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REVIEW

Prognostic value of endocan expression in cancers: evidence from meta-analysis

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Abstract: Endocan is a 50 kDa dermatan sulfate proteoglycan. Numerous previous studies have indicated that endocan might be an attractive prognostic tumor biomarker. However, the results of different studies are inconsistent. We conducted a meta-analysis to explore the association between endocan expression and cancer prognosis. A systematic, comprehensive search of the PubMed, Embase, and China National Knowledge Infrastructure databases was performed. Expression of endocan and its association with overall survival were evaluated by pooled hazard ratios (HRs) and their 95% confidence intervals (CIs). In total, 15 eligible studies of 1,464 patients were finally included in this meta-analysis. A significant association was found between elevated endocan expression and poorer overall survival (pooled HR: 2.48, 95% CI: 2.12–2.90, $P<0.001$). In the cancer-type subgroup, significant associations were detected for gastrointestinal (HR: 2.27, 95% CI: 1.77–2.91, $P<0.001$) and hepatocellular (HR: 2.61, 95% CI: 1.96–3.48, $P<0.001$) carcinoma. Our results demonstrate that endocan could be useful to exploit as a novel prognostic biomarker for patients with cancer.

Keywords: endocan, ESM-1, biomarker, cancer, prognosis, meta-analysis

Introduction

Endocan, previously called endothelial cell-specific molecule-1, was first cloned by Lassalle et al in 1996 from a human umbilical vein endothelial cell complementary DNA library.[1] It is a 50 kDa dermatan sulfate proteoglycan, and is secreted by activated vascular endothelial cells, including tumor endothelial cells.[2–4] Endocan can be upregulated by angiogenic factors and inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β.[1,2] In previous studies, endocan was found to induce tumor formation and to be closely associated with the conversion of dormant tumors into fast-growing angiogenic tumors.[5,6] Recent studies have shown that endocan is overexpressed at the messenger RNA and/or protein levels in various tumor types, including glioblastoma,[7] pituitary adenoma,[8,9] nonsmall cell lung cancer,[10] gastric cancer,[11–14] colorectal cancer,[15–17] renal cell cancer,[2,18] bladder cancer,[19] ovarian cancer,[20] and hepatocellular carcinoma.[21–23] Most studies also suggested that endocan overexpression was associated with aggressive tumor progression and poor outcomes.[7,11,13–17,20,21,23,24] However, conflicting results still exist.[12,19,22] Therefore, we conducted a meta-analysis of the available studies to investigate the relationship between endocan expression and prognosis of patients with cancer.

Materials and methods

Search and selection process

A systematic literature search was conducted of the PubMed, Embase, and China National Knowledge Infrastructure databases, covering all relevant studies published

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up to September 22, 2015, using the following keywords: "endocan" OR "ESM-1" AND "prognosis" OR "survival" OR "outcome" AND "cancer" OR "carcinoma" OR "neoplasm." The reference lists of the relevant publications were also carefully reviewed to obtain additional information.

Inclusion and exclusion criteria

To be eligible for inclusion, studies had to meet the following criteria: (a) published as a full paper in the English or Chinese literature; (b) investigated the association between endocan expression and cancer prognosis; and (c) included sufficient data for estimating hazard ratio (HR) with 95% confidence interval (CI). The major reasons for exclusion of studies were: (a) overlapping or duplicate data; (b) publication was either an abstract, comment, or review; and (c) without detailed data. The flow diagram for the study is shown in Figure 1.

Data extraction and quality assessment

Two reviewers (XH and XW) performed the search and identification independently using a standard approach.[25] The following items were extracted from each eligible publication: first author, year of publication, nationality, ethnicity (Asian or Caucasian), cancer type, quantitative method (enzyme-linked immunosorbent assay or immunohistochemistry), cutoff value, length of follow-up (months), HR with corresponding 95% CI for overall survival (OS) or recurrence-free survival (RFS), and total number of participants. In cases of discrepancy, another investigator (B-HR) was invited to check and discuss the original data until a consensus was reached. Quality assessment for each study included in the final analysis was carried out by the same two reviewers (XH and XW) according to the Newcastle–Ottawa quality assessment scale (NOS).[26] The Newcastle–Ottawa scores range from 0 to 9, and a score of ≥6 indicated good quality in the present study.

