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Review Article

Long noncoding RNA UCA1 can serve as a prognostic marker in human cancer: a meta-analysis

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Abstract: It has been reported that urothelial cancer associated 1 (UCA1) is dysregulated in various cancers. We performed this meta-analysis to clarify its promising functions as a prognosis marker in malignant tumors. Electronic databases, including PubMed, Medline, OVID, Cochrane Library, and Web of Science, were searched from inception to July 11, 2016. The hazard ratio (HR) and 95% confidence interval (CI) were calculated to explore the relationship between UCA1 expression and overall survival (OS), which were extracted from the eligible studies. The odds ratio (OR) was calculated to assess the association between UCA1 expression and pathological parameters using RevMan5.3 software. Twelve original studies were included in this meta-analysis that included 1,081 cancer patients. The pooled HR suggested that high UCA1 expression was significantly correlated with poor OS (pooled HR=1.80, 95% CI: 1.52-2.13) in cancer patients without obvious heterogeneity. UCA1 expression was found to be significantly related to lymph node metastasis (LNM) (OR=2.23, 95% CI: 1.52-3.28), distant metastasis (DM) (OR=3.32, 95% CI: 2.06-5.35) and tumor stage (OR=2.79, 95% CI: 2.15-3.62). Subgroup analysis showed that the type of cancer did not alter the significant predictive value of UCA1 in OS, LNM, DM and tumor stage from different types of cancer. This meta-analysis demonstrated that high UCA1 expression significantly predicts poor OS, lymph node metastasis, distant metastasis and high tumor stage, suggesting that high UCA1 expression may serve as a novel biomarker for poor prognosis in cancers.

Keywords: UCA1, neoplasms, prognosis, metastasis, meta-analysis

Introduction

It has been reported that 8.2 million people die from malignant tumors and 14.1 million people are diagnosed with cancer worldwide each year [1]. According to the American National Center for Health Statistics, approximately 600 thousand Americans will die of cancer in 2016 [2]. The five-year survival rate of most cancers is still low, and many scientists are looking for new biomarkers for the diagnosis or prognosis in cancer. Therefore, efforts to develop new prognostic markers should be made to help modify clinical application in cancers.

Long noncoding RNA (lncRNA) is defined as transcribed RNA molecules that lack an open reading frame of significant length, and the length of lncRNA is greater than 200 nucleotides [3]. LncRNA has many important functions in disease, including epigenetic regulation, and transcriptional and posttranscriptional regulation [4]. Recently, increasing studies have reported the dysregulation of lncRNAs in various types of cancer [5-8]. Some lncRNAs play a vital role in cancer progression, such as proliferation, invasion and metastasis [9, 10], and lncRNA may be regarded as a promising marker for the prognosis of cancer [11].

In 2006, urothelial cancer associated 1 (UCA1) was initially discovered in bladder cancer, and increased expression of UCA1 was examined by RT-PCR assay in bladder cancer tissues compared with that in normal bladder tissues [12]. Recently, more and more scientists have found that UCA1 might play important roles in cancer growth and metastasis [13], and UCA1 expression may have a relationship with prognosis and metastasis of human cancers. However, most studies reported so far are limited in discrete outcome and sample size. Therefore, we

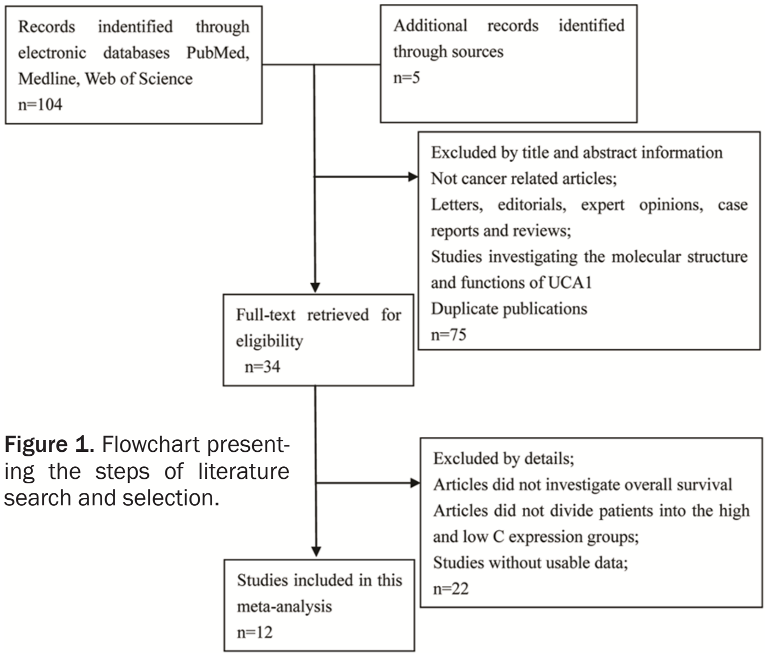

Figure 1. Flowchart presenting the steps of literature search and selection.

performed this updated meta-analysis to determine the prognostic value of UCA1 in cancer patients.

