

Review Article

Relationship between lincRNA-p21 expression and human cancer prognosis: a meta-analysis

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Abstract: Long intergenic noncoding RNA-p21 (lincRNA-p21) regulates key cell processes and is involved in the initiation and progression of human cancers. This meta-analysis explored the relationship between lincRNA-p21 expression and cancer prognosis. Firstly, we searched four electronic databases (Pubmed, Medline, Web of Science, and CochraneLibrary). Then, patient survival and clinicopathological features were extracted and analyzed as pooled hazard ratios (HRs) or odds ratios (ORs). Q and I² tests measured study heterogeneity. After that, we pooled HRs of overall survival (OS) and disease-free survival (DFS) using InHR and standard error, and assessed the association between lincRNA-p21 expression and clinicopathological features of tumors using ORs and 95% CIs. Begg's and Egger's tests assessed potential publication bias. A total of five studies comprised of 450 patients were included. Meta-analysis showed that, in most cancers, higher lincRNA-p21 expression was associated with better OS (P = 0.01) and DFS (P = 0.002). Higher lincRNA-p21 expression was also associated with better differentiation grade (P < 0.0001), but not vascular invasion (P = 0.39) or tumor, node, and metastasis stage (P = 0.95). Therefore, for most cancers, increased lincRNA-p21 expression was associated with better OS, DFS, and tumor differentiation grade, and may be a novel tool for cancer prognosis.

Keywords: LincRNA-p21, human cancers, prognostic indicator, meta-analysis

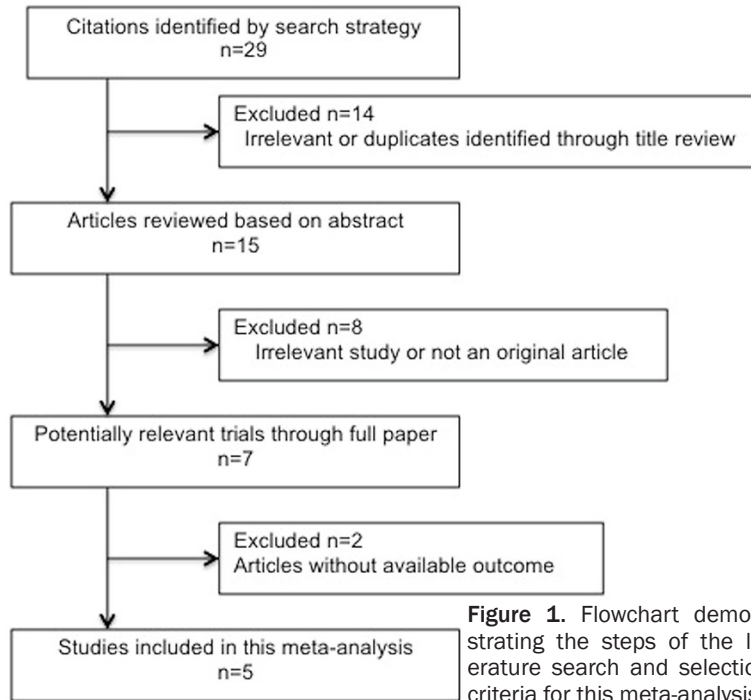
Introduction

Worldwide, cancer is a major public health problem and is the leading cause of human mortality. In China [1], there were approximately 4,292,000 new cancer cases and 2,814,000 cancer-related deaths in 2015. Lung, stomach, esophageal, liver, and colorectal cancer comprise the five major cancers in China [1]. In the US, the American National Center for Health Statistics estimates that there were nearly 600,000 cancer-related deaths in 2016 [2]. For most cancers, the standard treatment remains a combination of surgery, radiotherapy, and chemotherapy; however, this combination is not effective for all patients. Thus, continued research is necessary to identify novel diagnostic and prognostic markers and therapeutic targets that would increase therapeutic efficacy and patient survival.

One particularly viable set of potential markers and targets for cancer treatment are long non-

coding RNAs (lncRNAs). lncRNAs belong to a class of RNA molecules that are larger than 200 nucleotides with no protein-coding capability [3], and are transcribed pervasively in the human genome. Initially, they were thought to have no biological effect on gene transcription and were declared “noise” by scholars [4]. However, more recent studies have found that this genomic “dark matter” critically regulates biological processes by altering gene expression and signaling pathways [5]. Specifically, lncRNAs play key roles in physical function regulation and in the progression of various diseases including cancer [3, 6-8]. Despite accumulating evidence that the majority of lncRNAs are functional, only a relatively small proportion have been functionally annotated [6].

