative breast MRI to generate propensity scores (Table 4.3),

younger age, fewer comorbidities, lobular carcinoma, and positive hormone receptor status.

Also, women living in areas with fewer high school graduates or certain SEER regions such

as New Mexico, Seattle, and California were significantly more likely to get a breast MRI.

Women not covered by Medicare state-buy in supplemental insurance or who were

diagnosed more recently had significantly increased odds of receiving a breast MRI.

Women getting their surgeries at facilities that were cooperative group- or NCI-affiliated, and

a higher surgical volume were significantly more likely to have a breast MRI. Women with

poorly differentiated tumors compared to well differentiated tumors had significantly

decreased odds of a preoperative breast MRI.

After using inverse probability weighting, the observed clinical, sociodemographic,

and surgical facility variables were well balanced (Tables 4.1 and 4.2). In all analyses,

adjusting for the propensity scores demonstrated substantial improvement in covariate

balance across the groups with and without breast MRI. After weighting, the absolute

standardized differences (Appendix Figures A.1 and A.2) were reduced for all observed

covariates below the threshold of 10% in absolute value.[77] In all analyses, excluding patients with non-overlapping propensity scores or trimming patients at the three different cut points did not change the significance of our estimates, and only attenuated the effect of breast MRI slightly (See Appendix Table D.1 and D.2). Thus, we report the results without trimming. Figure 4.3 shows the propensity score distribution of the samples in our analyses.

   Time to surgery analysis. Overall, 89.2% of women had surgery, 88.6% of the group without a breast MRI and 93.7% of the group with MRI (p<0.001). Of the women who had surgery, The unadjusted median time to complete surgery was 53 days for patients without a breast MRI and 63 days for patients with a breast MRI (p<0.001). Unadjusted time to surgery curves and time to surgery curves adjusted with the use of inverse probability weighting are shown in Figure 4.4. Adjusting for inverse probability weighting, having a preoperative breast MRI was associated with a 15-day delay (95% CI: [11, 19]) in median days to complete surgery (No MRI group median: 53 days [95% CI: 53, 55]; MRI group median: 68 days [95% CI: 63, 71]). Using proportional hazard modeling (Table 4.4; for full models, see Appendix Table A.4), results were consistent with a delay in treatment for the MRI group. All adjusted models demonstrate that the hazard of having surgery was significantly lower for women receiving a breast MRI when compared to women not receiving a breast MRI. For example in the model with inverse probability weights, the hazard ratio was 0.90 (95% CI:[0.85, 0.95]).

   Type of initial surgery. Overall, in our main analysis, 22.3% of women in our sample had a mastectomy as their first surgical procedure compared to those women with BCS (No MRI group: 22.0%; MRI group 24.1%). After adjusting for covariates or using inverse probability weighting across all models, MRI was significantly associated with an increased likelihood of mastectomy (Table 4.5; for full models, see Appendix Table A.5). Having a breast MRI was associated with a 30% increase in the odds of having a

mastectomy in the model with inverse probability weights (Odds Ratio [OR]: 1.30 [95% CI: 1.12, 1.50]).

We found similar results in our sub-analysis of the association of preoperative breast MRI with the likelihood of a mastectomy compared to a partial mastectomy as the first surgical procedure. Again, MRI was significantly associated with increased odds of a mastectomy across all models when adjusted for covariates or using inverse probability weighting (Table 4.6, full models see Appendix Table A.7). In the model using inverse probability weights, women with breast MRI had a 20%-increase in the odds of having a mastectomy compared to the women who did not have a breast MRI (OR: 1.20 [95% CI: 1.02, 1.40]).

Discussion

Preoperative breast MRI is becoming more common for elderly women with breast cancer as evidenced by 20.5% of women in our sample diagnosed in 2007 receiving a preoperative breast MRI. In this large, population-based observational study of elderly women with breast cancer, we found that preoperative breast MRI was associated with a 15-day delay in the time to complete surgery. Additionally, we found that, when compared to women who did not receive a preoperative breast MRI, elderly women who underwent a preoperative breast MRI were more likely to have a mastectomy as their first surgical procedure. Because baseline characteristics of patients who received breast MRI differed from the group that did not receive breast MRI, we used multiple multivariable regression modeling techniques and propensity score adjustments to balance the groups with and without breast MRI on observed characteristics. Across multiple multivariable models and differing propensity score method adjustments, the association between breast MRI and treatment delay and the likelihood of a mastectomy persisted and remained significant.

Our results showed a significant delay in surgical treatment for those patients with breast MRI, however, the 15-day delay we estimated is shorter than the 22- to 41-day delay that previous studies have reported.[22-24] Our estimates may differ from previous research for several reasons. First, the estimated delay due to breast MRI may differ due to inconsistent definitions of the follow-up start date. Our study used the first claim with a breast-related diagnosis code that differed from studies using the actual date of diagnosis or the pathologically confirmed date of diagnosis. Second, the shorter delay we found may be attributed to the fact that previous studies were single institution studies that may have differing referral and diagnostic follow-up patterns than our national sample.

Although the delay we estimate is statistically significant, it is unclear how much it affects patient outcomes. The estimated delay we found would most likely not impact survival directly. Evidence suggests that a much larger delay in initial surgery, specifically, between three and eight months, is reported to have detrimental effects on five-year survival rates for breast cancer patients.[78,79] However, studies have shown that any delay in treatment can be anxiety-provoking to patients and leads to uncertainties related to the interpretation and management of additional findings.[79,80] The timeliness of surgery, specifically within 30 days of diagnosis, has been proposed as a quality metric[80-83] and, although we did not estimate the date of diagnosis, the estimated two-week delay experienced by the group with MRI generates concern these women are not having surgery in a timely manner.

Some studies have suggested that the delay in surgery may be due to the additional diagnostic work-up necessary for breast MRI.[23] Because of the low specificity of breast MRI, lesions visible on MRI alone should be followed up with MR-guided needle biopsy with pathological assessment and, if needed, pre-surgical localization.[20,80] Although not the goal of this study (See Chapter 6), we found that women with MRI had a higher proportion of biopsies and surgical procedures before their completed surgery than the group without

breast MRI. Women in the MRI group had a higher proportion of at least two or more biopsies (no MRI group: 2.7%, n=604 vs. MRI group: 10.7%, n=325, p<0.001) and at least one breast surgical procedure before complete surgery (no MRI group: 17.1%, n=3,766 vs. MRI group: 11.5%, n=349, p<0.001). This is concerning in the elderly population, especially if breast MRI is not associated with improved outcomes,[4,11,12,21-27] because additional biopsies and procedures may cause anxiety, increase complications in frail populations, and can be difficult to schedule for women with limited transportation options and access to care.

We found that the odds of having a mastectomy as a first surgical procedure were 1.30 times greater in the breast MRI group compared to the group without a breast MRI. This is consistent with previous literature showing that breast MRI was associated with an increased likelihood of mastectomy compared to breast conserving surgery,[12,18,25-30] including the randomized controlled trial from Great Britan.[20,31] Recent studies have reported that mastectomy rates for early-stage breast cancer patients have increased, and more patients with early-stage breast cancer are undergoing aggressive surgical treatment.[8,84-86] Though our estimates of the proportion of patients with a mastectomy (22.3% main analysis, 30.3% sub-analysis) may appear lower than estimates in the published literature,[8,38,84] it is important to note these studies use the *complete* or *most extensive* surgery as end points, which is what was captured in SEER data or reported in other studies using claims.[87] Conversely, we used the *initial* surgical procedure to examine the association between surgical planning and breast MRI. Though not reported, our estimates of the proportion of patients with mastectomy as a *complete* surgical procedure (33.7% main analysis, 37.4% sub-analysis) are consistent with previous estimates of mastectomy rates in the US elderly population.

Since evidence has shown that BCS plus radiation, or breast conserving therapy, and mastectomy yield equivalent survival outcomes for those patients who are clinically eligible for both treatments,[88] the decision regarding the type of initial surgery for early-stage

breast cancer has been considered a "preference-sensitive decision."[89,90] Treatment

decisions can be based on a wide range of biological, physical, emotional, economic, and

social factors.[91-96] Although it is possible that the increased rate of initial mastectomies may

reflect a shift in patient choice towards an aggressive, preventive surgical approach against

local recurrence and new initial breast cancers despite any expected survival benefit,[8] it is

also important for providers and patients to be aware of other factors, such as breast MRI,

that may influence the decision-making process and the choice of initial surgery, especially

in the absence of evidence of improved psychosocial and outcomes survival. For example,

evidence suggests that women with multi-focal invasive cancer, a type of cancer that breast

MRI is highly sensitive in detecting, treated with BCS and adjuvant therapy have an

equivalent survival and risk of recurrence as those patients treated with mastectomy due to .

advances in adjuvant systemic treatments and radiotherapy.[97-101] Thus, it is concerning if

patients and providers are basing their decision to have a mastectomy over breast

conserving surgery on additional lesions found with breast MRI that could have been

controlled with adjuvant systemic treatments and radiotherapy, and might not affect

recurrence or survival.

Our study is limited in several aspects. First, in the analysis evaluating the type of

first surgery, we were unable to differentiate breast excisions that were used as part of a

diagnostic work-up, as in the case of open biopsies, and those excisions that were intended

to be therapeutic lumpectomies using claims data. To address this limitation, we employed

two definitions of breast conserving therapy: (a) one that defined BCS liberally as a partial

mastectomy or breast excision; and (b) in a sub-analysis, one that defined BCS

conservatively as a partial mastectomy. In our main analyses, we used a definition of BCS

that was more specific than our second definition, but less sensitive because it considered

women who had open biopsies as having had BCS, regardless of whether they went on to

have a mastectomy. However, relatively few patients in our sample had a breast excision

and subsequent mastectomy in the initial treatment phase (7.2%, n=1,806), and only 6.3% (n=112) of them had a preoperative breast MRI. These patients would have been correctly classified if they had a breast excision as their planned surgical treatment followed by a re-excision (a mastectomy) to obtain clear tumor margins, or they might have been incorrectly classified as having BCS when they actually had an open biopsy followed by a mastectomy as their initial surgical treatment. To address this ambiguity, our second conservative definition of BCS was intended to mimic the decision between BCS and mastectomy as first surgery in a population in which we can be certain the surgery was intended to be a treatment. Despite this limitation, we found that, regardless of how we define BCS, women in the breast MRI group were more likely to have a mastectomy as their first surgical procedure.

Second, we do not know exactly how the MRI results influenced the decision-making process and course of treatment. As previously mentioned, patient preferences play a role in treatment selection and the decision-making process for a woman diagnosed with early-stage breast cancer is complex. We do not know based on claims data if the patient and physician decided on a mastectomy based on her MRI results or if the decision was based on her personal beliefs regarding mastectomy and BCT.

Third, there are limitations to our study due to the nature of the SEER-Medicare dataset. For example, because the SEER-Medicare data only include complete claims for fee-for-service and not for managed care patients, the results of the study may not be generalizable to all elderly women. Also, our measures of socioeconomic status were limited. Our measure of education was assessed at the census tract of residence, and we were unable to disaggregate whether the construct's effect was related to a person's personal wealth or education level, or if it was related to the resources of the community where the person lives. To attempt to mitigate this problem, we included one person-level

measure, state-buy in status, which indicated whether the patient ever applied for and was enrolled in the Medicare state buy-in program.[102]

Fourth, as in most observational studies, we were unable to control for unmeasured confounding. Using propensity score methods, we successfully balanced women with and without breast MRI on observed clinical, sociodemographic, and surgical facility variables; however, we were unable to balance the women on unobserved characteristics that may be associated with breast MRI and our outcomes, and thus we are concerned that our models are underspecified due to variables not available in our dataset. For example, unmeasured confounders could include access to care, care-seeking behavior, healthcare coordination, and patient and surgeon preferences regarding the initial type of surgery. These factors may be associated with breast MRI receipt and my also influence the likelihood of a mastectomy or the time to complete surgical treatment. Future research should apply novel statistical methods such as instrumental variable analysis that may more adequately control for unmeasured confounding and help strengthen our confidence in these findings that are based on the examination of observational data.

Fifth, we were unable to control for confounding by indication and differentiate between the women who received breast MRI as a part of routine work-up compared to those women who were inadequately imaged using conventional assessment (i.e., suspected of multifocal or multicentric cancers, had heterogeneously dense breast tissue, or experienced a situation where the radiologist read the mammogram or ultrasound and recommended that the patient get a breast MRI). Women who are inadequately imaged using conventional assessment, such as those women with invasive lobular carcinoma, may have a higher baseline risk for mastectomy;[17] thus, Future research, should explore confounding by indication in sub-analyses of women who are more likely to be inadequately imaged by conventional assessment.

As new and advanced imaging modalities, such as breast MRI, are introduced into clinical practice, it is important to generate evidence about their appropriateness and to inform their dissemination into practice. Given that preoperative breast MRI is associated with a slight surgical delay of surgery and increased odds of mastectomy for older women with breast cancer, healthcare providers and patients should consider breast MRI's impact on the patient's psychosocial outcomes, such as emotional distress, quality of life, satisfaction with the decision-making process, and preferences when deciding to use breast MRI preoperatively. Further research should examine the effectiveness of preoperative MRI in terms of outcomes, such as reoperation rates, recurrence, and survival in a population-based sample.

Figure 4.1. Inclusion/exclusion schematic for the time to surgery and initial type of surgery analyses

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│       Women diagnosed with their first primary breast cancer in SEER in 2004-2007* │
│                                  n= 39,652                                        │
└────────────────────────────────────────────────────────────────────────────────┘

              INCLUDED                                         EXCLUDED

┌──────────────────────────────────────┐      ┌──────────────────────────────────────┐
│ Known Stage I-IIIA disease, tumor size│      │ Stage 0 or IV disease, stage unknown; │
│ <5cm, histology codes indicating      │      │ tumor size greater than 5cm; histology│
│ malignant breast cancer               │      │ codes indicating in situ/ non-malignant│
│ N=26,751                              │      │ disease or non-breast primary tumors   │
│                                       │      │ n=12,901                              │
└──────────────────────────────────────┘      └──────────────────────────────────────┘

┌──────────────────────────────────────┐      ┌──────────────────────────────────────┐
│ Able to determine the first definitive│      │ Medicare claims identified conflicting │
│ surgical treatment and have no prior  │      │ surgical procedures on the same day;   │
│ cancer treatments before surgery      │      │ receipt of cancer treatments prior to  │
│ n= 25,669                             │      │ surgery                                │
│                                       │      │ n=1,082                               │
└──────────────────────────────────────┘      └──────────────────────────────────────┘

┌──────────────────────────────────────┐      ┌──────────────────────────────────────┐
│ Patients with a breast surgical       │      │ Unable to link patient to her surgical │
│ procedure Linkable to their surgical  │      │ provider                               │
│ provider                              │      │ n= 631                                 │
│ n= 25,038                             │      │                                        │
└──────────────────────────────────────┘      └──────────────────────────────────────┘

┌────────────────────────────────────────────────────────────────────────────────┐
│           Sample for the analysis examining time to surgery                      │
│                                  n= 25,038                                       │
│     Additional inclusion/ exclusion criteria for the initial type of surgery analysis: │
└────────────────────────────────────────────────────────────────────────────────┘

              INCLUDED                                         EXCLUDED

┌──────────────────────────────────────┐      ┌──────────────────────────────────────┐
│ Had a first biopsy or breast surgical │      │ First breast breast biopsy or surgical │
│ procedure† Within 4 months of SEER    │      │ procedure† claim more than 4 months    │
│ diagnosis month                       │      │ from SEER diagnosis month              │
│ n= 24,439                             │      │ n= 599                                 │
└──────────────────────────────────────┘      └──────────────────────────────────────┘

┌────────────────────────────────────────────────────────────────────────────────┐
│  Sample for the analysis examining the likelihood of a mastectomy as the initial surgery │
│                                  n= 24,439                                       │
└────────────────────────────────────────────────────────────────────────────────┘
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SEER, Surveillance, Epidemiology and End Results

* Meeting SEER-Medicare inclusion requirements of aged 66 or older at diagnosis, reporting source not autopsy or death certificate, laterality not bilateral or unknown, original reason for Medicare entitlement not disability or end stage renal disease, valid month of diagnosis, no health maintenance organization enrollment during study period, continuous enrollment in Part A & B during the study period, comorbidity score and was able to be matched to claims during the study period. Study period is defined here as the 12 months prior to diagnosis month till the end of data or death (For more details see Appendix Table A.1)

† Breast surgical procedure includes breast excision, partial/subtotal mastectomy and mastectomy

Figure 4. 2. First surgical procedure comparison group definitions for the main and sub-analyses
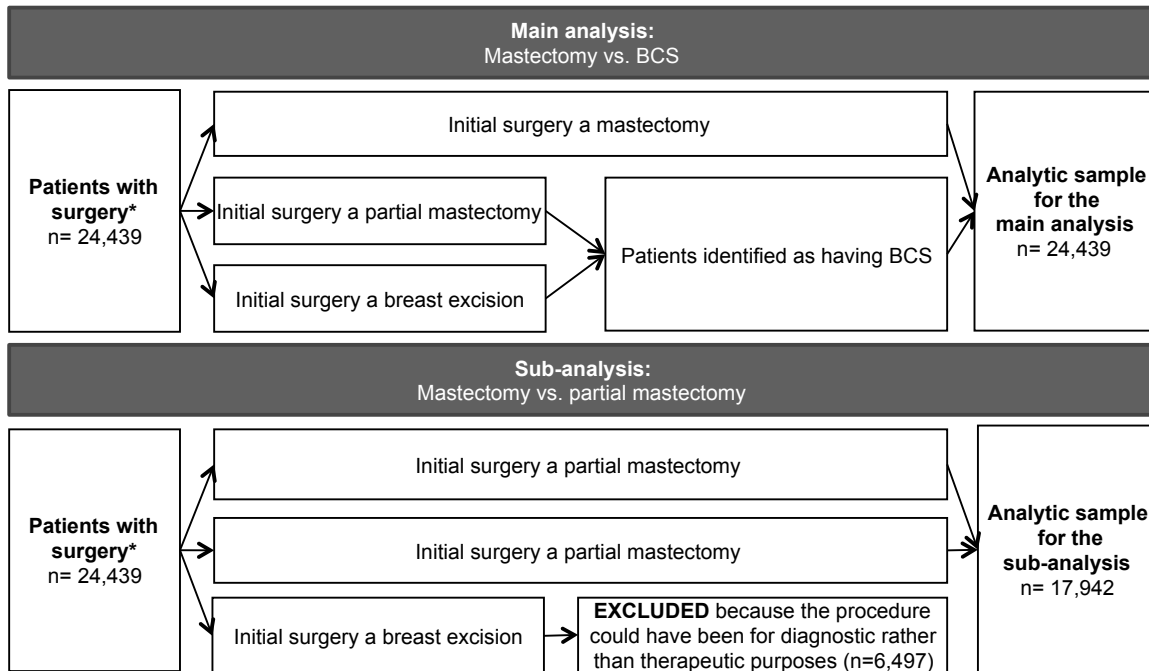
BCS, breast conserving therapy.

* Who meet our inclusion criteria

Table 4.1. Baseline characteristics of patients for the time to surgery analysis (n=25,038)

	Unadjusted data				Data adjusted using Inverse Probability Weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N=25,038	N=22,027	N=3,011		N=21,849	N=2,999	
Preoperative breast MRI (%)	12.0	0.0	100.0	<0.001	0	100	0.001
Had surgery (PM/TM)	89.2	88.6	93.7	<0.001	89.0	91.6	0.01
Time to complete surgery, days	84.8 (97.9)	82.0 (95.6)	104.1 (110.7)	<0.001	82.5 (95.6)	105.6 (110.5)	<0.001
Tumor size (%)				0.004			0.03
< 2cm	72.5	72.2	74.7		72.6	75.5	
≥ 2cm, < 5cm	27.5	27.8	25.3		27.4	24.5	
Tumor grade (%)				<0.001			0.95
Well differentiated	26.2	26.0	27.8		26.2	26.1	
Moderately differentiated	43.7	43.4	46.5		43.8	44.2	
Poorly differentiated	24.5	25.0	20.5		24.4	24.5	
Grade unknown	5.6	5.6	5.2		5.6	5.2	
Hormone receptor status (%)				0.005			0.67
Positive	78.9	78.6	80.8		78.9	78.3	
Negative	12.9	13.0	12.4		12.9	13.9	
Unknown	8.2	8.4	6.8		8.2	7.8	
Node positivity (%)	20.6	20.4	21.9	0.06	20.6	20.6	>0.99
Histology				<0.001			0.58
Ductal	73.8	74.9	66.3		73.8	74.0	
Lobular	9.8	8.9	16.1		9.8	9.0	
Mixed ductal/lobular	8.0	7.4	12.2		8.0	8.9	
Other	8.4	8.9	5.3		8.4	8.2	
NCI Comorbidity Index (%)				<0.001			0.80
0	63.3	62.0	73.0		63.5	62.4	
Between 0 and 1	28.0	28.7	23.0		28.0	28.9	
Greater than 1	8.7	9.3	4.0		8.5	8.6	
Age at diagnosis (%)				<0.001			0.69
65 to 69	20.3	18.5	33.5		20.4	20.8	
70 to 74	24.5	23.8	29.6		24.7	25.9	
75 to 79	24.1	24.5	20.9		24.2	24.5	
80 to 84	18.8	19.8	11.7		18.8	18.3	
85 and older	12.3	13.4	4.4		11.9	10.5	
Married (%)	45.4	44.2	54.6	<0.001	45.6	45.6	0.97
State buy-in coverage (%)				<0.001			0.43
No	89.0	88.2	94.6		89.2	90.1	
Yes	11.0	11.8	5.4		10.8	9.9	
Race (%)				<0.001			0.50
White	86.7	86.5	88.6		86.8	87.6	
Non-white	13.3	13.5	11.4		13.2	12.4	
Cooperative group affiliation of surgical facility (%)[†]	51.2	49.5	63.2	<0.001	51.4	50.8	0.69
NCI affiliation of surgical facility (%)	5.4	5.1	7.5	<0.001	5.4	5.7	0.68
Surgical facility a teaching hospital (or affiliated one)	52.6	52.1	56.8	<0.001	52.9	56.6	0.02

Table 4.1. Baseline characteristics of patients for the time to surgery analysis (cont.)

	Unadjusted data				Data adjusted using Inverse Probability Weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= 25,038	N= 22,027	N= 3,011		N=21,849	N=2,999	
Surgical volume of surgical facility (%)				<0.001			0.70
Low	49.7	52.1	32.3		49.4	50.0	
High	50.3	47.9	67.7		50.6	50.0	
Zip code proportion with at least high school education (% in each quartile)				<0.001			0.66
Low education	24.7	23.0	37.4		24.8	24.4	
Low-medium education	24.1	23.9	25.5		24.3	25.2	
Medium-high education	23.6	24.0	20.7		23.6	22.2	
High education	23.6	25.2	12.2		23.3	23.4	
Unknown education	4.0	4.0	4.3		4.0	4.7	
Year of diagnosis (%)				<0.001			0.13
2004	25.1	26.9	11.9		24.8	22.3	
2005	24.6	25.5	17.8		24.6	24.6	
2006	24.9	24.6	27.1		25	24.8	
2007	25.4	22.9	43.2		25.6	28.4	
SEER Region (%)				<0.001			0.33
California registries	32.5	31.5	39.7		32.7	32.2	
Northeast registries	23.3	22.7	27.2		23.5	26.5	
Georgia	3.3	3.4	2.9		3.3	2.6	
Detroit	6.9	7.2	4.8		6.9	6.9	
Iowa	7.2	7.8	2.8		7.2	5.9	
New Mexico	2.1	1.8	4.4		2.1	1.8	
Seattle	6.3	5.6	11.1		6.4	6.8	
Utah	2.7	2.8	2.3		2.7	2.1	
Kentucky	7.6	8.3	2.4		7.3	8.3	
Louisiana	6.9	7.5	2.2		6.8	5.7	
Hawaii	1.2	1.4	0.2		1.1	1.4	

p-values by t-test for continuous variables and chi2 test for binary / categorical variables, Mean (Standard Deviation) or %

MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; PM, Partial mastectomy; TM, Total mastectomy; NCI, National Cancer Institute

[†] NCI Cooperative Groups having breast cancer research portfolios

Table 4.2. Baseline characteristics of patients in the analysis examining the first surgical procedure (main analysis, n= 24,439)

		Unadjusted data			Data adjusted using Inverse Probability Weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= N= 24,439	N= 21,522	N= 2,917		N=21,373	N=2,909	
Preoperative breast MRI (%)	11.9	0	100	<0.001	0	100	<0.001
Mastectomy as the first surgical procedure	22.3	22.0	24.1	0.01	21.4	26.6	<0.001
Tumor size (%)				0.004			0.05
< 2cm	72.9	72.6	75.1		73	75.6	
≥ 2cm, < 5cm	27.1	27.4	24.9		27.0	24.4	
Tumor grade (%)				<0.001			0.99
Well differentiated	26.3	26.1	27.9		26.3	26.4	
Moderately differentiated	43.8	43.4	46.7		43.9	44.1	
Poorly differentiated	24.5	25	20.4		24.4	24.4	
Grade unknown	5.4	5.4	5.0		5.4	5.1	
Hormone receptor status (%)				0.004			0.72
Positive	78.9	78.6	81		79.0	78.4	
Negative	13	13.1	12.3		13.0	13.9	
Unknown	8.1	8.2	6.7		8.0	7.7	
Node positivity (%)	20.6	20.4	21.8	0.08	20.6	20.4	0.89
Histology				<0.001			0.57
Ductal	73.9	74.9	66.7		73.9	74.1	
Lobular	9.7	8.9	16		9.8	8.8	
Mixed ductal/lobular	8	7.4	12.2		8.0	8.8	
Other	8.3	8.8	5.1		8.3	8.2	
NCI Comorbidity Index (%)				<0.001			0.66
0	63.6	62.3	73.3		63.8	62.2	
Between 0 and 1	27.9	28.6	22.9		27.9	29.2	
Greater than 1	8.5	9.1	3.8		8.3	8.6	
Age at diagnosis (%)				<0.001			0.74
65 to 69	20.5	18.7	33.8		20.6	20.8	
70 to 74	24.7	24	29.6		24.8	26.0	
75 to 79	24.1	24.6	20.6		24.3	24.5	
80 to 84	18.8	19.7	11.7		18.8	18.2	
85 and older	12	13	4.3		11.6	10.4	
Married (%)	45.8	44.6	54.8	<0.001	45.9	45.8	0.96
State buy-in coverage (%)				<0.001			0.53
No	89.3	88.5	94.9		89.5	90.2	
Yes	10.7	11.5	5.1		10.5	9.8	
Race (%)				<0.001			0.56
White	87	86.7	88.9		87.1	87.8	
Non-white	13	13.3	11.1		12.9	12.2	
Cooperative group affiliation of surgical facility (%)[†]	51	49.3	63.1	<0.001	51.2	50.7	0.75
NCI affiliation of surgical facility (%)	5.2	4.9	7.1	<0.001	5.2	5.4	0.78
Surgical facility a teaching hospital or affiliated one, (%)	52.4	51.8	56.5	<0.001	52.6	56.6	0.01
Surgical volume of surgical facility (%)				<0.001			0.64
Low	49.8	52.2	32.0		49.6	50.3	
High	50.2	47.8	68.0		50.4	49.7	

Table 4.2. Baseline characteristics of patients in the analysis examining the first surgical procedure (cont.)

	Unadjusted data				Data adjusted using Inverse Probability Weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= N= 24,439	N= 21,522	N= 2,917		N=21,373	N=2,909	
Zip code proportion with at least high school education (% in each quartile)				<0.001			0.6
Low education	24.6	22.9	37.4		24.7	24.5	
Low-medium education	24.0	23.9	25.3		24.2	25.3	
Medium-high education	23.6	24.0	20.6		23.6	21.9	
High education	23.7	25.3	12.3		23.5	23.7	
Unknown education	4.0	3.9	4.3		4.0	4.6	
Year of diagnosis (%)				<0.001			0.12
2004	25.2	27.0	11.8		24.9	22.3	
2005	24.6	25.5	17.8		24.6	24.5	
2006	24.9	24.6	27.1		25.0	24.9	
2007	25.3	22.8	43.4		25.5	28.3	
SEER Region (%)				<0.001			0.28
California registries	32.3	31.4	39.5		32.5	31.7	
Northeast registries	23.3	22.7	27.4		23.5	26.9	
Georgia	3.3	3.3	2.8		3.3	2.5	
Detroit	6.9	7.1	5.0		6.9	6.8	
Iowa	7.4	8.0	2.8		7.3	5.9	
New Mexico	2.1	1.8	4.3		2.0	1.7	
Seattle	6.3	5.7	11.2		6.4	6.8	
Utah	2.7	2.8	2.3		2.8	2.1	
Kentucky	7.6	8.3	2.5		7.4	8.4	
Louisiana	6.9	7.5	2.2		6.8	5.8	
Hawaii	1.2	1.4	0.2		1.1	1.3	

* p<0.05, ** p<0.01, *** p<0.001"
Exponentiated coefficients
MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; NCI,
National Cancer Institute; AIC, Akaike information criterion
[†] NCI Cooperative Groups having breast cancer research portfolios

Table 4.3. Multivariate logistic regression to generate preoperative breast MRI propensity scores

	Time to surgery analysis		Type of first surgical procedure sample			
			Main analysis: Patients with a mastectomy or BCS (n=24,439)		Sub-analysis: Patients with a mastectomy or partial mastectomy (n=17,1942)	
	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval
Tumor size						
< 2cm	(ref.)		(ref.)		(ref.)	
≥ 2cm, < 5cm	0.97	[0.87, 1.07]	0.99	[0.89, 1.10]	0.92	[0.82, 1.03]
Tumor grade						
Well differentiated	(ref.)		(ref.)		(ref.)	
Moderately differentiated	1.02	[0.92, 1.13]	1.04	[0.94, 1.15]	0.99	[0.89, 1.12]
Poorly differentiated	0.81**	[0.71, 0.93]	0.85*	[0.74, 0.97]	0.84*	[0.72, 0.98]
Grade unknown	0.90	[0.74, 1.11]	0.90	[0.73, 1.11]	0.86	[0.67, 1.09]
Hormone receptor status						
Positive	(ref.)		(ref.)		(ref.)	
Negative	1.16*	[1.01, 1.34]	1.22**	[1.06, 1.40]	1.20*	[1.03, 1.40]
Unknown	1.03	[0.87, 1.21]	1.02	[0.86, 1.20]	0.96	[0.80, 1.16]
Node positivity	1.03	[0.92, 1.15]	1.11	[1.00, 1.24]	1.10	[0.98, 1.24]
Histology						
Ductal	(ref.)		(ref.)		(ref.)	
Lobular	2.18***	[1.92, 2.47]	2.13***	[1.88, 2.42]	2.16***	[1.87, 2.49]
Mixed ductal/lobular	1.69***	[1.48, 1.94]	1.69***	[1.47, 1.94]	1.66***	[1.42, 1.93]
Other	0.81*	[0.68, 0.97]	0.79*	[0.65, 0.95]	0.78*	[0.64, 0.96]
NCI Comorbidity Index						
0	(ref.)		(ref.)		(ref.)	
Between 0 and 1	0.79***	[0.72, 0.88]	0.79***	[0.71, 0.87]	0.78***	[0.70, 0.88]
Greater than 1	0.55***	[0.45, 0.67]	0.53***	[0.43, 0.66]	0.50***	[0.39, 0.64]
Age at diagnosis						
65 to 69	(ref.)		(ref.)		(ref.)	
70 to 74	0.69***	[0.62, 0.77]	0.68***	[0.61, 0.75]	0.67***	[0.60, 0.76]
75 to 79	0.49***	[0.43, 0.55]	0.46***	[0.41, 0.52]	0.45***	[0.40, 0.52]
80 to 84	0.34***	[0.30, 0.39]	0.32***	[0.28, 0.37]	0.33***	[0.28, 0.38]
85 and older	0.19***	[0.15, 0.23]	0.17***	[0.14, 0.21]	0.16***	[0.12, 0.20]
Married	1.10*	[1.01, 1.20]	1.10*	[1.01, 1.20]	1.15**	[1.05, 1.27]
State buy-in coverage						
No	(ref.)		(ref.)		(ref.)	
Yes	0.59***	[0.49, 0.71]	0.57***	[0.47, 0.69]	0.62***	[0.51, 0.76]
Race						
White	(ref.)		(ref.)		(ref.)	
Non-white	0.91	[0.79, 1.04]	0.91	[0.79, 1.04]	0.91	[0.78, 1.06]
Cooperative group affiliation of surgical facility[†]	1.36***	[1.24, 1.50]	1.35***	[1.23, 1.49]	1.34***	[1.20, 1.49]
NCI affiliation of surgical facility	1.26**	[1.06, 1.50]	1.19	[0.99, 1.42]	1.08	[0.88, 1.33]
Surgical facility a teaching hospital (or affiliated one)	0.94	[0.85, 1.04]	0.93	[0.84, 1.03]	0.84**	[0.75, 0.94]
Surgical volume of surgical facility						
Low	(ref.)		(ref.)		(ref.)	
High	1.98***	[1.79, 2.19]	2.00***	[1.81, 2.22]	2.01***	[1.79, 2.25]

Table 4.3. Multivariate logistic regression to generate preoperative breast MRI propensity scores (cont.)

| | Time to surgery analysis | | Type of first surgical procedure sample | | | |
| | | | Main analysis: Patients with a mastectomy or BCS (n=24,439) | | Sub-analysis: Patients with a mastectomy or partial mastectomy (n=17,1942) | |
	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval
Zip code proportion with at least a high school education (quartiles)						
Low education	(ref.)		(ref.)		(ref.)	
Low-medium education	0.70***	[0.63, 0.79]	0.70***	[0.63, 0.78]	0.70***	[0.62, 0.79]
Medium-high education	0.66***	[0.59, 0.75]	0.66***	[0.58, 0.74]	0.67***	[0.59, 0.77]
High education	0.48***	[0.41, 0.56]	0.48***	[0.41, 0.56]	0.49***	[0.41, 0.58]
Unknown education	0.70**	[0.57, 0.87]	0.71**	[0.57, 0.89]	0.71**	[0.56, 0.91]
Year of diagnosis						
2004	(ref.)		(ref.)		(ref.)	
2005	1.61***	[1.39, 1.85]	1.62***	[1.40, 1.87]	1.61***	[1.37, 1.90]
2006	2.67***	[2.33, 3.06]	2.69***	[2.35, 3.09]	2.74***	[2.35, 3.19]
2007	5.02***	[4.42, 5.72]	5.06***	[4.44, 5.77]	4.85***	[4.19, 5.63]
SEER Region						
California registries	(ref.)		(ref.)		(ref.)	
Northeast registries	1.04	[0.92, 1.18]	1.06	[0.93, 1.20]	1.18*	[1.02, 1.36]
Georgia	0.53***	[0.42, 0.68]	0.53***	[0.41, 0.67]	0.58***	[0.45, 0.74]
Detroit	0.55***	[0.45, 0.68]	0.58***	[0.47, 0.71]	0.63***	[0.49, 0.81]
Iowa	0.42***	[0.33, 0.54]	0.42***	[0.32, 0.54]	0.45***	[0.34, 0.60]
New Mexico	3.16***	[2.52, 3.96]	3.16***	[2.51, 3.97]	4.43***	[3.43, 5.72]
Seattle	1.68***	[1.43, 1.97]	1.67***	[1.42, 1.96]	1.92***	[1.61, 2.28]
Utah	0.62***	[0.47, 0.81]	0.63***	[0.48, 0.83]	0.77	[0.57, 1.03]
Kentucky	0.28***	[0.21, 0.36]	0.28***	[0.21, 0.37]	0.31***	[0.24, 0.42]
Louisiana	0.37***	[0.28, 0.49]	0.37***	[0.28, 0.49]	0.46***	[0.33, 0.62]
Hawaii	0.11***	[0.04, 0.28]	0.12***	[0.05, 0.30]	0.091***	[0.03, 0.30]
Observations	25,038		24,439		17,942	
AIC	15330.4		14905.2		11891.3	