Materials and methods

Literature collection

According to the standard guidelines of meta-analyses [14, 15], a systematic search was performed by two authors independently in the electronic databases of Medline, Pubmed, OVID, and Web of Science for relevant articles that concerned UCA1 as a prognostic biomarker for the survival of cancer patients. The latest search was updated on July 11, 2016. We performed literature search by both text word and MeSH strategy with the terms “UCA1”, “Urothelial cancer associated 1”, “hepatocellular carcinoma up-regulated long non-coding RNA”, “lncRNA” or “noncoding RNA” or “long intergenic noncoding RNA”, “carcinoma” or “neoplasm” or “tumor” or “cancer”, “prognostic” or “prognosis”, “outcome” or “survival or “recurrence”. The strategy was correspondingly adjusted in the different databases. In the retrieval process, we made a manual search using the reference lists of the relevant articles to include eligible studies.

Study selection

Two researchers (Yanghua Fan and Liyuan Xie) evaluated all of the included studies and extracted the data independently. The inclusion criteria were as follows: 1) the relationship between UCA1 expression and survival was measured in multiple human tumors; 2) the expression levels of UCA1 in human tumor tissue were measured, and the patients were grouped according to the expression levels of UCA1; 3) all of the tumors were confirmed by pathological or histological examinations, and the clinicopathologic parameters were described; 4) studies described sufficient information on the overall survival (OS) such as the hazard ratio (HR) and 95% confidence interval (CI).

The following studies were excluded: 1) reviews, letters, editorials, case reports and expert opinions; 2) non-English language and non-human studies; 3) studies without available data; and 4) laboratory studies with the molecular structure and functions of UCA1 only.

Data extraction

Two reviewers (Yanghua Fan and Lei Wu) independently extracted and examined the data from the original articles. Disagreements in the literature assessment were resolved through consensus with a third reviewer (Xingen Zhu). The following data were collected: surname of the first author, publication year, country, tumor type, sample size, the number of patients with lymph node metastasis and distant metastasis, HR and 95% CI of elevated UCA1 for OS, description of the cut-off value of UCA1, the NOS score, and detection method of UCA1.

The study quality was assessed in accordance with the Newcastle-Ottawa Scale (NOS). Nine items were extracted, and each item scored 1. The total scores ranged from 0 to 9. If the scores were ≥7, the study was considered as high quality.

Statistical methods

Statistical analyses were performed using RevMan version 5.3 software. The heterogeneity among different studies was measured by

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

Study	Year	Region	Tumor type	Sample size	UCA1 expression						Analysis	HR (95% CI)	Cut-off value	NOS	Method
					Low			High							
					Total	LNM	DM	Total	LNM	DM					
Bian ZH [18]	2016	China	CRC	90	45	23	4	45	30	8	Multivariate	2.395 (1.044-5.495)	Median	8	qRT-PCR
Han Y [19]	2014	China	CRC	80	43	18	7	37	17	7	Multivariate	1.330 (0.640-2.780)	Mean	8	qRT-PCR
Li J [20]	2014	China	ESCC	90	49	12		41	22		Multivariate	2.627 (1.416-5.874)	Mean	7	qRT-PCR
Li W [21]	2016	China	OSC	135	67		9	68		25	Multivariate	3.141 (1.249-7.899)	Median	7	qRT-PCR
Ni B [22]	2015	China	CRC	54	27	5	1	27	12	6	Multivariate	3.137 (1.180-9.326)	Median	8	qRT-PCR
Nie W [23]	2016	China	NSCLC	112	73	21		39	14		Multivariate	1.409 (1.077-1.844)	Youden index	8	qRT-PCR
Tao K [24]	2015	China	CRC	80	60	21		20	13		Multivariate	2.002 (1.007-3.981)	Fourth quartile	7	qRT-PCR
Wang F [25]	2015	China	HCC	98	49		11	49		30	Multivariate	1.859 (1.077-3.210)	Median	8	qRT-PCR
Wang H [26]	2015	China	NSCLC	60	24	8		36	26		Multivariate	1.936 (1.062-3.258)	Median	7	qRT-PCR
Yang YJ [27]	2016	China	OC	53	26	5		27	13		Multivariate	6.318 (1.119-35.679)	Median	8	qRT-PCR
Zhang L [28]	2016	China	OC	117	58	12		59	26		Multivariate	1.688 (1.005-2.834)	Median	8	qRT-PCR
Zheng Q [29]	2015	China	GC	112	56	37		56	35		Multivariate	2.350 (1.222-4.521)	Median	8	qRT-PCR