Among the lncRNAs associated with cancer progression is long intergenic noncoding RNA-p21 (lincRNA-p21). LincRNA-p21 is located approximately 15 kilobases (kb) upstream of the cell-cycle regulator gene, *p21* or *CDKN1A*,



and is ~3.0 kb in length. Early studies using mouse embryonic fibroblasts described lincRNA-p21 as a TP53-activated lincRNA [7]. LincRNA-p21 is regulated by p53 and serves as a repressor in p53-dependent transcriptional responses [8], while overexpression of lincRNA-p21 inhibits cell proliferation [9]. Thus, lincRNA-p21 expression may have relevance to tumor tissues and cancer progression; however, the relationship between these is controversial. Some studies report that the expression of lincRNA-p21 is significantly lower in tumor tissues compared with normal non-tumor tissues [8, 10-13], suggesting that lincRNA-p21 may function as a potential tumor suppressor in cancer cells. Alternatively, data from The Cancer Genome Atlas (TCGA, <http://cancergenome.nih.gov/>) suggest that high lincRNA-p21 expression is associated with shorter overall survival (OS) [11]. Furthermore, lincRNA-p21 expression is reduced in colorectal cancer (CRC) tumor tissues compared with normal controls, but is significantly elevated in stage II and III CRC tumors and vascular invasion [8]. This suggests that the function of lincRNA-p21 varies in different human cancers. Further research is necessary to clearly delineate the relationship between lincRNA-p21 expression and cancer progression. The goal of this study was to better determine this relationship and to evaluate the prognostic value of lincRNA-p21 in human can-

cer. Our meta-analysis revealed that higher lincRNA-p21 expression was associated with better OS, DFS, and tumor differentiation grade. Thus, lincRNA-p21 may be a novel prognostic tool for cancer patients.

Materials and methods

Literature search strategy for meta-analysis

A search of four electronic databases (Pubmed, Medline, Web of Science, and CochraneLibrary) was performed independently by two authors (Ye Li and Xingyu Chen) according to the standard guidelines for meta-analysis. The literature was searched from study inception until July 1,

2017 for articles that reported lincRNA-p21 expression as a probable prognostic marker for survival of cancer patients. The search strategy used both MeSH terms and free-text words to increase sensitivity. The following search terms were used: 'lincRNA-p21' or 'linc-p21' or 'TRP53COR1' or 'TP53COR1' and 'carcinoma' or 'neoplasm' or 'tumor' or 'cancer'. The strategy was adjusted for different databases to maximize search findings. Manual searches were performed using the reference lists of the relevant articles to retrieve additional eligible studies for inclusion.

Data inclusion and exclusion criteria

Two researchers (Ye Li and Xingyu Chen) independently evaluated all studies to select relevant data for meta-analysis. The inclusion criteria for this meta-analysis were: 1) the expression level of lincRNA-p21 was determined in human tumor tissue and patients were grouped according to the expression of lincRNA-p21; 2) the relationship between lincRNA-p21 expression and survival was measured in human tumors or the relationship between lincRNA-p21 expression and clinicopathological features of human tumors was measured; and 3) all tumors were confirmed by pathological or histological exam with pathologic parameters. The exclusion criteria were: 1) articles that were reviews, letters,

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Table 1. Main characteristics and data of the five studies included in this meta-analysis (A total of 450 patients were included in this meta-analysis)

Study	Year	Nation	Tumor type	Sample size	lincRNA-p21 expression								Survival Analysis	HR (95% CI)	NOS	Detection method
					High				Low							
					Total	VI	HTS	PTD	Total	VI	HTS	PTD				
Zhai	2013	USA	CRC	66	37	6	11	-	29	4	6	-	-	-	7	qRT-PCR
Yang	2015	China	HCC	70	32	14	7	23	38	27	22	36	OS	0.49 (0.24-1)	7	qRT-PCR
													DFS	0.56 (0.29-1.07)		
Castellano	2016	Spain	NSCLC	128	34	-	-	-	94	-	-	-	OS	1.65 (0.58-4.71)	8	qRT-PCR
													DFS	1.46 (0.8-2.65)		
Peng	2015	China	DLBCL	105	55	-	40	-	50	-	26	-	OS	0.27 (0.13-0.55)	8	qRT-PCR
													DFS	0.24 (0.13-0.44)		
Wang	2016	China	PSC	81	34	-	-	19	47	-	-	42	OS	0.5 (0.24-1.02)	7	qRT-PCR
													DFS	0.51 (0.29-0.88)		

Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; DLBCL, diffuse large B cell lymphoma; PSC, prostate carcinoma; VI, vascular invasion; HTS, higher tumor stage; PTD, poorer tumor differentiation grade; OS, overall survival; DFS, disease-free survival; NOS, Newcastle-Ottawa Scale.

editorials, case reports, and expert opinions; 2) non-English language and non-human studies; 3) studies lacking data listed in the inclusion criteria; and 4) basic characterization studies [14].

Literature screening and variable extraction

Two investigators (Ye Li and Xingyu Chen) independently extracted and examined the data from original articles. Disagreements in assessment were resolved through consensus with a third reviewer (Jian Zhou). For each study, the following details were collected: surname of the first author, publication year, nation, tumor type, sample number, the number of patients with higher tumor, node, and metastasis (TNM) stage, poorer tumor differentiation grade, and vascular invasion, hazard ratio (HR) and 95% CIs of elevated lincRNA-p21 for OS and disease-free survival (DFS), the Newcastle-Ottawa Scale (NOS) score, and the method used to detect lincRNA-p21.

Quality assessment score of the included studies

Study quality was assessed according to the NOS. The scale assigned 0-9 stars to each study based on three categories (selection, comparability, and outcome). Studies receiving ≥ 7 stars were considered high quality.

Statistical analysis

We either extracted HRs directly from the reported publication or estimated them from O-E statistics and variance. Otherwise, we calculated the HRs from Kaplan-Meier curves

using the continuous point method with the Engauge Digitizer software version 4.1. The extracted survival rates at specified times were entered into the excel spreadsheet of 1745-6215-8-16-S1 developed by Tierney JF [15]. Then, an approximated curve was produced and compared to published curves to confirm the accuracy of our data extraction. RevMan software version 5.3 was used for statistical analysis of pooled HRs or odds ratios (ORs). Heterogeneity among the different studies was measured by Q and I^2 tests. A probability value of $I^2 \geq 50\%$ indicated significant heterogeneity. Random effects or fixed effects models were selected based on study heterogeneity. Specifically, a random effects model was used if there was significant heterogeneity and a fixed effects model if there was not. Pooled HRs of OS and DFS were calculated using the lnHR and standard error (SE) values. ORs and their 95% CIs were used to assess the association between lincRNA-p21 expression and clinicopathological features of tumors. Potential publication bias was assessed using the Begg's funnel plot or Egger linear regression test using the Stata 14.0 software.

Results

Literature search results

As shown in **Figure 1**, a total of 29 studies were retrieved from the initial database search and 14 irrelevant or duplicate articles were excluded. After a detailed screening of the study abstracts, seven articles were reviewed in

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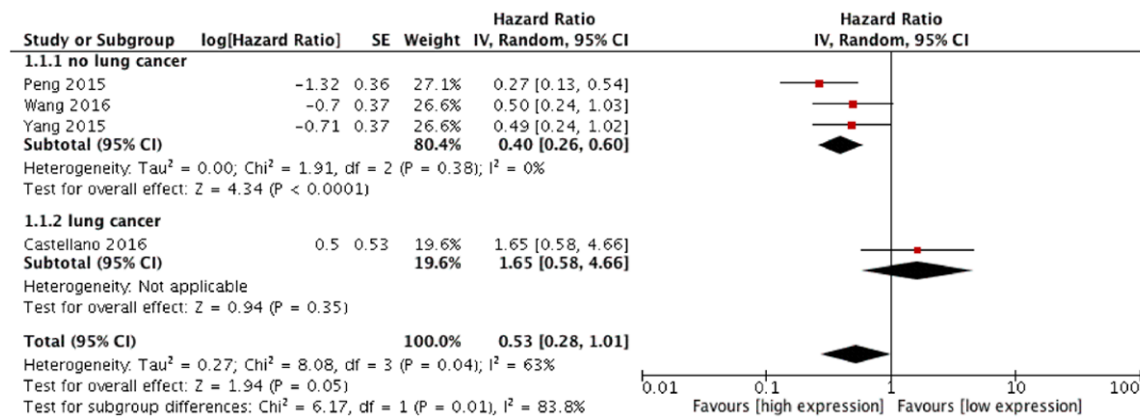


Figure 2. Forest plot showing the association between lincRNA-p21 expression and OS in different types of human cancer (Subgroup analysis showed that high levels of lincRNA-p21 were significantly correlated with better OS for patients with most types of cancer, except NSCLC).

detail by the full-text [8, 10-13, 16, 17]. Two papers were excluded because of insufficient data of grouping [16, 17]. Based on the inclusion and exclusion criteria, a total of five studies and 450 patients were included in this meta-analysis [8, 10-13].