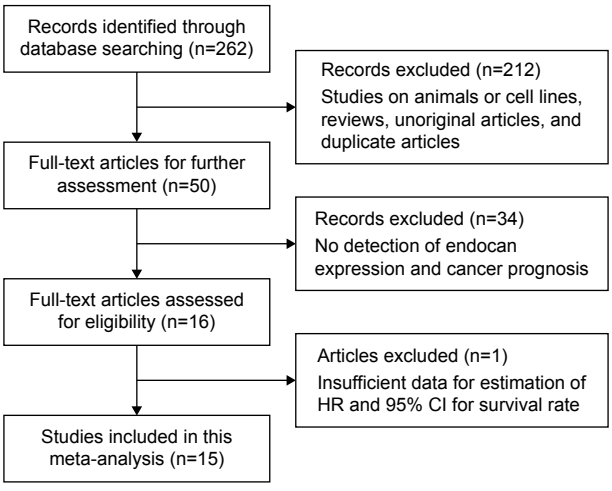

Figure 1 Study flow chart showing the process for selecting eligible publications.

Statistical analysis

HR with 95% CI was calculated for the association between endocan expression and cancer prognosis (OS and RFS). When the statistical variables were reported in the text or tables, we obtained them directly. Otherwise, the methods reported by Tierney[27] were used to calculate data from Kaplan–Meier survival curves. Heterogeneity between studies was checked using the χ^2-based Q-test and considered statistically significant at $I^2>50\%$ or $P<0.1$. The Mantel–Haenszel fixed-effects model was used if there was no significant heterogeneity; otherwise, the Der Simonian and Laird random effects model was utilized.[28] Subgroup analyses and logistic metaregression analyses were conducted to explore the source of heterogeneity between variables, such as cancer type, ethnicity, quantitative method, sample size, and study quality. Sensitivity analysis was carried out to identify the effect of data from each study on the pooled HRs. Publication bias was determined by Egger's test and Begg's funnel plots.[29] All statistical tests were conducted with STATA software version 12.0 (STATA Corporation, College Station, TX, USA), and $P<0.05$ was considered significant.

Results

Study characteristics

In total, 262 potentially relevant studies were identified after the initial database searches. After a rough review of the titles and abstracts of all studies, 212 studies were excluded, then, with a systematical review of the full texts, another 34 studies were excluded (Figure 1). After further screening, one article was excluded because of insufficient data.[10] Moreover, one study[22] included two different survival analyses separately. Therefore, 15 eligible studies of 1,464 patients were finally included in this meta-analysis.[7,11–17,19–24]

The main characteristics of the included studies are summarized in Tables 1 and 2. Of the 15 studies, 10 (1,157 patients: 79.0%) were performed in Asia,[11–17,21,23,24] and the remaining five studies (307 patients: 21.0%) were conducted in Europe and America.[7,19,20,22] All of these studies were retrospective in design. The malignant neoplasms assessed in these studies were colorectal cancer,[15–17] gastric cancer,[11–14] hepatocellular carcinoma,[21–23] nasopharyngeal carcinoma,[24] bladder cancer,[19] ovarian cancer,[20] and glioblastoma.[7] Enzyme-linked immunosorbent assay was used in eight studies,[7,12,13,15,17,21,22] and immunohistochemistry was used in the remaining six studies.[11,14,16,19,20,23,24]