* p<0.05, ** p<0.01, *** p<0.001"

MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute; AIC, Akaike information criterion

[†] NCI Cooperative Groups having breast cancer research portfolios

Figure 4.3a. Breast MRI propensity score distribution for the analysis examining time to surgery (n=25,038)
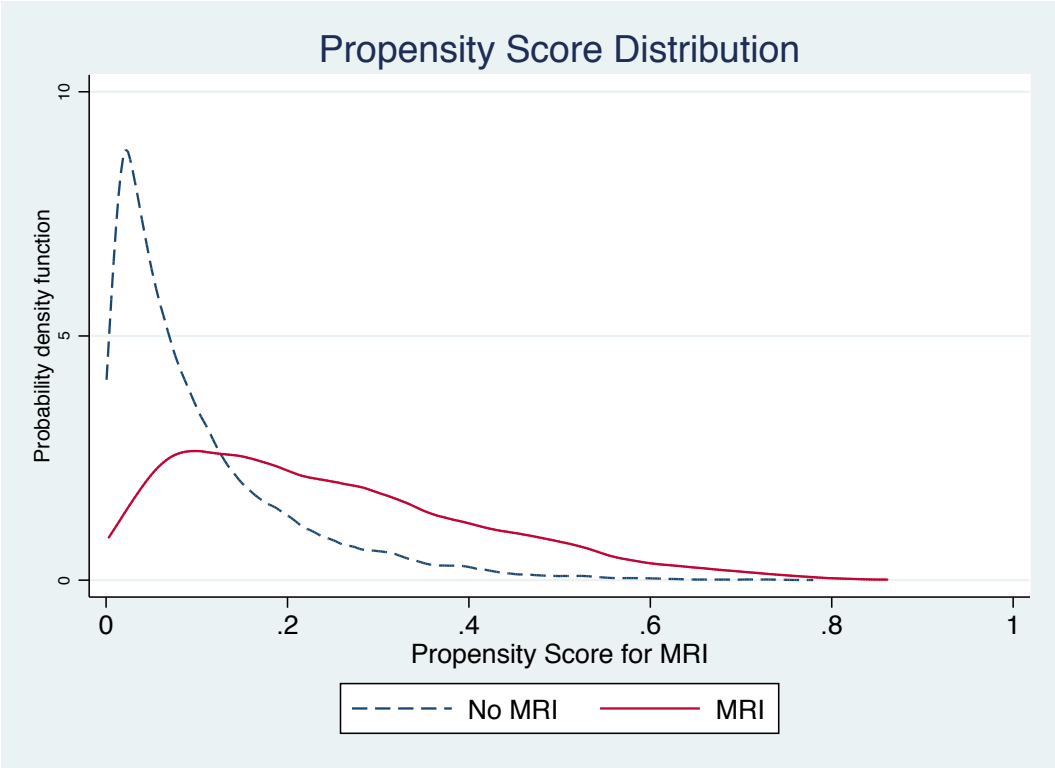
Figure 4.3b. Breast MRI propensity score distribution for the analysis examining the type of initial surgery (n=24,439)
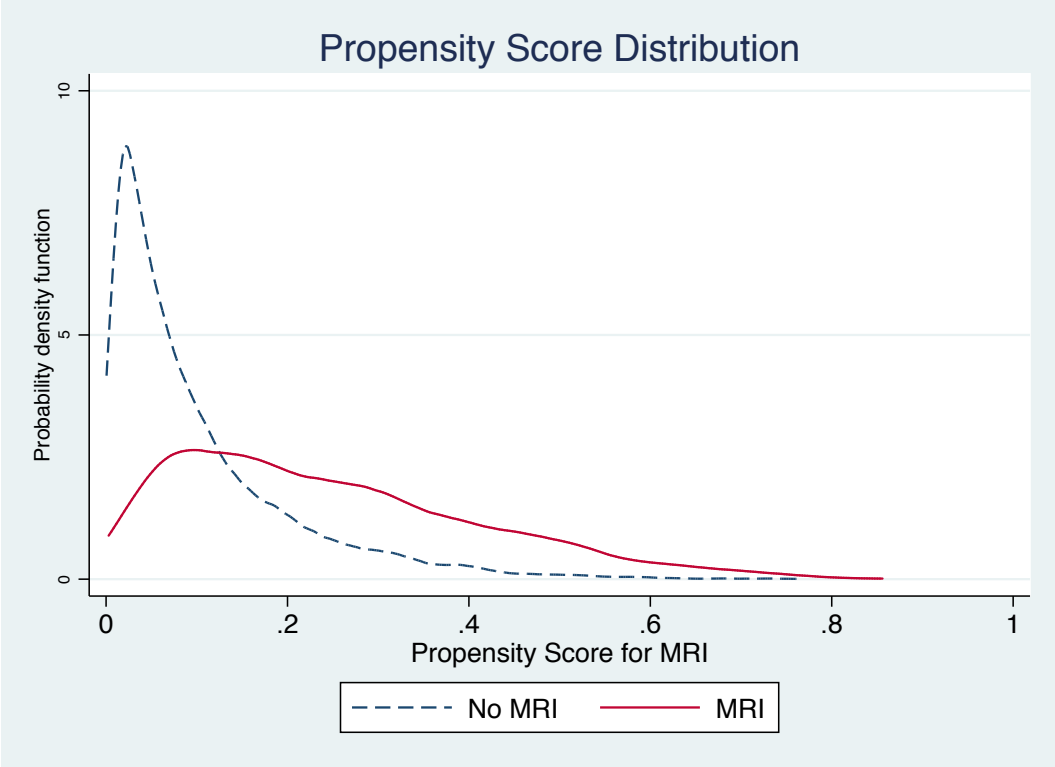
Figure 4.4. Time until surgery in populations with and without preoperative breast MRI, unadjusted vs. adjusted using IPW
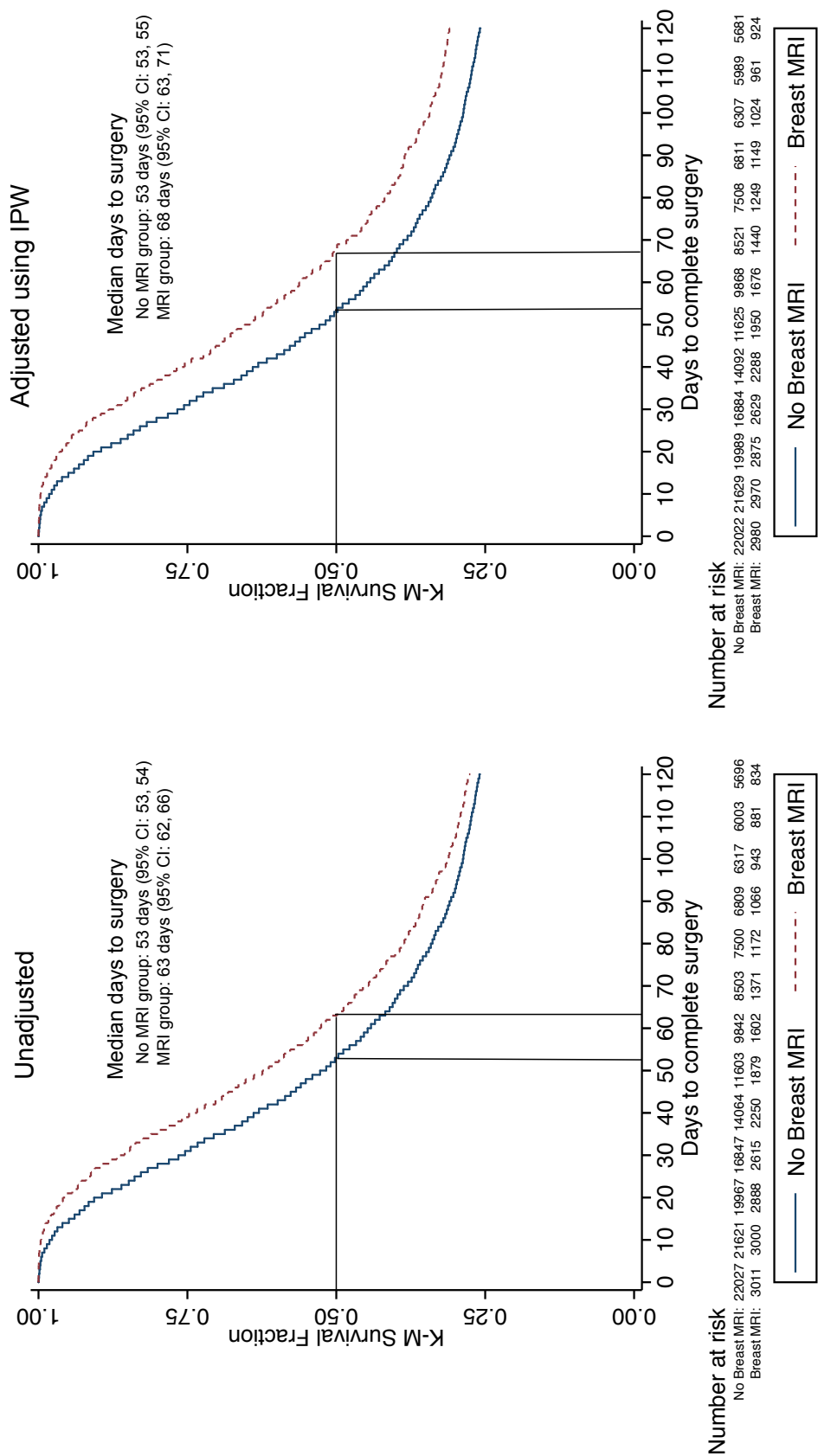
MRI, magnetic resonance imaging; IPW, inverse probability weights; CI, Confidence interval.
CIs constructed using bootstrapped standard errors and are bias corrected

Table 4.4. Impact of preoperative breast MRI on the time until complete surgery

	Hazard ratio	95% Conf. Interval	n
Unadjusted proportional hazard model	0.96	[0.93, 1.00]	25,038
Proportional hazard model adjusted for covariates†	0.93***	[0.89, 0.97]	25,038
Proportional hazard model with IPW¶	0.90***	[0.85, 0.95]	25,038

* p<0.05, ** p<0.01, *** p<0.001"
MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting
† See Appendix Table A.4 for the coefficients for the additional covariates
¶ Robust standard errors

Table 4.5. Impact of preoperative breast MRI on the likelihood of a mastectomy compared to BCS as the first surgical procedure (main analysis, n= 24,439)

	Odds ratio	95% Conf. Interval	n
Unadjusted logistic regression	1.12*	[1.03, 1.23]	24,439
Logistic regression adjusted for covariates†	1.55***	[1.40, 1.72]	24,439
Logistic regression with IPW‡	1.30***	[1.12, 1.50]	24,439

* p<0.05, ** p<0.01, *** p<0.001
MRI, Magnetic Resonance Imaging; BCS; breast conserving surgery; IPW, Inverse probability weighting
Note: BCS is defined as a breast excision or a partial mastectomy
† See Appendix Table A.5 for the coefficients of the additional included variables
‡ Robust standard errors

Table 4.6. Impact of preoperative breast MRI on the likelihood of a mastectomy compared to partial mastectomy as the first surgical procedure (sub-analysis, n=17,942)

	Odds ratio	95% Conf. Interval	n
Unadjusted logistic regression	0.93	[0.84, 1.02]	17,942
Logistic regression adjusted for covariates†	1.48***	[1.33, 1.65]	17,942
Logistic regression with IPW‡	1.20*	[1.02, 1.40]	17,942

* p<0.05, ** p<0.01, *** p<0.001
MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting
† See Appendix Table A.7 for the coefficients for the additional covariates
‡ Robust standard errors

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Overview

Breast magnetic resonance imaging (MRI) increasingly has been used in addition to conventional assessment in the preoperative evaluation of women with newly diagnosed breast cancer. Despite its rapid adoption, there is limited evidence to suggest that using MRI leads to improved short-term outcomes. The purpose of this study was to evaluate the relationship between preoperative breast MRI and the likelihood of a re-excision and a second breast cancer event in a large, population-based cohort of elderly women with early-stage breast cancer.

In this observational, retrospective analysis, we identified women diagnosed with early-stage (I-IIB) breast cancer from 2004-2007 in the Surveillance, Epidemiology, and End Results (SEER) registry data linked to Medicare claims. Cancer treatment and breast MRI receipt were identified from the Medicare claims. Women were considered eligible for a re-excision if their first surgical procedure was breast conserving surgery. A re-excision was defined as a claim submitted during the initial treatment phase for a breast surgical procedure, which was specified as a breast excision, partial mastectomy, or mastectomy, after the initial surgery. Second breast cancer events were identified through an algorithm validated in breast cancer patients using information regarding secondary cancers and surgical procedures from claims data and SEER registries. We used propensity score methods to control for measured confounders.

Twelve percent of women in our samples received a breast MRI. Of the 17,199 women who were considered eligible for re-excision, one-third of the patients in our sample

had an additional breast cancer surgical procedure after their initial surgical procedure (34.2% in the no MRI group vs. 29.2% of the MRI group [p<0.001]). Using inverse probability weighting, having a preoperative breast MRI was not significantly associated with the odds of having an additional surgical procedure (OR 1.11; 95% confidence interval (CI): [0.92, 1.35]). Of the 24,438 women who met our inclusion criteria and were included in our sample examining a second breast cancer event, 9.4% had a second breast cancer event (9.2% of the no MRI group; 11.0% of the MRI group, p<0.001). Using propensity score weighting, patients with a preoperative breast MRI were associated with an increased hazard of a second breast cancer event (HR: 1.37; 95% CI: [1.11, 1.68]) and were more likely to have a second breast cancer event one, three, and five years after their first suspected breast disorder when compared to women without preoperative breast MRI (OR: 2.13; 95% CI: [1.54, 2.94]; OR: 1.43; 95% CI: [1.12, 1.82]; OR: 1.57; 95% CI: [1.20, 2.07], respectively).

We did not find evidence that preoperative breast MRI was associated with improved short-term outcomes. Preoperative breast MRI receipt was not associated with a difference in the likelihood of re-excision, but was associated with an increased hazard of a second breast cancer event.

Introduction

Breast magnetic resonance imaging (MRI) is increasingly being used as a part of preoperative planning for patients with early-stage invasive breast cancer.[1-10] Breast MRI is able to identify lesions that are not detectable by conventional assessment, which includes clinical examination of the breasts, mammography, and ultrasonography.[11] However, there is limited evidence that the use of preoperative breast MRI improves short-term surgical outcomes for early-stage invasive breast cancer patients. Despite the paucity of definitive evidence for the use of preoperative breast MRI as a part of surgical planning, the

percentage of elderly breast cancer patients with preoperative breast MRI increased from 1.2% in 2002 to 18.8% in 2007.[12]

The effect of preoperative breast MRI on short-term surgical outcomes, such as re-excision rates and recurrence, has been examined in two randomized clinical trials (RCT)[13,14] and multiple retrospective, single institution studies.[11,15-22] Authors of one RCT from United Kingdom[13] (n=1,623) reported no significant difference in the re-excision rates between the MRI and non-MRI groups (10% vs. 11%; p=0.77) and no difference in the one-year, local recurrence-free interval rates. The other RCT from the Netherlands[14] (n=149) found a significantly higher re-excision rate for the MRI group (34%) compared to the no MRI group (12%; p=0.008) and was not powered to detect recurrence rate differences. These results are consistent with previous retrospective, single institution studies showing that preoperative breast MRI was not associated with reduced re-excision rates[8,21-23] or lower ipsilateral local recurrence rates.[8,16]

There is a dearth of evidence examining the association between preoperative breast MRI used as a part of preoperative surgical planning to measure the extent of disease and short-term surgical outcomes, which have not been examined in a population comparable to the US elderly population. The patients and medical groups in the RCTs and single institution studies conducted to date were highly selective and not generalizable to US elderly population. For example, the median and mean ages for the RCTs were 57[13] and 55.5 years,[14] almost two decades younger than the average age of breast cancer patients enrolled in Medicare[24] and the average patient in our study (76.1 years). Additionally, breast cancer treatment patterns, decision-making factors, health service/insurance structure, and fiscal considerations are different in the US compared to the European countries where the RCTs were conducted.[25-28]

Research has shown that baseline characteristics of elderly women in the US who receive breast MRI, such as age, race, and health service area resources, differ from

women who do not undergo breast imaging.[2] Although RCTs are the best method to control

for treatment selection biases, conducting an RCT in the US elderly population would be

expensive and would take years to generate results. Thus, an observational analysis using

a large, population-based dataset applying appropriate statistical methods would generate

breast MRI treatment effects that may reflect real world practice in the US elderly

population.

In this retrospective study, we used the population-based Surveillance,

Epidemiology, and End Results (SEER)-Medicare linked dataset and propensity score

methods to examine the effectiveness of preoperative breast MRI in reducing the likelihood

of re-excision and the hazard of a second breast cancer event for elderly breast cancer

patients with early-stage breast cancer.

Methods

Data

This retrospective study used the SEER-Medicare dataset, which links a consortium

of population-based cancer registries across the United States to Medicare administrative

data and healthcare claims.[29] The SEER data encompass 17 registries nationwide and

cover approximately 25% of the incident US cancer population. The data contain

demographic and incident cancer characteristics including histology, grade, and stage as

well as treatment information and vital statistics. The SEER data also contain ecological

measures of income, education, and other characteristics at each patient's census tract and

zip code of residence.[30] The sample covered by the program is comparable to the overall

US population with regard to measures of poverty and education.[29]

Medicare is the primary insurer for more than 97% of Americans aged 65 and

older.[31] Medicare covers hospital services, physician services, some drug therapy, and other

medical services. The Medicare claims provide information about the use and cost of health

care services and co-morbid health conditions. The National Cancer Institute (NCI) hospital file contains hospital-level information, including staffing, structure, research network affiliation, and information on accreditation.

Study Population

This study included women aged 66 or older with a primary diagnosis of unilateral, pathologically confirmed, stage I-IIB operable breast cancer (American Joint Committee on Cancer [AJCC] sixth edition, International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification [ICD-9-CM] code 174). Our sample included women diagnosed between January 1, 2004 and December 31, 2007. As we were only interested in elderly breast cancer patients, we focused our analysis on age-eligible women. Thus, we excluded women under the age of 65 who were eligible and enrolled in Medicare due to end-stage renal disease or disability only. We also excluded women with previous cancers, women who were not continuously enrolled in Medicare Part A and Part B, and women who were enrolled in a health maintenance organization (HMO) during the study period. We were concerned that these beneficiaries would have incomplete claims in the SEER-Medicare dataset and, therefore, we would be unable to examine their healthcare utilization in its entirety. A comorbidity index was calculated based on 12 months of claims prior to diagnosis; thus, women not enrolled 12 months prior to diagnosis were excluded (SEER-Medicare inclusion/exclusion table can be found in Appendix Table B.1).

We limited this analysis to women whose first definitive treatment was surgery, thus excluding women who received neoadjuvant chemotherapy prior to surgery (n=435). These women were excluded because breast MRI can also be used to measure tumor response to neoadjuvant chemotherapy,[32-36] and our research focuses on the use of breast MRI to measure extent of disease in the ipsilateral breast as a part of preoperative surgical planning. We also excluded patients who had conflicting claims for mastectomy and partial

mastectomy on the same day in the Medicare outpatient setting, inpatient setting, and physician files (n=647). We excluded these women because we were unable to determine the type of initial surgery. We also excluded women who had their first biopsy or breast surgical procedure more than four months before or after the SEER diagnosis month (n=599) because we were concerned that those surgical claims did not correspond to the first primary breast cancer identified from the SEER registry. Our study inclusion/exclusion criteria are presented in Figure 5.1.

Re-excision analysis (main analysis and sub-samples). For both the main and sub-analysis, we excluded those women who had a mastectomy as their first surgical procedure (n=4,631) because re-excisions after mastectomies are rare and unlikely.[37] In our sample of women who had a mastectomy as their first surgery, only 2.0% had a re-excision. Given that the rate of contralateral breast cancer has been estimated at about 1% these surgeries may have been on the contralateral breast after a single mastectomy and thus, may be validly excluded.

When examining re-excisions, we conducted both a main and sub-analysis using two different definitions of breast conserving surgery (BCS) to identify patients eligible for re-excisions (Figure 5.2). In our main analysis, we liberally defined BCS as a breast excision or partial mastectomy (for procedure codes see Appendix Table B.2), and included women whose first surgical procedure was either a breast excision or partial mastectomy. In our sub-analysis, we conservatively defined BCS as a partial mastectomy alone and excluded women whose first surgery was a breast excision (n=5,837).

We conducted both analyses because our study focuses on the use of preoperative breast MRI for *therapeutic* surgical planning; however, previous research has classified claims for breast excisions as both a diagnostic procedure[38,39] and breast conserving surgical treatment.[40-42] Based on claims data, it is not possible to differentiate between breast excisions that were intended to be curative (i.e., BCS) rather than diagnostic (i.e.,

open biopsy). Thus, the main analysis estimates the likelihood of re-excision after any surgical procedure (whether or not the first surgical intent was curative), and the sub-analysis limits our sample to women with definitive therapeutic surgeries (i.e., partial mastectomy). Furthermore, because re-excision after an initial breast excision could be intended as either the first definitive treatment (e.g., an open biopsy followed by a mastectomy) or as a second surgery to obtain clear margins (e.g., a lumpectomy followed by a mastectomy), we used the sub-analysis to limit our sample to examine re-excisions after surgical treatments with *definitive curative intent* (i.e., partial mastectomy).

Variables and Measures

We examined all claims in Medicare outpatient, inpatient, and physician claims files during each patient's initial treatment phase from 2004 through 2009. The initial treatment phase was defined to capture the diagnostic, preoperative, and initial treatment stages. The start of the initial treatment phase began on the date of the first claim for a suspected breast disorder[43] (e.g., lump or mass in breast, or abnormal mammogram; see Appendix Table B.2 for codes) 12 or fewer months prior to the SEER diagnosis month. We defined the end of the initial treatment phase as the last day of breast cancer treatment (i.e., partial mastectomy, mastectomy, radiation, or chemotherapy; for codes, see Appendix 4.II) before a treatment gap of more than 90 days,[44-46] the patient's death, or the end of the study period, which was December 31, 2009. Breast cancer treatments, including surgery, were identified in Medicare outpatient, inpatient, and physician claims files using the American Medical Association Current Procedural Terminology (CPT) and the Healthcare Common Procedure Classification System (HCPCS) codes (See Appendix Table B.2).

Our independent variable of interest was a binary indicator for whether or not the patient received a preoperative breast MRI. Patients were classified as having a preoperative breast MRI if they had a claim for a breast MRI (CPT: 76093-94, 77058-59,

HCPCS: C8903-C8908) on or after the first day of suspected breast disorder but before the date of their first surgical procedure. Though this approach may capture breast MRIs that were ordered for screening purposes, we are not concerned about including these breast MRIs as "preoperative" because breast images taken during the initial treatment phase, even for screening purposes, would most likely be used as a part of the surgical planning process (Dr. Keith Amos. Personal communication. May 23, 2012).

Re-excisions. A re-excision was defined as a claim for a breast surgical procedure (i.e., breast excision, partial mastectomy, or mastectomy [Appendix Table B.2]) after the initial surgery but during the initial treatment phase. Therefore, a re-excision could either have been an additional BCS after the initial surgery or conversion to mastectomy after the initial BCS.

Second breast cancer events. Since SEER registries do not capture cancer recurrence, we used a validated algorithm to identify second breast cancer events (Figure 5.3).[47] Our definition of a second breast cancer event was intended to include recurrence and second breast cancers because both may be associated with breast MRI receipt and affect cancer morbidity and mortality.[48-51] Further, no validated algorithm currently exists to identify each outcome separately. The algorithm was validated against medical record review in patients with early-stage invasive breast cancer.[47] We selected the algorithm with the highest specificity (99%) and positive predictive value (90%), which had a sensitivity of 89%. We selected this algorithm over other algorithms with higher sensitivity because it provided the highest likelihood of identifying only women who had a second breast cancer event.

To identify second breast cancer events, the study population (n=24,438) was first split by whether or not the patient had two visits with a code for a secondary malignant neoplasm within a 60-day period occurring more than 365 days after the primary breast cancer (for codes see Appendix Table B.2). For women who met this first criterion, they

were considered to have had a second breast event if they either did not have second cancer record in SEER or their second SEER cancer record was for breast cancer. Women who did not meet the first criterion were considered to have a second breast cancer event if: (a) they had a second breast cancer record in the SEER registry; or (b) they had a mastectomy 180 days after their SEER diagnosis, and the surgical procedure for the primary breast cancer reported in SEER was breast conserving surgery. Otherwise, it was assumed that women did not have a second breast cancer event.

For each patient, we created a continuous variable representing the time (in days) until a second breast cancer event. The time interval began on the date of the first suspected breast cancer and ended on the date of the second breast cancer event. The date of the second breast cancer was defined as the date of the procedure or diagnosis (Figure 5.3) that identified the patient as having a second breast cancer event. For example, if the patient was considered to have a second breast cancer based on having a second primary cancer in the SEER registries (n=759), we used first day of the SEER diagnosis month for the second primary cancer. Since SEER registries do not capture the date of surgery, the date of a patient's first mastectomy occurring more than 180 days after the primary breast cancer was used for women who were identified as having a second breast cancer based on the surgical procedure in SEER (n=161). For women who were identified as having a second breast cancer based on two visits with a code for a secondary malignant neoplasm within a 60-day period occurring more than 365 days after the primary breast cancer, the date of her second visit was used as the date of the second breast cancer event.

Additional covariates. We examined numerous variables that could potentially be associated with breast MRI receipt and confound the relationship between breast MRI and surgical outcomes. We included a variable for tumor histology (ductal, lobular, mixed ductal lobular, and other) because research has shown that lobular tumors are more likely to be mammographically occult and, thus, patients may be more likely to receive and/or benefit

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more from breast MRI.[52] Tumor characteristics examined included grade (well, moderately, poorly/undifferentiated, and undetermined), tumor size (≤ 2cm vs. > 2cm & ≤ 5cm), any node positivity (yes vs. no), and hormone receptor status identified from SEER data (positive [ER+/PR+, ER+/PR-, ER+/no PR data, ER-/PR+, or no ER data/PR+], negative, unknown). We used the NCI Combined Comorbidity Index method to address competing health demands and risks of complications that may have affected treatment selection (0, 0-1, >1).[53] Demographic characteristics examined included age group at diagnosis (in five-year intervals), marital status (married vs. unmarried), race (white vs. nonwhite), and SEER region. We evaluated two measures to represent socio-economic status, quartiles of median household income in county of residence, and a person-level indicator for Medicare state buy-in coverage (yes vs. no), and retained the stronger predictor in the final model.

We examined surgical facility characteristics that could be associated with breast MRI receipt and affect surgical outcomes. We identified the facility where the first surgical procedure took place and linked it to the NCI hospital file, which included measures for whether or not the organization was a teaching hospital (yes vs. no), was a designated NCI Cancer Center (yes vs. no), and had on-site radiation facilities (yes vs. no). We constructed a variable for whether or not the facility was affiliated (yes vs. no) with NCI Cooperative Groups having breast cancer research portfolios, including the American College of Surgeons Oncology Group (ACOSOG), Eastern Cooperative Oncology Group (ECOG), Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), and National Surgical Adjuvant Breast and Bowel Project (NSABP).[54] We also controlled for facility ownership type (for-profit vs. not-for-profit) and breast cancer surgical volume (low volume vs. high volume).

For the re-excision analysis, because having a biopsy prior to surgery may indicate improved surgical planning and may be associated a lower likelihood of a re-excision,[38,55-57] we considered including an indicator for whether or not the patient had a biopsy before her

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first surgical procedure. However, because guidelines recommend that all suspicious MRI findings be biopsied,[58] there is some concern that biopsy may be a mediating rather than a confounding variable. Thus, we explored whether to include a biopsy indicator in the model generating propensity scores (MRI OR 1.04, 95% CI [0.85,1.26]), in the second model examining the likelihood of a re-excision (MRI OR 01.08, 95% CI [0.89,1.31]) or omit the indicator from both models (MRI OR 0.93, 95% CI [0.78,1.11]). Since all models were qualitatively similar, we chose to consider biopsy a confounding variable and included it in the model to generate propensity scores.

For the second breast cancer event analysis, we included treatment variables that have been found to reduce the likelihood of a second breast cancer event. The indicators included whether or not the patient received chemotherapy and radiation as indicated in the Medicare claims (Appendix Table B.2). We also considered including whether the patient's most extensive surgery was a breast excision, partial mastectomy, or mastectomy. Based on the results in Chapter 4: Aim I, the type of initial surgery is a mediator and was not included in the model to generate propensity scores but instead, was included in the second model examining the second breast cancer event even though the effect on breast MRI was quantitatively similar regardless of when it was included in the propensity score model (HR: 1.32, 95% CI: [1.07,1.62]). It is worth noting that we were unable to control for oral hormone therapy receipt because it was not included in the Medicare database over the entire time period. However, as mentioned above, we included each patient's hormone receptor status as a proxy.

Statistical Analyses

We compared unadjusted baseline characteristics between the group of patients with and without a preoperative breast MRI using the Pearson chi-squared test for categorical variables and Student's t-test for continuous variables. We used multivariate logistic

regression to estimate the association of each covariate on the likelihood of receiving a breast MRI. We calculated odds ratios, 95% confidence intervals (CI), and two-sided p-values for each predictor.

Propensity score methods. Because elderly women who receive a preoperative breast MRI may differ systematically from women who do not, we used propensity score methods[59] to balance the groups of women with and without breast MRI on measured covariates and to control for potential confounders. Numerous studies have previously used propensity score methods to examine SEER-Medicare data.[60-64]

We used multivariate logistic regression to determine each patient's propensity for receipt of preoperative breast MRI on the basis of observed patient and hospital characteristics.[59] This process generated each patient's likelihood of breast MRI receipt based on the included covariates or, in other words, each patient's propensity score. Variables were selected based on their hypothesized relationship with breast MRI receipt and the outcome (either a re-excision or second breast cancer event).[65]

Inverse probability weighting (IPW) was used to account for measured baseline differences between the group that received a breast MRI and the group that did not.[66,67] Each patient with a breast MRI was weighted by the inverse of the probability that she would be selected for a breast MRI based on her covariates, and each patient without a breast MRI was weighted by the inverse of the probability that she would not have a breast MRI. We then stabilized these weights by multiplying the inverse probability weights by the marginal prevalence of the breast MRI receipt.[68,69]

We assessed the performance of the propensity model by examining the distribution of covariates and propensity scores between the two groups (MRI vs. no MRI), examining balance by decile of propensity score.[70] Additionally, we calculated the change in standardized difference for each variable before and after inverse probability weighting.[71] We examined excluding patients with non-overlapping propensity score distributions (i.e.,

women without a preoperative breast MRI who had a propensity score higher than the maximum or lower than the minimum propensity score of women with preoperative breast MRI).[70,66] To reduce bias due to unmeasured confounders, we also assessed asymmetrically trimming patients who were treated most contrary to prediction.[68] We examined trimming patients at three different cut points corresponding to the 1st and 99th percentiles, the 2.5th and 97.5[th] percentiles, and the 5th and 95th percentiles at the tails of the propensity score distribution in the treated (i.e., breast MRI) and untreated (i.e., no breast MRI) patients, respectively.

Analytic Approach. In our first analysis estimating the likelihood of a re-excision, we used multivariate logistic regression weighted with the inverse probability weights and robust standard errors.[66,72] Wald tests and 95% confidence intervals were used to examine the difference in the likelihood of a re-excision between those women with and without a breast MRI.

In the second analysis examining a second breast cancer event, we calculated the likelihood of a second breast cancer event within one, three, and five years after diagnosis. In these analyses, we used logistic regression using inverse probability weighting and robust standard errors. [66,72] Patients who had incomplete follow-up for each time period were excluded from each time period's respective analysis. We used a liberal definition to define women eligible for a second breast cancer event and included women who died before they experienced a second breast cancer event. We included these women because it is unlikely that many of them would have actually experienced a second breast cancer event had they lived (between 3-7%).[73] Results were quantitatively similar, however, when we explored using a more conservative definition of a second breast cancer event and excluded those women who died before one (MRI OR: 2.10, 95% CI:[1.52, 2.89]; n=23,907), three (MRI OR: 1.35, 95% CI:[1.06, 1.72]; n=17,696), and five years (MRI OR: 1.27, 95% CI:[0.95, 1.69];

n=7,115). This definition was more conservative because we included only women for which we could observe a second breast cancer event.

We estimated hazard ratios using the Cox proportional-hazards model,[74] generating unadjusted estimates and estimates: (a) adjusted for covariates; and (b) adjusted using inverse-probability weighting.[74-76] Women without a second breast cancer event who were alive at the end of follow-up or who died were censored at the end of follow-up (December 31, 2009) or their date of death. We evaluated the proportional hazards assumption by graphical methods using Schoenfeld residuals[77] and did not find any clear violations of the proportional hazard assumption. We estimated unadjusted survival curves using the Kaplan-Meier method[56] and adjusted survival curves using the inverse-probability weighting approach from Cole and Hernan.[75]

Diagnostic and procedure codes were identified and verified using medical literature, coding experts, EpiCoder (Yost Engineering Inc., Ohio), and the Integrated Cancer Information and Surveillance System coding references.[78] Analyses were performed using Stata version 12.0 (Stata Corporation, College Station, Texas). All tests were conducted using a minimum significance level of 0.05.

Results

Characteristics of the study population. Of the 39,652 women diagnosed with their first primary breast cancer in the SEER-Medicare dataset between 2004 and 2007, 24,438 women were included in our analysis examining second breast cancer events (Figure 5.1) and 17,199 women were identified as eligible for re-excision. Baseline characteristics for both samples were similar (Tables 5.1 and 5.2) with 11.6% of women receiving a preoperative breast MRI in the re-excision analysis and 11.9% in the second breast cancer event analysis. In the unadjusted bivariate analysis, women who received a

breast MRI differed significantly from women who did not on all baseline characteristics (except lymph node involvement and race in the second breast cancer event analysis).

