# A Population-Based Study on Liver Metastases in Women with Newly Diagnosed Breast Cancer

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## Abstract

**Background:** Population-based estimates for prognosis among patients with liver metastases in newly diagnosed breast cancer are not generally available.

**Methods:** Within the Surveillance, Epidemiology and End Results (SEER) database, we identified 298,370 patients with breast cancer and 4,285 patients diagnosed with initial liver metastases between 2010 and 2014. Data were stratified according to subtype, age, and race. Multivariate logistic and Cox regression were used to identify predictors for the presence of initial liver metastases and prognostic factors, respectively. Kaplan–Meier procedure was used for survival analysis.

**Results:** A total of 4,285 patients with initial liver metastases (1.4% of the entire cohort, 29.6% of the subset with metastatic disease) were identified. Patients with hormone receptor (HR)-negative human epidermal growth factor receptor 2 (HER2)-positive (4.4% of entire cohort, 52.5% of patients

with metastatic disease to any distant site) and HR-positive HER2-positive (2.8% of entire cohort, 40.4% of patients with metastatic disease to any distant site) subtypes had highest incidence proportions. The median survival of patients with liver metastases in the entire cohort was 15.0 months. Patients with HR-positive HER2-positive subtype showed the longest median survival (31.0 months); however, patients with triple-negative subtype showed the shortest median survival (8.0 months).

**Conclusions:** Our findings provide population-based estimates of epidemiologic characteristics and prognosis in breast cancer patients diagnosed with initial liver metastases.

**Impact:** This study lends support to the diagnosis of the liver among patients at high risk of liver metastases, including those with HER2-positive and other systemic metastases.

## Introduction

Breast cancer is the leading cause of cancer-related deaths in female patients worldwide (1). Approximately 20% of patients with breast cancer suffer from metastatic disease (2). Liver metastases develop in half of the women with metastatic breast cancer and represent a frequent cause of mortality among these patients (3–8). However, liver metastases usually present with nonspecific symptoms (e.g. upper abdominal fullness, a mass, ascites, jaundice, or weight loss) or present asymptomatically during a metastatic screen, and the survival time is only 4 to 8 months for patients with breast cancer if liver metastasis status was ignored (8, 9). Notably, liver metastases are present in only 3% to 8% of patients with breast cancer at the time of the initial diagnosis and are typically associated with metastases at other sites (10, 11). As a result, the changes caused by distant relapse and treatment exposure could be potential confounding factors in the prognostic assessment (12). In

addition, the prognosis of patients with liver metastases from breast cancer is usually extremely poor, with 5-year survival rates of only 3.8% to 12% (6, 13–15). Because liver metastases have a significant influence on the morbidity and prognosis of patients with breast cancer, the early detection of liver metastases is of utmost importance.

Population-based estimates for the prognosis in patients with newly diagnosed breast cancer and liver metastases are lacking. Data from several single institution experiences and retrospective studies (8, 16–23) yielded varying results. Duan and colleagues (23) reported on the outcome of 123 patients with breast cancer diagnosed with liver metastases; they found subtype remained an independent prognostic predictor among patients with breast cancer liver metastases, in which triple-negative breast cancer (TNBC) conferred the worst survival after diagnosis of liver metastases when compared with non–triple-negative subtypes. In addition, Eichbaum and colleagues (22) found a prognostic benefit for patients with a positive hormone receptor (HR) status and an expression of Ki-67 < 20%, p53 < 50%. However, Ge and colleagues (18) showed breast cancer subtypes were not associated with survival after liver metastases in 104 patients with breast cancer with liver metastases. Thus, the association of breast cancer subtypes and survival after liver metastases was unclear and remained controversial. Nevertheless, several studies suggested that the risk of liver metastases was subtype-dependent, and patients with HER2-positive experienced significantly higher rates of liver metastasis than patients (with HER2-negative) tumors (5, 24–26). Besides, other sociodemographic and clinical predictors of outcome

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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have not been well characterized on a population-based level, which makes the prognostic assessment and management very challenging.

The aim of this article was to characterize the incidence proportion of liver metastases in newly diagnosed breast cancer on a population level within the Surveillance, Epidemiology, and End Results (SEER) database. We also sought to calculate survival estimates and to assess sociodemographic and clinical predictors of poorer survival among patients with newly diagnosed breast cancer and liver metastases.

## Materials and Methods

### Study population

This study was based on data from the SEER program. The SEER program is a nation-wide cancer registry that collects data on cancer incidence, treatment, and survival for approximately 30% of the U.S. population (27). We analyzed data from the SEER database on cases of invasive breast cancer between January 1, 2010, and December 31, 2014. The detailed patient selection steps are illustrated in Fig. 1. Briefly, patients for whom the presence or absence of liver metastases at diagnosis was unknown were excluded. We also removed patients with unknown race and unknown age or younger than 18, and male patients, leaving 298,370 patients eligible for incidence analysis. Among these, 4,285 patients were diagnosed with initial liver metastases. Subsequently, we excluded patients with unknown follow-up, leaving 4,280 patients in the final cohort for survival analysis. The Institutional Review Boards at Nanfang Hospital of Southern Medical University (Guangzhou, China) approved this study and waived the need to obtain written informed consent.

