Original Article

Factors associated with bone metastasis in breast cancer: a systematic review and meta-analysis

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Background: To systematically evaluate and analyze the risk factors for breast cancer (BC) with bone metastasis (BM) and provide clinical evidence supporting the early prevention of BM.

Methods: We systematically retrieved databases from the Cochrane Library, PubMed, Web of Science, and EMBASE for BC with BM patient. Limited: publish cation between January 1, 2001, and December 31, 2019. Literature screening and evaluation were performed independently by 2 evaluators. The quality of all included studies was evaluated with the NOS. Studies with NOS ≥6 on factors related to the BM of BC were identified. Weighted odds ratio (OR) were used as the combined effects.

Results: We identified 18 articles with available data. The NOS scores ranged from 6–9. Progesterone receptor (PR)-positive BC patients had a relatively lower risk of BM [I^2=45.9%, OR =0.80, 95% confidence interval (CI): 0.72, 0.88, P<0.001]. HER2-positive BC patients had a relatively higher risk of BM (I^2=77.6%, OR =1.35, 95% CI: 1.04, 1.76, P=0.025). The risk of BM in patients with lymph node metastasis was higher than that in patients with no lymph node metastasis (I^2=99.7%, OR =2.60, 95% CI: 1.41, 4.80, P=0.002). The risk of BM in stage T2 BC patients was 1.99 times that in stage T1 BC patients (I^2=96.8%, OR =1.99, 95% CI: 1.03, 3.83, P=0.040). The risk of BM in stage T3 BC patients was 4.74 times that in stage T1 BC patients (I^2=95.6%, OR =4.74, 95% CI: 1.94, 11.57, P=0.001). The risk of BM in stage T4 BC patients was 14.57 times that in stage T1 BC patients (I^2=95.4%, OR =14.57, 95% CI: 4.16, 51.05, P<0.001). The incidence of BM in BC patients without lobular or ductal BC was significantly higher than that in patients with ductal BC (I^2=56.4%, OR =1.26, 95% CI: 1.09, 1.45, P=0.001).

Discussion: Patients with PR-positive BC have a relatively lower risk of BM. Patients with HER2-positive, lymph node metastasis-positive, nonlobular, or ductal BC have a relatively higher risk of BM. With increasing T stage, the risk of BM in BC patients also increases.

Keywords: Breast cancer (BC); bone metastasis (BM); relevant factors; meta-analysis

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Introduction

Breast cancer (BC) is one of the most common malignant tumors in women, and its incidence rate has increased in recent years. Bone tissue is the most common metastatic site of advanced BC, and the proportion of metastasis in the bone is much higher than the proportions of metastases in other organs. A meta-analysis in 2017 showed that the 5-year incidence of bone metastasis (BM) in patients with stages I–III BC was 12% (1). A SEER based study

found that BM of BC patients with distant metastasis was 51% (8,848/17,445), which is higher than lung metastasis 24% (4,167/17,445), liver metastasis 20% (3,434/17,445) and brain metastasis 6% (1,000/17,445) (2). Leone *et al.* reported that BM rate was 37.5%, visceral metastasis rate was 21%, and other site metastasis rate was 11.9% in 9,143 patients of IV BC at initial diagnosis (3).

BM of BC can induce anemia, fractures, paraplegia, pain, cachexia, and other conditions, and significantly reduces the quality of life of patients. Factors related to BM in BC patients can be used as screening tools for the prevention and treatment of BM, and are very important for reducing adverse events associated with BM and improving the quality of life of patients. BM of BC can occur in the ribs, vertebra, femur, ilium, and other bones. The process of the development of secondary bone tumors after tumor metastasis to the bone through the lymphatic system and blood circulation is extremely complicated, and the mechanism is still not completely clear. From the "seeds and soil" theory proposed 100 years ago to the "homing" theory suggested today, all theories support the specific rather than random metastasis of cancer cells.

Currently, the meta-analysis is mainly focuses on the treatment of BC patients with BM. Awan *et al.* analysed 5 clinical trials, and the results showed Zoledronate administration every 12 weeks compared to every 4 weeks for patients with 1 on-study SRE indicating similar efficacy (4). Yang *et al.* analyzed 4 articles to compare the efficacy of bisphosphonate treatment every 4 weeks to every 12 weeks, and there were no significant differences in skeletal-related events, renal dysfunction, and osteonecrosis of jaw (5).

With the continuous updating of clinical indicators, some new clinical indicators have been incorporated into the evaluation of BM, such as hormone receptors (HRs) and BC staging. The addition of these new indicators changes the traditional model, which had fewer indicators, such as tumor size and TNM stage, and improves the accuracy of the prediction of BC BM. Zhang *et al.* systematically extrapolated the occurrence, risk factor, prognostic characteristics, BM and SREs, but they did not calculate the odds ratio (OR) of each index (6). In this report, retrospective studies on the BM of BC were reviewed, and a meta-analysis was performed to evaluate the predictive indexes.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-21-438).

Methods

Retrieval strategy studies were retrieved from the Cochrane Library, PubMed, Web of Science, and EMBASE. Included articles were published between January 1, 2001, and December 31, 2019

The Cochrane Library search strategies (((Breast Neoplasms)OR(Breast Neoplasm)OR(Breast cancer) OR(Breast Carcinoma)OR(Breast Tumor))AND(Bone metastasis)OR(metastasis of Bone)OR((Skeletal metastasis) OR(Skeletal complication)OR(skeletal-related event)) AND(Publication Date from January 1st,2001 to December 31,2020)).

PubMed and EMBASE search strategies (((Breast Neoplasms[Mesh])OR(Breast Neoplasm)OR(Breast cancer) OR(Breast Carcinoma)OR(Breast Tumor))AND(Bone metastasis)OR(metastasis of Bone)OR((Skeletal metastasis) OR(Skeletal complication)OR(skeletal-related event)) AN D(limits:Humans,English;Publication Date from January 1st,2001 to December 31,2020)).

Web of Science search strategies (TS=((Breast Neoplasms[Mesh])OR(Breast Neoplasm)OR(Breast cancer)OR(Breast Carcinoma)OR(Breast Tumor)) AND(TS=((Bone metastasis)OR(metastasis of Bone) OR(Skeletal metastasis)OR(Skeletal complication) OR(skeletal-related event))) AND (DT=Article),AND (English,PY=(2001-2020)).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) the study subjects were diagnosed with BC, and patients with bone metastases were diagnosed by imaging or pathology; (II) complete data could be extracted, and the hazard ratio (HR) and 95% confidence interval (CI) could be directly or indirectly obtained; (III) more than 1 index was included; and (IV) the number of patients with bone metastases from BC was not fewer than 10.

The exclusion criteria were as follows: (I) duplicates, reviews, and case reports or studies for which the full text versions were unavailable; (II) the included patients had other tumors at the same time; (III) the data could not be extracted or were incomplete; and (IV) studies with a Newcastle-Ottawa scale (NOS) score ≤5.

