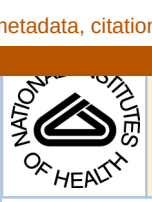

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Risk of Advanced-Stage Breast Cancer Among Older Women with Comorbidities

Shagufta Yasmeen[1], **Rebecca A. Hubbard**[2], **Patrick S. Romano**[1], **Weiwei Zhu**[2], **Berta M. Geller**[3], **Tracy Onega**[4], **Bonnie C. Yankaskas**[5], **Diana L. Miglioretti**[2], and **Karla Kerlikowske**[6]

[1]University of California Davis School of Medicine, Sacramento, CA

[2]Group Health Research Institute, Group Health Cooperative, Seattle, WA

[3]Health Promotion Research, University of Vermont, College of Medicine, Burlington, VT

[4]Department of Community and Family Medicine, Dartmouth Medical School, Norris Cotton Cancer Center, Lebanon, NH

[5]Department of Radiology, University of North Carolina, Chapel Hill, NC

[6]Department of Epidemiology and Biostatistics and General Internal Medicine Section, Department of Veterans Affairs, University of California, San Francisco, CA

Abstract

Background—Comorbidities have been suggested influencing mammography utilization and breast cancer stage at diagnosis. We compared mammography use, and overall and advanced-stage breast cancer rates, among female Medicare beneficiaries with different levels of comorbidity.

Methods—We used linked Breast Cancer Surveillance Consortium (BCSC) and Medicare claims data from 1998 through 2006 to ascertain comorbidities among 149,045 female Medicare beneficiaries age 67 and older who had mammography. We defined comorbidities as either “unstable” (life threatening or difficult to control) or “stable” (age-related with potential to affect daily activity) based on claims within two years before each mammogram.

Results—Having undergone two mammograms within 30 months was more common in women with stable comorbidities (86%) than in those with unstable (80.3%) or no (80.9%) comorbidities. Overall rates of advanced-stage breast cancer were lower among women with no comorbidities (0.5 per 1000 mammograms, 95% CI 0.3–0.8) than among those with stable comorbidities (0.8, 95% CI 0.7–0.9, p=0.065 compared to no comorbidities) or unstable comorbidities (1.1, 95% CI 0.9–1.3, p=0.002 compared to no comorbidities). Among women having undergone two mammograms within 4–18 months, those with unstable and stable comorbidities had significantly higher advanced cancer rates compared to those with no comorbidities (p=0.004 and p=0.03, respectively).

Conclusions—Comorbidities were associated with more frequent use of mammography, but also higher risk of advanced-stage disease at diagnosis among the subset of women who had the most frequent use of mammography.

Impact—Future studies need to examine whether specific comorbidities affect clinical progression of breast cancer.

Corresponding Author: Shagufta Yasmeen, MD, Department of Obstetrics/Gynecology and Internal Medicine, 4860 Y Street, Suite 2500, Sacramento CA 95817, Tel # (91 734-6929, Fax # (916) 734-6666, shagufta.yasmeen@ucdmc.ucdavis.edu.

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Keywords

Comorbidities; mammography; breast cancer screening; stage at diagnosis

Introduction

Breast cancer screening among older women is complicated because of the variation in the number and severity of comorbidities [1]. Studies examining the associations between comorbid conditions and mammography screening use and breast cancer outcomes have reported mixed results [2]. Some have reported a higher risk of advanced-stage cancer among women with comorbidities, [3] whereas others have reported a higher risk of advanced-stage cancer at diagnosis among women with no comorbidities [4, 5]. Age-related comorbid conditions may increase the frequency of physician visits, leading to higher mammography utilization and better follow-up of abnormal results, resulting in an earlier stage at diagnosis [6]. Alternatively, chronic disease management may constitute a "competing demand" during physician visits, diverting attention from the delivery of preventive services. A recent study of Medicare beneficiaries suggests that stable comorbidities are associated with lower likelihood of late stage diagnosis, whereas unstable comorbidities are associated with higher likelihood of late stage diagnosis, partially due to less use of mammography [7].

Many cancer screening guidelines recommend considering an older woman's health status when making screening decisions, as screening mammography is unlikely to benefit older women whose life expectancy is less than five years [8, 9]. However, it is unclear how these guidelines are applied in practice and to what extent cancer screening tests are actually targeted to healthy older women with sufficient life expectancy to reasonably benefit from screening mammography, and not offered to older women with multiple or severe comorbidities who have a life expectancy of less than 5 years and are unlikely to benefit from screening [10, 11].

Previous studies have used the linked Surveillance, Epidemiology, and End Results (SEER) program-Medicare data to assess comorbidities, mammography utilization, and breast cancer outcomes in older women [12]. A major limitation of these data is difficulty in distinguishing screening from diagnostic mammograms in cancer case cohorts,[13] given that most women eventually undergo diagnostic mammography evaluation before treatment begins. For instance, mammograms performed to evaluate breast symptoms can be mislabeled as screening instead of diagnostic, especially in older women with comorbidities who may not undergo regular screening mammography. Such misclassification can lead to overestimation of screening mammography usage, and may thereby bias epidemiologic analyses of factors associated with adequate screening. Claims-based algorithms to minimize this misclassification risk are useful but not entirely satisfactory [13].

