



Hepatitis B virus infection specially increases risk of liver metastasis in breast cancer patients: a propensity-matched analysis

Ping Yu[#], Peng Liu[#], Na Li[#], Xinhua Xie, Hailin Tang, Jiali Wu, Yanan Kong, Xiaoming Xie, Feng Ye

Department of Breast Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China

Contributions: (I) Conception and design: P Yu, P Liu, F Ye, X Xie; (II) Administrative support: F Ye, X Xie; (III) Provision of study materials or patients: F Ye, X Xie; (IV) Collection and assembly of data: J Wu, N Li; (V) Data analysis and interpretation: N Li, H Tang, X Xie, Y Kong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xiaoming Xie, Feng Ye. Department of Breast Oncology, State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, 651 East Dongfeng Road, Guangzhou 510060, China. Email: xiexm@sysucc.org.cn; yefeng@sysucc.org.cn.

Background: Breast cancer and hepatitis B virus (HBV) infection are serious public health issues in China. But the effect of HBV infection on breast cancer remains unclear. The objective was to assess whether HBV infection was associated with prognosis of breast cancer.

Methods: A retrospective database of 1,924 invasive breast cancer patients from Sun Yat-sen University Cancer Center from 2008 to 2010 was established. Propensity score matching method was applied to balance baseline parameters. Logistic regression was used for identifying the independent risk factors of liver metastasis. Prognostic outcomes were evaluated via Kaplan-Meier analysis and Cox model.

Results: Primary evaluation of gross data suggested HBV infection was associated with much higher rate of liver metastasis. 642 patients were matched for analysis. The median follow-up time was about 69 months. Patients with HBV surface antigen (HBsAg) (+) had a specially higher risk of liver metastasis aside of other distant organs than those with HBsAg (-). HBsAg (-/+) was identified to be an independent risk factor of liver metastasis [odds ratio (OR), 2.651; 95% confidence intervals (CI), 1.213–5.796; P=0.015]. HBsAg (+) was associated with liver metastasis significantly in stage III or in estrogen receptor (ER) (+) and/or progesterone receptor (PR) (+), human epidermal growth factor receptor-2 (HER-2) (-) subtype. Meanwhile, patients with HBsAg (+) had significant shorter liver metastasis-free survival (LMFS) compared with HBsAg (-) patients (P=0.041). But the difference of overall survival (OS) between the HBsAg (-) and HBsAg (+) groups reached statistically no significance (P=0.425). The multivariate analysis suggested HBsAg (+) could worsen the outcome of LMFS [hazards ratio (HR), 2.450; 95% CI, 1.169–5.135; P=0.018].

Conclusions: In breast cancer, HBsAg (+) was associated with specially a higher rate of liver metastasis and thus worsened the LMFS. HBsAg (-/+) was an independent risk factor of liver metastasis.

Keywords: Hepatitis B virus (HBV); breast cancer; liver metastasis; survival

Submitted Aug 27, 2019. Accepted for publication Dec 26, 2019.

doi: 10.21037/tcr.2020.01.63

View this article at: <http://dx.doi.org/10.21037/tcr.2020.01.63>

Introduction

Breast cancer (BC) is the most common malignancy in the world. Incidence rate for distant metastasis accounts for approximately 6% of breast cancer diagnoses during 2008 to 2014 in United States (1). Metastatic spread is still a great challenge in spite of the favorable results after receiving standard treatments for early stage breast cancer patients (2,3).

Hepatitis B virus (HBV) infection remains to be a serious global public health problem (4,5). According to the statistics, in recent years the overall hepatitis B surface antigen (HBsAg) seropositive rate is 3.61% worldwide affecting more than 240 million people. China has been known as the primary drive of global epidemic of HBV infection, devoting for about 1/3 of burden all over the world (4). A recent research on 15 million rural couples from China showed the HBsAg seropositive rate of 5.2% in 20–49 years old women (6).

Chronic infection with HBV is a kind of pathological status which can cause chronic liver damage such as changes of liver-related immunity and inflammation (7–11). HBV infection has been well recognized to be one of the major causes of hepatocellular cancer (HCC) and associated with non-Hodgkin's lymphoma (12–15). Moreover, some reports are obtainable regarding that whether HBV infection is associated with liver metastasis in some extrahepatic malignancies including colorectal cancer (CRC) and pancreatic cancer (PC). Interestingly, patients infected with HBV had lower liver metastasis rate than those without infection of HBV, but the extrahepatic metastases rate rose in patients with HBV infection in CRC (16,17). To the contrary, in PC patients synchronous liver metastasis rate increased along with HBV infection (18). Besides, studies revealed HBV infection also influenced the prognosis in CRC and PC (16–18). Nevertheless, in clinical practice many breast cancer patients with HBV infection occurred liver metastasis. The gap on the association between HBV infection and liver metastasis of breast cancer still exists, and the effect of HBV infection on prognosis in breast cancer remains unclear. Therefore, we conducted a cohort research to assess whether HBV infection was associated with liver metastasis and prognosis in breast cancer.