### Study variables

We defined patients' sociodemographic characteristics including age (18–40, 41–60, 61–80, and >80 years), race (white, black, Hispanic, Asian American, or other), marital status (unmarried, married, and unknown), insurance status (uninsured, insured, and unknown). In addition, we also defined variables including tumor size (<2.0 cm, 2.0–4.9 cm, $\geq$5.0 cm, and unknown), tumor grade (1, 2, 3/4, and unknown), American Joint Committee on Cancer (AJCC) stage (I, II, III, IV, and unknown), depth of invasion (T category: T1, T2, T3, T4, and unknown),
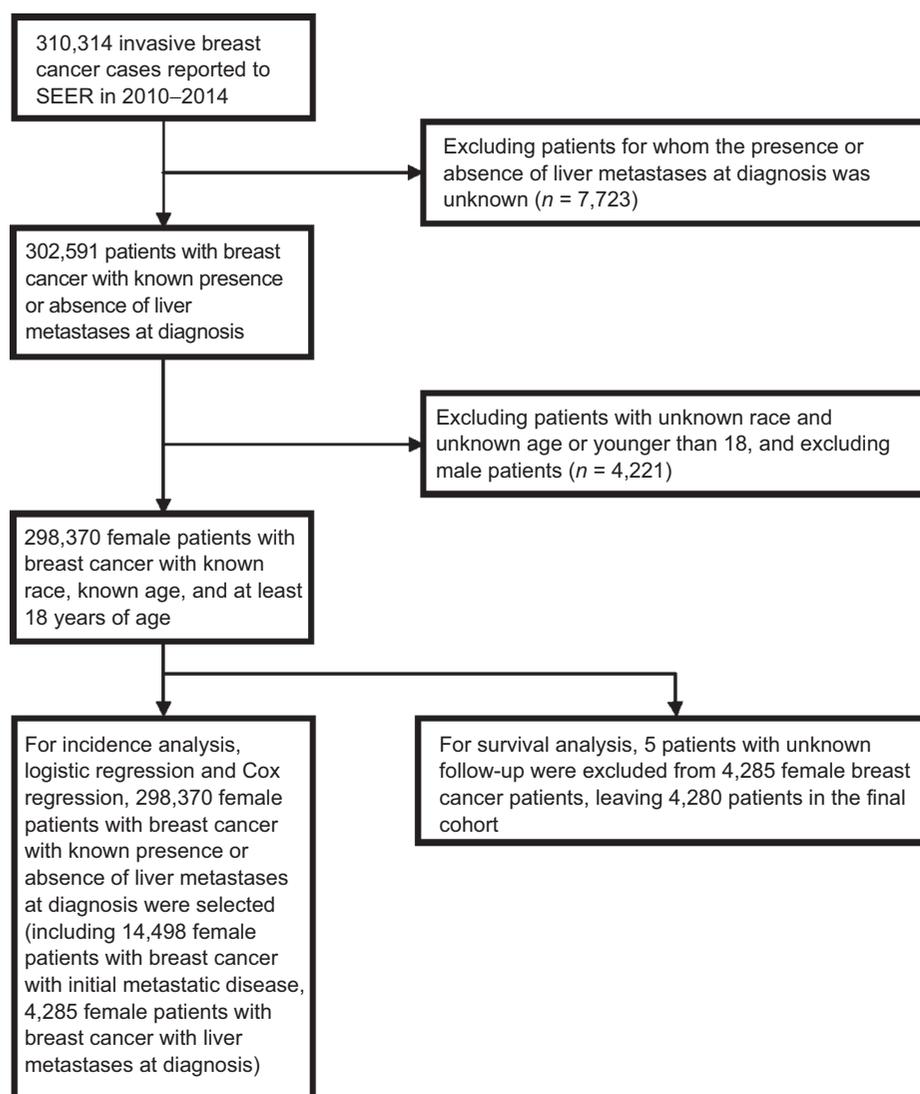


**Figure 1.**
Selection of patients diagnosed with invasive breast cancer in 2010–2014.

310,314 invasive breast cancer cases reported to SEER in 2010–2014

Excluding patients for whom the presence or absence of liver metastases at diagnosis was unknown ($n = 7,723$)

302,591 patients with breast cancer with known presence or absence of liver metastases at diagnosis

Excluding patients with unknown race and unknown age or younger than 18, and excluding male patients ($n = 4,221$)

298,370 female patients with breast cancer with known race, known age, and at least 18 years of age

For incidence analysis, logistic regression and Cox regression, 298,370 female patients with breast cancer with known presence or absence of liver metastases at diagnosis were selected (including 14,498 female patients with breast cancer with initial metastatic disease, 4,285 female patients with breast cancer with liver metastases at diagnosis)

For survival analysis, 5 patients with unknown follow-up were excluded from 4,285 female breast cancer patients, leaving 4,280 patients in the final cohort

and number of metastasis nodes (N category: N0, N1, N2, N3, and unknown). Whether to receive adjuvant therapy such as radiation or chemotherapy was also considered in the study. Molecular subtypes of breast cancer were classified as HR-positive HER2-negative, HR-positive HER2-positive, HR-negative HER2-positive, and triple-negative (HR-negative HER2-negative). The extent of systemic disease was characterized by the presence of lung, brain, and bone metastases among patients in this study (28, 29).

### Statistical analysis

Absolute numbers and incidence proportions were computed among patients with breast cancer with initial liver metastases; incidence proportions were also evaluated after stratification with age and race. We defined incidence of liver metastases as the number of patients with breast cancer diagnosed with initial liver metastases divided by the number of patients in the entire cohort. Incidence proportion was also calculated for patients with breast cancer with distant metastases.

Univariate logistic regression was performed with each variable to determine its association with the presence of liver metastases at diagnosis. ORs with 95% confidence intervals (CIs) were calculated. Variables with $P < 0.05$ were incorporated into a multivariate logistic regression to calculate the adjusted ORs. Each variable was first analyzed with univariate Cox regression. Variables shown by univariate Cox regression analysis to be significantly ($P < 0.05$) associated with survival were entered into multivariate Cox regression model. Interactions between the HER2 subtype and the variables were also detected by means of the logistic model and the Cox model, respectively. Survival estimates were calculated using the Kaplan–Meier approach. Breast cancer cases between 2010 and 2014 in the SEER public access database and their corresponding details were retrieved with the use of SEER*Stat software version 8.3.4. Statistical analyses were performed using SPSS statistical software version 21.

## Results

### Incidence

The number and incidence proportions of initial liver metastases in patients diagnosed with breast cancer are provided in Table 1, as stratified by breast cancer subtype. Of the 298,370 patients diagnosed with invasive breast cancer between 2010 and 2014, 67.9%, 9.5%, 4.1%, 10.6%, and 7.9% had HR-positive HER2-negative, HR-positive HER2-positive, HR-negative HER2-positive, triple-negative, and unknown subtypes, respectively. Of the 14,498 patients with metastatic disease, 51.0%, 13.8%, 7.1%, 11.2%, and 15.9% had HR-positive HER2-negative,

HR-positive HER2-positive, HR-negative HER2-positive, triple-negative, and unknown subtypes, respectively. A total of 4,285 patients with initial liver metastases were identified, accounting for 1.4% of the entire cohort and 29.6% of the subset with metastatic disease. The incidence proportions of liver metastases were highest among patients with HR-negative HER2-positive (4.4% of the entire cohort, 52.5% of the subset with metastatic disease) and HR-positive HER2-positive (2.8% of the entire cohort, 40.4% of the subset with metastatic disease) subtypes.