Table 1 summarizes the main characteristics of the five included studies. A total of 450 patients were included, ranging from 66 to 128. The accrual period of these studies ranged from 2013 to 2016, and the studies were published by research groups throughout the world: three from China, one from Spain, and one from the United States. Of the five studies, one focused on colorectal cancer [8], one on hepatocellular cancer [10], one on non-small cell lung cancer (NSCLC) [11], one on diffuse large B cell lymphoma [12], and one on prostate cancer [13]. The expression of lincRNA-p21 was measured in cancer specimen. The diagnosis of TNM stage, tumor differentiation grade, and vascular invasion depended on pathology. HRs and 95% CIs were calculated using the excel spreadsheet 1745-6215-8-16-S1. The NOS scores of all five studies were ≥ 7 .

Association between lincRNA-p21 expression and OS

The association between OS and lincRNA-p21 expression was reported in four studies with a total of 384 patients. We performed a cumulative meta-analysis to determine the relationship between lincRNA-p21 and OS (**Figure 2**). The random effects model was adopted due to

significant heterogeneity between studies ($I^2 = 63\%$, $P = 0.04$). Due to the presence of heterogeneity, a sensitivity analysis was performed. After excluding the Castellano study [11], study heterogeneity was no longer significant ($I^2 = 0\%$, $P = 0.38$). Subgroup analysis showed that high levels of lincRNA-p21 were significantly correlated with better OS for patients with most types of cancer, except NSCLC (pooled HR = 0.40, 95% CI: 0.26-0.60, $P = 0.01$). To analyze publication bias, we performed Begg's and Egger's bias analyses. No obvious asymmetry was found using a Begg's funnel plot (**Figure 3A**) and no significant publication bias was identified through Egger's bias analysis (**Figure 3B**; $P = 0.129$). Therefore, our data demonstrated that lincRNA-p21 was an independent predictive factor for OS of cancer patients. Specifically, higher lincRNA-p21 expression was associated with better OS.

Association between lincRNA-p21 expression and DFS

We next performed a cumulative meta-analysis to determine the role of lincRNA-p21 in the DFS of 384 patients (**Figure 4**). The random effects model was adopted because of significant heterogeneity between studies ($I^2 = 82\%$, $P = 0.0008$). After excluding the Castellano study [11], subgroup analysis showed that higher levels of lincRNA-p21 significantly correlated with better DFS for patients with most cancers, except for NSCLC (pooled HR = 0.41, 95% CI: 0.24-0.68, $P = 0.002$). No obvious asymmetry was found in the Begg's funnel plot (**Figure 5A**)

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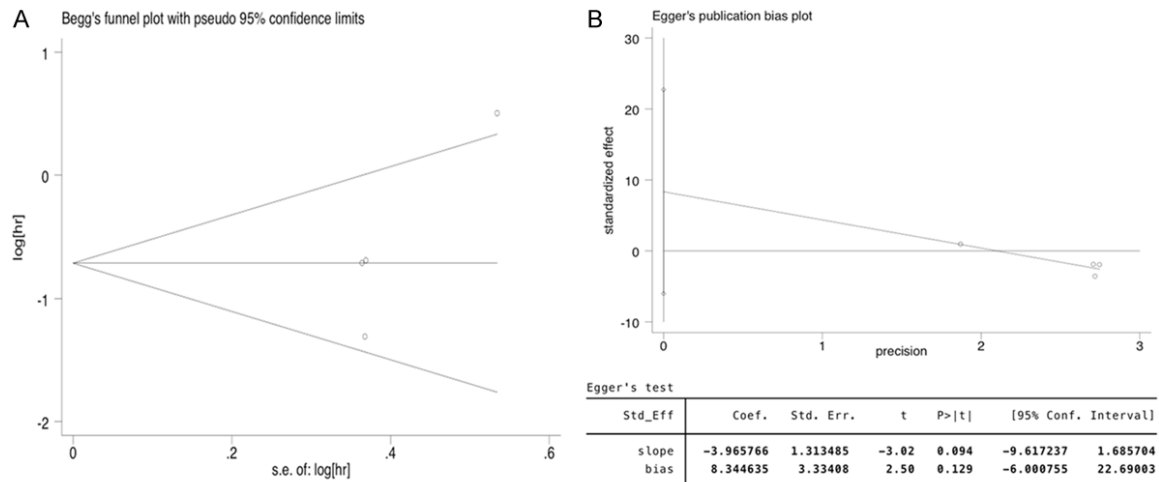