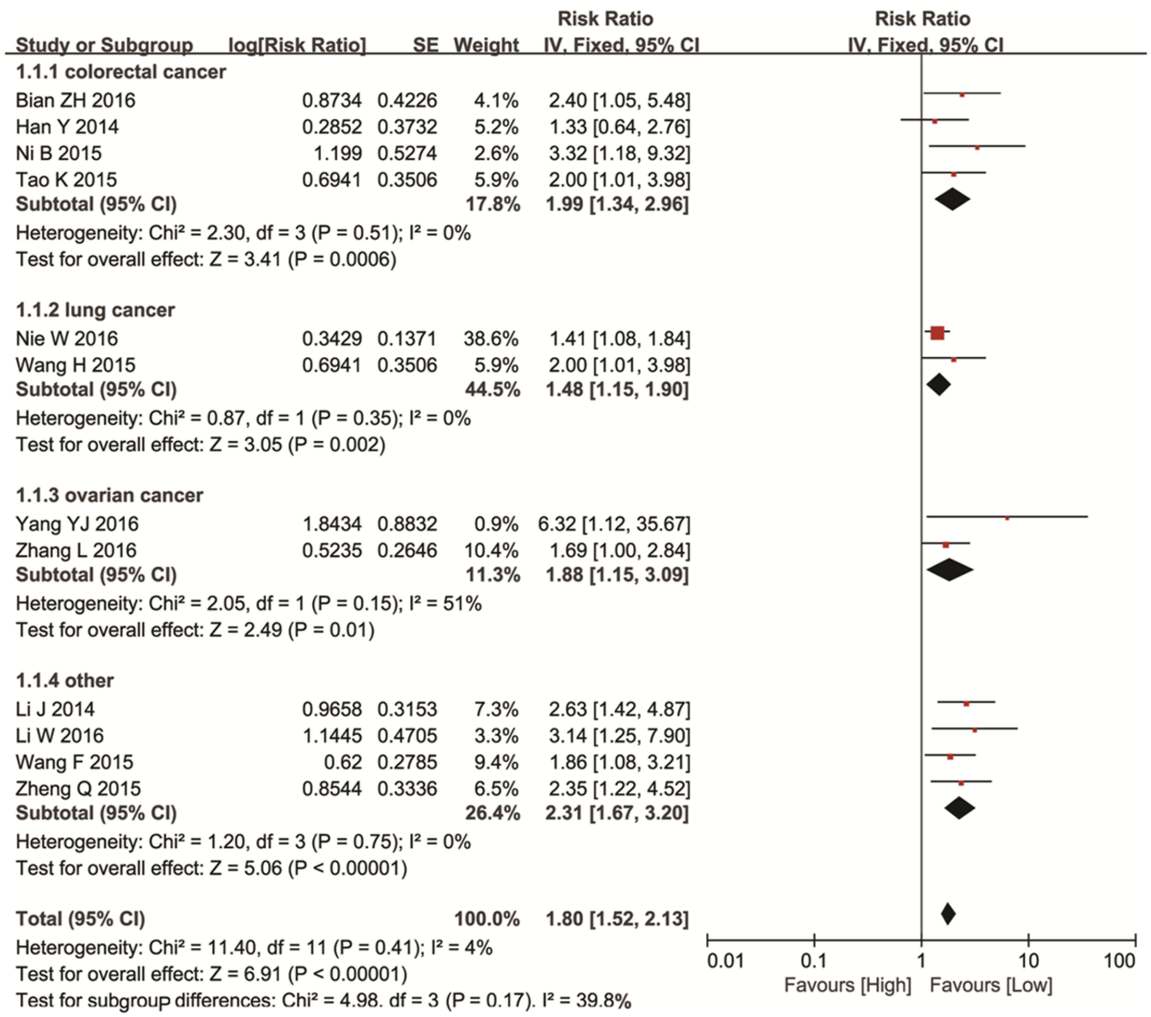

Figure 2. Forest plot showing the subgroup analyses of the pooled HRs of OS with elevated UCA1 expression in the different types of cancer.