Table 1 Main characteristics of studies included in the meta-analysis

Authors	Publication year	Case nationality	Dominant ethnicity	Sample size	Mean age	Malignant disease	Survival analysis	Source of HR	Follow-up months	NOS score
Jiang et al[15]	2015	People's Republic of China	Asian	89	NA	Colorectal cancer	OS	Reported	NA	7
Zhao et al[11]	2014	People's Republic of China	Asian	255	NA	Gastric cancer	OS	Reported	300	7
Sun et al[12]	2014	People's Republic of China	Asian	102	59	Gastric cancer	OS	SC	NA	5
Ozaki et al[21]	2014	Japan	Asian	64	71	Hepatocellular Carcinoma	OS	Reported	109	8
Lv et al[13]	2014	People's Republic of China	Asian	114	NA	Gastric cancer	OS	Reported	84	8
Yu et al[24]	2013	People's Republic of China	Asian	41	47.3	Nasopharyngeal carcinoma	OS	Reported	NA	5
Roudnicky et al[19]	2013	Switzerland	Caucasian	40	NA	Bladder cancer	RFS	SC	NA	4
Nault1 et al[22]	2013	France	Caucasian	58	NA	Early hepatocellular carcinoma	OS/RFS	SC	30	7
Nault2 et al[22]	2013	France	Caucasian	67	NA	Advanced hepatocellular carcinoma	OS	Reported	13.6	7
El Behery et al[20]	2013	Egypt	Caucasian	100	50.1	Ovarian cancer	OS	Reported	36	8
Kim et al[16]	2012	Korea	Asian	143	NA	Colon carcinoma	OS/RFS	Reported	80.7	9
Liu et al[14]	2010	People's Republic of China	Asian	159	57.2	Gastric cancer	OS	Reported	111	7
Ji et al[17]	2010	Korea	Asian	100	NA	Colorectal cancer	OS	Reported	NA	6
Maurage et al[7]	2009	USA	Caucasian	42	NA	Glioblastomas	OS	SC	NA	5
Huang et al[23]	2009	People's Republic of China	Asian	90	51	Hepatocellular carcinoma	OS	Reported	50	8

Abbreviations: NA, not available; NOS, Newcastle–Ottawa; OS, overall survival; RFS, recurrence-free survival; SC, survival curve.

Meta-analysis

Endocan expression and OS

Fourteen studies with a total of 1,424 patients provided survival results in the form of OS. As the heterogeneity was not statistically significant (I^2=25.80%, P=0.176), the fixed-effects model was used to pool HRs. The result revealed that high endocan expression predicts poor OS in various carcinomas, with a pooled HR of 2.48 (95% CI: 2.12–2.90, $P<0.001$) (Figure 2).

To determine the prognostic role of endocan in different cancers, studies were divided into subgroups by cancer types. The results indicated that high endocan expression

Table 2 HRs and 95% CIs for patient survival (OS) in association with endocan expression in enrolled studies

Authors	Publication year	Detecting method	Cutoff value	Case number		HR (95% CI)	
				High expression	Low expression	OS	RFS
Jiang et al[15]	2015	ELISA	68.4 pg/mL	45	44	4.09 (2.27–10.88) M	NA
Zhao et al[14]	2014	IHC	1%	64	191	1.719 (1.103–3.028) M	NA
Sun et al[12]	2014	ELISA	0.826 ng/mL	NA	NA	1.912 (0.991–3.688) U	NA
Ozaki et al[21]	2014	ELISA	2.20 ng/mL	48	16	2.36 (1.22–5.36) M	NA
Lv et al[13]	2014	ELISA	84.2 pg/mL	NA	NA	2.493 (1.065–6.021) M	NA
Yu et al[24]	2013	IHC	10%	21	20	3.140 (1.078–9.142) M	NA
Roudnicky et al[19]	2013	IHC	Score ≥2	12	28	NA	1.83 (0.70–4.74) U*
Nault1 et al[22]	2013	ELISA	5 ng/mL	23	35	1.74 (0.75–4.04) U*	2.17 (1.1–4.27) U*
Nault2 et al[22]	2013	ELISA	5 ng/mL	38	29	1.16 (0.48–2.79) M	NA
El Behery et al[20]	2013	IHC	Score ≥73.5	NA	NA	3.31 (2.10–4.35) M	NA
Kim et al[16]	2012	IHC	25%	76	67	3.531 (1.632–7.644) M	2.109 (1.196–3.716) M
Liu et al	2010	IHC	25%	92	67	1.88 (1.15–3.08) M	NA
Ji et al[17]	2010	ELISA	76 pg/mL	NA	NA	3.394 (1.285–8.963) M	NA
Maurage et al[7]	2009	ELISA	NA	15	27	1.68 (1.02–2.77) U*	NA
Huang et al[23]	2009	IHC	Score ≥73.5	NA	NA	3.31 (2.10–4.35) M	NA

Notes: The source of HR and 95% CI is described as derived from univariate analysis (U) or multivariate analysis (M). *HR and 95% CI calculated from survival curves.
Abbreviations: CI, confidence intervals; ELISA, enzyme-linked immunosorbent assay; HR, hazard ratio; IHC, immunohistochemistry; NA, not available; OS, overall survival; RFS, recurrence-free survival.