In the multivariate logistic regression predicting MRI receipt to generate propensity scores (Appendix Table B.3), younger age, more recent diagnosis, fewer comorbidities, and SEER region were significant predictors of MRI receipt. Women with lobular carcinomas were more likely to have received a breast MRI when compared to women diagnosed with ductal carcinomas. Women living in areas with fewer high school graduates and not covered by Medicare state-buy-in supplemental insurance were significantly more likely to have a breast MRI. Women having their surgeries at facilities that were affiliated with cooperative groups and a high surgical volume had significantly increased odds of receiving a breast MRI. In the re-excision analysis, women with a biopsy before their first surgical procedure and a breast excision instead of a partial mastectomy as their first surgical procedure were more likely to have had a breast MRI. In the analysis examining second breast cancer events, women who received chemotherapy were more likely to have had a breast MRI.

After adjustment using inverse probability weighting, the observed clinical, socio-demographic, and surgical facility variables were well balanced (Tables 5.1 and 5.2). In all analyses, adjusting for the propensity scores demonstrated substantial improvement in covariate balance across the groups with and without breast MRI. In both samples in our final analysis, adjusting for the propensity scores reduced standardized differences (Appendix Figures B.1 and B.2) for all observed covariates below the threshold of 10% in absolute value, demonstrating substantial improvement in covariate balance across the groups with and without breast MRI.[79] In all analyses, excluding patients with non-overlapping propensity scores or trimming patients at the three different cut points did not change the significance of our estimates, and only attenuated the effect of breast MRI slightly (See Appendix Table D.3 and D.4). Thus, we report the results without trimming. Figure 5.4 shows the propensity score distribution of the samples in our analyses.

Re-excisions*.* Overall, 33.6% of women had a re-excision after their first surgical procedure, which included 34.2% of women without a breast MRI and 29.2% of women with a breast MRI (p<0.001). For all models adjusted for covariates or using propensity score methods in our main analysis (Table 5.3), the likelihood of a re-excision after BCS was comparable for those women with and without preoperative breast MRI (IPW model: OR: 1.11; 95% CI: 0.92, 1.35). In our sub-analysis examining the likelihood of a re-excision after partial mastectomy (Table 5.4), the association between breast MRI and the likelihood of a re-excision was also found to be non-significant (IPW model: OR: 0.67; 95% CI: 0.78, 1.27).

Second breast cancer events*.* Our median follow-up time from first suspected breast disorder to study end or death was 3.9 years (interquartile range [IQR]: 2.86-4.99) for the group without breast MRI and 3.32 years (IQR: 2.63-4.35) for the group with breast MRI. We identified a second breast cancer event in 11.9% of women in our sample. Of the women in the group without a breast MRI, 9.4% had a second breast cancer event compared to 11.0% in the group with an MRI (p<0.001). Across all models adjusting for covariates or using propensity score methods (Table 5.5), breast MRI receipt was significantly associated with a second breast cancer event. The unadjusted and adjusted time to event curves are presented in Figure 5.5. In the hazard model using IPW, women with a breast MRI were associated with an increased hazard of a second breast cancer event compared to those without a breast MRI (Hazard ratio [HR]: 1.37 95% CI: 1.11, 1.68). In the logistic regressions using IPW to examine the likelihood of a second breast cancer event (Table 5.5), women with breast MRI were more likely to experience a second breast cancer event within one year (OR: 2.13; 95% CI: [1.54, 2.94]), three years (OR: 1.43; 95% CI: [1.12, 1.82]) and five years (OR: 1.57; 95% CI: [1.20, 2.07]) than women without a breast MRI.

Discussion

In this large, population-based observational study of elderly women with breast cancer, we found that preoperative breast MRI was not significantly associated with a reduction in the likelihood of a re-excision after breast conserving surgery and was associated with an increased hazard of a second breast cancer. Because baseline characteristics for the group of patients who received a breast MRI differed from those who did not receive a breast MRI, we used multiple multivariable regression modeling techniques and propensity score adjustments to balance the two groups on these observed characteristics. Across all multivariable models and differing propensity score method adjustments, the association between breast MRI and re-excision remained statistically non-significant and, for all models, women who received a preoperative breast MRI were consistently more likely to have a second breast cancer event than those women who did not.

Our findings are largely consistent with previous RCTs and multiple single institution studies reporting that breast MRI did not significantly improve short-term surgical outcomes, such as re-excisions[8,21-23] and recurrence.[8,16] Our findings were discordant with only two small, retrospective studies examining re-excisions[15] and recurrence.[18] However, one of these studies did not adjust for measured confounders[18] and the other was conducted in two institutions in the Netherlands, a population more homogenous and perhaps not generalizable to the US elderly breast cancer population.[15]

Re-excisions after breast conserving surgery are an important surgical outcome. Re-excisions have been found to occur in 17-60%[37,80-84] of women who have already undergone breast conserving surgery, and in our study, we found that 34.4% of patients had a re-excision. Re-excisions have multiple negative consequences, including a worsened cosmetic outcome, delay in adjuvant therapy, increased anxiety, possible increased rates of recurrence, and higher costs associated with the additional treatment.[81,82,85-87] Reoperation

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rates are also an important clinical issue in the elderly population. Operations and reoperations are more problematic for elderly women who more likely have co-morbidities and for whom it is riskier to undergo anesthesia. Furthermore, recovery from surgery is much more difficult for elderly women.

Studies of younger populations of early-stage breast cancer patients have shown that recurrence rates after the completion of adjuvant therapy are between 6–13%,[88-90] and the likelihood of recurrence has been reported to peak within the first five years after primary treatment.[45,46,91] We found that 9.4% of our sample had a second breast cancer event identified from Medicare claims, which is consistent with previous findings. A second breast cancer event is an important, short-term breast cancer outcome because of its effect on overall survival[48] and the physiological and physical distress of additional cancer treatments. Additionally, anxiety from fear of recurrence or a second breast cancer is one of the most prevalent, long-term psychological consequences of breast cancer.[92-94]

The results of this study have two potentially differing interpretations. The first is that women receiving breast MRI were inadequately imaged using conventional assessment (i.e., mammogram and ultrasound) and have higher baseline risk for re-excisions and/or recurrence. In this scenario, the addition of breast MRI improved surgical planning and produced similar re-excision outcomes compared to women who may have been adequately imaged using conventional imaging and had a lower risk of re-excision. The use of MRI did not, however, result in a similar risk of a second breast cancer event since the MRI group had a higher likelihood of such an occurrence. Based on evidence from our study, this scenario may be plausible because women with invasive lobular carcinoma, a histology type that is more prone to multifocal and muticentric disease,[95] mammographically occult tumors,[52,96,97] and higher re-excision rates,[80,98-101] were more likely to receive an MRI compared to women with ductal carcinoma (OR 2.22; 95% CI: [1.89, 2.57]).

The second interpretation of our results is that breast MRI is being overutilized in women who may not benefit from it and, thus, we do not see benefit from its routine use at a population level. Evidence from our study suggests that this scenario may also be plausible because breast MRI is being rapidly adopted (20.5% of the women diagnosed in 2007 from our study sample had received a preoperative breast MRI) and the variability we see by provider and SEER region suggests that it is unlikely that breast MRI's utilization is based solely on whether or not the woman was adequately imaged using conventional assessment. Furthermore, our study focuses on breast cancer in elderly women, a population that is most likely to be adequately imaged by conventional assessment.[102]

We are unable to say definitively which scenario is true based on claims data and, in fact, both scenarios may be happening simultaneously. However, our results provide evidence against the use of breast MRI as a part of routine work-up in the elderly population for either scenario because only certain sub-populations may benefit (first scenario) and there is no evidence of benefit at a population level (second scenario). Future research should endeavor to identify sub-populations that are most likely to benefit and provide guidelines about the appropriate use of breast MRI in elderly breast cancer patients.

In the absence of evidence assessing clinical benefit, it is important to examine potential side effects associated with the use of preoperative breast MRI. Preoperative breast MRIs may contribute to greater use of unnecessary tests and morbidity from diagnostic procedures and initial treatments. Studies have found that breast MRI may be associated with more downstream imaging, such as follow-up ultrasounds, more biopsies, more extensive surgeries, and treatment delay.[1,23,103] Furthermore, it is concerning that women may be electing or surgeons may be recommending more extensive surgery (Chapter 4: Aim I) based on additional lesions detected by MRI that may be adequately managed by radiation and systemic therapy.[10] The increased morbidity that is possibly associated with breast MRI in absence of clinical benefit is troubling as more breast cancer

patients are having comparatively favorable prognoses, and many clinicians are focusing on reducing treatment burden and morbidity.[104]

Limitations

Our study has several limitations. As SEER registries do not capture recurrence, identification of second breast cancer events was limited to our algorithm. The validation study for the algorithm was conducted using a single non-profit, health-care system in a slightly younger population (mean age was 62.8 years compared to 76.1 years in our study). Thus, it is possible that coding practices, care-seeking behaviors, and access to care may differ in our study population when compared to a validated study population and the algorithm might be less sensitive and/ or specific. To analyze this limitation, we also examined models using additional algorithms with a high sensitivity for identifying second breast cancer events (Appendix Figure B.3) to examine whether the association between breast MRI and the likelihood of a second breast cancer event changed, which it did not (results not reported). It is also worth noting that the algorithm we used was not verified to identify the date of the second breast cancer event. However, since women who had a breast MRI were more likely to be diagnosed in recent years, we had a differential follow-up time for the groups with and without breast MRI and were required to establish a date of a second breast cancer recurrence. Despite this limitation, we believe our estimated date of a second breast cancer event is acceptable because when we stratified by year of diagnosis (results not shown), the association between breast MRI and the likelihood of a second breast cancer event was consistent with our reported results. Despite these limitations, we believe the algorithm, validated against medical record review in patients with early-stage invasive breast cancer, is an improvement over previous research examining recurrence with claims data that used a gap in treatment to identify recurrence.[44-46]

Additionally, we were unable to differentiate breast cancer surgeries that were on the ipsilateral versus the contralateral breast due to missing laterality (i.e., side) information. We believe this effect to be small because of the small rate of contralateral breast cancer, estimated to be less than 1% per year,[105] but worth noting because MRI increases the likelihood of contralateral breast cancer detection.[10] We found that the claims data inconsistently reported the laterality of the breast cancer surgical procedure with more than 40% of the surgical claims missing breast laterality. We were uncertain of the direction of the bias that would be introduced if we included only observations with the non-missing laterality information. Not having laterality information affects our estimates of re-excisions because we were unable to discern whether the additional surgery was on the ipsilateral or contralateral breast.

Propensity score methods are only able to balance the groups with and without breast MRI on *observed* characteristics, and any remaining unmeasured confounders associated with our outcomes and/or breast MRI receipt could have influenced our findings. For example, we were unable to adjust the two groups for several re-excision and recurrence risk factors such as multifocal disease, mammographic density and micro-calcifications, and the difference in tumor size between MRI and ultrasonography.[106-108] We were, nevertheless, able to control for tumor grade and histology, age, advanced stage, hormone receptor negative status, and radiation and chemotherapy receipt, which have also been reported as re-excision and/or second breast cancer event risk factors.[46,106] However, our estimates showing that women with a breast MRI have an increased risk of a second breast cancer event indicate that we did not control for all variables confounding the relationship between breast MRI receipt and our outcome of interest because we did not hypothesize that breast MRI may cause an a second breast cancer event. Future research should apply novel statistical methods such as instrumental variable analysis that may more adequately control for unmeasured confounding.

Our study involves the usual limitations of SEER-Medicare data, including concern about the generalizability to all elderly breast cancer patients due to exclusion of patients who are not continuously enrolled in fee-for-service Medicare. Additionally, as in most observational studies, we were unable to directly control for patient preferences, functional status, socioeconomic status, and social support, all of which may be correlated with breast MRI receipt and outcomes. However, we used variables such as the NCI Comorbidity Index, state buy-in coverage, and marriage to mitigate these biases.

Conclusion

Given the persistent finding that breast MRI was not significantly associated with improved short-term outcomes across models and statistical techniques, we believe our study findings contribute to the growing literature about the efficacy and effectiveness of breast MRI. To our knowledge, our study is one of the first to use nationally representative data to investigate the effect of preoperative breast MRI on short-term surgical outcomes in elderly women in the US. Our findings are supported by results from other studies, including two randomized control trials. Proponents for the use of preoperative breast MRI believe that it can improve surgical planning, however, this analysis, along with other studies, show that this assumption may not be the case in the general population. Based on our results, we are unable to suggest the optimum proportion of elderly breast cancer patients that should receive breast MRI. Thus, more research should be conducted to identify sub-populations of breast cancer patients that may have improved short- and long-term benefits from preoperative assessment with MRI. In the absence of evidence suggesting that breast MRI may improve short-term surgical outcomes, the decision whether or not to use the imaging procedure should be based on conversations with informed patients discussing patient preferences and the potential harms and realistic benefits of breast MRI.

Figure 5.1. Inclusion/exclusion schematic

Women diagnosed with their first primary breast cancer in SEER in 2004-2007*
n= 39,652

INCLUDED

EXCLUDED

Known Stage I-IIIA disease, tumor size <5cm, histology codes indicating malignant breast cancer
N=26,751

Stage 0 or IV disease, stage unknown; tumor size greater than 5cm; histology codes indicating in situ/ non-malignant disease or non-breast primary tumors
n=12,901

Able to determine the first definitive surgical treatment and have no prior cancer treatments before surgery
n= 25,669

Medicare claims identified conflicting surgical procedures on the same day; receipt of cancer treatments prior to surgery
n=1,082

Patients with a breast surgical procedure Linkable to their surgical provider
n= 25,038

Unable to link patient to her surgical provider
n= 631

Had a first biopsy or breast surgical procedure within 4 months of SEER diagnosis month
n= 24,439

First breast breast biopsy or surgical procedure claim more than 4 months from SEER diagnosis month
n= 599

Sample for the analysis examining the hazard of a second breast cancer event[†]
n= 24,439
Additional inclusion/ exclusion criteria for the re-excision analysis:

INCLUDED

EXCLUDED

Did not have a second primary cancer identified in SEER
n= 22,348

Had a second primary cancer identified in SEER within 12 months of diagnosis
n= 2,091

Alive 12 months after diagnosis
n= 21,830

Died within 12 months of diagnosis
n= 518

Had breast conserving surgery[‡] as the first surgical procedure
n= 17,199

Had mastectomy as the first surgical procedure
n= 4,631

Sample for the analysis examining the likelihood of a re-excision
n= 17,199

SEER, Surveillance, Epidemiology and End Results

 * Meeting SEER-Medicare inclusion requirements of aged 66 or older at diagnosis, reporting source not autopsy or death certificate, laterality not bilateral or unknown, original reason for Medicare entitlement not disability or end stage renal disease, valid month of diagnosis, no health maintenance organization enrollment during study period, continuous enrollment in Parts A & B during the study period, comorbidity score and was able to be matched to claims during the study period. Study period is defined here as the 12 months prior to diagnosis month till the end of data or death (For more details see Appendix 5.I).

† Note: This was the sample size for the hazard of a second breast cancer event analysis; women were censored (1) at the day of the end of follow-up if they were alive and had yet to experience a second breast cancer event or (2) at their date of death if they died before they experienced a second breast cancer event. In the logistic regressions examining a second breast cancer event at 1, 3, and 5 years, we excluded women who did not have complete follow-up at 3 or 5 years (n=4,617 and 14,161, respectively).

‡ Breast conserving surgery is defined as breast excision or partial/ subtotal mastectomy

Figure 5.2. Patient sample eligible for a re-excision in the main and sub-analyses
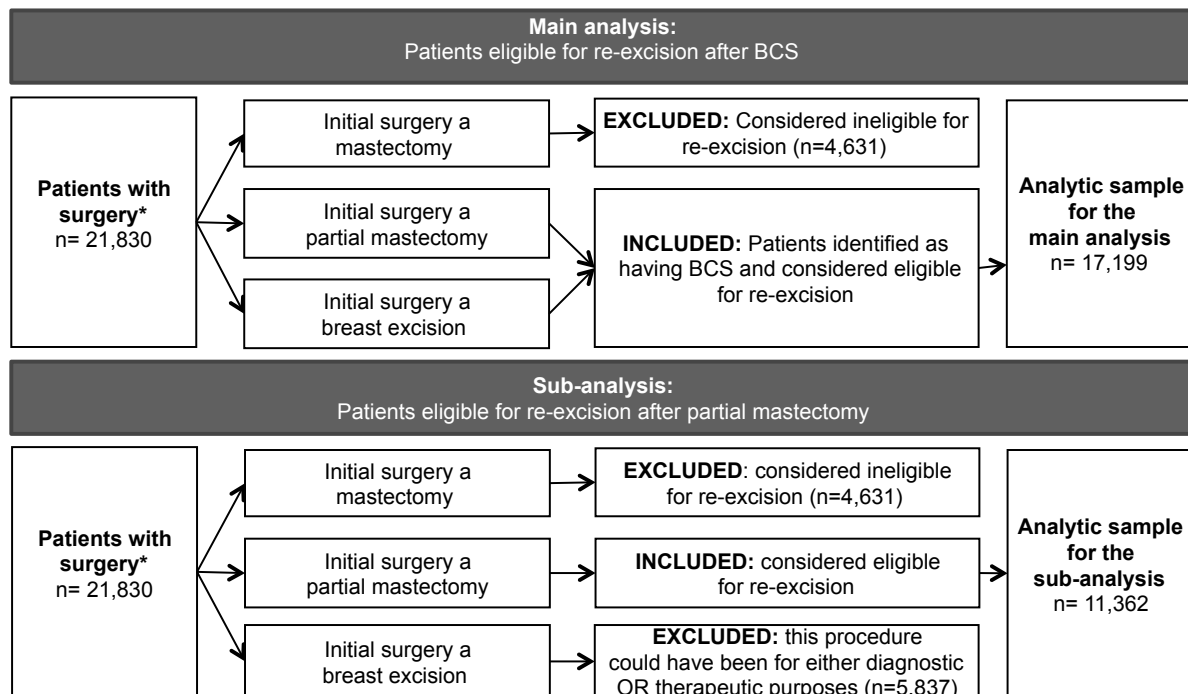
BCS, breast conserving therapy.

* Who meet our inclusion criteria

Figure 5.3. Algorithm for identifying a second breast cancer event

Two visits with a code for a secondary malignant neoplasm within a 60 day period occurring >365 days after the primary breast cancer
(n = 24,439)

No → A second breast cancer record in the SEER registry (n=22,733)

Yes → A non-breast cancer record in the SEER registry after the primary breast cancer (n = 1706)

From "A second breast cancer record in the SEER registry":

No → A mastectomy >180 days after the primary breast cancer (n= 21,974)

Yes → **Second breast cancer event (n=759)**

From "A non-breast cancer record in the SEER registry":

No → **Second breast cancer event (n=1,377)**

Yes → **No second breast cancer event (n=329)**

From "A mastectomy >180 days after the primary breast cancer":

No → **No second breast cancer event (n=21,684)**

Yes → Surgical procedure for the primary breast cancer (SEER registry) (n=290)*

From "Surgical procedure for the primary breast cancer":

Mastectomy → **No second breast cancer event (n=128)**

BCS → **Second breast cancer event (n=161)**

Figure created with permission from Chubak J, Yu O, Pocobelli G, et al: Administrative Data Algorithms to Identify Second Breast Cancer Events Following Early-Stage Invasive Breast Cancer. J Natl Cancer Inst 104:931-940, 2012.

Note: This algorithm was selected due to its estimated high specificity (99%) and positive predictive value (90%). Sensitivity (89%) based on a validation study using a different study population (Chubak et al. 2012). See Appendix 5.VIII for additional algorithms examined.

BCS, breast conserving surgery (i.e. breast excision or partial mastectomy); SEER, Surveillance, Epidemiology and End Results

* One woman did not have a surgery that was either a mastectomy or BCS and was excluded from the analysis, thus, our sample size went from 24,439 to 24,438 based on our definition of recurrence.

Table 5.1. Baseline characteristics of patients for the re-excision analysis (main analysis)

	Unadjusted data				Data adjusted using inverse probability weighting		
	Overall N= 17,199	No breast MRI N= 15,198	Breast MRI N= 2,001	p-value	No breast MRI N=15,045	Breast MRI N= 1,992	p-value
Preoperative breast MRI (%)	11.6	0	100	<0.001			
Re-excision after first surgical procedure	33.6	34.2	29.2	<0.001	33.6	35.7	0.34
Biopsy before first surgical procedure	60.8	58.2	80.3	<0.001	61.2	59.5	0.45
Initial BCS procedure				<0.001			0.16
Partial Mastectomy	66.1	64.4	78.3		66.3	63.3	
Breast Excision	33.9	35.6	21.7		33.7	36.7	
Tumor size (%)				0.04			0.34
≤ 2cm	79.4	79.2	81.1		79.6	81.1	
> 2cm, ≤ 5cm	20.6	20.8	18.9		20.4	18.9	
Tumor grade (%)				<0.001			0.98
Well differentiated	28.2	28	29.7		28.1	27.5	
Moderately differentiated	44.1	43.7	46.7		44.0	44.7	
Poorly differentiated	22.4	22.9	18.7		22.5	22.3	
Grade unknown	5.4	5.5	4.9		5.4	5.5	
Hormone receptor status (%)				0.02			0.19
Positive	81.0	80.7	83.3		81.0	77.5	
Negative	11.8	12	10.5		11.9	14.7	
Unknown	7.2	7.3	6.2		7.1	7.9	
Node positivity (%)	16.5	16.3	17.5	0.17	16.5	17.5	0.50
Histology				<0.001			0.43
Ductal	74.1	74.9	67.9		74.5	73.7	
Lobular	9.4	8.5	15.8		9.1	7.8	
Mixed ductal/lobular	7.8	7.4	10.8		7.8	8.7	
Other	8.7	9.2	5.5		8.6	9.9	
NCI Comorbidity Index (%)				<0.001			0.75
0	65.6	64.5	73.3		65.8	64.7	
Between 0 and 1	27.2	27.8	22.9		27.1	27.4	
Greater than 1	7.3	7.7	3.8		7.1	7.9	
Age at diagnosis (%)				<0.001			0.81
65 to 69	22.2	20.5	35.1		22.0	21.4	
70 to 74	25.6	25.1	29.2		25.9	28.0	
75 to 79	24.1	24.7	19.5		24.3	24.2	
80 to 84	17.6	18.3	11.6		17.6	16.9	
85 and older	10.6	11.4	4.5		10.3	9.6	
Married (%)	47.7	46.7	54.8	<0.001	47.9	46.1	0.38
State buy-in coverage (%)				<0.001			0.61
No	90.6	90	95.1		90.9	91.5	
Yes	9.4	10	4.9		9.1	8.5	
Race (%)				0.13			0.68
White	87.2	87.1	88.3		87.5	88.0	
Non-white	12.8	12.9	11.7		12.5	12.0	
Cooperative group affiliation of surgical facility (%)[†]	51.5	50	63.1	<0.001	51.8	50.3	0.46
NCI affiliation of surgical facility (%)	5.6	5.4	7.5	<0.001	5.6	6.3	0.38

Table 5.1. Baseline characteristics (cont.)

	Unadjusted data				Data adjusted using inverse probability weighting		
	Overall N= 17,199	No breast MRI N= 15,198	Breast MRI N= 2,001	p-value	No breast MRI N=15,045	Breast MRI N= 1,992	p-value
Surgical facility a teaching hospital (or affiliated one)	53.3	52.9	56.5	0.002	53.9	56.6	0.19
Surgical volume of surgical facility (%)				<0.001			0.2
Low	48.6	50.9	30.8		48.4	51.0	
High	51.4	49.1	69.2		51.6	49.0	
Zip code proportion with at least high school education (% in each quartile)				<0.001			0.49
Low education	25.5	24.0	37.1		25.5	24.2	
Low-medium education	24.4	24.1	26.4		24.7	26.4	
Medium-high education	23.6	23.9	20.9		23.5	21.2	
High education	22.6	24.0	11.8		22.3	23.4	
Unknown education	3.9	3.9	3.8		4.0	4.8	
Year of diagnosis (%)				<0.001			0.78
2004	24.6	26.3	11.5		24.3	22.8	
2005	24.2	25.1	16.9		24.4	25.0	
2006	25.6	25.4	26.9		26.0	25.5	
2007	25.6	23.1	44.6		25.4	26.6	
SEER Region (%)				<0.001			0.57
California registries	32.9	31.9	40.6		33.3	32.0	
Northeast registries	25	24.5	28.6		25.5	28.4	
Georgia	3.2	3.3	2.4		3.3	2.6	
Detroit	7.3	7.6	5.1		7.5	7.2	
Iowa	6.4	6.9	2.5		6.4	6.0	
New Mexico	2.1	1.8	4.5		2.0	1.3	
Seattle	6.1	5.6	10.2		6.0	6.2	
Utah	2.6	2.7	2.1		2.7	2.1	
Kentucky	6.8	7.4	1.6		6.3	7.5	
Louisiana	6.2	6.7	2		6.1	5.0	
Hawaii	1.4	1.5	0.1		1.1	1.7	

p-values by t-test for continuous variables and chi2 test for binary / categorical variables, Mean (Standard Deviation) or %

BCS, breast conserving surgery; MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute

[†] NCI Cooperative Groups having breast cancer research portfolios

Table 5.2. Baseline characteristics of patients for the second breast cancer event analysis

		Unadjusted data			Data adjusted using inverse probability weighting[†]		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= 24,438	N= 21,521	N= 2,917		N= 21,3521	N= 2,917	
Preoperative breast MRI (%)	11.9	0.0	100.0	<0.001			
Second breast cancer event	9.4	9.2	11.0	0.001	9.1	12.3	0.002
Time to second breast event (years)	1.8 (1.4)	1.9 (1.4)	1.3 (1.3)	<0.001	1.8 (1.4)	1.8 (1.6)	0.82
Most extensive surgery*				<0.001			0.005
Breast excision	10.0	10.6	5.5		10.3	7.3	
Partial mastectomy	56.2	55.4	62.3		56.7	56.3	
Mastectomy	33.8	34.0	32.2		33.0	36.4	
Received radiation	51.9	50.5	62.4	<0.001	52.2	54.3	0.24
Received chemotherapy	20.6	19.9	26.1	<0.001	20.7	20.6	0.92
Tumor size (%)				0.004			0.02
≤ 2cm	72.9	72.6	75.1		73.0	76.1	
> 2cm, ≤ 5cm	27.1	27.4	24.9		27.0	23.9	
Tumor grade (%)				<0.001			0.68
Well differentiated	26.3	26.1	27.9		26.3	25.8	
Moderately differentiated	43.8	43.4	46.7		43.9	43.5	
Poorly differentiated	24.5	25.0	20.4		24.4	24.2	
Grade unknown	5.4	5.4	5.0		5.4	6.5	
Hormone receptor status (%)				0.004			0.52
Positive	78.9	78.6	81.0		79.0	77.1	
Negative	13.0	13.1	12.3		13.0	13.7	
Unknown	8.1	8.2	6.7		8.0	9.2	
Node positivity (%)	20.6	20.4	21.8	0.08	20.5	20.3	0.84
Histology				<0.001			0.41
Ductal	73.9	74.9	66.7		73.9	72.9	
Lobular	9.7	8.9	16.0		9.8	8.7	
Mixed ductal/lobular	8.0	7.4	12.2		8.0	8.7	
Other	8.3	8.8	5.1		8.3	9.6	
NCI Comorbidity Index (%)				<0.001			0.42
0	63.6	62.3	73.3		63.9	61.4	
Between 0 and 1	27.9	28.6	22.9		27.9	30.2	
Greater than 1	8.5	9.1	3.8		8.3	8.4	
Age at diagnosis (%)				<0.001			0.93
65 to 69	20.5	18.7	33.8		20.6	20.4	
70 to 74	24.7	24.0	29.6		24.8	25.8	
75 to 79	24.1	24.6	20.6		24.3	24.1	
80 to 84	18.8	19.7	11.7		18.8	17.9	
85 and older	12.0	13.0	4.3		11.6	11.7	
Married (%)	45.8	44.6	54.8	<0.001	45.9	45.3	0.70
State buy-in coverage (%)				<0.001			0.49
No	89.3	88.5	94.9		89.5	90.3	
Yes	10.7	11.5	5.1		10.5	9.7	
Race (%)				<0.001			0.47
White	87.0	86.7	88.9		87.1	87.9	
Non-white	13.0	13.3	11.1		12.9	12.1	

Table 5.2. Baseline characteristics of patients for the second breast cancer event analysis (cont.)

	Unadjusted data				Data adjusted using inverse probability weighting[†]		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= 24,438	N= 21,521	N= 2,917		N= 21,3521	N= 2,917	
Cooperative group affiliation of surgical facility (%)[†]	51.0	49.3	63.1	<0.001	51.2	49.8	0.42
NCI affiliation of surgical facility (%)	5.2	4.9	7.1	<0.001	5.3	5.4	0.85
Surgical facility a teaching hospital (or affiliated one, %)	52.4	51.8	56.5	<0.001	52.8	54.7	0.28
Surgical volume of surgical facility (%)				<0.001			0.44
Low	49.8	52.2	32.0		49.5	50.9	
High	50.2	47.8	68.0		50.5	49.1	
Zip code proportion with at least high school education (% in each quartile)				<0.001			0.48
Low education	24.6	22.9	37.4		24.7	24.0	
Low-medium education	24.0	23.9	25.3		24.2	24.9	
Medium-high education	23.6	24.0	20.6		23.6	21.7	
High education	23.7	25.3	12.3		23.5	24.9	
Unknown education	4.0	3.9	4.3		4.0	4.6	
Year of diagnosis (%)				<0.001			0.17
2004	25.2	27.0	11.8		24.9	22.0	
2005	24.6	25.5	17.8		24.6	25.6	
2006	24.9	24.6	27.1		25.0	24.5	
2007	25.3	22.8	43.4		25.5	27.9	
SEER Region (%)				<0.001			0.59
California registries	32.3	31.4	39.5		32.5	31.1	
Northeast registries	23.3	22.7	27.4		23.5	26.4	
Georgia	3.3	3.3	2.8		3.3	2.5	
Detroit	6.9	7.1	5.0		6.9	6.8	
Iowa	7.4	8.0	2.8		7.3	7.4	
New Mexico	2.1	1.8	4.3		2.0	1.7	
Seattle	6.3	5.7	11.2		6.4	6.7	
Utah	2.7	2.8	2.3		2.8	2.0	
Kentucky	7.6	8.3	2.5		7.4	8.2	
Louisiana	6.9	7.5	2.2		6.8	5.8	
Hawaii	1.2	1.4	0.2		1.1	1.4	

P-values by t-test for continuous variables and chi2 test for binary / categorical variables, Mear (Standard Deviation) or %

BCS, breast conserving surgery; MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute

[*] Variable not included in model generating inverse probability weights

[†] NCI Cooperative Groups having breast cancer research portfolios

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Figure 5.4a. Breast MRI propensity score distribution for the analysis examining re-excisions (n=17,199)

Propensity Score Distribution
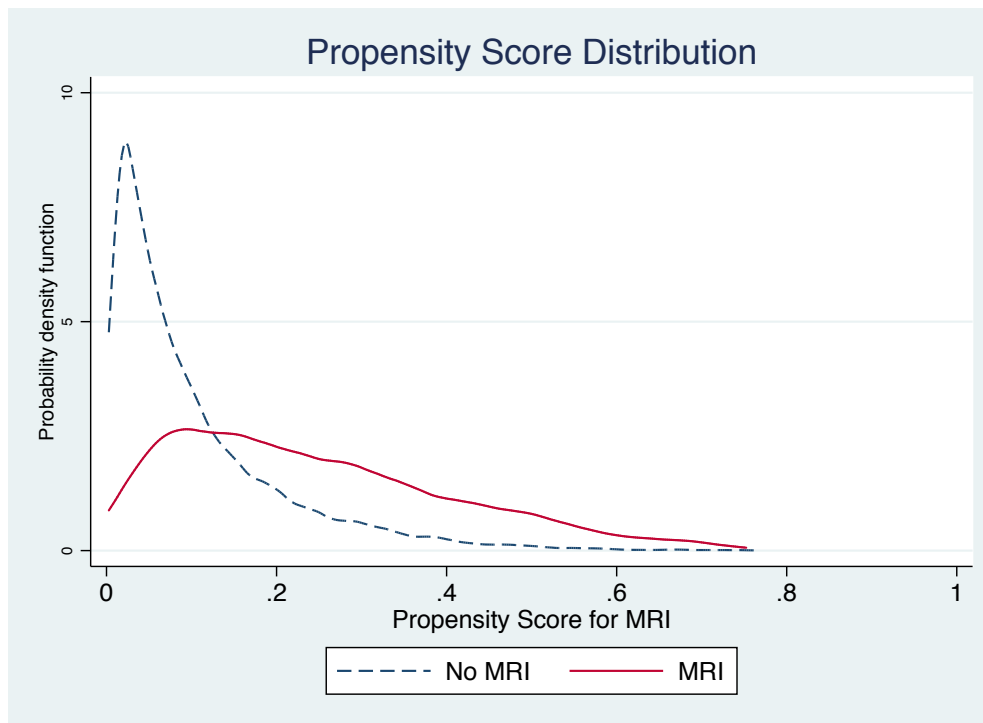
Figure 5.4b. Breast MRI propensity score distribution for the analysis examining second breast cancer events (n=24,438)

Propensity Score Distribution
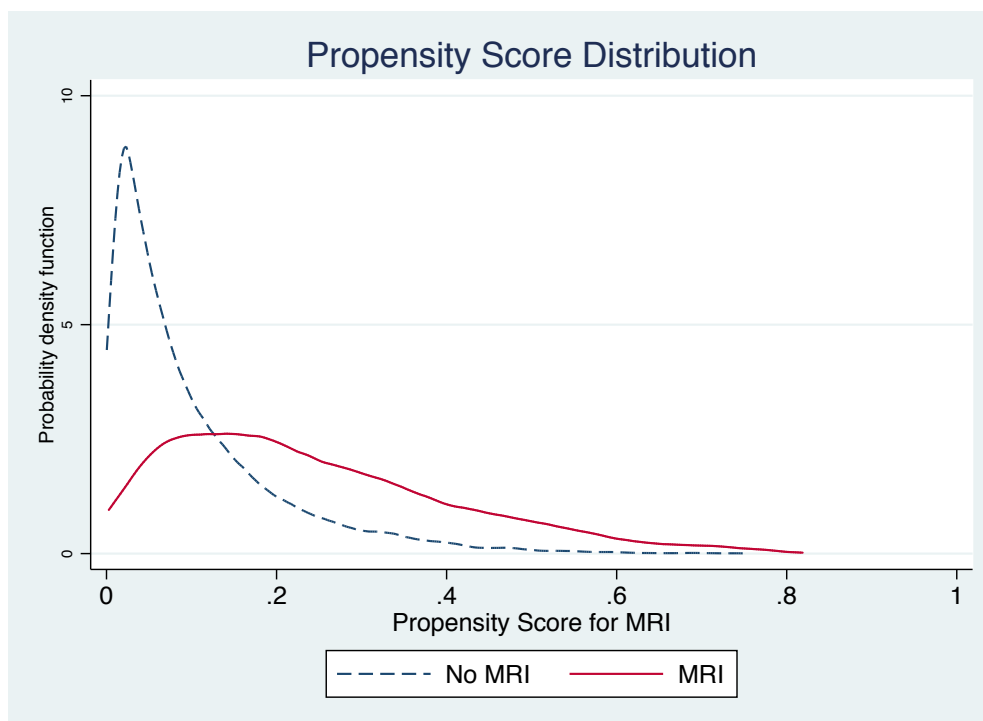
Table 5.3. Impact of preoperative breast MRI on the likelihood of a re-excision after BCS (main analysis, n=17,199)

	Odds ratio	95% Conf. Interval	n
Unadjusted logistic regression	0.80***	[0.72, 0.88]	17,199
Logistic regression adjusted for covariates[†]	1.04	[0.93, 1.17]	17,199
Logistic regression using IPW[‡]	1.11	[0.92, 1.35]	17,199

* p<0.05, ** p<0.01, *** p<0.001
BCS, breast conserving surgery (i.e., breast excision or partial mastectomy) MRI, Magnetic Resonance Imaging;
  IPW, Inverse probability weighting
[†] See Appendix Table B.4 for the coefficients of the additional included variables
[‡] Robust standard errors

Table 5.4. Impact of preoperative breast MRI on the likelihood of a re-excision after partial mastectomy (sub-analysis, n=11,362)

	Odds ratio	95% Conf. Interval	n
Unadjusted logistic regression	1.01	[0.88, 1.16]	11,362
Logistic regression adjusted for covariates[†]	0.92	[0.79, 1.07]	11,362
Logistic regression using IPW[‡]	0.67	[0.78, 1.47]	11,362

* p<0.05, ** p<0.01, *** p<0.001
MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting
† See Appendix Table B.7 for the coefficients for the additional covariates
[‡] Robust standard errors

Table 5.5. Association between breast MRI and a second breast cancer event

	Hazard/ odds ratio	95% Conf. Interval	n
Hazard of a second breast cancer event			
Unadjusted proportional hazard model	1.31***	[1.17, 1.48]	24,438
Proportional hazard model adjusted for covariates[†]	1.29***	[1.14, 1.46]	24,438
Proportional hazard model with IPW	1.37***	[1.11, 1.68]	24,438
Proportional hazard model with IPW, adjusted for the first surgical treatment after estimating the IPW[†]	1.32**	[1.07, 1.63]	24,438
Likelihood of a second breast cancer event within 1 year[§]			
Unadjusted logistic regression	2.39***	[1.99, 2.86]	24,438
Logistic regression adjusted for covariates[‡]	2.16***	[1.76, 2.64]	24,438
Logistic regression using IPW	2.13***	[1.54, 2.94]	24,438
Logistic regression using IPW, adjusted for the first surgical treatment after estimating the IPW	2.07***	[1.51, 2.84]	24,438
Likelihood of a second breast cancer event within 3 years[§]			
Unadjusted logistic regression	1.74***	[1.50, 2.01]	19,821
Logistic regression adjusted for covariates[‡]	1.66***	[1.42, 1.95]	19,821
Logistic regression using IPW	1.43**	[1.12, 1.82]	19,821
Logistic regression using IPW, adjusted for the complete treatment after estimating the IPW	1.39**	[1.10, 1.76]	19,821
Likelihood of a second breast cancer event within 5 years[§]			
Unadjusted logistic regression	2.86***	[2.44, 3.36]	10,278
Logistic regression adjusted for covariates[‡]	2.11***	[1.77, 2.52]	10,278
Logistic regression using IPW	1.57**	[1.20, 2.07]	10,278
Logistic regression using IPW, adjusted for the complete treatment after estimating the IPW	1.57**	[1.20, 2.05]	10,278

Note: IPW analyses use robust standard errors
* p<0.05, ** p<0.01, *** p<0.001"
MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting
[†] See Appendix Table B.5 for the coefficients for the additional covariates
[‡] See Appendix Table B.5 for covariates included in the models (coefficients not reported).
[§] Sample size reflects excluding due to limited follow-up. We excluded women who did not have complete follow-up at 3 (n=4,617) or 5 years (n=14,160).