Association between initial liver metastases and variables assessed by univariate logistic regression analysis is presented in Supplementary Table S1. Univariate factors with $P < 0.05$ were analyzed using multivariate logistic regression. On multivariate logistic regression (Table 2) among patients with breast cancer with metastatic disease, grade 2 (vs. grade 1; OR, 1.22; 95% CI, 1.01–1.47; $P = 0.035$), grade 3/4 (vs. grade 1; OR, 1.57; 95% CI, 1.30–1.89; $P < 0.001$), N3 (vs. N0; OR, 0.85; 95% CI, 0.74–0.98, $P = 0.026$), metastatic disease to 2 extrahepatic sites (vs. 0 or 1 site; OR, 1.56; 95% CI, 1.42–1.71; $P < 0.001$) or 3 extrahepatic sites (vs. 0 or 1 site; OR, 3.36; 95% CI, 2.69–4.20; $P < 0.001$), without radiation (vs. with radiation; OR, 1.76; 95% CI, 1.62–1.92; $P < 0.001$), and HR-positive HER2-positive (vs. HR-positive HER2-negative subtype; OR, 2.05; 95% CI, 1.84–2.29; $P < 0.001$), HR-negative HER2-positive (vs. HR-positive HER2-negative subtype; OR, 3.16; 95% CI, 2.74–3.64; $P < 0.001$), and triple-negative subtypes (vs. HR-positive HER2-negative subtype; OR, 1.49; 95% CI, 1.31–1.69; $P < 0.001$) were associated with significantly greater odds of having liver metastases at diagnosis. Age 41 to 60 years (vs. age 18–40 years; OR, 0.81; 95% CI, 0.70–0.94; $P = 0.004$), age 61 to 80 years (vs. age 18–40 years; OR, 0.59; 95% CI, 0.51–0.69; $P < 0.001$) and age greater than 80 years (vs. age 18–40 years; OR, 0.49; 95% CI, 0.41–0.59; $P < 0.001$), Hispanic race (vs. white; OR, 0.76; 95% CI, 0.67–0.86; $P < 0.001$), and without chemotherapy (vs. with chemotherapy; OR, 0.72; 95% CI, 0.66–0.78; $P < 0.001$), were associated with remarkably lower odds of liver metastases at diagnosis. Marital status, insurance status, tumor size, and T stage were not associated with a risk of liver metastasis at diagnosis in the multivariate model. Results are presented in Table 2. The association of sociodemographic and clinical characteristics for the presence of liver metastases at diagnosis of breast cancer stratified by HER2 status is presented in Supplementary Tables S2 and S3.

### Survival

Median survival among patients in the survival cohort ($n = 4,280$) with breast cancer and identified liver metastases at

**Table 1.** Incidence proportion and median survival of patients with breast cancer with identified liver metastases at diagnosis by subtype

| Subtype | Patients, no. (%) | | | Incidence proportion of liver metastases, % | | Survival among patients with liver metastases, median (IQR), mo |
|---|---|---|---|---|---|---|
| | With breast cancer | With metastatic disease | With liver metastases | Among entire cohort | Among subset with metastatic disease | |
| HR+/HER2− | 202,713 (67.9) | 7,539 (51.0) | 1,652 (38.6) | 0.8 | 21.9 | 19.0 (5.0–41.0) |
| HR+/HER2+ | 28,453 (9.5) | 1,995 (13.8) | 806 (18.8) | 2.8 | 40.4 | 31.0 (7.0–NR) |
| HR−/HER2+ | 12,321 (4.1) | 1,034 (7.1) | 543 (12.7) | 4.4 | 52.5 | 22.0 (4.0–47.0) |
| Triple-negative | 31,632 (10.6) | 1,627 (11.2) | 548 (12.8) | 1.7 | 33.7 | 8.0 (2.0–15.0) |
| Unknown | 23,251 (7.9) | 2,303 (15.9) | 736 (17.1) | 3.2 | 32.0 | 3.0 (0–18.0) |
| All subtypes | 298,370 (100) | 14,498 (100) | 4,285 (100) | 1.4 | 29.6 | 15.0 (3.0–39.0) |

Abbreviations. IQR, interquartile range; mo, month; NR, not reached.

