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Surveillance mammography and the risk of death among elderly breast cancer patients

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Abstract Purpose To examine the benefits of mammography for elderly breast cancer survivors in community settings. Methods Using the 1991-1999 linked SEER-Medicare data, we examined if mammography reduced the risk of breast-cancer-specific and all-cause mortality among women age 66 or older who were diagnosed with first primary breast cancer (FPBC) at stages 0-III and survived at least 30 months. To analyze the influence of mammography (both within one year and within two years prior to death/censoring) on the risk of breast-cancer-specific mortality, we compared women who died of breast cancer (cases) with women who died of other causes or were censored (controls). For an analysis of all-cause mortality, we compared women who died from any cause (cases) with women who were censored (controls). Propensity scores were used to adjust for tumor-related, treatment-related, and sociodemographic confounders. Results Among 1351 breast cancer deaths (cases) and 5,262 controls, women who had a mammogram during a one or

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R. Aft John Cochran VA Medical Center, Saint Louis, MO, USA two-year time interval were less likely to die from breast cancer than women who did not have any mammograms during this time period in propensity-score-adjusted analysis (within one year odds ratio [OR]: 0.83, 95% confidence interval [CI]: 0.72–0.95; within two years OR: 0.80, 95% CI: 0.70–0.92). Similarly, risk of all-cause mortality was reduced among women who had mammograms during one- or two-year intervals. *Conclusions* In community settings, mammography use during a one- or two-year time interval was associated with a small-reduced risk of breast-cancer-specific and all-cause mortality among elderly breast cancer survivors.

Keywords Elderly · Mammography · Breast cancer survivors · Effectiveness

Introduction

Screening mammography reduces the risk of breast-cancerspecific mortality in women age 65 and older in the general population [1–4]. Several national organizations and agencies recommend annual mammography among elderly women in the general population with or without upper age limit [5, 6]. Due to earlier detection of breast cancers through screening and improved survival through more effective treatment, an estimated one million women age 65 or older who have previously been diagnosed with breast cancer [7], a number that is expected to increase over time as the baby boomer generation ages.

Contrary to studies of screening mammography among elderly women in the general population, few observational [8–10] and no randomized studies have examined whether mammography reduces risk of death among elderly breast cancer survivors in the years after breast cancer treatment (surveillance mammography). Generalizing results from these observational studies among women in the general population is not possible since breast cancer survivors were specifically excluded from participation. As a result of the lack of available evidence, the benefit of surveillance mammography for older women is unclear [8], although some organizations, including the American Society for Clinical Oncology and the National Comprehensive Cancer Network, have made recommendations about screening after breast cancer treatment [11–14]. To fill this gap in knowledge, we examined the effect of surveillance mammography on risk of breast-cancer-specific and all-cause mortality in breast cancer survivors age 66 or older, using the 1991–1999 linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data.

Methods

Sample selection

The sample for this case-control study was obtained from a database that links data of cancer patients from the 1992 to 1999 National Cancer Institute's SEER program with 1991–1999 Medicare claims files from the Centers for Medicare and Medicaid (CMS). In the linked data, women (n = 71,523) were included in the study when diagnosed with a first primary breast cancer (FPBC) from 1992 to 1999. Of these, 34,644 women were at least 66 years of age at the time of stage 0-III FPBC diagnosis and had survived at least 30 months. Women must have survived at least 30 months in order to allow for the possibility of having a maximum of two mammograms during a 24-month surveillance period starting seven months after diagnosis. Since it is not always obvious in the SEER-Medicare data when a woman's initial treatment phase ends and surveillance begins, we began the surveillance period six months after diagnosis to allow time for the patient to complete surgical and systemic treatments, similar to other studies using the SEER-Medicare data [15, 16]. We excluded 7,494 women who (1) were enrolled in a health maintenance organization (HMO) at any point during the 1991-1999 study period, since claims data would not be available; (2) were not covered by Medicare Parts A and B during the time between FPBC diagnosis and study end point (date of death or December 31, 1999); (3) were identified by death certificate only; (4) had bilateral mastectomy; and (5) were age 65 at diagnosis in order to obtain comorbidity from Medicare data around the time of diagnosis beginning in 1991. This left 27,150 patients available for the remainder of the study.

