All-Cause Mortality Is Decreased in Women Undergoing Annual Mammography Before Breast Cancer Diagnosis

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OBJECTIVE. The value of annual mammography remains an area of debate because of concerns regarding risk versus benefit. The potential for harm due to overdiagnosis and treatment of clinically insignificant cancers may not be captured by breast cancer–specific mortality. Instead, we examined all-cause mortality as a function of missed annual mammography examinations before breast cancer diagnosis.

MATERIALS AND METHODS. Primary breast cancer cases diagnosed in the Marshfield Clinic Health System from 2002 through 2008 were identified for retrospective review, and whether annual mammography examinations had been performed in the 5 years before diagnosis was assessed.

RESULTS. Analyses were performed on 1421 women with breast cancer. After adjustment of data for age, comorbidity status, a family history of breast cancer, insurance status, medical encounter frequency, and the calendar year, women who had missed any of the previous five annual mammography examinations had a 2.3-fold increased risk of all-cause mortality compared with subjects with no missed mammography examinations (hazard ratio = 2.28; 95% CI, 1.58–3.30; $p < 0.0001$). Additionally, an analysis by the number of missed annual mammography examinations showed a progressive increase in hazard as the number of missed mammography studies increased.

CONCLUSION. These results suggest that annual mammography before breast cancer diagnosis is predictive of increased overall survival. A stepwise decline in overall survival was noted for each additional missed mammography examination. These results are similar to findings in the literature for breast cancer–specific mortality and illustrate the importance of recommending annual mammography to all eligible women.

Keywords: breast cancer, mammography, mortality

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Breast cancer is the most commonly diagnosed cancer in U.S. women, excluding nonmelanoma skin cancers, and has one of the highest cancer mortality rates in women, accounting for more than 40,000 deaths in the United States in 2013 [1]. Thus, breast cancer has become an important public health concern, and preventive measures, including mammography, have been implemented to detect breast cancer at an early stage. Randomized control trials conducted in the 1970s and 1980s fueled the implementation of regular mammographic screening, citing a 25–30% decrease in breast cancer–specific mortality [2]. Similar decreases in breast cancer–specific mortality were noted after nearly 30 years of follow-up in the Swedish Two-County Trial [3], and several subsequent studies have provided additional evidence of a reduction in breast cancer–specific mortality with regular screening mammography [3–11].

Despite the large body of evidence supporting routine mammography, the benefits of screening mammography are not universally accepted and remain under scrutiny. Critics of annual mammography suggest that the observed decreases in breast cancer–specific mortality are minimal compared with the harm inflicted by screening [12–15]. The major criticisms of routine mammography screening relate to overdiagnosis and subsequent treatment of clinically insignificant cancers in addition to issues of radiation exposure and the potential psychologic harm to patients with false-positive results [16, 17]. In theory, overdiagnosis may lead to increases in the incidence of breast cancer and unnecessary treatment of breast cancers that might not have progressed even in the absence of treatment. Including these can-

cers may, therefore, influence breast cancer–specific mortality statistics [12–15]. Additionally, cancer treatment is associated with considerable morbidity and may inflict harm, potentially affecting overall mortality rates, and biases related to the classification of breast cancer–related deaths may also influence breast cancer–specific mortality studies [18, 19]. Thus, a number of groups have proposed the analysis of all-cause mortality rather than breast cancer–specific mortality [18–22]. To date, few studies have compared all-cause mortality in breast cancer patients who undergo routine screening mammography versus those who miss routine screening opportunities [18, 19, 23], and these studies have yielded mixed results. Therefore, we sought to determine all-cause mortality rates in women diagnosed with breast cancer as a function of annual mammography.