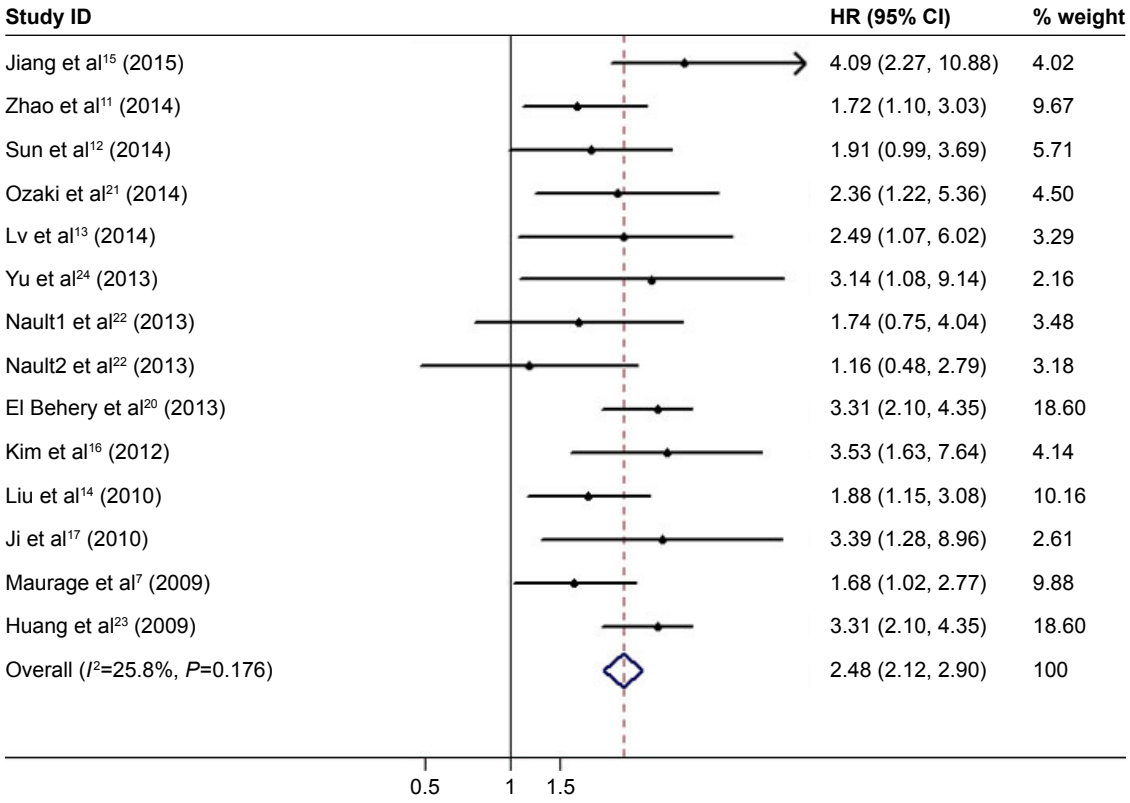

Figure 2 Forest plot of HRs for the association between high endocan expression and OS in patients with malignant tumors.
Abbreviations: HRs, hazard ratios; OS, overall survival.

was an unfavorable prognostic indicator in both gastrointestinal (HR: 2.27, 95% CI: 1.77–2.91, $P<0.001$) and hepatocellular (HR: 2.61, 95% CI: 1.96–3.48, $P<0.001$) carcinoma (Figure 3).

Subgroup analyses by ethnicity revealed that endocan was a negative predictor of OS for both Asian (HR: 2.56, 95% CI: 2.11–3.11, $P<0.001$) and Caucasian (HR: 1.99, 95% CI: 1.22–3.26, $P=0.006$) populations. When considering differences in sample type, high endocan level was a poor prognostic marker for sera (HR: 2.08, 95% CI: 1.61–2.70, $P<0.001$) and tissue (HR: 2.74, 95% CI: 2.25–3.34, $P<0.001$). In addition, subgroup analyses showed that an elevated endocan level predicted poor prognosis, regardless of sample size and the study quality (Table 3).

Endocan expression and RFS

Three studies[16,19,22] were used for RFS analysis with a fixed-effects model ($I^2=0.00\%$, $P=0.958$). Our results indicated that elevated endocan predicted a worse outcome for RFS, with a combined HR of 2.08 (95% CI: 1.40–3.09, $P<0.001$). Subgroup analysis, metaregression analysis, and sensitivity analysis were not applicable because of the limited number of studies.