The goal of this study was to determine whether the presence and severity of comorbid conditions affect screening mammography utilization and breast cancer stage at diagnosis. We examined data from four mammography registries in the Breast Cancer Surveillance Consortium (BCSC) [14] and linked Medicare claims data from 1998 to 2006 to estimate the relationship between the presence and severity of comorbid conditions and use of mammography, breast cancer stage at diagnosis, and tumor characteristics. We used an updated approach to classifying comorbidities that has been shown to separate comorbidities associated with increased versus decreased mammography utilization in the Medicare population [7].

Materials and Methods

Data Source

The BCSC is a collaborative effort between seven geographically dispersed mammography registries [14]. Details regarding the BCSC have been provided elsewhere [15, 16]. Data were obtained from four BCSC mammography registries (Carolina Mammography Registry; New Hampshire Mammography Network; San Francisco Mammography Registry; and Vermont Breast Cancer Surveillance System) that participated in linking BCSC records and Medicare claims data. Registries collected demographic, risk factor, and clinical information at each mammogram, including radiologists' indication for examination and recommendations based on the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS®). Data were pooled at a central Statistical Coordinating Center (SCC) at Group Health Research Institute (Seattle, Washington) [14, 16]. BCSC registries and the SCC received Institutional Review Board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analysis. All procedures were Health Insurance Portability and Accountability Act (HIPAA) compliant, and registries and the SCC received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities.

Women participating in these four mammography registries who were also enrolled in Medicare were linked to the Center for Medicare & Medicaid Services' (CMS) Medicare Program Master Enrollment file by identifiers such as name, date of birth, and social security number. Breast cancer diagnoses and tumor characteristics were obtained through linkage with state tumor registries or regional SEER programs [17] and additional linkage to hospital-based pathology services at three of the four mammography registries [16].

Study population

The study population included all women who were 67 years of age and older who had undergone mammography in the BCSC database from the four sites between January 1, 2000 and December 31, 2006. We limited the study to women with at least two years of continuous Medicare enrollment in Part A and Part B and who were not enrolled in Medicare Advantage for two years before a mammogram in the BCSC database, and with no previous history of breast cancer. We required two years of continuous Medicare enrollment before a mammogram to ensure complete capture of claims during the period used to assess presence of comorbidities. To further ensure complete capture of Medicare claims, we excluded mammograms included in the BCSC database for which a corresponding Medicare claim for a mammogram could not be found within 7 days before or after the exam date recorded in the BCSC database. Approximately 426,295 mammograms meeting inclusion criteria were identified in the BCSC database from 2000 to 2006 and 415,078 (97.4%) had a matching Medicare mammogram claim within 7 days of BCSC examination date. Of those with matching mammogram claims 3316 (2.2%) had a breast cancer diagnosis within 12 months of mammography.

Measurements and Definitions

We characterized each mammogram included in the study according to type of examination (screening versus diagnostic) and time interval between that examination and a woman's most recent prior examination. A screening mammogram was defined using the standard BCSC definition as a bilateral mammogram with a physician-stated indication for routine screening and no mammography within the past 9 months. Mammography intervals were categorized as: 4 to 18 months; 19 to 30 months; or 31 to 42 months.[15, 16, 18] Estimates for the number of months between mammograms were calculated by using the most recent of the dates of previous mammography in the BCSC database or the self-reported date given

by the participant. All mammograms occurring within a 4-month period were considered to represent a single diagnostic series and our analyses included only the first mammogram in the series.

We applied a recently refined list of 38 comorbid conditions [7], classified by organ system and severity, using ICD-9-CM codes listed in previously published comorbidity measures developed for Medicare claims data by Klabunde et al [19], Fleming et al.[12], and Elixhauser [20]. We updated these measures to more recent versions of ICD-9-CM and distinguished "stable" and "unstable" comorbidities based on clinical significance, judgment of seriousness, and whether the condition predicted five-year mortality in prior studies. This distinction was previously shown to be useful in understanding variation in mammography use [7]. We defined comorbidities that are life threatening or difficult to control such as severe heart failure, cardiac arrhythmias, and end-stage liver disease as "unstable," and age-related conditions that could affect daily function, such as arthritis, osteoporosis, depression, and diabetes as "stable" (Appendix 1).

Inpatient, outpatient, and physician-supplier claims were reviewed for two years before the most recent mammogram in the BCSC database and used to determine the prevalence of comorbidities during that period, excluding the month of diagnosis in cancer cases. If a qualifying comorbid diagnosis code appeared only once in physician claims during that period, and an identical code was not present in inpatient hospital claims, then the condition was not counted as a comorbidity [21]. Likewise, if a code appeared more than once in physician claims within a 30-day period, but never appeared again in either inpatient hospital or physician claims, then the condition was not counted [22]. This approach was based on prior studies showing poor agreement between medical records and Medicare claims when looser methods were used to capture diagnostic information [21, 22].