The indicators of interest were as follows: (I) estrogen receptor (ER) expression; (II) progesterone receptor (PR) expression; (III) HR expression, with positive ER or PR expression indicating positive HR expression; (IV) human

epidermal growth factor receptor-2 (HER2) expression; (V) luminal A, luminal B, HER2 overexpression, and triple-negative breast cancer (TNBC) subtypes; (VI) premenopausal and postmenopausal status; (VII) histological grades I, II, and III; (VIII) positive or negative lymph node metastasis status, where negative status indicated that the number of lymph node metastases was 0 or the N stage was N0, and positive status indicated that the number of lymph node metastases was ≥1 or the N stage was N1–N4; (IX) tumor size; (X) TNM T stage (T1, T2, T3, T4); and (XI) histological types determined by pathology, including ductal, lobular, and others (mixed ductal and lobular, mucinous, papillary, carcinoma)

Study screening and evaluation

Literature screening and evaluation were performed independently by 2 evaluators. First, irrelevant documents were excluded by reading the title and abstract. Then the full texts of the remaining documents were read, and the final selection was made based on the inclusion and exclusion criteria. The quality of the included studies was evaluated with the NOS as recommended by the Cochrane Collaboration Network (cohort study) (7). The maximum score was 9, and studies with scores ≥6 were high-quality studies, while those with scores ≤5 were low-quality studies. In cases of disputes, the evaluations were negotiated or assessed by an experienced third party.

Data extraction

The extracted data were the title, year of publication, author, study design, and observation index. The statistics of indicators were extracted directly from the text when available; otherwise, they were calculated indirectly. The data entry was performed by 2 evaluators independently. If the data entered was inconsistent, the data was discussed and corrected through negotiation or adjudication by an experienced third party. If there were subjects from the same region (database) in the same period in more than 1 study, only data from 1 of the studies was included for each indicator of interest.

Statistical methods

The original data was entered into Excel 2006. Data conversion and statistical analyses of the indicators of interest were performed with Stata 12.0 statistical software. The weighted mean difference (WMD) was used for measurement data, and the OR was used for count data. If the original data were HRs and 95% CI, then the HR was considered to be equivalent to the OR. All effect indexes are presented with the corresponding 95% CIs. The natural logarithm of the OR (lnOR) and the natural logarithm of the 95% CI (lnLL, lnUL) were calculated. Then, the natural logarithm of the standard error was calculated with the following equation: SElnOR = ln(lnUL-lnLL)/3.92. Heterogeneity was tested using the chi-square test. If I^2 was <50%, the heterogeneity was acceptable, and the fixed effect model was used for the analysis. If I^2 was greater than 50%, the level of heterogeneity was high, and a random effect model was used for the analysis. Publication bias was tested by the Begg's rank correlation method. $P<0.05$ was statistically significant.

Results

Results of the literature search

The searches of PubMed, Web of Science, EMBASE, and the Cochrane Library yielded 3,157 articles. Batch and manual checks for duplicates were performed using EndNote software. A total of 1,921 documents remained after eliminating duplicate documents, and 1,625 irrelevant documents were excluded after reading the title and abstract. Of the 69 documents that remained, 51 were removed after reading the full texts and assessing the study quality. Finally, 18 documents were included in the meta-analysis (*Figure 1*).

Basic information (Table 1)

Eighteen studies (8-25) were included from 13 countries, including China, France, Germany, Denmark, the UK, Italy, Indonesia, Canada, the US, Belgium, Spain, Iran, and Japan. An additional 6 European countries (Belgium, France, Germany, Italy, Spain, and the UK) were included in the study by Von Moos *et al.* in 2018 (21) and other studies. Gong *et al.* in 2018 collected 229,195 subjects from the Surveillance, Epidemiology, and End Results (SEER) database between January 2010 and December 2014 (14). Xiong *et al.* in 2018 collected 245,707 subjects from the SEER database between January 2010 and December 2013 (23). There was obvious overlap between the 2 research datasets. This study mainly used the data from the study by Xiong *et al.* in 2018 (23). Data on subtypes,

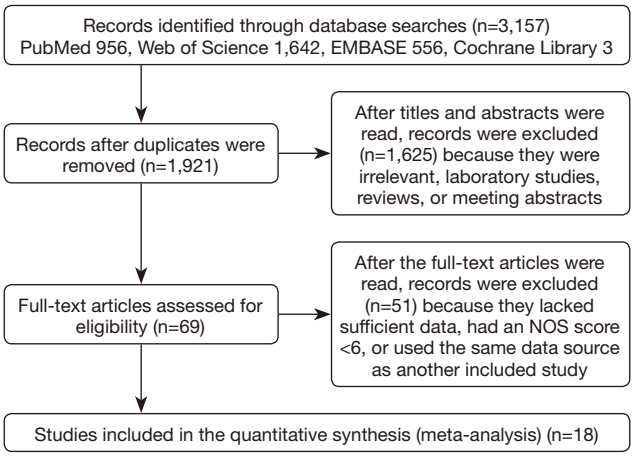

Figure 1 Flow chart of the literature search process.

histological grades, nodal metastasis, T stages, and other indicators of interest were collected. The use of the histological type obtained from pathological reports in the study by Gong *et al.* in 2018 (14) was intended to maximize the data and prevent the inclusion of duplicate data in the meta-analysis. Eleven retrospective studies and 6 cross-sectional studies were included.

Quality assessment

The NOS scores ranged from 6–9, including 7 studies scoring 6 points, 5 studies scoring 7 points, 4 studies scoring 8 points, and 2 studies scoring 9 points (*Table 2*).

Meta-analysis overview

Eleven indicators were included in this study. Tumor size was only preliminarily analyzed because of a lack of standard definitions in the literature. Among the other 10 indicators, subgroup analyses were performed for the subtype, histological grade, and T stage, etc. Nodal metastasis was defined as the presence of metastatic lymph nodes and was further grouped based on the cutoff value of ≥3 involved lymph nodes. The I^2 for PR was 45.9%, and a fixed effect model was used. The I^2 values for the other 9 indicators were all >50%, and random effects models were used. Begg's test showed that there was no statistically significant bias caused by any study, and the meta-analysis was performed by pooling the data (*Table 3*).

Analysis results

ER

Eight studies (8,9,13,15-17,19,20) reported the effect of ER status on BM of BC. No significant differences were observed in the incidence of BM between ER-positive and ER-negative BC patients (I^2=77.4%, OR =1.23, 95% CI: 0.93, 1.62, P=0.140) (*Figure 2*).

PR

Seven studies (8,9,15,16,19,20,24) reported the effect of PR status on BM of BC. The results showed that the risk of BM was lower in PR-positive than in PR-negative BC patients (I^2=45.9%, OR =0.80, 95% CI: 0.72, 0.88, P<0.001) (*Figure 3*).