Sensitivity analysis

We adopted the "leave-one-out" scheme (ie, analysis is conducted using all studies but one) to explore the influence of individual studies on the pooled HRs. The results showed that the pooled HRs were not materially altered, which suggested that no individual study significantly affected the pooled results (Figure 4).

Publication bias

Begg's funnel plot and the Egger's linear regression test were conducted to evaluate the publication bias of the literature. In the pooled analyses of OS and RFS, the Egger's test P-values were 0.466 and 0.372, respectively, as shown by symmetric funnel plots (Figure 5). Therefore, no evidence of publication bias was noted.

Discussion

Endocan is a soluble dermatan sulfate (DS) proteoglycan, which is secreted by the vascular endothelium and freely circulates in the bloodstream.[1] Accumulating evidence shows that endocan is related to the regulation of major processes such as cell adhesion, inflammatory disorders, and tumor progression.[30–32] Inflammatory cytokines, such

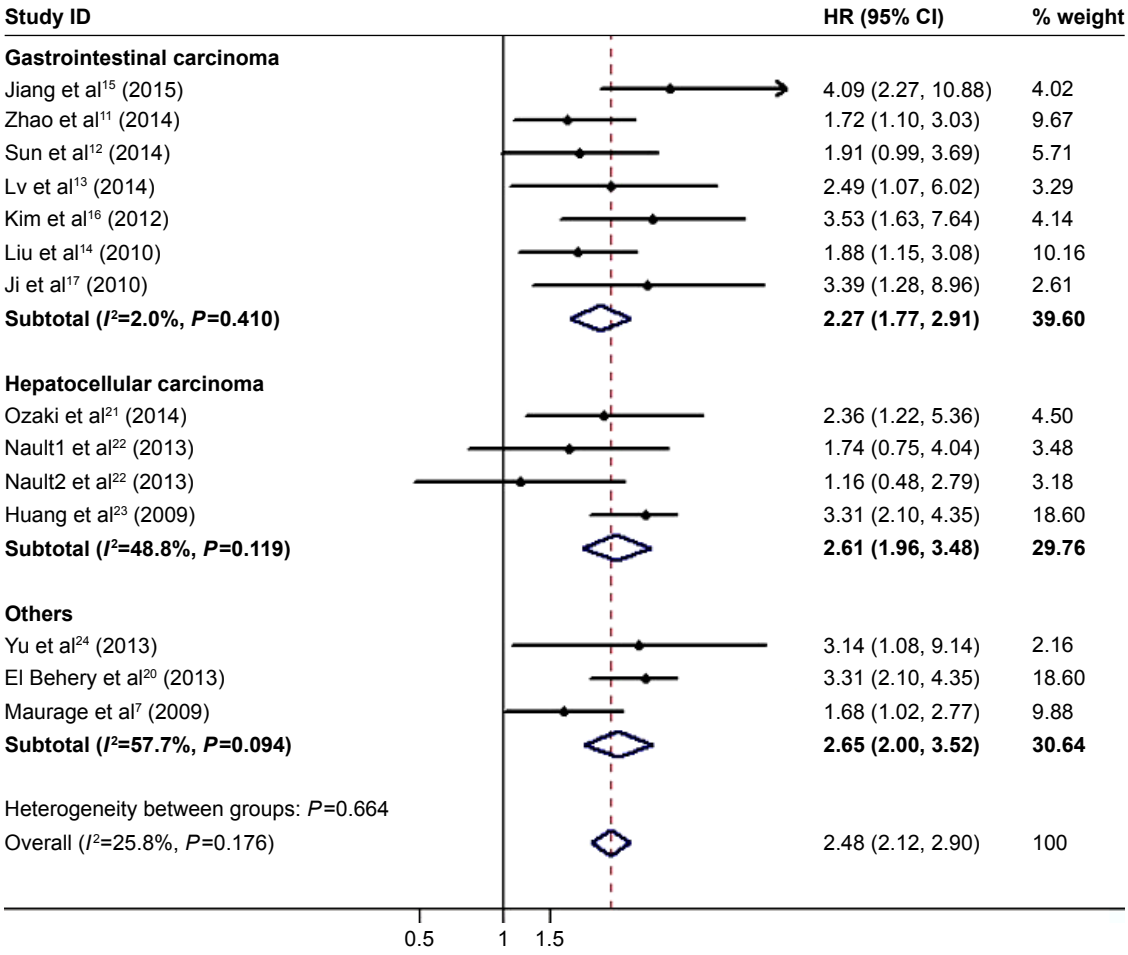

Figure 3 Meta-analysis (forest plot) of the evaluable studies assessing endocan expression and OS, stratified by cancer type.
Abbreviation: OS, overall survival.