To estimate total comorbidity burden, we grouped stable and unstable comorbidities as absent or present. We then counted the number of stable comorbid conditions. Unstable comorbidities were collapsed into a single group as the prevalence of multiple unstable conditions was very low.

Breast cancer stage at diagnosis was classified according to the Tumor, Node, Metastasis (TNM) system based on the criteria of the American Joint Committee on Cancer as stage 0, I, IIA, IIB, III or IV. Invasive tumors of stages IIB, III, and IV were considered to be advanced-stage disease [23]. This definition of advanced-stage disease has been used as a proxy outcome among women with breast cancer because only 5% to 12% of Stage I/II patients die within 10 years after diagnosis, compared with over 60% of Stage III patients and over 90% of Stage IV patients [24].

Statistical Analysis

We estimated the overall prevalence of stable and unstable comorbidities in our study population. We summarized demographic characteristics stratified by comorbidity status: no comorbid conditions, stable conditions only (aggregating women with one or more conditions, due to their similar characteristics), or unstable conditions with or without additional stable conditions. Among women diagnosed with cancer, demographic characteristics, comorbidity burden, mammography utilization rates, and tumor characteristics were compared between comorbidity groups using chi-squared tests with statistical significance defined at $P<0.05$.

We calculated stratum-specific frequency distributions for previous mammography use based on a single mammogram per woman to prevent over-representation of women who were frequent mammography users [15]. We selected the mammogram closest to the date of

diagnosis for cancer cases and a randomly selected mammogram for non-cancer cases. For mammograms followed by a cancer diagnosis, we calculated the proportion of tumors that were invasive and the distribution of tumor size, stage, grade, and estrogen receptor status.

We explored differences in previous mammography use by comorbidity status using logistic regression models for the binary outcome "adequately screened," which we defined as having two mammography examinations within 30 months. This model was adjusted for age, race/ethnicity, year, and BCSC registry. In this analysis we selected one mammogram to include in the analysis per woman as described above.

We used logistic regression to estimate overall and advanced cancer rates per 1000 mammograms by comorbidity status, adjusting for age, race/ethnicity, year of diagnosis, and BCSC registry using generalized estimating equations (GEE). In these analyses, we excluded diagnostic mammograms with no prior mammogram within 42 months. The unit of analysis in these models was the mammogram, with women potentially contributing multiple mammograms. The method of GEE accounts for clustering among mammograms from the same woman. Adjusted cancer rates were estimated using the method of indirect standardization [25, 26]. Confidence intervals were estimated using the delta method. Models were also fit including interaction terms for previous mammography use and comorbidity status to examine variation in the association between comorbidity status and cancer rates across previous mammography use groups. Adjusted cancer rates from these models are reported for each comorbidity and previous mammography use group. We also computed the mean time from the most recent prior mammography examination to cancer diagnosis to evaluate possible diagnostic delays among women by comorbidity status. All statistical analyses were carried out using R statistical software.

Results

We identified 415,078 eligible mammograms among 149,045 women between 2000 and 2006 in the linked BCSC-Medicare data (Table 1). Comorbidities were identified in 133,227 (89.4%) women: 93,428 (62.7%) had stable and 39,799 (26.7%) had unstable or both stable and unstable comorbidities. Overall, 83.9% of women had two mammograms within 30 months; these proportions were slightly higher among those with stable comorbidities (86.0%) and than among those with no comorbidities (80.9%) or unstable comorbidities (80.3%) (Table 1). The Appendices show the prevalence of stable comorbidities by organ system.

A total of 3,316 (2.2%) women were diagnosed with primary incident breast cancer (Table 2). Comorbidities were identified in 89.4% of the cancer cohort; 60.8% had stable comorbidities and 28.6% had unstable only or both stable and unstable comorbidities. Women with comorbidities were significantly older and more likely to have recent mammography compared to women with no comorbidities ($p<0.001$) (Table 2). Overall, 77.1% of these women had a mammogram within 4–30 months of cancer diagnosis; these proportions were lower among women with no comorbidities (68.5%) and higher among those with stable (80.6%) or unstable comorbidities (72.7%) ($p<0.001$).

Overall, 84.9% of the tumors detected were invasive, and 15.1% were ductal carcinoma in situ (DCIS). Among women with invasive cancers, those with stable comorbidities had significantly higher proportions of stage I cancers and women with unstable and stable comorbidities had the highest proportions of stage IIB tumors compared to women with no comorbidities. Women with unstable or no comorbidities had a higher proportion of advanced-stage cancers compared to those with stable comorbidities (21.8% and 20.4% versus 17.3%, respectively). Women with no comorbidities showed higher prevalence of

well differentiated tumors than women with stable and unstable comorbidities (p=0.034) (Table 2).

As displayed in Table 3, overall women with stable comorbidities were more likely to have had a mammogram within 4–18 months than women with either unstable or no comorbidities (70% versus 62.4% and 64.1%) respectively and this pattern was similar among women less than age 75 and aged 75 and older.