Methods

Study population

Consecutive invasive breast cancer patients in Sun Yat-

sen University Cancer Center (SYSUCC) from January 2008 to December 2010 were reviewed retrospectively. Other inclusion criteria were included: received surgery in hospital; female. Exclusion criteria were as below: undergone surgery before admission; bilateral breast cancer; with second cancers other than breast cancer; had recurrence or metastasis; complicated with other types of hepatitis. They were followed up until June 30, 2017 or date of any cause death. This study passed the approval of the Research Ethics Committee in SYSUCC and informed consent was signed by every patient.

Data collection

Baseline parameters were collected including age, menstrual condition, family history, pathological type, histologic grade, tumor size, number of metastatic axillary lymph nodes, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2), surgical method, HBsAg status and date of distant metastases including liver metastasis, death or last follow-up.

Clinical or pathological staging and intrinsic subtyping

The clinical or pathological stages of the disease were determined by TNM staging according to the seventh edition of the American Joint Committee on Cancer (AJCC) system (19).

Information on ER, PR and HER-2 was extracted according to American Society of Clinical Oncology guideline recommendations (20,21). ER, PR positive was defined as $\geq 1\%$ tumor cells presenting positive nuclear staining by immunohistochemistry (IHC) assay. HER-2 positive was determined as IHC 3+ or fluorescence in situ hybridization positive (HER-2 amplification). The breast cancer molecular subtypes were grouped as below: ER (+) and/or PR (+), HER-2 (–); ER (+) and/or PR (+), HER-2 (+); ER (–) and PR (–), HER-2 (+); ER (–) and PR (–), HER-2 (–).

HBsAg test

All patients received routine serum test for HBV infection before surgery by immunoenzyme labeling method. Serum samples were gathered and then centrifuged for using. The diagnostic kit from Shanghai Kehua Bioengineering Company was approved for clinical diagnostic usage.

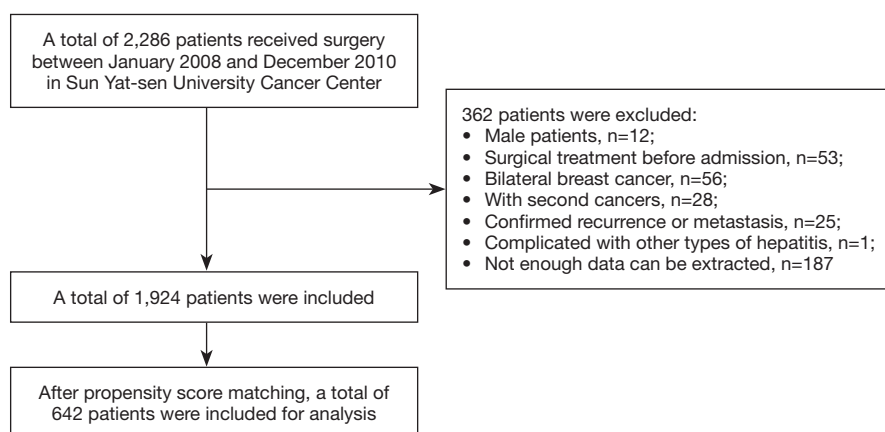


Figure 1 Flow chart of the patient selection.

Follow-up and assessment of disease

Patients' follow-up was performed via outpatient medical records and telephone counseling. Generally, according to National Comprehensive Cancer Network (NCCN) Guidelines of invasive breast cancer, patients received routine examinations including blood regular and biochemistry test, tumor biomarkers and ultrasonography of breast, abdomen, uterus and adnexa for follow-up visit. When liver metastases were suspected, a specific examination such as a computed tomography scan, magnetic resonance imaging or pathological biopsy was added. All of the liver metastatic patients were diagnosed according to serology test [carcino-embryonic antigen (CEA), carbohydrate antigen 153 (CA153), alpha fetoprotein (AFP)] and imaging test [computed tomography (CT) scan or magnetic resonance imaging (MRI) scan or positron emission tomography-computed tomography (PET-CT) scan] and confirmed through pathological biopsy and latter anti-tumor treatment and long-term follow-up.

