Lead Time Bias as a Factor in Mammography Detected Invasive Breast Cancer Survival in an Institutional Cohort

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Research article

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Abstract

**Background:** Lead time, the interval between screen detection and when a disease would have become clinically evident, is commonly cited to explain longer survival times in mammography detected breast cancer cases (BC).

**Methods:** An institutional retrospective cohort study of BC outcomes related to detection method (mammography (MamD) vs. patient (PtD)). Cases were first primary invasive stage I-III BC, age 40-74 years (n = 6603), 1999-2016. Survival time was divided into 1) distant disease-free interval (DDFI) and 2) distant disease-specific survival (DDSS) as two separate time interval outcomes. We measured statistical association between detection method and diagnostic, treatment and outcome variables using bivariate comparisons, Cox proportional hazards analyses and mean comparisons. Outcomes were distant recurrence (n=422), DDFI and DDSS.

**Results:** 39% of cases were PtD (n = 2566) and 61% were MamD (n = 4037). MamD cases had a higher percentage of Stage I tumors [MamD 69% stage I vs. PtD 31%, p<.001]. Rate of distant recurrence was 11% among PtD BC cases (n=289) vs. 3% of MamD (n=133) (p<.001). Order of factor entry into the distant recurrence time interval (DDFI) model was 1) TNM stage (p<.001), 2) HR/HER2 status (p<.001), 3) histologic grade (p=.005) and 4) detection method (p<.001). Unadjusted PtD DDFI mean time was 4.34 years and MamD 5.52 years (p<.001) however when stratified by stage, the most significant factor relative to distant recurrence, there was no significant difference between PtD and MamD BC. Distant disease specific survival time did not differ by detection method.

**Conclusion:** We observed breast cancer survival differential lead time to be a function of stage at diagnosis and tumor characteristics with marginal contribution of detection method. Patient and mammography detected breast cancer time to distant recurrence did not differ stratified by stage indicating survival difference is more likely related to early diagnosis than lead time bias. Lead time bias associated with breast cancer detection method appears to have marginal influence on survival in the current diagnostic and treatment era.

Introduction

The incidence of recurrent metastatic breast cancer (rMBC) has decreased in recent years coincident with an improvement in breast cancer survival in part due to successful adjuvant therapy improvement for stage I-III disease.1,2,3 Debate and analysis continue about the relative contribution of early detection of breast cancer by mammography screening to improved survival. From reports of national mammography screening program surveillance reports, mammography detected tumors are more often smaller and lower stage with better survival but these reports lack comparative evidence as to whether this is a real contributor to improved survival or the result of bias.4 Lead time bias is the time between screening detection and when the disease would have become clinically evident without screening. Lead time interval when added to the time over which evident disease progresses, makes it appear that screen detected cases have longer survival than if screening had not taken place.5,6,7,8,9

We are now in a time of accepted validity for mammography screening with evidence-based guidelines adopted and promoted in the United States and Europe.10,11,12 Mammography screening is not institutionalized in the United States where it is an opportunistic choice based on health care access, screening guideline knowledge, insurance coverage and care giver recommendation.13

Timing and incidence of invasive breast cancer distant disease recurrence provides an opportunity to measure lead time by comparing time to distant recurrence after initial diagnosis and post recurrence survival as a function of detection method. In this study of invasive breast cancer in a retrospective institutional cohort, we reviewed breast
cancer characteristics by method of detection with time to and incidence of distant disease recurrence and death as the outcomes of interest to assess contribution of lead time to survival.

**Methods**

To assess the contribution of lead time to survival among mammography detected BC cases we conducted lead time analysis comparing mammography (MamD) to patient detected (PtD) BC using time to distant recurrence as the first interval (DDFI) and time from distant recurrence to last follow up or death from disease as the second interval (distant disease specific survival (DDSS)) separately and combined. We compared distant recurrence lead time by detection method to DDFI and DDSS, the two component time intervals of disease specific survival, and modeled the relative contribution of detection method to DDFI. We also assessed relative rMBC incidence by detection method.

