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Review Article

Decreased long non-coding RNA MEG3 expression is associated with survival outcome and lymph node metastasis: a meta-analysis

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Abstract: Abnormal expressions of long non-coding RNAs (lncRNAs) are observed in several cancers. The novel lncRNA maternally expressed gene 3 (MEG3) has been observed to widely express in multiple cancers, and accumulated evidence have confirmed its role of a tumor suppressor. However, the association between MEG3 expression and survival outcome/metastasis status remains controversial. Here we performed a meta-analysis including 11 studies of 911 patients by searching PubMed, Web of Science and Embase online databases. Hazard ratios (HRs) or odds ratios (ORs) and their 95% confidence intervals (CIs) for overall survival (OS)/relapse free survival (RFS[1])/recurrence free survival (RFS[2]) were adopted to evaluate the strength of the association. Our results revealed that cancer patients with high MEG3 expression had a long survival outcome. Besides, decreased MEG3 expression was negatively associated with lymph node metastasis (LNM) (HR=0.58, 95% CI: 0.37-0.90, P=0.018). Moreover, subgroup analysis found that lower MEG3 expression was related to shorter OS for patients with nondigestive system cancers (HR=0.41, 95% CI: 0.24-0.70, P<0.001) and digestive system cancers (HR=0.40, 95% CI: 0.26-0.61, P=0.001). The similar results were revealed in other subgroups, when divided by HR resource and sample size. In a word, our results statistically demonstrated that decreased MEG3 expression significantly predicted poorer survival/metastasis outcomes in patients with multiple cancers.

Keywords: lncRNAs, MEG3, prognosis, cancer

Introduction

When long non-coding RNAs (lncRNAs) were identified with extraordinary performances even though they were entitled with "dark mass" in biology history [1], the theory of "one gene, one protein" was demonstrated to be incorrect. Compared with 20,000 protein-coding genes, the quantity of non-coding genes occupied more than 98% of human genes [2]. LncRNAs are RNA polymerase II transcripts without protein-coding capacity and their length are exceeded 200 nucleotide. Their various kinds of different roles in gene transcription at the transcriptional, post-transcriptional and epigenetic levels have been highlighted [3-5], but the underlying mechanism for the function of lncRNAs has not been reported so far.

The burden of global cancer remains sharply increased, there are nearly 1,700,000 new cases and 600,000 deaths in the US in 2016 [6]. Carcinogenesis is a clinically and genetically diverse procedure, any tiny dysregulation arising during this system could trigger the start keys. Due to the differential expression between normal tissue and tumor, lncRNAs have been linked with cancers [7]. Recently, some lncRNAs have been associated with clinicopathological parameters. For instance, Wang et al. [8] revealed that H19 promoted cell invasion and EMT in gallbladder cancer (GBC) cells, and highly expressed H19 in GBC was significantly cor-

related with tumor size, lymph metastasis (LNM) and tumor status, which always hinted poorer outcome of patients with cancer.

At first, human lncRNA maternally expressed gene 3 (MEG3) was identified as the ortholog of gene trap locus2 (Gtl2) in mice. It located on chromosome 14q32, a region observed to contain putative tumor suppressors [9]. Decreased expression of MEG3 was widely identified in many types of cancer and it interacted with miRNAs as a competing endogenous RNA and participated in regulating the signal pathways during carcinogenesis [10]. Cao et al. [11] have demonstrated a strong association between MEG3 polymorphisms and high risk of colorectal cancer in Chinese. In addition, a series of articles have reported that expression of MEG3 might be associated with the clinical outcomes of patients with cancer [12-14].

Here we conducted a meta-analysis to statistically evaluate the performance of MEG3 to exam whether it could be a potential biomarker to predict the prognosis in a variety of cancers.

Material and methods

Search strategy

We searched online databases including PubMed, Web of Science and Embase before December 29, 2016, using "long non-coding RNA MEG3" or "lncRNA MRG3" or "MEG3" or "maternally expressed gene 3" as key words. At the same time, the potential relevant reviews and references were manually searched to ensure the statistical integrity.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) study searched on patients with cancer; (2) none of patients received radiotherapy or chemotherapy treatment before operation; (3) evaluated MEG3 expression by quantitative real-time polymerase chain reaction (qRT-PCR) using $2^{-\Delta\Delta Ct}$ method or other measurement techniques; (4) the cut-off value of MEG3 expression was given definitely; (5) assessed the relationship between MEG3 expression and overall survival (OS)/relapse free survival (RFS1)/recurrence free survival (RFS2) or LNM of patients with cancer. The following were excluded: (1) reviews, letters, comments, case reports or laboratory articles; (2) duplicated publications; (3) articles published in languages other than English.