Statistical analysis

Propensity scores were calculated for every patient by logistic regression using the covariates: age, menstrual condition, family history, pathological type, histologic grade, tumor size, number of metastatic lymph nodes, ER, PR, HER-2, surgical method with 1 to 2 matching ratios. The main end points in the research were liver metastasis-free survival (LMFS) and overall survival (OS). LMFS determined as time to liver metastasis, was calculated from the date of diagnosis to the date of liver metastasis or last

follow-up. OS was figured up from the date of diagnosis to the date of any cause death or last follow-up. The continuous data were described via median and range. The categorical data were exhibited by numbers and percentages. Chi-square test was adopted to evaluate categorical data. Logistic regression model was used to evaluate odds ratio (OR) and 95% confidence intervals (CIs) for identifying the independent risk factors associated with liver metastasis. Age, menstrual condition, family history, histologic grade, tumor size, number of metastatic lymph nodes, ER, PR, HER-2, surgical method and HBsAg (–/+) were included as variables. Kaplan-Meier curve was estimated for survival analyses, meanwhile the differences between the groups were evaluated by log-rank test. A Cox proportional hazards model was used to identify the independent factors associated with LMFS, OS. A two-tailed P value of <0.05 was deemed to significant statistically. All the statistical analyses were carried out by the SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

In total, 1,924 consecutive patients diagnosed invasive breast cancer were enrolled, including 215 (11.2%) HBsAg (+) patients; 642 patients were selected for analysis by propensity score matching (PSM) including 214 (33.3%) HBsAg (+) patients. The whole selection process was shown in *Figure 1*. The median age was 48 years (rang, 22–85 years); 416 (64.8%) patients were younger than 50 years. Patient characteristics and correlations between HBsAg

(-/+) and clinicopathological parameters before and after PSM were shown in *Tables 1,2*. For the matched cohort, there was no significant difference demonstrated concerning age, menstrual condition, family history, pathological type, histologic grade, tumor size, number of metastatic lymph nodes, ER, PR, HER-2, surgical methods between HBsAg (-) and HBsAg (+) groups (all $P>0.05$). Moreover, compared with HBsAg (-) group, HBsAg (+) group suffered more liver metastasis in both original and selected cohort ($P<0.05$). There was no difference on extrahepatic metastases observed between two groups in selected data ($P=0.199$).

Failure patterns

The median follow-up time was about 69 months (range, 1–119 months). Death and liver metastasis happened in 81 (12.6%), 31 (4.8%) of the 642 patients. Up to the last time of follow-up, 16/214 (7.5%) patients in HBsAg (-) group and 15/428 (3.5%) patients in HBsAg (+) group developed liver metastasis. Moreover, 31/214 (14.5%) patients and 50/428 (11.7%) patients died in HBsAg (-) and HBsAg (+) group, respectively.

Association between HBsAg (-/+) and liver metastasis

In the univariate logistic regression analysis, there was a significant association statistically found between HBsAg (-/+), tumor size, number of metastatic lymph nodes and liver metastasis (*Table 3*, all $P<0.05$). Meanwhile, to adjust for various risk factors, multivariate analysis was performed, which result accorded with that of the univariate analysis. It revealed that HBsAg (-/+) could be identified as an independent risk factor of liver metastasis (OR, 2.651; 95% CI, 1.213–5.796; $P=0.015$). Patients in HBsAg (+) group had a much higher risk of liver metastasis than those in HBsAg (-) group. In addition, tumor size, number of metastatic lymph nodes were also independent risk factors of liver metastasis.

After stratified according to clinical stages, multivariate analysis revealed that HBsAg (+) was related with liver metastasis significantly in breast cancer patients of stage III (OR, 3.892; 95% CI, 1.450–10.451; $P=0.007$; *Table 4*), and the results of patients with HBsAg (+) in stage I, II had no significantly difference from those with HBsAg (-) ($P=0.488$). Besides, HBsAg (-/+) was identified to be a risk

Table 1 Baseline characteristics of breast cancer patients with or serum HBsAg (-/+) before matched

Characteristic	Patients before matched, n (%)			P*
	All	HBsAg (+)	HBsAg (-)	
No. of patients	1,924	215 (11.2)	1,709 (88.8)	
Age, years				0.042
≤50	1,111 (57.7)	138 (64.2)	973 (56.9)	
>50	813 (42.3)	77 (35.8)	736 (43.1)	
Menstrual status				0.005
Premenstrual	1,200 (62.4)	153 (71.2)	1,047 (61.3)	
Postmenstrual	724 (37.6)	62 (28.8)	662 (38.7)	
Family history				0.343
Breast or ovarian carcinoma	86 (4.5)	9 (4.2)	77 (4.5)	
Other carcinomas	204 (10.6)	29 (13.5)	175 (10.2)	
No	1,634 (84.9)	177 (82.3)	1,457 (85.3)	
Tumor type				0.272
IDC	1,806 (93.6)	207 (96.3)	1,599 (93.6)	
ILC	35 (1.8)	3 (1.4)	32 (1.9)	
Others	83 (4.3)	5 (2.3)	78 (4.6)	

Table 1 (continued)

Table 1 (continued)