**Study Design**

We conducted a retrospective cohort analysis of all first primary stage I-III invasive BC cases age 40–74 from 1990–2016, with follow-up through 2018 for distant recurrence and vital status (n = 6603). Age 40–74 years was selected based on screening recommendations during this time period. Non-surgical cases (n = 18), patients who refused recommended treatment other than surgery (n = 24), cases with unknown method of detection (n = 11) and cases with unknown cancer status at follow up (n = 139) were excluded from the analysis. Inflammatory breast cancer (T4) cases were excluded (n = 125), as the diagnosis is symptom based and not detected by mammography. Patient (PtD) and mammography detected (MamD) BC was included and BC found by a medical professional from a lump or abnormality during routine physical examination were excluded (n = 295). (Fig. 1)

Our institutional breast cancer registry database contains detailed information on diagnosis, pathology, staging, treatment, tumor markers, and vital status at follow up including cause-specific death. Incident BC cases are entered at time of diagnosis into the HIPAA compliant and IRB approved registry. Patient vital and disease status including date, site and type of recurrence and date and cause of death are collected prospectively through annual updates by a certified cancer registrar complete through 2018 for this cohort. Follow-up status was obtained from 1) electronic chart review, 2) IRB-approved physician directed follow-up letter, 3) the institution's cancer registry, and 4) SEER Seattle-Puget Sound Registry.

Distant disease recurrence (rMBC) was restricted to first presentation of distant disease excluding dates of subsequent disease progression. Hormone receptor positivity was estrogen and/or progesterone receptor positive (HR positive) and HR negative if negative for both. Self-reported race was coded white/non-white. All cases were coded to AJCC 7 classic anatomic staging across all years. TNM stage 0 were excluded from the analysis as few were patient detected and distant recurrence was a rare event. Distant recurrence (rMBC) was designated if distant disease diagnosis occurred three months or more post initial diagnosis.

Breast cancer detection method was obtained by medical record review by a certified cancer registrar. Mammography detected was assigned to breast cancer discovered by routine mammography in the absence of complaints or known physical findings or as a repeat or diagnostic mammogram to verify a previous equivocal mammography finding. Patient detection was assigned if the patient presented with personally detected breast symptoms, such as a palpable lump, pain, swelling, nipple discharge, or bleeding which prompted a doctor visit. Patients with self-detected tumors may have subsequently had a mammogram or ultrasound done but would still be
categorized as a patient-detected breast cancer from first presentation. Detection method was recorded by the physician at time of diagnosis and was only assigned if it was certain from the record.

Pearson chi-square test comparisons of categorical characteristics by detection method and mean comparisons for continuous variables were used (F statistic). Distant disease-free interval (DDFI) was time from primary BC diagnosis to distant recurrence, distant disease specific survival (DDSS) was time from distant recurrence (rMBC) to last follow-up or death from this disease, and disease specific survival (DSS) was total time from initial BC diagnosis to last follow-up or death from this disease. By dividing DSS into two component parts, time to distant disease recurrence (DDFI) and time from distant disease recurrence to last follow up or death from disease (DDSS), we are able to identify which portion of survival time is affected by lead time and evaluate accordingly. Kaplan-Meier estimation was used to calculate 5-year DDFI, DDSS and DSS rates (log rank tests).

Covariates significant by detection method were used to build the model, informed by the chi-square analysis and tested a priori using stepwise entry. The multivariable Cox proportional hazards model was used to estimate adjusted hazard ratios (HzR) and corresponding 95% confidence intervals (CI) using DDFI as the outcome. We evaluated the proportional hazards assumption by plotting ln{−ln(survival)} curves for the ordinal covariate of diagnosis year versus ln (at risk time) and on the basis of Schoenfeld residuals after fitting individual Cox models. We found no evidence suggesting substantial violation of the proportionality assumption graphically or in tests for interaction with the logarithm of survival time. Effect modification was evident from the Cox proportional hazards analysis with stage the dominant variable in the model. Therefore, lead time analysis was stratified by stage to compare detection method differences in survival. All p-values were 2-sided and analyses were conducted using SPSS v.26.