Overall, the presence of either stable or unstable comorbidities was associated with significantly higher odds of adequate mammography use (defined as a prior mammogram within 30 months) after adjusting for patient characteristics (age, race, year, and BCSC registry). The odds ratio (OR) for adequate mammography use among women with stable comorbidities compared to no comorbidities was 1.60 (95% confidence interval [CI]: 1.52–1.67) and for unstable comorbidities compared to no comorbidities was 1.14 (95% CI: 1.08–1.19).

Adjusted overall breast cancer rates (DCIS and invasive combined) and advanced-stage cancer rates per 1000 mammograms by comorbidity status and prior mammography use are displayed in Table 4. Overall cancer rates per 1000 mammograms are highest among women with unstable comorbidities (7.5, 95% CI [7.0–8.1]) and lower among women with stable comorbidities (6.7, 95% CI [6.4, 7.0]) or no comorbidities (6.6, 95% CI [5.8, 7.5]). On comparing cancer rates per 1000 mammograms by comorbidity status there were no significant differences in cancer rates among women with stable and unstable comorbidities compared to women with no comorbidities (Table 4). Women were more likely to be diagnosed with breast cancer when mammogram intervals were more than 42 months than with shorter intervals of 31–42 months, 19–30 months, or 4–18 months (14.6 versus 9.9, 8.1, and 6.1 per 1000 mammograms, respectively).

Advanced-stage cancer rates per 1000 mammograms were highest among women with unstable comorbidities (1.1, 95% CI [0.9, 1.3]) and lower among those with stable comorbidities (0.8, 95% CI [0.7,0.9]) and those with no comorbidities (0.5, 95% CI [0.3,0.8]) (Table 5). Advanced-stage breast cancers were more likely to occur among women with intervals of more than 42 months between mammography examinations compared to shorter intervals of 31–42 months, 19–30 months, or 4–18 months (1.7 versus 1.6, 0.9, and 0.7 per 1000 mammograms, respectively). The likelihood of diagnosis with advanced-stage cancer was highest among women with unstable comorbidities (1.1, 95% CI [0.9, 1.3]) and lower among those with stable (0.8, 95% CI [0.7, 0.9]) or no comorbidities (0.5, 95% CI [0.3, 0.8]) (Table 5). Overall, advanced-stage cancer rates per 1000 mammograms were significantly higher for women with unstable comorbidities compared to women with no comorbidities (p=0.002) (Table 5). After stratifying on prior mammography utilization, the only significant difference across comorbidity groups was that among women with an interval of 4–18 months between mammograms. In this group, advanced-stage cancer was more frequent among those with unstable (0.9, 95% CI [0.7, 1.2], p=0.004) and stable comorbidities (0.7, 95% CI [0.6, 0.8], p=0.03) than among those with no comorbidities (0.3, 95% CI [0.2, 0.6]).

The mean number of days between mammography and cancer diagnosis was not significantly different between women with stable and unstable comorbidities compared to those with no comorbidities. The mean number of days was 46.8 (95% CI: 39.6–59.9), 54.4 (95% CI: 51.1–57.8), and 50.9 (95% CI: 46.4–55.6) among women with no comorbidities, stable and unstable comorbidities respectively.

Discussion

This is a large population–based study of linked BCSC-Medicare data reporting on mammography use and rates of advanced-stage breast cancer relative to presence and severity of comorbidities. It adds to prior research in this field by using better methods to distinguish screening from diagnostic mammograms, and to distinguish stable from unstable comorbidities, as the later may contraindicate offering screening mammography due to limited life expectancy. In adjusted analysis overall breast cancer rates per 1000 mammograms did not differ across comorbidity groups, after stratifying by similar mammography use. However, among women who received mammography within 4–18 months of diagnosis, advanced-stage cancer rates were significantly higher among those with either unstable or stable comorbidities than among those without comorbidities.

Based on prior research [7], we hypothesized that women with unstable comorbidities would be less likely to undergo mammography and more likely to be diagnosed with advanced-stage disease. Conversely, women with stable comorbidities were hypothesized to be more likely to undergo mammography [4], and less likely to be diagnosed with advanced-stage disease, than women without comorbidities. In this cohort, which was limited to women who had at least one mammogram during the study period, we found the expected association between stable comorbidities and increased mammography use, but unexpectedly high mammography use among women with unstable comorbidities (e.g., 77.6% of women aged 75 years or more had a mammogram within 30 months), who are less likely to live long enough to benefit from screening. After adjusting for demographic characteristics, stable and unstable comorbidities were associated with 1.60 and 1.14 times higher odds, respectively, compared to women without comorbidities of having received a prior mammogram within 30 months. Given these findings, we expected stable comorbidities to be associated with lower unadjusted rates of advanced-stage breast cancer, and unstable comorbidities to be associated with similar rates, but these associations should diminish or disappear after stratifying on mammography interval [7]. In fact, among women who had prior mammography within 4–18 months of cancer diagnosis, the rates of advanced-stage cancer were higher among those with either stable or unstable comorbidities than among those without comorbidities.

