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ORIGINAL RESEARCH

HOXB7 as a promising molecular marker for metastasis in cancers: a meta-analysis

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Abstract: Numerous studies on carcinoma have revealed that the expression level of *HOXB7* in cancerous tissues was significantly higher than that in noncancerous tissues. Elevated expression of *HOXB7* is associated with the susceptibility to lymph node metastasis and distant metastasis in various tumors. In this study, a meta-analysis was performed to involve majority of relevant articles and explore the association of *HOXB7* expression level with metastasis in cancer patients. Literature retrieval was conducted by searching in a number of electronic databases (up to December 1, 2015). The meta-analysis was conducted with RevMan 5.3 software and Stata SE12.0. A total of 1,532 patients with carcinoma from 14 studies were included in analysis. The results of meta-analysis demonstrated that lymph node metastasis was observed more frequently in the patients group with high expression level of *HOXB7* than in the patients group with low expression level of *HOXB7* (odds ratio =2.17, 95% CI: 1.74–2.71, $P<0.00001$, fixed-effects model). In addition, a similar result was observed in the association between *HOXB7* expression and distant metastasis; the odds ratio was 1.77 (95% CI: 1.09–2.88, $P=0.02$, fixed-effects model). This meta-analysis demonstrated that the overexpression of *HOXB7* was significantly associated with metastasis in cancer patients, which may be served as a common molecular marker for indicating cancer metastasis.

Keywords: homeobox gene, *HOXB7*, carcinoma, metastasis, meta-analysis

Introduction

Nowadays, cancer is a leading cause of mortality. According to a recent survey, 8.2 million people die from cancer each year and 14.1 million new cases were diagnosed with cancer worldwide.[1] A majority of the cancer cases can ultimately develop metastases, which included lymph node metastases (LNM) and distant metastases (DM). The occurrence of metastasis was a critical indicator for survival, which indicated poor prognosis in most cancers.[2,3] In addition, the treatment measures were also determined by whether there was metastasis or not. Until now, the precise mechanism on metastasis in cancer cells is still unclear. In recent years, molecular biomarkers, as a hotspot in cancer research, have raised a revolution in the prediction and treatment of cancer.[4–6] Until now, we still know nothing about the role of *HOXB7* in predicting metastases of various cancers, although it may act as a common molecular marker for both LNM and DM.

HOX genes belong to an important component of superfamily of homeobox genes. A large family of transcriptional factors were encoded, and the expression of many downstream target genes was regulated by *HOX* genes.[7,8] Human *HOX* genes can be divided into two classes. In class I, there were four paralogous clusters of *HOX* genes, and they were defined as *HOXA*, *HOXB*, *HOXC*, and *HOXD*, which were arranged in 2, 12, 17, and 7 chromosomes in turn.[9–11] Many studies have reported that *HOX* genes

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were frequently deregulated in cancers, which could widely make effects on cellular functions, including proliferation, differentiation, and apoptosis.[12–15] *HOX* genes were also involved in tumor initiation and progression.[16,17]

HOXB7, as one of class I *HOX* genes, was found to participate in the process of various cancers, such as gastric cancer, breast cancer (BC), and pancreatic carcinoma.[18–20] Some studies revealed that *HOXB7* played a crucial role in tumorigenesis and was closely related to the viability, invasion, and metastasis of tumor cells.[21,22] A number of studies have demonstrated that the expression level of *HOXB7* was upregulated in cancerous tissues and was associated with some clinical features, including LNM and DM.[23–25] Therefore, in this study, we collected relevant literatures and performed the meta-analysis. It aimed to explore the relationship between the *HOXB7* expression and metastasis and further determine whether *HOXB7* could be applied as a putative biomarker for indicating metastasis in cancer patients.

Methods

Literatures' retrieval strategy

For obtaining potentially eligible studies, integrated online literature retrieval was performed against multiple databases, including PubMed, Springer, Google Scholar, China National Knowledge Infrastructure (CNKI), Chongqing VIP Information Network, and Wanfang. The deadline of retrieval period was up to December 1, 2015. The keywords for the search were as follows: "Homeobox B7", "HOXB7", "cancer", "carcinoma", and "neoplasm". In addition, other relevant articles were also obtained by manually viewing the reference list.