Materials and Methods

All-cause mortality was evaluated in a cohort of women seen in the Marshfield Clinic Health System with an initial primary breast cancer as previously described by Onitilo et al. [24]. The Marshfield Clinic Health System is the largest private group medical practice in Wisconsin serving the predominantly rural northern, central, and western portions of the state at more than 50 locations with more than 80 different medical specialties. In many of its service areas, the Marshfield Clinic Health System is the only health care provider available. Primary breast cancer cases were identified between January 1, 2002, and December 30, 2008, using a multicenter cancer registry accredited by the American College of Surgeons Commission on Cancer, and these cases were followed for all-cause mortality through December 31, 2010. Patients diagnosed with breast cancer at another facility, male breast cancer patients, and patients who live outside the Marshfield Clinic service area of Wisconsin and the surrounding states of Illinois, Michigan, and Minnesota were excluded.

Data were obtained by electronic abstraction from the cancer registry and from electronic medical records with extensive manual abstraction, including manual review of all mammography reports within 5 years of breast cancer diagnosis. Manual validation of 10% of the electronically abstracted data was performed. Patient demographics and additional data including the number of medical encounters within the 5 years before the breast cancer diagnosis, the number of annual mammography examinations performed within 5 years before the breast cancer diagnosis, breast cancer stage, insurance status, medical and family history, comorbidities at the time of the breast cancer diagnosis, and patient residence were obtained. This study was approved by the institutional review board of the Marshfield Clinic Research Foundation.

Mammographic data were obtained through an electronic search for related procedure codes; International Classification of Diseases, ninth revision (ICD-9) [25], codes; and 31 mammography-related appointment types. Procedures codes related to computer mammography add-on, mammary duct radiography, mammography (one breast, both breasts, or screening), computer-aided detection on diagnostic or screening mammography, multiple mammary ductography or galactography studies, unilateral or bilateral mammography, bilateral or digital screening mammography, and digital diagnostic mammography were used. ICD-9 codes included 793.8x for unspecified abnormal mammography, mammographic microcalcifications, inconclusive mammography, or other abnormal radiographic findings; V76.11 for high-risk patient screening mammography; and V76.12 for other screening mammography examinations.

Most mammography examinations in our patient group were detected through at least two sources (procedure codes, ICD-9 codes, or appointment type), and the remaining 11.3% of identified mammography studies that had only one source were manually checked to ensure accuracy. After identification and confirmation of all mammography examinations performed on included subjects, the examinations performed for screening and diagnostic purposes were considered for data analysis. Mammography examinations were annualized in the 5 years before diagnosis by examining each 365-day time period for evidence of a mammography study. Subjects were stratified as "yes" if at least one mammography examination was performed per time period or "no" if mammography was not performed during the corresponding time period.

Cox regression models with the backward elimination method were generated to analyze the association between all-cause mortality and annual mammography. For these analyses, missed mammography examinations, age group (< 50, 50–75, > 75 years), insurance status, the number of medical encounters, comorbidity status, family history, the calendar year, and the interaction of age and missed mammography examinations were considered as potential predictive variables. Adjustment of data for medical comorbidity status used the Charlson comorbidity index [26]. The supremum test was used to assess the proportional hazards assumption. SAS software (version 9.2, SAS Institute) was used for all statistical analyses with $p < 0.05$ considered statistically significant.

TABLE 1: Patient Demographics and Disease Characteristics

Characteristic	No. of Patients	Value
Age at diagnosis (y), median (interquartile range)	1421	62.6 (22.3)
Stage at diagnosis, no. (%) of patients	1421	
Stage 0		302 (21.3)
Stage I		599 (42.2)
Stage II		303 (21.3)
Stage III		112 (7.9)
Stage IV		52 (3.7)
Stage was missing from medical record		53 (3.7)
Charlson comorbidity index score ≥ 1, no. (%) of patients	1421	600 (42.2)
No. of medical encounters in 5 y before breast cancer diagnosis, median (interquartile range)	1272	33 (48)
Family history of breast cancer, no. (%) of patients	1421	
Yes		573 (40.3)
Insurance, no. (%) of patients	1421	
Yes		829 (58.3)