the Q and I^2 tests. A probability value of $I^2 \geq 50\%$, and $P<0.1$ indicated the existence of significant heterogeneity [16]. A random effects model or fixed effects model was used depending on the results of heterogeneity analysis. If there was a significant heterogeneity among the studies, the random-effects model was adopted. The potential publication bias was assessed by the Begg's funnel plot. Pooled HRs and ORs were extracted from the published data. Because the HRs can be obtained directly from the publication, we used crude ones. While the HR and 95% CI were not directly reported in the studies, survival information was extracted from Kaplan-Meier curves and was used to estimate the HR. The log HR and standard error (SE) were used to summarize the outcome of overall survival [17]. Odds ratios (ORs) and their 95% CIs were combined to assess the association between UCA1 expression and clinicopathological parameters, including LNM, DM and tumor stage.

Results

Study characteristics

The detailed screening process is shown in detail in **Figure 1**. According to the inclusion and exclusion criteria, twelve studies and 1,081 patients were included in the meta-analysis [18-29]. Additionally, the characteristics of the 12 studies included in the present meta-analysis are summarized in **Table 1**. The subject number of 12 studies ranged from 55 to 135, with a mean sample size of 90.1. The studies were all from China. The publication time of the

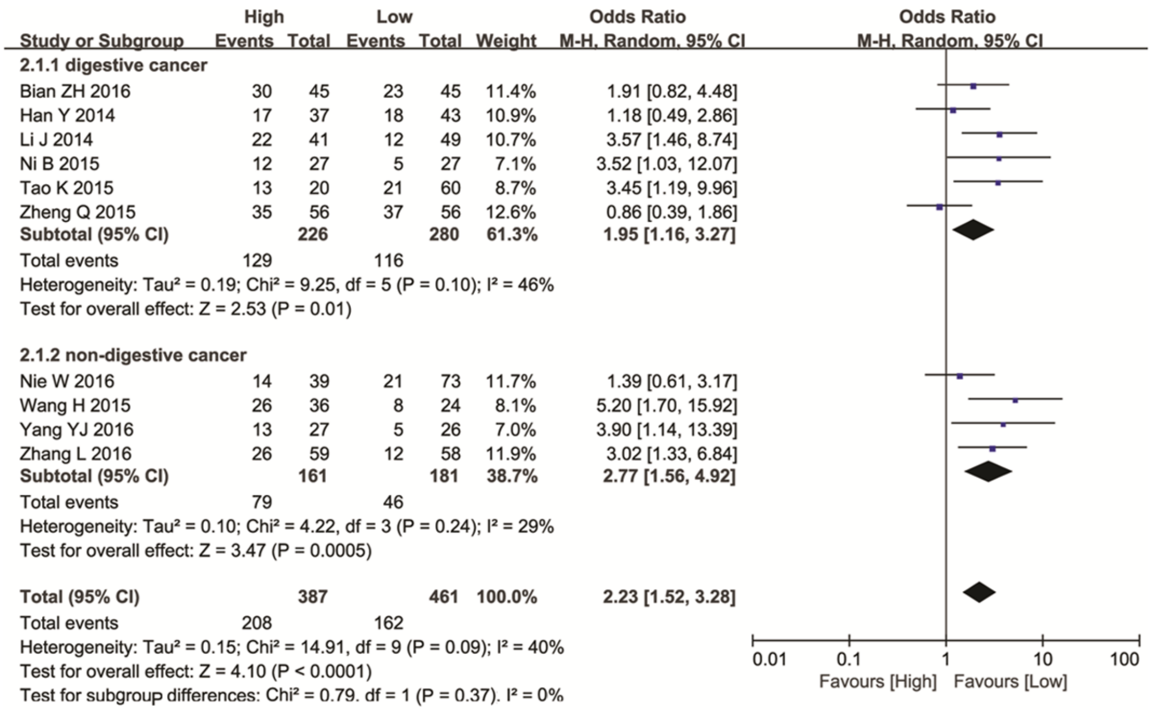

Figure 3. Forest plot for the association between the UCA1 expression levels with lymph node metastasis.