Inclusion and exclusion criteria

Inclusion criteria for the articles were as follows: 1) the role of *HOXB7* in the development of human cancer was investigated; 2) related clinicopathologic parameters were described; 3) the expression level of *HOXB7* in primary cancerous tissue was measured; and 4) patients were grouped according to the expression level of *HOXB7*.

Exclusion criteria for the articles were as follows: 1) duplicate publications; 2) studies without valuable data; and 3) reviews, letters, case reports, and expert opinions.

Date extraction

The data and information from all eligible studies were independently extracted by two investigators (YX O and GP Z). The following data and information were collected from each study: author, publication year, country, race, cancer type, total number of patients, number of high *HOXB7* expression group and low *HOXB7* expression group, number of patients with LNM and DM in each group, and the criteria of high *HOXB7* expression. If there were disagreements, a consensus was reached by a third investigator (CQ).

Statistical methods

The present meta-analysis was conducted using RevMan5.3 software and Stata SE12.0. The heterogeneity among eligible studies was determined with the chi-square-based Q-test and I^2 statistics; a P-value for Q-test <0.05 and I^2-value $>50\%$ were considered severe heterogeneity. The random-effects model was applied in studies with a significant heterogeneity ($P_Q \leq 0.05$, $I^2 \geq 50\%$); otherwise, the fixed-effects model was adopted ($P_Q > 0.05$, $I^2 < 50\%$). Potential publication bias was assessed with a funnel plot, and sensitivity analysis was also performed to ensure the reliability of results. The P-value <0.05 was considered statistically significant.

Result

Studies' characteristics

The process of literature retrieval is shown in detail in Figure 1. A total of 14 studies were finally identified to be eligible according to the criteria for selection.[23–36] A total of 1,532 patients were included in the current meta-analysis, and the mean sample size of patients was 109.4 (range: 35–280). Among the 14 studies, 12 were from the People's Republic of China, two were from Brazil, and one was from the USA. Eight different cancer types were evaluated in this meta-analysis, with two BC, three esophagus cancer, one gastric cancer, one lung cancer, two pancreatic cancer, two colorectal cancer, two oral cancer, and one malignant ovarian germ cell tumor. All cancerous specimens were well preserved before RNA extraction. The diagnoses of LNM and DM were all based on pathology.

There were two studies that reported on the association between the expression of *HOXB7* mRNA and LNM,[23,29] and the rest 12 articles have paid attention on the association of *HOXB7* protein expression and metastases. Two detection methods (reverse transcription polymerase chain reaction and immunohistochemical staining) were applied to determine the expression levels of *HOXB7* in cancerous tissues. The criteria of high *HOXB7* expression in all included studies are shown in Table 1. All studies were divided into two groups (high *HOXB7* expression group and low *HOXB7* expression group). For unifying the result for further analysis, positive expression of *HOXB7* was regarded as high expression and negative expression of *HOXB7* was classified into low expression group.