**Table 2.** Multivariate logistic regression for the presence of liver metastases at diagnosis of breast cancer[a]

| | Patients, no. | | Among entire cohort | | Among subset with metastatic disease | |
| | Patients (n = 298,370) | With liver metastases (n = 4,285) | | | | |
| Variable | | | OR (95% CI) | P | OR (95% CI) | P |
|---|---|---|---|---|---|---|
| Age at diagnosis, y[b] | | | | | | |
| 18–40 | 16,957 | 404 | 1 (Reference) | | 1 (Reference) | |
| 41–60 | 122,483 | 1,886 | 0.81 (0.72–0.91) | <0.001 | 0.81(0.70–0.94) | 0.004 |
| 61–80 | 130,478 | 1,608 | 0.69 (0.61–0.78) | <0.001 | 0.59(0.51–0.69) | <0.001 |
| >80 | 28,452 | 387 | 0.54 (0.46–0.64) | <0.001 | 0.49(0.41–0.59) | <0.001 |
| Race[b] | | | | | | |
| White | 206,898 | 2,773 | 1 (Reference) | | 1 (Reference) | |
| Black | 32,687 | 769 | 1.08 (0.98–1.18) | 0.117 | 0.99(0.89–1.10) | 0.858 |
| Hispanic | 31,953 | 410 | 0.64 (0.57–0.72) | <0.001 | 0.76(0.67–0.86) | <0.001 |
| Asian | 24,580 | 300 | 0.74 (0.65–0.85) | <0.001 | 0.97(0.83–1.13) | 0.697 |
| Other | 2,252 | 33 | 0.86 (0.59–1.25) | 0.426 | 1.02(0.66–1.56) | 0.937 |
| Marital status | | | | | | |
| Unmarried | 121,864 | 2,196 | 1 (Reference) | | 1 (Reference) | |
| Married | 159,687 | 1,812 | 0.87 (0.81–0.93) | <0.001 | 1.01 (0.93–1.09) | 0.865 |
| Unknown | 16,819 | 277 | 0.95 (0.82–1.10) | 0.498 | 1.12 (0.95–1.31) | 0.184 |
| Insurance status | | | | | | |
| Uninsured | 5,251 | 222 | 1 (Reference) | | 1 (Reference) | |
| Insured | 287,373 | 3,954 | 0.82 (0.70–0.97) | 0.023 | 0.89 (0.74–1.06) | 0.192 |
| Unknown | 5,746 | 109 | 0.58 (0.44–0.76) | <0.001 | 0.86 (0.64–1.16) | 0.334 |
| Tumor size | | | | | | |
| <2.0 cm | 158,893 | 489 | 1 (Reference) | | 1 (Reference) | |
| 2.0–4.9 cm | 97,757 | 1,435 | 1.19 (0.98–1.44) | 0.075 | 1.07 (0.88–1.31) | 0.512 |
| ≥5.0 cm | 25,401 | 1,266 | 1.43 (1.17–1.74) | <0.001 | 1.12 (0.91–1.38) | 0.284 |
| Unknown | 16,319 | 1,095 | 1.25 (1.03–1.52) | 0.022 | 1.06 (0.86–1.31) | 0.578 |
| Grade | | | | | | |
| I | 64,645 | 167 | 1 (Reference) | | 1 (Reference) | |
| II | 123,484 | 1,195 | 1.70 (1.43–2.02) | <0.001 | 1.22 (1.01–1.47) | 0.035 |
| III/IV | 91,612 | 1,845 | 1.98 (1.67–2.35) | <0.001 | 1.57 (1.30–1.89) | <0.001 |
| Unknown | 18,629 | 1,078 | 3.16 (2.63–3.79) | <0.001 | 1.36 (1.12–1.65) | 0.002 |
| T | | | | | | |
| T1 | 172,939 | 469 | 1 (Reference) | | 1 (Reference) | |
| T2 | 85,733 | 1,108 | 2.20 (1.80–2.67) | <0.001 | 0.94 (0.76–1.16) | 0.581 |
| T3 | 17,787 | 567 | 3.36 (2.70–4.17) | <0.001 | 0.83 (0.66–1.05) | 0.113 |
| T4 | 12,391 | 1281 | 6.52 (5.39–7.90) | <0.001 | 0.89 (0.73–1.10) | 0.279 |
| Unknown | 9,520 | 860 | 6.58 (5.36–8.07) | <0.001 | 1.16 (0.93–1.44) | 0.190 |
| N | | | | | | |
| N0 | 202,600 | 971 | 1 (Reference) | | 1 (Reference) | |
| N1 | 66,606 | 1,847 | 2.40 (2.20–2.63) | <0.001 | 1.08 (0.98–1.19) | 0.126 |
| N2 | 15,067 | 417 | 2.09 (1.83–2.39) | <0.001 | 0.97 (0.84–1.13) | 0.713 |
| N3 | 9,633 | 473 | 2.56 (2.24–2.92) | <0.001 | 0.85 (0.74–0.98) | 0.026 |
| Unknown | 4,464 | 577 | 3.42 (2.97–3.93) | <0.001 | 1.16 (1.01–1.33) | 0.032 |
| Extrahepatic metastatic sites to lung, brain, and bone, no. | | | | | | |
| 0/1 | 284,444 | 2,816 | 1 (Reference) | | 1 (Reference) | |
| 2 | 2,763 | 962 | 15.66 (14.17–17.29) | <0.001 | 1.56 (1.42–1.71) | <0.001 |
| All 3 | 361 | 187 | 42.60 (33.41–54.32) | <0.001 | 3.36 (2.69–4.20) | <0.001 |
| Unknown | 802 | 320 | 16.32 (13.80–19.29) | <0.001 | 1.81 (1.55–2.11) | <0.001 |
| Radiation | | | | | | |
| Yes | 138,318 | 1,054 | 1 (Reference) | | 1 (Reference) | |
| No/Unknown | 160,052 | 3,231 | 2.46 (2.28–2.67) | <0.001 | 1.76 (1.62–1.92) | <0.001 |
| Chemotherapy | | | | | | |
| Yes | 115,409 | 2,407 | 1 (Reference) | | 1 (Reference) | |
| No/Unknown | 182,961 | 1,878 | 0.79 (0.73–0.86) | <0.001 | 0.72 (0.66–0.78) | <0.001 |
| Subtype | | | | | | |
| HR$^+$/HER2$^-$ | 202,713 | 1,652 | 1 (Reference) | | 1 (Reference) | |
| HR$^+$/HER2$^+$ | 28,453 | 806 | 2.30 (2.09–2.54) | <0.001 | 2.05 (1.84–2.29) | <0.001 |
| HR$^-$/HER2$^+$ | 12,321 | 543 | 2.97 (2.64–3.33) | <0.001 | 3.16 (2.74–3.64) | <0.001 |
| Triple-negative | 31,632 | 548 | 1.32 (1.18–1.48) | <0.001 | 1.49 (1.31–1.69) | <0.001 |
| Unknown | 23,251 | 736 | 1.36 (1.22–1.53) | <0.001 | 1.51 (1.34–1.70) | <0.001 |

[a]$P < 0.05$ was considered statistically significant.
[b]Unknown age and unknown race removed from model owing to nonconvergence (n = 1,055).
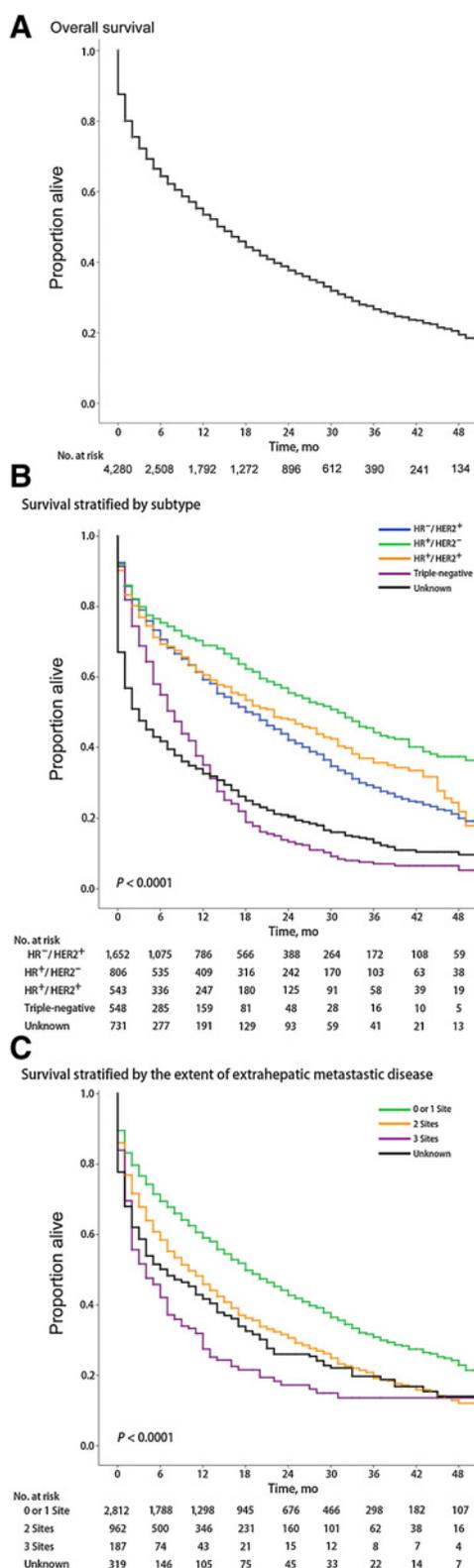
**Figure 2.**
Overall survival among patients with breast cancer and liver metastases at diagnosis. Extent of extrahepatic metastatic disease is classified by the number of metastatic sites to the brain, bone, or lung.