included studies ranged from 2014 to 2016. Among the twelve studies, four [18, 19, 22, 24] focused on colorectal cancer (CRC), two [23, 26] focused on non-small cell lung cancer (NSCLC), two [27, 28] on ovarian cancer (OC), one [20] on esophageal squamous cell carcinoma (ESCC), one [25] on hepatocellular carcinoma (HCC), one [21] on osteosarcoma (OSC), and one [29] on gastric cancer (GC). UCA1 expression was measured in cancerous specimens. All of the diagnoses of LNM, DM and tumor stage were all dependent on the pathology. The cut-off values of the high and low expression of UCA1 in these studies were found to be inconsistent, including median [18, 21, 22, 25-29], mean [19, 20], fourth quartile [24] of the expression level of UCA1 and Youden index [23]. The NOS scores of all the included studies were ≥7.

Association between the UCA1 expression level and OS

We performed a cumulative meta-analysis to assess the function of UCA1 for overall survival (OS) in patients with cancer. Additionally, all of the included studies with 1,081 patients reported the relationship between OS and UCA1. A significant association was observed between UCA1 and OS in cancer patients (pooled HR=1.80, 95% CI: 1.52-2.13; **Figure 2**). In addition, we found no significant heterogeneity among the studies (I^2=4%, P_Q=0.41). Furthermore, the subgroups were analyzed based on the cancer type and revealed a significant association between UCA1 and OS in colorectal cancer (HR=1.99, 95% CI: 1.34-2.96), lung cancer (HR=1.48, 95% CI: 1.15-1.90, P=0.002), ovarian cancer (HR=1.88, 95% CI: 1.15-3.09) and other cancer types (HR=2.31, 95% CI: 1.67-3.20).

This result demonstrated that cancer patients with a high expression of lncRNA-UCA1 might be correlated with a shorter OS. Thus, we found that lncRNA-UCA1 was an independent factor of OS among patients with cancer.

Association between the UCA1 expression level and LNM

Eight hundred forty-eight patients with cancer from 10 eligible studies were collected and analyzed. The random effects model was used for significant heterogeneity (I^2=40%, P_Q=0.09). The odds ratio (OR), expressed as the high UCA1 expression group versus low UCA1 expression group was 2.23 (95% CI: 1.52-3.28, P<0.0001; **Figure 3**). Meta-regression analysis and subgroup analysis (digestive or non-diges-

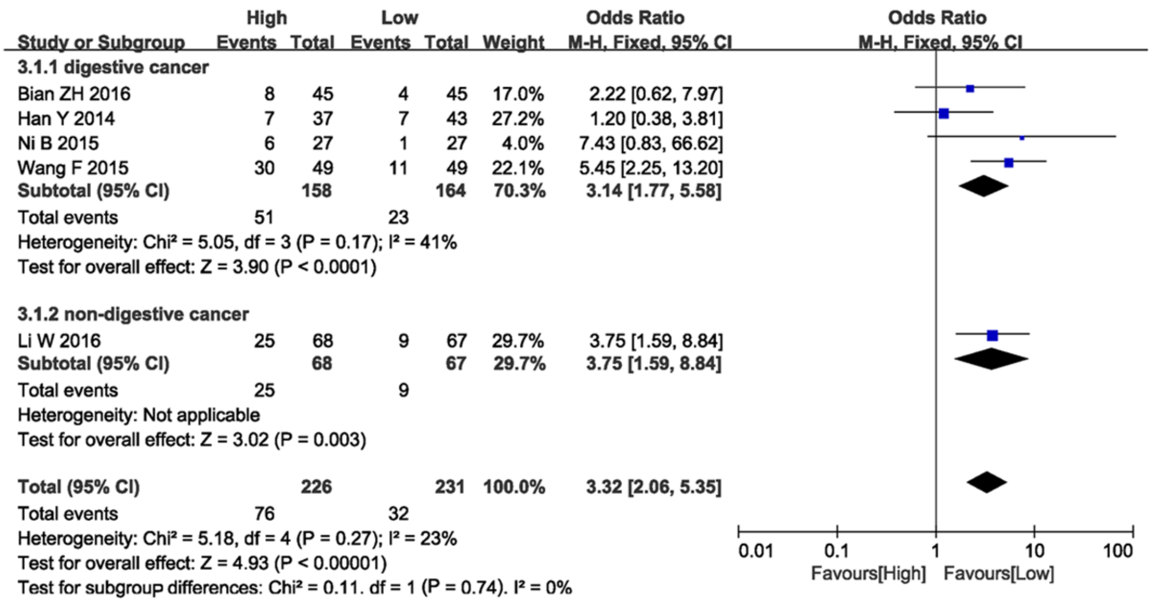

Figure 4. Forest plots for the association between UCA1 expression and distant metastasis.