There are two plausible sets of explanations for these findings: health system-related and biologic. Health system-related explanations could be due to delays or errors in mammographic interpretation, and delays or errors in diagnostic evaluation after an abnormal mammogram due to competing health concerns as uncontrolled comorbidities may lead to rescheduling or cancellation of diagnostic tests, or difficulties in the referral process. To explore whether advanced-stage disease can be explained by delay in diagnosis we examined the time interval (mean number of days) between mammography and cancer diagnosis by comorbidity status. We found no statistically significant differences in time to diagnosis among women with no comorbidities compared to those with stable and unstable comorbidities.

Biologic explanations for differences in advanced-stage cancer rates focus on the interaction of aging and comorbidities with cancer risk, disease progression, treatment and survival [27]. Comorbid conditions related to syndromes with common pathophysiologic mechanisms (e.g., metabolic disorders) are associated with more aggressive cancer [28, 29]. Diabetes (largely Type II diabetes) is associated with a significantly higher risk for breast cancer. A meta-analysis of 20 case-control studies has reported a 20% increased risk of breast cancer (RR,1.20; 95% CI, 1.12–1.28) among women with diabetes versus those no diabetes [30]. Hyperinsulinemia is associated with poor disease-specific survival in breast cancer [31]. Insulin resistance has been associated with hyperinsulinemia, increased growth

factors (including insulin-like growth factor [IGF]-1), activation of the NFκB antiapoptotic pathway via activation of the IκB kinase β (IKKβ), and activation of peroxisome proliferator-activated receptors [32]. Other potential mechanisms are induction of the receptor for advanced glycation end-products (RAGE), modulation of the protein kinase B/atypical protein kinase C zeta, and immune mechanisms [32].

Obesity is associated with increased incidence of breast cancer and worse prognosis among postmenopausal women, perhaps due to increased levels of leptin, which can act as a growth factor on cancer cells. Other cytokines that might synergize with leptin are interleukin (IL)-6, IGF-1 and the free portion of IGF-1, which increase with weight [28, 29]. Even in the absence of overt diseases, aging is associated with increased levels of several inflammatory markers, such as IL-6, C-reactive protein, and sedimentation rate, [33] and nonspecific markers of autoimmunity, such as antinuclear antibodies. Studies examining the interaction of autoimmune disease and cancer among older patients provide conflicting evidence for solid tumors such as breast cancer, but do suggest increased incidence of hematologic malignancies [27].

Adequate mammography use among women age ≥67 years in this sample (84%) exceeded previously published reports (66% to 68%), including a recent report on mammography trends from 2000 to 2008 (68%) [34, 35]. Our higher utilization rates could be because we focused on women who had prior mammography. The prevalence of multiple comorbidities in this study resembled earlier studies using SEER-Medicare data [36] but was somewhat lower than reported by Fleming et al [7, 12]. This difference is probably due to our rigorous classification of ICD-9-CM codes, thus capturing only clinician-assigned diagnoses requiring either multiple outpatient visits or inpatient care.

This is the first large population-based study of the linked BCSC-Medicare data reporting on comorbidities, mammography use among women with and without cancer, and advanced breast cancer rates among older women by comorbidity status. Its strengths include better ascertainment of screening mammography than is possible from claims data alone, minimizing misclassification of screening and diagnostic mammograms. This study's other strengths include its large sample size; geographic, racial, and ethnic diversity; and use of two years of prior inpatient and outpatient claims to estimate comorbidity burden and severity. These data cover a large population with detailed data on mammography use, cancer diagnosis, and ICD-9-CM codes for comorbid diagnoses. These data are generalizable to older U.S. women with breast cancer, as they reflect community-based, usual care for older women.

This study's limitations include potential underreporting of chronic conditions, a well-recognized limitation of administrative data. Because Medicare claims data are collected primarily for payment, and the diagnoses on claims come from medical records, comorbidities are not always reported, especially among patients who have multiple diagnoses and have been seen only as outpatients. This study did not assess longer-term outcomes such as mortality and survival. We also did not address patient preferences and values related to stopping mammography, although Satariano and Regland [37] concluded that early diagnosis of breast cancer would confer little or no survival benefits on women with multiple comorbidities.

Conclusions

We found that older women with stable and unstable comorbidities were significantly more likely to have received mammography within the past 30 months than were those without comorbidities although mammography utilization was high in all groups. Unadjusted rates

of advanced-stage cancer were highest among women with unstable comorbidities, intermediate among women with stable comorbidities, and lowest among those with no comorbidities. After stratifying by prior mammography use, women with and without comorbidities did not differ on overall cancer rates. However, both unstable and stable comorbidities were associated with higher rates of advanced-stage disease at diagnosis among older women who had the most frequent use of mammography. The higher rates of advanced-stage tumors among women with comorbidities cannot be explained by differences in their use of mammography. Future studies need to examine whether specific comorbidities affect clinical progression of breast cancer.