HR

Five studies (11,12,18,21,22) analyzed the effect of HR status on BM of BC. The results showed that the risk of BM was higher in HR-positive than in HR-negative BC patients (I^2=87.7%, OR =1.39, 95% CI: 0.90, 2.16, P=0.142) (*Figure 4*).

HER2

Ten studies (8,9,11,12,15,16,18,19,22,24) evaluated the risk of HER2 on BM from BC. The results showed that HER2-positive BC patients had a relatively higher risk of BM (I^2=77.6%, OR =1.35, 95% CI: 1.04, 1.76, P=0.025) (*Figure 5*).

Table 1 Basic study information

Author, year	Country or region	Dates	Study design	Indicators	Research subjects			Age, years (range, percentage)	Follow-up duration (years)
					Total	BM	nBM		
Chen 2013 (8)	China	Jan 2006 to Jan 2009	CS	①②④⑥⑦⑧	362	108	254	22–77 (100%)	NA
Chen 2014 (9)	China	Jan 2000 to July 2010	RS	①②④⑦⑧⑩	3,411	46	3,365	18–75 (100%)	NA
Chen 2017 (10)	China	Jan 2005 to Dec 2015	RS	⑥⑧⑪	2,133	327	1,806	(48.13±10.6)	NA
Delpech 2015 (11)	France	Jan 1997 to Dec 2004	RS	③④⑥⑧⑩⑪	972	314	658	19–91 (100%)	0.25–3.31
Diessner 2016 (12)	Germany	1992 to 2008	RS	③④⑤⑥⑦⑧⑩	886	226	660	22–96 (100%)	≥10
Cronin-Fenton 2018 (13)	Denmark	Jan 1999 to Dec 2011	RS	①	23,478	519	22,959	40–69 (69.3%)	1–5
Gong 2018 (14)	SEER database	Jan 2010 to Dec 2014	CS	⑪	229,195	8,295	220,900	18–64 (62%)	NA
Harries 2014 (15)	UK	1975 to 2006	RS	①②④⑦⑧⑨⑪	7,064	1,589	5,475	40–69 (71.2%)	9.4 (mean)
Irawan 2008 (16)	Indonesia	1998 to 2002	CS	①②④⑪	197	48	149	28–77 (100%)	NA
James 2003 (17)	UK	Jul 1997 to Dec 2001	CS	①⑦⑧⑨⑪	492	267	225	41–70 (100%)	NA
Li 2015 (18)	China	NA	RS	③④⑤⑥⑧⑨	613	126	487	26–88 (100%)	2.46 (mean)
Liede 2016 (19)	Canada	1992 to 2008	RS	①②④⑦⑧⑨	2,097	257	1,840	22–94 (100%)	0.06–27
Mihai 2006 (20)	UK	Jun 1998 to Jun 2003	CS	①②	65	42	23	35–90 (100%)	NA
von Moos 2018 (21)	Six European countries	February to April 2015	RS	③⑥	2,984	1,408	1,576	63.1 (mean)	0.25–3
Valsecchi 2009 (22)	US	Jan 1999 to Dec 2005	RS	③④⑥⑨	692	75	617	59 (mean)	3.9
Xiong 2018 (23)	SEER	Jan 2010 to Dec 2013	CS	⑤⑦⑧⑩	245,707	89,01	236,806	18–80 (89.9%)	≥1
Yamashiro 2014 (24)	Japan	Aug 2010 to Jan 2011	RS	②④⑤⑥⑦⑧⑨⑩	1,024	193	831	24–93 (100%)	0.04–8.12
Yazdani 2019 (25)	Iran	2002 to 2012	CS	⑥⑧⑨	1,690	123	1,567	47.26±11.31	NA

Six European countries: Belgium, France, Germany, Italy, Spain, and the UK. Indicators: ① ER; ② PR; ③ HR; ④ HER2; ⑤ subtype; ⑥ menopausal status; ⑦ histological grade; ⑧ nodal metastasis; ⑨ tumor size; ⑩ T stage; ⑪ histological type. CS, cross-sectional study; RS, retrospective study; BM, bone metastasis; nBM, no bone metastasis; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; TNBC, triple-negative breast cancer.

Table 2 Quality assessment according to the Newcastle-Ottawa (Case-Control Star Template)

Study	NOS score			
	Selection	Comparability	Exposure	Total
Chen 2013 (8)	3	2	2	7
Chen 2014 (9)	3	2	2	7
Chen 2017 (10)	4	2	2	8
Delpech 2015 (11)	3	1	2	6
Diessner 2016 (12)	4	2	2	8
Cronin-Fenton 2018 (13)	3	1	2	6
Gong 2018 (14)	3	2	2	7
Harries 2014 (15)	4	1	3	8
Irawan 2008 (16)	3	1	2	6
James 2003 (17)	3	1	2	6
Li 2015 (18)	4	1	2	7
Liede 2016 (19)	4	2	3	9
Mihai 2006 (20)	3	1	2	6
von Moos 2018 (21)	2	2	2	6
Valsecchi 2009 (22)	4	2	2	8
Xiong 2018 (23)	3	2	2	7
Yamashiro 2014 (24)	4	2	3	9
Yazdani 2019 (25)	2	2	2	6

Subtype

Four studies (12,18,23,24) evaluated the risk of BM in patients with different subtypes of BC. The results showed that the incidence of BM in patients with luminal A BC was not significantly different from that in patients with the following subtypes: luminal B (I^2=82.3%, OR =1.19, 95% CI: 0.81, 1.75, P=0.362), HER2 overexpression (I^2=91.8%, OR =0.85, 95% CI: 0.37, 1.96, P=0.703), and TNBC (I^2=89.9%, OR =0.64, 95% CI: 0.32, 1.29, P=0.212) (*Figure 6*).

Menopausal status

Nine studies (8,9,11,12,18,21,22,24,25) reported the effect of menopause on BM in BC patients. The results showed that the risk of BM in postmenopausal BC patients was not significantly different from that in premenopausal patients (I^2=68.4%, OR =1.07, 95% CI: 0.85, 1.35, P=0.994) (*Figure 7*).

Histological grade

Eight studies (8,9,12,15,17,19,23,24) reported the risk of BM in patients with different histological grades of BC. No significant difference was observed in the incidence of BM between patients with grade 2 (I^2=86.6%, OR =1.55, 95% CI: 0.99, 2.42, P=0.055) or grade 3 BC (I^2=91.0%, OR =1.43, 95% CI: 0.84, 2.45, P=0.190) and those with grade 1 BC (*Figure 8*).