Data extraction and quality assessment

Ying Wang and Rongwei Li extracted data individually from the finally included articles. The first author's name, publication year, country, cancer type, sample size, MEG3 expression measurement method, age, sex, follow-up time, cut-off value, number of patients with LNM in high or low MEG3 expression group, the HRs of MEG3 for OS/RFS[1]/RFS[2] and 95% confidence intervals (CIs) were extracted. If HR and its 95% CI were not reported, we estimated from the Kaplan-Meier curves by extracting some survival rates at specified times using methods reported previously [15]. Two investigators independently calculated these data with Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/, a free downloaded software). Any discontent was discussed and eventually reached a consensus among all authors. According to the Newcastle-Ottawa Scale (NOS) [16], each study was evaluated with a score from 0 to 9 to assess the quality, and an NOS score >5 indicated high quality.

Statistical analysis

Stata SE12.0 (StataCorp, College Station, TX, USA) was used to perform all statistical analyses. The relationship between MEG3 expression and survival outcome was evaluated by the HRs (95% CI), and the effect of MEG3 expression on LNM was presented as the odds ratios (OR) (95% CI). If HRs were supplied for both multivariate analyses and univariate analyses, the former data were adopted. Heterogeneity between studies was assessed by chi-square-based Q-test and I^2 index. When $P_Q \geq 0.05$ or $I^2 \leq 50\%$, the fixed effects model was used to calculate the pooled HRs, otherwise, the random effects model was used. We considered that the decreased expression of MEG3 predicted poor survival in patients with any type of cancer while pooled HR was lower than 1. The stability of the results was conducted by the sensitivity analysis by removing each individual study. Publication bias was performed by Begg's and Egger's linear regression tests. All *P* values <0.05 were defined to be statistically significant, which determined by a two-sided test.

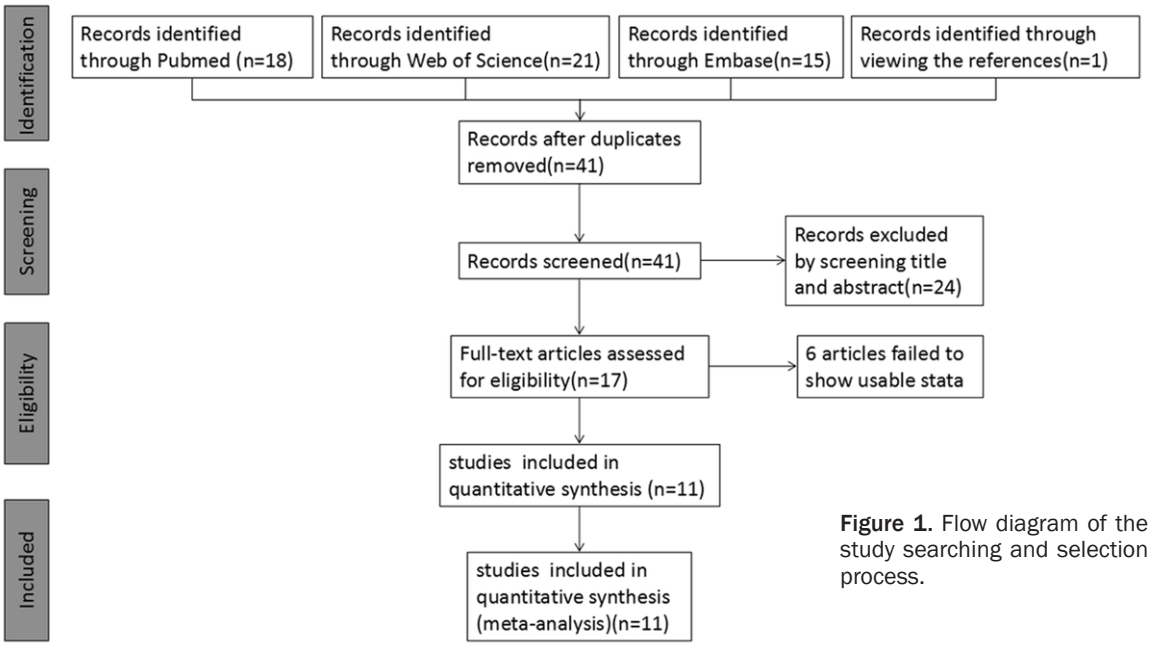

Figure 1. Flow diagram of the study searching and selection process.