Figure 5.5. Rates of second breast cancer events in populations with and without preoperative breast MRI, unadjusted vs. adjusted with the use of inverse probability weighting
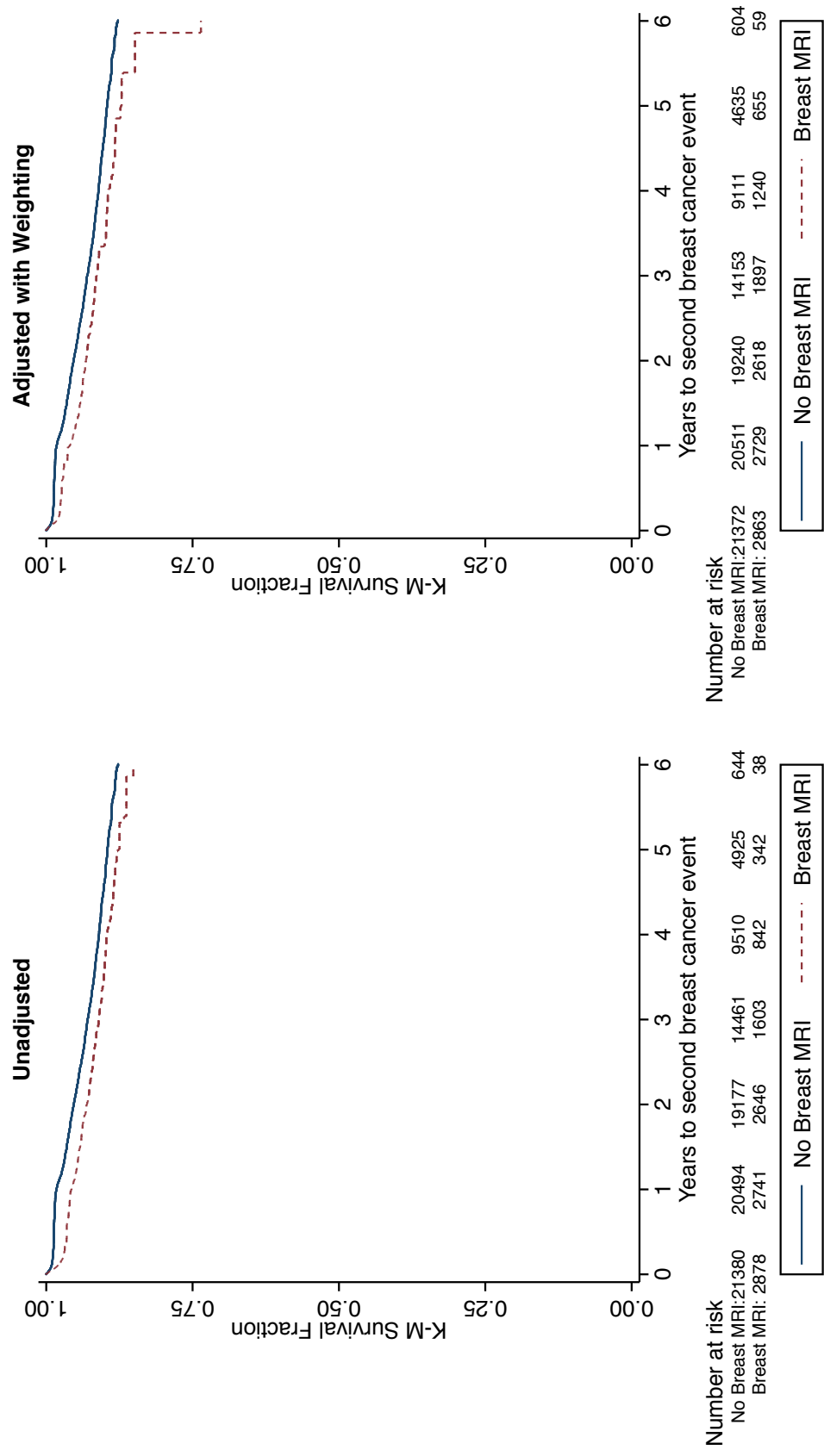
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CHAPTER 6: ESTIMATING THE COSTS OF INITIAL CANCER TREATMENT RELATED TO PREOPERATIVE BREAST MRI IN ELDERLY BREAST CANCER PATIENTS

Overview

Background: The cost of breast cancer care is escalating. Evidence suggests that growing breast cancer prevalence, changing treatment patterns, and use of advanced imaging are all contributing to the increasing cost burden. Research has shown that preoperative breast magnetic resonance imaging (MRI), an advanced imaging procedure being adopted rapidly, may change treatment patterns through additional diagnostic work-up and an increased likelihood of more extensive surgery. However, to date, there is a dearth of literature examining the cost associated with breast preoperative MRI in the United States. The goal of this analysis was to estimate the costs associated with breast MRI for elderly breast cancer patients in the United States from the perspective of Medicare.

In this large, population-based, observational study, we identified women diagnosed between 2004-2007 with early-stage (I-IIB), operable breast cancer from the Surveillance, Epidemiology, and End Results-Medicare dataset. Using claims from 2004 through 2009, we identified Medicare payments during the initial treatment phase, which included the diagnostic, preoperative, surgical, and adjuvant therapy stages of care. For women with and without a preoperative breast MRI, we examined unadjusted total all-cause and breast cancer-attributable Medicare payments per-patient during the initial treatment phase. Further, we used generalized linear models to estimate the adjusted multiplicative and marginal effects of preoperative breast MRI on all-cause or breast cancer-attributable Medicare payments.

Of the 22,974 women included in our sample, twelve percent (n=2,751) had a preoperative breast MRI. Women with breast MRI, on average, had higher unadjusted, per-person Medicare payments than those without MRI during the initial treatment phase, which lasted an average of 4.9 months. The average all-cause Medicare payment was $23,683—$22,987 for the non-MRI group and $28,795 for the MRI group (p-value <0.001). The average per-patient, breast cancer-attributable payment was $19,749, $19,025 for the non-MRI group and $25,075 for the MRI group (p-value <0.001). In our multivariate models, we found that preoperative breast MRI was associated with 10%-higher all-cause payments [95% CI: (1.08, 1.13)] and 14%-greater breast cancer-attributable payments [95% CI: (1.12, 1.16)] during the initial treatment phase. The average marginal effect of breast MRI was $2,348 for all-cause payments and $2,619 for breast cancer-attributable payments [95% CI: ($1,771, $2,924), ($2,208, $3,030)]. Payments not attributable to breast cancer during the initial treatment phase did not significantly differ by MRI receipt

The additional cost to Medicare associated with breast MRI should be evaluated in concert with preoperative breast MRI effectiveness data to inform policy makers about the value of breast MRI in the elderly breast cancer population.

Introduction

Breast cancer is the most common cancer among women, with an estimated 3.5 million breast cancer survivors in the US as of 2020. Its prevalence is expected to grow to 4.5 million by 2010.[1] With an estimated $16.5 billion spent nationally on breast cancer, it is the most expensive cancer site with costs comprising 13.3% of total healthcare spending on cancer. Based on US population changes alone, it has been estimated that national expenditures for breast cancer will increase by 24.2% and reach $20.5 billion by 2020.[1] Spending on breast cancer is not only growing due to increased prevalence, but also due to escalating treatment costs per-patient. [2-4] It has been estimated that the inflation-adjusted

cost of the initial phase of care for each breast cancer patient increased by 25% from $16,775 in 1991 to $20,964 in 2002.[5]

Given the increasing cost burden of breast cancer, it is important to examine what factors drive the cost of breast cancer care. The rising cost of breast cancer treatment has been attributed to changes in treatment patterns and to the increased use of targeted therapies and supportive medicine.[2-4] Additionally, it has been estimated that the growing use of advanced imaging contributes to the accelerating cost, which are increasing at a greater rate than the total costs among Medicare beneficiaries with cancer.[6,7]

Breast magnetic resonance imaging (MRI) is an example of an advanced imaging modality that is being rapidly adopted.[6,8-20] The percentage of elderly breast cancer patients with preoperative breast MRI increased from 1.2% in 2002 to 18.8% in 2007.[17] However, evidence suggests that breast MRI may not be associated with improved outcomes, such as fewer reoperations[21-26] or lower recurrence rates[10,20,24-27] (see results from Chapter 5). Preoperative breast MRI is used in addition to conventional assessment (i.e., mammogram and ultrasound, as needed)[27] to measure the extent of disease as a part of surgical planning in women with newly diagnosed breast cancer. It is worth noting that, breast MRI is used for other, non-preoperative indications such as to screen high risk women [16,27-34] or to monitor responses to neoadjuvant therapy;[35-41] however, these uses are not the focus of the present study.

Research has shown that preoperative breast MRI may change treatment patterns in ways that can affect the cost of the initial treatment phase. First, breast MRI has been associated with additional diagnostic procedures, such as second-look ultrasounds and MR- or ultrasound-guided biopsies,[25,42,43] which is consistent with guidelines recommending that suspicious lesions identified on breast MRI should be pathologically confirmed with a biopsy.[27,36,44,45] As well, evidence suggests that breast MRI is associated with an increased likelihood of a mastectomy as the first surgical procedure[21-25] (Chapter 4), a more extensive

and expensive surgery compared to breast conserving surgery (BCS). Additionally, one of the purported benefits of breast MRI is that it improves surgical planning and reduces the likelihood of re-excision; however, research has shown that women with and without a preoperative breast MRI have a similar likelihood of re-excision[21-26] (Chapter 5), suggesting that there will be no difference in costs for re-excision for women with and without preoperative breast MRI.

To our knowledge, no study has examined the association between breast MRI and the cost of initial treatment in the United States. The only study to examine the cost of breast MRI is a randomized controlled trial conducted in the United Kingdom,[46] which found a small difference in cost between women who received breast MRI and those women who did not (£5,508 compared with £5,214). After controlling for other covariates, however, this difference was not statistically significant. However, because breast cancer treatment patterns, payment structures, and decision-making factors are different in the United States compared to the United Kingdom,[47-51] it is important that the cost of breast MRI be examined in the United States.

The purpose of this analysis was to estimate the costs associated with preoperative breast MRI during the initial treatment phase for elderly breast cancer patients. Using Medicare claims from 2004 through 2009, we identified all-cause and breast cancer-attributable Medicare payments during the initial treatment phase (mean 4.9 months), which we defined to include the diagnostic, preoperative, surgical, and adjuvant therapy stages of care (See Table 6.1). We compared unadjusted all-cause and breast cancer-attributable payments during the initial treatment phase for women with and without preoperative breast MRI. Further, we used multivariate generalized linear models to generate the adjusted multiplicative and marginal effects of preoperative breast MRI on all-cause and breast cancer-attributable Medicare payments. We hypothesized that breast MRI would be associated with increased costs to Medicare in the initial treatment phase due to the

additional cost of the procedure itself, along with its association with supplementary

diagnostic work-up and more extensive surgeries.

Methods

Data

We used the SEER-Medicare dataset to conduct this retrospective study. The SEER-

Medicare dataset links 17 population-based cancer registries across the United States to

Medicare administrative data and healthcare claims.[52] The SEER registries cover

approximately 25% of the incident US cancer population. The SEER-Medicare dataset is

comparable to the overall US population with regard to measures of poverty and

education.[52] SEER registry data capture demographic and incident cancer characteristics,

including stage, grade, and histology as well as treatment information and vital statistics.[53]

The SEER data also contain ecological measures of income, education, and other

characteristics at each patient's census tract and zip code of residence. The Medicare data

cover claims for hospital services, physician services, some drug therapy, and other medical

services. Medicare data include information about the use and cost of health care services

and co-morbid health conditions. The National Cancer Institute (NCI) hospital file contains

hospital-level information, including staffing, structure, research network affiliation, and

information on accreditation.

Study Population

The present study included women with a primary diagnosis of unilateral,

pathologically confirmed, stage I-IIB operable breast cancer identified from SEER-Medicare

data (with staging determined by the American Joint Committee on Cancer [AJCC] sixth

edition, International Statistical Classification of Diseases and Related Health Problems, 9th

revision, clinical modification [ICD-9-CM] code 147). Women were included if they were

diagnosed with their first primary breast cancer between January 1, 2004 and December 31,

2007, and had no previous cancers. Focusing on elderly breast cancer patients, we excluded women who were younger than 66 at diagnosis or enrolled in Medicare for renal disease or disability. We also excluded women who were not continuously enrolled in Medicare Part A and Part B, and who were enrolled in a health maintenance organization (HMO) during the study period because these beneficiaries would have incomplete claims in the SEER-Medicare dataset, and we would be unable to examine their healthcare utilization in its entirety. The National Cancer Institute (NCI) comorbidity index[54] was calculated based on 12 months of claims. Thus, women not enrolled 12 months prior to diagnosis were excluded (SEER-Medicare inclusion/exclusion table can be found in Appendix Table C.1).

We limited this analysis to women whose first definitive treatment was surgery, thus excluding women who received neoadjuvant chemotherapy prior to surgery. These women were excluded because breast MRI can also be used to measure tumor response to neoadjuvant chemotherapy,[37-41] which is not the focus of this study. We also excluded patients who had conflicting claims for mastectomy and partial mastectomy on the same day in the Medicare outpatient, inpatient, and physician files. We excluded these women because we were unable to determine the type of initial surgery. We also excluded women who had their first biopsy or breast surgical procedure more than four months before or after the SEER diagnosis month because we were concerned that these surgical claims did not correspond to the first primary breast cancer identified from the SEER registry. We eliminated women who died within 12 months of diagnosis or women who died during treatment because research has shown that healthcare utilization and cost is significantly different in the terminal phase of care than in the initial phase of care,[55-61] which is the focus of the present study. Study inclusion/exclusion criteria are presented in Figure 6.1.

Variables and Measures

We examined all claims during the initial treatment phase (Table 6.1) from 2004 through 2009. The initial treatment phase was defined to capture the diagnostic,

preoperative, and initial treatment stages and to include all costs from when the patient was

first suspected of having breast cancer up through the end of the patient's initial treatment

and lasted an average of 4.9 months. Specifically, the start of the initial treatment phase

began on the date of the first claim for a suspected breast disorder (e.g., lump or mass in

breast, or abnormal mammogram; see Appendix Table C.2 for codes) 12 or fewer months

prior to the SEER diagnosis month. We defined the end of the initial treatment phase as the

last day of breast cancer treatment (i.e., partial mastectomy, mastectomy, radiation, or

chemotherapy; for codes, see Appendix Table C.2) before a treatment gap of more than 90

days,[62-64] the patient's death, or the end of the study period, which was December 31, 2009.

We identified healthcare utilization, breast cancer events, and Medicare payments using the

Medicare outpatient, carrier, and Medicare Provider Analysis And Review (MEDPAR) files

using American Medical Association Current Procedural Terminology (CPT), Healthcare

Common Procedure Classification System (HCPCS) and International Classification of

Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for codes (See Appendix Table

C.2).

Our independent variable of interest was a binary indicator for whether or not the

patient received a preoperative breast MRI. Patients were classified as having a

preoperative breast MRI if they had a claim for a breast MRI (CPT: 76093-94, 77058-59,

HCPCS: C8903-C8908) on or after the first day of suspected breast disorder but before the

date of their first surgical procedure. Though this approach may capture breast MRIs that

were ordered for screening purposes, we are not concerned about including these breast

MRIs as "preoperative" because breast images taken during the initial treatment phase,

even for screening purposes, would most likely be used as a part of the surgical planning

process (Dr. Keith Amos. Personal communication. May 23, 2012).

Healthcare utilization during the initial treatment phase. To examine whether

differential breast cancer-attributable healthcare utilization exists for women with and without

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breast MRI, we identified breast cancer diagnostic and therapeutic services (See Table C.2 for HCPCS and ICD-9-CM codes). We included diagnostic procedures such as mammograms, ultrasounds, and biopsies, and surgical procedures, such as the receipt of a mastectomy, as the initial surgery and adjuvant, post-surgical treatments, such as radiation and chemotherapy.

Initial treatment phase costs. Our main dependent variable of interest was cost from a Medicare perspective. Thus, we defined cost as the amount paid by Medicare. This approach is consistent with previous SEER–Medicare cost of care studies.[5,55,65] Medicare payments, unlike Medicare charges, are an appropriate proxy for medical care costs because they are payments derived from reimbursement formulas intended to reflect the average resource utilization for that health service.[5] However, Medicare payments do not include healthcare payments from private insurance or supplemental insurers, such as Medigap or Medicaid, and do not include the beneficiary's co-insurance amount or deductible. Costs not included in our estimates include costs for oral prescription medications such as oral chemotherapy, patient prescription drugs, and chemotherapy not administered by a physician. All costs were adjusted to 2012 dollars using the Consumer Price Index for medical care to account for medical inflation.[66]

We examined several different estimates of cost per-patient during the initial treatment phase (Table 6.1), including total all-cause and total breast cancer-attributable Medicare payments. For each patient, the total all-cause Medicare payment was defined as the sum of Medicare payments during the initial treatment phase for all claims found in the outpatient, carrier, and MEDPAR files. The total breast cancer-attributable Medicare payment was the sum of each patient's Medicare payments during the initial treatment phase from claims for breast biopsy, breast surgery, chemotherapy, radiation, mammogram, ultrasound, breast MRI, or from a claim with a breast diagnosis code within the claim's first four diagnosis codes from the outpatient and carrier files. To examine if non-cancer related

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care costs differ by MRI receipt, we defined payments not attributable to breast cancer as the difference between all-cause and breast cancer-attributable payments.

Additional covariates. We examined numerous variables that could potentially be associated with breast MRI receipt and confound the relationship between breast MRI and cost. We included a variable for tumor histology (ductal, lobular, mixed ductal lobular, and other) because research has shown that lobular tumors are more likely to be mammographically occult and, thus, patients may be more likely to receive and/or benefit more from breast MRI.[67] Tumor characteristics examined included grade (well, moderately, poorly/undifferentiated, and undetermined), tumor size (≤ 2cm vs. > 2cm & ≤ 5cm), any node positivity (yes vs. no), and hormone receptor status identified from SEER data (positive [ER+/PR+, ER+/PR-, ER+/no PR data, ER-/PR+, or no ER data/PR+], negative, unknown). We used the NCI Combined Comorbidity Index method to address competing health demands and risks of complications that may affect treatment selection (0, 0-1, >1).[54] Demographic characteristics examined included age group at diagnosis (in 5-year increments), marital status (married vs. unmarried), race (white vs. nonwhite), Medicare state buy-in coverage (yes vs. no), residence in a metropolitan zip code (yes vs. no), and SEER region. We also included surgical facility characteristics, such as whether it was a designated NCI Cancer Center (yes vs. no) or whether or not the facility was affiliated (yes vs. no) with NCI Cooperative Groups having breast cancer research portfolios (i.e., American College of Surgeons Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, Southwest Oncology Group, and the National Surgical Adjuvant Breast and Bowel Project).[68]

Additionally, we included indicators for other diagnostic procedures and treatments in our models that may confound the relationship between breast MRI and cost. Previous research has shown that breast MRI is associated with the receipt of additional advanced imaging tests[41] that may increase the cost of the initial treatment phase. Thus, we included

an indicator for whether or not the patient had a claim for an "advanced imaging" test defined by previous research[7,69] (i.e., computed tomography [CT], positron emission tomography, bone scan, brain magnetic resonance imaging, or nuclear medicine). Because chemotherapy and radiation therapy represent a large proportion of the initial treatment episode's cost,[70,71] we also included indicators for whether the patient had chemotherapy or radiation. Although these diagnostic procedures and treatments are correlated with breast MRI and cost, we assumed breast MRI receipt did not cause the receipt of advanced imaging, chemotherapy, and radiation.

Because a mastectomy is an extensive inpatient procedure, women with mastectomies may have higher surgical costs than women with BCS. Additionally, women receiving a breast MRI may be converted to mastectomy from BCS based on additional MRI findings,[21] and research has shown that women with a breast MRI are more likely to undergo a mastectomy as their initial surgery (Chapter 4).[21-25] Thus, we considered including an indicator for whether or not the patient had a mastectomy as her initial treatment. We also examined whether stratifying by mastectomy receipt was appropriate. The effect of breast MRI was quantitatively similar, regardless of the model used (no mastectomy indicator 1.14, 95% CI: [1.12 1.16], mastectomy indicator included in the model, 1.13, 95% CI: [1.10 1.15], patients with mastectomies only 1.14, 95% CI: [1.10 1.19], patients with BCS only 1.13, 95% CI: [1.09 1.15])), but slightly lower when we controlled for mastectomy receipt. Based on the hypothesized relationship between breast MRI and mastectomy, we assumed that mastectomy was a mediator and on the causal pathway from MRI to cost, and thus, we omitted mastectomy from our final model.

Statistical Analyses

Descriptive statistics were calculated for patients with and without a preoperative breast MRI. We tested for differences in the clinical, demographic, and treatment

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characteristics across patients with and without breast MRI using the Pearson chi-squared test for categorical variables and the Student's t-test for continuous variables. We also used t-tests and chi-squared tests in our bivariate analyses of breast MRI receipt and different measures of healthcare utilization and cost.

In our multivariate analyses examining the association between breast MRI and cost, we fitted a generalized linear model (GLM) with a log-link and gamma distribution variance function with robust standard errors.[72,73] We used a log transformation to normalize the cost distribution, which is typically highly skewed.[44] Because all of the women in our sample had surgery within our study's timeframe, almost all women had Medicare payments during the initial treatment phase and two-part models were not required.[74,75] (Note: Ten women did not have any Medicare payments, which may be due to the fact that some private insurers may pay before Medicare.[76])

Diagnostic and procedure codes were identified and verified using the medical literature, coding experts, EpiCoder (Yost Engineering Inc., Ohio) and the Integrated Cancer Information and Surveillance System coding references.[77] Analyses were performed using Stata version 12.0 (Stata Corporation, College Station, Texas). All tests were conducted using a minimum significance level of 0.05.

Sensitivity Analysis

Much of the previous literature examining the cost of the initial breast cancer treatment phase with SEER-Medicare data uses a 12-month window beginning with diagnosis.[60,78] Since our definition of initial treatment phase comprised an average of 4.9 months, in order to make our results comparable, we replicated all of the analyses described above using a 12-month time frame. Rather than included all claims from the first claim for a suspected breast disorder to the end of treatment as was done in the main analysis, in the sensitivity analysis, we included all claims from the 12 months after the first claim for a suspected breast disorder. Other than capturing a different time frame, the cost definitions

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remained the same (i.e., for all-cause and breast cancer-attributable payments) and identical covariates were included in the multivariate models.

Results

Of the 26,751 women diagnosed with stage I-IIB breast cancer between 2004-2007 from SEER-Medicare data, 22,974 women were included in our sample (Figure 6.1). Twelve percent (12.0%) of women in our sample received a preoperative breast MRI (Table 6.2). The initial treatment phase lasted an average of 4.9 months, 4.8 months for women who received an MRI and 5.9 months for women who did not. On average, when compared to patients that did not receive a breast MRI, patients with breast MRI were more likely to experience longer treatment duration, have invasive lobular carcinoma, have a hormone receptor-positive tumor, be healthier, younger, white, married, and not in a Medicare state buy-in program. Patients with a breast MRI also were more likely to be diagnosed more recently, live in a metropolitan zip code, and had surgery at a breast cancer Cooperative Group and NCI-affiliated facility. MRI receipt also significantly differed by SEER region.

Patients with breast MRI had different healthcare utilization patterns compared with women who had not undergone preoperative breast MRI with respect to services received during diagnosis and initial treatment (Table 6.3). Women with breast MRI were more likely to have a claim for a mammogram, ultrasound, biopsy, and advanced imaging, such as nuclear medicine tests, CT and PET scans. Women with breast MRI, on average, were more likely to have a mastectomy as their first surgical procedure and to receive radiation and chemotherapy.

In analyses examining unadjusted costs during the initial treatment phase (Table 6.4), women with preoperative breast MRI were significantly more likely to have higher costs than those women who had not undergone preoperative breast MRI with the exception of payments not attributable to breast cancer. Overall, the mean per-patient, all-cause

payment during the initial treatment phase was, on average, $23,683, which amounted to $22,987 for women without a preoperative breast MRI and $28,795 for women with a breast MRI (p <0.001). The mean per-patient, breast cancer-attributable payment was $19,749 for all patients, which amounted to $19,025 for women without a preoperative breast MRI and $25,075 for women with a breast MRI (p <0.001). The difference in costs for other causes was not statistically significant (p=0.31) and accounted for roughly $3,900 for all patients.

Multivariate analyses. In our multivariate models, breast MRI was significantly associated with an increase in Medicare payments for all-cause and breast cancer-attributable payments (Table 6.5) in the initial treatment phase. On average, women with a breast MRI had 10%-higher total all-cause payments (95% confidence interval [CI]: 1.08, 1.13) and 14%-higher breast cancer-attributable payments (95% CI: 1.12, 1.16), The average marginal effect of breast MRI on all-cause Medicare payments was $2,348 (95% CI: $1,771, $2,924) and $2,619 for breast cancer-attributable payments (95% CI: $2,208, $3,030). Medicare payments in the initial treatment phase not attributable to breast cancer were not significantly different according to preoperative breast MRI receipt.

Sensitivity analysis. In our sensitivity analysis we repeated analyses using a 12-month time frame rather than what we defined as the initial treatment phase earlier, which lasted on average of 4.9 months. All payments in all categories (i.e., all-cause, breast cancer-attributable, non-breast cancer-attributable) were higher than those in our main sample (See Table 6.4), most likely due to the extended time frame. In the multivariate analyses (Table 6.5), the effect of breast MRI on breast cancer-attributable payments was similar to results from our main analysis (1.11, 95% CI: 1.08, 1.12). However, breast MRI was not significantly associated with increased all-cause Medicare payments (1.03, 95% CI: 1.00, 1.06). Thus, the increases in breast cancer-attributable payments may have been offset by reductions in costs for other causes since breast MRI receipts was significantly

associated with a reduction in payments not attributable to breast cancer (0.86, 95% CI: 0.79, 0.94).

Discussion

In this large, population-based, observational study of elderly women with breast cancer, we found that breast MRI was significantly associated with increased total all-cause and breast cancer-attributable Medicare payments during the initial treatment phase, which lasted on average 4.9 months. Breast MRI was associated with 10%-higher all-cause payments and 14%-higher breast cancer-attributable payments during the initial treatment phase. On average, breast MRI reciept was associated with an increase of $2,348 for all-cause payments and $2,619 for breast cancer-attributable payments. Payments not attributable to breast cancer during the initial treatment phase did not significantly differ according to MRI receipt.

We believe that Medicare costs during the initial treatment phase are higher among women receiving breast MRI than in women who did not receive breast MRI for several reasons. First, since breast MRI augments rather than replaces some or all of conventional assessment, there is the additional upfront cost of the procedure, an average of $617. Second, breast MRI may influence treatment patterns in ways that increases costs. Consistent with previous literature,[25,42,43] our analyses demonstrated that breast MRI is associated with additional diagnostic procedures, such as ultrasounds and biopsies, which is consistent with guidelines recommending that suspicious lesions identified by breast MRI should be followed up with second-look ultrasound and pathologically confirmed with a biopsy before implementing changes in clinical management.[27,36,44,45] Additionally, breast MRI may have affected surgical treatment by causing conversion from BCS to mastectomy based on the additional findings of the MRI,[21] which would result in higher surgical treatment costs. We observed this effect when we controlled for mastectomy receipt in the models,

and the effect of breast MRI was attenuated (OR 1.14, 95% CI: [1.12,1.16] main model, breast cancer-attributable payments; OR 1.13, 95% CI: [1.10,1.15] model controlling for mastectomy receipt). Furthermore, although one of the purported benefits of breast MRI is that it improves surgical planning, women with and without a preoperative breast MRI may have a similar likelihood of re-excision (Chapter 5 and other studies[21-26]), suggesting that women who received a preoperative breast MRI may not have fewer re-excision costs than those who did not receive a preoperative breast MRI.

Our estimates of breast cancer treatment costs are comparable to other sources using SEER-Medicare data with breast-cancer attributable costs amounting to $23,683 during the initial treatment phase.[1,5,79] When examining breast MRI compared to other drivers of high-cost cancer care, the effect of breast MRI on costs was not as strong as other breast cancer services, such as chemotherapy and radiation therapy. Women receiving radiation therapy had a 61% increase in breast cancer-attributable payments (95% CI: 1.59, 1.64), and women receiving chemotherapy had a 138% increase in breast cancer-attributable payments (95% CI: 2.32, 2.44). The results are shown in Appendix Table C.3.

Although breast MRI might not be a primary driver of breast cancer costs, the used of this procedure is costly to Medicare. Breast MRI is being rapidly adopted with the percentage of older women receiving breast MRI increasing from 2.5% in 2004 to 20.5% in 2007. If MRI utilization remains constant at the 2007 level (roughly 20%), Medicare would spend an average of $11.4 million on breast MRI procedures and experience an additional $48.1 million for breast cancer care annually. With the projected increase in breast cancer prevalence,[1] we would expect these figures to rise to $14.8 million and $62.9 million, respectively by 2020.

The increased cost to Medicare associated with preoperative breast MRI is concerning given the mounting evidence suggesting that breast MRI does not improve patient outcomes. Two randomized controlled trials, numerous retrospective single

institution studies, several meta-analyses, and one observational study using the elderly SEER-Medicare breast cancer population (Chapter 5) have shown that breast MRI does not significantly improve short-term surgical outcomes, such as fewer reoperations[21-26] or lower recurrence rates[10,20,24-27] (see results from Chapter 5). In the absence of survival or recurrence differences, quality of life would have to significantly improved to justify its routine use. However, recent evidence suggests that quality of life may not be improved,[80-83] as breast MRI has been shown to be associated with an increased likelihood of mastectomy compared to BCS (Chapter 4).[21-25] Additionally, two studies have shown that preoperative breast MRI does not improve quality-adjusted life expectancy.[46,84] Furthermore, the one randomized controlled trial that examined the cost-effectiveness of breast MRI in the United Kingdom determined that "the addition of MRI to triple assessment did not result in a reduction in operation rates, and the use of MRI would thus consume extra resources with few or no benefits in terms of cost-effectiveness or health-related quality of life (p. iv)."[46]

Though it is unlikely that breast MRI is cost-effective based on our findings in Chapter 5 as well as mounting efficacy and effectiveness data, future research could use our cost data in combination with efficacy and effectiveness data to examine the cost-effectiveness of breast MRI. Future research could utilize our estimates of the per-person cost to assess the upfront cost of the procedure and the downstream effects of breast MRI on cancer costs in combination with outcome data, such as disease-free survival, overall survival, and health related quality of life. By quantifying the costs and benefits of breast MRI using a common measure, such as quality adjusted life years or years of life saved, we could then compare the cost-effectiveness of breast MRI to the cost-effectiveness of other breast cancer diagnostic procedures and treatments.