Characteristic	Patients before matched, n (%)			P*
	All	HBsAg (+)	HBsAg (–)	
Histologic grade				0.694
G1	52 (2.7)	6 (2.8)	46 (2.7)	
G2	1,126 (58.5)	121 (56.3)	1,005 (58.8)	
G3	492 (25.6)	62 (28.8)	430 (25.2)	
Unknown	254 (13.2)	26 (12.1)	228 (13.3)	
Tumor size				0.432
T1	754 (39.2)	75 (34.9)	679 (39.7)	
T2	979 (50.9)	112 (52.1)	867 (50.7)	
T3	93 (4.8)	13 (6.0)	80 (4.7)	
T4	89 (4.6)	14 (6.5)	75 (4.4)	
Unknown	9 (0.5)	1 (0.5)	8 (0.5)	
Lymph node status				0.278
N0	995 (51.7)	98 (45.6)	897 (52.5)	
N1	470 (24.4)	59 (27.4)	411 (24.0)	
N2	273 (14.2)	33 (15.3)	240 (14.0)	
N3	186 (9.7)	25 (11.6)	161 (9.5)	
ER				0.345
Positive	1,351 (70.2)	145 (67.4)	1,206 (70.6)	
Negative	573 (29.8)	70 (32.6)	503 (29.4)	
PR				0.461
Positive	1,357 (70.5)	147 (68.4)	1,210 (70.8)	
Negative	567 (29.5)	68 (31.6)	499 (29.2)	
HER-2				0.865
Positive	368 (19.1)	40 (18.6)	328 (19.2)	
Negative	1,444 (75.1)	164 (76.3)	1,280 (74.9)	
Unknown	112 (5.8)	11 (5.1)	101 (5.9)	
Surgery				0.148
Modified radical mastectomy	1,775 (92.3)	193 (89.8)	1,582 (92.6)	
Breast conserving surgery	149 (7.7)	22 (10.2)	127 (7.4)	
Liver metastasis				0.025
Yes	86 (4.5)	16 (7.4)	70 (4.1)	
No	1,838 (95.5)	199 (92.6)	1,639 (95.9)	

*, using Chi-squared test, $P < 0.05$ was considered statistically significant. IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor, PR, progesterone receptor, HER-2, human epidermal growth factor receptor-2; HBsAg, hepatitis B surface antigen.

Table 2 Baseline characteristics of breast cancer patients with serum HBsAg (–/+) after matched

Characteristic	Patients after matched, n (%)			P*
	All	HBsAg (+)	HBsAg (–)	
No. of patients	642 (100.0)	214 (33.3)	428 (66.7)	
Age, years				0.770
≤50	416 (64.8)	137 (64.0)	279 (65.2)	
>50	226 (35.2)	77 (36.0)	149 (34.8)	
Menstrual status				0.618
Premenstrual	464 (72.3)	152 (71.0)	312 (72.9)	
Postmenstrual	178 (27.7)	62 (29.0)	116 (27.1)	
Family history				0.635
Breast or ovarian carcinoma	28 (4.4)	9 (4.2)	19 (4.4)	
Other carcinomas	76 (11.8)	29 (13.6)	47 (11.0)	
No	538 (83.8)	176 (82.2)	362 (84.6)	
Tumor type				0.865
IDC	620 (96.6)	206 (96.3)	414 (96.7)	
ILC	7 (1.1)	2 (0.9)	4 (0.9)	
Others	15 (2.3)	5 (2.3)	10 (2.3)	
Histologic grade				0.464
G1	14 (2.2)	6 (2.8)	8 (1.9)	
G2	365 (56.9)	120 (56.1)	245 (57.2)	
G3	199 (31.0)	62 (29.0)	137 (32.0)	
Unknown	64 (10.0)	26 (12.1)	38 (8.9)	
Tumor size				0.833
T1	234 (36.4)	75 (35.0)	159 (37.1)	
T2	322 (50.2)	112 (52.3)	210 (49.1)	
T3	47 (7.3)	13 (6.1)	34 (7.9)	
T4	37 (5.8)	13 (6.1)	24 (5.6)	
Unknown	2 (0.3)	1 (0.5)	1 (0.3)	
Lymph node status				0.913
N0	292 (45.5)	98 (45.8)	194 (45.3)	
N1	174 (27.1)	59 (27.6)	115 (26.9)	
N2	108 (16.8)	33 (15.4)	75 (17.5)	
N3	68 (10.6)	24 (11.2)	44 (10.3)	
ER				0.636
Positive	427 (66.5)	145 (67.8)	282 (65.9)	
Negative	215 (33.5)	69 (32.2)	146 (34.1)	

Table 2 (continued)

Table 2 (continued)