Results

Between 1999 and 2016, 39% of invasive stage I-III breast cancer cases were patient detected (n = 2566) and 61% were mammography detected (n = 4037). Seventy eight percent of MamD BC cases were stage I at diagnosis, 27% stage II and 4% stage III. Thirty one percent of PtD BC were stage I at diagnosis, 51% stage II and 18% stage III (p < .001). PtD BC patients trended to younger age at diagnosis, 37% age 40–49 years vs. 19% MamD and MamD cases trended older [mean age PtD = 58 years vs MamD = 54 years (p < .001)]. More MamD BC cases identified as white race (84% vs 77%). Table 1.
|                  | PtD          | MamD         | p value |
|------------------|--------------|--------------|---------|
| Stage I          | 792 (31%)    | 2772 (69%)   | < .001 |
| Stage II         | 1314 (51%)   | 1108 (27%)   |         |
| Stage III        | 460 (18%)    | 157 (4%)     |         |
| Age 40–49        | 950 (55%)    | 765 (45%)    | < .001 |
| Age 50–64        | 1216 (36%)   | 2189 (64%)   |         |
| Age 65–74        | 400 (27%)    | 1083 (73%)   |         |
| Mean age (range, F statistic) | 54 (40–74) | 58 (40–74)   | < .001 |
| Race White       | 1986 (37%)   | 3388 (63%)   | < .001 |
| Race Non-White   | 580 (47%)    | 649 (53%)    |         |
| Hormone receptor status HR+ | 2081 (36%) | 3641 (64%)   | < .001 |
| HER2 status      | 458 (46%)    | 534 (54%)    | < .001 |
| HR+/HER2-        | 1718 (36%)   | 3110 (64%)   | < .001 |
| HR+/HER2+        | 332 (45%)    | 399 (55%)    |         |
| HR-/HER2-        | 340 (61%)    | 216 (39%)    |         |
| HR-/HER2+        | 126 (49%)    | 134 (51%)    |         |
| Histologic type initial primary breast tumor Ductal | 2122 (39%) | 3312 (61%) | .287 |
| Lobular          | 258 (39%)    | 411 (61%)    |         |
| Lobular/Ductal Mixed | 120 (40%) | 177 (60%)    |         |
| Other Cancer     | 64 (33%)     | 133 (67%)    |         |
| Nuclear grade initial primary breast tumor |          |              |         |
|                          | PtD          | MamD         | p    |
|--------------------------|--------------|--------------|------|
| Low/Intermediate         | 1189 (31%)   | 2675 (69%)   | <.001|
| High                     | 1340 (51%)   | 1289 (49%)   |      |
| Histologic grade initial |              |              |      |
| primary breast tumor     |              |              |      |
| Low/Intermediate         | 583 (29%)    | 1447 (71%)   | <.001|
| High                     | 1943 (44%)   | 2498 (56%)   |      |
| Tumor size (mean, range, | 2.91 (.10, 18.00) | 1.51 (.05, 17.00) | <.001|
| F statistic              |              |              |      |
| # positive nodes (mean,  | 1.67 (0–44)  | .57 (0–35)   | <.001|
| range, F statistic       |              |              |      |
| Treatment                |              |              |      |
| surgery only             | 339 (36%)    | 614 (64%)    | <.001|
| surgery/radiation        | 575 (22%)    | 1997 (78%)   |      |
| surgery/chemotherapy     | 412 (53%)    | 372 (47%)    |      |
| surgery/radiation/chemo  | 1240 (54%)   | 1054 (46%)   |      |
| therapy                  |              |              |      |
| Distant Recurrence       |              |              |      |
| yes                      | 289 (68%)    | 133 (32%)    | <.001|