Limitations

Our study has several limitations. First, as in all observational studies, we are concerned with omitted variable bias. Women who received breast MRI may differ from women who did not receive breast MRI based on unobserved characteristics such as unmeasured tumor biology, health seeking-behavior, access to healthcare, and patient and provider preferences for certain diagnostic procedures and treatments. These unmeasured, omitted variables may be associated with healthcare utilization and initial treatment costs and, thus, have the potential to bias our estimates. For example, who received breast MRI may have higher initial treatment phase costs because they have more invasive or complicated cancers[17] than those women who do not undergo breast MRI. These women may have undergone a breast MRI because their tumor was inadequately imaged with conventional assessment.[26,35,43,44] Thus, these women may have needed additional diagnostic mammograms, ultrasounds, or nuclear medicine tests in addition to the breast MRI that assisted in determining the extent of disease.[85,86] We attempted to control for cancer tumor biology by including tumor size, grade, histology, nodal status, and adjuvant therapy receipt in our models. When compared to women who did not receive a breast MRI, women who undergo breast MRI may be more likely to have access to more expensive cancer care technologies in addition to MRI,[69,87] which may increase the likelihood of receiving these procedures[68,81] and increase initial treatment phase costs, regardless of a perceived indication of clinical benefit. We attempted to control access to and use of expensive cancer technologies/therapies by including indicators in our models for whether or not the patient received advanced imaging, chemotherapy and/or radiation therapy. By examining payments not attributable to breast cancer care, we assessed whether women with breast MRI had a higher baseline propensity for overall healthcare utilization, independent of their cancer treatment, which would bias our all-cause initial treatment phase costs. However, we do not believe that is the case since the association between breast

MRI and non-cancer related payments in the initial treatment phase was statistically non significant (Table 6.4), and breast MRI was associated with a reduction in non-cancer payments during the first 12 months after the first suspicion of breast cancer in the sensitivity analysis. Despite our best efforts to mitigate omitted variable bias, we were unable to control for all factors that potentially confound the relationship between breast MRI and cost and, thus, we are unable to conclude that the observed effect is due to the impact of preoperative breast MRI on treatment patterns alone.

Second, for our estimate of cancer care cost, we included only those costs directly related to cancer management, rather than using a comparison group without cancer. Though we were concerned that this may somewhat underestimate the costs by possibly not capturing the side effects associated with cancer treatment, we employed several measures to ensure this was not the case. First, for our main analysis we included only costs during the first treatment phase (~4.9 months) rather than the entire first year of diagnosis to provide a more accurate estimate of costs incurred when the patient was actually in the preoperative phase or in active treatment. Second, when identifying "breast cancer-attributable" claims, we conducted a sensitivity analysis (not reported) to determine the appropriate diagnosis code position (i.e. first through tenth) that would most likely capture services for breast cancer. We conducted this sensitivity analysis because we were concerned that women may have a breast cancer diagnosis code in later diagnosis code positions even if the claim was for something non-cancer related because they were in the initial breast cancer treatment phase. In our sensitivity analysis, we compared the costs in claims with breast cancer diagnosis code in the first position compared to the cost in claims with a breast cancer code in the sixth diagnosis code position or lower. We determined that claims with a breast cancer diagnosis code in the first through fourth positions were appropriate to capture cancer costs.

Third, because we used SEER-Medicare data, we were limited in that we were only able to focus on costs reimbursed by Medicare. We were unable to capture breast cancer services not paid for by Medicare, such as care provided by private health insurance through an employer or services for which Medicare does not reimburse. We also were unable to include any insurance payments secondary to Medicare or co-insurance or deductibles paid by the beneficiary. We did not capture other indirect costs, such as productivity loss. Additionally, our study has the usual SEER-Medicare dataset limitations, including concern about the generalizability to all elderly breast cancer patients due to the exclusion of patients who are not continuously enrolled in fee-for-service Medicare.

Conclusion

Recent concerns about the increasing use of advanced imaging, changing treatment patterns, and escalating cancer costs prompted us to undertake this study estimating the effect of breast MRI on costs of cancer care among elderly women enrolled in Medicare.[4,6,7,69] Proponents of healthcare cost containment strategies have stressed the importance of using evidence-based medicine to address the increasing costs of cancer care.[2,51] The adoption of preoperative breast MRI is an example of just the opposite, an additive advanced imaging modality with limited evidence that it improves patient outcomes that changes treatment patterns. In this study, we found that breast MRI was significantly associated with increased all-cause and breast cancer-attributable Medicare payments. The additional costs of breast MRI should be evaluated in concert with breast MRI effectiveness data to inform policy makers about the value of breast MRI in the elderly breast cancer population.

Table 6.1: Initial phase of care and cost definitions

Term	Definition
Initial treatment phase	All claims from the date of the first claim for a suspected breast disorder (i.e. lump or mass in breast, abnormal mammogram, see Appendix Table C.2) 12 or fewer months prior to the SEER diagnosis month to the last day of a treatment claim before a gap in treatment claims of at least 90 days. The average initial treatment phase lasted 4.9 months.
All-cause payments	The sum of Medicare payments from all claims during the initial treatment phase from the outpatient, carrier, and MEDPAR files (including claims for ED, long and short-term inpatient, and skilled nursing facility stays).
Breast cancer-attributable payments	The sum of Medicare payments from claims with breast biopsy, breast surgery, chemotherapy, radiation, mammogram, ultrasound, breast MRI or from a claim with a breast diagnosis code within the claim's first four diagnosis codes during the initial treatment phase. Claims from the outpatient, carrier, and MEDPAR files were included.
Payments not attributable to breast cancer care	Difference between all-cause and breast cancer-attributable payments

SEER, Surveillance, Epidemiology, and End Results; ED, emergency department; MEDPAR, Medicare Provider Analysis And Review.

Figure 6.1. Inclusion/exclusion schematic

Women diagnosed with their first primary breast cancer in SEER in 2004-2007* n= 39,652	
INCLUDED	**EXCLUDED**
Known Stage I-IIIA disease, tumor size <5cm, histology codes indicating malignant breast cancer N=26,751	Stage 0 or IV disease, stage unknown; tumor size greater than 5cm; histology codes indicating in situ/ non-malignant disease or non-breast primary tumors n=12,901
Able to determine the first definitive surgical treatment and have no prior cancer treatments before surgery n= 25,669	Medicare claims identified conflicting surgical procedures on the same day; receipt of cancer treatments prior to surgery n=1,082
Patients with linkable to her surgical provider n= 25,038	Unable to link patient to her surgical provider n= 631
Had a breast surgical procedure† within 4 months of SEER diagnosis month n= 24,439	Did not have a breast surgical procedure† or had one > 4 months before/after SEER diagnosis month n= 599
Had a breast surgical procedure† within within a year of the first claim for a suspected breast disorder n= 23,593	Did not have a breast surgical procedure† within a year of the first claim for a suspected breast disorder n= 846
Alive for a year after diagnosis and did not die while in active treatment n= 22,974	Died within a year of diagnosis or while in active treatment n= 629
Analytical Sample n= 22,974	

SEER, Surveillance, Epidemiology and End Results

* Meeting SEER-Medicare inclusion requirements of aged 66 or older at diagnosis, reporting source not autopsy or death certificate, laterality not bilateral or unknown, original reason for Medicare entitlement not disability or end stage renal disease, valid month of diagnosis, no health maintenance organization enrollment during study period, continuous enrollment in Part A&B during the study period, comorbidity score, and was able to be matched to claims during the study period. Study period is defined here as the 12 months prior to diagnosis month till the end of data or death (For more details see Appendix Table C.1).

† Breast surgical procedure includes breast excision, partial/subtotal mastectomy, and mastectomy

Table 6.2. Baseline characteristics

	Overall (N=22,974)	No breast MRI (N= 20,223)	Breast MRI (N=2,751)	p-value
Preoperative breast MRI receipt	12.0	0	100.0	<0.001
Treatment length (months)	4.9 (4.3)	4.8 (4.2)	5.9 (4.6)	<0.001
Tumor size between 2 and 5 cm	26.6	26.8	25.2	0.07
Tumor grade (%)				<0.001
Well differentiated	26.4	26.2	27.8	
Moderately differentiated	44	43.6	46.9	
Poorly differentiated	24.2	24.8	20.3	
Grade unknown	5.4	5.5	5.0	
Hormone receptor status (%)				0.006
Positive	79.2	78.9	81.2	
Negative	12.8	12.9	12.2	
Unknown	8.0	8.2	6.6	
Node positivity (%)	20.3	20.1	21.8	0.04
Histology				
Ductal	73.9	74.9	67.0	<0.001
Lobular	9.8	8.9	16.0	
Mixed ductal/lobular	7.9	7.4	11.9	
Other	8.4	8.8	5.1	
NCI comorbidity index (%)				<0.001
0	64.2	63	73.2	
Between 0 and 1	27.8	28.5	22.9	
Greater than 1	8.0	8.5	3.8	
Age at diagnosis (%)				<0.001
65 to 69	20.7	18.9	34.0	
70 to 74	24.7	24.2	29.0	
75 to 79	24.3	24.8	20.8	
80 to 84	18.6	19.6	11.8	
85 and older	11.6	12.6	4.4	
State buy-in coverage (%)				<0.001
No	89.5	88.7	95.0	
Yes	10.5	11.3	5.0	
Race (%)				<0.001
White	86.9	86.6	89.2	
Non-white	13.1	13.4	10.8	
Married (%)	46.2	45.0	54.6	<0.001
Zip code of residence (%)				<0.001
Metropolitan	84.7	83.7	92.7	
Non-metropolitan	15.3	16.3	7.3	

Table 6.2. Baseline characteristics (cont.)

	Overall (N=22,974)	No breast MRI (N= 20,223)	Breast MRI (N=2,751)	p-value
Cooperative group affiliation of surgical facility (%)†	51.2	49.5	63.2	<0.001
NCI affiliation of surgical facility (%)	5.1	4.9	6.9	<0.001
Year of diagnosis (%)				<0.001
2004	25.2	27.1	11.7	
2005	24.6	25.5	18.1	
2006	24.8	24.5	27.0	
2007	25.4	22.9	43.2	
SEER Region (%)				<0.001
California registries	32.4	31.4	39.5	
Northeast registries	23.2	22.7	27.3	
Georgia	3.3	3.3	2.7	
Detroit	6.9	7.1	5.0	
Iowa	7.3	8.0	2.8	
New Mexico	2.1	1.8	4.4	
Seattle	6.4	5.7	11.3	
Utah	2.7	2.8	2.3	
Kentucky	7.6	8.3	2.5	
Louisiana	6.8	7.5	2.2	
Hawaii	1.2	1.4	0.1	

Mean (Standard Deviation) or %, P-values by t-test for continuous variables and chi-squared test for binary / categorical variables

† NCI Cooperative Groups having breast cancer research portfolios

MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute.

Table 6.3. Healthcare utilization and Medicare payments during the initial treatment phase, by patients with and without preoperative breast MRI

	Percent with utilization (%)			
	Overall (N=22,974)	No MRI (N=20,223)	MRI (N= 2,751)	p-value
Diagnostic/ preoperative procedures				
Mammogram	93.2	92.8	96.3	<0.001
Ultrasound	78.8	77.3	89.9	<0.001
Biopsy	73.1	70.9	89.7	<0.001
Advanced Imaging	64.3	62.3	78.6	<0.001
Bone scan	19.0	18.3	24.3	<0.001
Brain MRI	2.7	2.6	3.3	0.03
CT scan	24.7	23.7	31.6	<0.001
PET scan	9.2	8.2	16.0	<0.001
Nuclear medicine	49.4	47.5	63.2	<0.001
Treatments				
Mastectomy as first surgery	21.8	21.6	23.7	0.01
Radiation	55.2	54.0	63.9	<0.001
Chemotherapy	15.9	15.2	21.2	<0.001

P-values from chi-squared test

CT, Computed tomography; MRI, Magnetic resonance imaging; PET, Positron emission tomography.

Note: If a claim for a biopsy occurred on the same day as a breast excision it was considered a breast excision. If a claim for a breast excision occurred on the same day as a partial mastectomy or a mastectomy, it was considered a partial mastectomy or a mastectomy, respectively. If there were conflicting claims for a partial mastectomy and a mastectomy on the same day, the patient was excluded

Table 6.4. Unadjusted Medicare payments, by breast MRI receipt

	Overall (N=27,935)	No breast MRI (N=25,065)	Breast MRI (N=2,870)	p-value
Payments during the initial treatment phase				
All Payments	$23,683 ($22,525)	$22,987 ($22,208)	$28,795 ($24,131)	<0.001
Breast cancer-attributable payments*	$19,749 ($16,827)	$19,025 ($16,383)	$25,075 ($18,956)	<0.001
Payments not attributable to breast cancer**	$3,933 ($11,792)	$3,962 ($11,971)	$3,720 ($10,377)	0.31
Payments during first 12 months of diagnosis and treatment (sensitivity analysis)[***]				
All Payments	$31,297 ($30,339)	$31,062 ($31,050)	$33,024 ($24,420)	0.001
Breast cancer-attributable payments*	$20,557 ($15,330)	$19,936 ($15,104)	$25,124 ($16,185)	<0.001
Payments not attributable to breast cancer**	$10,740 ($25,181)	$11,127 ($26,104)	$7,900 ($16,638)	<0.001

Note: Mean (Standard Deviation), P-values by t-test

MRI, Magnetic resonance imaging.

* Breast cancer-attributable payments include total Medicare payments from claims associated with breast cancer diagnosis or treatment or from claims with a breast diagnosis code within the claim's first four diagnosis codes.

** Payments not attributable to breast cancer are the difference between all payments and breast cancer-attributable payments

*** First 12 months of diagnosis and treatment defined as all claims for 12 months after the first claim with a breast diagnosis code

Table 6.5. Multivariate models examining the effect of preoperative breast MRI on Medicare payments and average marginal effect estimates

	All Medicare payments	Breast cancer-attributable payments[†]	Payments not attributable to breast cancer[‡]
Payments during the initial treatment phase			
Multiplicative effect of preoperative breast MRI	1.10*** [1.08, 1.13]	1.14*** [1.12, 1.16]	0.98 [0.88, 1.10]
Average marginal effect of preoperative breast MRI	$2,344*** [$1,767, $2,921]	$2,617*** [$2,206, $3,027]	$-65 [$-491, $360]
Payments during first 12 months of diagnosis and treatment (sensitivity analysis)			
Multiplicative effect of preoperative breast MRI	1.03 [1.00, 1.06]	1.11*** [1.09, 1.14]	0.86*** [0.79, 0.94]
Average marginal effect of preoperative breast MRI	$804 [-$79, $1,687]	$2,241*** [$1,824, $2,657]	-$1592*** [-$2,494, -$690]
N	22,974	22,974	22,974
AIC, main analysis	5.0e+05	5.0e+05	4.2e+05
AIC, sensitivity analysis	5.2e+05	4.9e+05	4.7e+05

* p<0.05 ** p<0.01 *** p<0.001

95% confidence intervals in brackets, generalized linear models use log-link and gamma distribution with robust standard errors.

MRI, Magnetic resonance imaging; AIC, Akaike information criterion

Models control for treatment variables (whether or not the patient had radiation, chemotherapy, advanced Imaging), patient characteristics (tumor stage, nodal status, hormone receptor status, histology, NCI Comorbidity, age, state buy-in coverage, race), metropolitan zip code of residence, SEER region, year, and whether or not the women had her surgery at a facility having NCI Cooperative Groups breast cancer research portfolios or that is NCI affiliated. For full results see Appendix Table C.3 and C.4.

[†] Total Medicare payments from claims associated with breast cancer diagnosis or treatment or from a claim with a breast diagnosis code within the claim's first four diagnosis codes

[‡] Controlling for non-cancer related characteristics (see Appendix Table C.3 and C.4)

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Summary of findings

Breast magnetic resonance imaging (MRI) has been increasingly used in the preoperative evaluation of women with newly diagnosed breast cancer, with almost one-fifth of elderly breast cancer patients receiving a preoperative breast MRI by 2007. Despite its rapid adoption, limited evidence exists to support the routine use of breast MRI, creating controversy in breast cancer management.[1-20] Numerous single institution studies, several meta-analyses, and two randomized controlled trials suggest that breast MRI changes treatment patterns, leading to surgical treatment delay and more extensive surgeries. However, breast MRI may not produce improved outcomes in terms of fewer re-excisions[4,11,21-23] or lower recurrence rates.[12,21,24-27] There is a dearth of evidence examining the effect of breast MRI on surgical planning and outcomes in elderly women with breast cancer, and few studies assess breast MRI at a population level. This study is one of the first to examine the association between preoperative breast MRI and surgical planning, short-term outcomes, and cost in the elderly breast cancer population using SEER-Medicare data.

In Chapter 4, we examined the association between preoperative breast MRI and surgical planning in elderly women with early-stage, invasive breast cancer and found that preoperative breast MRI was associated with treatment delay and more extensive initial surgeries. Women who received preoperative breast MRI differed from women who did not in terms of baseline patient, tumor, and surgical facility characteristics. We used propensity score methods to reduce the risk of bias that could result from factors associated with initial

receipt of MRI, as differentiated from factors associated with subsequent treatment and timing of care. The median time from the first suspicion of breast cancer to complete surgery was 53 days for patients without a breast MRI and 63 days for patients with a breast MRI (p<0.001), and we found that preoperative breast MRI was associated with a median 15-day delay in the time to complete surgery using propensity score methods. More than 20% of women in our sample had a mastectomy as their first surgical procedure and, after adjustment using propensity scores, receipt of a breast MRI was associated with significantly greater odds of having a mastectomy as the initial surgery (OR: 1.30, 95% CI [1.12, 1.50]). This finding is consistent with previous literature documenting breast MRI's association with treatment delay[28-30] and more extensive surgeries.[4,11,21-23]

In Chapter 5, we examined whether preoperative breast MRI was associated with improved short-term outcomes. We found that breast MRI was not associated significantly with re-excision rates, but was associated with an increased hazard of a second breast cancer event (i.e., recurrence or a second primary breast cancer). We defined a re-excision as an additional breast surgical procedure after breast conserving surgery (BCS) during the initial treatment phase (i.e., before a gap in treatment of 90 days). One-third of patients in our sample had a re-excision and, after adjustment using propensity score methods, receipt of a preoperative breast MRI was not associated with the odds of having a re-excision. We identified second breast cancer events through a validated algorithm[31] using information regarding secondary cancers and surgical procedures from claims data and SEER registries. We found that 9.4% of our sample had a second breast cancer event. Using propensity score methods, undergoing a preoperative breast MRI was associated with an increased hazard of a second breast cancer event. These women were significantly more likely to have experienced a second breast cancer event one, three, and five years after the first suspected breast cancer compared to women who did not receive preoperative breast

MRI. Our results add to the mounting evidence[4,11,12,21-27] that breast MRI is not associated with improved outcomes vis-à-vis fewer re-excisions and lower recurrence rates.

In Chapter 6, we examined the costs associated with preoperative breast MRI during the initial treatment phase from the perspective of Medicare. We found that women with breast MRI had higher total all-cause and breast cancer-attributable costs than those women without MRI. We defined costs during the initial treatment phase as Medicare payments for all claims from the date of the first suspected breast disorder to the last day of treatment before a gap in treatment of at least 90 days. We also examined breast cancer-attributable costs using Medicare payments for breast cancer procedures and claims with breast cancer diagnosis codes. The average per-patient, all-cause cost during the initial treatment episode was $23,683, which equated to $22,987 for those who did not receive an MRI and $28,795 for those who did (p-value <0.001). The average per-patient, breast cancer-attributable payment was $19,749, which meant $19,025 for those who did not receive an MRI and $25,075 for those who did (p-value <0.001). In our multivariate models, we found that preoperative breast MRI was associated with 10% higher all-cause costs [95% CI: (1.08, 1.13)] and 14% higher breast cancer-attributable costs [95% CI: (1.12, 1.16)] during the initial treatment phase. The average marginal effect of breast MRI was $2,348 for all-cause costs and $2,619 for breast cancer-attributable costs [95% CI: ($1,771, $2,924), ($2,208, $3,030)]. Costs not attributable to breast cancer during the initial treatment phase did not significantly differ by MRI receipt in either our unadjusted or adjusted models. We conclude that the increased cost to Medicare associated with preoperative breast MRI is cause for concern in light of the mounting evidence suggesting that breast MRI is associated with a treatment delay and more extensive initial surgeries (Chapter 4) in the absence of improved outcomes (Chapter 5).

Contributions to existing literature, and policy and practice implications

   This dissertation makes several important contributions to the existing literature examining preoperative breast MRI. First, few studies have examined the use of preoperative breast MRI in elderly women. Most of the existing research examined breast MRI in younger breast cancer populations.[22] For example, the average participant in the two RCTs examining breast MRI was in their mid-50s,[21,23] two decades younger than the average age of breast cancer patients enrolled in Medicare[32] and the average patient in our study (76.1 years). Given that older women are likely to be underrepresented in clinical trials,[33] effectiveness research, like this dissertation, is warranted to inform patients and their providers about the risks and benefits of breast MRI specific to their age group. This information, in turn, can be used in the decision-making process by elderly women and their providers about whether or not to use breast MRI. Furthermore, older age may be associated with clinical heterogeneity[40,41] and influence the magnitude of the effect of breast MRI. Specifically, older patients, in addition to having complex co-morbidities and cognitive or functional impairment, are more likely to have less dense breasts and, therefore, fewer occult tumors with conventional assessment.[34-39] Thus, they may be least likely to experience any benefit from imaging technology, but more likely to experience harm from more extensive surgeries associated with breast MRI. Evidence from our studies about the effectiveness of breast MRI specific to elderly breast cancer patients is intended to help clinicians and patients understand which patients will benefit most, who is least likely to benefit, and who is at greatest risk of experiencing adverse outcomes.

   Second, a dearth of evidence exists examining the impact of breast MRI on surgical planning or short-term outcomes at the US population level. As previously mentioned, much of the existing literature examining breast MRI is based on multiple studies from single institutions and two randomized controlled trials, and does not use population-level data. The RCTs and single institution studies were highly selective and restrictive in their inclusion

criteria; thus, the study populations were not comparable to the US elderly population. Furthermore, the two RCTs were conducted in Europe[21,23] where physician practice patterns and patient treatment preferences differ significantly from the US.[40-42] Our study is novel in that it uses the SEER-Medicare dataset, a large, population-based dataset to examine the association between breast MRI and surgical planning and outcomes at a population level using rich information about patient and tumor characteristics as well as healthcare utilization. Information from our study can be used as a part of the decision-making process to inform elderly women with breast cancer and their providers about the potential risks and benefits of using breast MRI.

Third, no study, to our knowledge, has examined the association between breast MRI and the cost of initial breast cancer treatment in the United States. The only study to examine the cost of breast MRI was a randomized controlled trial conducted in the United Kingdom[43] where treatment patterns, payment structures, and fiscal considerations are different.[40-42,44,45] Our study findings are among the first cost estimates that could be used in concert with effectiveness data to generate information about the comparative cost-effectiveness of breast MRI.

This study has several policy and clinical practice implications. The results of this study have the potential to improve the quality of breast cancer care by generating additional evidence about the appropriate use of preoperative breast MRI. The Institute of Medicine (IOM) has defined overuse as a quality of care problem,[46] and recent publications document unnecessary overtreatment for breast cancer.[47-50] These studies have shown that more extensive treatment does not necessarily improve outcomes and, in fact, may increase the risk for complications and the cost to treat the incident breast cancer. Our study results suggest that breast MRI may be an example of an overuse of technology. Indeed, the addition of breast MRI to conventional assessment was not associated with improvement in short-term outcomes, but was associated with an increased likelihood of a mastectomy and

higher cancer treatment costs. The scientific evidence generated by our study may be used to inform new policies and strategies to help determine when breast MRI is appropriate. Additionally, the results of this study add to the growing evidence about the risks and benefits of breast MRI and, thus, may contribute to the likelihood of consistently delivering appropriate care. The more definitive the evidence for (or against) breast MRI, the more likely that it will be consistently used (or abandoned) in clinical practice.[51] Our findings also have the potential to improve patient outcomes by reducing morbidity from unnecessary biopsies and more extensive surgeries.

This dissertation responds to the IOM's call for more comparative effectiveness research (CER) to improve quality of care.[52] According to the IOM, "CER is the generation and synthesis of evidence that compares the potential benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."[53] The evidence generated by our study can be used to inform new policies and strategies for delivering appropriate care to this cancer population. Based on a population-level, 'real-world' setting, this study will assist healthcare providers and patients in making informed decisions about whether or not to use breast MRI in older women with breast cancer and may encourage more appropriate, targeted imaging of patients. Thus, the indirect effect of this new information may benefit the many thousands of elderly women who are diagnosed with breast cancer each year.

Examining the cost of care is increasingly important given the concern over the cost of Medicare and its contribution to our national deficit.[54] One of the goals of the Affordable Care Act of 2010 was to cut overspending on healthcare and rein in costs to improve the US deficit and increase longevity of the Medicare program. This dissertation informs policy makers about the additional cost of using breast MRI in the preoperative evaluation of

elderly breast cancer patients and may allow for improved use of Centers for Medicare and Medicaid's resources. Future research, as discussed later in this chapter, should combine our cost estimates with effectiveness data to generate information about the comparative cost effectiveness of breast MRI to inform policy makers who determine Medicare reimbursement policies.

Limitations

First, although the SEER-Medicare dataset is among the strengths of this dissertation, the dataset is not without limitations. In order to capture the complete claims experience for each patient, we excluded women who were not continuously enrolled in Medicare Part A and B, and not enrolled in a health maintenance organization during the study period. Despite the fact that the SEER-Medicare dataset covers approximately 25% of the incident US cancer population, it is not perfectly generalizable to the US elderly population. For example, women in SEER regions are slightly more likely to be affluent, well educated, and reside in urban areas than the general elderly population.[55]

Second, our study sample may not reflect the most current breast cancer diagnosis and treatment approaches because data for women diagnosed after 2007 were not yet available. Thus, our findings may have limited generalizability to more recent years as breast MRI technology improves, and radiologists and surgeons become more experienced with imaging. Additionally, our study sample does not capture possible changes in breast MRI utilization after publication of the two randomized trials in 2010 and 2011.

Third, because the use of breast MRI is more prevalent in the later years of our study, we have limited follow-up for women who received a breast MRI and were unable to examine the likelihood of a second breast cancer event beyond five years. Due to the high survival rate of early-stage breast cancer patients, including those in our sample, we were unable to draw conclusions about the association between breast MRI and survival. More

studies are needed as the data accumulate with extended follow-up periods. However, we believe our study results are valuable because women are most likely to experience cancer recurrence during the first five years after a primary diagnosis.[56-58]

Fourth, because we used claims data, we were unable to explicitly control for the reasons why the MRI was ordered and are concerned about confounding by indication. Results from our study suggest that some women in our sample may have received a breast MRI as a part of routine preoperative work-up and other women may have received an MRI because they were inadequately imaged using conventional assessment (See Discussion, Chapter 5). Women who are inadequately imaged using conventional assessment, such as those women with invasive lobular carcinoma, may have a higher baseline risk for mastectomy, re-excisions, and/or recurrence[59-66] than women who were adequately imaged. Future research, described in the next section, should explore confounding by indication in sub-analyses of women who are more likely to be inadequately imaged by conventional assessment.

Fifth, because this was an observational study, we were unable to control for all patient and surgeon characteristics that may have influenced surgical planning, short-term outcomes, and cost. Using propensity score methods as described in Chapters 4 and 5, we were able to balance the observed characteristic of women who did and did not receive a breast MRI. However, we were unable to balance these groups based on unobserved characteristics. Specifically, as explained in Chapter 4, we were unable to control for patient preferences regarding surgery and whether or not women preferred to have mastectomy compared to BCS. We also were unable to observe surgeon preferences for one procedure over another. Chapter 5 indicates that we were unable to adjust the two groups based on several re-excision and recurrence risk factors such as multifocal disease, mammographic density and microcalcifications, and the difference in tumor size between MRI and ultrasonography.[67-69] Also, we were unable to control for surgeon experience and practice

style, which may be correlated with breast MRI and re-excisions.[70,71] As noted in Chapter 6, we were unable to balance the women on patient factors, such as family history and care-seeking behavior as well as on physician behaviors, such as their tendency to use more intensive cancer care. Future research, described in the next section, should explore the use of instrumental variables to diminish the effect of these potential unobserved confounders.

Future research

This dissertation sets the foundation for important future work. We examined the effect of breast MRI as a part of routine diagnostic work-up for all women with early-stage invasive breast cancer, but future research should determine whether breast MRI is associated with improved surgical planning and outcomes in subsets of women that may benefit from breast MRI because they may be likely to be inadequately imaged using conventional assessment. For example, some evidence suggests that breast MRI may improve surgical outcomes in women with invasive lobular carcinoma (ILC),[22,72] which comprised 9.5% of our sample. Thus, we could assess potential confounding by indication by restricting our analysis to elderly women with ILC. Further examination of subsets of women most likely to benefit from breast MRI may be clarified through linkage to, or explicit examination of, additional datasets beyond SEER-Medicare such as the Breast Cancer Surveillance Consortium, which has more detailed clinical information and data on radiological results. With additional information, including breast density and radiologist's recommendations, we would be able to examine the association between breast MRI and outcomes in women for which breast MRI may have been indicated[73] (i.e., patients with conflicting mammogram and ultrasound results or for women with possible multifocal or multicentric disease).

Future research should also focus on the effect of breast MRI in more recent years because, as with most technologies, its use may vary over time. First, RCT results from 2010-2011 indicated that breast MRI did not improve outcomes.[21,23] Second, due in part to the RCT findings and additional publications, breast MRI has become an increasingly controversial topic in breast cancer management.[2-5,7-20] Third, it is important to continue to examine breast MRI as surgeons and radiologists gain experience with the technology. This evolution in our understanding of the association between MRI and outcomes, and our appreciation of balancing harms, benefits, and costs, is likely to have had an effect on the utilization of this service in more recent years. Furthermore, as data accumulate, it is important to examine the likelihood of a second breast cancer event with longer follow-up periods. With additional years of data, we also may be able to examine the association between breast MRI and survival.

Future research should apply novel statistical methods that may more adequately control for unmeasured confounding and help strengthen our confidence in these findings that are based on the examination of observational data. For example, instrumental variable analysis[74,75] may be useful, however, a key challenge is in finding one or more suitable instruments that are substantially correlated with the endogenous explanatory variable (MRI use) and only correlated with our outcomes via their impact through MRI use. Two potential instruments we plan to examine in future research are the volume of breast MRI at the patient's surgical facility and surgical facility affiliation with the American College of Radiology Imaging Network (ACRIN), the NCI Cooperative Group that conducts radiology trials.

Future research should combine our cost estimates (Chapter 6) with our effectiveness results (Chapters 4 and 5) to model the cost-effectiveness of preoperative breast MRI for elderly women with breast cancer. Information about quality-adjusted life expectancy from previously published studies examining breast MRI[43,76] should be

considered in this analysis. Additional data regarding baseline patient clinical, social, and demographic information as well as patient-reported outcomes, quality of life, and long-term outcomes associated with breast MRI in elderly women with breast cancer would also be useful in understanding MRI utilization, other treatment decisions, and outcomes. By quantifying the costs and benefits of breast MRI using a common measure, such as an incremental cost-effectiveness ratio in US dollars per quality adjusted life year, we then could compare the cost-effectiveness of breast MRI to other breast cancer diagnostic procedures and treatments. The results from this analysis could help decision-makers determine how to best use resources and inform policy makers that define Medicare reimbursement policies.

Conclusion

Findings from this dissertation indicate that breast MRI was associated with a slight surgical delay and increased likelihood of a mastectomy as the initial surgery in elderly breast cancer patients. We did not find that breast MRI was associated with improved short-term outcomes, such as a decreased likelihood of a re-excision or second breast cancer event. Furthermore, we found that breast MRI was associated with increased all-cause and breast cancer-attributable costs during the initial treatment phase. Our findings are supported by results from numerous studies, including two randomized controlled trials.[4,11,12,21-27] This study contributes to the existing literature by being one of the first to examine preoperative breast MRI and surgical planning, outcomes, or cost using a population-level dataset composed exclusively of elderly breast cancer patients. Given that preoperative breast MRI was associated with a slight delay in surgery and an increased likelihood of mastectomy in the absence of evidence for improved short-term outcomes, healthcare providers and their patients should consider these factors when making informed decisions about the use of breast MRI for elderly women with breast cancer. Furthermore,

results from this study are intended to inform Medicare policy decision-makers about the

risks, benefits, and costs of routine preoperative breast MRI in the elderly breast cancer

population.

Note: References for this chapter appear after the appendices on page 256.

Table A.1: SEER-Medicare inclusion/exclusion criteria

Inclusion Criteria	Included	Excluded
Breast cancer diagnosis in SEER	260,079	
Diagnosed between 2003 and 2007 (inclusive)	143,757	116,322
First or initial cancer	131,974	11,783
Age 66 or older at diagnosis	86,127	45,847
Female	85,367	760
Reporting source not autopsy or death certificate	84,466	901
Laterality is not bilateral or unknown	83,659	807
Original reason for Medicare entitlement not disability or ESRD	79,355	4,304
Has valid month of diagnosis	79,114	241
Has no HMO enrollment during study period*	56,652	22,462
Has continuous enrollment in Part A&B during the study period*	52,038	4,614
Has comorbidity score and was able to be matched to claims during the study period*	48,283	3,755
Diagnosed between 2004 and 2007**	39,652	8,631

ESRD, end stage renal disease; HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology and End Results

* Study period is 12 months prior to diagnosis month until the end of data or death

** We excluded patients diagnosed in 2003 because few patients (n=148) had a breast MRI, and were unable to be balanced using propensity scores.