Nodal metastasis

Twelve studies (8-12,15,17-19,23-25) compared the effect of nodal metastasis on the BM of BC. Chen *et al.* [2014] (9), Xiong *et al.* [2018] (23), Yamashiro *et al.* [2014] (24), and Yazdani *et al.* [2019] (25) reported the N stage. The results showed that the risk of BM in patients with lymph node metastasis was higher than that in patients with no lymph node metastasis, and the difference was statistically significant (I^2=99.7%, OR =2.60, 95% CI: 1.41, 4.80,

Table 3 Summary of the results of the meta-analysis and the evaluation of publication bias for the included indicators

Indicator	Comparison	Amount	Heterogeneity test		Effect model	OR (95%)	P	Begg's test	
			I^2	P				Z	P
ER	Positive *vs.* negative	8	77.4%	<0.001	R	1.23 (0.93, 1.62)	0.140	1.11	0.266
PR	Positive *vs.* negative	7	45.9%	0.085	F	0.80 (0.72, 0.88)	<0.001	1.20	0.230
HR	Positive *vs.* negative	5	87.7%	<0.001	R	1.39 (0.90, 2.16)	0.142	–0.24	1.000
HER2	Positive *vs.* negative	10	77.6%	<0.001	R	1.35 (1.04, 1.76)	0.025	0.54	0.592
Subtype	Luminal B *vs.* luminal A	4	82.3%	0.001	R	1.19 (0.81, 1.75)	0.362	–0.34	1.000
	HER2 overexpression *vs.* luminal A	4	91.8%	<0.001	R	0.85 (0.37, 1.96)	0.703	0.34	0.734
	TNBC *vs.* luminal A	4	89.9%	<0.001	R	0.64 (0.32, 1.29)	0.212	0.34	1.000
Menopausal status	Post- *vs.* pre-	9	68.4%	0.001	R	1.07 (0.85, 1.35)	0.994	–0.83	0.730
Histological grade	Grade 2 *vs.* grade 1	8	86.6%	<0.001	R	1.55 (0.99, 2.42)	0.055	–0.12	1.000
	Grade 3 *vs.* grade 1	8	91.0%	<0.001	R	1.43 (0.84, 2.45)	0.190	0.62	0.536
Nodal metastasis	Metastasis yes *vs.* no	12	99.7%	<0.001	R	2.60 (1.41, 4.80)	0.002	–1.51	1.440
	Metastatic nodes ≥3 *vs.* <3	5	94.3%	<0.001	R	1.57 (0.90, 2.75)	0.113	0.73	0.462
T stage	T2 *vs.* T1	5	96.8%	<0.001	R	1.99 (1.03, 3.83)	0.040	–0.24	1.000
	T3 *vs.* T1	4	95.6%	<0.001	R	4.74 (1.94, 11.57)	0.001	–0.34	1.000
	T4 *vs.* T1	3	95.4%	<0.001	R	14.57 (4.16, 51.05)	<0.001	NA	NA
	T3/T4 *vs.* T1	1	NA	NA	NA	1.29 (0.80, 2.07)	0.30	NA	NA
Histological type	Lobular *vs.* ductal	6	93.6%	<0.001	R	1.33 (0.89, 1.97)	0.16	0.38	0.707
	Others *vs.* ductal	4	56.4%	0.076	R	1.26 (1.09, 1.45)	0.001	0.34	0.734

ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; TNBC, triple-negative breast cancer.

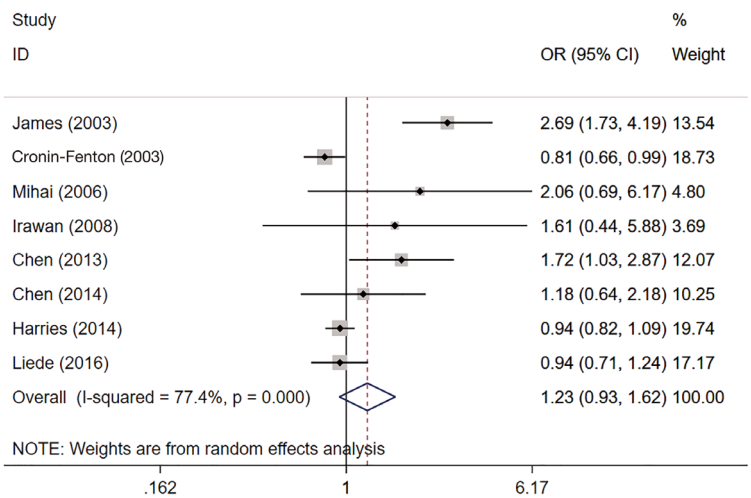

Figure 2 Effect of ER status on bone metastasis of breast cancer. ER, estrogen receptor.

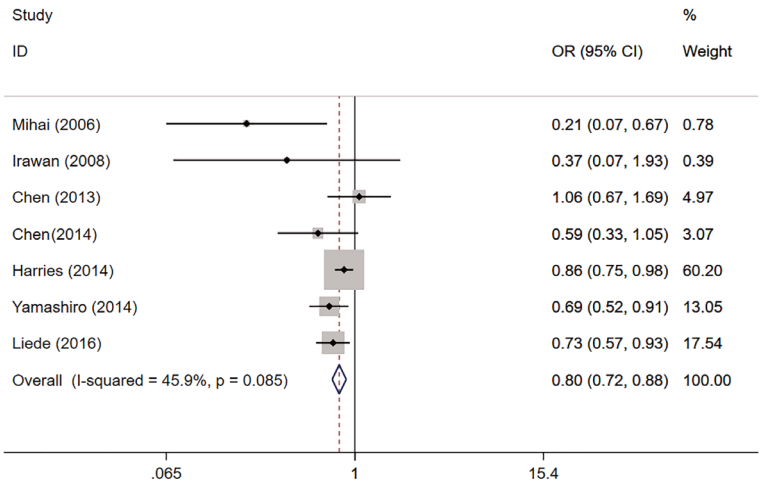

Figure 3 Effect of PR status on bone metastasis of breast cancer. PR, progesterone receptor.

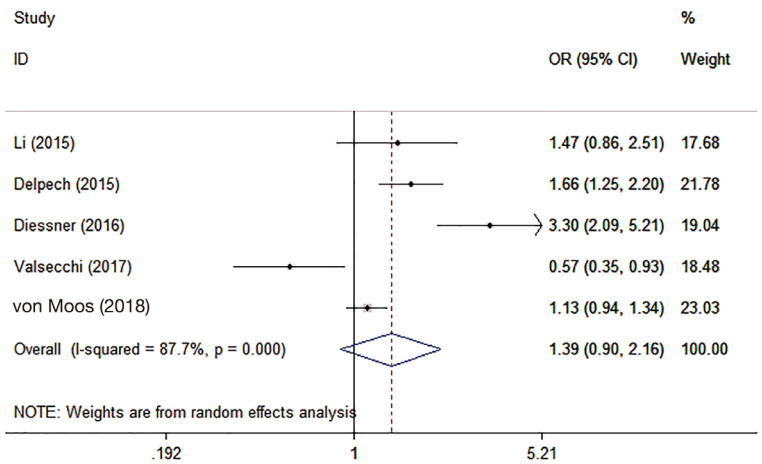

Figure 4 Effect of HR status on bone metastasis of breast cancer. HR, hormone receptor.