Results

Characteristics of eligible studies

As shown in **Figure 1**, a total number of 54 records were potentially related to MEG3 expression and cancers by searching from the online database, while one additional article was adopted from references. After duplicates removed, 41 records were screened the title and abstract and 30 articles were abandoned when the exclusion criteria applied. Finally, 11 studies in recent four years were included in this meta-analysis. Compared with the normal tissues, the expression of MEG3 was saliently decreased in tumor tissues within these studies and these whose expression levels under the cutoff values came into low MEG3 expression group. The high level MEG3 expression in tumor tissues was relatively quantified by qRT-PCR using $2^{-\Delta\Delta Ct}$ method. Jia et al. [17] supplied the risk ratio (RR) for OS after a follow-up time of 48 months. Based on "Quantitative methods in the review of epidemiologic literature" [18], we transformed its original data into HR directly. The major characteristics of all eligible studies were shown in **Table 1**. There were altogether 911 Chinese patients with different kinds of cancers in 11 studies, including 1 breast cancer (BC) [19], 1 gastric cancer (GC) [20], 1 osteosarcoma [21], 1 colorectal cancer (CRC) [22], 1 hepatocellular carcinoma (HCC) [23], 1 retinoblastoma [24], 1 gallbladder cancer (GBC) [25], 1 non-small cell lung cancer (NSCLC) [26], 1 tongue squamous cell carcinoma (TSCC) [17], 1 prostate cancer (PC) [27] and 1 esophageal squamous cell cancer (ESCC) [28]. All studies were assessed to be high quantity.

Meta-analysis

The pooled HRs were 0.40 (95% CI: 0.29-0.56, P<0.001) for OS (**Figure 2**) and 0.33 (95% CI: 0.18-0.63, P=0.001) for RFS^1/RFS^2 (**Figure 3**) with a fixed-effect model because no obviously significant heterogeneity was found (I^2=0.00%, P_Q>0.05), which meant decreased expression of MEG3 associated with poor prognosis for patients with cancer. Moreover, we evaluated the correlation of MEG3 expression with LNM and found that the combined OR of three studies comprising 350 patients was 0.58 (95% CI: 0.37-0.90, P=0.018) without statistically significant heterogeneity (I^2=36.3%, P_Q=0.208) (**Figure 4**).

Subsequently, studies were divided into subgroups based on similar characteristics (**Table 2**). Regardless of sample size, results from both subgroups indicated that increased MEG3 expression meat long survival term (HR=0.40, 95% CI: 0.27-0.59, P<0.001; HR=0.41, 95% CI: 0.21-0.79, P=0.008). Similar outcome was found in multivariate analyses subgroup and

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

Author	Year	Country	Cancer type	Num.	Method	Age	Man (%)	Follow-up (m)	Cut-off	Out-come	HR 95% CI	HR estimate	LNM	MEG3 expression	
														High	Low
Shi	2016	China	BC	257	Rt-PCR	45	0	NR	Δct=8.065	OS/RFS[1]	Univariate/Multivariate	Reported	Yes	39	96
													No	50	72
Sun	2014	China	GC	72	Rt-PCR	60	58.3	NR	Median ratio	OS	Multivariate	Survival curve	Yes	14	26
													No	18	14
Tian	2015	China	Osteosar-coma	64	Rt-PCR	25	56.3	NR	Median level	OS	Univariate/Multivariate	Reported	Yes	-	-
													No	-	-
Yin	2015	China	CRC	62	Rt-PCR	60	58.1	NR	Mean level	OS	Univariate/Multivariate	Reported	Yes	-	-
													No	-	-
Zhou	2016	China	HCC	72	Rt-PCR	60	81.9	NR	Median level	OS	Univariate/Multivariate	Reported	Yes	-	-
													No	-	-
Jia	2014	China	TSCC	76	Rt-PCR	60	52.6	48	T/N=0.373	OS	Multivariate	Reported	Yes	-	-
													No	-	-
Liu	2016	China	GBC	84	Rt-PCR	59.51±8.95	29.8	60	Median level	OS	Multivariate	Survival curve	Yes	-	-
													No	-	-
Lu	2013	China	NSCLC	44	Rt-PCR	NR	77.3	NR	Mean ratio	OS	Multivariate	Survival curve	Yes	-	-
													No	-	-
Luo	2015	China	PC	21	Rt-PCR	65	100	NR	T/N=0.5	NR	Multivariate	-	Yes	2	1
													No	5	13
Gao	2016	China	Retinoblastoma	63	Rt-PCR	2.5	55.6	NR	Median level	RFS[2]	Univariate/Multivariate	Reported	Yes	-	-
													No	-	-
Lv	2016	China	ESCC	96	Rt-PCR	60	80.21	NR	NR	OS	Multivariate	Reported	Yes	-	-
													No	-	-

Num: sample size; OS: overall survival; RFS[1]: relapse free survival; RFS[2]: recurrence free survival; HR: hazard ratio; CI: confidence interval; LNM: lymph node metastasis; BC: breast cancer; GC: gastric cancer; CRC: colorectal cancer; HCC: hepatocellular carcinoma; TSCC: tongue squamous cell carcinoma; GBC: gallbladder cancer; NSCLC: non-small cell lung cancer; PC: prostate cancer; ESCC: esophageal squamous cell cancer; qRT-PCR: quantitative real-time polymerase chain reaction; T/N: tumor/normal ratio; NR: not reported.