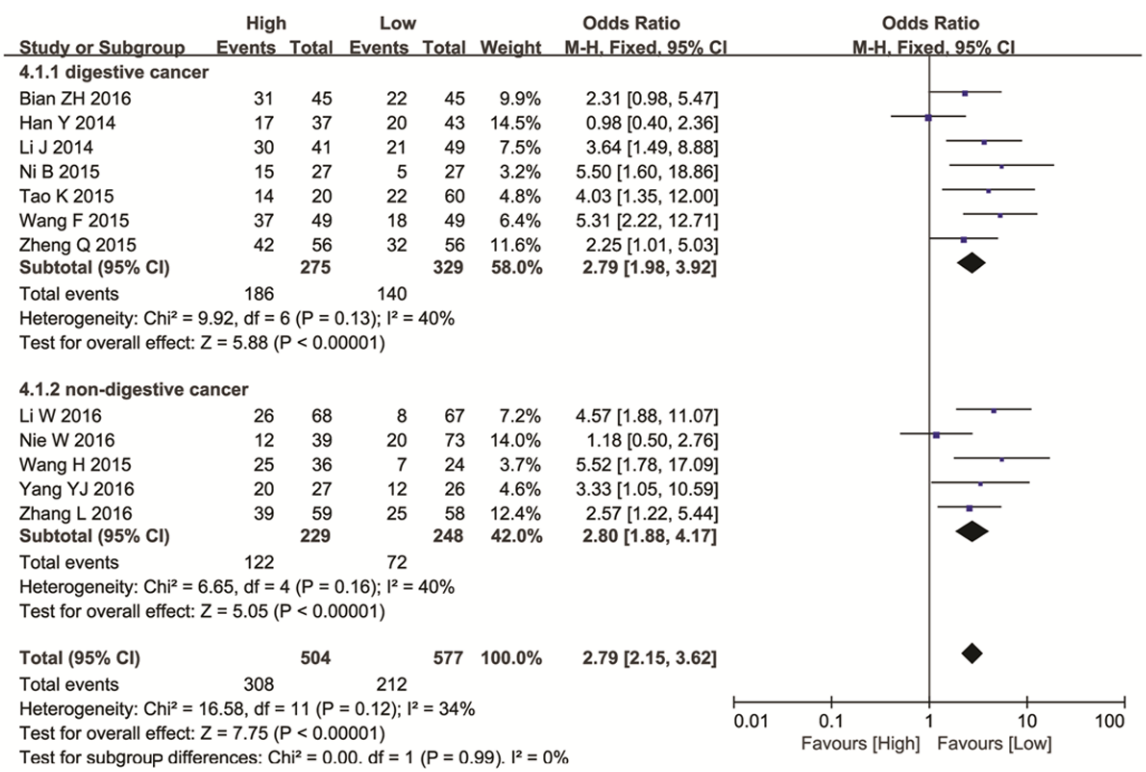

Figure 5. Forest plot showing meta-analysis of the independent role of UCA1 in tumor stage in the different types of cancer.

tive cancer) were performed to explore the sources of heterogeneity. In the subgroup analysis, there was a significant association between UCA1 and LNM in digestive cancer (OR=1.95, 95% CI: 1.16-3.27, P=0.01) and non-digestive cancer patients (OR=2.77, 95% CI: 1.56-4.92, P=0.0005).

According to the result, there was a significant difference in the LNM incidence between the