P=0.002) (*Figure 9*).

Five studies (8,10,12,15,17) evaluated the effect of the number of metastatic lymph nodes on the BM of BC. The results showed that there was no significant difference between patients with ≥3 and <3 metastatic lymph nodes (I^2=94.3%, OR =1.57, 95% CI: 0.90, 2.75, P=0.113) (*Figure 10*).

Tumor size

Seven studies (15,17-19,22,24,25) reported the effect of tumor size on BM in BC patients (*Table 4*). The subjects in 6 studies (15,18,19,22,24,25) were all stage I–IV BC patients. The results suggest that the larger the tumor is, the higher the risk of BM. Since the parameters used to stratify the tumor sizes in each study were different, the data were not combined. James *et al.* showed that BC patients with tumor metastasis with tumors ≥1.5 cm had a lower probability of BM than patients with tumors <1.5 cm (17).

T stage

Five studies (1,9,12,23,24) reported the risk of BM in BC patients with different T stages (*Figure 11*). The results showed that the higher the T stage, the higher the risk of BM. Data from 5 studies (7,9,11,23,24) showed that the risk of BM in stage T2 BC patients was 1.99 times that of patients with stage T1 BC (I^2=96.8%, OR =1.99, 95% CI: 1.03, 3.83,

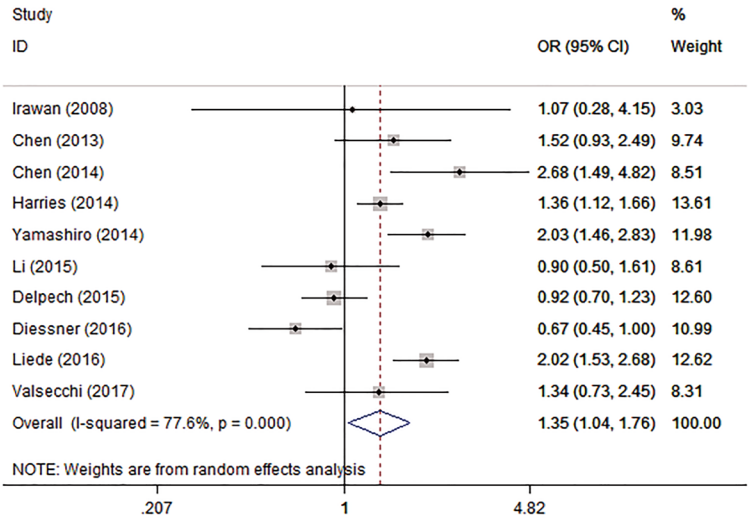

Figure 5 Effect of HER2 on bone metastasis of breast cancer. HER2, human epidermal growth factor receptor-2.

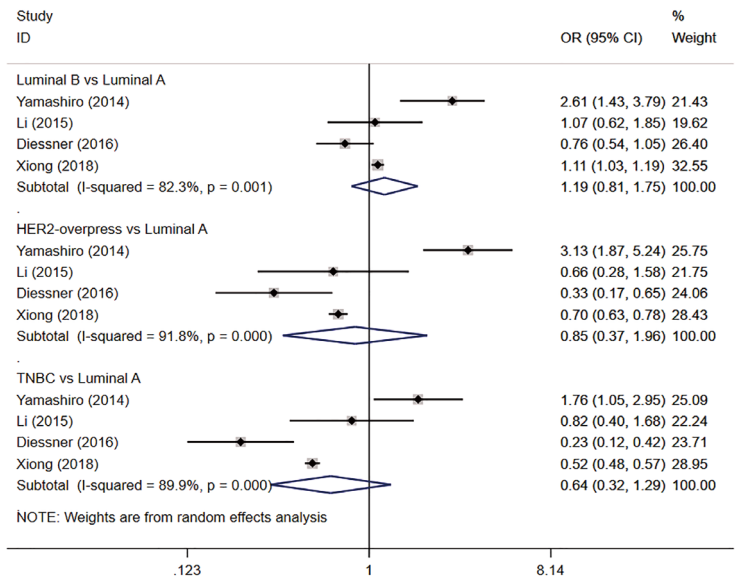

Figure 6 Meta-analysis of bone metastasis risk in patients with different subtypes of breast cancer.

P=0.040). The data from 4 studies (9,11,23,24) showed that the risk of BM of stage T3 BC patients was 4.74 times that of stage T1 BC patients (I^2=95.6%, OR =4.74, 95% CI: 1.94, 11.57, P=0.001). The combined data of 3 studies (9,23,24) showed that the risk of BM in stage T4 BC patients was 14.57 times that of stage T1 BC patients (I^2=95.4%, OR =14.57, 95% CI: 4.16, 51.05, P<0.001). One (12) study reported that the BM rate of stage T3/T4 BC patients was not significantly different from that of stage T1 BC patients (OR =1.29, 95% CI: 0.80, 2.07, P=0.30).

Histological type

Six studies (10,11,14-17) compared the risk of BM in patients with BC of different histological types (*Figure 12*). The meta-analysis results of 6 studies (10,11,14-17) showed that the incidence of BM in lobular BC patients was not significantly different from that in ductal BC patients (I^2=93.6%, OR =1.33, 95% CI: 0.89,

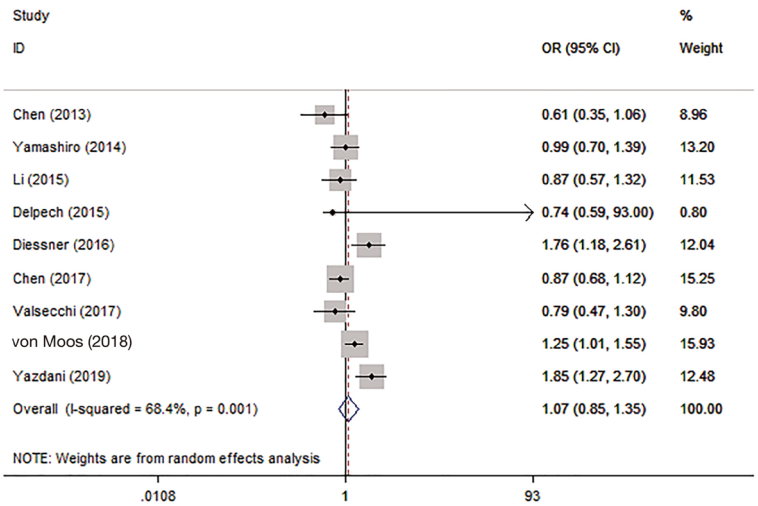

Figure 7 Effect of menopause on bone metastasis of breast cancer.