Figure 3. Begg's and Egger's bias analyses to determine publication bias for the effect of lincRNA-p21 on OS. A. No obvious asymmetry was found in Begg's funnel plot. B. No significant publication bias was found in Egger's bias analysis ($P = 0.129$).

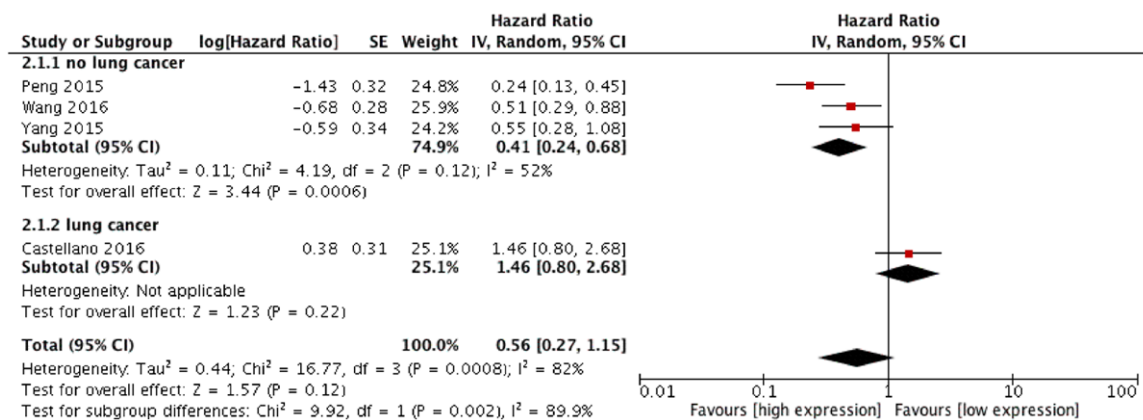


Figure 4. Forest plot showing the association between lincRNA-p21 expression and DFS in different types of human cancer.

and no significant publication bias was found through Egger's bias analysis (**Figure 5B**; $P = 0.954$). As with OS, we demonstrated that lincRNA-p21 was an independent predictive factor for DFS of cancer patients, and its high expression was associated with greater DFS.

Association between lincRNA-p21 expression and vascular invasion

Overexpression of lincRNA-p21 can induce aberrant neoangiogenesis. We performed a cumulative meta-analysis to determine the role of lincRNA-p21 in vascular invasion of 136 cancer patients (**Figure 6**). The random effects model was used because of significant study heterogeneity ($I^2 = 59\%$, $P = 0.12$). Meta-an-

alysis showed that higher expression of lincRNA-p21 did not predict higher vascular invasion in human tumors (pooled OR = 0.57, 95% CI: 0.15-2.09, $P = 0.39$).

Association between lincRNA-p21 expression and TNM stage

We performed a cumulative meta-analysis to determine the role of lincRNA-p21 in the TNM stage of 241 cancer patients (**Figure 7**). The random effects model was used because of significant heterogeneity ($I^2 = 86\%$, $P = 0.0009$). Meta-analysis showed that high levels of lincRNA-p21 did not correlate with higher TNM stage (pooled OR = 0.95, 95% CI 0.21-4.37, $P = 0.95$). Therefore, the results demonstrate that