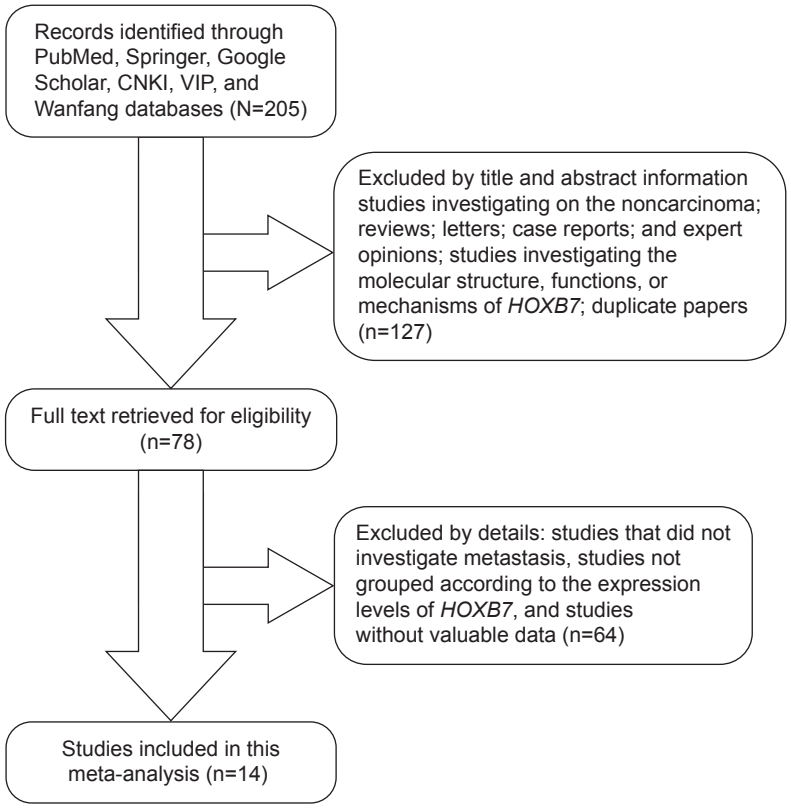

Figure 1 A flowchart presenting the steps of literature retrieval and selection.
Abbreviations: CKNI, China National Knowledge Infrastructure; VIP, Chongqing VIP Information Network.

Association between HOXB7 expression level and LNM

All 14 studies provided the number of patients with LNM based on different *HOXB7* expression levels in a total of 1,532 patients. The fixed-effects model was adopted as there was limited heterogeneity across studies (I^2=0%, P_Q=0.59). The odds ratio (OR), expressed as high *HOXB7* expression group versus low *HOXB7* expression group, was 2.17 (95% CI: 1.74–2.71, $P<0.00001$; Figure 2). In the subgroup analysis, the result showed that there was a significant association between the expression level of *HOXB7* mRNA and LNM (OR =2.22, 95% CI: 1.26–3.91, P=0.006). For the association between the expression level of *HOXB7* protein and LNM, the OR, expressed as high *HOXB7* protein expression group versus low *HOXB7* protein expression group, was 2.16 (95% CI: 1.70–2.76, $P<0.00001$). From the analysis results, when the LNM incidence of cancers was compared between the two groups, we found that there was a significant difference in the LNM incidence between the high and low expression groups. This result demonstrated that cancer patients determined with high *HOXB7* expression (including mRNA and protein) in cancerous tissues were more prone to developing LNM.

Association between HOXB7 expression level and DM

Five studies reported the number of patients with DM based on different *HOXB7* protein expression levels in a total of 544 patients. There was no significant heterogeneity among the studies (I^2=15%, P_Q=0.32); thus, the fixed-effects model was adopted. Analysis showed a pooled OR =1.77 (95% CI: 1.09–2.88, P=0.02; Figure 3). Compared with the low *HOXB7* expression group, the DM rate was significantly increased in the high *HOXB7* expression group. The result showed that patients with high *HOXB7* protein expression level in tumor tissues may indicate an increased risk of developing DM.

In addition, sensitivity analysis and assessment of publication bias were not performed due to the relatively small heterogeneity across studies in distant metastasis and limited number of included studies.

Publication bias

For meta-analysis of the association between *HOXB7* expression level and LNM, the funnel plot was slightly asymmetrical (Figure 4), and then, the trim and fill method was applied to test for publication bias. The results showed that there was no significant publication bias across these studies.