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Table 1

Characteristics of female Medicare beneficiaries who underwent mammography examinations in the linked BCSC-Medicare data from 2000–2006 (N= 149,045)

	All women		No comorbidities (N = 15,818)		Stable [a] comorbidities (N = 93,428)		Unstable [b] only or both stable and unstable comorbidities (N = 39,799)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age at mammography examination								
67–74	82777	(55.5)	10894	(68.9)	52567	(56.3)	19316	(48.5)
75–79	34836	(23.4)	3042	(19.2)	21659	(23.2)	10135	(25.5)
80–84	20998	(14.1)	1387	(8.8)	12862	(13.8)	6749	(17.0)
≥85	10434	(7.0)	495	(3.1)	6340	(6.8)	3599	(9.0)
Race/Ethnicity								
White	114181	(76.6)	12863	(81.3)	72438	(77.5)	28880	(72.6)
Black	11957	(8.0)	737	(4.7)	6903	(7.4)	4317	(10.8)
Hispanic	2505	(1.7)	252	(1.6)	1542	(1.7)	711	(1.8)
Asian/PI	5277	(3.5)	440	(2.8)	3442	(3.7)	1395	(3.5)
American Indian	868	(0.6)	51	(0.3)	448	(0.5)	369	(0.9)
Other/Unknown	14257	(9.6)	1475	(9.3)	8655	(9.3)	4127	(10.4)
Number of comorbid conditions								
None (0)	15818	(10.6)	15818	(100)	-		-	
1	24426	(16.4)	-		23907	(25.6)	519	(1.3)
2	26761	(18.0)	-		24523	(26.2)	2238	(5.6)
3	22951	(15.4)	-		18680	(20.0)	4271	(10.7)
4	17310	(11.6)	-		12008	(12.9)	5302	(13.3)
5	12125	(8.1)	-		6770	(7.2)	5355	(13.5)
>5	29654	(19.9)	-		7540	(8.1)	22114	(55.6)
Mammography use (time between mammography examinations)[c]								
4–18 months	92536	(67.3)	9251	(64.1)	60718	(70.0)	22567	(62.4)
19–30 months	22746	(16.6)	2426	(16.8)	13848	(16.0)	6472	(17.9)
31–42 months	8529	(6.2)	969	(6.7)	4886	(5.6)	2674	(7.4)
>42 months or first screen [d]	11893	(8.7)	1575	(10.9)	6481	(7.5)	3837	(10.6)

	All women		No comorbidities (N = 15,818)		Stable [a] comorbidities (N = 93,428)		Unstable [b] only or both stable and unstable comorbidities (N = 39,799)	
	n	(%)	n	(%)	n	(%)	n	(%)
>42 months or first diagnostic [e]	1710	(1.2)	209	(1.4)	858	(1)	643	(1.8)

[a]Stable comorbidities are defined as age-related conditions with no influence on predicted 5 year mortality. Examples include arthritis, osteoporosis, depression, diabetes, thyroid disorders, stable coronary artery disease, and peptic ulcer disease (Appendix 1).

[b]Unstable comorbidities are defined as life threatening or difficult to control with less than 5 year predicted mortality. Examples include severe heart failure, end-stage pulmonary disease, end-stage liver disease, renal disease, and diabetes with complications (Appendix 1).

[c]Mammography use was categorized according to type of examination and time between mammography examinations. Time to prior mammogram was calculated using last mammogram before cancer diagnosis for women with a cancer diagnosis and a randomly selected mammogram for women with no cancer diagnosis.

[d]>42 months or first screen is defined as a screening mammogram with no prior mammogram within 42 months.

[e]>42 months or first diagnostic is defined as a diagnostic mammogram with no prior within 42 months.

Table 2

Characteristics of female Medicare beneficiaries diagnosed with breast cancer in the linked BCSC-Medicare data from 2000–2006 (N=3316)

	All cancer cases		No comorbidities (N = 350)		Stable [a] comorbidities (N = 2,018)		Unstable [b] only or both stable and unstable co-morbidities (N = 948)		
	n	(%)	n	(%)	n	(%)	n	(%)	*P*
Age at diagnosis									<0.001
67–74	1516	(45.7)	192	(54.9)	942	(46.7)	382	(40.3)	
75–79	918	(27.7)	95	(27.1)	538	(26.7)	285	(30.1)	
80–84	562	(16.9)	42	(12)	346	(17.1)	174	(18.4)	
≥85	320	(9.7)	21	(6)	192	(9.5)	107	(11.3)	
Race/Ethnicity									0.0159
White	2628	(79.3)	296	(84.6)	1610	(79.8)	722	(76.2)	
Black	270	(8.1)	19	(5.4)	161	(8)	90	(9.5)	
Other/Unknown[c]	418	(12.6)	35	(10.0)	247	(12.2)	136	(14.3)	
Number of comorbid conditions									0.001
None (0)	350	(10.6)	350	(100)	-		-		
1	553	(16.7)	-		545	(27)	55	(5.8)	
2	580	(17.5)	-		533	(26.4)			
3	506	(15.3)	-		396	(19.6)	110	(11.6)	
4	354	(10.7)	-		244	(12.1)	110	(11.6)	
5	276	(8.3)	-		149	(7.4)	127	(13.4)	
>5	697	(21)	-		151	(7.5)	546	(57.6)	
Mammography use (time between mammography examinations)[d]									<0.001
4–18 months	1898	(63.0)	164	(54.5)	1240	(66.7)	494	(58.1)	
19–30 months	425	(14.1)	42	(14.0)	259	(13.9)	124	(14.6)	
31–42 months	157	(5.2)	14	(4.7)	91	(4.9)	52	(6.1)	
>42 months or first screen [e]	249	(8.3)	33	(11.0)	138	(7.4)	78	(9.2)	
>42 months or first diagnostic[f]	282	(9.4)	48	(15.9)	132	(7.1)	102	(12.0)	
Tumor characteristics									0.479
In Situ	501	(15.1)	49	(14.0)	317	(15.7)	135	(14.2)	
Invasive	2814	(84.9)	301	(86.0)	1700	(84.3)	813	(85.8)	

