

The role of lncRNA CASC2 on prognosis of malignant tumors: a meta-analysis and bioinformatics

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Background: Cancer susceptibility candidate 2 (CASC2) is characterized as a tumor suppressor, which was first identified to be downregulated in endometrial carcinoma. Accumulating evidence was provided to testify the function of CASC2 in malignant tumors. However, a systematic and quantitative assessment is not available. The present study was designed to evaluate the role of CASC2 in multiple carcinomas through meta-analysis and bioinformatics.

Materials and methods: A systematic assessment of the relationship of CASC2 with tumors was performed by using several computerized databases from inception to December 1, 2017. Pooled HR with 95% CI was calculated to summarize the effect. The data on prognosis of malignant tumors were also downloaded from The Cancer Genome Atlas (TCGA) project, OncoLnc, TANRIC and lncRNAtor database.

Results: A total of 13 studies with 966 cancer patients were pooled in the analysis to evaluate the prognostic value of CASC2 in multiple tumors and the clinical features. The results of the meta-analysis revealed that low expression levels of CASC2 were associated with poor overall survival (OS) (pooled HR=0.39, 95% CI: 0.28–0.53, $P<0.0001$). CASC2 obviously has a negative correlation with advanced tumor node metastasis (TNM) stage, lymph node metastasis (LNM) and T stage, respectively ($P<0.05$). There was, however, no significant difference in gender, distant metastasis and high differentiation ($P>0.05$). In the Kaplan–Meier curves with log-rank analysis, higher expression of CASC2 was positively correlated with longer survival time than patients with a lower level ($P<0.05$), including kidney renal clear cell carcinoma, brain lower grade glioma, pancreatic adenocarcinoma and sarcoma.

Conclusion: Findings from this meta-analysis suggest that lower expression of CASC2 is associated with poorer prognosis of cancers, as well as advanced TNM, LNM and T stage. Data from the bioinformatics analysis revealed that higher expression of CASC2 was related to longer OS in patients with malignant tumors.

Keywords: CASC2, malignant tumors, prognosis, meta-analysis, bioinformatics

Introduction

There is ample epidemiological evidence indicating malignant tumors as the leading cause of mortality and morbidity worldwide, with ~8.2 million people dying from cancers and 14.1 million people being diagnosed with cancer every year according to the “global cancer report 2012” released by the World Health Organization (WHO).^{1–3} And worst of all, the number of new cases is expected to rise by about 70% over the next two decades.⁴ The latest research from the American Cancer Society showed that ~1.7 million new cancer cases and 600,000 cancer deaths were expected to occur in the USA in 2017.⁵ Despite advances in the level of health care, oncotherapy is

still confronted with great challenges due to the delayed diagnosis, poor prognosis, recurrence or metastasis, as well as cancer associated mutation.^{6,7} Tumor molecular markers, a class of chemical substances that specifically reflect the existence and growth of malignant tumors, can effectively and greatly evaluate tumor screening, diagnosis, prognosis, and recrudescence and, to date, have been widely used in clinical treatment of tumors.⁸ Therefore, analysis and measurement of the specific biomarkers in malignant tumors, specifically the connection between the expression levels of biomarkers and tumor progression, may provide insights into opportunities and priorities for prevention, research, and clinical treatment of tumors.

Long non-coding RNAs (lncRNAs) are defined as a group of nonprotein-coding RNAs, but interacting with proteins, with a length of >200 nucleotides that can regulate gene expression at the transcriptional or posttranscriptional level.^{9,10} Accumulating evidence suggests that lncRNA played an important role in various cellular biological processes, including cell growth, cell cycle, proliferation, differentiation, apoptosis, metabolism, and carcinogenesis.^{11–16} Recently, human genomic sequence data have shown that more than 90% of the human genomic sequences are transcribed to produce lncRNAs.^{17–19} Furthermore, studies have demonstrated that there are 18% of lncRNAs associating with human tumors, obviously higher than those of 9% of human protein-coding genes which only account for 1% of the total genomic sequences.^{20,21} All these suggested that lncRNAs might act as major contributors to carcinogenesis and cancer progression and the dysregulated lncRNAs in most cancers may be used as markers for cancer diagnosis and prognosis, as well as potential therapeutic targets.

The lncRNA cancer susceptibility candidate 2 (CASC2), which is located on chromosome 10q26, is a novel lncRNA initially identified to be downregulated in endometrial cancer and has been characterized as a tumor suppressor.^{22,23} An increasing number of studies have shown that CASC2 is abnormally expressed in various malignancies and plays a tumor-suppressive role through inhibiting cell proliferation, migration, invasion, and inducing apoptosis, such as glioma, gastric cancer, nonsmall-cell lung cancer, colorectal cancer, renal cell carcinoma, and endometrial cancer.^{24–37} These results have provided new insights into the role of CASC2 in the development of cancers and indicated the potential application of CASC2 as a prognostic marker and therapeutic target. To date, however, there are few reports concerning the relationship between the novel lncRNA, CASC2, by functioning as a tumor suppressor in various

cancers and patient outcomes. Furthermore, there were limitations in most individual studies assessing the implication of CASC2 levels in cancer due to small sample sizes and discrete outcome. And, to the best of our knowledge, there has not been a systematic and quantitative assessment of the published studies available. Therefore, in the present study, we performed a correlation analysis based on meta-analysis and bioinformatics methods to explore the relationship between the expression of CASC2 and the prognosis of malignant tumors.