Table 3 Main results of meta-analysis

Categories	Studies	Patients	HRs	95% CI	Heterogeneity		*P*-value
					I^2 (%)	P_h	
Overall	14	1,424	2.48	2.12–2.90	25.80	0.176	<0.001
Cancer type							
Gastrointestinal carcinoma	7	962	2.27	1.77–2.91	2.00	0.41	<0.001
Hepatocellular carcinoma	4	279	2.61	1.96–3.48	48.80	0.119	<0.001
Others	3	183	2.54	1.53–4.20	57.70	0.094	<0.001
Ethnicity							
Asian	10	1,157	2.56	2.11–3.11	1.40	0.426	<0.001
Caucasian	4	267	1.99	1.22–3.26	62.90	0.044	0.006
Sample type							
Sera	8	636	2.08	1.61–2.70	0.00	0.456	<0.001
Tissue	6	788	2.74	2.25–3.34	38.00	0.153	<0.001
Sample size							
Large	7	973	2.47	2.00–3.06	19.60	0.28	<0.001
Small	7	451	2.49	1.97–3.14	40.40	0.122	<0.001
Study quality							
High	11	1,239	2.63	2.21–3.13	28.40	0.175	<0.001
Low	3	185	1.89	1.30–2.74	0.00	0.582	0.001

Abbreviations: CI, confidence interval; HRs, hazard ratios; P_h, $P_{Heterogeneity}$.

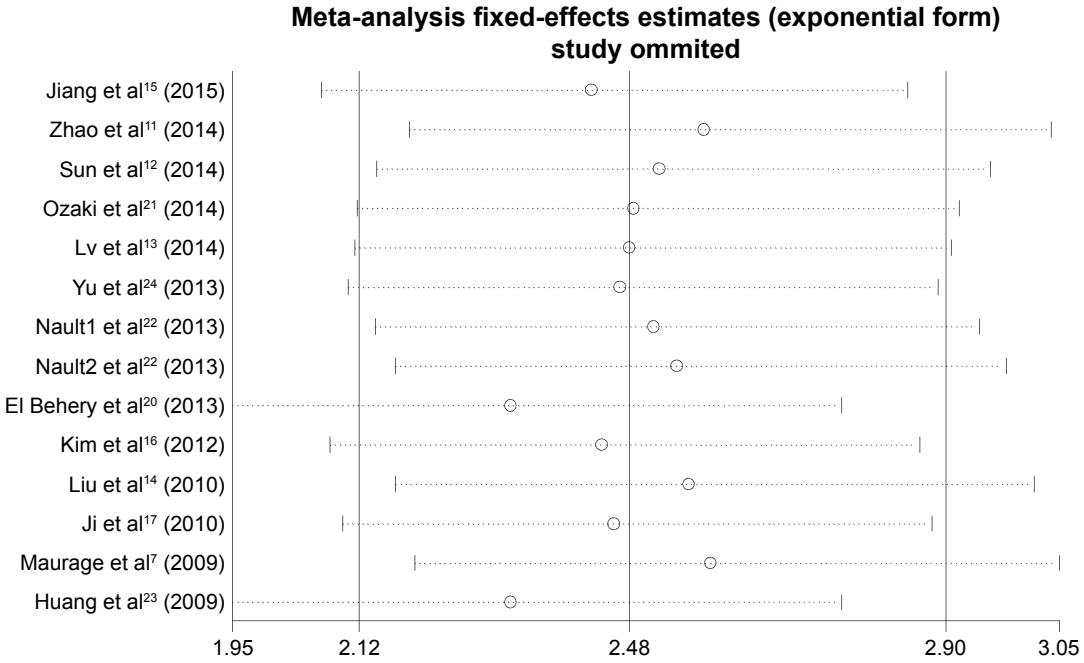

Figure 4 Sensitivity analysis for OS: effect of individual studies on pooled HRs for patients with cancer.
Abbreviations: HRs, hazard ratios; OS, overall survival.