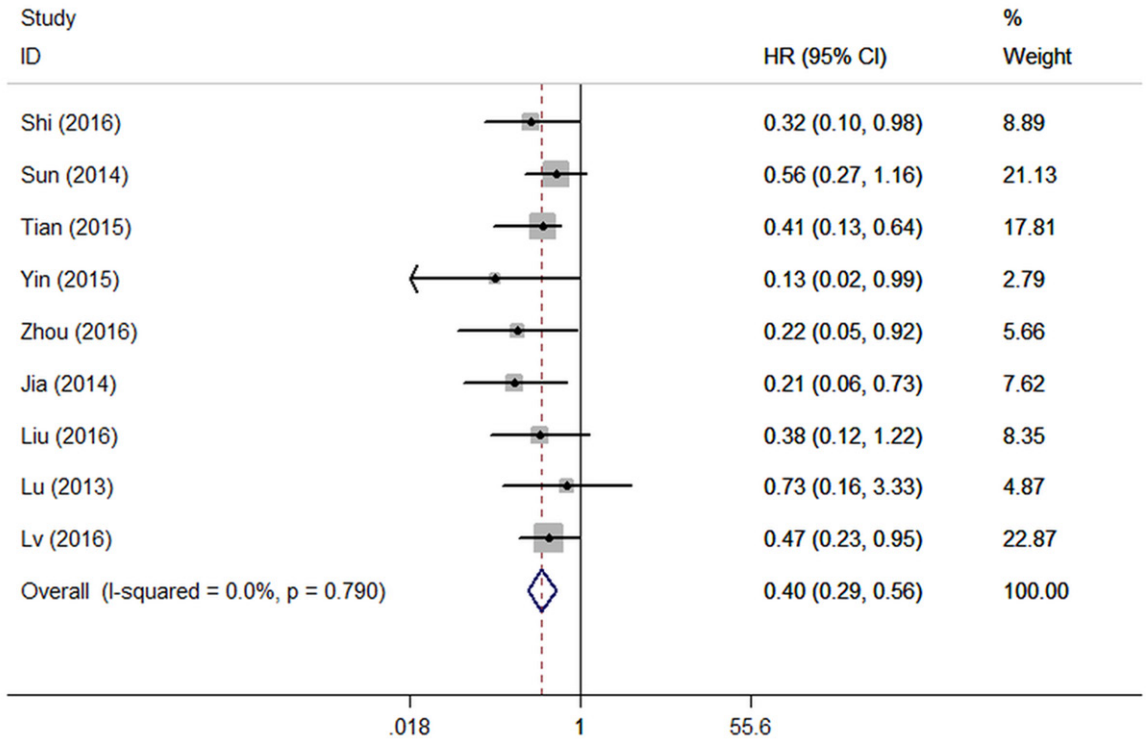

Figure 2. Forest plots for association between MEG3 expression and OS.