Table 1 The basic information and data of all included studies in the meta-analysis

Author (year)	Country	Race	Cancer type	Total number	HOXB7 expression						Detection method	High expression
					High LNM	High DM	High	Low LNM	Low DM	Low		
Zhu et al[23] (2015)	People's Republic of China	Asian	BC	48	18	–	33	3	–	15	RT-PCR	HOTAIR/GAPDH ≥1.0
Li et al[24] (2015)	People's Republic of China	Asian	EC	280	81	–	185	26	–	95	IHC	Positive cells >25%
Tu et al[25] (2015)	People's Republic of China	Asian	GC	96	47	4	66	16	1	30	IHC	Sum of the intensity and extent scores ≥2
Yuan et al[26] (2014)	People's Republic of China	Asian	LC	75	36	3	57	5	2	18	IHC	Sum of the intensity and extent scores ≥3
Long et al[27] (2014)	People's Republic of China	Asian	EC	76	26	3	41	21	3	35	IHC	Sum of the intensity and extent scores ≥2
Zhang et al[28] (2014)	People's Republic of China	Asian	PC	44	17	–	29	3	–	15	IHC	Sum of the intensity and extent scores ≥2
Xie et al[29] (2013)	People's Republic of China	Asian	EC	179	63	–	115	25	–	64	RT-PCR	Above the cutoff value (0.25)
Nguyen et al[30] (2013)	USA	Caucasian	PC	145	35	–	55	41	–	90	IHC	Histoscore >110
Wang et al[31] (2013)	People's Republic of China	Asian	CC	73	21	11	47	9	1	26	IHC	Sum of the intensity and extent scores ≥2
Bitu et al[32] (2012)	Brazil	Mixed	OC	115	31	–	55	20	–	60	IHC	Positive cells ≥31%
Liao et al[33] (2011)	People's Republic of China	Asian	CRC	224	59	46	121	38	26	103	IHC	Intensity score ≥2 with positive cells ≥50%
De Souza Setubal Destro et al[34] (2010)	Brazil	Mixed	OC	35	14	–	19	7	–	16	IHC	Positive cells >38.2%
Ding[35] (2010)	People's Republic of China	Asian	MOGC	85	3	–	24	0	–	61	IHC	Product of the intensity and extent scores ≥8
Chen et al[36] (2009)	People's Republic of China	Asian	BC	57	25	–	41	5	–	16	IHC	Sum of the intensity and extent scores ≥3

Note: The dashes represent no data.

Abbreviations: BC, breast cancer; CC, colon cancer; CRC, colorectal cancer; DM, distant metastases; EC, esophagus cancer; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GC, gastric cancer; IHC, immunohistochemistry; LC, lung cancer; LNM, lymph node metastases; MOGC, malignant ovarian germ cell tumor; OC, oral cancer; PC, pancreatic cancer; RT-PCR, reverse transcription polymerase chain reaction.