Characteristic	Patients after matched, n (%)			P*
	All	HBsAg (+)	HBsAg (–)	
PR				0.904
Positive	443 (69.0)	147 (68.7)	296 (69.2)	
Negative	199 (31.0)	67 (31.3)	132 (30.8)	
HER-2				0.958
Positive	116 (18.1)	40 (18.7)	76 (17.8)	
Negative	493 (76.8)	163 (76.2)	330 (77.1)	
Unknown	33 (5.1)	11 (5.1)	22 (5.1)	
Surgery				0.565
Modified radical mastectomy	582 (90.7)	192 (89.7)	390 (91.1)	
Breast conserving surgery	60 (9.3)	22 (10.3)	38 (8.9)	
Liver metastasis				0.027
Yes	31 (4.8)	16 (7.5)	15 (3.5)	
No	611 (95.2)	198 (92.5)	413 (96.5)	
Extrahepatic metastases				0.199
Yes	56 (8.7)	23 (10.7)	33 (7.7)	
No	586 (91.3)	191 (89.3)	395 (92.3)	

*, using Chi-squared test, $P < 0.05$ was considered statistically significant. IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor, PR, progesterone receptor, HER-2, human epidermal growth factor receptor-2; HBsAg, hepatitis B surface antigen.

factor for the patients of ER (+) and/or PR (+) HER-2 (–) subtype ($P = 0.020$, Table 4), and there was a very slight trend in ER (+) and/or PR (+) HER-2 (+) subtype ($P = 0.352$). No statistically significance was found in ER (–) and PR (–) HER-2 (+), ER (–) and PR (–) HER-2 (–) subtypes (all $P > 0.05$)

Survival analysis

For the matched 642 patients, the 5-year OS, LMFS rates were 88.0% and 95.0% respectively. Besides the 5-year LMFS (96.6% *vs.* 92.3%; $P = 0.041$; Figure 2A) rate for patients with HBsAg (–) was significantly slightly higher than that for patients with HBsAg (+). However, the difference in the 5-year OS (88.2% *vs.* 85.9%; $P = 0.425$; Figure 2B) rates between the HBsAg (–) and HBsAg (+) groups reached no statistical significance. Adjusting for various prognostic factors, multivariate analysis showed the result that patients with HBsAg (+) could worsen the

outcome of LMFS [hazards ratio (HR), 2.450; 95% CI, 1.169–5.135; $P = 0.018$] (Table 5).

Discussion

HBV infection has been already reported to be associated with liver metastasis of some malignancies. However, the effect of HBV infection upon breast cancer patients remains unclear.

In our study, the liver metastasis and survival condition of 642 breast cancer cases were analyzed retrospectively using propensity score matching method. HBsAg (+) was associated with specially higher rate liver metastasis in breast cancer and thus worsened the LMFS. HBsAg (–/+) was an independent risk factor of liver metastasis in breast cancer.

Considering the number of HBsAg (–) group was far more than that of HBsAg (+) group and the imbalance between two groups' covariates existed in original data,

Table 3 Logistic regression of factors associated with liver metastasis

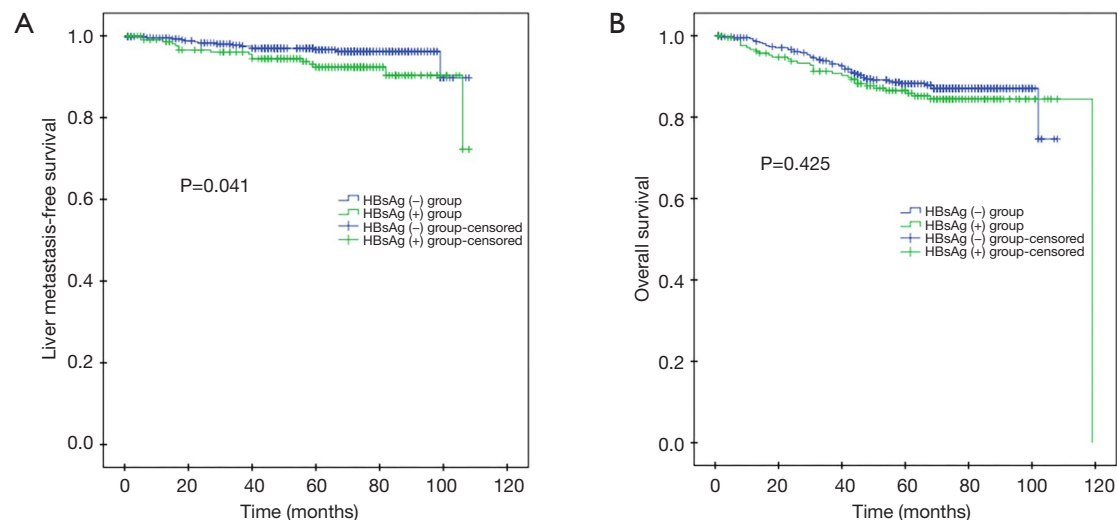
Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P*
Age	1.013 (0.476–2.154)	0.973		
Menstrual status	0.613 (0.247–1.519)	0.290		
Family history				
No	1 (reference)			
BC or OC	0.627 (0.082–4.773)	0.652		
Other carcinomas	0.754 (0.316–3.189)	0.897		
Histologic grade				
G1/unknown	1 (reference)		1 (reference)	
G2	0.443 (0.163–1.205)	0.111	0.352 (0.108–1.142)	0.082
G3	0.770 (0.279–2.129)	0.615	0.530 (0.159–1.766)	0.301
Tumor size				
T1/unknown	1 (reference)		1 (reference)	
T2	4.329 (1.254–14.974)	0.020	4.468 (1.236–16.151)	0.022
T3	11.366 (2.733–47.262)	0.001	8.288 (1.760–39.026)	0.007
T4	12.135 (2.767–53.219)	0.001	4.801 (0.938–24.578)	0.050
Lymph node status				
N0	1 (reference)		1 (reference)	
N1	6.501 (1.788–23.639)	0.004	6.045 (1.579–23.134)	0.009
N2	9.830 (2.651–36.446)	0.001	7.414 (1.802–30.511)	0.006
N3	11.055 (2.780–43.959)	0.001	8.875 (1.984–39.704)	0.004
ER	0.595 (0.288–1.232)	0.162		
PR	0.808 (0.380–1.720)	0.580		
HER-2				
Negative	1 (reference)			
Positive	2.098 (0.924–4.766)	0.077		
Unknown	2.495 (0.699–8.904)	0.159		
Surgery	1.082 (0.318–3.678)	0.900		
HBsAg	2.225 (1.078–4.592)	0.031	2.651 (1.213–5.796)	0.015