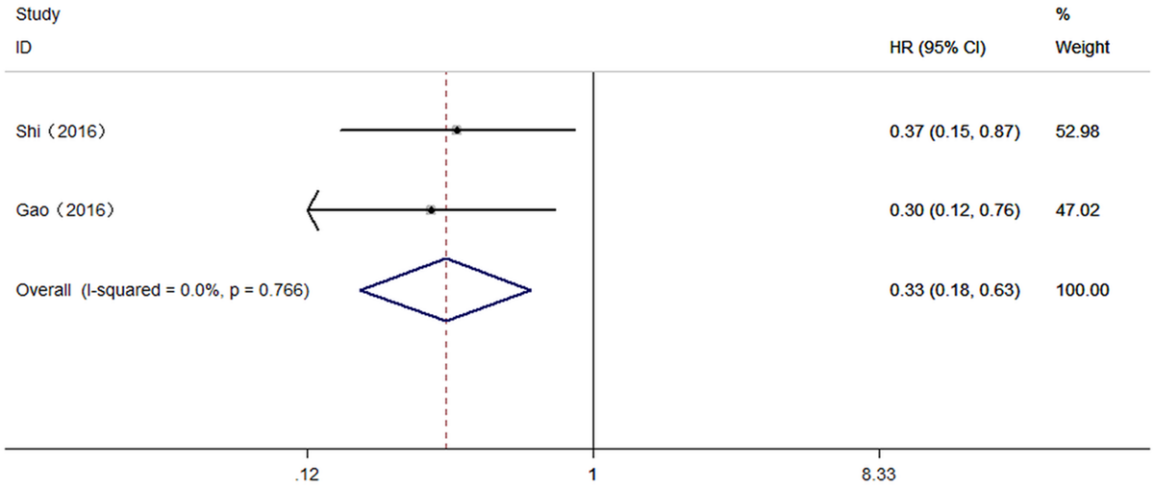

Figure 3. Forest plots for association between MEG3 expression and RFS[1]/RFS[2].

uinivariate analyses subgroup (HR=0.46, 95% CI: 0.30-0.69, P<0.001; HR=0.32, 95% CI: 0.18-0.56, P<0.001). Additionally, compared with patients with non-digestive system cancers (HR=0.41, 95% CI: 0.24-0.70, P<0.001), the effect of MEG3 expression seemed to be alike for patients with digestive system cancers (HR=0.40, 95% CI: 0.26-0.61, P=0.001).

Sensitivity analyses and publication bias

The sensitivity analyses were performed by removing each individual study to assess the stability of these results (**Figure 5**). In order to evaluate the publication bias of the studies included, both Begg's funnel plot and the Egger's linear regression test were conducted.

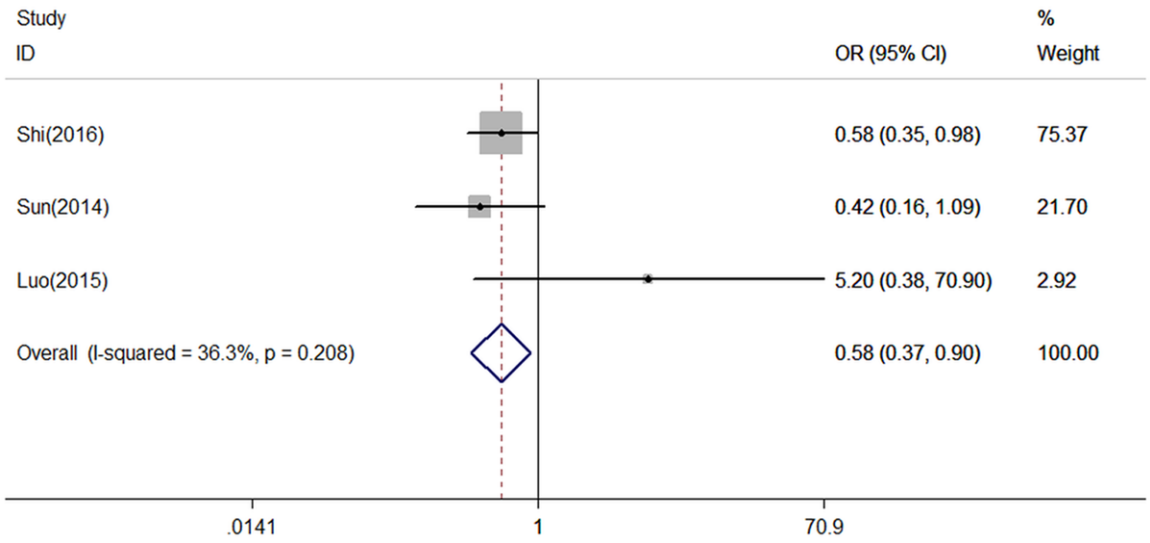

Figure 4. Forest plots for association between MEG3 expression and LNM.

Table 2. Subgroup analysis of pooled HRs of OS

Subgroup Factor	Divided Standard	Number	Pooled HR 95% CI	*P*-value	I^2 value (%)	*P*-value for Heterogeneity
Survival analysis	Univariate analysis	4	0.32 (0.18, 0.56)	<0.001	0.0	0.710
	Multivariate analysis	5	0.46 (0.30, 0.69)	<0.001	0.0	0.672
Cancer type	Non-digestive system	4	0.41 (0.24, 0.70)	<0.001	0.0	0.855
	Digestive system	5	0.40 (0.26, 0.61)	0.001	0.0	0.419
Patients' number	Number ≥70	6	0.40 (0.27, 0.59)	<0.001	0.0	0.711
	Number <70	3	0.41 (0.21, 0.79)	0.008	0.0	0.414