diagnosis, stratified by subtype, is presented in Table 1. The median survival among the entire cohort was 15.0 months, with patients with HR-positive HER2-positive subtype experiencing the longest median survival (31.0 months) and patients with triple-negative subtype experiencing the shortest median survival (8.0 months). Survival estimates overall (Fig. 2A) and as stratified by subtype (Fig. 2B) and by extent of extrahepatic metastatic disease (Fig. 2C) are graphically displayed in Fig. 2. Median survival for patients with breast cancer with liver metastases varied significantly by subtype ($P < 0.0001$). Survival was poorer among patients with more extensive systemic disease at diagnosis ($P < 0.0001$).

Variables associated with the survival evaluated by the univariate Cox regression analysis are presented in Supplementary Table S4. The significant factors ($P < 0.05$) were included in the multivariate Cox regression analysis. On multivariate Cox regression (Table 3) for all-cause mortality among patients with liver metastases at diagnosis, age 41 to 60 years (vs. age 18–40 years; HR, 1.46; 95% CI, 1.23–1.73; $P < 0.001$), age 61 to 80 years (vs. age 18–40 years; HR, 1.97; 95% CI, 1.66–2.35; $P < 0.001$) and age greater than 80 years (vs. age 18–40 years; HR, 3.05; 95%CI, 2.49–3.75; $P < 0.001$), black race (vs white; HR, 1.18; 95%CI, 1.06–1.31; $P < 0.001$), grade 3/4 (vs. grade I, HR, 1.43; 95% CI, 1.14–1.79; $P = 0.002$), without radiation (vs. with radiation; HR, 1.17; 95% CI, 1.06–1.29; $P = 0.001$), without chemotherapy (vs. with chemotherapy; HR, 1.76; 95% CI, 1.62–1.92; $P < 0.001$), metastatic disease to 2 extrahepatic sites (vs. 0 or 1 site; HR, 1.41; 95% CI, 1.28–1.55; $P < 0.001$) and 3 extrahepatic sites (vs. 0 or 1 site; HR, 2.01; 95% CI, 1.68–2.41; $P < 0.001$) and triple-negative subtype (vs. HR-positive HER2-negative subtype; HR, 2.20; 95% CI, 1.94–2.48; $P < 0.001$) were significantly associated with an increased all-cause mortality. Married social status (vs. unmarried social status; HR, 0.88; 95% CI, 0.81–0.96; $P = 0.004$), insured social status (vs. uninsured social status; HR, 0.64; 95% CI, 0.54–0.76; $P < 0.001$), N1 (vs. N0; HR, 0.82; 95% CI, 0.74–0.91, $P < 0.001$), N2 (vs. N0; HR, 0.83; 95% CI, 0.71–0.97, $P = 0.019$), N3 (vs. N0; HR, 0.82; 95% CI, 0.70–0.95, $P = 0.009$), and HR-positive HER2-positive (vs. HR-positive HER2-negative subtype; HR, 0.86; 95% CI, 0.76–0.98; $P = 0.019$) were significantly associated with a decreased all-cause mortality. Breast cancer–specific mortality among patients with breast cancer and liver metastases at diagnosis is also presented in Table 3. The association of sociodemographic and clinical characteristics for mortality among patients with liver metastases stratified by HER2 status is shown in Supplementary Tables S5 and S6. Table 4 displays median survival by subtype as stratified by the extent of systemic disease. In general, survival was poorer among patients with more extensive systemic disease at diagnosis. We also found that the presence of liver metastases at initial diagnosis was associated with shorter survival time compared with patients presenting with *de novo* metastatic disease without baseline liver involvement (Table 4).

## Discussion

In this article, we described the incidence of patients with liver metastases at diagnosis of breast cancer and examined the subsequent survival of such patients. This study reports for the first time, to the best of our knowledge, the survival outcomes

**Table 3.** Multivariate Cox regression for all-cause mortality and breast cancer–specific mortality among patients with liver metastases[a]