Materials and methods

Literature search and study design

A meta-analysis was conducted and reported according to standard guidelines of the meta-analysis of original studies.^{38,39} We performed a systematic search of published studies before December 1, 2017 in PubMed, Embase, Web of Science and Cochrane Library by using the following medical subject headings and terms without restrictions: (“long noncoding RNA” OR “lnc RNA” OR “cancer susceptibility candidate 2” OR “CASC2”) AND (“cancer” OR “tumor” OR “neoplasm” OR “carcinoma”) AND (“survival” OR “prognosis” OR “prognostic” OR “metastasis”). Searching was done without restriction on publication years. The strategy was adjusted for each database to maximize the chances of finding the appropriate articles. In addition, we reviewed the reference lists of retrieved articles to identify any studies that were not identified from the preliminary literature searches.

Selection criteria for study inclusion

Two researchers evaluated all of the included studies and extracted the data independently. Studies were included in the meta-analysis if they met the following predetermined inclusion criteria: 1) reported original data and published as a full peer-reviewed article; 2) all tumors had to be confirmed by clinical diagnosis; 3) the subjects in every study included cancer samples and normal controls; 4) published in the English language; 5) the relationship between CASC2 expression and OS, or pathological parameters such as lymph node metastasis (LNM), advanced tumor node metastasis (TNM) stage, or the difference of gender, with respect to CASC2 expression; 6) the level of CASC2 expression was measured in human tumor tissue by RT-PCR, and patients were grouped according to CASC2 level; 7) provided estimates of HR or OR with 95% CI.

The exclusion criteria were as follows: 1) cell or animal experiments, and letters, case reports, reviews, conference

reports or commentaries; 2) the required data could not be extracted from the original article, the article was not found in full or had been published repeatedly; 3) only the latest publication was included if the same data subsets were reported; 4) only the single subunit of the CASC2 gene was studied.

Data extraction

Data extraction was conducted independently by two investigators from each retrieved article according to the selection standards. Decisions were made and any disagreements regarding decisions were resolved by discussion and consensus with a third reviewer. The following information was extracted from the studies: name of the first author, year of publication, country of origin, tumor type, sample size of cases, the number of patients with high difference (HD), LNM and distant metastasis (DM) in high or low expression of CASC2, HR and 95% CI of CASC2 value for OS, the reference gene and detection method of CASC2. Then, a database was established after the selected data were arranged and verified.

Statistical analysis

We pooled HR with 95% CI from each study separately for each outcome using a fixed effects meta-analysis. ORs with 95% CIs were used to assess the associations between CASC2 expression and tumor parameters, including gender, TNM, LNM, DM, T stage and HD. A fixed or random effect model was applied depending on the heterogeneity analysis results in this meta-analysis, and the fixed effect model was used when a significant Q test with $P > 0.05$ or $I^2 < 50\%$. Begg's funnel plots and Egger's was used to examine the underlying publication bias. All statistical analysis were done with Stata Software 12.0 version, $P < 0.05$ was considered significant.

Bioinformatics analysis

The expression of CASC2 and its effect on the prognosis of malignant tumors were analyzed and downloaded from the Cancer Genome Atlas (TCGA) project, OncoLnc, TANRIC and lncRNAtor database (<http://cancergenome.nih.gov/>). Cox proportional hazards regression models were generated for OS of tumors, which incorporated multiple variables. CASC2 expression was then analyzed through the raw data and compared with the prognostic data of the patients with malignant tumors. Additionally, the prognostic significance of CASC2 was also analyzed using Kaplan–Meier plotter (<http://kmpplot.com>).

Results

Included literatures

We retrieved 62 articles from our preliminary search initially. After duplicate articles had been removed, 42 articles were left and these articles were then screened. Of these, 20 articles were excluded based on titles and abstracts that did not satisfy some or all of the inclusion criteria and 22 articles were identified for full review. Nine studies were then excluded due to lack of specific report on the association of CASC2 with malignant tumor or insufficient data in the original studies. Finally, the remaining 13 articles were included in the meta-analysis. The results of the literature search are shown in Figure 1.

Characteristics of eligible studies

The characteristics of the 13 articles are summarized in Table 1. Among these 13 studies, a total of 966 patients were represented, with a mean sample size of 74.3 (with a range from 47 to 133). All studies were conducted in China and were published between 2016 and 2017. There were 11 types of carcinomas in this meta-analysis, including hepatocellular carcinoma (HCC),^{29,35} glioma,^{30,31} non-small-cell lung cancer (NSCLC),²⁵ colorectal cancer (CRC),²⁶ esophageal squamous cell carcinoma (ESCC),⁴⁰ thyroid carcinoma (TC),³⁴ pancreatic cancer (PC),³² lung adenocarcinoma (LAC),⁴¹ pituitary adenoma (PA),⁴² cervical cancer (CC),²⁸ and gastric cancer (GC).³³ All these patients were divided into two groups (high and low expression of CASC2) according to the CASC2 measurement results by RT-PCR in cancerous specimens. All of the diagnoses of TNM, DM, LNM, T stage and HD were dependent on individual pathology. The reference gene of CASC2 in these studies was found to be inconsistent, including GAPDH,^{26,28–30,34,35,37} RNU6B,³² and β -actin.^{25,33} The Newcastle-Ottawa Scale confirmed that all studies were of good quality.