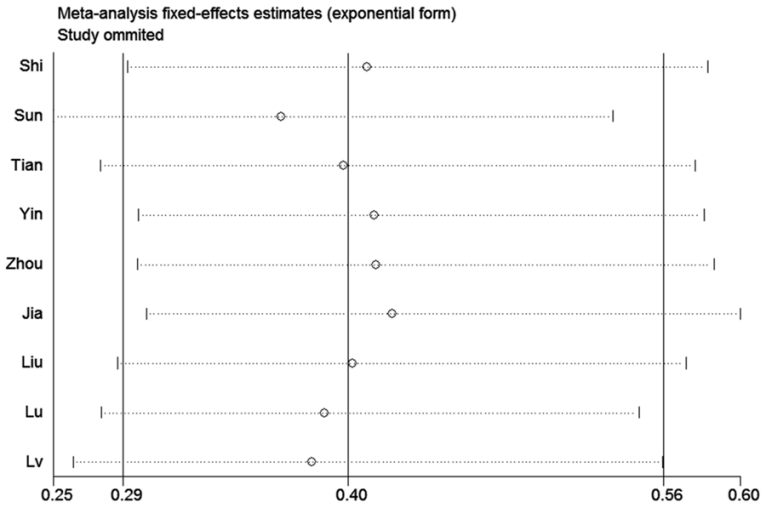

Figure 5. Sensitivity analysis of the pooled HRs and OS for studies included.

There was no evidence of obvious publication bias for OS using the Begg's test (P=0.076) and the Egger's test (P=0.065) (**Figure 6**).

Discussion

In the past few decades, accumulated evidence has confirmed that aberrant expression of lncRNAs was an important prognostic element in majority tumors [29]. HOTAIR, which was a well-known lncRNA transcribed from the antisense stand of the HOXC gene locus, has been explored to be an oncogene in several types of cancer. For overall survival of patients with cancer, the higher the level of HOTAIR was, the higher HR was [30]. In HCC, not only HOTAIR expression was a potential predictor for prognosis, but also

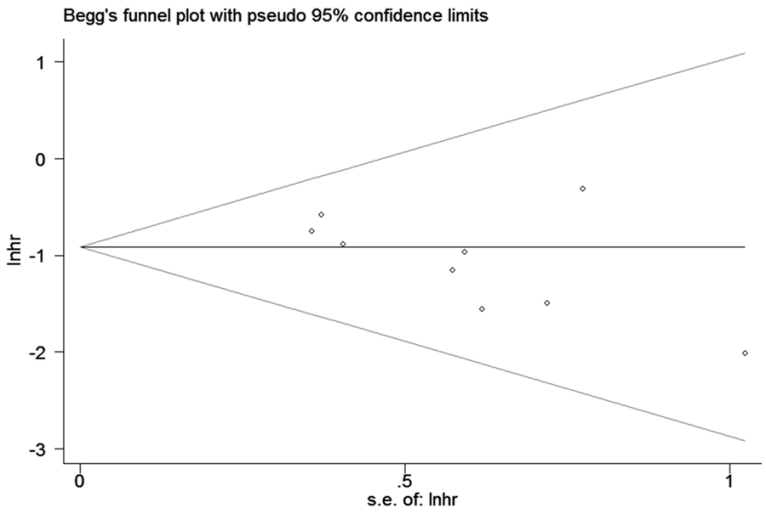

Figure 6. Begg's Funnel plot analysis of potential bias for OS.

associated with tumor differentiation, metastasis and early recurrence. Besides, by activating the Wnt/β-catenin signaling pathway, the overexpressed HOTAIR enhanced the progression of HCC [31]. MALAT-1 was initially identified to predict the survival of stage I NSCLC patients. Recently, it was reported that the malignant behaviors of gastric cancer cells would be inhibited when knocked down MALAT1, which was proposed to correlate with miR-122-IGF-1R signaling [32]. ANRIL was highly expressed in epithelial ovarian cancer (EOC) and served as an independent predictor for OS. Additionally, it partially promoted EOC cell proliferation by decreasing P15INK4B and increasing Bcl-2 expression [33]. To our best knowledge, this is the first meta-analysis investigated the prognostic role of MEG3 in multiple cancers.

MEG3 served important roles in a wide range of cancers. Sun et al. [20] found that the expression of MEG3 was significantly correlated with TNM stages, depth of invasion and tumor size, what's more, patients with decreased MEG3 experienced a relatively poor prognosis. Another study by Sun et al. [34] showed that overexpressed MEG3 in breast cancer cells of MCF7 and MB231 resulted lower proliferation, colony formation, migration and invasion capacities. They considered it might activate the target genes of p53 including p21, Maspin and KAI1, thus stabilized and accumulated p53 expression. Zhou et al. [35] reported the positive correlation between miR-141 and MEG3, interestingly, results in vivo confirmed this relationship and highlighted this novel interconnection between miRNAs and lncRNAs.