When assessing the effect of surveillance mammography on risk of breast-cancer-specific mortality, cases included women who met all inclusion criteria and none of the exclusion criteria and who subsequently died of breast cancer. Controls included women who met all inclusion and none of the exclusion criteria and who died from other causes, who were censored due to the end of the study period, or who were lost to follow-up. Controls were frequency matched (1 case: 4 controls) based on survival time and randomly selected. Matching on survival time reduces the potential for length-time bias. Because of the prognostic importance of stage at diagnosis, we also matched on stage in addition to survival time in sensitivity analysis.

We also assessed the effect of surveillance mammography on risk of all-cause mortality, which avoids ascertainment bias of disease-specific mortality and is often viewed as the most robust endpoint in clinical trials [17, 18]. Cases included women who met all inclusion and none of the exclusion criteria and who died of any cause. Controls included women who met all inclusion and none of the exclusion criteria and who were censored due to the end of the study period or loss to follow-up. For this analysis, controls were frequency matched (1 case: 3 controls) based on survival time. Fewer controls per case were included based on the number of available controls. A waiver of informed consent was obtained from the Washington University IRB.

Use of mammography

Mammograms were identified from the Medicare data by the CPT-4 codes of 76090, 76091, and 76092 starting at seven months after diagnosis. Since the procedure codes distinguish poorly between screening and diagnostic mammograms [19, 20], we counted two mammograms within one month of each other as one screening mammogram. For claims with a screening mammography code (76092), there had to be a screening diagnosis code in the physician's claim (V10.3, V15.89, V16.3, V72.5, or V76.1) [21, 22]. There is high concordance between claims data and medical record data for mammography use among breast cancer survivors [23].

To examine the effect of surveillance mammography use during the period starting at seven months after the date of diagnosis until date of death or censoring (the surveillance period), we determined whether or not women had received a mammogram within one year prior to death/ censoring and also whether or not women had received a mammogram within two years of death/censoring. Each of these groups of women who received a mammogram was compared with women who did not have any mammograms within one (or two) year(s) prior to death/censoring, respectively.

Covariates

Several covariates were examined to determine the adjusted effect of mammography use on risk of breast cancer death or all-cause mortality. Covariates obtained from the SEER data included: tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, or unknown); estrogen receptor status (positive, negative, or unknown); histology (ductal, lobular, mixed, or other/inflammatory); type of surgery (none, breast conserving, mastectomy, or unknown); receipt of radiation therapy (yes, no, or unknown); race (white, African American, or other); marital status (married, not married, unknown); year of diagnosis (1992–1999); and SEER program (registry site). All were obtained near the time of FPBC diagnosis.

From the Medicare data, we obtained information about comorbidity, chemotherapy, primary-care visit, oncologist visit, ambulatory-care sensitive hospitalizations (ACSH), and development of metastases. We used the Deyo adaptation of the Charlson comorbidity index to measure comorbidity [24, 25] as follows. We searched all available ICD-9 CM codes in the Medicare files (inpatient, outpatient, physician claims) to identify women who had a history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild to severe liver disease, diabetes with or without end-organ damage, hemiplegia, moderate or severe renal disease, or AIDS from 365 days before to 120 days after their FPBC diagnosis. Each category was weighted according to the Charlson index. Women who had no Medicare claims during this period were categorized as having unknown comorbidity.

Chemotherapy was obtained from the Medicare claims data, which appear to be of adequate validity and completeness [26]. The following codes were used to define chemotherapy: International Classification of Disease (ICD)-9-CM procedure code 9925 for a hospital inpatient or outpatient facility claim of chemotherapy, the Common Procedure Terminology codes 96400–96549, J9000–J9999, and Q0083–Q0085 for a physician or outpatient claim, revenue center codes 0331, 0332, and 0335 for an outpatient claim, and the ICD-9-CM V codes V58.1, V66.2, or V67.2 [27]. Women were considered to have received chemotherapy for breast cancer if there was at least one claim present after the date of diagnosis; other women were coded as not having received chemotherapy.