Association between the CASC2 expression and OS

The association between the CASC2 expression and overall survival (OS) is shown in Figure 2. We performed a cumulative meta-analysis to assess the function of CASC2 for OS in patients with cancers. There were 5 of 13 included studies with 995 patients reporting the relationship between OS and CASC2. The fixed effects model was used because no heterogeneity was found among those five studies (unadjusted $I^2 = 34.2\%$, $P = 0.193$; adjusted $I^2 = 0.00\%$, $P = 0.452$). There was a graded reduction in unadjusted event rates for OS from high to low expression of CASC2 (pooled HR=0.40,

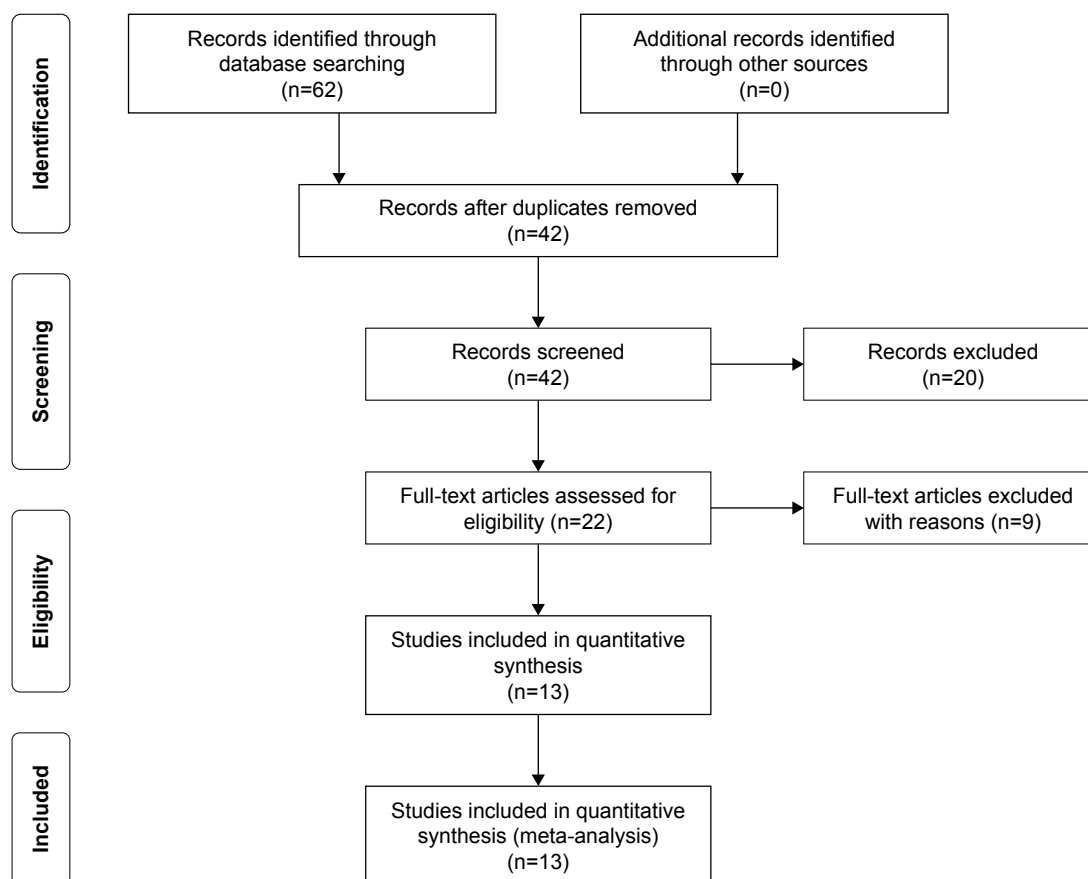


Figure 1 Flow diagram of the study search and selection process in the meta-analysis.

95% CI: 0.29–0.54, $P < 0.0001$) (Figure 2A). After further adjustment, the difference still existed that the OS of patients with lower expression of CASC2 was obviously decreased (pooled HR=0.39, 95% CI: 0.28–0.53, $P < 0.0001$) (Figure 2B). These results from our meta-analysis study suggested that the expression of CASC2 was independently associated with OS among patients with cancers.

Association between CASC2 expression and clinicopathological parameters of malignant tumors

The correlations between CASC2 expression and cancers in gender, TNM, LNM, DM, T stage and HD are presented in Figure 3. There was no obvious heterogeneity in these studies, and the fixed effects model was used ($I^2=0.0\%$, $P=0.304$; $I^2=11.8\%$, $P=0.332$; $I^2=13.4\%$, $P=0.327$; $I^2=16.4\%$, $P=0.309$; $I^2=00.0\%$, $P=0.623$; $I^2=00.0\%$, $P=0.866$). As it shown, we observed that there was no difference in CASC2 expression between the male and female patients with malignant tumors (pooled OR=0.86, 95% CI: 0.65–1.14, $P > 0.05$) (Figure 3A). People with TNM stage III–IV malignancies showed lower

expression of CASC2, compared with those with stage I–II (pooled OR=0.36, 95% CI: 0.26–0.48, $P < 0.001$) (Figure 3B). CASC2 expression was also negatively related to LNM of cancer and T stage in cancer patients (pooled OR=0.62, 95% CI: 0.43–0.89, $P < 0.01$; pooled OR=0.42, 95% CI: 0.25–0.72, $P < 0.01$) (Figure 3C and E). However, no significant difference was observed between the two groups in the DM and HD incidence (pooled OR=0.59, 95% CI: 0.33–1.07, $P > 0.05$; pooled OR=0.64, 95% CI: 0.41–1.00, $P > 0.05$) (Figure 3D and F). These results indicated that low CASC2 expression in patients with malignant tumors may predict increased probability of DM, LNM and T stage.