Results

A total of 1428 women diagnosed with primary breast cancer during the study period were identified. Analyses were conducted on 1421 of these subjects; the remaining seven patients were excluded because of incomplete or missing mammography dates. The median age at the time of breast cancer diagnosis was 62.6 years. Most (≈ 85%) women were diagnosed with early-stage (0–II) breast cancer (Table 1). Cancer stage as a function of annual mammography in this population was previously addressed [24]. In total, 252 patients died during follow-up

(median age at death, 77.9 years). Additional patient information concerning comorbidities, the number of medical encounters, insurance status, residence, and family history of breast cancer is shown in Table 1.

Manual validation of 10% of the electronically abstracted data revealed a 0.27% error rate and no significant difference among the variables used to identify mammography examinations. Because the rate of agreement between manually validated data and electronically captured data was 99.7%, no further action was taken.

Cox regression analyses revealed that missed mammography examinations ($p < 0.0001$), age ($p < 0.0001$), comorbidity status ($p < 0.0001$), and a family history of breast cancer ($p = 0.004$) were significant independent risk factors for all-cause mortality. The supremum test showed that age, a family history of breast cancer, and comorbidity status were not in violation of the proportional hazards assumption. When data were adjusted for age, a family history of breast cancer, and comorbidity status, Cox regression analyses showed that subjects with at least one missing annual mammography examination in the 5 years before the breast cancer diagnosis resulted in a hazard ratio (HR) for all-cause mortality of 2.28 (95% CI, 1.58–3.30; $p < 0.0001$) compared with subjects who participated in five of five annual mammography studies before diagnosis (Fig. 1). When subjects were analyzed by number of missed annual mammography examinations in the 5 years before diagnosis, Cox regression analyses revealed a progressive increase in the HR for all-cause mortality with each additional missed mammography examination (Table 2). A significant increase in the HR for all-cause mortality began with two missed annual mammography examinations (HR = 1.97; 95% CI, 1.18–3.29; $p = 0.0096$) and increased progressively. Five missed mammography examinations yielded an HR of 3.55 (95% CI, 2.38–5.30; $p < 0.0001$).

TABLE 2: Hazard Ratio (HR) for All-Cause Mortality by Number of Annual Mammography Examinations Missed

No. of Annual Mammography Examinations Missed	No. of Patients	HR[a]	95% CI	*p*
0	283	Reference		
1	253	1.37	0.84–2.22	0.2052
2	156	1.97	1.18–3.29	0.0096
3	131	2.07	1.23–3.47	0.0061
4	187	2.15	1.29–3.57	0.0033
5	411	3.55	2.38–5.30	< 0.0001

[a]Adjusted for age, family history of breast cancer, comorbidity status, number of medical encounters, and calendar year.

Discussion

Despite ample evidence showing that mammography reduces breast cancer–specific mortality [2–11, 27–30], the risk-versus-benefit balance of mammography as a screening tool remains under scrutiny [12–15]. Some concerns center around the effects that overdiagnosis and treatment advances have had on decreases in breast cancer–specific mortality previously attributed to successful screening mammography programs [12–15]. Other concerns involve the potential for harm as a result of overtreatment of cancers that might not have progressed or biases related to the classification of breast cancer–related deaths when analyzing breast cancer–specific mortality [18, 19]. The assessment of all-cause mortality, rather than disease-specific mortality, as a function of annual mammography frequency offers additional insights into the utility of mammography.

To date, three studies have examined the relationship between mammography frequency and all-cause mortality [18–20], and these studies have yielded mixed results. Gøtzsche and Olsen [18] and Black et al. [19] reviewed randomized controlled trials of screening mammography published between 1998 and 2000 and identified inconsistencies between breast cancer–specific mortality and all-cause mortality in several of the studies. Both studies were met with significant criticism, primarily concerning poor reasoning for the inclusion or exclusion of the trials assessed and the use of unadjusted data [31–39]. In 2002, Tabár et al. [23], authors of the long-running Swedish Two-County Trial, conducted a breast cancer–specific and all-cause mortality analysis of 2468 breast cancer patients followed for an average of 10 years after breast cancer diagnosis. Their results indicated a significant 19% reduction in all-cause mortality and a 31% reduction in breast cancer–specific mortality for breast cancer patients who underwent regular mammography [23].