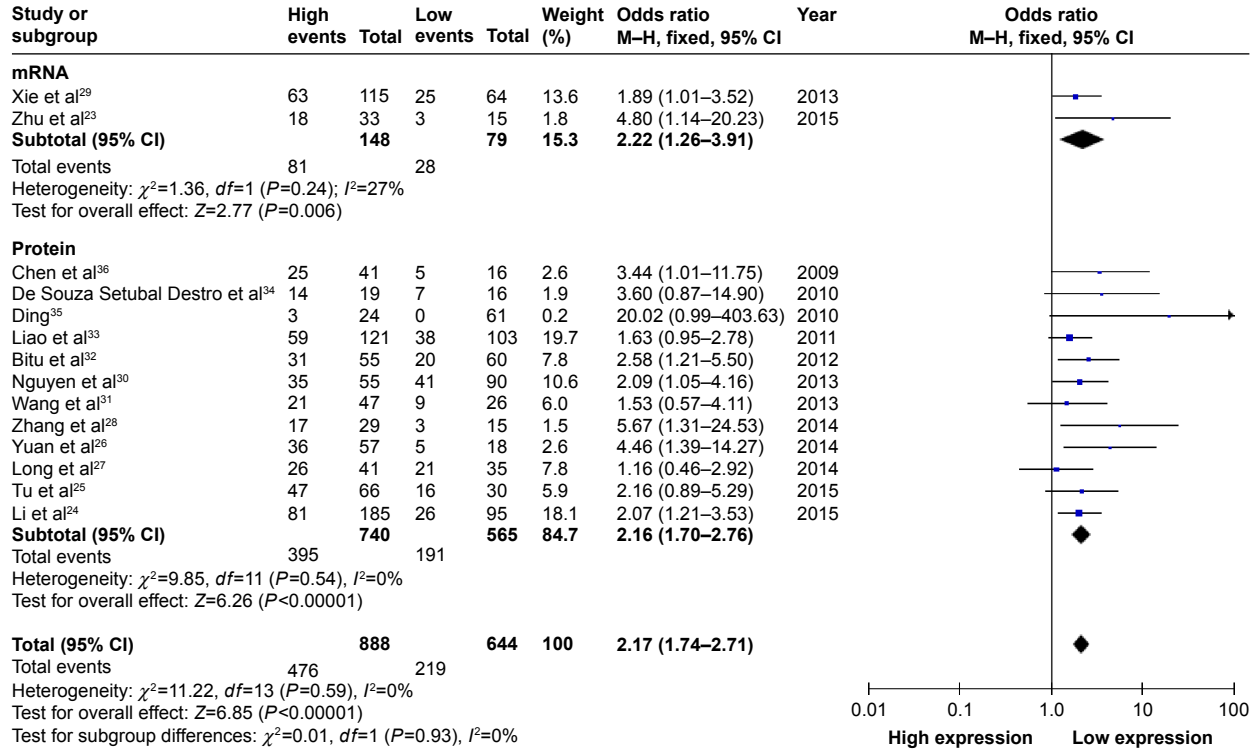

Figure 2 A forest plot for the association between HOXB7 expression levels with LNM.
Abbreviations: *df*, degrees of freedom; LNM, lymph node metastases; M–H, Mantel–Haenszel test.

Sensitivity analysis

For meta-analysis of the association between *HOXB7* expression level and LNM, sensitivity analysis was performed by deleting each study in turn from the pooled analysis. It aimed to test the influence of the removed data set on the overall ORs. The result was not significantly influenced by the exclusion of each study, suggesting that the result of synthetic analysis was robust.

Discussion

As we all know, cancer is a severe threat to human health, and there are millions of people who die from cancer every year. The LNM is the most common metastasis pathway in most cancers, and distant metastasis often occurs in the later stages of cancer. LNM and DM are positively significant for diagnosis in tumor–node–metastasis staging and treatment for cancer patients, as well as are important indicators for predicting prognosis. Thereby, further discovery of new molecular markers to predict metastasis for cancer is still essential and full of clinical significance.

A growing number of researches have showed that the expression of *HOXB7* was higher in cancerous tissues compared with paired noncancerous tissues. There were associations between *HOXB7* expression and certain clinical

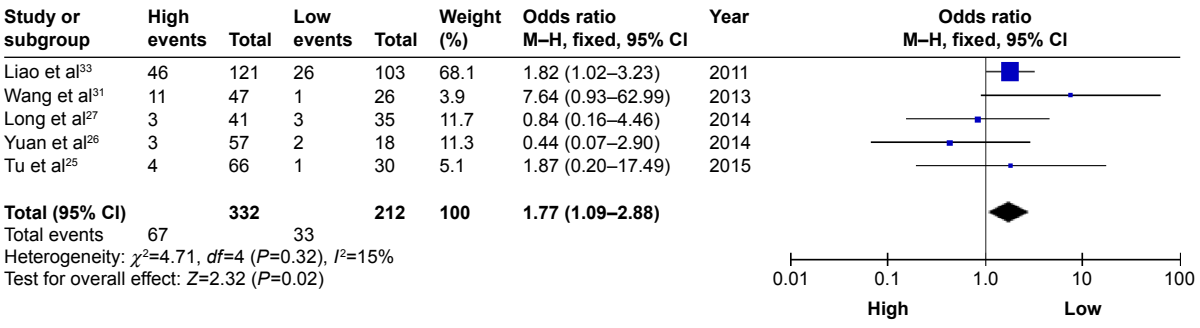

Figure 3 A forest plot for the association between *HOXB7* expression levels with DM.
Abbreviations: *df*, degrees of freedom; DM, distant metastases; M–H, Mantel–Haenszel test.