*, using Chi-squared test, $P < 0.05$ was considered statistically significant. IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor, PR, progesterone receptor, HER-2, human epidermal growth factor receptor-2; HBsAg, hepatitis B surface antigen; BC, breast carcinoma; OC, ovarian carcinoma.

Table 4 Univariate and multivariate logistic regression analyses for the association between serum HBsAg (–/+) and liver metastasis in various clinical stages and intrinsic subtypes

Subgroup	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Clinical stages*				
I/II	1.567 (0.415–5.924)	0.508	1.631 (0.409–6.493)	0.488
III	2.931 (1.193–7.202)	0.019	3.892 (1.450–10.451)	0.007
Intrinsic subtypes[#]				
ER (+) and/or PR (+) HER-2 (–)	2.571 (0.937–7.056)	0.067	4.248 (1.250–14.433)	0.020
ER (+) and/or PR (+) HER-2 (+)	1.087 (0.186–6.367)	0.926	6.084 (0.136–272.056)	0.352
ER (–) and PR (–) HER-2 (+)	3.692 (0.305–44.692)	0.305	1.304 (0.098–8.672)	0.977
ER (–) and PR (–) HER-2 (–)	1.300 (0.112–15.144)	0.834	0.587 (0.024–14.354)	0.744
Unknown	4.667 (0.374–58.248)	0.232	1.455 (1.011–7.989)	0.965

*, tumor size and lymph node status were not involved in the multivariate analyses; [#], hormone receptor status and HER-2 status were not involved in the multivariate analyses. ER, estrogen receptor, PR, progesterone receptor, HER-2, human epidermal growth factor receptor-2; HBsAg, hepatitis B surface antigen.

**Figure 2** Kaplan-Meier OS (A), LMFS (B) curves for the 642 patients with HBsAg (–/+). OS, overall survival; LMFS, liver metastasis-free survival; HBsAg, hepatitis B surface antigen.

PSM method was used to equilibrate baseline parameters and then match patients in order to eliminate these errors.

Tumor development is derived from the complicated interactions among tumor intrinsic properties, the host microenvironment and inflammatory response (22–24). Under the drive of some factors the tumor cells leave the original site, migrate via the bloodstream and lymphatic drainage, settled in the suitable target organ, and then

invade the surrounding tissue to form a new metastatic site (22,25). HBV, as one of oncogenic viruses, has been found not only to participate in the etiology of cancers and also to play the vital part in cancer metastasis (26). Several possible mechanisms are considered to be connected with the progression and migration of tumor cells. Firstly, HBV directly assists breast cancer cells colonization to the liver. Binding with HBV X-interacting protein (HBXIP) which

Table 5 Cox regression analyses of serum HBsAg (–/+) for LMFS in 642 patients

Variable	Univariate (P value)	Multivariate	
		HR (95% CI)	P
Age	0.831		
Menstrual status	0.312		
Family history	0.804		
Histologic grade	0.238		
Tumor size	0.001	1.586 (1.098–2.292)	0.014
Lymph node status	0.002	1.911 (1.315–2.778)	0.001
ER	0.094		
PR	0.352		
HER-2	0.077		
Surgery	0.934		
HBsAg	0.046	2.450 (1.169–5.135)	0.018

ER, estrogen receptor, PR, progesterone receptor, HER-2, human epidermal growth factor receptor-2; HBsAg, hepatitis B surface antigen, LMFS, liver metastasis-free survival.