Similar to other studies, we used Medicare claims data to identify ACSH, as an indicator of adequate, timely, efficient, and high-quality ambulatory care [28, 29]. Women who had one or more ACSH at any time following their breast cancer diagnosis were considered to have less adequate, timely, efficient, or high-quality ambulatory care. This group of women was compared with women who did not have any ACSH following their breast cancer diagnosis. The International Classification of Disease (ICD)-9-CM codes reported as a first or primary diagnosis for each hospitalization were used to determine if a hospitalization could be classified as ACSH [28, 30].

We used the Health Care Financing Administration (HCFA) provider specialty code in Medicare to categorize breast cancer survivors' visits to primary care physicians and oncologists following their diagnosis [31]. We included the following provider specialty codes: 01—general practice; 11—internal medicine; 08—family practice; 16—obstetrics/gynecology; 38—geriatric medicine; and 70—multispecialty group practices. Using HCFA specialty codes, oncology specialists were defined as subspecialists in medical oncology or hematology-oncology (codes 83 or 90), radiation oncologists (code 92), or surgeons (code 02 for general surgery or 91 for surgical oncology).

We used Medicare's ICD-9-CM codes (196.0–196.9, 197.0–198.81, and 199.0) to identify metastases of secondary/unspecified malignant neoplasms of lymph nodes, respiratory/digestive systems, or of other unspecified sites [32].

Data from the 1990 census were used to obtain indicators of socioeconomic and sociodemographic conditions at the census-tract level, recognizing that this is an imperfect measure of individual-level socioeconomic condition. Covariates from the census included percentage of residents who were below federal poverty level, African American, and age 25 or older without a high school education.

Statistical analysis

We examined the effectiveness of mammography use on risk of breast-cancer-specific mortality using logistic regression. First, we calculated unadjusted odds ratios and 95% confidence intervals (95% CI). Next, we used propensity scores to calculate adjusted odds ratios by balancing covariates on mammography use since it may depend on patient characteristics, tumor characteristics, type of treatment received, and comorbidity [33, 34].

Multivariable logistic regression may be limited in its ability to control for confounders in studies of mammography effects when there are fewer than 10 events per variable analyzed [35]. The use of propensity scores has been proposed as an alternative that may be especially useful when multiple confounders are involved [36].

The propensity score is defined as the conditional probability of a woman having a mammogram, given all observed covariates (patient characteristics, tumor characteristics, type of treatment received, and comorbidity). The propensity score can be thought of as a measure of the likelihood based solely on covariate information that a woman will be classified in one of the two mammography groups (having a mammogram during the time period or not). To calculate the propensity score, a logistic regression model was constructed in which the dependent variable was the use of mammography within one year versus no mammography and the independent variables were the covariates associated with mammography use. We included only variables associated with mammography use in the calculation of propensity scores [37]. Next, we grouped the subjects into ten strata representing deciles of the propensity score, which is usually adequate to remove more than 90% of the bias due to each of the covariates in a fully specified model [34]. We then determined if the conditional distribution of the characteristics given the propensity score is the same for two groups [38]. This was the case, suggesting appropriate adjustment for all covariates (patient characteristics, tumor characteristics, type of treatment received, and comorbidity) included. Receiver operating characteristic (ROC) curves were generated for each model and their performance assessed by the c-statistic, which is akin to the area under the curve, recognizing the limitation this goodness-of-fit measure may not identify missing confounders [39]. The risk of breast-cancerspecific mortality based on mammography use was then calculated adjusting for propensity score deciles. Separate analyses were done for having a mammogram within two years and to examine the effect of mammography use on risk of all-cause mortality.

To minimize the likelihood of including mammography that had not been performed for routine surveillance purposes shortly before death/censoring, we shifted the entire 30-month time period to six months earlier as part of a sensitivity analysis. The time period of interest now started six-months before death or censoring and extended to 36months prior to death or censoring. Because of its skewed distribution between both groups, we also frequency matched on stage in addition to survival time as part of a sensitivity analysis.