Publication bias

The potential publication bias of the present meta-analysis was evaluated by funnel plot and Beggs indicator test in Figure 4. The results showed no evidence of publication bias was detected in the gender analysis with the expression of CASC2 ($P > 0.05$) as well as LNM ($P > 0.05$) (Figure 4A and C). Similar results occurred in the shape of the Begg's indicator test, which did not reveal any evidence of obvious

Table 1 Summary of the 13 included articles

Study	Region	Tumor type	Sample size	CASC2 expression						OS			Reference gene	Method
				High			Low			HR (95% CI) (UA)	HR (95% CI) (MA)			
				Total	HD	LNM	DM	Total	HD			LNM		
Feng et al, 2017 ²⁸	China	CC	60	30	NA	15	NA	30	NA	NA	NA	NA	GAPDH	RT-PCR
Gan et al, 2017 ²⁹	China	HCC	50	19	11	4	2	31	20	8	2	NA	GAPDH	RT-PCR
He et al, 2016 ²⁵	China	NSCLC	76	38	7	19	NA	38	14	21	NA	0.192 (0.070–0.528)	GAPDH	RT-PCR
Huang et al, 2016 ²⁶	China	GC	68	34	14	18	NA	34	23	21	NA	NA	GAPDH	RT-PCR
Liao et al, 2017 ³⁰	China	Glioma	57	29	9	NA	NA	28	18	NA	NA	0.571 (0.305–1.069)	GAPDH	RT-PCR
Wang et al, 2017 ³⁵	China	Glioma	47	22	6	NA	NA	25	16	NA	NA	0.492 (0.278–0.843)	β-actin	RT-PCR
Wang et al, 2017 ³⁵	China	HCC	75	38	4	NA	NA	37	15	NA	NA	NA	β-actin	RT-PCR
Xiong et al, 2017 ³⁴	China	TC	86	70	18	37	2	16	11	6	1	0.058 (0.006–0.588)	GAPDH	RT-PCR
Yu et al, 2017 ³²	China	PC	110	56	26	NA	25	54	28	NA	28	0.368 (0.219–0.619)	RNU6B	RT-PCR
Zhou et al, 2017 ³³	China	GC	69	34	4	NA	3	35	15	NA	11	NA	GAPDH	RT-PCR
Wang et al, 2017 ³⁵	China	LAC	63	29	10	13	NA	34	21	24	NA	NA	GAPDH	RT-PCR
He et al, 2017 ⁴⁰	China	ESCC	133	47	14	21	NA	86	45	57	NA	NA	GAPDH	RT-PCR
Chen et al 2017 ⁴²	China	PA	72	36	NA	NA	NA	36	NA	NA	NA	NA	GAPDH	RT-PCR

Abbreviations: CC, cervical cancer; CRC, colorectal cancer; DM, distant metastasis; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HD, high difference; LAC, lung adenocarcinoma; LNM, lymph node metastasis; MA, multivariate analysis; NA, not available; NSCLC, nonsmall-cell lung cancer; OS, overall survival; PA, pituitary adenoma; PC, pancreatic cancer; RT-PCR, reverse transcription polymerase chain reaction; TC, thyroid carcinoma; UA, univariate analysis.

asymmetry (Figure 4D and F). For the analysis of TNM, but, there was certain publication bias in these 11 articles and the funnel plot and the Begg’s indicator test revealed asymmetry ($P<0.05$) (Figure 4B and E).

Sensitivity analysis

The stability of the crude results was evaluated by sensitivity analysis in Figure 5. The results suggested that the conclusions are stable and robust because the pooled HR was not significantly affected by the exclusion of any single study.

The prognostic significance of CASC2 expression in malignant tumors

Bioinformatics analysis was performed to gain insight into the functional impact of the expression of CASC2 on cancers. As summarized in Figure 6, we performed multivariate analysis using Cox’s hazard proportional model to evaluate whether CASC2 expression was an independent prognostic factor for malignant tumors, and four types of tumors were found with a significant difference, including KIRC, LGG, PAAD and SARC. Then, Kaplan–Meier curves with log-rank analysis were further used to explore the relationship between the expression of CASC2 and the OS rates of these patients in Figure 7. Similar to the results of our meta-analysis, we found that a higher CASC2 expression was positively correlated with longer survival time than in patients with lower CASC2 expression ($P<0.05$) (Figure 7A–D). These results suggested that CASC2 may be an independent predictor of tumors.

Discussion

Accumulating evidence has demonstrated that lncRNAs could play oncogenetic, tumor suppressive roles or both under different circumstances and in different tissues and cells, and they may promise to be the new tumor marker for diagnostic and prognosis of tumors.^{9,43} CASC2, which was considered to be a tumor suppressor, has been reported by several original articles negatively relating to poor prognosis of cancers through its regulation of diverse cellular processes, including migration, invasion, proliferation, differentiation, and apoptosis.^{28,30,31} Our results from the meta-analysis and bioinformatics analysis also suggested that the lower expression of CASC2 was consistently associated with poor prognosis of malignant tumors. The value of meta-analysis is illustrated by the fact that most studies individually lacked precision, a problem alleviated by pooling.