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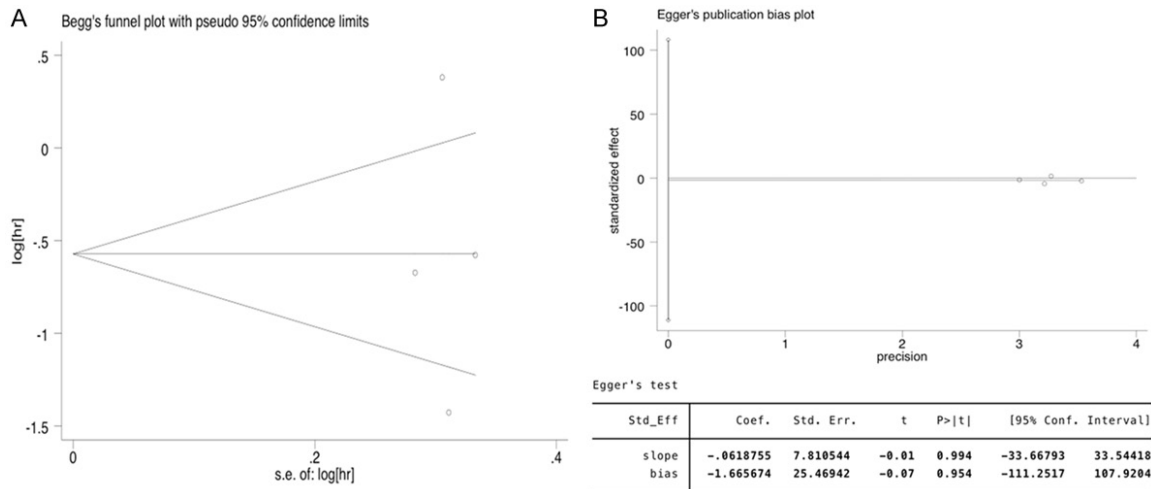


Figure 5. Begg's and Egger's bias analyses to determine publication bias for the effect of lincRNA-p21 on DFS. A. No obvious asymmetry was found in Begg's funnel plot. B. No significant publication bias was found in Egger's bias analysis ($P = 0.954$).

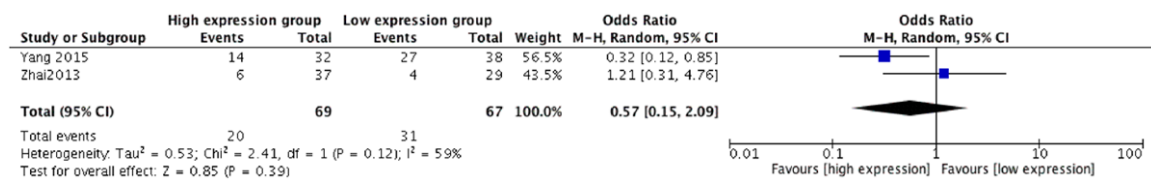


Figure 6. Forest plot showing the association between lincRNA-p21 expression and vascular invasion in human cancers.

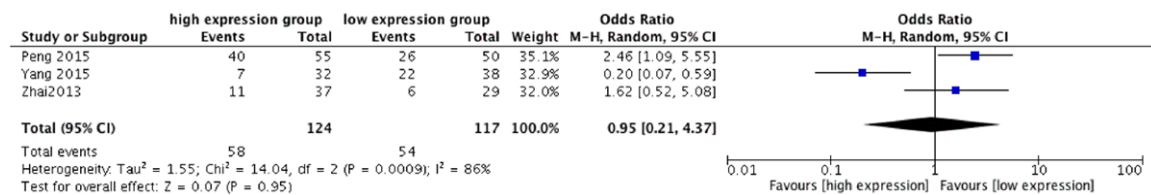


Figure 7. Forest plot showing the association between lincRNA-p21 expression and TNM stage.

higher expression of lincRNA-p21 did not predict TNM stage in human tumors.

Association between lincRNA-p21 expression and tumor differentiation grade

To determine the relationship between lincRNA-p21 expression and tumor differentiation grade, we performed a cumulative meta-analysis in 151 cancer patients (**Figure 8**). The fixed effects model was adopted ($I^2 = 0\%$, $P = 0.95$). Meta-analysis showed that high levels of lincRNA-p21 significantly correlated with a better differentiation grade for tumor patients (pooled OR = 0.15, 95% CI: 0.06-0.38, $P < 0.0001$).

Therefore, our findings demonstrate that high expression of lincRNA-p21 was an independent predictive factor for tumor differentiation grade.