The fit of the logistic models was analyzed by calculation of the Hosmer–Lemeshow goodness-of-fit statistic. The explained variance was based on Nagelkerke's R^2 . We used SAS software, version 9.1, for all analyses.

Results

Breast-cancer-specific mortality

This analysis included 1351 cases who died from breast cancer and 5262 controls who survived at least 30 months after their date of diagnosis. The average surveillance period for cases and controls starting at 7 months after diagnosis was 48.9 months (median: 45.0 months; range: 30.0–95.0 months). Cases and controls were well matched on surveillance time (Table 1).

Cases were more likely to be older, to be African American, to have two or more comorbid conditions, to have been diagnosed at a more advanced stage of breast cancer, to have received chemotherapy, and to not have received radiotherapy (Table 2). About 28% of cases had a mammogram within one year prior to death compared with 39.7% of controls prior to death/censoring (P < 0.0001). About 54% of cases had a mammogram within two years prior to death compared with 71.2% of controls prior to censoring (P < 0.0001).

In unadjusted analysis, women who had a mammogram within one year were 0.59 times as likely to die from breast cancer as women who did not have any mammograms during this time period (Table 3). We then calculated propensity scores by having a mammogram versus not having a mammogram within one year as the dependent variable. The area under the ROC curve was 0.65, indicating reasonable discrimination between women in the two categories of mammography use. No statistically significant differences in the component covariates by mammography use were observed when controlling for propensity score strata, suggesting equivalent distributions of covariates across the two-mammography groups. In propensity-score-adjusted analysis, women who had a mammogram within one year were 0.83 times as likely to die from breast cancer as women who did not have any mammograms during this time period.

In unadjusted analysis, women who had a mammogram within two years were 0.48 times as likely to die from breast cancer as women who did not have any mammograms (Table 3). We then calculated propensity scores by modeling having a mammogram versus not having a mammogram within two years. The area under the ROC curve was 0.76, indicating good discrimination between

 Table 1
 Proportion of cases and controls age 66 or older who survived at least 30 months after diagnosis in the 1991–1999 linked

 SEER-Medicare database, by surveillance time (years)

Survival time (years)	Cases n = 1,351 (%)	Controls n = 5,262 (%)	All women <i>n</i> = 6,613 (%)	
3	41.1	41.6	41.5	
4	26.2	25.8	25.9	
5	17.9	17.4	17.5	
6	9.3	9.2	9.2	
7	4.8	5.1	5.1	
8	0.7	0.8	0.8	

Cases are women who died of breast cancer

 Table 2
 Selected characteristics of the sample of women age 66 or older who survived at least 30 months past FPBC diagnosis in the 1991–1999

 SEER-Medicare database

Variables	Cases $n = 1,351 \ (\%)$	Controls $n = 5,262 \ (\%)$	All women n = 6,613 (%)
Age (years)*			
66–69	22.2	23.7	23.4
70–74	27.4	31.0	30.2
75–79	21.8	23.2	22.9
80-84	16.9	13.8	14.5
85+	11.8	8.3	9.0
Race*			
White	87.8	90.6	90.0
African American	9.5	5.2	6.1
Other	2.7	3.8	3.6
Unknown	0.0	0.5	0.4
Comorbidity*			
None	52.0	53.4	53.1
One	26.3	28.2	27.8
Two or more	20.1	16.7	17.3
Unknown	1.7	1.8	1.7
AJCC stage*			
0 (in situ)	1.6	14.7	12.1
Ι	22.0	51.8	45.7
П	54.7	29.2	34.4
III	20.0	3.7	6.9
Radiotherapy recei	ved*		
Yes	29.4	36.4	35.0
No	68.2	62.2	63.4
Unknown	2.4	1.4	1.6
Chemotherapy rece	eived*		
Yes	46.1	11.8	18.8
No	53.9	88.2	81.2

FPBC: first primary breast cancer. AJCC: American Joint Commission on Cancer

Cases: Women who died of breast cancer

* P < 0.05

women in the two categories of mammography use. No statistically significant differences in the component covariates by mammography use were observed when controlling for propensity score strata, suggesting equivalent distributions of covariates across the twomammography groups. In propensity-score-adjusted analysis, women who had a mammogram within two years were 0.80 times as likely to die from breast cancer as women who did not have any mammograms during this time period. Both sensitivity analyses did not change the results appreciably.