In our study, we found that sarcoma patients from 13 remaining articles presented poor OS, including HCC,

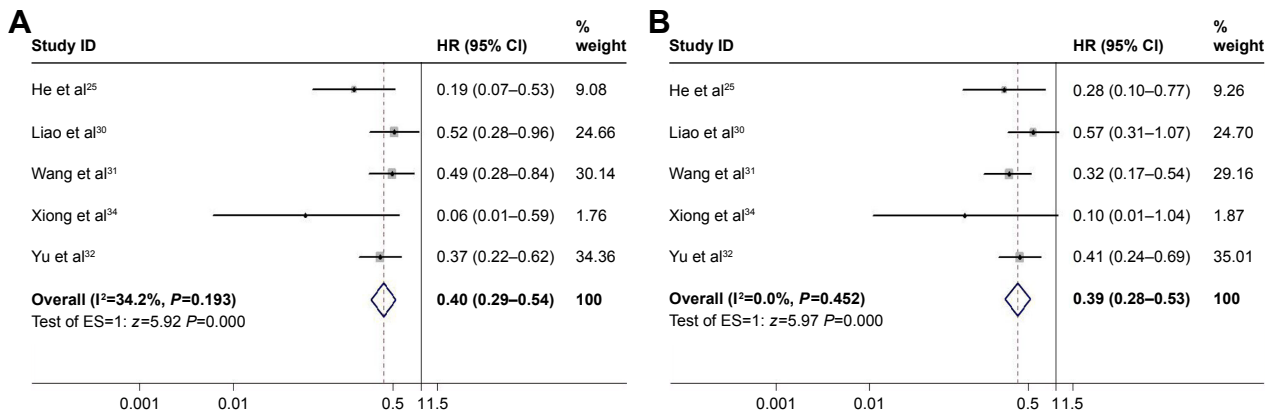


Figure 2 Forest plot for the association between CASC2 expression and OS. **Notes:** (A) Unadjusted event rates for OS, (B) adjusted event rates for OS. **Abbreviations:** ES, effect size; OS, overall survival; CASC2, cancer susceptibility candidate 2.

glioma, NSCLC, CRC, ESCC, TC, PC, LAC, PA, CC and GC, when the level of CASC2 expression downregulated in tumor tissue. Meanwhile, patients with higher CASC2 expression often displayed better prognosis and less clinicopathologic features, the same phenomenon were

shown in tumor cell lines. Since the lncRNA CASC2 was originally found to be downregulated in endometrial cancer in 2004 as a tumor suppressor,²³ there have been an increasing number of studies demonstrating that CASC2 expression was related to the prognosis of malignant tumors

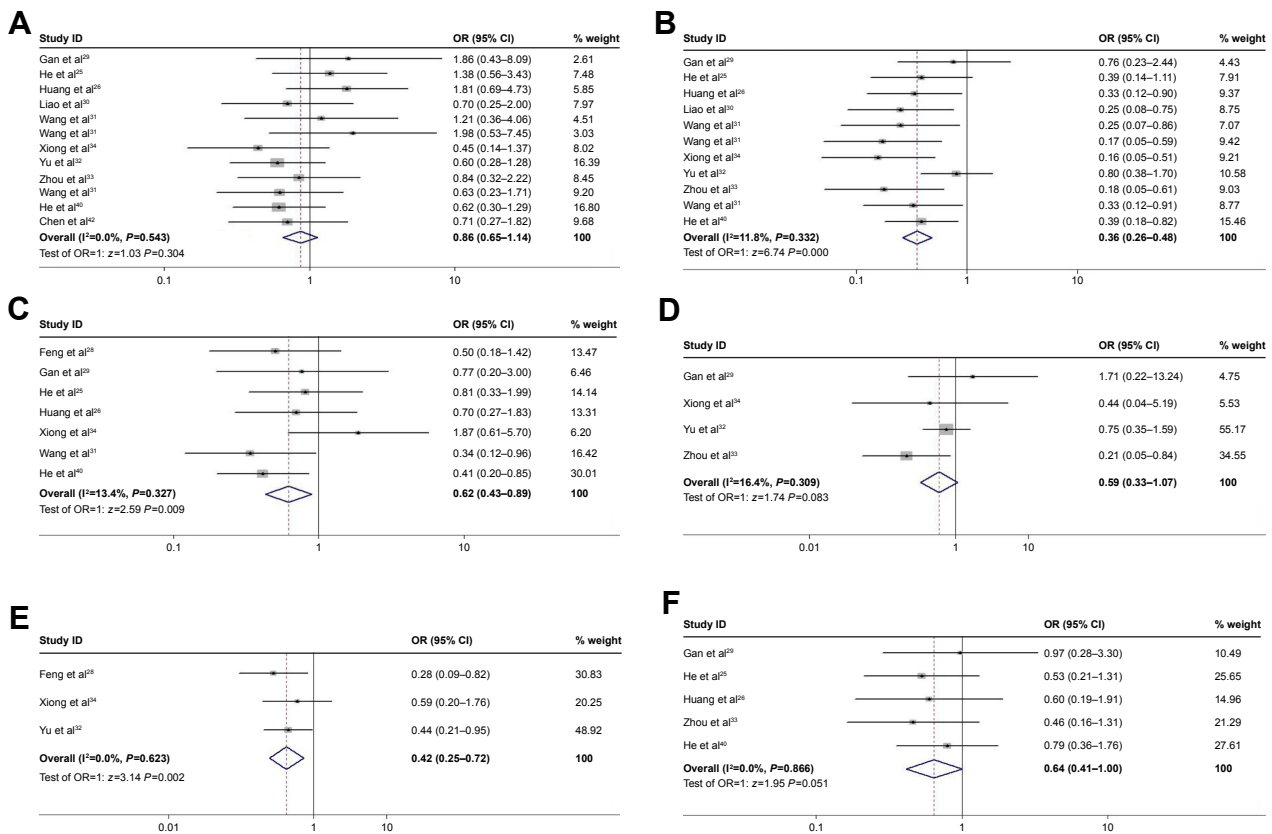


Figure 3 Forest plot for the association between CASC2 expression and clinicopathological parameters of malignant tumors. **Notes:** (A) Correlation between gender and CASC2 expression (female vs male), (B) correlation between TNM and CASC2 expression (stage III–IV vs stage I–II), (C) correlation between LNM and CASC2 expression, (D) correlation between DM and CASC2 expression, (E) correlation between T stage and CASC2 expression, (F) correlation between HD and CASC2 expression. **Abbreviations:** LNM, lymph node metastasis; DM, distant metastasis; TNM, tumor node metastasis.