	All cancer cases		No comorbidities (N = 350)		Stable [a] comorbidities (N = 2,018)		Unstable [b] only or both stable and unstable co-morbidities (N = 948)		
	n	(%)	n	(%)	n	(%)	n	(%)	*P*
Stage [g]									0.001
Stage I	1458	(59.8)	138	(53.1)	922	(61.9)	398	(57.6)	
Stage IIA	519	(21.3)	69	(26.5)	308	(20.7)	142	(20.5)	
Stage IIB	195	(8.0)	20	(7.7)	97	(6.5)	78	(11.3)	
Stage III, IV	268	(11.0)	33	(12.7)	162	(10.9)	73	(10.6)	
Tumor size									0.028
<10 mm	854	(29.2)	81	(26.8)	540	(30.2)	233	(27.9)	
11–15 mm	860	(29.4)	86	(28.5)	549	(30.7)	225	(26.9)	
>=16 mm	1210	(41.2)	135	(44.7)	697	(39)	378	(45.2)	
Tumor grade									0.034
Well differentiated	610	(23.0)	81	(29.9)	370	(22.8)	159	(20.9)	
Moderately differentiated	1233	(46.4)	112	(41.3)	768	(47.3)	353	(46.4)	
Poorly differentiated/Undifferentiated	812	(30.6)	78	(28.8)	485	(29.9)	248	(32.6)	
Estrogen Receptor Status									0.761
Positive	1964	(84.5)	202	(85.6)	1194	(84.1)	568	(85.0)	
Negative	360	(15.5)	34	(14.4)	226	(15.9)	100	(15.0)	

[a] Stable comorbidities are defined as age-related conditions with no influence on predicted 5 year mortality. Examples include arthritis, osteoporosis, depression, diabetes, thyroid disorders, stable coronary artery disease, and peptic ulcer disease (Appendix 1).

[b] Unstable comorbidities are defined as life threatening or difficult to control with less than 5 year predicted mortality. Examples include severe heart failure, end-stage pulmonary disease, end-stage liver disease, renal disease, and diabetes with complications (Appendix 1).

[c] Groups collapsed due to small cell sizes.

[d] Mammography use was categorized according to type of examination and time between mammography examinations. Time to prior mammogram was calculated using last mammogram before cancer diagnosis for women with a cancer diagnosis and a randomly selected mammogram for women with no cancer diagnosis.

[e] >42 months or first screen is defined as a screening mammogram with no prior mammogram within 42 months.

[f] >42 months years or first diagnostic is defined as a diagnostic mammogram with no prior within 42 months.

[g] Breast cancer stage at diagnosis is classified on TNM staging system (tumor, node, and metastasis) which is based on the criteria of the American Joint Commission. Stage distribution was computed among invasive tumors only.

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Table 3

Mammography examinations by comorbidity status among female Medicare beneficiaries in the linked BCSC-Medicare data from 2000–2006 (N= 149,045)

Mammography Use [a]	**1 year 4–18 months**		**2 years 19–30 months**		**3 years 31–42 months**		**> 42 months or first screening mammogram** [d]		**> 42 months or first diagnostic mammogram** [e]	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
All										
Stable [b] comorbidities	60718	(70)	13848	(16)	4886	(5.6)	6481	(7.5)	858	(1)
Unstable [c] comorbidities	22567	(62.4)	6472	(17.9)	2674	(7.4)	3837	(10.6)	643	(1.8)
No comorbidities	9251	(64.1)	2426	(16.8)	969	(6.7)	1575	(10.9)	209	(1.4)
Age < 75										
Stable [b] comorbidities	35874	(72.8)	7477	(15.2)	2482	(5.0)	3104	(6.3)	330	(0.7)
Unstable [c] comorbidities	11670	(65.5)	3111	(17.2)	1235	(6.9)	1594	(8.9)	220	(1.2)
No comorbidities	6638	(66.1)	1642	(16.4)	635	(6.3)	1002	(10.0)	118	(1.2)
Age ≥ 75										
Stable [b] comorbidities	24844	(66.2)	6371	(17.0)	2404	(6.4)	3377	(9.0)	528	(1)
Unstable [c] comorbidities	10897	(59.3)	3361	(18.3)	1439	(7.8)	2243	(12.2)	423	(2)
No comorbidities	2613	(59.5)	784	(17.8)	334	(7.6)	573	(13.0)	91	(2)

[a] Mammography use was categorized according to type of examination and time between mammography examination.

[b] Stable comorbidities are defined as age-related conditions with no influence on predicted 5 year mortality.