All-cause mortality

Cases and controls were well matched on surveillance time (data not shown). In unadjusted analysis, women who had a mammogram within one year were 0.52 times as likely to die as women who did not have any mammograms during this time period (Table 4). We then calculated propensity scores by modeling having a mammogram versus not having a mammogram within one year. The area under the ROC curve for mammography use within one year was 0.66. Equivalent distributions of covariates across mammography groups when controlling for propensity score strata were observed. In propensity-score-adjusted analyses, women who had a mammogram within one year were less likely to die from any cause (OR: 0.83) relative to women who did not have any mammograms during this time period.

In unadjusted analysis, women who had a mammogram within two years were 0.34 times as likely to die from any cause as women who did not have any mammograms during this time period (Table 4). We then calculated propensity scores by modeling having a mammogram versus not having a mammogram within one year. The area under the ROC curve for mammography use within two years was 0.77. Women who had a mammogram within two years were less likely (OR: 0.70) to die from any cause compared with women who did not have any mammograms during this time period. Both sensitivity analyses did not change the results appreciably.

Discussion

In this case-control study, women age 66 or older diagnosed with breast cancer who received a mammogram during either a one- or two-year time interval were at reduced risk of breast-cancer-specific and all-cause mortality compared with women who did not have any mammograms during these time periods. Our results extend the literature about the effects of mammography among women in the general population [40] to breast cancer survivors.

The reduction in risk of breast-cancer-specific mortality was similar for elderly women receiving mammograms during a one- or two-year time interval. Comparable results have been reported among elderly women in the general population [22, 41]. The lack of a difference in risk of breast-cancer-specific mortality between the one- and twoyear time intervals in our study may be the result of the low tumor growth rate in the elderly. Based on our results, women who received a mammogram during a two-year interval could expect the same reduction in risk of death due to breast cancer or to all causes as women who

	Mammography during surveillance period before death/censoring		
	Within 1 year vs. no mammogram	Within 2 years vs. no mammogram	
Unadjusted OR (95% CI)	0.59 (0.52–0.67)	0.48 (0.42–0.54)	
Nagelkerke R^2	0.015	0.033	
c-statistic	0.559	0.586	
Propensity-score adjusted OR (95% CI)	0.83 (0.72–0.95)*	0.80 (0.70-0.92)**	
Nagelkerke R^2	0.165	0.163	
c-statistic	0.720	0.722	
Hosmer-Lemeshow goodness-of-fit	0.693	0.880	

Table 3 Logistic regression models evaluating the influence of surveillance mammography on the risk of breast cancer-specific mortality

OR: Odds ratio; CI: Confidence interval

* Variables included in the propensity score: stage, year of diagnosis, age group, tumor grade, radiotherapy, type of surgery, race, comorbidity, tumor histology, marital status, primary care visit, oncologist visit, ambulatory care sensitive visit, registry site

** Variables included in the propensity score: stage, year of diagnosis, age group, race, tumor grade, radiotherapy, type of surgery, chemotherapy, comorbidity, tumor histology, percent without high school degree, percent African Americans, primary care visit, oncologist visit, ambulatory care sensitive visit

received a mammogram during a one-year interval. Thus, our findings do not support the current recommendation for annual surveillance mammography following breast cancer diagnosis among women over age 65 [11, 14]. However, Lash and colleagues recently showed that the benefit goes up with the number of surveillance mammograms [9].

Although a majority of breast cancer survivors received mammography during the two-year time interval (71.2% among controls and 54.0% among cases [i.e., women who ultimately died from breast cancer]), little is known about why some women do not undergo surveillance mammography beyond factors traditionally found in cancer registry data [42, 43]. Further research is needed to identify other factors associated with use of surveillance mammography and to develop interventions to increase use of surveillance mammography among breast cancer survivors.