| | Patients, no. | | All-cause mortality | | Breast cancer–specific mortality | |
| | Patients | With liver metastases | | | | |
| Variable | (n = 298,370) | (n = 4,285) | HR (95% CI) | P | HR (95% CI) | P |
|---|---|---|---|---|---|---|
| Age at diagnosis, y[b] | | | | | | |
| 18–40 | 16,957 | 404 | 1 (Reference) | | 1 (Reference) | |
| 41–60 | 122,483 | 1,886 | 1.46 (1.23–1.73) | <0.001 | 1.45 (1.21–1.74) | <0.001 |
| 61–80 | 130,478 | 1,608 | 1.97 (1.66–2.35) | <0.001 | 1.91 (1.59–2.29) | <0.001 |
| >80 | 28,452 | 387 | 3.05 (2.49–3.75) | <0.001 | 2.78 (2.23–3.46) | <0.001 |
| Race[b] | | | | | | |
| White | 206,898 | 2,773 | 1 (Reference) | | 1 (Reference) | |
| Black | 32,687 | 769 | 1.18 (1.06–1.31) | <0.001 | 1.15 (1.03–1.29) | 0.014 |
| Hispanic | 31,953 | 410 | 1.00 (0.87–1.16) | 0.953 | 0.95 (0.81–1.11) | 0.489 |
| Asian | 24,580 | 300 | 0.99 (0.84–1.17) | 0.911 | 0.91 (0.76–1.08) | 0.286 |
| Other | 2,252 | 33 | 0.62 (0.38–1.02) | 0.060 | 0.59 (0.34–1.00) | 0.051 |
| Marital status | | | | | | |
| Unmarried | 121,864 | 2,196 | 1 (Reference) | | 1 (Reference) | |
| Married | 159,687 | 1,812 | 0.88 (0.81–0.96) | 0.004 | 0.89 (0.81–0.97) | 0.010 |
| Unknown | 16,819 | 277 | 0.98 (0.83–1.16) | 0.803 | 0.97 (0.81–1.16) | 0.762 |
| Insurance status | | | | | | |
| Uninsured | 5,251 | 222 | 1 (Reference) | | 1 (Reference) | |
| Insured | 287,373 | 3,954 | 0.64 (0.54–0.76) | <0.001 | 0.66 (0.55–0.80) | <0.001 |
| Unknown | 5,746 | 109 | 0.53 (0.39–0.71) | <0.001 | 0.63 (0.46–0.86) | 0.004 |
| Tumor size | | | | | | |
| <2.0 cm | 158,893 | 489 | 1 (Reference) | | 1 (Reference) | |
| 2.0–4.9 cm | 97,757 | 1,435 | 1.09 (0.87–1.36) | 0.451 | 1.21 (0.95–1.55) | 0.115 |
| ≥5.0 cm | 25,401 | 1,266 | 1.18 (0.94–1.48) | 0.154 | 1.34 (1.04–1.72) | 0.023 |
| Unknown | 16,319 | 1,095 | 1.14 (0.91–1.42) | 0.251 | 1.34 (1.04–1.71) | 0.022 |
| Grade | | | | | | |
| I | 64,645 | 167 | 1 (Reference) | | 1 (Reference) | |
| II | 123,484 | 1,195 | 1.16 (0.93–1.46) | 0.194 | 1.30 (1.01–1.68) | 0.042 |
| III/IV | 91,612 | 1,845 | 1.43 (1.14–1.79) | 0.002 | 1.59 (1.23–2.04) | <0.001 |
| Unknown | 18,629 | 1,078 | 1.42 (1.13–1.79) | 0.003 | 1.52 (1.17–1.97) | 0.002 |
| T | | | | | | |
| T1 | 172,939 | 469 | 1 (Reference) | | 1 (Reference) | |
| T2 | 85,733 | 1,108 | 0.98 (0.77–1.24) | 0.852 | 0.92 (0.71–1.19) | 0.517 |
| T3 | 17,787 | 567 | 0.98 (0.76–1.26) | 0.857 | 0.96 (0.73–1.27) | 0.795 |
| T4 | 12,391 | 1281 | 1.17 (0.93–1.46) | 0.182 | 1.11 (0.87–1.42) | 0.393 |
| Unknown | 9,520 | 860 | 1.30 (1.03–1.64) | 0.028 | 1.20 (0.93–1.55) | 0.157 |
| N | | | | | | |
| N0 | 202,600 | 971 | 1 (Reference) | | 1 (Reference) | |
| N1 | 66,606 | 1,847 | 0.82 (0.74–0.91) | <0.001 | 0.87 (0.78–0.98) | 0.018 |
| N2 | 15,067 | 417 | 0.83 (0.71–0.97) | 0.019 | 0.90 (0.76–1.06) | 0.196 |
| N3 | 9,633 | 473 | 0.82 (0.70–0.95) | 0.009 | 0.86 (0.74–1.01) | 0.074 |
| Unknown | 4,464 | 577 | 0.89 (0.78–1.02) | 0.092 | 0.91 (0.78–1.05) | 0.203 |
| Extrahepatic metastatic sites to lung, brain and bone, no. | | | | | | |
| 0/1 | 284,444 | 2,816 | 1 (Reference) | | 1 (Reference) | |
| 2 | 2,763 | 962 | 1.41 (1.28–1.55) | <0.001 | 1.41 (1.28–1.57) | <0.001 |
| All 3 | 361 | 187 | 2.01 (1.68–2.41) | <0.001 | 1.89 (1.55–2.30) | <0.001 |
| Unknown | 802 | 320 | 1.23 (1.06–1.42) | 0.005 | 1.25 (1.06–1.46) | 0.006 |
| Radiation | | | | | | |
| Yes | 138,318 | 1,054 | 1 (Reference) | | 1 (Reference) | |
| No/Unknown | 160,052 | 3,231 | 1.17 (1.06–1.29) | 0.001 | 1.15 (1.03–1.27) | 0.009 |
| Chemotherapy | | | | | | |
| Yes | 115,409 | 2,407 | 1 (Reference) | | 1 (Reference) | |
| No/Unknown | 182,961 | 1,878 | 1.76 (1.62–1.92) | <0.001 | 1.73 (1.58–1.90) | <0.001 |
| Subtype | | | | | | |
| HR+/HER2− | 202,713 | 1,652 | 1 (Reference) | | 1 (Reference) | |
| HR+/HER2+ | 28,453 | 806 | 0.86 (0.76–0.98) | 0.019 | 0.85 (0.74–0.97) | 0.018 |
| HR−/HER2+ | 12,321 | 543 | 1.13 (0.98–1.30) | 0.083 | 1.12 (0.97–1.30) | 0.132 |
| Triple-negative | 31,632 | 548 | 2.20 (1.94–2.48) | <0.001 | 2.16 (1.89–2.46) | <0.001 |
| Unknown | 23,251 | 736 | 1.58 (1.40–1.77) | <0.001 | 1.49 (1.31–1.69) | <0.001 |

[a]P < 0.05 was considered statistically significant.
[b]Unknown age and unknown race removed from model owing to nonconvergence (n = 1,055).