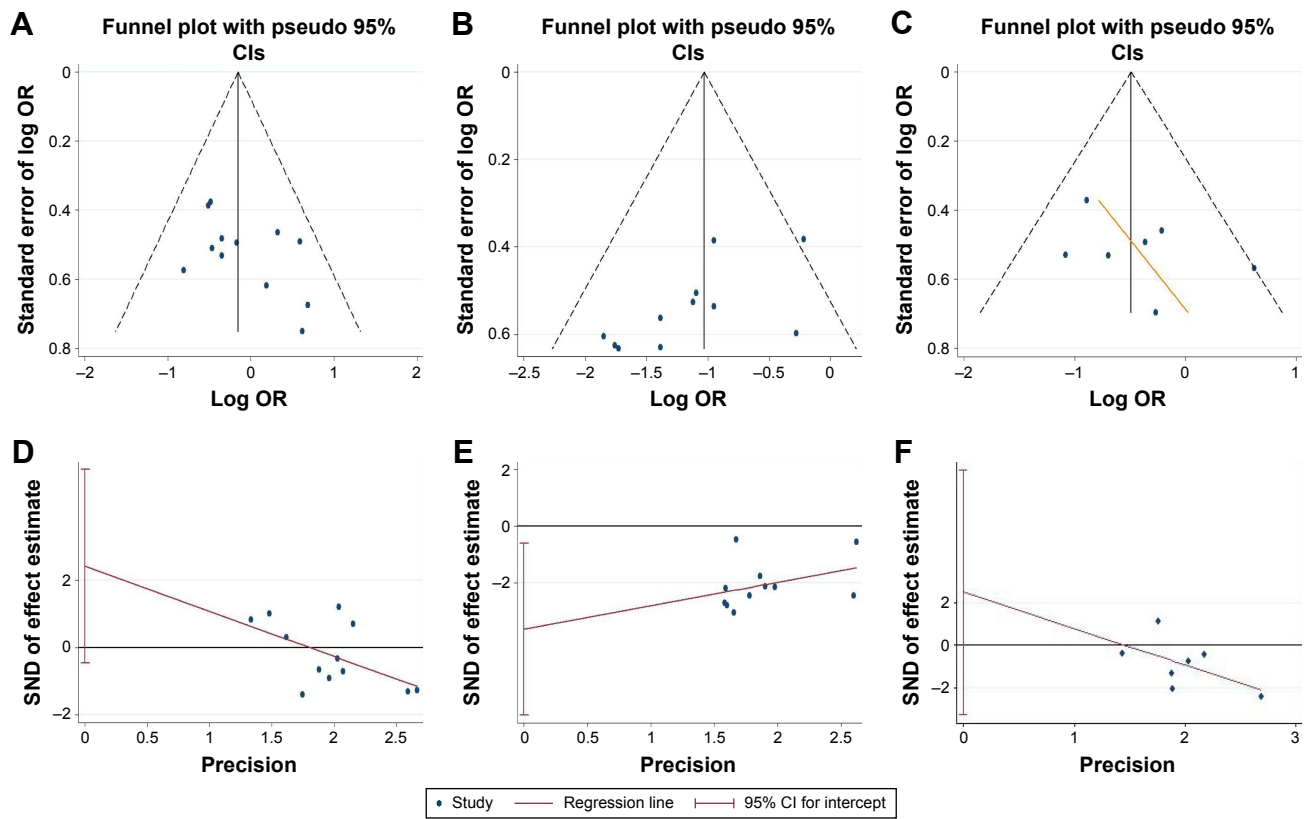


Figure 4 Funnel plot and Begg's indicator tests of the publication bias.

Notes: (A) Funnel plot for gender, (B) funnel plot for TNM, (C) funnel plot for LNM, (D) Begg's indicator test for gender, (E) Begg's indicator test for TNM, (F) Begg's indicator test for LNM.

Abbreviations: LNM, lymph node metastasis; SND, standard normal deviate; TNM, tumor node metastasis.