Tumor characteristics differed with MamD BC cases more likely HR+/HER2- [64% vs. 36% PtD BC] and the reverse for TNBC [39% MamD BC vs 61% PtD BC] (p < .001). MamD tumors were smaller and more often < = 2 cm in size (77%) vs. 42% of PtD BC cases (p < .001) [mean tumor size: MamD = 1.51 cm, PtD = 2.16 cm (p < .001)]. Twenty one percent of MamD BC had positive lymph nodes vs 44% of PtD BC patients (p < .001). Histologic type was not significantly different. PtD BC nuclear grade was more often high grade than MamD BC (52% vs. 32%). PtD and MamD cases were both majority high grade, PtD 76% and MamD 62% (p < .001). 15% or fewer of each group had surgery treatment only, with the majority of MamD BC cases receiving surgery/radiation treatment (50%) and the majority of PtD BC cases receiving surgery/radiation/chemotherapy treatment (54%) (p < .001). Table 1.

Average follow up was 9 years [range 1.7 to 20.4 years]. Eleven percent of PtD BC cases had a distant recurrence (rMBC) (n = 289) compared to 3% of MamD BC (n = 133). Five-year disease specific survival was 99% for MamD BC and 95% for PtD BC (p < .001). Five-year overall survival was 97% for MamD BC and 93% for PtD BC (p < .001). Figure 2.

Using all cases in the analytic set (n = 6333) the distant disease-free interval five-year survival rate was 98% for MamD BC and 92% for PtD BC (p < .001). Figure 3. For the subset of patients with distant recurrence (rMBC = 422), distant disease-free interval five-year survival was 43% for MamD BC and 30% for PtD BC (p < .001) [DDFI: time from initial diagnosis to last follow-up or distant disease]. Distant disease specific five-year survival was 11% for rMBC MamD BC and 10% for rMBC PtD BC (not significant) (n = 422) [DDSS: time from distant recurrence to death from disease or last follow-up]. Figure 4.
In the forward conditional Cox proportional hazards model of time to distant recurrence (DDFI) using rMBC as the outcome (n = 6603), variable order of entry into the model at < .05 significance level was 1) TNM stage 2) HR/HER2 status, 3) histologic grade, and 4) detection method. The majority chi-square change in the model by order of entry was attributable to TNM stage I-III at diagnosis (Wald chi-square change = 353.10) and least of all to detection method (Wald chi-square change = 8.67) although detection method was significant and retained in the model in last position. The model was adjusted for age, race, and diagnosis year which were not significant. Table 2.

### Table 2

| By order of entry into the model: | HzR (95% CI) | p value | Wald chi-square | Model Chi-square change | df |
|----------------------------------|-------------|---------|----------------|-------------------------|----|
| TNM Stage I                      | reference   | < .001  | 200.86         | 353.10                  | 2  |
| TNM Stage II                     | 3.30 (2.47, 4.42) | 64.96  |                |                         |    |
| TNM Stage III                    | 9.19 (6.70, 12.60) | 190.03 |                |                         |    |
| HR/HER2 status:                  |             |         |                |                         |    |
| initial diagnosis                |             |         |                |                         |    |
| HR+/HER2-                        | reference   | < .001  | 48.50          | 55.00                   | 2  |
| HR + or HR-/HER2+                | .86 (.66, 1.13) | 1.13  |                |                         |    |
| HR-/HER2-                        | 2.22 (1.73, 2.84) | 40.31 |                |                         |    |
| Histological grade primary tumor |             |         |                |                         |    |
| Low/Intermediate                 | reference   | < .001  | 7.89           | 29.04                   | 1  |
| High                             | 1.49 (1.13, 1.98) |        |                |                         |    |
| Detection method                 |             |         |                |                         |    |
| MamD                             | reference   | < .001  | 25.84          | 8.51                    | 1  |
| PtD                              | 1.80 (1.43, 2.25) |        |                |                         |    |

*adjusted for age, race and diagnosis year (not significant in the model)