**Table 4.** Median survival of patients with breast cancer by extent of systemic metastatic disease

| | | Survival, median (IQR), mo | |
|---|---|---|---|
| Subtype | Type of metastasis | Extrahepatic systemic disease only | Extrahepatic systemic disease and liver metastases |
| HR$^+$/HER2$^-$ | Lung | 35.0 (14.0–NR) | 14.0 (3.0–33.0) |
| | Brain | 11.0 (4.0–NR) | 7.0 (3.0–18.0) |
| | Bone | 38.0 (20.0–NR) | 23.0 (7.0–41.0) |
| | 2 of 3 | 26.0 (9.0–55.0) | 13.0 (4.0–34.0) |
| | All 3 | 18.0 (4.0–40.0) | 6.0 (1.0–28.0) |
| HR$^+$/HER2$^+$ | Lung | 48.0 (21.0–NR) | 15.0 (2.0–NR) |
| | Brain | 34.0 (8.0–NR) | NR (32.0–NR) |
| | Bone | 48.0 (25.0–NR) | 34.0 (10.0–51.0) |
| | 2 of 3 | 36.0 (18.0–NR) | 20.0 (4.0–NR) |
| | All 3 | 17.0 (5.0–40.0) | 9.0 (2.0–NR) |
| HR$^-$/HER2$^+$ | Lung | 25.0 (11.0–51.0) | 25.0 (4.0–48.0) |
| | Brain | 14.0 (8.0–38.0) | 4.0 (0–6.0) |
| | Bone | NR (15.0–NR) | 23.0 (6.0–45.0) |
| | 2 of 3 | 17.0 (6.0–NR) | 13.0 (3.0–34.0) |
| | All 3 | 9.0 (3.0–24.0) | 4.0 (1.0–12.0) |
| Triple-negative | Lung | 13.0 (5.0–26.0) | 10.0 (3.0–18.0) |
| | Brain | 5.0 (2.0–15.0) | 3.0 (3.0–14.0) |
| | Bone | 13.0 (4.0–32.0) | 7.0 (4.0–13.0) |
| | 2 of 3 | 8.0 (3.0–16.0) | 5.0 (1.0–10.0) |
| | All 3 | 5.0 (3.0–8.0) | 3.0 (1.0–11.0) |
| Unknown | Lung | 5.0 (1.0–28.0) | 1.0 (0–18.0) |
| | Brain | 5.0 (1.0–20.0) | 0 (0–1.0) |
| | Bone | 20.0 (4.0–47.0) | 6.0 (0–24.0) |
| | 2 of 3 | 7.0 (1.0–29.0) | 2.0 (0–17.0) |
| | All 3 | 2.0 (0–18.0) | 1.0 (0–2.0) |
| All subtypes | Lung | 22.0 (7.0–52.0) | 11.0 (2.0–30.0) |
| | Brain | 10.0 (2.0–30.0) | 6.0 (1.0–22.0) |
| | Bone | 36.0 (15.0–NR) | 19.0 (5.0–41.0) |
| | 2 of 3 | 21.0 (5.0–49.0) | 10.0 (2.0–30.0) |
| | All 3 | 12.0 (3.0–35.0) | 4.0 (1.0–14.0) |

Abbreviations: IQR, interquartile range; NR, not reached.

according to tumor subtype among patients with liver metastases at the initial diagnosis of breast cancer using national-level data from the United States. We found that patients with HR-negative HER2-positive status had a better survival compared with those with other breast cancer subtypes. HER2-positive status and black race were risk factors of the initial liver metastases, whereas HER2-negative status, Hispanic race, and young age (≤40) patients were protective factors. Remarkably, a higher incidence of liver metastases was found in patients with breast cancer with HER2-positive status. This is consistent with previous studies that showed organ specificity associated with specific gene (14, 25, 30, 31). An early study suggested that decreased or abnormal expression of a number of cell adhesion/junctional proteins, including claudin 4, 7, ZO-1, and γ-catenin, correlated with breast cancer liver metastases (30). An aforementioned study demonstrated that CLDN2, which was significantly upregulated in liver metastases, was an independent prognostic factor for early liver recurrence in breast cancer (31). A recent study identified a 17-gene signature enriched for extracellular matrix or stroma genes, the majority of which were selectively downregulated in breast cancer liver metastases (14).

Liver is one of the most common metastatic sites of breast cancer (5, 6, 13, 20, 32). Soni and colleagues (5) reported on the common sites of distant metastasis in 531 consecutive patients with advanced breast cancer; they found that the liver was the second most common organ of breast cancer metastatic involvement, representing 27% of the patients with breast cancer. Tampellini and colleagues (32) reported on patient demography

in 312 patients with advanced breast cancer, they found 77 patients (25%) had the initial recurrence in liver. Consistently, our study indicated 29.6% of patients with initial metastatic breast cancer were with liver metastases, similar to previous studies. However, the true incidence of liver metastases in patients with breast cancer is likely underestimated by the results in this study, in part due to liver metastases usually present with non-specific symptoms (e.g. upper abdominal fullness, a mass, ascites, jaundice, or weight loss). Besides, predicting liver metastases of early-stage breast cancer is important as it significantly influences the prognosis of advanced disease (31). Consequently, improving personalized management of breast cancer warrants further investigation in larger population-based cohorts which better capture the heterogeneity in biology and outcome of breast cancer.

Our results confirmed previous work in a population-based sample of patients with newly diagnosed breast cancer and liver metastases, demonstrating that the HER2-positive subtype was significantly associated with liver metastases compared with HER2-negative subtypes. In a retrospective case–control study of 103 patients with metastatic breast cancer, Buonomo and colleagues (33) showed that HER2-positive subtypes had a stronger association with systemic spread (OR, 2.127; 95% CI, 1.2–3.8) than other subgroups. In a retrospective study of 1,350 patients from referral centers in Turkey, Kaplan and colleagues (24) indicated that liver was the most frequent site of first metastases among HER2-overexpressing patients. Besides, results from other two studies suggested that HER2-rich subtypes have a liver-homing (OR = 2.99) characteristic (5, 26). In a Finnish study of 234 patients with breast cancer diagnosed with distant

metastases from 1991 to 1992, Sihto et al. (25) also indicated that HER2 subtype had a propensity to give rise to first distant metastases at liver, though no statistically significant difference was found. Nonetheless, the role of HER2 overexpression or amplification in liver metastases from breast cancer remains uncertain and needs elucidation (5). Li and colleagues (34) reported that HER2 overexpression mediated a chemokine receptor, CXCR4-associated metastases. Taken together, in line with previous studies, our observations demonstrated that the HER2 subtype of breast cancer preferentially metastasized to the liver. Further study to clarify the molecular mechanism of this relationship may provide substantial clinical utility.