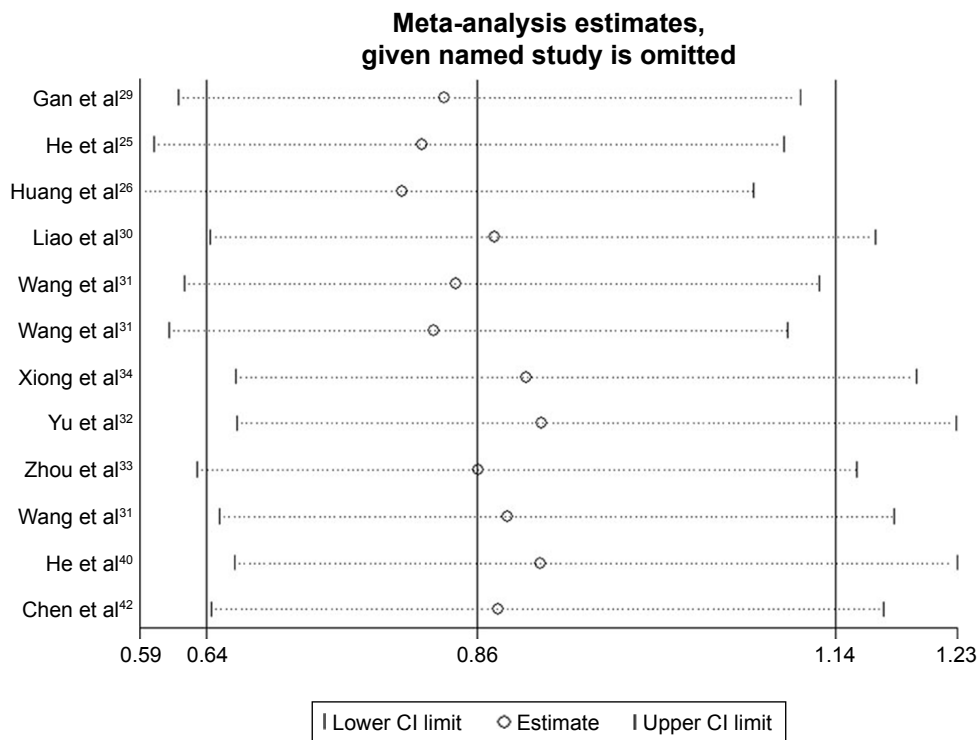


Figure 5 Sensitivity analyses of studies concerning CASC2.

Abbreviation: CASC2, cancer susceptibility candidate 2.

Cancer ▲▼	Coefficient ▲▼	P-value ▲▼	Corrected ▲▼	Rank ▲▼	Expression ▲▼	Expression ▲▼
BLCA	-0.004	9.60e-01	9.82e-01	15,920	23.08	27.71
BRCA	-0.087	3.00e-01	6.69e-01	7,314	48.98	55.35
CECSC	-0.125	3.10e-01	6.52e-01	7,650	26.12	35.81
COAD	-0.094	3.40e-01	7.24e-01	7,578	34.95	38.82
ESCA	-0.033	7.90e-01	9.87e-01	13,347	35.25	42.46
GBM	-0.038	6.60e-01	9.54e-01	11,523	77.38	90.36
HNSC	0.01	8.90e-01	9.64e-01	15,299	15.01	18.75
KIRC	-0.06	4.40e-01	5.69e-01	12,832	60.19	67.45
KIRP	-0.25	1.00e-01	2.33e-01	6,934	116.2	121.43
LAML	-0.082	4.30e-01	7.71e-01	8,396	11.65	16.29
LGG	-0.034	7.10e-01	7.81e-01	15,242	122.12	139.94
LIHC	0.054	5.50e-01	7.69e-01	11,258	6.37	9.57
LUAD	-0.068	3.60e-01	6.00e-01	9,964	37.86	48.16
LUSC	0.062	3.90e-01	8.22e-01	7,920	24.27	29.61
OV	-0.01	8.90e-01	9.81e-01	15,228	68.99	83.88
PAAD	-0.268	1.60e-02	9.75e-02	2,765	44.57	52.83
READ	0.178	3.90e-01	9.57e-01	6,575	37.04	40.24
SARC	-0.265	1.50e-02	1.27e-01	1,863	26.58	33.0
SKCM	-0.073	2.90e-01	4.98e-01	9,253	13.39	17.42
STAD	-0.049	5.60e-01	8.46e-01	11,107	49.51	58.94
UCEC	0.011	9.20e-01	9.95e-01	15,224	64.61	80.28

Figure 6 Cox regression results of CASC2 expression in malignant tumors.

Abbreviations: BLCA, Bladder urothelial carcinoma; BRCA, Breast invasive carcinoma; CESC, Cervical and endocervical cancers; COAD, Colon adenocarcinoma; ESCA, Esophageal carcinoma; GBM, Glioblastoma multiforme; HNSC, Head and Neck squamous cell carcinoma; KIRC, kidney renal clear cell carcinoma; KIRP, Kidney renal papillary cell carcinoma; LGG, Brain Lower Grade Glioma; LAML, Acute Myeloid Leukemia; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; PAAD, Pancreatic adenocarcinoma; OV, Ovarian serous cystadenocarcinoma; READ, Rectum adenocarcinoma; SARC, Sarcoma; SKCM, Liver hepatocellular carcinoma; STAD, Stomach adenocarcinoma; UCEC, Uterine Corpus Endometrial Carcinoma.

through different mechanisms. For example, one of the most prominent events was the increased ability of tumor cell proliferation in NSCLC, HCC, CC, CRC, glioma, TC, PC, and GC, where patients presented with low levels of CASC2 expression.^{25,26,28–35} Decreased CASC2 expression in PC, GC, LAC and ESCC was associated with LNM and DM.^{32,33,40,41} And, in HCC, CRC, glioma, GC and PA, a low level of CASC2 was related to migration and invasion.^{29,30,31,33,35,42} Additionally, CASC2 expression was observed to be significantly correlated with TNM and T stage in NSCLC, CC, TC, PC, GC, LAC and ESCC.^{25,26,32–34,40,41} On the contrary, in HCC, NSCLC, CC, CRC, glioma, TC and PA cells, a higher expression of CASC2 exerted significant tumor suppressing functions through promoting cell apoptosis and arresting cell cycle in vitro, as well as inhibiting tumor cell growth and reducing tumor size.^{25,26,29–31,34,35,42} In the meantime, we

further strengthened the results of our meta-analysis by bioinformatics. In the Kaplan–Meier curves with log-rank analysis, we found that the OS of patients with KIRC, LGG, PAAD and SARC was longer compared with those who had lower CASC2 expression. Those results all illustrated that CASC2 might play the role of tumor suppressor in various tumors. A new therapeutic strategy through upregulating the CASC2 expression may benefit cancer patients.