Mean unadjusted time to distant recurrence (DDFI) was significantly different [MamD 5.52 years, PtD 4.34 years (p = .001) (difference 1.18 years)]. Figure 5. Mean times to distant disease recurrence for PtD and MamD BC stratified by stage to adjust for effect modification were not statistically significantly different [stage I 5.74 years: MamD 6.02
years, PtD 5.35 years (p = .902) (difference .67 years); stage II 4.99 years: MamD 5.66 years, PtD 4.69 years (p = .537) (difference .97 years); Stage III 3.83 years: MamD 4.49 years, PtD 3.67 years (p = .597) (difference .82 years)]. Mean time from distant disease recurrence to death or last follow up (DDSS) did not differ by detection method overall [MamD 2.27 years, PtD 2.38 years (p = .154)]. Figure 5.

Discussion

The majority of distant disease recurrence (68%) occurred among patient-detected cases with an incidence rate of 11% compared to 3% distant recurrence among mammography detected breast cancer cases. Mean time to distant recurrence was shorter for patient-detected BC than it was for mammography-detected BC but did not differ significantly when stratified by the effect modifier stage at diagnosis which was more strongly associated with the outcome distant recurrence than other factors in the model including detection method. There was no difference in time from distant disease recurrence to last follow-up or death from disease by detection method

Time from initial diagnosis to distant recurrence is the first interval and time from distant recurrence to last follow-up or death is the second interval in disease progression and disease specific survival. Time to disease progression would be equivalent between screening and symptomatic presentation if lead time bias was not present. Although there were small differences in DDFI mean time comparisons by stage, the differences were not significant. In the model adjusted for stage, HR/HER2 status and histologic grade, detection method ranked last in the model with a small but significant effect as measured by the Wald chi-square statistic. Lead time bias appears to be a marginal factor in distant disease-free interval as other factors related to early diagnosis, stage, HR/HER2 status and histologic grade, represent the majority of effect on distant disease-free interval superseding the effect of detection method.

A strictly binary evaluation of survival by detection method creates a false dichotomy of the effect of mammography. Stage at diagnosis, histologic grade, and hormone receptor/HER2 status are not evenly distributed between patient and mammography detected invasive breast cancer cases. Stage at diagnosis is most strongly associated with the outcome, distant disease recurrence, in the Cox proportional hazards model. Factors associated with mammography detection of breast cancer dominate the model introducing bias in the form of effect modification. The magnitude of the effect of detection method, on the outcome, length of time to distant recurrence, differs substantially by stage at diagnosis. Stratified analysis adjusts for the effect measure modification and gives a more accurate assessment of differential lead time by detection method. The natural ordering of stage at diagnosis lends itself to a linear approach to the stratified analysis.

Strengths and Limitations

Mammography screening in the United States relies on opportunistic mammography screens based on United States Preventive Services Task Force, the American Cancer Society and other organizations recommendations unlike countries with organized screening programs. \(^\text{14, 15, 22, 23}\) Screening is therefore predicated on self-initiation of screening mammography or prompted by a care provider or health care system. In the absence of a national screening program and as screening participation data connected to outcomes is not readily available, we tested the lead time bias hypothesis using an institutional cohort and mammography detected breast cancer as a proxy for screen detection compared to patient detected breast cancer.
Mammography screening participation rate reported in the year prior to 2012 was 57% in Washington State, very close to our observed rate of 61% mammography detection. We do not have information regarding age appropriate mammography screening program participation or time interval between last non-diagnostic mammogram and breast cancer discovered by mammography. While it has been speculated that some mammography screen detected cancer would not become clinically evident in a woman’s life time, to date there are no published reports of screen detected breast cancer regression or spontaneous disappearance. Only invasive breast cancer stage I-III were included in the analysis as stage 0 may be interpreted as an overdiagnosis category detected by mammography and therefore not compatible with survival comparison by detection method.