Among the entire cohort, Hispanic patients (vs. white patients) had markedly lower odds of having liver metastases (OR, 0.64; 95% CI, 0.57–0.72; $P < 0.001$), and this association was also seen among the cohort with metastatic disease (OR, 0.76; 95% CI, 0.67–0.86; $P < 0.001$). These results suggest that Hispanic patients are likely being diagnosed at an earlier stage compared with white patients. Another major cause for concern is that we found that black patients with liver metastases had worse overall median survival, with a significant HR of 1.18 (95% CI, 1.06–1.31; $P < 0.001$) despite adjustment for socio-demographic factors, insurance status, tumor grade, stage, extent of systemic disease, treatment, and subtype. Biochemical, cellular and molecular factors may promote cancer growth and metastasis among African American women (35, 36). In addition, altered metabolic and inflammatory profile might be involved in the high prevalence rates of comorbid conditions (e.g., obesity, diabetes or chronic stress) and adverse cancer outcomes in African Americans (37–41). A better understanding of racial/ethnic differences in de novo metastases sites and survival outcomes is required.

Liver metastases are typically associated with metastases at other sites (11). In this study, 66.3% (2,841/4,285) patients with liver metastases also developed extrahepatic metastases, and we also found that the presence of liver metastases at initial diagnosis was associated with shorter survival time compared with patients presenting with de novo metastatic disease without baseline liver involvement. Liver metastasis patients of old age (>60) were correlated with higher mortality risk, whereas those Asian, married, or insured patients had lower mortality risk. Because SEER data cover nearly 30% of the U.S. population, the incidence proportions and median survivals we presented are remarkably generalizable compared with previously reported data focused mainly on patients received treatment at academic cancer centers.

We found that median survival for patients with breast cancer with liver metastases varied significantly by subtype, with triple-negative breast cancer being associated with the poorest survival (median survival, 8.0 months). HR-positive HER2-positive patients had the longest survival (median survival, 31.0 months). Braunstein and colleagues reported similar results for disease-free survival in patients with locoregional recurrence after breast-conserving therapy (42). In 82 patients with local recurrence, triple-negative subtype experienced significantly worse overall survival compared with Luminal A subtype (35% vs. 85% at 5 years; $P < 0.001$). Probable explanations for poorer overall survival in triple-negative subtype include ineffectiveness of hormonal therapy or HER2-directed agents. Nevertheless, results from a single institution study (104 patients) showed that breast cancer subtypes were not associated with survival after liver metastases (18), which are less likely to be generalizable. Our data are consistent with some of the general trends reported in academic center-based retrospective studies (24, 33, 42). Importantly, given the potential referral bias and other biases that can be presented in academic center-based series, we confirmed in a population-based sample of patients with newly diagnosed breast cancer and liver metastases that a median survival of nearly 3 years after diagnosis is now achieved in patients with HR-positive HER2-positive tumors.

Liver metastasis from breast cancer is a heterogeneous disease and its outcome varies significantly among tumor subtypes (12). In our study, the median survival among these patients with HR-positive HER2-positive and HR-negative HER2-positive subtype were 31.0 months and 22.0 months, respectively, experiencing longer median survival than other subtypes. The improvements in prognosis seen in HER2-positive patients could be explained in part by the efficacy of HER2-targeted agents. Historically, HER2-positive patients with breast cancer had poor prognosis, with response rates to chemotherapy ranging from 17% to 42% (43). Now with the advent of HER2-targeted therapy, patient prognosis was remarkably improved (44–47). Pertuzumab, one of the most promising HER2-targeted interventions, may act in synergy with trastuzumab to antagonize HER2 signaling by inhibiting HER2 heterodimerization and activating antibody-dependent cell-mediated cytotoxicity (46). Moreover, dual anti-HER2 therapy is shown to improve prognosis of HER2-positive patients with breast cancer. In the CLEOPATRA study, 80.2% of patients randomized to the pertuzumab group (docetaxel, trastuzumab, and pertuzumab) had an objective tumor response compared with 69.3% in the control group (docetaxel and trastuzumab; ref. 47). Given the high rates of tumor response to HER2-targeted therapy, we foresee that in the future, prognosis will be even further improved in patients with HER2-positive breast cancer liver metastases.

We also found that survival was poorer among patients with more extensive systemic disease at diagnosis ($P < 0.0001$). Similarly, a few aforementioned studies also suggested that patients with liver-only metastatic disease may experience longer survival compared with patients harboring liver metastases in parallel with metastases in other organs (14, 15, 19, 20, 48). In a prospective, randomized phase III trial study of 304 women diagnosed with locally advanced (inoperable) or metastatic breast cancer, patients with liver-only metastatic disease experienced longer survival compared with patients harboring liver metastases in parallel with metastases in other organs [log-rank, $P = 0.01$, multivariate Cox model $P < 0.001$ adjusting for age (>50 years or ≤50 years), metastasis-free interval (≤52 years or >2 years); ref. 14]. In a retrospective review in 80 consecutive patients who were treated for breast cancer liver metastases, the presence of extrahepatic metastases was found to worsen prognosis in breast cancer liver metastases (HR = 14.21; 95% CI, 1.08–186.94; $P = 0.044$; ref. 19). As a result, treatment options for liver oligometastases include surgery or stereotactic radiotherapy may hold great value, and more randomized controlled trials are needed to investigate the efficacy of these treatments (14).

The major limitations of this study were its retrospective setting and relatively small and heterogeneous population. First, information about disease recurrence or subsequent sites of disease involvement were not recorded in SEER

database; in addition, the sites of distant metastases, including bone, brain, lung, and liver, are recorded in the SEER database; however, other metastatic sites were not documented in detail; thus, we were unable to evaluate patients who developed liver metastases later or other metastatic sites, which were not available in SEER database in their disease course. Second, as for treatment, the subjects with "no/unknown" radiation or chemotherapy were not guaranteed as not receiving these treatments or just missing the information. Third, information relating to individual level socioeconomic status, use of mammography screening, family history, or other lifestyle factors was not recorded in the current dataset. Future studies using alternative data sources should be carried out to address these limitations.

In summary, this study offers insights into the epidemiology of liver metastases for patients presenting with newly diagnosed breast cancer in the United States. It lends support to consideration of studies evaluating the clinical utility of diagnosis of the liver among patients at high risk of liver metastases, including those with HER2-positive or triple-negative disease and other systemic metastases. Further investigation is warranted to determine the degree to which earlier screening may have an influence on crucial outcomes.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** J. Xie, Z. Xu
**Development of methodology:** J. Xie
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** J. Xie
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** J. Xie
**Writing, review, and/or revision of the manuscript:** J. Xie, Z. Xu
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** J. Xie, Z. Xu
**Study supervision:** Z. Xu

## Acknowledgments

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# BLOOD CANCER DISCOVERY

# A Population-Based Study on Liver Metastases in Women with Newly Diagnosed Breast Cancer

Jingjing Xie and Zhongyuan Xu

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