Limitation and strengths

There were some limitations in this meta-analysis. First, the potential publication bias suggested that the tests were likely to be underpowered. Second, the relatively small number of studies which only came from China limited our ability to identify the relationships between the CASC2 and malignant tumors. The small number of studies also limited the

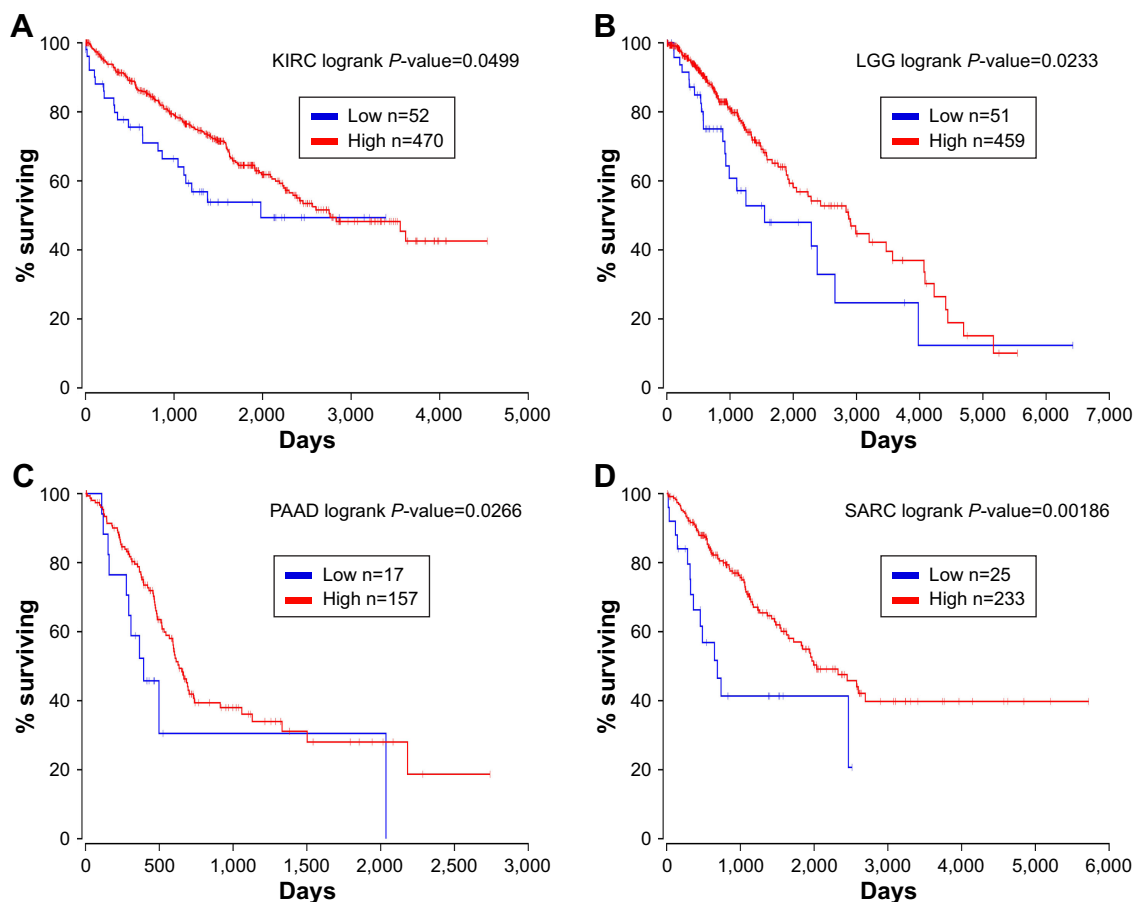


Figure 7 The prognostic significance of CASC2 expression in malignant tumors from TCGA data.

Notes: (A) The survival curve of patients with KIRC, (B) the survival curve of patients with LGG, (C) the survival curve of patients with PAAD, (D) the survival curve of patients with SARC.

Abbreviations: KIRC, kidney renal clear cell carcinoma; LGG, brain lower grade glioma; PAAD, pancreatic adenocarcinoma; SARC, sarcoma; TCGA, The Cancer Genome Atlas.

assessment of heterogeneity related to study quality, and our data may not represent global populations. Third, there is a significant correlation between the status of prognosis and the treatment of patients, and these differences might have a great impact on HR. Finally, unpublished data, non-English language studies, and missed studies may exist and might have influenced our results. Therefore, more studies are needed to make reliable quantitative statements about the relation of CASC2 to malignant tumors. Despite the limitations of the present study, the observed results may be viewed as hypotheses generating and supporting further studies.

Conclusion

In conclusion, results from this meta-analysis supported a recent and growing body of evidence that the expression of CASC2 is negatively correlated with the prognosis of cancers. Moreover, bioinformatics analysis revealed the correlation between the higher expression of CASC2 and longer OS in patients with malignant tumors. Our findings

indicated that CASC2 might be a powerful tool for predicting the progression and prognosis of malignant tumor patients. More studies are needed to determine whether overexpression of CASC2 can benefit patients with various tumors in the future. Future studies focused on CASC2 are also needed to explore mechanisms for tumor initiation and progression.

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Author contributions

LY and SC are co-first authors on this manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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