Interpretation: comparison to other studies

In a study of 233 patients diagnosed in 1988 of patients with stage 0-IV breast cancer, mammography screen-detected (MSDG) breast cancer had superior prognosis primarily due to the mammography detected better prognosis, low stage breast cancer at diagnosis compared to the non-mammography screening screen detected group. Superior prognosis was mainly because of the lower stage at diagnosis among the screened group as adjusting for stage removed the difference as we observed in our study. In a study of screen and non-screen detected breast cancer by Lawrence et al, 1988–2004, uncorrected 10-year disease-specific survival was 86% for screened and 64% in non-screened symptomatic cases. Corrected for lead time using the method by Duffy et al, 10 year DSS was 81%. Comparing screen detected to interval cancers the ten-year survival was 86–72%. In a similar study by O’Brien et al in 2006–2011 using stage I-IV breast cancers corrected for lead time bias and adjusting for stage, subtype, and grade, no significant survival difference was observed between screen-detected, interval and non-screening participants breast cancer.

Corrections for and explanation of lead time bias largely rely on modelling and/or statistical estimates applied to population data and lack information on time to distant recurrence and time to death from distant disease. In our institutional cohort with distant recurrence date and distant disease survival time we have a different approach to evaluate lead time using real, as opposed to modelled, data. Lead time bias is the time between screening detection and when disease would become clinically evident without screening, assuming the same disease evolution regardless of detection method. Lead time added to evident disease progression time, makes it appear screen-detected cases have longer survival than would occur absent screening. We observed no difference in distant disease survival by detection method indicating lead time bias only factors in the first time-interval of disease progression and once distant metastatic disease is present disease progression is the same.

Generalizability

The Seattle-Puget Sound region where the study was conducted has high socioeconomic status (SES) with ready access to care and high insured percentage. Patients treated at this institution may not be comparable to other U.S. geographic areas. Our breast cancer survival rates have been documented by national comparisons to have greater improvement over time than national rates.

Conclusion
From our analysis, mammography detected breast cancer was associated with earlier stage, higher percentage HR+/Her2- subtype and lower histologic grade disease, factors associated with better outcomes and reduced distant recurrence. However, once distant disease occurred, no distant disease survival time difference was observed in spite of more unfavorable PtD breast cancer initial phenotypes. Time to distant recurrence did not differ significantly by detection method stratified by stage and had marginal significance in distant disease occurrence modelling. The combined modelling analysis and comparison of lead times suggest lead time bias presence but marginal significance compared to other diagnostic characteristics related to survival.

Lead time bias may have been a factor to a greater degree and more significant effect in decades preceding current diagnostic and tumor specific treatment options. Without comparative studies of time from diagnosis to distant recurrence and distant recurrence to death from earlier decades, we do not know prior magnitude of effect. However, in the modern era of diagnosis and treatment it appears lead time bias related to method of detection is not a dominant factor affecting survival relative to other breast cancer characteristics. Early diagnosis, measured by earlier stage breast cancer at diagnosis irrespective of how the breast cancer was detected, is most directly associated with better outcomes and survival. Importantly it appears lead time bias is a phenomenon related to earlier stage diagnosis by mammography, which as the aim of screening is to find disease at an earlier more treatable stage appears to have been accomplished.

Declarations

Ethics approval and consent to participate: All work on this analysis and publication was IRB approved by the Providence Institutional Review Board. As the analysis only used de-identified data no additional approval from patients was required and the study had exempt status.

Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests to report. HK, JM, MA

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Authors' contributions: Each author has made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it and have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. HK, JM, MA

Data availability: The dataset analysed during the current study are not publicly available due HIPAA Security Rules regarding patient data at the institution where the registry was created and is kept and are not available from the corresponding author on reasonable request.

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Figure 1

CONSORT diagram
Figure 2

DSS and OS by detection method
Figure 3

DDFI survival: all cases (n=6603)

Figure 4

DDFI survival and DDSS by Detection Method: rMBC only (n=422)
Figure 5

rMBC disease survival time by detection method and DDFI+DDSS stratified by stage and detection method (n=422)