Examples include arthritis, osteoporosis, depression, diabetes, thyroid disorders, stable coronary artery disease, and peptic ulcer disease (Appendix 1).

[c] Unstable comorbidities are defined as life threatening or difficult to control with less than 5 year predicted mortality. Examples include severe heart failure, end-stage pulmonary disease, end-stage liver disease, renal disease, and diabetes with complications (Appendix 1).

[d] >42 months or first screen is defined as a screening mammogram with no prior mammogram within 42 months.

[e] >42 months or first diagnostic is defined as a diagnostic mammogram with no prior within 42 months.

Table 4

Overall breast cancer rates per 1000 mammograms by comorbidity status and time to previous mammogram [c] (N=3316)

	Overall		4–18 Months		19–30 months		31–42 months		>42 months/first screening [d]	
	Rate (95% CI)	p	Rate (95% CI)	p	Rate (95% CI)	p	Rate (95%CI)	p	Rate (95% CI)	p
All	6.9 (6.6,7.2)	--	6.1 (5.9,6.4)	--	8.1 (7.8, 8.9)	--	9.9 (8.5,11.6)	--	14.6 (13.4,15.9)	--
No comorbidities	6.6 (5.8,7.5)	Ref	5.7 (4.9, 6.6)	Ref	8.0 (5.9,10.8)	Ref	8.0 (4.7, 13.5)	Ref	14.6 (10.4,20.4)	Ref
Stable [a] comorbidities	6.7 (6.4,7.0)	0.821	6.0 (5.7, 6.4)	0.489	8.0 (7.1, 9.0)	0.76	9.9 (8.0, 12.1)	0.60	14.7 (12.4, 17.3)	0.814
Unstable [b] comorbidities	7.5 (7.0,8.1)	0.084	6.6 (6.1, 7.2)	0.086	8.3 (7.0, 10)	0.58	10.8 (8.3,14.2)	0.63	14.5 (11.6, 18.1)	0.481

Results adjusted for covariates (age, race/ethnicity/BCSC registry)

[a] Stable comorbidities are defined as age-related conditions with no influence on predicted 5 year mortality. Examples include arthritis, osteoporosis, depression, diabetes, thyroid disorders, stable coronary artery disease, and peptic ulcer disease (Appendix 1).

[b] Unstable comorbidities are defined as life threatening or difficult to control with less than 5 year predicted mortality. Examples include severe heart failure, end-stage pulmonary disease, end-stage liver disease, renal disease, and diabetes with complications (Appendix 1).

[c] Mammography use was categorized according to type of examination and time between mammography examination. Time to prior mammogram was calculated using last mammogram before cancer diagnosis for women with a cancer diagnosis and a randomly selected mammogram for women with no cancer diagnosis.

[d] >42 months or first screen is defined as a screening mammogram with no prior mammogram within 42 months.

Table 5

Advanced stage breast cancer rates per 1000 mammograms by comorbidity status and time to previous mammogram [c] (N=3316)

	Overall		4–18 Months		19–30 months		31–42 months		>42 months/first screening [d]	
	Rate (95% CI)	p	Rate (95% CI)	p	Rate (95% CI)	p	Rate (95% CI)	p	Rate (95% CI)	p
All	0.8 (0.7,0.9)	--	0.7 (0.6,0.8)	--	0.9 (0.7,1.2)	--	1.6 (1.1,2.4)	--	1.7 (1.2,2.4)	--
No comorbidities	0.5 (0.3,0.8)	Ref	0.3 (0.2, 0.6)	Ref	0.4 (0.1, 1.5)	Ref	2.2 (0.8, 5.9)	Ref	1.3 (0.4, 3.9)	Ref
Stable [a] comorbidities	0.8 (0.7,0.9)	0.065	0.7 (0.6, 0.8)	.03	0.9 (0.6, 1.3)	0.803	1.0 (0.5, 1.9)	0.024	1.5 (0.9, 2.5)	0.422
Unstable [b] comorbidities	1.1(0.9,1.3)	0.002	0.9 (0.7, 1.2)	0.004	1.0 (0.6, 1.6)	0.975	2.7 (1.6, 4.7)	0.242	2.2 (1.3, 3.9)	0.562

Results adjusted for covariates (age, race/ethnicity/BCSC registry)

[a] Stable comorbidities are defined as age-related conditions with no influence on predicted 5 year mortality. Examples include arthritis, osteoporosis, depression, diabetes, thyroid disorders, stable coronary artery disease, and peptic ulcer disease (Appendix 1).

[b] Unstable comorbidities are defined as life threatening or difficult to control with less than 5 year predicted mortality. Examples include severe heart failure, end-stage pulmonary disease, end-stage liver disease, renal disease, and diabetes with complications (Appendix 1).

[c] Mammography use was categorized according to type of examination and time between mammography examination time interval since the prior mammography examination. Time to prior mammogram was calculated using last mammogram before cancer diagnosis for women with a cancer diagnosis and a randomly selected mammogram for women with no cancer diagnosis.

[d] >42 months or first screen is defined as a screening mammogram with no prior mammogram within 42 months.

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