Our study has both strengths and limitations. Strengths include the population-based nature of the study, the large number of breast cancer deaths included in the analysis relative to other studies, and the use of propensity score analysis to control for lack of random assignment of mammography [34]. Population-based data can provide valuable insights into the practical effectiveness of mammography that either cannot be tested in or obtained from results of a clinical trial [44]. Participants in clinical trials do not represent all patients who may become candidates for treatment. For example, patients who are older or have significant comorbidities are generally excluded or exclude

Table 4 Logistic regression models evaluating the influence of surveillance mammography on the risk of all-cause mortality

	Mammography during surveillance period before death/censoring		
	Within 1 year vs. no mammogram	Within 2 years vs. no mammogram	
Unadjusted OR (95% CI)	0.52 (0.49–0.56)	0.34 (0.32–0.37)	
Nagelkerke R^2	0.025	0.073	
c-statistic	0.571	0.624	
Propensity-score adjusted OR (95% CI)	0.83 (0.76-0.90)*	0.72 (0.66–0.78)**	
Nagelkerke R^2	0.232	0.321	
c-statistic	0.761	0.807	
Hosmer-Lemeshow goodness-of-fit	1.000	0.374	

OR: Odds ratio; CI: Confidence interval

* Variables included in the propensity score: stage, year of diagnosis, age group, tumor grade, radiotherapy, type of surgery, chemotherapy, comorbidity, tumor histology, metastases, poverty rate, percent without high school degree, percent African American, marital status, primary care visit, oncologist visit, ambulatory care sensitive visit, registry site

** Variables included in the propensity score: stage, year of diagnosis, age group, race, tumor grade, radiotherapy, type of surgery, chemotherapy, comorbidity, estrogen receptor status, primary care visit, oncologist visit, ambulatory care sensitive visit themselves from clinical trials. In addition, the process of care is strictly maintained within the clinical trial setting with frequent follow-up and protocols for disease management. On the other hand, outside clinical trials, physicians care for patients with possible comorbidities, exhibit variations in practice patterns, and must consider patients' treatment preferences. Moreover, clinical trial data are typically obtained from larger hospitals, thereby reducing the generalizability to patients who may not have access to these hospitals for various reasons (e.g., rural women). Trial results may differ from actual treatment outcomes in everyday practice in other ways as well. Therefore, highquality observational data, such as the SEER-Medicare program data, can provide important insights into the effectiveness of mammography in community settings especially among older breast cancer patients [45].

Our study also has some limitations. First, our reliance on Medicare claims data may have underestimated the use of mammography if some women paid for the test themselves. Although there are some differences in mammography rates between Medicare data and self-reported data [20], it is difficult to determine the direction and magnitude this bias would exert on our findings. A second limitation is the inability to distinguish between screening and diagnostic mammograms in the Medicare data. It is possible that women who sought a mammogram may have had symptoms. This potential bias would have been nondifferential and likely underestimated our findings. This potential bias was reduced by our considering that two mammograms within one month of each other to be one mammogram and by the fact that 87% of community mammograms are considered to be screening mammograms [46]. Third, since claims data were used, we did not have information about the use of clinical breast examination (CBE). Although some women in the control group may have received a CBE, its effect on breast cancer mortality from randomized trials is inconclusive [47]. Thus, it is unclear how CBE use would have affected our findings. Fourth, we assessed mammography use only a relatively short time interval (two years) prior to death similar to other studies [22]. Irrespective of the relatively short time interval, we show important and immediate effects of mammography use shortly before death/censoring. From our results, it is unclear how repeated mammograms would affect the risk of death. Lash and colleagues recently showed that the risk of death is reduced with increasing number of mammograms after diagnosis [9], but they did not evaluate the interval between mammograms. Fifth, generalizability is limited to the study population included, namely women age 66 or older with fee-for-service Medicare insurance and diagnosed with FPBC during 1992-1999. Extrapolation to younger women and to elderly women with HMO insurance remains unclear.

In summary, this study provides evidence that, in the community setting, the use of mammography following FPBC diagnosis was associated with a small reduction in risk of breast-cancer-specific and all-cause mortality. Breast cancer survivors age 66 or older should be encouraged to receive mammography at least every 2 years after diagnosis.

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