Discussion

Genome-wide analysis has shown that approximately 80% of transcription is associated with lncRNAs [18]. lncRNAs modulate various biological processes, including cancer progression and metastasis, through chromosome remodeling, transcription, and post-transcriptional processing [5, 19]. lncRNAs also make promising cancer biomarkers as some are specifically expressed in tumor development, and are dif-

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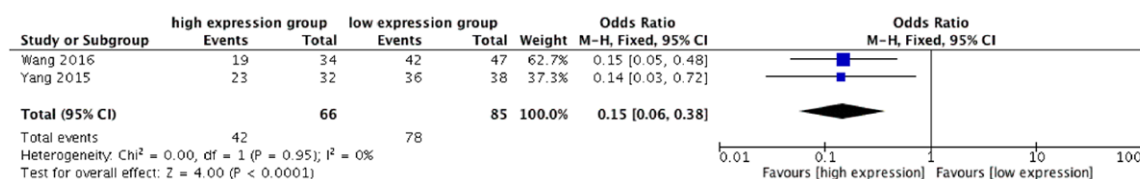


Figure 8. Forest plot showing the association between lincRNA-p21 expression and tumor differentiation grade.

ferentially expressed in body fluids and tumor tissues [20]. Therefore, characterization of cancer-related lncRNAs is a viable method for identifying novel tools of cancer diagnosis, treatment, and prognosis.

Data from a variety of human cancers, including colorectal [8], hepatocellular [10], NSCLC [11], diffuse large B cell lymphoma [12], prostate [13], lymphocytic leukemia [21], and skin tumors [22], indicate that lincRNA-p21 expression is significantly lower in cancer tissues compared with corresponding normal ones [18]. Jia et al. [16, 17] found that lincRNA-p21 expression inhibits the invasion and metastasis of hepatocellular carcinoma. This occurs through regulation of the Notch signaling-induced epithelial-mesenchymal transition. Furthermore, Yoon et al. found that lincRNA-p21 acts as a post-transcriptional inhibitor of translation [7]. Specifically, under reduced HuR levels, lincRNA-p21 accumulates in human cervical carcinoma HeLa cells, increases its association with *JUNB* and *CTNNB1* mRNAs, and selectively attenuates their translation [7]. Together these studies suggest that lincRNA-p21 is a potential prognostic marker and candidate drug target for human cancers.

However, the role of lincRNA-p21 in human cancer progression is controversial. Yang et al. [10] found that lincRNA-p21 promotes tumorigenesis by associating with the HIF1A-mediated hypoxic response and enhancing the Warburg effect in cancer cells. Thus, under hypoxic conditions, lincRNA-p21 may regulate angiogenesis and the Warburg effect. Alternatively, Castellano et al. [11] found that under normoxic conditions, lincRNA-p21 enhances TP53-mediated apoptosis, and represses somatic reprogramming, silencing the expression of pluripotency genes. Given the clear complexity in the role of lincRNA-p21 in human cancers and the potential for lncRNAs as cancer biomarkers, our study explored the prognostic value of lincRNA-p21 in cancer patients.

In this meta-analysis, we have examined the prognostic efficacy of lincRNA-p21 in cancer and the relationship between lincRNA-p21 and clinicopathological characteristics of tumors. To the best of our knowledge, this is the first meta-analysis to investigate the relationship between lincRNA-p21 expression and cancer prognosis. We included studies from both Asian and Western countries, which increases the population covered by this meta-research. Our data revealed that higher lincRNA-p21 expression predicts better prognosis. Due to significant heterogeneity among the included studies, subgroup analysis and sensitivity analysis were conducted according to cancer type. After excluding the Castellano study [11], study heterogeneity was no longer significant, and there was a significant difference in OS and DFS between high and low lincRNA-p21 expression groups. Specifically, higher lincRNA-p21 expression was associated with better OS (**Figure 2**), DFS (**Figure 4**), and tumor differentiation grade (**Figure 8**). These results demonstrate that the expression of lincRNA-p21 can be a new prognostic indicator for cancer patients.

There were several limitations in our meta-analysis. First, our study included relatively few studies covering a small number of cancer types and samples. Further investigation including a larger number of studies and cancer types is needed to confirm our results. Second, most of the HRs could not be directly obtained from the primary studies, and instead were estimated from reported survival curves. This may introduce some error. Third, the cut-off value used to separate high and low lincRNA-p21 expression varied across studies and it was difficult to reach a consensus value. Finally, our meta-analysis only included articles published in English, which may introduce additional bias. Therefore, well-designed and high quality studies are needed to confirm these preliminary findings, and we will update our meta-analysis accordingly.

Conclusions

In most cancers, increased expression of lincRNA-p21 was associated with better OS, DFS, and tumor differentiation grade. LincRNA-p21 expression may be a novel tool for cancer prognosis.

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Disclosure of conflict of interest

None.

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