expresses in breast cancer (27), HBV-encoded X antigen (HBx) could mediate epithelial–mesenchymal transition (EMT) program, therefore facilitating tumor invasion and migration. The EMT program is started through activating the TWIST promoter and the protein kinase B/phosphatidylinositol 3-kinase/glycogen synthase kinase-3b (Akt/PI3-K/GSK-3b) signaling pathway by HBx (28–31). Secondly, chronic inflammation caused by HBV infection contributes to imbalance of cytokines such as interleukin 6 (IL-6) (32), IL-27 (33), transforming growth factor beta (TGF- β) (34) in the liver microenvironment, participating in tumor cells EMT program and promoting metastases (35–38). For example, IL-6 produced by immune cells activates the Src homology 2 (SH2)-containing protein tyrosine phosphatase-2 (SHP-2)-Ras-extracellular signal-regulated kinase (ERK), Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) and PI3K-Akt pathways, leading to tumor cells proliferation, EMT, invasion, angiogenesis and finally metastasis (36). Thirdly, chronic HBV infection triggers immune tolerance in liver, which creates a favorable environment for cancer cells survival. During long-term chronic HBV antigenic stimulation, virus-specific T cells become exhausted and functionally impaired. Meanwhile, regulatory T cells (Tregs) produced via activation of Notch pathway suppress CD4/

CD8 T cells in reverse via releasing IL-10, TGF- β . These together lead to tolerance, allowing tumor cells colonization without immune clearance (9,39,40).

HBV infection also had some impact on survival in several malignancies. So far people couldn't draw a coincident conclusion about the effect of HBV infection on survival of CRC in previous studies (16,17). Interestingly, Wei *et al.* found chronic hepatitis B and non-HBV infection group showed significantly better OS than inactive HBsAg carriers group (18). In our study, HBsAg (+) group showed significant worse LMFS than HBsAg (–) group, which was in line with higher liver metastasis rate in HBsAg (+) group. The overall survival between the HBsAg (–) and HBsAg (+) groups reached no statistical difference, which might attribute to the small size of sample and need prospective studies to figure it out.

On account of the retrospective feature of our study, there were some deficiencies. Above all, although consecutive patients were chosen and eligibility criteria were carried out to minimize the bias, a selection bias was inevitable. In addition, the size of sample was limited and from one center, much bigger samples and work are included in future.

Therefore, further prospective trials and basic laboratory experiments on mechanisms are required to make certain

how HBV infection affects breast cancer progression, which may provide clinicians a new strategy to evaluate and prevent the risks for liver metastasis and death.

Conclusions

HBsAg (+) was associated with a specially higher rate liver metastasis in breast cancer and thus worsened the LMFS. HBsAg (-/+) could be an independent risk factor of liver metastasis in breast cancer patients. By far, it is the first research to demonstrate the effect of HBV infection on liver metastasis in breast cancer.

Acknowledgments

We thank the patients, their families, and the investigators who participated in this study.

Funding: This work was sponsored by funds from the National Natural Science Foundation of China (81872152, to X Xie), the Natural Science Foundation of Guangdong (2018A0303130285, to F Ye) and Science and Technology Planning Projects of Guangdong (2017A020215197, to F Ye).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.01.63>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study passed the approval of the Research Ethics Committee in Sun Yat-sen University Cancer Center and informed consent was signed by every patient.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7-34.
2. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin* 2019;69:438-51.
3. Schwartz RS, Erban JK. Timing of Metastasis in Breast Cancer. *N Engl J Med* 2017;376:2486-8.
4. Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015;386:1546-55.
5. Ott JJ, Horn J, Krause G, et al. Time trends of chronic HBV infection over prior decades - A global analysis. *J Hepatol* 2017;66:48-54.
6. Long Z, Wang YY, Huang YJ, et al. Status of HBsAg seroprevalence in 15 million rural couples in China: a cross-sectional study. *Sci Rep* 2017;7:42822.
7. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008;48:335-52.
8. Jung MC, Pape GR. Immunology of hepatitis B infection. *Lancet Infect Dis* 2002;2:43-50.
9. Shin EC, Sung PS, Park SH. Immune responses and immunopathology in acute and chronic viral hepatitis. *Nat Rev Immunol* 2016;16:509.
10. Gish RG, Given BD, Lai CL, et al. Chronic hepatitis B: Virology, natural history, current management and a glimpse at future opportunities. *Antiviral Res* 2015;121:47-58.
11. Gil-Garcia AI, Madejon A, Francisco-Recuero I, et al. Prevalence of hepatocarcinoma-related hepatitis B virus mutants in patients in grey zone of treatment. *World J Gastroenterol* 2019;25:5883-96.
12. Engels EA, Cho ER, Sun HJ. Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: a cohort study. *Lancet Oncol* 2010;11:827-34.
13. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142:1264-73.e1.
14. Baatarkhuu O, Gerelchimeg T, Munkh-Orshikh D, et al. Epidemiology, Genotype Distribution, Prognosis, Control, and Management of Viral Hepatitis B, C, D, and Hepatocellular Carcinoma in Mongolia. *Euroasian J Hepatogastroenterol* 2018;8:57-62.
15. Kim M, Kyung Lee Y, Park B, et al. Hepatitis virus B and C infections are associated with an increased risk of non-Hodgkin lymphoma: A nested case-control study using a national sample cohort. *J Med Virol* 2019. [Epub ahead of