Though the underlying mechanism of dysregulated MEG3 in cancer was not clear, hepermethylation of differentially methylated regions (DMRs) has been observed to related to MEG3 expression. In clinically nonfunctioning pituitary tumors, Zhao et al. [36] hypothesized that hypermethylation of the MEG3 region was associated with the decreased MEG3 expression. Lately, in GC miR-148a was found to regulate MEG3 expression by influencing DNA methlytransferase 1 (DNMT-1), which belonged to DNA methyltransferases (DNMTs) and accounted for DNA methylation patterns [37].

In this meta-analysis, we explored the association between MEG3 expression level and prognostic/clinicopathological outcomes in patients with cancer. The results showed a negative relationship between decreased MEG3 expression and survival/metastasis outcomes, for there was no evidently significant heterogeneity. However, there were still some weaknesses which needed to be addressed. Firstly, the sample sizes of these included studies were limited, and patients were all coming from China, the results might only represent the cases of Chinese patients with cancer. Secondly, we have spared no effort to find the original data, unfortunately, we performed a more rudimentary analysis from 3 studies using Kaplan-Meier curves. Besides, sensitivity analysis and publication bias evaluation tests were not conducted for RFS^1/RFS^2 or LNM because of confined studies. Finally, due to the publications limitation, we only discussed the role of MEG3 expression in solid tumors, other malignancy such as epithelial carcinoma was not considered. Further functional studies of MEG3 would help us to answer the question whether increased MEG3 expression has effect on patients' prognosis.

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Disclosure of conflict of interest

None.

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References

[1] Lee JT. Epigenetic regulation by long noncoding RNAs. Science 2012; 338: 1435-1439.
[2] International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. Cah Rev The 2004; 431: 931-945.
[3] Gutschner T and Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. RNA Biol 2012; 9: 703-719.
[4] Quinn JJ and Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet 2016; 17: 47-62.
[5] Flynn RA and Chang HY. Long noncoding RNAs in cell-fate programming and reprogramming. Cell Stem Cell 2014; 14: 752-761.
[6] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.
[7] Rachmilewitz J, Elkin M, Rosensaft J, Gelman-Kohan Z, Ariel I, Lustig O, Schneider T, Goshen R, Biran H and de Groot N. H19 expression and tumorigenicity of choriocarcinoma derived cell lines. Oncogene 1995; 11: 863-870.
[8] Wang SH, Wu XC, Zhang MD, Weng MZ, Zhou D and Quan ZW. Upregulation of H19 indicates a poor prognosis in gallbladder carcinoma and promotes epithelial-mesenchymal transition. Am J Cancer Res 2016; 6: 15-26.
[9] Bando T, Kato Y, Ihara Y, Yamagishi F, Tsukada K and Isobe M. Loss of heterozygosity of 14q32 in colorectal carcinoma. Cancer Genet Cytogenet 1999; 111: 161-165.
[10] Guo Q, Qian Z, Yan D, Li L and Huang L. LncRNA-MEG3 inhibits cell proliferation of endometrial carcinoma by repressing Notch signaling. Biomed Pharmacother 2016; 82: 589-594.
[11] Cao X, Zhuang S, Hu Y, Xi L, Deng L, Sheng H and Shen W. Associations between polymorphisms of long non-coding RNA MEG3 and risk of colorectal cancer in Chinese. Oncotarget 2016; 7: 19054-19059.
[12] Binse I, Ueberberg B, Sandalcioglu IE, Flitsch J, Luedecke DK, Mann K and Petersenn S. Expression analysis of GADD45gamma, MEG3, and p8 in pituitary adenomas. Horm Metab Res 2014; 46: 644-650.
[13] Wang P, Ren Z and Sun P. Overexpression of the long non-coding RNA MEG3 impairs in vitro glioma cell proliferation. J Cell Biochem 2012; 113: 1868-1874.
[14] Zhuang W, Ge X, Yang S, Huang M, Zhuang W, Chen P, Zhang X, Fu J, Qu J and Li B. Upregulation of lncRNA MEG3 promotes osteogenic differentiation of mesenchymal stem cells from multiple myeloma patients by targeting BMP4 transcription. Stem Cells 2015; 33: 1985-1997.
[15] Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.
[16] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.
[17] Jia LF, Wei SB, Gan YH, Guo Y, Gong K, Mitchelson K, Cheng J and Yu GY. Expression, regulation and roles of miR-26a and MEG3 in tongue squamous cell carcinoma. Int J Cancer 2014; 135: 2282-2293.
[18] Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9: 1-30.
[19] Shi WF, Xia SH, Yin Y, Qi XW and Xing CG. Decreased expression of lncRNA MEG3 in breast cancer is associated with poor prognosis. Int J Clin Exp Pathol 2016; 9: 5327-5333.
[20] Sun M, Xia R, Jin F, Xu T, Liu Z, De W and Liu X. Downregulated long noncoding RNA MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer. Tumour Biol 2014; 35: 1065-1073.
[21] Tian ZZ, Guo XJ, Zhao YM and Fang Y. Decreased expression of long non-coding RNA MEG3 acts as a potential predictor biomarker in progression and poor prognosis of osteosarcoma. Int J Clin Exp Pathol 2015; 8: 15138-15142.
[22] Yin DD, Liu ZJ, Zhang E, Kong R, Zhang ZH and Guo RH. Decreased expression of long noncoding RNA MEG3 affects cell proliferation and predicts a poor prognosis in patients with colorectal cancer. Tumour Biol 2015; 36: 4851-4859.