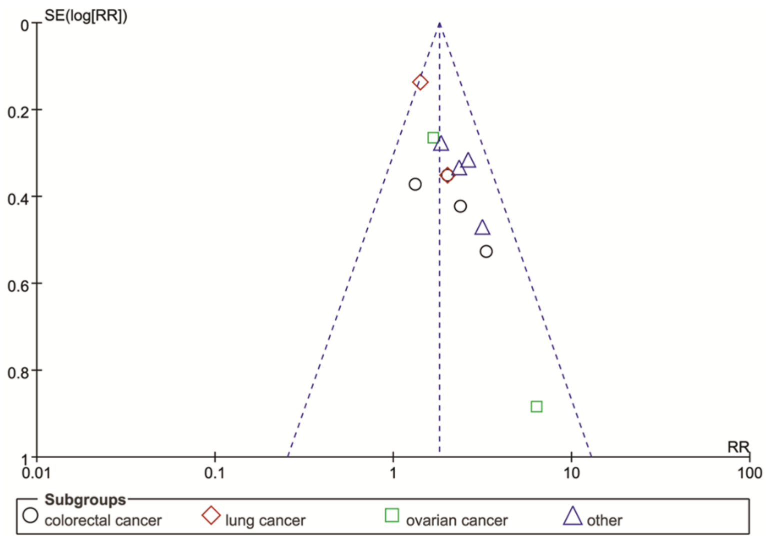

Figure 6. Funnel plot of the publication bias for the analysis of the independent role of UCA1 in OS in the different types of cancer.

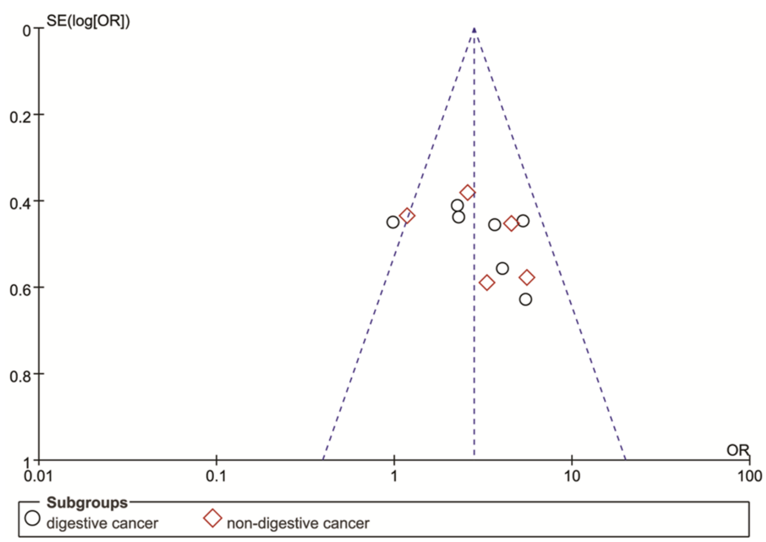

Figure 7. Funnel plot of the publication bias for the analysis of the independent role of UCA1 in tumor stage in the different types of cancer.

two groups. Additionally, the results demonstrated that a high expression of UCA1 significantly predicted a higher tendency to develop LNM in patients with cancer.

Association between the UCA1 expression level and DM

The correlations between UCA1 expression and distant metastasis (DM) are presented in **Figure 4**. Five studies with 457 patients declared the association between the UCA1 expression levels and number of cancer patients with DM. In these studies, there was no significant heterogeneity, and the fixed-effects model was used (I^2=23%, P_Q=0.27). The analysis showed a pooled OR=3.32 (95% CI: 2.06-5.35, P<0.00001; high versus low UCA1 expression; **Figure 4**). Subgroup analysis showed that UCA1 was an independent factor for DM in Chinese digestive cancer (OR=3.14, 95% CI: 1.77-5.58, P<0.0001) and non-digestive cancer (OR=3.75, 95% CI: 1.59-8.84, P=0.003) patients.

As a result, the patients with DM were significantly increased in the high UCA1 expression group. The result revealed that patients with a high UCA1 expression level in tumor tissues may indicate an increased probability of DM.

Association between the UCA1 expression level and tumor stage

One thousand eighty-one patients in all eligible studies were included to detect the relationship between the UCA1 expression levels and tumor stage in this meta-analysis. The fix effects model was used for limited heterogeneity (I^2=34%, P_Q=0.12). A significant connection was found between a high UCA1 expression level and high tumor stage in cancer patients (pooled OR=2.79, 95% CI: 2.15-3.62, P<0.00001; **Figure 5**). From the subgroup analysis, the elevated expression of UCA1 was found to be significantly associated with tumor stage in patients with digestive cancer (OR=2.79; 95% CI: 1.98-3.92) and non-digestive cancer (OR=2.80; 95% CI: 1.88-4.17). In addition, we found no significant heterogeneity among the digestive cancer group (I^2=40%, P_Q=0.13) and non-digestive cancer group (I^2=40%, P_Q=0.12).

From the analysis results, the tumor stage was significantly increased in the high UCA1 expression group compared with that in the low UCA1 expression group, and the results demonstrated that a high expression of UCA1 significantly increased the risk of high tumor stage.