Similar to the findings reported by Tabár et al. [23] more than a decade ago, the results of the current study show decreased all-cause mortality in breast cancer patients who underwent routine mammography before diagnosis compared with those with missed annual mammography examinations. This significant difference persisted when the data were controlled for age, insurance status, the number of medical encounters, comorbidity status, a family history of breast cancer, and the calendar year. Although we were able to show a significant difference,

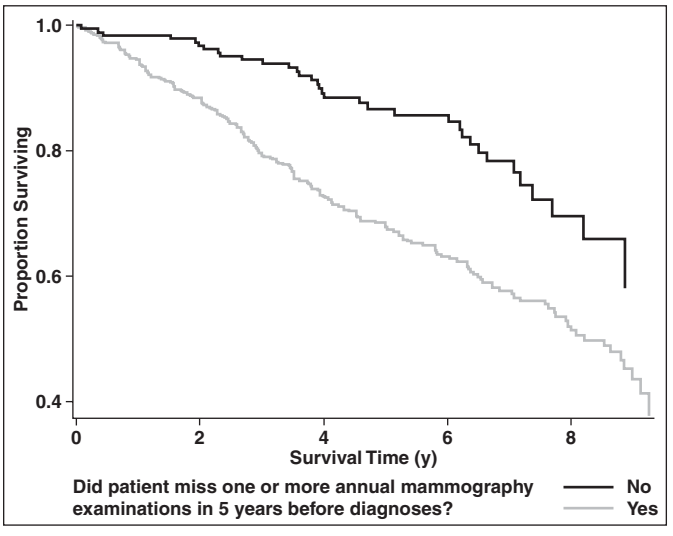

Fig. 1—Cox regression survival curves for all-cause mortality stratified by whether or not patients had one or more annual mammography examinations in 5 years before breast cancer diagnosis: yes (*gray line*, $n = 1138$ patients) or no (*black line*, $n = 283$ patients). Data were adjusted for age, family history of breast cancer, comorbidity status, number of medical encounters, and calendar year. Hazard ratio for all-cause mortality was 2.28 (95% CI, 1.58–3.30; $p < 0.0001$).

this benefit may be underestimated. Both screening imaging and diagnostic imaging were considered for analysis, and any mammography examination performed per 365-day period classified a patient as having undergone annual mammography. Therefore, women who did not undergo regular screening mammography but presented with symptoms and subsequently underwent diagnostic mammography were considered as having undergone mammography that year. Recent evidence suggests that breast cancers detected clinically are likely to be more aggressive than those detected by screening mammography [40]. The potential increased risk of mortality associated with diagnostic mammography–detected breast cancers included in this study may have falsely increased all-cause mortality in the group of subjects who underwent annual mammography.

An additional analysis revealed a direct relationship between the number of missed annual mammography examinations during the previous 5 years and all-cause mortality with progressively increasing HRs for each additional year of missed mammography. A trend toward increased all-cause mortality was found in women who missed one annual mammography examination (HR = 1.37; 95% CI, 0.84–2.22; $p = 0.2052$) with a significant difference in all-cause mortality beginning in women who missed two annual mammography examinations. Although a significant difference with one missed mammography examination was not seen, this HR may be underestimated. For study purposes, we chose a cutoff of 12 months per annualized mammography study. Therefore, women who underwent mammography at 13 or 14 months were classified as having missed an annual mammography examination and may, consequently, have an influential effect on decreasing all-cause mortality in this group.