[23] Zhuo H, Tang J, Lin Z, Jiang R, Zhang X, Ji J, Wang P and Sun B. The aberrant expression of MEG3 regulated by UHRF1 predicts the prognosis of hepatocellular carcinoma. Mol Carcinog 2016; 55: 209-219.
[24] Gao Y and Lu X. Decreased expression of MEG3 contributes to retinoblastoma progression and affects retinoblastoma cell growth by regulating the activity of Wnt/beta-catenin pathway. Tumour Biol 2016; 37: 1461-1469.
[25] Liu B, Shen ED, Liao MM, Hu YB, Wu K, Yang P, Zhou L and Chen WD. Expression and mechanisms of long non-coding RNA genes MEG3 and ANRIL in gallbladder cancer. Tumour Biol 2016; 37: 9875-9886.
[26] Lu KH, Li W, Liu XH, Sun M, Zhang ML, Wu WQ, Xie WP and Hou YY. Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. BMC Cancer 2013; 13: 461.
[27] Luo G, Wang M, Wu X, Tao D, Xiao X, Wang L, Min F, Zeng F and Jiang G. Long non-coding RNA MEG3 inhibits cell proliferation and induces apoptosis in prostate cancer. Cell Physiol Biochem 2015; 37: 2209-2220.
[28] Lv D, Sun R, Yu Q and Zhang X. The long noncoding RNA maternally expressed gene 3 activates p53 and is downregulated in esophageal squamous cell cancer. Tumour Biol 2016; [Epub ahead of print].
[29] Serghiou S, Kyriakopoulou A and Ioannidis JP. Long noncoding RNAs as novel predictors of survival in human cancer: a systematic review and meta-analysis. Mol Cancer 2016; 15: 50.
[30] Miao Z, Ding J, Chen B, Yang Y and Chen Y. HOTAIR overexpression correlated with worse survival in patients with solid tumors. Minerva Med 2016; 107: 392-400.
[31] Gao JZ, Li J, Du JL and Li XL. Long non-coding RNA HOTAIR is a marker for hepatocellular carcinoma progression and tumor recurrence. Oncol Lett 2016; 11: 1791-1798.
[32] Wang J, Xu AM, Zhang JY, He XM, Pan YS, Cheng G, Qin C, Hua LX and Wang ZJ. Prognostic significance of long non-coding RNA MALAT-1 in various human carcinomas: a meta-analysis. Genet Mol Res 2016; 15.
[33] Qiu JJ, Wang Y, Liu YL, Zhang Y, Ding JX and Hua KQ. The long non-coding RNA ANRIL promotes proliferation and cell cycle progression and inhibits apoptosis and senescence in epithelial ovarian cancer. Oncotarget 2016; 7: 32478-32492.
[34] Sun L, Li Y and Yang B. Downregulated long non-coding RNA MEG3 in breast cancer regulates proliferation, migration and invasion by depending on p53's transcriptional activity. Biochem Biophys Res Commun 2016; 478: 323-329.
[35] Zhou X, Ji G, Ke X, Gu H, Jin W and Zhang G. MiR-141 inhibits gastric cancer proliferation by interacting with long noncoding RNA MEG3 and down-regulating E2F3 expression. Dig Dis Sci 2015; 60: 3271-3282.
[36] Zhao J, Dahle D, Zhou Y, Zhang X and Klibanski A. Hypermethylation of the promoter region is associated with the loss of MEG3 gene expression in human pituitary tumors. J Clin Endocrinol Metab 2005; 90: 2179-2186.
[37] Okano M, Bell DW, Haber DA and Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell 1999; 99: 247-257.