Publication bias

Next, a Begg's funnel plot was constructed to evaluate publication bias. The Begg's funnel plot (**Figure 6**) showed no evidence of obvious asymmetry for overall survival. Similarly, there was no evidence for significant publication bias in terms of tumor stage (**Figure 7**).

Discussion

Cancer remains a serious threat to human health, and the incidence of cancer has increased gradually in recent years [2]. Most cancers could eventually progress to metastasis, including lymph node metastasis (LNM) and distant metastasis (DM). The occurrence of metastasis was an important indicator for survival, indicating that these cancers have a poor prognosis [30, 31]. Moreover, LNM and DM have an important significance in the diagnosis of TNM (tumor-node-metastasis) staging for cancer patients, as well as are important indicators for predicting prognosis. Hitherto, the precise mechanism underlying metastasis remains uncertain in cancer patients. Currently, cancer research hotspot-molecular biomarkers play a critical role in the prediction and treatment of cancer [32, 33]. Therefore, it is still necessary and significant to identify new molecular markers to predict tumor metastasis and prognosis.

Recently, genome-wide studies have found that the mammalian genome is transcribed abundantly and that more than 80% of this transcription is associated with lncRNAs [34]. Mounting evidence has shown that lncRNAs play a central role in the regulation of differentiation, cell development and proliferation [25, 35]. Due to the specific expression of lncRNAs in the occurrence and development of tumors, lncRNAs can be used as promising biomarkers to diagnose and monitor tumors and could be collected easily from body fluids and tumor tissues [36]. Thus, the identification of tumor-related lncRNAs is important to understanding their function in tumorigenesis, and lncRNAs may be regarded as promising biomarkers for the prognosis of cancer.

The UCA1 gene is located on the human chromosome 19p13.12 positive strand [13]. UCA1 was first reported in bladder cancer and showed extensive regulatory functions in cell proliferation, apoptosis, invasion, cell cycle, and drug resistance by different mechanisms [12, 22]. In recent years, increasing evidence has revealed the contribution of UCA1 in playing oncogenic roles in tumorigenesis, and UCA1 is dysregulated in many tumors, including gastric cancer, colorectal cancer, bladder cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma and ovarian cancer [12, 13, 18-29]. Additionally, these studies have revealed that HULC has potential prognostic value for the prognosis in patients with cancer.

However, the underlying mechanisms concerning the role of UCA1 in human cancer remain largely unclear, and UCA1 may act as a common molecular biomarker. Therefore, through this meta-analysis, we explored the clinicopathologic significance and prognostic value of UCA1 in cancer patients.

One thousand eighty-one patients with cancer from 12 eligible studies were collected and analyzed in this study. A random-effects model or fixed-effects model was used depending on the results of heterogeneity analysis. We found that high UCA1 expression may indicate a worse prognosis in cancer patients. By combining HRs from Cox multivariate analyses, there was a significant difference in OS between the high and low UCA1 expression level groups (pooled HR 1.80, 95% CI: 1.52-2.13). Additionally, the results showed that different types of cancer, including CRC, NSCLC, OC and other cancers, did not change the significant predictive value of UCA1 in overall survival.

Furthermore, we found that high UCA1 expression in tumor tissues was significant correlated with lymph node metastasis. Due to the presence of heterogeneity, we performed sensitivity analysis; the heterogeneity disappeared after the study by Zheng et al [29] was excluded, but the results did not change. Next, we revealed that high UCA1 expression was significantly correlated with distant metastasis. In this meta-analysis, 12 studies reported the correlation between the UCA1 expression level and tumor stage. We found that high UCA1 expression was significantly associated with high tumor stage without obvious heterogeneity in the different types of cancer. Taken together, subgroup analysis showed that the type of cancer (digestive or non-digestive cancer) did not alter the significant predictive value of UCA1 in LNM, DM and tumor stage compared with different types of cancer.

Nevertheless, several limitations must be considered while interpreting the conclusions of the present meta-analysis. First, all of the included studies were from China; thus, the results may only represent Chinese patients with cancer. Additionally, the included type and number of cancers were small, so better-designed studies are necessary to verify the obtained results. Third, the criteria for high expression were different in these studies. Therefore, further well-designed and high-quality studies are needed to confirm the function of UCA1 in various cancers.

Conclusion

High levels of UCA1 expression in multiple cancers are significantly correlated with poor OS, LNM, DM and tumor stage. Therefore, UCA1 expression may serve as a promising biomarker for predicting prognosis in cancer patients.

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Disclosure of conflict of interest

None.

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