Table A.2: Codes for identifying breast cancer events and surgical procedures

Study time frame	Definition
Initial treatment phase	The date of the first claim with a breast-related diagnosis code to the end of the initial treatment as defined as the last day of treatment before a gap in treatment of 90 days or more or the end of the study period (December 31, 2009) or the patient's death.
First suspected breast disorder date	**Definition**
Suspected breast disorder diagnosis codes	174.* Malignant neoplasm of female breast 217. Benign neoplasm of breast 233.0 Carcinoma in situ of breast 238.3 Neoplasm of uncertain behavior of breast 239.3 Neoplasms of unspecified nature breast 610.0 Solitary cyst of breast 610.1 Diffuse cystic mastopathy 610.2 Fibroadenosis of breast 610.3 Fibrosclerosis of breast 610.9 Benign mammary dysplasia, unspecified 611.0 Inflammatory disease of breast 611.1 Hypertrophy of breast 611.3 Fat necrosis of breast 611.8 Other specified disorders of breast 611.9 Unspecified breast disorder 611.71 Signs and symptoms in breast 611.72 Lump or mass in breast 611.79 Signs and symptoms in breast 793.80 Abnormal mammogram, unspecified 793.81 Mammographic microcalcification 793.89 Other (abnormal) findings on radiological examination of breast V711 Observation for suspected malignant neoplasm
First suspected breast disorder date	The day of the first breast-related diagnosis code listed above within one year prior to the SEER diagnosis month
Surgical Procedure	**Code identified in claims**
Breast excision	ICD-9-CM: 85.20-85.22; HCPCS: 19120, 19125, 19126, 19300
Partial mastectomy	ICD-9-CM: 85.23; HCPCS: 19160/2, 19301/2
Mastectomy	ICD-9-CM: 85.4X; HCPCS: 19180, 19182, 19200, 19220, 19240, 19303-7
Histology	**Code identified in SEER**
Ductal	ICD-O-3: 8500, 8521, 8523, 8514, 8541
Lobular	ICD-O-3: 8520, 8524
Mixed ductal/ lobular	ICD-O-3: 8522
Other*	ICD-O-3: 8480, 8211, 8010, 8140, 8201, 8255, 8401, 8510, 8000, 8022, 8031, 8032, 8033, 8035, 8050, 8141, 8260, 8310, 8323, 8513, 8540, 8560, 8570, 8571, 8572, 8573, 8574, 8575, 8980, 8982, 9020,
Excluded**	8501, 8502, 8503, 8504, 8507, 8508, 8230, 8525, 8543, 8012, 8013, 8041, 8070, 8074, 8200, 8251, 8490

SEER, Surveillance, Epidemiology and End Results; HCPCS, Healthcare Common Procedure Classification System; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

*Note: Two-thirds of "other histology" were mucinous or tubular adenocarcinomas

** Excluded do to pre-malignant (in situ) or non-malignant lesions histologies indicating non-breast initial tumors

Table A.3. First breast-related diagnosis code distributions and the time to event by first breast-related diagnosis code

First breast-related diagnosis code	Number, %			Days to SEER diagnosis month				Days to "path diagnosis"***				Days to 1st surgical procedure**				Days to complete surgery*			
	NO MRI	MRI	Total	NO MRI Mean	SD	MRI Mean	SD	NO MRI Mean	SD	MRI Mean	SD	NO MRI Mean	SD	MRI Mean	SD	NO MRI Mean	SD	MRI Mean	SD
Lump or mass in breast 611.72	13,742 53%	1,253 43%	14,995 52%	17	(81)	20	(62)	33	(80)	36	(60)	50	(81)	65	(61)	57	(84)	71	(64)
Abnormal mammogram, unspecified 793.80	4,204 16%	570 18%	4,774 16%	25	(67)	30	(76)	41	(65)	46	(74)	60	(66)	75	(74)	68	(67)	84	(80)
Other (abnormal) findings on radiological examination of breast 793.89	1,155 4%	207 8%	1,362 5%	27	(67)	26	(70)	43	(66)	40	(69)	61	(66)	71	(72)	68	(66)	76	(73)
Mammographic microcalcification 793.81	1,034 4%	180 6%	1,214 4%	38	(78)	42	(77)	54	(76)	56	(77)	74	(78)	86	(77)	84	(79)	95	(78)
Malignant neoplasm of breast 174.9	945 4%	96 3%	1,041 4%	28	(87)	27	(93)	47	(86)	43	(91)	64	(86)	73	(91)	70	(89)	75	(92)
Signs and symptoms in breast 611.79	685 3%	104 4%	789 3%	41	(81)	29	(65)	58	(80)	43	(65)	75	(81)	74	(67)	85	(84)	79	(70)
Other specified disorders of breast 611.8	944 4%	121 4%	1,065 4%	39	(80)	52	(92)	55	(78)	70	(90)	74	(79)	97	(88)	82	(80)	108	(97)
Diffuse cystic mastopathy 610.1	601 2%	91 3%	692 2%	86	(103)	117	(121)	101	(102)	133	(117)	118	(102)	163	(116)	128	(102)	172	(119)
Signs and symptoms in breast 611.71	531 2%	85 3%	616 2%	57	(91)	73	(94)	72	(90)	88	(96)	91	(89)	115	(98)	97	(91)	123	(99)
Unspecified breast disorder 611.9	411 2%	35 1%	446 2%	22	(61)	62	(100)	39	(61)	77	(95)	58	(61)	104	(95)	65	(63)	108	(94)
Other breast diagnosis code***	1575 7%	146 7%	1721 7%	43	(92)	45	(98)	59	(91)	58	(98)	83	(93)	96	(98)	81	(93)	91	(96)
Total/ Average	25,827	2,888	28,715	38		48		55		63		73		92		80		98	

DX, diagnosis; Path, pathological Note: This sample is from women that meet the overall inclusion/exclusion criteria (2003-2007) (n=28,715)
*First biopsy, excision, or definitive breast cancer surgery; ** First breast excision, partial mastectomy or total mastectomy
***174.0-174.8, 217, 233.0, 238.3, 239.0, 610.0, 610.2-610.9, 611.0-611.7, 793.8, V71.1

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Figure A.1. Absolute standardized differences before and after adjusting with inverse probability weights for the time to surgery analysis
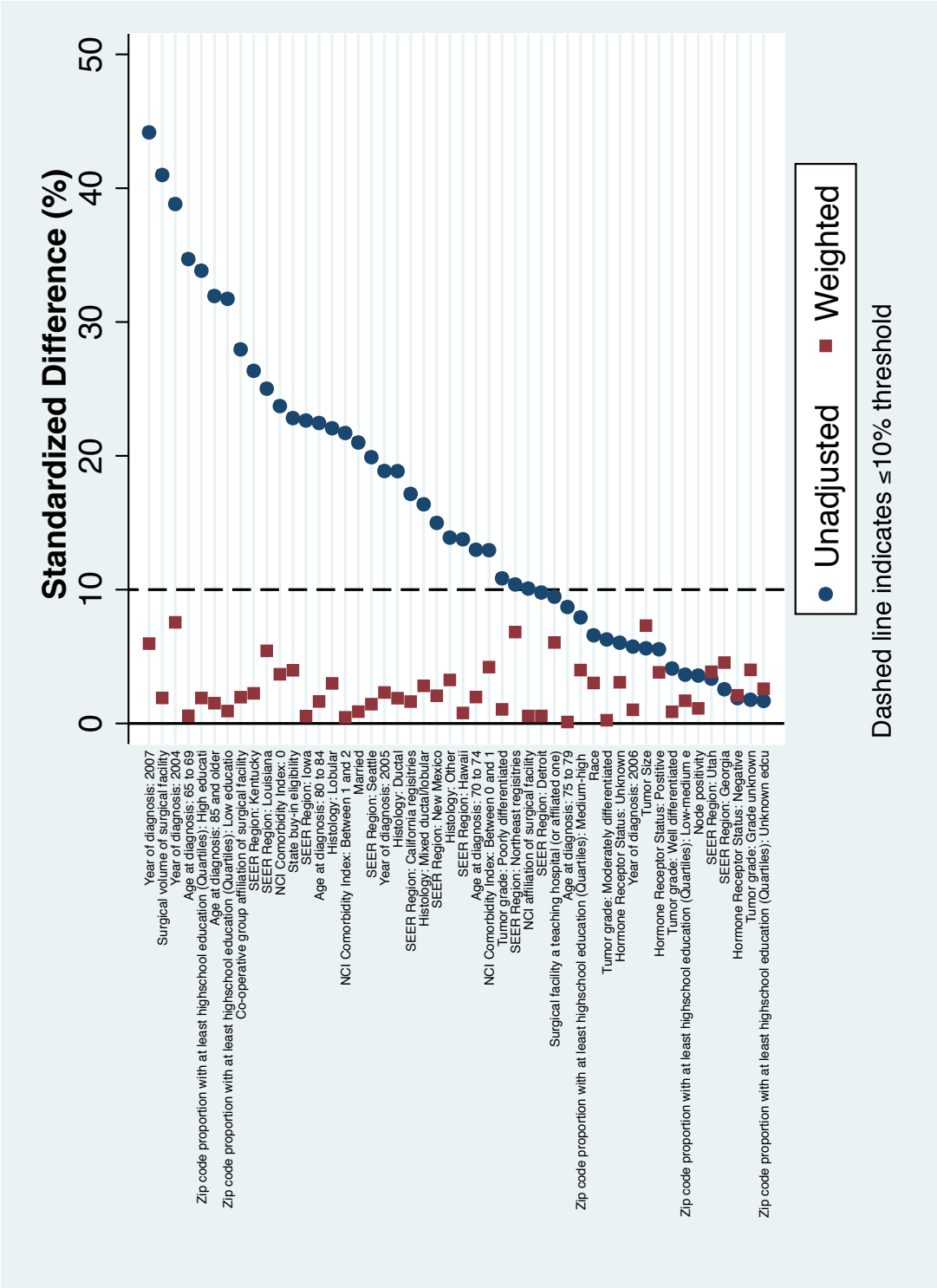
Figure A.2. Absolute standardized differences before and after adjusting with inverse probability weights for the first surgical procedure (main analysis, n= 24,439)
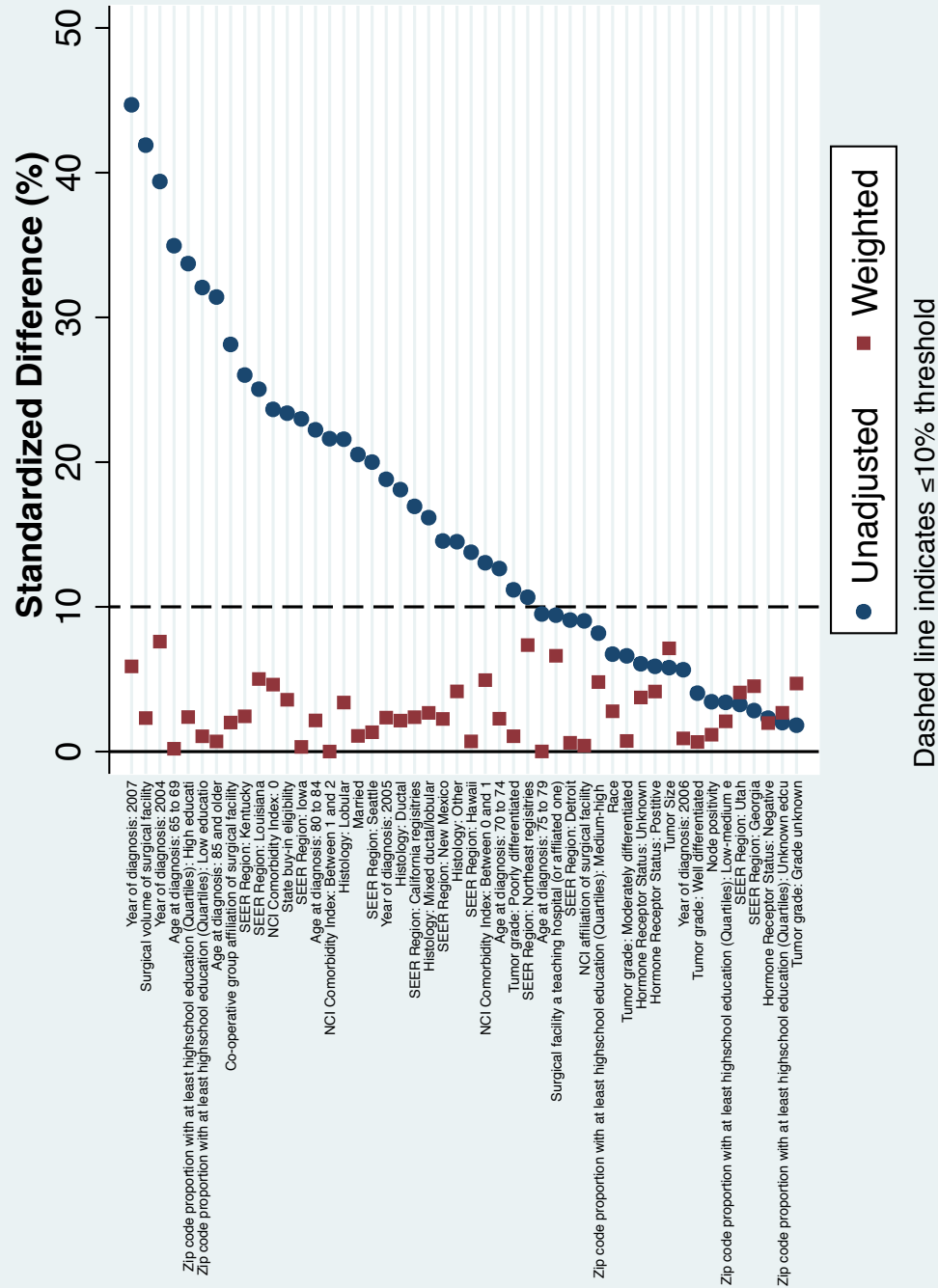
Table A.4. Multivariate proportional hazard model examining the time to complete surgery

	Hazard Ratio	95% Conf. Interval
Preoperative breast MRI	0.93***	[0.89, 0.97]
Tumor size		
< 2cm	(ref.)	
≥ 2cm, < 5cm	1.17***	[1.14, 1.21]
Tumor grade		
Well differentiated	(ref.)	
Moderately differentiated	1.05**	[1.02, 1.09]
Poorly differentiated	1.07**	[1.02, 1.11]
Grade unknown	0.84***	[0.79, 0.90]
Hormone Receptor Status		
Positive	(ref.)	
Negative	1.01	[0.97, 1.05]
Unknown	0.97	[0.92, 1.01]
Node positivity	1.06**	[1.02, 1.10]
Histology		
Ductal	(ref.)	
Lobular	0.95*	[0.91, 1.00]
Mixed ductal/lobular	0.95*	[0.90, 0.99]
Other	0.97	[0.92, 1.02]
NCI Comorbidity Index		
0	(ref.)	
Between 0 and 1	0.94***	[0.91, 0.97]
Greater than 1	0.91***	[0.86, 0.95]
Age at diagnosis		
65 to 69	(ref.)	
70 to 74	1.00	[0.96, 1.04]
75 to 79	1.03	[0.99, 1.07]
80 to 84	1.04	[0.99, 1.09]
85 and older	1.05	[1.00, 1.11]
Married	1.03*	[1.01, 1.06]
State buy-in coverage		
No	(ref.)	
Yes	0.93**	[0.89, 0.97]
Race		
White	(ref.)	
Non-white	0.91	[0.79, 1.04]
Cooperative group affiliation of surgical facility[†]	0.97	[0.94, 1.00]
NCI affiliation of surgical facility	0.76***	[0.72, 0.81]
Surgical facility a teaching hospital (or affiliated one)	0.95**	[0.93, 0.98]
Surgical volume of surgical facility		
Low	(ref.)	
High	1.02	[0.99, 1.05]
Zip code proportion with at least a high school education (quartiles)		
Low education	(ref.)	
Low-medium education	0.98	[0.94, 1.01]
Medium-high education	0.97	[0.93, 1.01]
High education	1.01	[0.97, 1.06]
Unknown education	0.96	[0.89, 1.03]

Table A.4. Multivariate proportional hazard model examining the time to complete surgery (cont.)

	Hazard Ratio	95% Conf. Interval
Year of diagnosis		
2004	(ref.)	
2005	1.00	[0.96, 1.04]
2006	0.96*	[0.92, 0.99]
2007	0.97	[0.93, 1.01]
SEER Region		
California registries	(ref.)	
Northeast registries	0.98	[0.93, 1.02]
Georgia	1.02	[0.94, 1.10]
Detroit	0.99	[0.93, 1.05]
Iowa	1.55***	[1.45, 1.65]
New Mexico	1.09	[0.99, 1.20]
Seattle	1.07*	[1.01, 1.14]
Utah	1.44***	[1.32, 1.57]
Kentucky	1.23***	[1.16, 1.30]
Louisiana	1.36***	[1.28, 1.44]
Hawaii	1.13	[1.00, 1.29]
Observations	25,038	
AIC	418911.7	

* p<0.05, ** p<0.01, *** p<0.001

MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute; AIC, Akaike information criterion

† Robust standard errors

‡ NCI Cooperative Groups having breast cancer research portfolios

Table A.5. Multivariate logistic regression examining the likelihood of a mastectomy as the first surgical procedure (main analysis, n= 24,439) †

	Odds Ratio	95% Conf. Interval
Preoperative breast MRI	1.55***	[1.40, 1.72]
Tumor size		
< 2cm	(ref.)	
≥ 2cm, < 5cm	2.84***	[2.65, 3.05]
Tumor grade		
Well differentiated	(ref.)	
Moderately differentiated	1.11*	[1.02, 1.21]
Poorly differentiated	1.23***	[1.11, 1.36]
Grade unknown	1.18*	[1.01, 1.39]
Hormone receptor status		
Positive	(ref.)	
Negative	1.32***	[1.19, 1.46]
Unknown	1.57***	[1.40, 1.76]
Node positivity	1.93***	[1.79, 2.08]
Histology		
Ductal	(ref.)	
Lobular	1.14*	[1.02, 1.27]
Mixed ductal/lobular	1.11	[0.98, 1.25]
Other	0.83**	[0.73, 0.95]
NCI Comorbidity Index		
0	(ref.)	
Between 0 and 1	1.09*	[1.01, 1.17]
Greater than 1	1.25***	[1.12, 1.40]
Age at diagnosis		
65 to 69	(ref.)	
70 to 74	1.19***	[1.08, 1.32]
75 to 79	1.42***	[1.28, 1.58]
80 to 84	1.79***	[1.61, 2.00]
85 and older	1.80***	[1.59, 2.03]
Married	1.10*	[1.01, 1.20]
State buy-in coverage		
No	(ref.)	
Yes	1.28***	[1.15, 1.43]
Race		
White	(ref.)	
Non-white	1.13*	[1.01, 1.25]
Cooperative group affiliation of surgical facility†	1.14***	[1.06, 1.23]
NCI affiliation of surgical facility	0.73***	[0.62, 0.87]
Surgical facility a teaching hospital (or affiliated one)	0.97	[0.90, 1.05]
Surgical volume of surgical facility		
Low	(ref.)	
High	0.91*	[0.85, 0.98]
Zip code proportion with at least a high school education (quartiles)		
Low education	(ref.)	
Low-medium education	1.12*	[1.01, 1.23]
Medium-high education	1.16**	[1.05, 1.29]
High education	1.18**	
Unknown education	1.28**	[1.07, 1.52]

Table A.5. Multivariate logistic regression examining the likelihood of a mastectomy (cont.)

	Odds Ratio	95% Conf. Interval
Year of diagnosis		
2004	(ref.)	
2005	1.03	[0.94, 1.13]
2006	0.98	[0.90, 1.08]
2007	1.07	[0.97, 1.17]
SEER Region		
California registries	(ref.)	
Northeast registries	0.62***	[0.55, 0.69]
Georgia	1.31**	[1.09, 1.57]
Detroit	0.73***	[0.62, 0.85]
Iowa	2.02***	[1.75, 2.34]
New Mexico	0.87	[0.68, 1.11]
Seattle	1.13	[0.98, 1.29]
Utah	1.13	[0.92, 1.38]
Kentucky	1.75***	[1.53, 2.02]
Louisiana	1.36***	[1.18, 1.56]
Hawaii	0.91	[0.66, 1.25]
Observations	24,439	
AIC	23223.7	

MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting; SEER, Surveillance, Epidemiology and End Results; AIC, Akaike information criterion; NCI, National Cancer Institute

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

† Robust standard errors

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Table A.6. Baseline characteristics of patients in the analysis examining the first surgical procedure (sub-analysis, n= 17,942)

	Unadjusted data				Data adjusted using Inverse Probability Weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= 17,942	N= 15,514	N= 2,428		N= 15,431	N= 2,416	
Preoperative breast MRI (%)	13.5	0.0	100.0	<0.001	0.0	100.0	<0.001
Mastectomy as the first surgical procedure	30.3	30.6	29.0	0.01	29.3	34.0	0.008
Tumor size (%)				<0.001			0.05
< 2cm	69.2	68.6	73.5		69.4	72.4	
≥ 2cm, < 5cm	30.8	31.4	26.5		30.6	27.6	
Tumor grade (%)				<0.001			0.98
Well differentiated	25.3	24.9	28.0		25.3	25.8	
Moderately differentiated	44.0	43.7	46.0		44.0	43.8	
Poorly differentiated	26.0	26.7	21.4		25.9	25.8	
Grade unknown	4.8	4.8	4.6		4.8	4.5	
Hormone receptor status (%)				0.004			0.32
Positive	78.1	77.7	80.4		78.1	78.8	
Negative	13.6	13.7	12.8		13.6	14.2	
Unknown	8.3	8.5	6.8		8.2	7.0	
Node positivity (%)	22.5	22.4	23.0	0.47	22.4	22.2	0.86
Histology				<0.001			0.5
Ductal	74.3	75.4	67.2		74.3	74.7	
Lobular	9.8	8.9	15.7		9.8	9.3	
Mixed ductal/lobular	8.3	7.7	12.2		8.4	9.3	
Other	7.6	8.0	4.9		7.5	6.7	
NCI Comorbidity Index (%)				<0.001			0.78
0	64.3	62.8	74.0		64.4	63.3	
Between 0 and 1	27.4	28.2	22.4		27.4	28.6	
Greater than 1	8.3	9.1	3.5		8.2	8.1	
Age at diagnosis (%)				<0.001			0.61
65 to 69	20.0	17.9	33.6		20.1	19.7	
70 to 74	24.3	23.5	29.6		24.5	26.6	
75 to 79	23.8	24.3	20.5		23.9	23.8	
80 to 84	19.1	20.2	12.2		19.1	18.8	
85 and older	12.7	14.1	4.1		12.4	11.1	
Married (%)	45.3	43.8	55.2	<0.001	45.4	46.5	0.49
State buy-in coverage (%)				<0.001			0.1
No	89.6	88.8	94.8		89.7	91.5	
Yes	10.4	11.2	5.2		10.3	8.5	
Race (%)				0.002			0.24
White	87.2	86.9	89.2		87.4	88.7	
Non-white	12.8	13.1	10.8		12.6	11.3	
Cooperative group affiliation of surgical facility (%)[‡]	53.6	52.0	63.7	<0.001	53.8	54.0	0.88
NCI affiliation of surgical facility (%)	5.2	5.0	6.0	0.05	5.2	5.0	0.72
Surgical facility a teaching hospital or affiliated one	53.0	52.7	54.7	0.07	53.2	56.8	0.03

Table A.6. Baseline characteristics of patients in the analysis examining the first surgical procedure (sub-analysis, cont.)

	Unadjusted data				Data adjusted using Inverse Probability Weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= 17,942	N= 15,514	N= 2,428		N= 15,431	N= 2,416	
Surgical volume of surgical facility (%)				<0.001			0.84
Low	46.0	48.6	29.9		45.9	46.2	
High	54.0	51.4	70.1		54.1	53.8	
Zip code proportion with at least high school education (% in each quartile)				<0.001			0.48
Low education	27.2	25.4	38.6		27.3	27.1	
Low-medium education	24.9	24.8	25.5		25.0	26.0	
Medium-high education	22.6	23.0	20.1		22.6	20.8	
High education	21.3	22.9	11.5		21.1	21.1	
Unknown education	3.9	3.9	4.3		4.0	5.0	
Year of diagnosis (%)				<0.001			0.21
2004	23.1	25.0	11.2		22.9	20.2	
2005	24.1	25.1	17.5		24.1	24.1	
2006	26.0	25.6	28.3		26.0	26.4	
2007	26.8	24.3	43.0		27.0	29.3	
SEER Region (%)				<0.001			0.45
California registries	34.8	34.1	39.7		34.9	33.9	
Northeast registries	22.6	22.1	26.0		22.8	25.9	
Georgia	3.7	3.7	3.2		3.6	2.9	
Detroit	6.1	6.4	4.4		6.2	6.3	
Iowa	6.9	7.5	2.6		6.8	5.3	
New Mexico	1.9	1.5	4.8		1.9	1.7	
Seattle	6.7	5.9	12.0		6.8	6.8	
Utah	2.7	2.7	2.4		2.7	2.3	
Kentucky	7.5	8.3	2.7		7.4	8.8	
Louisiana	5.8	6.4	2.1		5.8	4.9	
Hawaii	1.2	1.4	0.1		1.1	1.2	

P-values by t-test for continuous variables and chi2 test for binary / categorical variables, Mean (Standard Deviation) or %

MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; PM, Partial mastectomy; TM, Total mastectomy; NCI, National Cancer Institute

‡ NCI Cooperative Groups having breast cancer research portfolios

Table A.7. Multivariate logistic regression examining the likelihood of a mastectomy as the first surgical procedure (sub-analysis, n=17, 942) †

	Odds Ratio	95% Conf. Interval
Preoperative breast MRI	1.48***	[1.33, 1.65]
Tumor size		
< 2cm	(ref.)	
≥ 2cm, < 5cm	2.54***	[2.36, 2.74]
Tumor grade		
Well differentiated	(ref.)	
Moderately differentiated	1.09	[0.99, 1.19]
Poorly differentiated	1.18**	[1.05, 1.31]
Grade unknown	1.37***	[1.15, 1.63]
Hormone receptor status		
Positive	(ref.)	
Negative	1.31***	[1.18, 1.46]
Unknown	1.49***	[1.32, 1.68]
Node positivity	1.92***	[1.77, 2.08]
Histology		
Ductal	(ref.)	
Lobular	1.17*	[1.04, 1.31]
Mixed ductal/lobular	1.12	[0.98, 1.27]
Other	0.90	[0.78, 1.03]
NCI Comorbidity Index		
0	(ref.)	
Between 0 and 1	1.12**	[1.04, 1.21]
Greater than 1	1.35***	[1.19, 1.52]
Age at diagnosis		
65 to 69	(ref.)	
70 to 74	1.19**	[1.06, 1.33]
75 to 79	1.45***	[1.30, 1.61]
80 to 84	1.79***	[1.59, 2.01]
85 and older	1.69***	[1.48, 1.93]
Married	0.93*	[0.86, 1.00]
State buy-in coverage		
No	(ref.)	
Yes	1.40***	[1.25, 1.57]
Race		
White	(ref.)	
Non-white	1.23***	[1.10, 1.38]
Cooperative group affiliation of surgical facility[†]	1.04	[0.96, 1.12]
NCI affiliation of surgical facility	0.74**	[0.62, 0.89]
Surgical facility a teaching hospital (or affiliated)	0.94	[0.86, 1.01]
Surgical volume of surgical facility		
Low	(ref.)	
High	1.98***	[1.79, 2.19]
Zip code proportion with at least a high school education (quartiles)		
Low education	(ref.)	
Low-medium education	1.16**	[1.05, 1.28]
Medium-high education	1.31***	[1.17, 1.47]
High education	1.45***	[1.28, 1.64]
Unknown education	1.46***	[1.22, 1.75]

Table A.7. Multivariate logistic regression examining the likelihood of a mastectomy as the first surgical procedure (cont.)

	Odds Ratio	95% Conf. Interval
Year of diagnosis		
2004	(ref.)	
2005	0.93	[0.84, 1.03]
2006	0.80***	[0.73, 0.89]
2007	0.87**	[0.79, 0.96]
SEER Region		
California registries	(ref.)	
Northeast registries	0.67***	[0.60, 0.75]
Georgia	1.33**	[1.10, 1.61]
Detroit	0.93	[0.79, 1.11]
Iowa	2.53***	[2.15, 2.98]
New Mexico	0.96	[0.74, 1.24]
Seattle	1.15	[0.99, 1.34]
Utah	1.29*	[1.04, 1.60]
Kentucky	1.98***	[1.70, 2.30]
Louisiana	1.95***	[1.67, 2.28]
Hawaii	0.83	[0.59, 1.17]
Observations		17,942
AIC		19507.9

MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; AIC, Akaike information criterion; NCI, National Cancer Institute
* $p<0.05$, ** $p<0.01$, *** $p<0.001$
† Robust standard errors

Figure A.3. Breast MRI propensity score distribution for the analysis examining the first surgical procedure (sub-analysis, n=17,942)
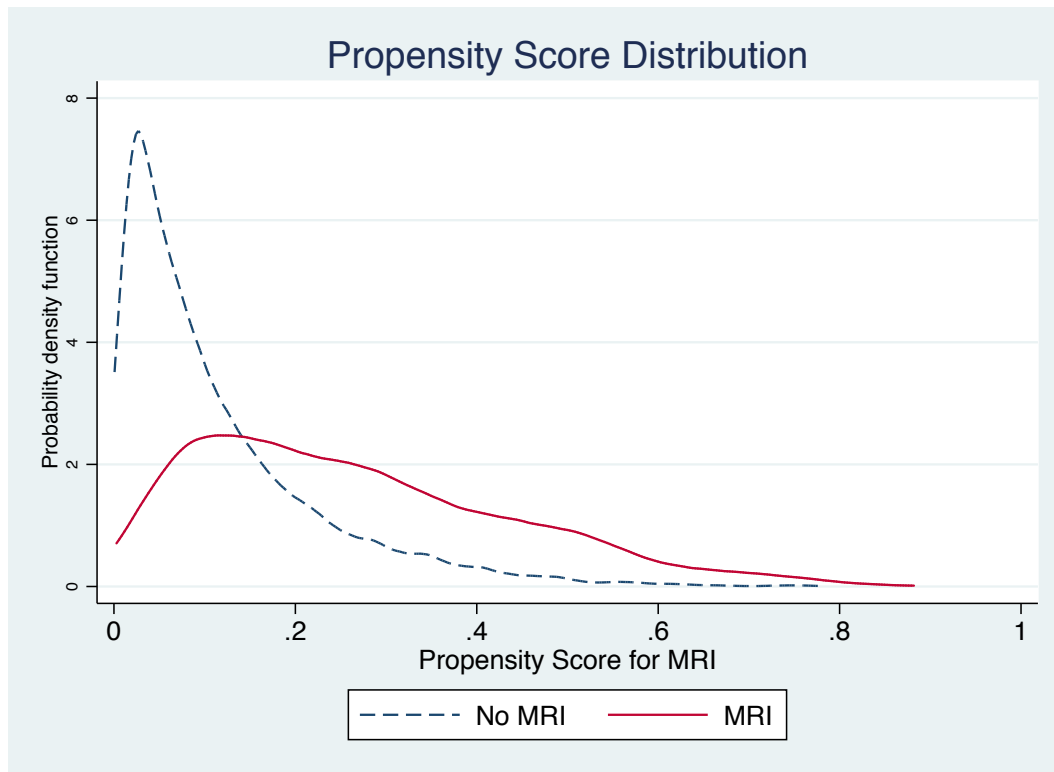
Figure A.4. Absolute standardized differences before and after adjusting with inverse probability weights for the first surgical procedure (sub-analysis, n= 17,942)
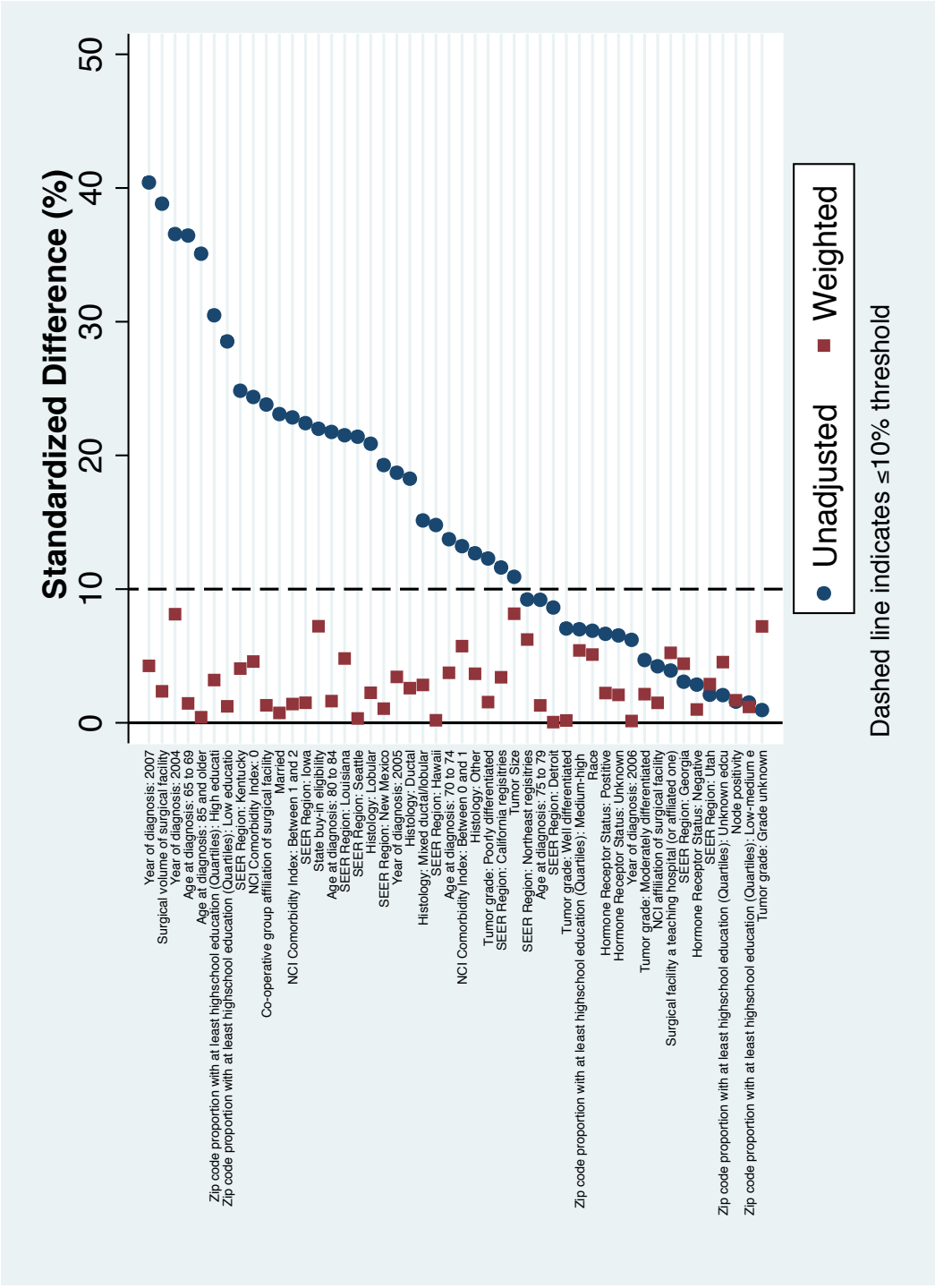
Table B.1. SEER-Medicare inclusion/exclusion criteria

Inclusion Criteria	Included	Excluded
Breast cancer diagnosis in SEER	260,079	
Diagnosed between 2003 and 2007 (inclusive)	143,757	116,322
First or primary cancer	131,974	11,783
Age 66 or older at diagnosis	86,127	45,847
Female	85,367	760
Reporting source not autopsy or death certificate	84,466	901
Laterality is not bilateral or unknown	83,659	807
Original reason for Medicare entitlement not disability or ESRD	79,355	4,304
Has valid month of diagnosis	79,114	241
Has no HMO enrollment during study period*	56,652	22,462
Has continuous enrollment in Part A&B during the study period*	52,038	4,614
Has comorbidity score and was able to be matched to claims during the study period*	48,283	3,755
Diagnosed between 2004 and 2007**	39,652	8,631

*Study period is 12 months prior to diagnosis month until the end of data or death
ESRD, end stage renal disease; HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology and End Results
** We excluded patients diagnosed in 2003 because few patients (n=148) had a breast MRI, and were unable to be balanced using propensity scores.