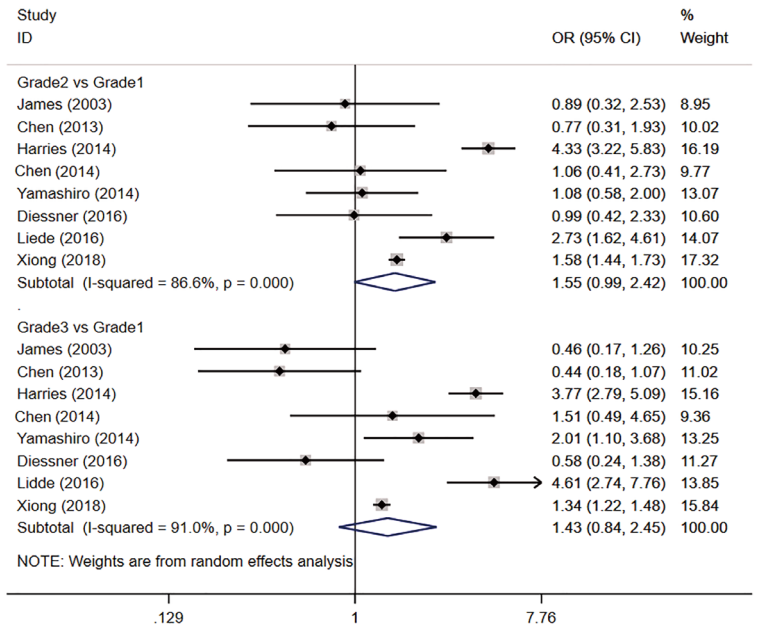

Figure 8 Effect of histological grade on bone metastasis of breast cancer.

1.97, P=0.16). Four studies (11,14,15,17) showed that the incidence of BM in non-lobular and non-ductal BC patients was higher than that in patients with ductal or lobular BC, and the difference was statistically significant (I^2=56.4%, OR =1.26, 95% CI: 1.09, 1.45, P=0.001).

Sensitivity analysis

In this study, the heterogeneity of PR was small (I^2=45.9%, P=0.085), and the heterogeneity of other indicators was large (I^2>50%, P<0.05). After the sensitivity analysis using the elimination method, the I^2 value and the scale of combined effect did not change significantly, indicating that the research results are robust.

Publication bias

In this paper, we conducted Begg's test on the indexes with

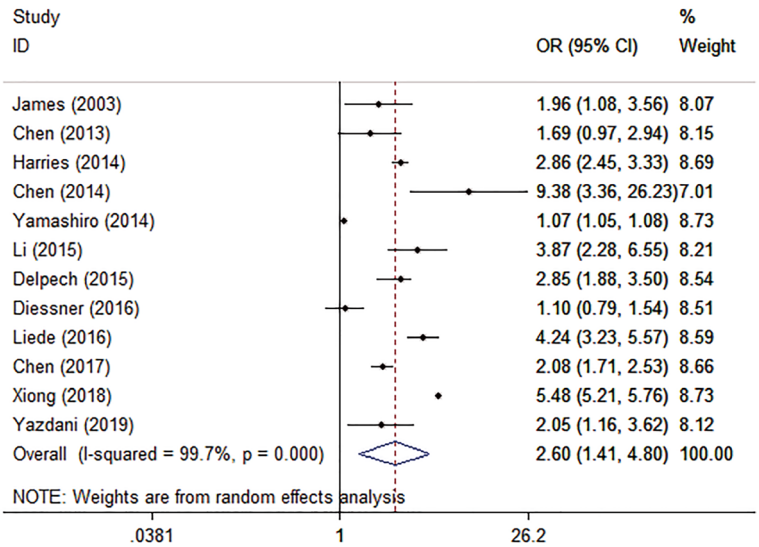

Figure 9 Effect of nodal metastasis on bone metastasis of breast cancer.

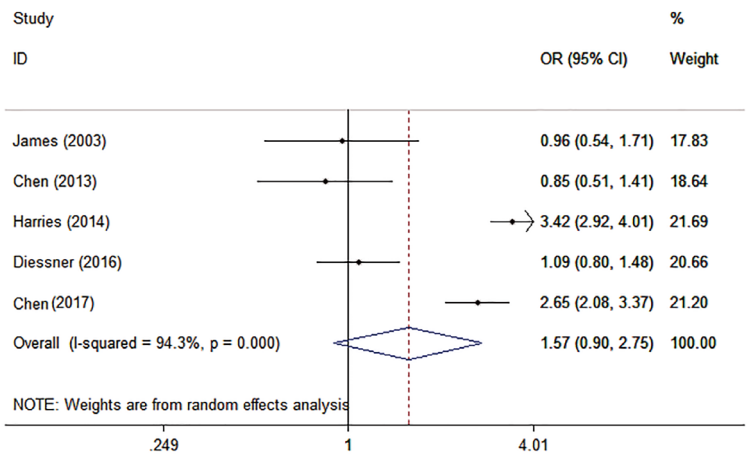

Figure 10 Effect of metastatic lymph nodes ≥3 on bone metastasis of breast cancer.

more than 4 included studies, and the results showed no obvious publication bias (*Table 3*).

Discussion

HR

The breast is a target organ of sex hormones. Under normal circumstances, estrogen and androgen receptors exist in breast tissue. The expression of ERs and androgen receptors is reduced or completely disappears when breast epithelial cancer occurs (17,26). In patients with the expression of estrogen and androgen receptors in breast tissue, endocrine therapy is effective, suggesting that these tumors are regulated by the endocrine system (27). In this study, ER-positive and/or PR-positive patients were considered to be HR-positive. The results showed that the risk of BM was relatively higher in HR-positive BC patients. Further analysis showed that the risk of BM was higher in ER-positive BC patients and lower in PR-positive BC patients, which suggests that the PR may be a protective factor against BM in BC patients. The risk of BM may be higher in BC patients who are positive for ER and negative for PR,

Table 4 Effect of tumor size on bone metastasis in breast cancer patients.

Variables (all breast cancer)	Study	OR (95% CI)
For every 1 cm increase	Yamashiro 2014	1.28 (1.202, 1.368)
<2 cm		1
2–5 cm	Li 2015	1.69 (1.08, 2.64)
	Harries 2014	2.25 (2.00, 2.53)
	Yazdani 2019	2.00 (0.93, 4.32)
	Subtotal	2.20 (1.90, 2.47)
>5 cm	Li 2015	3.59 (1.94, 6.66)
	Harries 2014	2.88 (2.46, 3.37)
	Yazdani 2019	4.01 (1.75, 9.17)
	Subtotal	2.95 (2.54, 3.43)
>2 cm	Valsecchi 2019	2.88 (1.35, 6.13)
≤1 cm		1
1.1–2 cm	Liede 2016	2.01 (1.28, 3.14)
2.1–5 cm	Liede 2016	5.17 (3.42, 7.83)
>5 cm	Liede 2016	6.84 (3.71, 12.60)
Metastatic breast cancer		
<1.5 cm		1
1.5–3 cm	James 2003	0.67 (0.48, 0.75)
>3 cm	James 2003	0.73 (0.50, 1.07)

OR, odds ratio; CI, confidence interval.

which is similar to the conclusions drawn by Wei *et al.* (28).