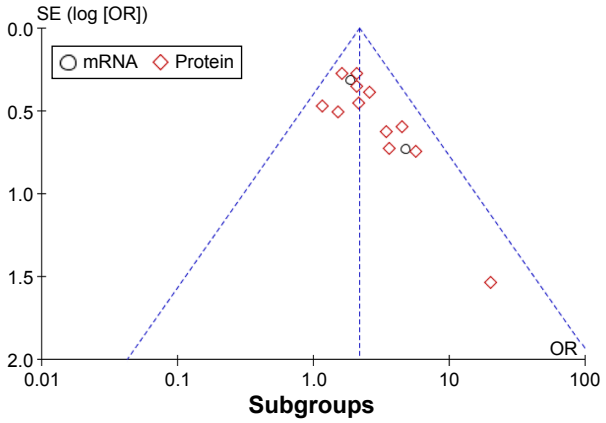

Figure 4 A funnel plot analysis of potential publication bias.
Abbreviations: SE, standard error; OR, odds ratio.

characteristics of cancer patients. The patients with high expression levels of *HOXB7* had an increased risk of metastasis as well as a poor overall survival.[26–28] Furthermore, the overexpression of *HOXB7* was closely related to the aggressive behavior of tumor cells. However, the exact mechanism of how *HOXB7* makes effects on promoting tumor cell invasion and metastasis has not been clear and is still in research stage. Wu et al[37] found that tumor invasion in BC could be promoted by *HOXB7* through Ras/Rho pathway activation after upregulating basic fibroblast growth factor (bFGF), which was a known transcriptional target of *HOXB7*. In the malignant melanoma, it has demonstrated that miR-196a was a central regulator of *HOXB7* expression, which played an important role in melanoma progression.[38] Recently, a study by Liu et al[39] showed that the migration and invasion of BC cells may be increased by overexpression of *HOXB7*, and this result could be reversed by knockdown of transforming growth factor (TGF)β2 or pharmacologic inhibition of TGFβ signaling. It suggested that *HOXB7* may make effects on promoting tumor malignant progression through the activation of TGFβ signaling pathway.[42–44] *HOXB7* was also found to promote the migration and metastasis in lung adenocarcinoma through activation of the TGFβ/SMAD3 signaling.[40] Chile et al[41] reported that *HOXB7* was also involved in cell proliferation and viability. Cell cycle arrest and apoptosis could be induced by the knockdown of *HOXB7* in pancreatic ductal adenocarcinomas, while decreased protein level could significantly lead to the increased apoptosis rate. *HOXB7* may be a promising target for future cancer therapies.

Conclusion

This meta-analysis has explored the relation between *HOXB7* expression levels with LNM and DM for carcinoma. From the results of this current meta-analysis, we found that the occurrence probability of LNM and DM was higher in cancer patients with high *HOXB7* expression, comparing with that of those with low *HOXB7* expression. Nevertheless, we also found that there were some limitations in this meta-analysis. Firstly, the included number of cancer patients has been still relatively small, hence larger and better design studies would be necessary to confirm the obtained results. Besides, most patients included in this meta-analysis have been Asian, the patients of other races accounted for a small percentage. Additionally, potential publication bias may exist, although no significant publication bias was observed based on trim and fill method and the sensitivity analysis have also showed the results were robust. Furthermore, the criterion of high *HOXB7* expression was varied in these studies. Therefore, more larger size, multicenter, and higher quality studies are needed for further research, based on a unified criterion for classifying *HOXB7* expression groups.

Author contributions

H-L Luo and P-Q Zhu were involved in the design of this meta-analysis and revision of this manuscript; they have also given final approval for submission. Y-X Ou, G-P Zhang, and C Qiu were involved in publication collection. F-T Liu was involved in data analysis of the study and manuscript writing. He has also assisted in the design of this work. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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