Mammography programs were developed to detect breast cancers at an earlier, easier-to-treat stage with the overarching goal of reducing breast cancer–related mortality. Recent studies have indicated that missed opportunities for screening mammography increase the risk of breast cancer diagnosis at a later stage [24, 41, 42]. The results of a recent study by Onitilo et al. [24] suggested that missing even one mammography examination in the year before breast cancer diagnosis made a difference in cancer stage. If a patient opts for a mastectomy rather than lumpectomy followed by radiation, patients with stage 0, stage I, and some stage II breast cancers may be treated with surgery alone (or in combination with endocrine therapy if hormone receptor–positive), whereas most breast cancers that are stage II or higher typically require the addition of chemotherapy, radiation, and endocrine therapy if hormone receptor–positive [43]. Cancer treatment is not without side effects and may result in significant morbidity and, in some cases, may contribute to subsequent mortality. Radiation, chemotherapy, and endocrine therapy can each cause significant long-term side effects, including the possible development of secondary cancers [44]. We speculate that the more aggressive therapy necessary to treat advanced breast cancers diagnosed in women who do not undergo annual mammography increases the risk of side effects and associated increases in all-cause mortality rates.

Certain limitations of the current study must be acknowledged. First, the follow-up period of the included breast cancer subjects is relatively short and many treatment side effects, such as those associated with radiation exposure, may take years to develop [45, 46]. Although the median follow-up time in our study was 5.2 years with a maximum of 9.5 years, our results are similar to those reported by Tabár et al. [23], who observed a 19% reduction in all-cause mortality among women who underwent screening when followed for an average of 10 years after breast cancer diagnosis. Second, the cohort size in our study is rather small. Proponents of using breast cancer–specific mortality argue that disease-specific mortality is small and that the benefits of screening may be significantly diluted when analyzing all-cause mortality without a large cohort size [23, 47]. However, we were able to detect a significant difference in survival between those who underwent annual mammography and those who did not. Third, because this analysis is retrospective, our study was limited to information available in the electronic medical records at the Marshfield Clinic facilities. Despite this limitation, we believe that most of the mammographic information for our study patients was documented and available. Our institution follows specific protocols to ensure the completeness of mammographic records. Inquiries regarding mammographic history are made when patients schedule mammography and again when patients present for mammography. Any gaps in mammographic examinations are questioned; when a woman indicates that she underwent mammography at another facility, staff members contact that facility to obtain the mammography records from the previous 5 years for comparison. Fourth, we did not analyze all-cause mortality in relation to specific cancer treatments, tumor characteristics, exposure to hormone replacement therapy, breast density, prior breast biopsies, or stage of cancer and are consequently unable to address the role that these factors may play in overall survival of the included breast cancer patients. Last, our mortality analysis included only women diagnosed with breast cancer and, therefore, cannot address risks associated with mammography experienced by women who are not diagnosed with breast cancer. However, overdiagnosis is unlikely to be a concern in these women.

The benefits of mammography are well documented, with numerous studies finding a significant decrease in breast cancer–specific mortality [2–11, 27–30]. Despite this clear evidence, concerns regarding the use of the proper endpoint have been raised. Criticisms regarding the overdiagnosis of clinically insignificant cancers, harms inflicted by cancer treatment, and potential biases related to the classification of breast cancer–related deaths have led some to suggest that all-cause mortality, rather than breast cancer–specific mortality, be used as an endpoint when evaluating the value of routine mammography [18–22]. Consistent with the 2002 study by Tabár et al. [23], our study shows a significant overall decrease in all-cause mortality among women with breast cancer who underwent annual mammography. These findings suggest that annual mammography before breast cancer diagnosis is predictive of increased overall survival. Moreover, a stepwise decline in overall survival was observed for each additional missed annual mammography examination in the 5 years before breast cancer diagnosis. Our results are similar to the findings in the literature for breast cancer–specific mortality and emphasize the importance of recommending annual mammography to all eligible women.

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