Table B.2. Codes for identifying breast cancer events and treatments

Study time frame	Definition
Initial treatment phase for the re-excision analysis	The date of the first claim with a breast-related diagnosis code to the end of the initial treatment as defined as the last day of treatment before a gap in treatment of 90 days or more or the end of the study period (December 31, 2009) or the patient's death.
Date of second breast cancer event	The date of the event (Figure 5.3) that identified the patient as having a second breast cancer event. For example, if the patient was considered to have a second breast cancer based on having a second primary in the SEER registries (n=759), the SEER date of the second primary was used. For women who were identified as having a second breast cancer based on the surgical procedure in SEER (n=161), the date of her mastectomy >180 days after the primary breast cancer was used because SEER does not capture the date of surgery. For women who were identified as having a second breast cancer based on two visits with a code for a secondary malignant neoplasm within 60 days and >365 days after the primary breast cancer, the date of her second visit was used as the date of the second breast cancer event.

First breast-related diagnosis code date	Definition
Breast-related diagnosis code	174.* Malignant neoplasm of female breast 217. Benign neoplasm of breast 233.0 Carcinoma in situ of breast 238.3 Neoplasm of uncertain behavior of breast 239.3 Neoplasms of unspecified nature breast 610.0 Solitary cyst of breast 610.1 Diffuse cystic mastopathy 610.2 Fibroadenosis of breast 610.3 Fibrosclerosis of breast 610.9 Benign mammary dysplasia, unspecified 611.0 Inflammatory disease of breast 611.1 Hypertrophy of breast 611.3 Fat necrosis of breast 611.8 Other specified disorders of breast 611.9 Unspecified breast disorder 611.71 Signs and symptoms in breast 611.72 Lump or mass in breast 611.79 Signs and symptoms in breast 793.80 Abnormal mammogram, unspecified 793.81 Mammographic microcalcification 793.89 Other (abnormal) findings on radiological examination of breast V711 Observation for suspected malignant neoplasm
First breast-related diagnosis code date	The day of the first breast-related diagnosis code listed above within one year prior to the SEER diagnosis month

Surgical Procedure	Code identified in claims
Breast Excision	ICD-9-CM: 85.20-85.22; HCPCS: 19120, 19125, 19126, 19300
Partial Mastectomy	ICD-9-CM: 85.23; HCPCS: 19160/2, 19301/2
Mastectomy	ICD-9-CM: 85.4X; HCPCS: 19180, 19182, 19200, 19220, 19240, 19303-7

SEER, Surveillance, Epidemiology and End Results; HCPCS, Healthcare Common Procedure Classification System; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; CPT, Current Procedural Terminology; DRG, Diagnosis-related group.

- Algorithm and codes defined by Chubak et al. (2012).

Table B.2. Codes for identifying breast cancer events and treatments (cont.)

Other treatment	Code identified in claims
Radiation	ICD-9-CM: 92.2X. 93.3, 92.4 HCPCS: 77401-77499, 77520, 77522, 77523, 77525, 77373, 77750-77799; G0243; G0174, G0251, G0339, G0340 Revenue Center Code: 0333 DRG: 409 Other: V58.0, V66.1, V67.1
Chemotherapy	ICD-9-CM procedure: 99.25, 285.3, 999.81 CPT/HCPCS: 51720, 96400–96549, 99555, Q008–3Q0085 (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
Second breast cancer event diagnosis codes*	**Code identified in claims**
Secondary malignant neoplasm	ICD-9-CM: 196.x, 197.x, 198.x, 199.x
Secondary non-breast malignant neoplasm	ICD-9-CM: 197.x, 198.x excluding 198.2 & 198.81

SEER, Surveillance, Epidemiology and End Results; HCPCS, Healthcare Common Procedure Classification System; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; CPT, Current Procedural Terminology; DRG, Diagnosis-related group.

* Algorithm and codes defined by Chubak et al. (2012).

Table B.3. Multivariate logistic regression to generate preoperative breast MRI propensity scores

| | Analysis examining re-excisions | | | | Analysis examining second breast cancer events (n=24,438) | |
| | Main analysis: Patients with initial BCS eligible for re-excision (n=17,199) | | Sub-analysis: Patients with an partial mastectomy eligible for re-excision (n=11,362) | | | |
	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval
Biopsy before first surgical procedure	2.00***	[1.77, 2.27]	3.63***	[2.73, 4.83]		
Received radiation therapy					1.04	[0.95, 1.14]
Received chemotherapy					1.30***	[1.16, 1.46]
Tumor size						
≤ 2cm	(ref.)		(ref.)		(ref.)	
> 2cm, ≤ 5cm	0.90	[0.79, 1.04]	0.85*	[0.73, 0.99]	0.95	[0.86, 1.06]
Tumor grade						
Well differentiated	(ref.)		(ref.)		(ref.)	
Moderately differentiated	1.05	[0.93, 1.19]	1.03	[0.90, 1.19]	1.02	[0.92, 1.13]
Poorly differentiated	0.86	[0.73, 1.01]	0.90	[0.75, 1.09]	0.80**	[0.70, 0.92]
Grade unknown	0.93	[0.71, 1.19]	0.85	[0.62, 1.16]	0.89	[0.72, 1.10]
Hormone receptor status						
Positive	(ref.)		(ref.)		(ref.)	
Negative	1.09	[0.91, 1.30]	1.03	[0.84, 1.27]	1.15	[1.00, 1.32]
Unknown	1.03	[0.83, 1.27]	0.97	[0.76, 1.24]	1.02	[0.86, 1.21]
Node positivity	1.07	[0.93, 1.23]	1.10	[0.94, 1.29]	1.03	[0.92, 1.15]
Histology						
Ductal	(ref.)		(ref.)		(ref.)	
Lobular	2.22***	[1.89, 2.57]	2.27***	[1.89, 2.72]	2.13***	[1.88, 2.42]
Mixed ductal/lobular	1.50***	[1.25, 1.77]	1.43***	[1.17, 1.74]	1.68***	[1.46, 1.92]
Other	0.82	[0.66, 1.02]	0.80	[0.62, 1.02]	0.79*	[0.65, 0.94]
NCI Comorbidity Index						
0	(ref.)		(ref.)		(ref.)	
Between 0 and 1	0.85**	[0.75, 0.95]	0.85*	[0.74, 0.98]	0.79***	[0.71, 0.87]
Greater than 1	0.63***	[0.49, 0.82]	0.61**	[0.45, 0.83]	0.54***	[0.44, 0.67]
Age at diagnosis						
65 to 69	(ref.)		(ref.)		(ref.)	
70 to 74	0.68***	[0.60, 0.78]	0.68***	[0.58, 0.78]	0.69***	[0.62, 0.77]
75 to 79	0.47***	[0.41, 0.55]	0.46***	[0.39, 0.54]	0.48***	[0.43, 0.54]
80 to 84	0.36***	[0.31, 0.43]	0.38***	[0.31, 0.46]	0.35***	[0.30, 0.40]
85 and older	0.23***	[0.18, 0.29]	0.21***	[0.16, 0.28]	0.19***	[0.15, 0.23]
Married	1.07	[0.96, 1.18]	1.13	[1.00, 1.27]	1.10*	[1.00, 1.19]
State buy-in coverage						
No	(ref.)		(ref.)		(ref.)	
Yes	0.61***	[0.49, 0.77]	0.71*	[0.55, 0.92]	0.57***	[0.47, 0.69]
Race						
White	(ref.)		(ref.)		(ref.)	
Non-white	1.00	[0.85, 1.18]	1.00	[0.82, 1.21]	0.90	[0.78, 1.03]
Cooperative group affiliation of surgical facility[†]	1.32***	[1.18, 1.48]	1.35***	[1.18, 1.54]	1.34***	[1.22, 1.48]

Table B.3. Multivariate logistic regression to generate preoperative breast MRI propensity scores (cont.)

	Analysis examining re-excisions				Analysis examining second breast cancer events	
	Main analysis: Patients with initial BCS eligible for re-excision (n=17,199)		Sub-analysis: Patients with an partial mastectomy eligible for re-excision (n=11,362)		(n=24,438)	
	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval	Odds Ratio	95% Conf. Interval
NCI affiliation of surgical facility	1.19	[0.96, 1.46]	0.98	[0.76, 1.26]	1.17	[0.98, 1.39]
Surgical volume of surgical facility						
Low	(ref.)		(ref.)		(ref.)	
High	1.91***	[1.69, 2.14]	1.96***	[1.71, 2.25]	1.98***	[1.79, 2.18]
Zip code proportion with at least a high school education (quartiles)						
Low education	(ref.)		(ref.)		(ref.)	
Low-medium education	0.77***	[0.68, 0.88]	0.78***	[0.67, 0.90]	0.70***	[0.63, 0.78]
Medium-high education	0.74***	[0.64, 0.86]	0.76**	[0.64, 0.90]	0.66***	[0.58, 0.75]
High education	0.54***	[0.45, 0.65]	0.55***	[0.44, 0.69]	0.48***	[0.41, 0.56]
Unknown education	0.68**	[0.51, 0.89]	0.65**	[0.47, 0.89]	0.72**	[0.58, 0.90]
Year of diagnosis						
2004	(ref.)		(ref.)		(ref.)	
2005	1.53***	[1.27, 1.82]	1.50***	[1.21, 1.85]	1.62***	[1.40, 1.88]
2006	2.42***	[2.05, 2.86]	2.55***	[2.10, 3.09]	2.70***	[2.35, 3.09]
2007	4.70***	[4.01, 5.52]	4.61***	[3.83, 5.56]	5.09***	[4.46, 5.80]
SEER Region						
California registries	(ref.)		(ref.)		(ref.)	
Northeast registries	1.06	[0.91, 1.22]	1.12	[0.94, 1.32]	1.03	[0.91, 1.17]
Georgia	0.45***	[0.33, 0.62]	0.51***	[0.36, 0.71]	0.52***	[0.41, 0.66]
Detroit	0.54***	[0.42, 0.69]	0.51***	[0.38, 0.68]	0.55***	[0.45, 0.68]
Iowa	0.44***	[0.32, 0.61]	0.45***	[0.31, 0.65]	0.41***	[0.32, 0.52]
New Mexico	3.48***	[2.66, 4.55]	5.43***	[3.98, 7.41]	3.10***	[2.46, 3.90]
Seattle	1.56***	[1.29, 1.90]	1.71***	[1.38, 2.12]	1.67***	[1.42, 1.96]
Utah	0.62**	[0.44, 0.87]	0.76	[0.51, 1.11]	0.62***	[0.47, 0.81]
Kentucky	0.22***	[0.15, 0.32]	0.23***	[0.15, 0.35]	0.28***	[0.21, 0.36]
Louisiana	0.39***	[0.27, 0.55]	0.49***	[0.33, 0.74]	0.37***	[0.28, 0.48]
Hawaii	0.082***	[0.02, 0.27]	0.036**	[0.00, 0.27]	0.11***	[0.05, 0.29]
Observations	17,199		11,362		24,438	
AIC	10345.1		7682.5		14887.5	

* p<0.05, ** p<0.01, *** p<0.001"

BCS, Brest conserving surgery (i.e. partial mastectomy or breast excision); MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute; AIC, Akaike information criterion

[†] NCI Cooperative Groups having breast cancer research portfolios

Table B.4. Multivariate logistic regression examining the likelihood of a re-excision after BCS (main analysis, n=17,199)

	Odds Ratio	95% Conf. Interval
Preoperative breast MRI	0.97	[0.86, 1.09]
Biopsy before first surgical procedure	1.56***	[1.38, 1.77]
Initial BCS procedure was a breast excision	11.0***	[9.67, 12.45]
Tumor size		
≤ 2cm	(ref.)	
> 2cm, ≤ 5cm	1.39***	[1.27, 1.53]
Tumor grade		
Well differentiated	(ref.)	
Moderately differentiated	1.14**	[1.04, 1.24]
Poorly differentiated	1.25***	[1.11, 1.40]
Grade unknown	1.22*	[1.03, 1.46]
Hormone receptor status		
Positive	(ref.)	
Negative	1.03	[0.92, 1.17]
Unknown	1.13	[0.98, 1.29]
Node positivity	1.55***	[1.40, 1.71]
Histology		
Ductal	(ref.)	
Lobular	1.52***	[1.34, 1.73]
Mixed ductal/lobular	1.36***	[1.19, 1.57]
Other	1.04	[0.91, 1.19]
NCI Comorbidity Index		
0	(ref.)	
Between 0 and 1	1.04	[0.96, 1.13]
Greater than 1	0.99	[0.85, 1.14]
Age at diagnosis		
65 to 69	(ref.)	
70 to 74	0.93	[0.84, 1.03]
75 to 79	0.87**	[0.78, 0.96]
80 to 84	0.80***	[0.71, 0.90]
85 and older	0.54***	[0.47, 0.63]
Married	1.07	[0.99, 1.15]
State buy-in coverage		
No	(ref.)	
Yes	1.00	[0.87, 1.14]
Race		
White	(ref.)	
Non-white	1.00	[0.85, 1.18]
Cooperative group affiliation of surgical facility[†]	0.86***	[0.79, 0.93]
NCI affiliation of surgical facility	0.97	[0.82, 1.15]
Surgical volume of surgical facility		
Low volume	(ref.)	
High volume	1.09*	[1.01, 1.19]
Zip code proportion with at least a high school education (quartiles)		
Low education	(ref.)	
Low-medium education	0.95	[0.85, 1.05]
Medium-high education	0.98	[0.88, 1.10]
High education	1.11	[0.98, 1.25]
Unknown education	0.84	[0.69, 1.04]

Table B.4. Multivariate logistic regression examining the likelihood of a re-excision for patients with a BCS (cont.)

	Odds Ratio	95% Conf. Interval
Year of diagnosis		
2004	(ref.)	
2005	1.04	[0.94, 1.15]
2006	1.15**	[1.04, 1.27]
2007	1.00	[0.90, 1.10]
SEER Region		
California registries	(ref.)	
Northeast registries	1.32***	[1.18, 1.48]
Georgia	1.31*	[1.06, 1.63]
Detroit	2.19***	[1.88, 2.56]
Iowa	0.76**	[0.64, 0.91]
New Mexico	1.61***	[1.27, 2.05]
Seattle	0.81*	[0.68, 0.98]
Utah	0.94	[0.74, 1.20]
Kentucky	1.02	[0.87, 1.20]
Louisiana	1.73***	[1.48, 2.03]
Hawaii	0.94	[0.66, 1.33]
Observations	17,199	
AIC	18022.7	

BCS, breast conserving surgery (i.e. breast excision or partial mastectomy); MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute; AIC, Akaike information criterion

* p<0.05, ** p<0.01, *** p<0.001

Table B.5. Multivariate proportional hazard regression analysis of second breast cancer events

	Model adjusted for covariates		Model with IPW, adjusted for the first surgical treatment after estimating the IPW	
	Hazard Ratio	95% Conf. Interval	Hazard Ratio	95% Conf. Interval
Preoperative breast MRI	1.29***	[1.14, 1.46]	1.32*	[1.07, 1.63]
Complete surgery				
Breast conserving surgery	(ref.)		(ref.)	
Mastectomy	1.41***	[1.14, 1.46]	1.92***	[1.73, 2.13]
Received radiation therapy	1.40***	[1.23, 1.58]		
Received chemotherapy	2.16***	[1.94, 2.40]		
Tumor size				
≤ 2cm	(ref.)			
> 2cm, ≤ 5cm	1.32***	[1.19, 1.45]		
Tumor grade				
Well differentiated	(ref.)			
Moderately differentiated	1.11	[0.98, 1.25]		
Poorly differentiated	1.36***	[1.18, 1.56]		
Grade unknown	1.13	[0.90, 1.42]		
Hormone receptor status				
Positive	(ref.)			
Negative	1.37***	[1.22, 1.54]		
Unknown	1.20*	[1.02, 1.40]		
Node positivity	1.55***	[1.40, 1.72]		
Histology				
Ductal	(ref.)			
Lobular	0.88	[0.75, 1.04]		
Mixed ductal/lobular	1.21*	[1.05, 1.40]		
Other	0.81*	[0.67, 0.98]		
NCI Comorbidity Index				
0	(ref.)			
Between 0 and 1	1.15**	[1.06, 1.29]		
Greater than 1	1.35***	[1.19, 1.61]		
Age at diagnosis				
65 to 69	(ref.)			
70 to 74	1.04	[0.91, 1.18]		
75 to 79	1.28***	[1.11, 1.44]		
80 to 84	1.30***	[1.11, 1.49]		
85 and older	1.37***	[1.25, 1.78]		
Married	0.96	[0.85, 1.02]		
State buy-in coverage				
No	(ref.)			
Yes	1.17*	[1.02, 1.34]		
Race				
White	(ref.)			
Non-white	0.90	[0.79, 1.03]		
Cooperative group affiliation of surgical facility[†]	1.04	[0.95, 1.15]		
NCI affiliation of surgical facility	1.19	[1.00, 1.43]		
Surgical volume of surgical facility				
Low	(ref.)			
High	1.01	[0.92, 1.12]		

Table B.5. Multivariate proportional hazard regression analysis of second breast cancer events (cont.)

	Model adjusted for covariates		Model with IPW, adjusted for the first surgical treatment after estimating the IPW	
	Hazard Ratio	95% Conf. Interval	Hazard Ratio	95% Conf. Interval
Zip code proportion with at least a high school education (quartiles)				
Low education	(ref.)			
Low-medium education	0.94	[0.87, 1.12]		
Medium-high education	0.93	[0.84, 1.11]		
High education	0.97	[0.84, 1.14]		
Unknown education	1.16	[0.94, 1.46]		
Year of diagnosis				
2004	(ref.)			
2005	0.90	[0.80, 1.01]		
2006	0.94	[0.83, 1.06]		
2007	0.95	[0.81, 1.06]		
SEER Region				
California registries	(ref.)			
Northeast registries	1.18*	[1.04, 1.34]		
Georgia	0.93	[0.72, 1.21]		
Detroit	1.07	[0.89, 1.28]		
Iowa	1.12	[0.91, 1.34]		
New Mexico	1.18	[0.89, 1.56]		
Seattle	1.11	[0.92, 1.33]		
Utah	0.95	[0.72, 1.25]		
Kentucky	1.21*	[1.01, 1.45]		
Louisiana	1.03	[0.85, 1.24]		
Hawaii	0.71	[0.43, 1.18]		
Observations	24,438		24,438	
AIC	44,257.7		45,192.9	

MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute; AIC, Akaike information criterion

[†] NCI Cooperative Groups having breast cancer research portfolios

Figure B.1. Absolute standardized differences before and after adjusting with inverse probability weights for the re-excision analysis (main analysis)

Standardized Difference (%)
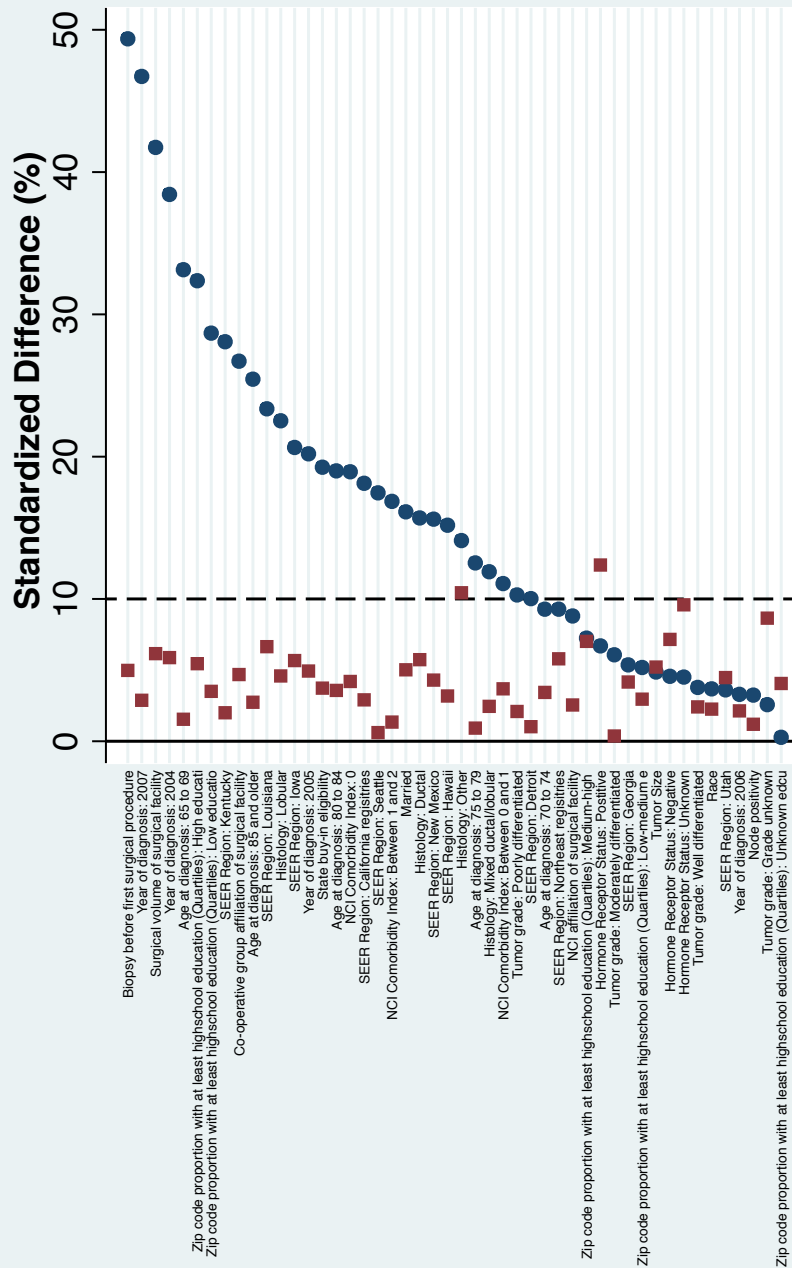
Unadjusted   Weighted

Dashed line indicates ≤10% threshold

Figure B.2. Absolute standardized differences before and after adjusting with inverse probability weights for the second breast cancer event analysis

Dashed line indicates ≤10% threshold
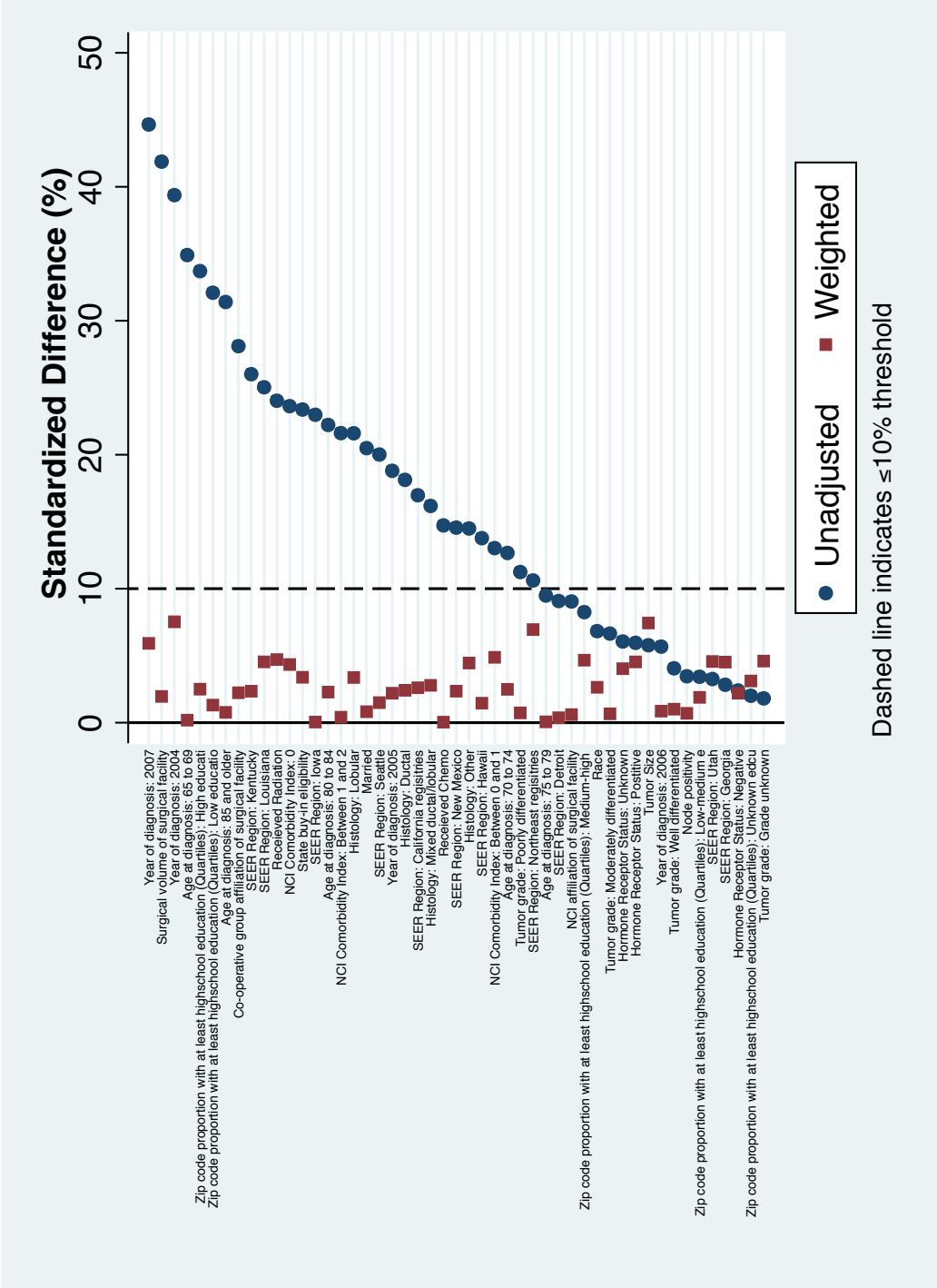
Figure B.3. Additional algorithms for identifying a second breast cancer event

A. Algorithm with estimated high sensitivity

Two visits with a code for a secondary malignant neoplasm within a 60 day period occurring >365 days after the primary breast cancer
(n = 24,439)

No → A second breast cancer record in the SEER registry (n=22,733)

Yes → **Second breast cancer event (n=1,706)**

No → A mastectomy >180 days after the primary breast cancer (n= 21,974)

Yes → **Second breast cancer event (n=759)**

No → A code for a secondary non-breast malignant neoplasm >180 days after the primary breast cancer (n= 21,684)

Yes → **Second breast cancer event (n=290)**

No → **No second breast cancer event (n=20,939)**

Yes → **Second breast cancer event (n=745)**

Sensitivity was estimated to be 96%, specificity 95%, and positive predictive value 74% based on validation study using a different study population (Chubak et al. 2012)

Figure created with permission from Chubak J, Yu O, Pocobelli G, et al: Administrative Data Algorithms to Identify Second Breast Cancer Events Following Early-Stage Invasive Breast Cancer. J Natl Cancer Inst 104:931-940, 2012.

Figure B.3. Additional algorithms for identifying a second breast cancer event (cont.)

B. Algorithm with estimated extremely high sensitivity

A code for a secondary malignant neoplasm >365 days after the primary breast cancer
(n = 24,439)

No — Breast surgery >180 days after the primary breast cancer (n=21,124)

Yes — **Second breast cancer event** (n=3,315)

No — Maximum time between two consecutive visits for chemotherapy (n= 19,922)

Yes — **Second breast cancer event** (n=1,202)

< 43 days — A second breast cancer record in the SEER registry (n= 19,012)

>43 days — **Second breast cancer event** (n=910)

No — **No second breast cancer event** (n=18,480)

Yes — **Second breast cancer event** (n=532)

Sensitivity was estimated to be 99%, specificity 81%, and positive predictive value 43% based on validation study using a different study population (Chubak et al. 2012)

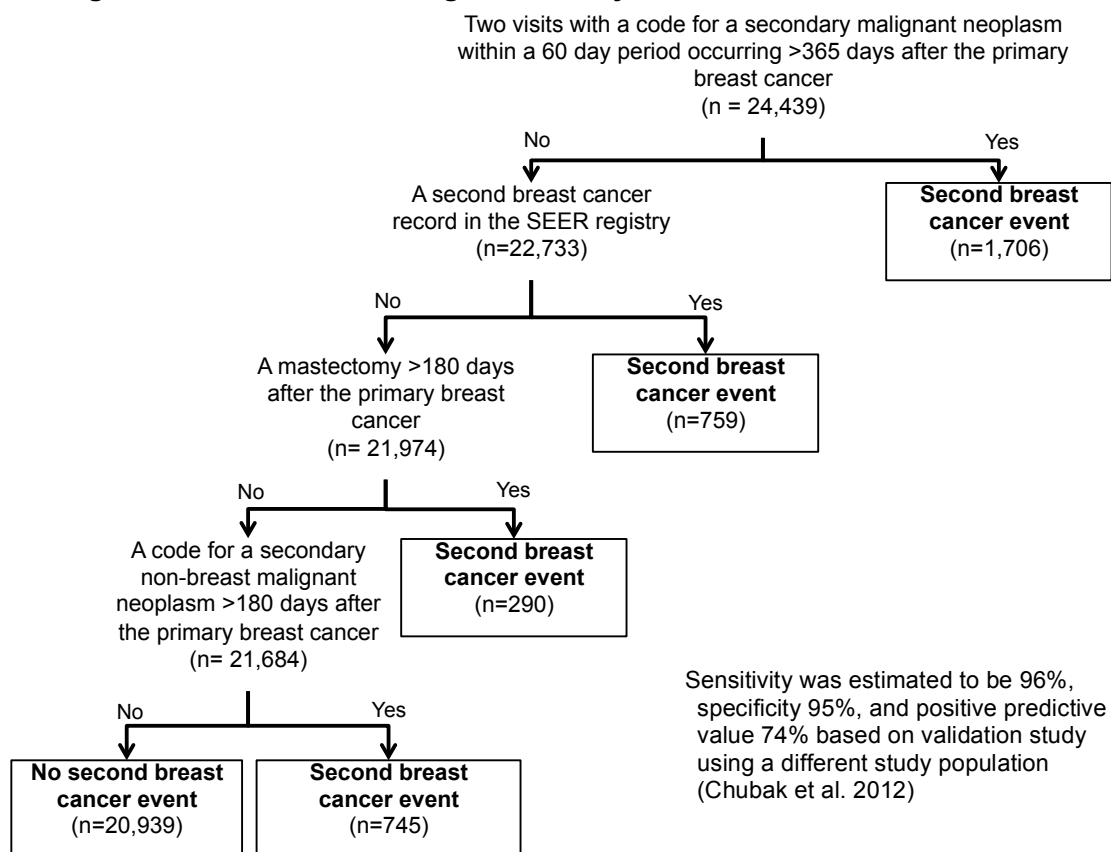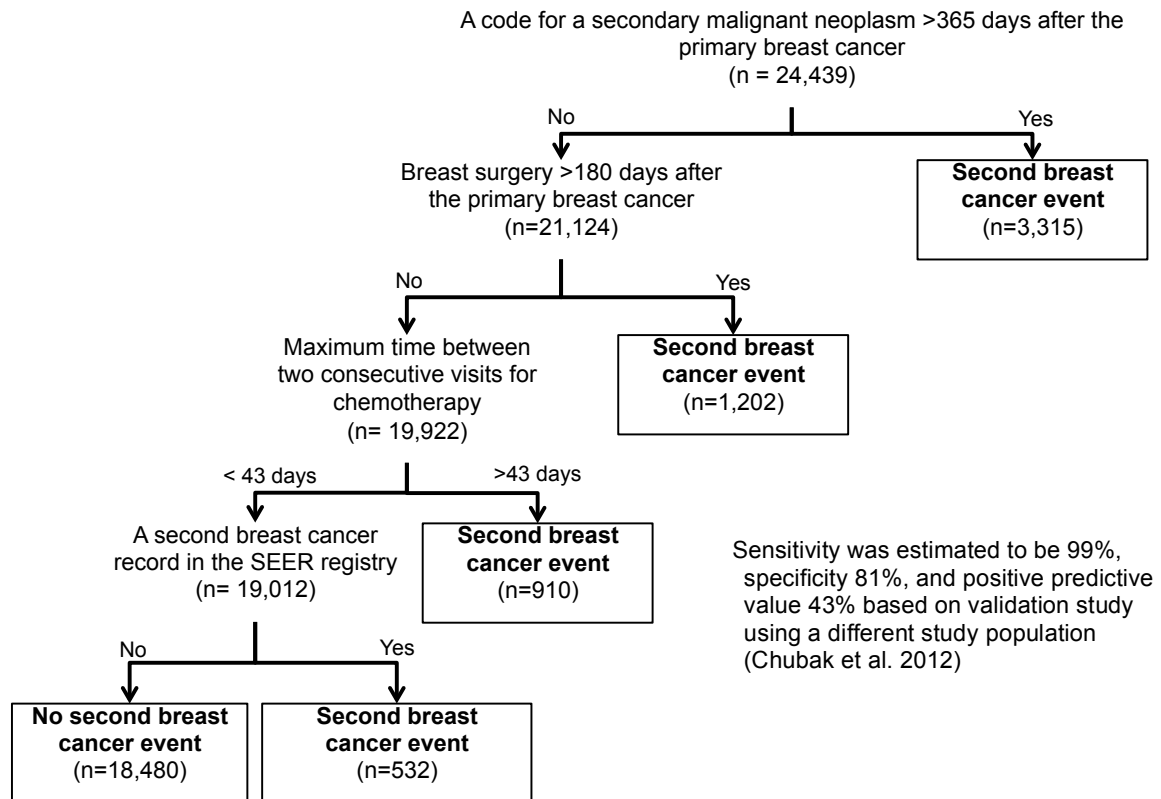Figure created with permission from Chubak J, Yu O, Pocobelli G, et al: Administrative Data Algorithms to Identify Second Breast Cancer Events Following Early-Stage Invasive Breast Cancer. J Natl Cancer Inst 104:931-940, 2012.