as tumor necrosis factor-α and interleukin-1, strongly increase the expression and secretion of endocan.[1,4] Endocan also plays vital roles during angiogenesis.[33] The study by Shin et al[34] showed that endocan level is increased in endothelial cells treated with vascular endothelial growth factor-A, and that its expression can induce tumor formation. Moreover, treatment of cultured endothelial cells with anti-angiogenic drugs or multityrosine kinase inhibitors can abolish the vascular endothelial growth factor-induced secretion of endocan.[35] Furthermore, Béchard et al reported a possible feedback mechanism in which tumor epithelial cells secrete growth factors that stimulate endothelial cell proliferation and endocan secretion, then endocan further stimulates tumor cell proliferation and secretion of growth factors and also promotes the proliferation of blood vessels.[3] Based on these results, it would be of great interest to use endocan expression as a biomarker for the screening of patients susceptible to angiogenesis-targeted therapies and to explore the prognostic value of endocan in various types of cancer.[7,11–17,19–24,36] However, the results remain controversial for many conditions. The aim of the current study was therefore to evaluate the prognostic value of endocan. To the best of our knowledge, this is the first meta-analysis to evaluate the correlation between endocan overexpression and survival in various cancers.

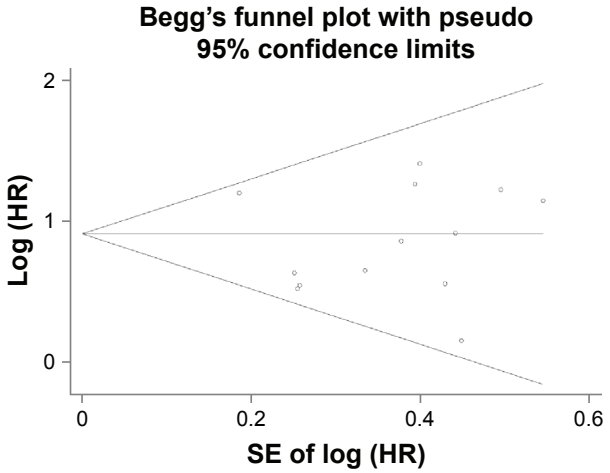

Figure 5 Begg's funnel plot of endocan expression and OS in patients with tumors.
Abbreviations: HR, hazard ratio; OS, overall survival; SE, standard error.

Meta-analysis is a useful tool to detect effects that may be missed by individual studies.[37] In the current meta-analysis, we combined 15 publications on 1,464 patients to yield statistics, indicating a statistically significant role of endocan in cancers. Combined HRs suggested that elevated endocan significantly predicts poor OS (HR: 2.48, 95% CI: 2.12–2.90, $P<0.001$) and RFS (HR: 2.08, 95% CI: 1.40–3.09, $P<0.001$) in patients with cancer. In addition, the significance of this association was not changed in a sensitivity analysis that removed individual studies. Subgroup analyses showed that the trend toward worse OS with higher endocan level was present in both Asian and Caucasian patients. We performed

subgroup analyses based on sample type, and found that patients with low endocan level had better OS compared with those with elevated endocan level, regardless of the sample type. Subgroup analysis stratified by sample size (ie, large or small) and study quality (ie, high or low) also revealed that endocan had a negative effect on OS.

To understand our findings better, some limitations should be considered. First, this meta-analysis was limited to articles published in English and Chinese and could not include studies that were not published because of negative or useless results. Second, our meta-analysis data did not include information on tumor stage, treatment, age, or physical condition, which might result in confounding bias. Third, immunohistochemistry was used as the detecting method in six studies, but it is a relatively complicated technique with many steps and is observer dependent. Fourth, some survival data were not presented directly, so we had to extract HR from survival curves in some enrolled studies,[7,19] and these HRs and 95% CIs might be less reliable than those given directly by the authors. Fifth, the applied methods for detecting endocan expression and the cutoff values were different in different studies, which could cause heterogeneity between the enrolled studies.

In conclusion, despite the limitations of the present study and heterogeneity across the included studies, our meta-analysis suggests that high endocan expression is negatively associated with prognosis of cancer. Future larger scale prospective and standard investigations should be conducted to confirm our results.

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Disclosure

The authors report no conflicts of interest in this work.

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