- print].
16. Zhao Y, Lin J, Peng J, et al. Hepatitis B Virus Infection Predicts Better Survival In Patients With Colorectal Liver-only Metastases Undergoing Liver Resection. *J Cancer* 2018;9:1560-7.
 17. Qiu HB, Zhang LY, Zeng ZL, et al. HBV infection decreases risk of liver metastasis in patients with colorectal cancer: A cohort study. *World J Gastroenterol* 2011;17:804-8.
 18. Wei XL, Qiu MZ, Chen WW, et al. The status of HBV infection influences metastatic pattern and survival in Chinese patients with pancreatic cancer. *J Transl Med* 2013;11:249.
 19. Edge SB, Compton CC. Edge SB, Compton CCThe American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 17(6): 1471-1474. *Ann Surg Oncol* 2010;17:1471-4.
 20. Lambein K, Van BM, Denys H, et al. 2013 update of the American Society of Clinical Oncology/College of American Pathologists guideline for human epidermal growth factor receptor 2 testing: impact on immunohistochemistry-negative breast cancers. *J Clin Oncol* 2014;32:1856-7.
 21. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol* 2010;28:2784-95.
 22. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nat Rev Cancer* 2003;3:453.
 23. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001;357:539-45.
 24. Mueller MM, Fusenig NE. Friends or foes - bipolar effects of the tumour stroma in cancer. *Nat Rev Cancer* 2004;4:839-49.
 25. Hosseini H, Obradović MM, Hoffmann M, et al. Early dissemination seeds metastasis in breast cancer. *Nature* 2017;540.
 26. Akram N, Imran M, Noreen M, et al. Oncogenic Role of Tumor Viruses in Humans. *Viral Immunol* 2017;30:20-7.
 27. Fujii R, Zhu C, Wen Y, et al. HBXIP, cellular target of hepatitis B virus oncoprotein, is a regulator of centrosome dynamics and cytokinesis. *Cancer Res* 2006;66:9099.
 28. Ye X, Brabletz T, Kang Y, et al. Upholding a role for EMT in breast cancer metastasis. *Nature* 2017;547:E1-E3.
 29. Yu M, Bardia A, Wittner BS, et al. Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition. *Science* 2013;339:580-4.
 30. Chen X, Bode AM, Dong Z, et al. The epithelial-mesenchymal transition (EMT) is regulated by oncoviruses in cancer. *FASEB J* 2016;30:3001.
 31. Ellis H, Ma CX. PI3K Inhibitors in Breast Cancer Therapy. *Curr Oncol Rep* 2019;21:110.
 32. Xia C, Liu Y, Chen Z, et al. Involvement of Interleukin 6 in Hepatitis B Viral Infection. *Cell Physiol Biochem* 2015;37:677-86.
 33. Jung-Ta K, Lai HC, Shu-Mei T, et al. Rather than interleukin-27, interleukin-6 expresses positive correlation with liver severity in naïve hepatitis B infection patients. *Liver Int* 2012;32:928-36.
 34. Argentou N, Germanidis G, Hytioglou P, et al. TGF- β signaling is activated in patients with chronic HBV infection and repressed by SMAD7 overexpression after successful antiviral treatment. *Inflamm Res* 2016;65:355-65.
 35. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol* 2014;15:178-96.
 36. Taniguchi K, Karin M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. *Semin Immunol* 2014;26:54-74.
 37. Feng X, Ke J, Li S, et al. FAF1 phosphorylation by AKT accumulates TGF- β type II receptor and drives breast cancer metastasis. *Nat Commun* 2017;8:15021.
 38. Tsai JH, Yang J. Epithelial-mesenchymal plasticity in carcinoma metastasis. *Genes Dev* 2013;27:2192-206.
 39. Liu Y, Cheng LS, Wu SD, et al. IL-10-producing regulatory B-cells suppressed effector T-cells but enhanced regulatory T-cells in chronic HBV infection. *Clin Sci* 2016;130:907.
 40. Trehanpati N, Vyas AK. Immune Regulation by T Regulatory Cells in Hepatitis B Virus-Related Inflammation and Cancer. *Scand J Immunol* 2017;85:175-81.

Cite this article as: Yu P, Liu P, Li N, Xie X, Tang H, Wu J, Kong Y, Xie X, Ye F. Hepatitis B virus infection specially increases risk of liver metastasis in breast cancer patients: a propensity-matched analysis. *Transl Cancer Res* 2020;9(3):1506-1517. doi: 10.21037/tcr.2020.01.63