HER2 expression

HER2 participates in the regulation of cell growth, proliferation, and differentiation. The HER2 gene, also known as the c-erbB-2 gene, is located on chromosome 17q21 and has intracellular tyrosine kinase activity. It is a commonly used gene marker for BC because of its frequent changes after tumor occurrence. Approximately 20–25% of BC cells overexpress HER2 (29) (HER2-positive BC). Compared with other types of BC, HER2-positive BC has distinct clinical characteristics (30), such as a higher risk of recurrence and metastasis and insensitivity to chemotherapeutic drugs (31). Some researchers believe that HER2 overexpression (c-erbB-2 positive) is more useful than HR expression and tumor size for the prognostic evaluation of BC patients, and has a certain correlation with nodal metastasis (32). Ten studies were included in this analysis. The results showed that BC patients with HER2 expression had a relatively higher risk of BM.

Subtype

According to the expression of PR, ER, and HER2, the subtypes of BC can be divided into luminal A, luminal B, HER2, and TBNC. Until now, there have been few studies evaluating the risk of BM in patients with different subtypes of BC, and the results were inconclusive. Yamashiro *et al.* (24) showed that patients with luminal A BC had the lowest risk of BM, and the risk was significantly lower than that in patients with the other 3 subtypes of BC. In the study by Diessner *et al.* (12), the highest incidence of BM was in patients with luminal A BC (32.7%). Research data from Xiong *et al.* (23) showed that the risk of BM in patients with luminal B BC was higher

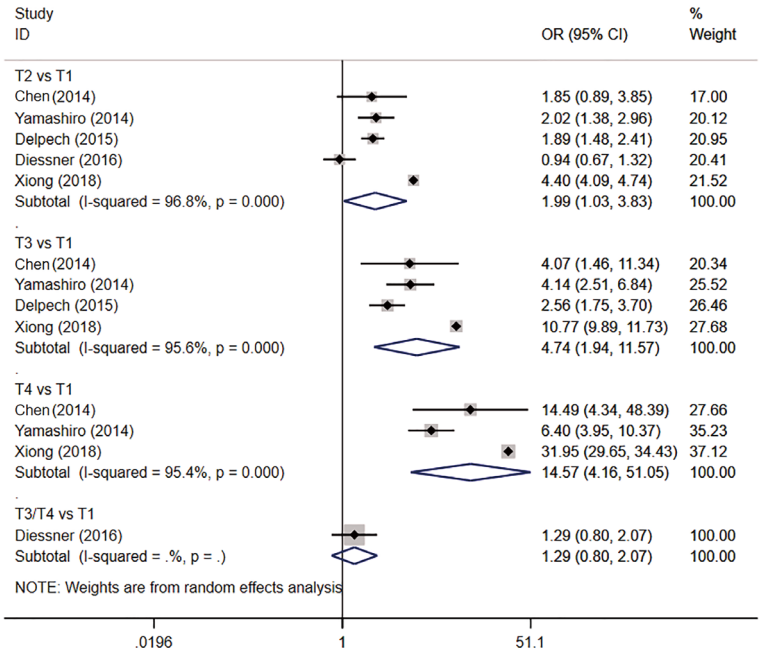

Figure 11 Effect of T stage on bone metastasis of breast cancer.

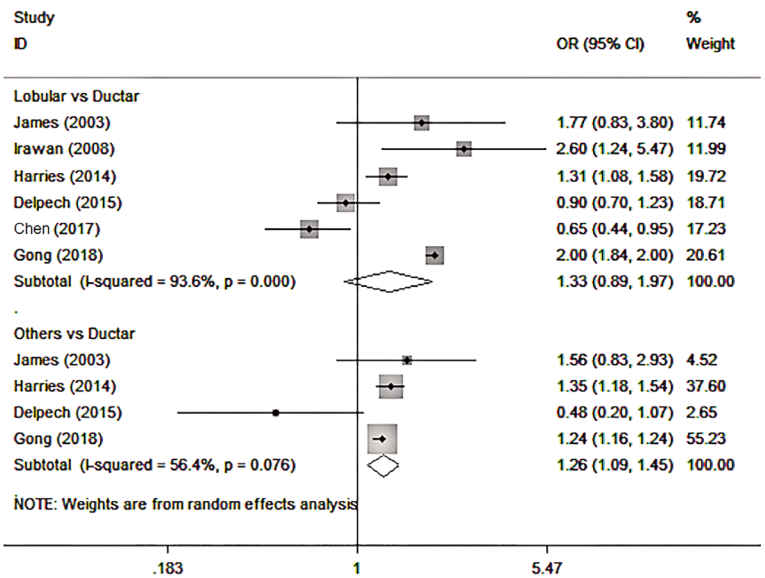

Figure 12 Effect of histological type on bone metastasis of breast cancer.

than that in patients with luminal A BC. The risk of BM in patients with HER2 BC and TNBC was lower than that in patients with luminal A. Li *et al.* showed that there was no difference in the risk of BM among the above 4 subtypes of BC (18). Ossovskaya *et al.* found that TNBC was characterized by early bone and visceral metastases (33). The results of this study showed that there were no differences among the 4 reports included in this meta-analysis, and it cannot be confirmed whether subtypes have an effect on the BM of BC.

Menopausal status

The menopausal status of women is an important factor affecting sex hormone levels and blood calcium levels. Bisphosphate has a good therapeutic effect on postmenopausal BC patients, suggesting that menopausal status is directly related to disease progression and the therapeutic effect in BC patients (34). The results of this study showed that the relationship between menopausal status and BM of BC was not significant, which may be due to the close relationship between the menopausal status and factors such as age and sex hormone levels, and the combined effect of multiple factors is unclear (35).

Histological grade

The histological grade of BC reflects the invasive ability of the tumor cells. The histological grade of BC is related to recurrence, metastasis, and prognosis (36). In this paper, data on the tumor grade from 8 studies were included in the meta-analysis. The results showed that the incidence of BM in patients with grade 2 and grade 3 cancer were not significantly different from that in patients with grade 1 cancer. Reports from Harries *et al.* (15), Liede *et al.* (19), and Xiong *et al.* (23) found that the incidence rates of BM in patients with grade 2 and grade 3 cancer were significantly higher than in patients with grade 1 cancer, while other studies showed no significant differences. This suggests that histological grade is not suitable for evaluating the risk of BM in BC.