Table B.6. Baseline characteristics in the re-excision sub-analysis (n=11,362)

		Unadjusted data			Data adjusted using inverse probability weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= 11,362	N= 9,795	N= 1,567		N=9,765	N=1,560	
Preoperative breast MRI (%)	13.8	0	100	<0.001	0	100	<0.001
Re-excision after first surgical procedure	18.7	18.7	18.8	0.87	18.8	20.4	0.58
Biopsy before first surgical procedure	86	84.3	96.3	<0.001	86.0	84.4	0.54
Tumor size (%)				<0.001			0.37
≤ 2cm	77.3	76.8	80.7		77.3	79.2	
> 2cm, ≤ 5cm	22.7	23.2	19.3		22.7	20.8	
Tumor grade (%)				<0.001			0.71
Well differentiated	27.7	27.3	30.1		27.6	27.0	
Moderately differentiated	44.4	44.1	46.1		44.2	43.1	
Poorly differentiated	23.4	24.0	19.7		23.6	25.8	
Grade unknown	4.5	4.6	4.1		4.6	4.0	
Hormone receptor status (%)				0.03			0.37
Positive	80.8	80.4	83.2		80.8	78.0	
Negative	12.0	12.3	10.5		12.1	15.1	
Unknown	7.2	7.3	6.3		7.2	6.9	
Node positivity (%)	17.1	16.9	18.4	0.16	17.2	19.6	0.22
Histology				<0.001			0.43
Ductal	74.6	75.5	69.0		75.1	75.1	
Lobular	9.3	8.3	15.3		8.9	7.9	
Mixed ductal/lobular	8.2	7.8	10.6		8.1	9.9	
Other	7.9	8.3	5.2		7.9	7.1	
NCI Comorbidity Index (%)				<0.001			0.79
0	67.0	65.8	74.0		66.8	65.3	
Between 0 and 1	26.2	26.8	22.5		26.3	26.7	
Greater than 1	6.8	7.4	3.5		6.9	7.9	
Age at diagnosis (%)				<0.001			0.31
65 to 69	22.2	20.1	35.4		21.7	20.7	
70 to 74	25.6	25.0	29.3		25.7	30.5	
75 to 79	23.5	24.3	18.9		23.8	22.2	
80 to 84	17.6	18.4	12.2		17.7	17.1	
85 and older	11.1	12.2	4.3		11.1	9.5	
Married (%)	47.9	46.7	55.5	<0.001	47.8	50.8	0.24
State buy-in coverage (%)				<0.001			0.06
No	91.6	91.1	94.9		91.6	93.7	
Yes	8.4	8.9	5.1		8.4	6.3	
Race (%)				0.28			0.03
White	87.8	87.7	88.6		87.9	90.5	
Non-white	12.2	12.3	11.4		12.1	9.5	
Cooperative group affiliation of surgical facility (%)[‡]	55.5	54.1	64.4	<0.001	55.4	55.9	0.86
NCI affiliation of surgical facility (%)	5.8	5.7	6.2	0.47	5.8	5.6	0.8
Surgical facility a teaching hospital (or affiliated one)	54.7	54.8	54.2	0.66	55.4	53.4	0.46

Table B.6. Baseline characteristics in the re-excision sub-analysis (cont.)

	Unadjusted data				Data adjusted using inverse probability weighting		
	Overall	No breast MRI	Breast MRI	p-value	No breast MRI	Breast MRI	p-value
	N= 11,362	N= 9,795	N= 1,567		N=9,765	N=1,560	
Surgical volume of surgical facility (%)				<0.001			0.45
Low	42.5	44.9	27.4		42.8	44.8	
High	57.5	55.1	72.6		57.2	55.2	
Zip code proportion with at least high school education (% in each quartile)				<0.001			0.27
Low education	29.6	28.1	38.6		29.4	28.3	
Low-medium education	25.7	25.6	26.7		25.7	28.0	
Medium-high education	22.3	22.6	20.2		22.2	19.4	
High education	18.7	19.9	10.7		18.8	18.0	
Unknown education	3.8	3.8	3.8		3.8	6.4	
Year of diagnosis (%)				<0.001			0.61
2004	21.6	23.4	10.7		21.8	19.3	
2005	23.4	24.5	16.2		23.6	24.2	
2006	27.3	27.1	28.7		27.5	29.6	
2007	27.7	25.0	44.4		27.2	26.8	
SEER Region (%)				<0.001			0.73
California registries	36.6	35.9	41.0		36.7	34.7	
Northeast registries	25.0	24.6	27.2		25.2	27.5	
Georgia	3.7	3.8	2.9		3.8	3.2	
Detroit	6.5	6.8	4.5		6.6	6.1	
Iowa	5.2	5.7	2.2		5.3	5.2	
New Mexico	1.9	1.3	5.4		1.6	1.5	
Seattle	6.7	6.0	11.0		6.5	6.2	
Utah	2.4	2.5	2.3		2.5	2.2	
Kentucky	6.2	7.0	1.7		6.3	6.5	
Louisiana	4.3	4.7	1.9		4.3	4.2	
Hawaii	1.4	1.7	0.1		1.3	2.7	

P-values by t-test for continuous variables and chi2 test for binary / categorical variables, Mea (Standard Deviation) or %

MRI, Magnetic Resonance Imaging; SEER, Surveillance, Epidemiology and End Results; PM, Partial mastectomy; TM, Total mastectomy; NCI, National Cancer Institute

‡ NCI Cooperative Groups having breast cancer research portfolios

Table B.7. Likelihood of a re-excision after a partial mastectomy (sub-analysis, n=11,362)

	Odds Ratio	95% Conf. Interval
Preoperative breast MRI	0.92	[0.79, 1.07]
Biopsy before first surgical procedure	0.56***	[0.49, 0.64]
Tumor size		
≤ 2cm	(ref.)	
> 2cm, ≤ 5cm	1.25***	[1.11, 1.41]
Tumor grade		
Well differentiated	(ref.)	
Moderately differentiated	1.21**	[1.06, 1.36]
Poorly differentiated	1.26**	[1.08, 1.47]
Grade unknown	1.57***	[1.24, 1.99]
Hormone receptor status		
Positive	(ref.)	
Negative	1.03	[0.87, 1.21]
Unknown	1.00	[0.83, 1.22]
Node positivity	1.45***	[1.29, 1.64]
Histology		
Ductal	(ref.)	
Lobular	1.64***	[1.39, 1.92]
Mixed ductal/lobular	1.64***	[1.39, 1.93]
Other	1.01	[0.83, 1.23]
NCI Comorbidity Index (%)		
0	(ref.)	
Between 0 and 1	0.99	[0.88, 1.10]
Greater than 1	1.04	[0.85, 1.26]
Age at diagnosis		
65 to 69	(ref.)	
70 to 74	0.89	[0.78, 1.02]
75 to 79	0.78***	[0.68, 0.90]
80 to 84	0.74***	[0.64, 0.87]
85 and older	0.48***	[0.39, 0.59]
Married	1.09	[0.98, 1.20]
State buy-in coverage		
No	(ref.)	
Yes	0.98	[0.81, 1.18]
Race		
White	(ref.)	
Non-white	1.03	[0.88, 1.21]
Cooperative group affiliation of surgical facility[†]	1.02	[0.91, 1.13]
NCI affiliation of surgical facility	1.08	[0.87, 1.32]
Surgical volume of surgical facility		
Low	(ref.)	
High	1.04	[0.93, 1.15]
Zip code proportion with at least a high school education (quartiles)		
Low education	(ref.)	
Low-medium education	1.01	[0.89, 1.16]
Medium-high education	0.89	[0.77, 1.03]
High education	0.92	[0.78, 1.09]
Unknown education	0.89	[0.68, 1.16]

Table B.7. Likelihood of a re-excision after a partial mastectomy (cont.)

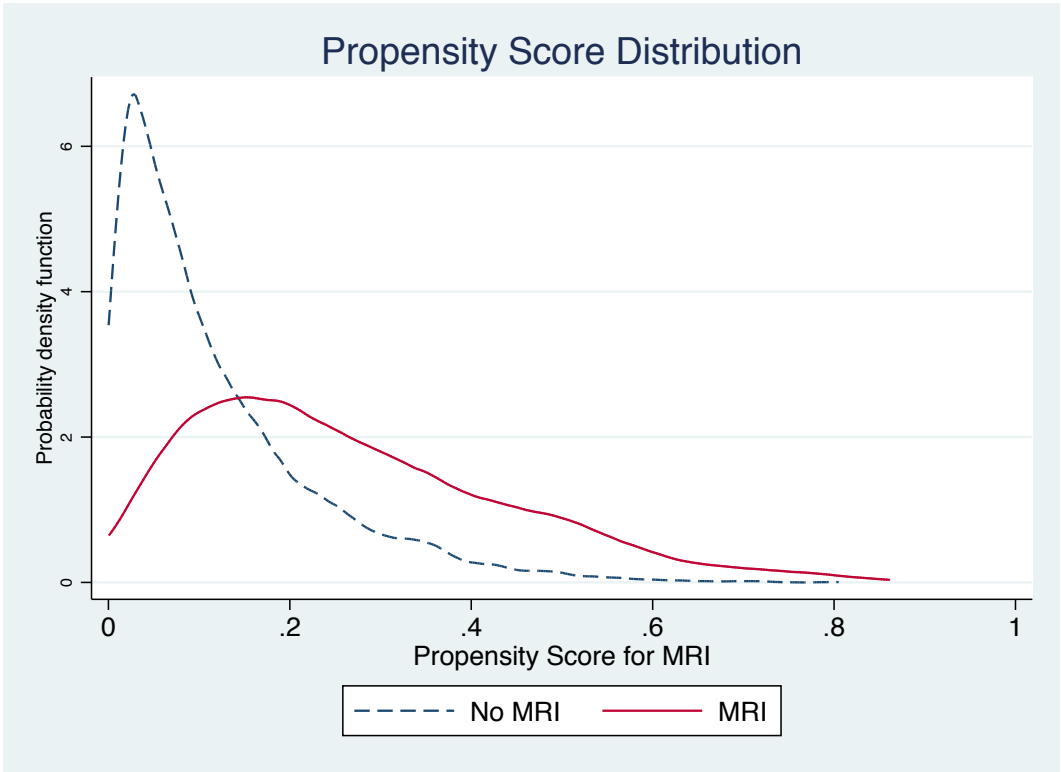|	Odds Ratio	95% Conf. Interval
Year of diagnosis		
2004	(ref.)	
2005	1.05	[0.91, 1.21]
2006	1.20*	[1.04, 1.37]
2007	1.06	[0.92, 1.22]
SEER Region		
California registries	(ref.)	
Northeast registries	1.16	[1.00, 1.35]
Georgia	1.21	[0.93, 1.59]
Detroit	2.24***	[1.84, 2.72]
Iowa	0.77	[0.58, 1.02]
New Mexico	1.25	[0.88, 1.79]
Seattle	1.19	[0.97, 1.47]
Utah	0.96	[0.69, 1.33]
Kentucky	0.75*	[0.58, 0.96]
Louisiana	1.07	[0.83, 1.38]
Hawaii	1.01	[0.64, 1.58]
Observations	11,362	
AIC	10,610.1	

MRI, Magnetic Resonance Imaging; IPW, Inverse probability weighting; SEER, Surveillance, Epidemiology and End Results; NCI, National Cancer Institute; AIC, Akaike information criterion

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[†] NCI Cooperative Groups having breast cancer research portfolios

[§] 383 groups (1,056 observations) were excluded because they had all patients with or all patients without re-excisions

Figure B.4. Brest MRI propensity score distribution (sub-analysis, n=11,362)

Figure B.5. Absolute standardized differences before and after adjusting with inverse probability weights for the sub-analysis examining re-excision (n=11,362)

Table C.1. SEER-Medicare inclusion/exclusion criteria

Inclusion Criteria	Included	Excluded
Breast cancer diagnosis in SEER	260,079	
Diagnosed between 2003 and 2007 (inclusive)	143,757	116,322
First or primary cancer	131,974	11,783
Age 66 or older at diagnosis	86,127	45,847
Female	85,367	760
Reporting source not autopsy or death certificate	84,466	901
Laterality is not bilateral or unknown	83,659	807
Original reason for Medicare entitlement not disability or ESRD	79,355	4,304
Has valid month of diagnosis	79,114	241
Has no HMO enrollment during study period*	56,652	22,462
Has continuous enrollment in Part A & B during the study period*	52,038	4,614
Has comorbidity score and was able to be matched to claims during the study period*	48,283	3,755
Diagnosed between 2004 and 2007**	39,652	8,631

*Study period is 12 months prior to diagnosis month until the end of data or death
ESRD, end stage renal disease; HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology and End Results
** We excluded patients diagnosed in 2003 because few patients (n=148) recieved a breast MRI

Table C.2. Codes for identifying breast cancer events

Time frame	Definition
Initial treatment phase (main analysis)	All claims from the first claim with a breast diagnosis code to the end of the initial treatment as defined as the last day of treatment before a gap in treatment of 90 days or more, the end of the study period (December 31, 2009), or patient's death.
Initial 12 months (sensitivity analysis)	All claims from 12 months after the first claim with a breast diagnosis code.

First breast diagnosis code date	Definition
Breast diagnosis code	174.* Malignant neoplasm of female breast 217. Benign neoplasm of breast 233.0 Carcinoma in situ of breast 238.3 Neoplasm of uncertain behavior of breast 239.3 Neoplasms of unspecified nature breast 610.0 Solitary cyst of breast 610.1 Diffuse cystic mastopathy 610.2 Fibroadenosis of breast 610.3 Fibrosclerosis of breast 610.9 Benign mammary dysplasia, unspecified 611.0 Inflammatory disease of breast 611.1 Hypertrophy of breast 611.3 Fat necrosis of breast 611.8 Other specified disorders of breast 611.9 Unspecified breast disorder 611.71 Signs and symptoms in breast 611.72 Lump or mass in breast 611.79 Signs and symptoms in breast 793.80 Abnormal mammogram, unspecified 793.81 Mammographic microcalcification 793.89 Other (abnormal) findings on radiological examination of breast V711 Observation for suspected malignant neoplasm
First breast diagnosis code date	The day of the first breast diagnosis code listed above within 12 or fewer months prior to the SEER diagnosis month

Procedures	Code identified in claims:
Breast MRI	**HCPCS**: 76093, 76094, 77058, 77059, C8903, C8904, C8905, C8906, C8907, C8908
Biopsy*	**HCPCS**: 19100, 19101, 19102, 19103, 10021, 10022 **ICD-9-CM:** 85.1, 85.11, 85.12, 85.19
Breast excision*	**HCPCS**: 19120, 19125, 19126, 19300 **ICD-9-CM:** 85.20, 85.21, 85.22, 85.2
Partial mastectomy*	**HCPCS:** 19160, 19162, 19301, 19302 **ICD-9-CM:** 85.23
Mastectomy*	**HCPCS:** 19180, 19182, 19200, 19220, 19240, 19303, 19304, 19305, 19306, 19307 **ICD-9-CM:** 85.4
Radiation	**HCPCS:** G0243, 77520, 77522, 77523, 77525, G0174, G0251, G0339, G0340, 77371, 77373, V580*, V661*, V671*, 774**, 77520, 77522, 77523, 77525, 77750, 7776*, 7777*, 7778*, 7779* **ICD-9-CM**: 92.2

Table C.2. Codes for identifying breast cancer events (cont.)

Procedures	Code identified in claims:
Chemotherapy	**HCPCS**: V581*, 96523", "96521", "96522", 0331, 0332, 0335, 410, 492, V662*, V672* 964**, 9654*, C1167, C8953, C8954, C8955, C9127, C9214, C9240, C9257, C9280, C9414, C9415, C9418, C9420, C9421, C9425, C9431, C9438, C9440, G0359, G0360, G902, G9031, G9032,G0355, G0357, G0358, G0359, G0360, G0361, G0362, S9329, S9330, S9331, Q0083, Q0084, Q0085, J8520, J8521, J8530, J8540, J8560, J8579, J8610, J8999, or any code beginning with J9 **ICD-9-CM**: 99.25
Mammogram	**HCPCS**: 76090, 76091, 76092, 76098, 77051, 77052, 77055, 77056, 77057, G0202, G0204, G0206 **ICD-9-CM**: 87.37
Ultrasound	**HCPCS**: 76645 **ICD-9-CM**: 88.72, 88.73
Lymph node procedure	**HCPCS**: 38308, 38500, 38505, 38510, 38525, 38530, 38740, 38745, 38792 **ICD-9-CM**: 40.0, 40.2, 40.3, 40.4, 40.6, 40.11, 40.19, 40.23
Bone Scan	**HCPCS**: 78305, 78306, 78300, 78315, 78399 **ICD-9-CM**: 92.14
Brain MRI	**HCPCS**: 70551, 70552, 70553 **ICD-9-CM**: 88.91
CT scan	**HCPCS**: 70480-82, 70486-88, 70490-92, 71250, 71260, 71270, 72125-33, 72192-4, 73200-2, 73700, 73701, 73702, 74150, 74160, 74170, 74176-8, 76497
PET and PET CT	**HCPCS**: 78811-78816, 78890, 78891, 78999, G0235, G0253, G0254 **ICD-9-CM**: 92.11, 92.12, 92.18, 92.19
Nuclear medicine test	**HCPCS**: 78195, 78320, 78464, 78465, 78472, 78473, 78478, 78480, 78585, 78800, 78801 **ICD-9-CM**: 92.16
Office visit/ consultation	**HCPCS**: 99201-05, 99211-15, 99241-45, 99251-55, 99273-5, G0101 **ICD-9-CM**: 87.44

HCPCS, Healthcare Common Procedure Classification System; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; MRI, Magnetic resonance imaging; PET, Positron emission tomography; CT, Computed tomography; SEER, Surveillance, Epidemiology and End Results

* If a claim for a biopsy occurred on the same day as a breast excision it was considered a breast excision. If a claim for a breast excision occurred on the same day as a partial mastectomy or a mastectomy, it was considered a partial mastectomy or a mastectomy, respectively. If there were conflicting claims for a partial mastectomy and a mastectomy on the same day, the patient was excluded.

Table C.3. Adjusted multiplicative effects on Medicare payments during the initial treatment phase

	All payments		Breast cancer-attributable payments†		Payments not attributable to breast cancer	
Preoperative breast MRI receipt	1.10***	[1.08, 1.13]	1.14***	[1.12, 1.16]	0.98	[0.88, 1.10]
Radiation receipt	1.54***	[1.51, 1.57]	1.61***	[1.59, 1.64]		
Chemotherapy receipt	2.49***	[2.42, 2.56]	2.38***	[2.32, 2.44]		
Advanced Imaging receipt	1.26***	[1.23, 1.29]	1.16***	[1.14, 1.18]		
Tumor size between 2 and 5 cm	1.09***	[1.07, 1.12]	1.08***	[1.06, 1.10]		
Tumor grade						
Well differentiated	(ref.)		(ref.)			
Moderately differentiated	1.00	[0.98, 1.02]	1.02	[1.00, 1.04]		
Poorly differentiated	1.02	[0.99, 1.05]	1.07***	[1.04, 1.09]		
Grade unknown	1.03	[0.99, 1.08]	1.03	[0.99, 1.07]		
Hormone receptor status						
Positive	(ref.)		(ref.)			
Negative	1.04**	[1.01, 1.07]	1.02	[1.00, 1.05]		
Unknown	1.02	[0.99, 1.06]	1.02	[0.99, 1.05]		
Node positivity	1.16***	[1.13, 1.19]	1.17***	[1.14, 1.19]		
Histology						
Ductal	(ref.)		(ref.)			
Lobular	1.03	[0.99, 1.06]	1.01	[0.99, 1.04]		
Mixed ductal/lobular	1.01	[0.98, 1.05]	1.03	[1.00, 1.06]		
Other	0.96**	[0.92, 0.99]	0.97	[0.94, 1.00]		
Positive nodal status	1.16***	[1.13, 1.19]	1.17***	[1.14, 1.19]		
NCI Comorbidity Index						
0	(ref.)		(ref.)		(ref.)	
Between 0 and 1	1.08***	[1.06, 1.11]	1.02*	[1.00, 1.04]	1.49***	[1.37, 1.62]
Greater than 1	1.34***	[1.28, 1.41]	1.03	[0.99, 1.06]	2.71***	[2.40, 3.06]
Age at diagnosis						
65 to 69	(ref.)		(ref.)		(ref.)	
70 to 74	1.03*	[1.00, 1.05]	1.02	[1.00, 1.04]	0.93	[0.85, 1.03]
75 to 79	1.01	[0.98, 1.03]	0.98	[0.96, 1.00]	0.84**	[0.76, 0.94]
80 to 84	1.00	[0.97, 1.03]	0.97**	[0.94, 0.99]	0.74***	[0.66, 0.83]
85 and older	0.88***	[0.85, 0.92]	0.82***	[0.79, 0.84]	0.64***	[0.55, 0.73]
State buy-in coverage						
No	(ref.)		(ref.)		(ref.)	
Yes	1.09***	[1.05, 1.14]	1.01	[0.99, 1.04]	1.41***	[1.25, 1.60]
Race						
White	(ref.)		(ref.)		(ref.)	
Non-white	1.01	[0.98, 1.04]	1.01	[0.98, 1.03]	1.05	[0.94, 1.17]
Married	1.00	[0.98, 1.01]	1.00	[0.99, 1.02]	1.00	[0.98, 1.01]

Table C.3 Adjusted multiplicative effects on Medicare payments during the initial treatment phase (cont.)

	All payments		Breast cancer-attributable payments†		Payments not attributable to breast cancer	
Zip residence						
Metropolitan	(ref.)		(ref.)		(ref.)	
Non-Metropolitan	0.96**	[0.93, 0.98]	0.98	[0.96, 1.00]	0.87*	[0.77, 0.98]
Surgical facility variables: Cooperative group affiliation§	1.02	[1.00, 1.04]	1.03***	[1.01, 1.05]		
NCI affiliation	0.98	[0.94, 1.01]	0.99	[0.96, 1.03]		
Year of diagnosis						
2004	(ref.)		(ref.)		(ref.)	
2005	1.04**	[1.01, 1.06]	1.02	[1.00, 1.04]	1.14**	[1.04, 1.26]
2006	1.06***	[1.03, 1.09]	1.04***	[1.02, 1.06]	1.18**	[1.07, 1.31]
2007	1.04**	[1.01, 1.06]	1.03*	[1.01, 1.05]	1.15**	[1.03, 1.27]
SEER region						
California registries	(ref.)		(ref.)		(ref.)	
Northeast registries	1.03*	[1.01, 1.06]	1.00	[0.98, 1.02]	1.25***	[1.14, 1.38]
Georgia	0.97	[0.92, 1.01]	0.96*	[0.92, 1.00]	0.93	[0.76, 1.13]
Detroit	1.04	[1.00, 1.09]	1.00	[0.97, 1.03]	1.40***	[1.21, 1.63]
Iowa	0.83***	[0.80, 0.86]	0.83***	[0.81, 0.86]	0.70***	[0.60, 0.83]
New Mexico	0.90**	[0.85, 0.96]	0.90***	[0.86, 0.95]	0.97	[0.75, 1.26]
Seattle	0.86***	[0.83, 0.89]	0.89***	[0.86, 0.91]	0.75***	[0.64, 0.89]
Utah	0.81***	[0.76, 0.86]	0.79***	[0.76, 0.83]	1.01	[0.77, 1.31]
Kentucky	0.86***	[0.83, 0.90]	0.82***	[0.79, 0.85]	1.11	[0.94, 1.30]
Louisiana	0.89***	[0.85, 0.93]	0.90***	[0.87, 0.93]	0.95	[0.82, 1.11]
Hawaii	0.80***	[0.74, 0.87]	0.81***	[0.75, 0.86]	0.74*	[0.55, 1.00]
N	22974		22974		22974	
AIC	5.0e+05		4.9e+05		4.2e+05	

* p<0.05 ** p<0.01   *** p<0.001

MRI, Magnetic resonance imaging; NCI, National Cancer Institute; AIC, Akaike information criterion,
95% confidence intervals in brackets, All models are generalized linear models using log-link gamma with robust standard errors.

† Breast cancer-attributable payments include total Medicare payments from claims associated with breast cancer diagnosis or treatment or from claims with a breast cancer diagnosis code within the claim's first four diagnosis codes.

§ NCI Cooperative Groups having breast cancer research portfolios

Table C.4. Sensitivity analysis: Adjusted multiplicative effects on Medicare payments during the first 12 months of diagnosis and treatment

	All payments		Breast cancer-attributable payments†		Payments not attributable to breast cancer	
Preoperative breast MRI receipt	1.03	[1.00, 1.06]	1.11***	[1.09, 1.14]	0.86***	[0.79, 0.94]
Radiation receipt	1.18***	[1.15, 1.21]	1.50***	[1.47, 1.52]		
Chemotherapy receipt	1.81***	[1.76, 1.87]	2.05***	[2.00, 2.09]		
Advanced Imaging receipt	1.38***	[1.34, 1.42]	1.17***	[1.14, 1.19]		
Tumor size between 2 and 5 cm	1.08***	[1.05, 1.11]	1.09***	[1.07, 1.11]		
Tumor grade						
Well differentiated	(ref.)		(ref.)			
Moderately differentiated	0.99	[0.96, 1.02]	1.02*	[1.01, 1.04]		
Poorly differentiated	1.04	[1.00, 1.08]	1.06***	[1.04, 1.09]		
Grade unknown	1.04	[0.98, 1.10]	1.04	[0.99, 1.09]		
Hormone receptor status						
Positive	(ref.)		(ref.)			
Negative	1.01	[0.97, 1.04]	1.03*	[1.00, 1.05]		
Unknown	1.02	[0.97, 1.06]	1.01	[0.98, 1.04]		
Node positivity						
Histology						
Ductal	(ref.)		(ref.)			
Lobular	1.00	[0.96, 1.04]	1.02	[1.00, 1.05]		
Mixed ductal/lobular	1.03	[0.99, 1.08]	1.04*	[1.01, 1.07]		
Other	0.93***	[0.90, 0.97]	0.97	[0.95, 1.00]		
Positive nodal status	1.16***	[1.13, 1.20]	1.20***	[1.18, 1.22]		
NCI Comorbidity Index						
0	(ref.)		(ref.)		(ref.)	
Between 0 and 1	1.18***	[1.15, 1.21]	1.03**	[1.01, 1.04]	1.60***	[1.50, 1.71]
Greater than 1	1.67***	[1.58, 1.76]	1.04*	[1.01, 1.08]	2.93***	[2.68, 3.21]
Age at diagnosis						
65 to 69	(ref.)		(ref.)		(ref.)	
70 to 74	1.02	[0.99, 1.05]	1.00	[0.98, 1.02]	1.08	[0.99, 1.17]
75 to 79	1.04*	[1.00, 1.07]	0.97*	[0.95, 0.99]	1.17***	[1.07, 1.28]
80 to 84	1.06**	[1.02, 1.10]	0.94***	[0.92, 0.97]	1.25***	[1.14, 1.38]
85 and older	1.07*	[1.01, 1.12]	0.80***	[0.77, 0.83]	1.47***	[1.32, 1.63]
State buy-in coverage						
No	(ref.)		(ref.)		(ref.)	
Yes	1.17***	[1.11, 1.22]	1.03*	[1.00, 1.06]	1.43***	[1.29, 1.58]
Race						
White	(ref.)		(ref.)		(ref.)	
Non-white	0.97	[0.93, 1.02]	1.01	[0.98, 1.03]	0.94	[0.85, 1.04]

Table C.4. Sensitivity analysis: Adjusted multiplicative effects on Medicare payments during the first 12 months (cont.)

	All payments		Breast cancer-attributable payments†		Payments not attributable to breast cancer	
Married	0.99	[0.96, 1.01]	1.00	[0.98, 1.02]	0.95	[0.89, 1.01]
Zip code of residence						
Metropolitan	(ref.)		(ref.)		(ref.)	
Non-metropolitan	0.96	[0.93, 1.00]	0.99	[0.96, 1.01]	0.94	[0.86, 1.04]
Cooperative group affiliation of surgical facility†	1.01	[0.99, 1.04]	1.03**	[1.01, 1.04]		
NCI affiliation of surgical facility	1.00	[0.95, 1.06]	0.99	[0.96, 1.03]		
Year of diagnosis						
2004	(ref.)		(ref.)		(ref.)	
2005	1.03*	[1.00, 1.07]	1.01	[0.99, 1.03]	1.09*	[1.01, 1.18]
2006	1.05**	[1.02, 1.08]	1.03**	[1.01, 1.05]	1.08*	[1.00, 1.18]
2007	1.02	[0.99, 1.05]	1.02*	[1.00, 1.05]	1.04	[0.96, 1.13]
SEER Region						
California registries	(ref.)		(ref.)		(ref.)	
Northeast registries	1.02	[0.99, 1.05]	1.01	[0.99, 1.03]	1.06	[0.98, 1.14]
Georgia	0.93**	[0.88, 0.98]	0.95**	[0.91, 0.99]	0.82**	[0.70, 0.95]
Detroit	1.06*	[1.00, 1.11]	0.99	[0.96, 1.02]	1.23**	[1.08, 1.39]
Iowa	0.81***	[0.78, 0.85]	0.82***	[0.80, 0.85]	0.74***	[0.65, 0.83]
New Mexico	0.84***	[0.78, 0.90]	0.90***	[0.86, 0.95]	0.78*	[0.62, 0.97]
Seattle	0.87***	[0.83, 0.91]	0.90***	[0.87, 0.92]	0.86*	[0.76, 0.97]
Utah	0.84***	[0.79, 0.90]	0.78***	[0.75, 0.81]	0.90	[0.76, 1.06]
Kentucky	0.86***	[0.82, 0.90]	0.81***	[0.78, 0.83]	0.94	[0.83, 1.05]
Louisiana	0.92**	[0.87, 0.97]	0.89***	[0.86, 0.92]	1.02	[0.90, 1.15]
Hawaii	0.73***	[0.67, 0.80]	0.80***	[0.75, 0.85]	0.61***	[0.48, 0.78]
N	22,974		22,974		22,974	
AIC	5.2e+05		5.0e+05		4.7e+05	

* p<0.05 ** p<0.01   *** p<0.001

MRI, Magnetic resonance imaging; NCI, National cancer institute; OLS, Ordinary least-squares regression; AIC, Akaike information criterion,

95% confidence intervals in brackets, All models are generalized linear models using log-link gamma with robust standard errors.

† Breast cancer-attributable payments include total Medicare payments from claims associated with breast cancer diagnosis or treatment or from claims with a breast

diagnosis code within the claim's first four diagnosis codes.

§ NCI Cooperative Groups having breast cancer research portfolios

Table D.1. Impact of preoperative breast MRI on the time until complete surgery, results of propensity score trimming

	Hazard Ratio	95% CI		Included, n	Excluded, n Withheld treatment	Last resort
Full proportional hazard model with IPW	0.90	[0.85	0.95]	25,038		
Limited to overlapping PS distributions[†]	0.90	[0.84	0.95]	24,867	171[†]	
Trimmed at 1% and 99%[§]	0.91	[0.86	0.96]	24,944	93	1
Trimmed at 2.5% and 97.5%[§]	0.91	[0.86	0.96]	24,779	258	1
Trimmed at 5% and 95%[§]	0.92	[0.87	0.97]	24,409	626	3

MRI, magnetic resonance Imaging; PS, propensity scores; IPW, inverse probability weighting

Note: all models use IPW.

[†] This model excluded women with non-overlapping propensity score distributions (i.e., women without a preoperative breast MRI who had a propensity score higher than the maximum or lower than the minimum propensity score of women with preoperative breast MRI)

[§] These models trimmed patients at three different cut points at the tails of the propensity score distribution in the treated (i.e., breast MRI) and untreated (i.e., no breast MRI) patients corresponding to the 1st and 99th percentiles, the 2.5th and 97.5th percentiles, and the 5th and 95th percentiles, respectively. Patients with an MRI and a PS below the lower cut point were considered to be "last resort." Patients with no MRI and a PS above upper cut point were considered to be "withheld treatment"

Table D.2. Impact of preoperative breast MRI on the likelihood of a mastectomy compared to BCS, results of propensity score trimming

	Odds Ratio	95% CI		Included, n	Excluded, n Withheld treatment	Last resort
Full logistic regression model with IPW	1.30	[1.12	1.51]	24,339		
Limited to overlapping PS distributions[†]	1.31	[1.13	1.52]	24,283	156[†]	
Trimmed at 1% and 99%[§]	1.33	[1.15	1.53]	24,346	92	1
Trimmed at 2.5% and 97.5%[§]	1.31	[1.13	1.52]	24,182	256	1
Trimmed at 5% and 95%[§]	1.28	[1.11	1.47]	23,829	607	3

MRI, magnetic resonance Imaging; PS, propensity scores; IPW, inverse probability weighting; BCS, breast conserving surgery (i.e., breast excision or a partial mastectomy)

Note: All models use IPW.

[†] This model excluded women with non-overlapping propensity score distributions (i.e., women without a preoperative breast MRI who had a propensity score higher than the maximum or lower than the minimum propensity score of women with preoperative breast MRI)

[§] These models trimmed patients at three different cut points at the tails of the propensity score distribution in the treated (i.e., breast MRI) and untreated (i.e., no breast MRI) patients corresponding to the 1st and 99th percentiles, the 2.5th and 97.5th percentiles, and the 5th and 95th percentiles, respectively. Patients with an MRI and a PS below the lower cut point were considered to be "last resort." Patients with no MRI and a PS above upper cut point were considered to be "withheld treatment"

Table D.3. Impact of preoperative breast MRI on the likelihood of a re-excision, results of propensity score trimming

	Odds Ratio	95% CI		Included, n	Excluded, n	
					Withheld treatment	Last resort
Full logistic regression model with IPW	1.11	[0.92	1.35]	24,339		
Limited to overlapping PS distributions[†]	1.12	[0.92	1.36]	24,283	148[†]	
Trimmed at 1% and 99%[§]	1.16	[0.96	1.39]	24,346	92	1
Trimmed at 2.5% and 97.5%[§]	1.10	[0.93	1.30]	24,182	256	1
Trimmed at 5% and 95%[§]	1.07	[0.91	1.26]	23,829	607	3

MRI, magnetic resonance Imaging; PS, propensity scores; IPW, inverse probability weighting
Note: All models use IPW.
[†] This model excluded women with non-overlapping propensity score distributions (i.e., women without a preoperative breast MRI who had a propensity score higher than the maximum or lower than the minimum propensity score of women with preoperative breast MRI)
[§] These models trimmed patients at three different cut points at the tails of the propensity score distribution in the treated (i.e., breast MRI) and untreated (i.e., no breast MRI) patients corresponding to the 1st and 99th percentiles, the 2.5th and 97.5th percentiles, and the 5th and 95th percentiles, respectively. Patients with an MRI and a PS below the lower cut point were considered to be "last resort." Patients with no MRI and a PS above upper cut point were considered to be "withheld treatment"

Table D.4. Impact of preoperative breast MRI on the time until a second breast cancer event, results of propensity score trimming

	Hazard Ratio	95% CI		Included, n	Excluded, n	
					Withheld treatment	Last resort
Full proportional hazard model with IPW	1.37	[1.11	1.68]	24,438		
Limited to overlapping PS distributions[†]	1.40	[1.14	1.71]	24,267	171[†]	
Trimmed at 1% and 99%[§]	1.39	[1.14	1.70]	24,345	92	1
Trimmed at 2.5% and 97.5%[§]	1.40	[1.13	1.70]	24,175	262	1
Trimmed at 5% and 95%[§]	1.27	[1.06	1.52]	23,829	606	3

MRI, magnetic resonance Imaging; PS, propensity scores; IPW, inverse probability weighting
Note: all models use IPW.
[†] This model excluded women with non-overlapping propensity score distributions (i.e., women without a preoperative breast MRI who had a propensity score higher than the maximum or lower than the minimum propensity score of women with preoperative breast MRI)
[§] These models trimmed patients at three different cut points at the tails of the propensity score distribution in the treated (i.e., breast MRI) and untreated (i.e., no breast MRI) patients corresponding to the 1st and 99th percentiles, the 2.5th and 97.5th percentiles, and the 5th and 95th percentiles, respectively. Patients with an MRI and a PS below the lower cut point were considered to be "last resort." Patients with no MRI and a PS above upper cut point were considered to be "withheld treatment"

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