Nodal metastasis

Axillary nodal metastasis is closely related to local recurrence, recurrence time, and distant metastasis in BC patients. The metastatic routes of BC are mainly lymphatic metastasis, blood flow metastasis, and direct invasion. Tumor cells can enter the blood circulation directly or through the lymphatic route to transfer to the lung, bone, and liver. Approximately 50–75% of the lymph is drained through the axillary lymph duct, which is why BC patients are relatively more prone to axillary nodal metastasis. In addition, the inhibition of cancer cells by regional lymph nodes depends on the immune function of the body and the number and invasiveness of cancer cells. Nodal metastasis reflects the immune function of the body to a certain extent, so if the number of axillary nodal metastases increases, the chance of distant metastasis of BC increases. A retrospective analysis showed that the incidence of BM in patients with metastatic lymph nodes was significantly higher than that in patients with no lymph node metastasis within 5 years after surgery (37). Rosa *et al.* (38) defined the number of lymph node metastases as an indicator, and the number of metastases that was predictive of early bone and visceral metastasis was 1–3. Han *et al.* (39) found that the number of lymph nodes had good predictive value for postoperative recurrence and metastasis after balancing the tumor size and HR expression. The International BC Study Group (IBCSG) (40) reported that when the number of axillary nodal metastases was ≥4, 12.2% had bone metastases within the first 2 years after the operation, and 26.8% had bone metastases within 10 years after the operation. The results of this study showed that the risk of BM in BC patients with lymph node metastasis was 3.65 times higher than that in patients without lymph node metastasis. There was no significant difference in the incidence of BM between BC patients with ≥3 metastatic lymph nodes and those with 0–2 metastatic lymph nodes. This suggests that the occurrence of nodal metastasis is a risk factor for BM in BC patients and the cutoff value of ≥3 is suitable for evaluating the prognosis of BC patients, but not for evaluating the risk of BM.

Tumor size

Tumor size is an independent risk factor for the prognosis of BC patients (41,42), and patients with larger tumors are more prone to relapse and metastasis. The reason is that tumor growth is accompanied by the formation of new blood vessels, and these new blood vessels often lack complete basement membranes, form arteriovenous anastomosis or blind ends, and are distorted in shape. Their capillary permeability is also higher than that of normal vessels. Brown *et al.* suggested that this mechanism may be involved in BM (43). Whether the tumor diameter exceeds 2 cm is one of the parameters considered in the diagnosis and treatment of BC (44). In this study, the criteria for stratification and statistical methods in the 3 reports on tumor size evaluation were different. Yamashiro *et al.* (24) showed that the larger the tumor was, the higher the risk of BM, based on continuous data analysis. Li *et al.* (18) and Harries *et al.* (15) divided the tumor size into 3 levels using the cutoffs of 2 and 5 cm. The results showed that the risk of BM in patients with a tumor diameter of 2–5 cm was higher than that in patients with a tumor diameter less than 2 cm, and the risk of BM was higher in patients

with a tumor diameter above 5 cm. Liede *et al.* (19) further stratified the patients by tumor diameter and found that the risk of BM was higher in patients with tumor diameters of 1.1–2 cm than in patients with diameters ≤1 cm, while the risk of BM was higher in patients with diameters of 2.1–5 and ≥5 cm. James *et al.* (17) showed that in stage IV BC patients, the larger the tumor diameter was, the lower the incidence of BM. The prognosis of BC patients with bone metastases is generally better than that of patients with metastases of other organs. This result suggests that tumor size has good predictive value for the prognosis of BC patients and is suitable for the prediction of BM in patients with stage I to stage III BC. The predictive value may be reduced in patients with stage IV BC.

T stage

In TNM staging of BC, T stage is classified mainly based on tumor size. Among them, T0 is tumor-free, a tumor diameter of ≤2 cm is classified as T1, a tumor diameter of 2–5 cm is classified as T2, a tumor diameter of >5 cm is classified as T3, and the T4 tumor directly affects the chest and/or the skin, regardless of the size of the tumor. Compared with tumor size, T4 increases the ability of T stage to judge the clinical invasion of BC (45). The results of the meta-analysis of 5 studies included in this study showed that the risks of bone metastases in patients with stages T2, T3, and T4 BC were 1.99 times, 4.74 times, and 14.57 times that of stage T1 BC patients, respectively. At the same time, it also suggests that the higher the T stage is, the higher the risk of BM. Compared with tumor size, T stage is more useful for predicting the BM of BC.

Pathological types

The pathological types of BC include invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), mixed carcinoma, mucinous carcinoma, and papillary carcinoma, among which IDC and ILC account for the majority. Some studies have found that the proportion of ILC patients positive for ER and PR was higher than the proportion of IDC patients positive for ER and PR. Fewer patients with ILC than with IDC were positive for HER2, and the tumor volume was larger in ILC patients than in IDC patients (46). Therefore, it is generally believed that BM is relatively more common in ILC patients. In this meta-analysis, 6 studies compared the incidence of BM in patients with ILC and IDC. The results showed that there was no significant difference. However, 4 studies compared the risk of BM in BC patients with pathological types other than ILC and IDC (such as mixed type, mucinous cancer, and papillary cancer) and found that the risk was higher than in patients with IDC.

Research limitations

This study has the following limitations: (I) although 18 articles were included in this study, only HER2 and lymph node metastasis were analyzed in ≥10 studies, thereby increasing the heterogeneity, and Begg's rank correlation test results indicated the presence of bias. (II) The original data were reported as the number and OR (HR). After the data conversion process, the meta-analysis was performed with OR and 95% CI. The conversion of some data (such as tumor size) could have produced errors. (III) For comparisons among multiple sets of data, considering the small number of included studies, this study adopted the subgroup analysis method, i.e., performed a comparative analysis with the same control group. However, a meta-analysis was not performed, and comprehensive comparisons were not made. (IV) Given the large fluctuations in serological indicators and the small sample size for the genetic factors, serological indicators and genetic factors associated with BM from BC were not included in this study. (V) The inclusion criteria of this study were commonly used to evaluate the risk of distant metastasis in BC patients. At present, there were few studies on specific biomarkers of BM, which is not enough for systematic evaluation. BC is prone to BM, but the prognosis of patients with BM is better than that of patients with lung metastasis and brain metastasis. Therefore, the index screening for the recurrence, metastasis, and prognosis of BC patients is different from the evaluation of BM. The indicators included in this study have mostly been confirmed to have a strong relationship with the prognosis of BC patients. However, the meta-analysis results showed that ER, HR, menopausal status, molecular type, and histological grade were not closely related to the occurrence of BM. PR-positive BC patients have a relatively lower risk of BM. Patients with HER2-positive, nonlobular, and nonductal BC with metastatic lymph nodes have a relatively higher risk of BM. Nodal metastasis can be regarded as a risk factor for BM in BC patients, and ≥3 metastatic lymph nodes was a suitable cutoff value for evaluating the prognosis of BC patients, but not for evaluating the risk of BM. With increasing T stage, the risk of BM in BC patients

also increases.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist http://dx.doi.org/10.21037/apm-21-438

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-438). 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.

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