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ORIGINAL RESEARCH

Long noncoding RNA DANCR in various cancers: a meta-analysis and bioinformatics

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Background: Differentiation antagonizing non-protein-coding RNA (DANCR) is a novel long noncoding RNA. Recent studies have shown that DANCR is aberrantly expressed in several types of cancer and is associated with poor outcomes. However, the clinical diagnostic significance of DANCR in tumors is not completely understood.

Methods: We searched the PubMed, Medline, Web of Science, EMBASE, Cochrane Library, and Ovid databases (up to December 30, 2018) for relevant literature. A total of 11 studies with 945 cancer patients were included in the present meta-analysis. We further validated the results using The Cancer Genome Atlas (TCGA) dataset.

Results: High expression of DANCR significantly predicted poor overall survival (low expression group vs high expression group; HR =0.56, 95% CI=[0.43, 0.72], =0.000); this was validated using TCGA. Moreover, DANCR expression was associated with advanced tumor node metastasis stage (I+II:III+IV; OR=0.22, 95% CI=[0.14, 0.35], *P*=0.001) and lymph node metastasis (no:yes; OR=0.21, 95% CI=[0.13, 0.35], *P*=0.001).

Conclusion: Our results suggest that elevated DANCR is related to poor clinical outcomes and could serve as a potential prognostic biomarker of cancer.

Keywords: cancer, overall survival, TCGA, long noncoding RNA, DANCR, meta-analysis

Introduction

Cancer is expected to rank as the leading cause of mortality and morbidity worldwide, with approximately 14 million new cases and 8 million cancer-related deaths every year, affecting populations in all countries and all regions.[1,2] Despite the rapid development of science and technology, oncotherapy continues to face great challenges, including delayed diagnosis and poor prognosis, mainly due to the lack of specific biomarkers.[3,4] Therefore, study of specific biomarkers in cancer, particularly the relationships between cancer progression and expression levels of biomarkers, may provide novel diagnostic methods and potential therapeutic targets for cancer.

Long noncoding RNAs (lncRNAs), a group of RNA molecules without protein-coding capacity and more than 200 nucleotides in length, can regulate gene expression at the transcriptional or post-transcriptional level.[5,6] Increasing numbers of studies have implicated dysregulation of lncRNAs in cancers, including in proliferation, invasion, and metastasis, and shown that they can function as either tumor suppressors or oncogenes.[7–10] Previous studies have demonstrated that 18% of lncRNAs are associated with tumors; much higher than the corresponding proportion (9%) of protein-coding genes.[11] Moreover, some lncRNAs have been confirmed as specific prognostic biomarkers for cancers. Previous meta-analyses indicated a connection between

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expression levels of ZEB1-AS1[12] and PCAT-1[13] and prognosis of cancer. All these results suggest an important role for lncRNAs in carcinogenesis and cancer progression. They may thus represent promising novel prognostic biomarkers for tumors. LncRNA differentiation antagonizing non-protein-coding RNA (DANCR) is located on chromosome 4, with the closest adjacent annotated genes being USP46 and ERVMER34-1. DANCR was originally identified as a suppressor in the progression of epidermal cell differentiation,[14] and it functions as an oncogenic driver in several types of cancer.[15,16] Several studies have reported that DANCR is abnormally expressed in multiple tumors and associated with tumor proliferation, invasion, and metastasis. Further, there is increasing evidence that high expression levels of DANCR are related to clinicopathological features such as tumor size, lymph node metastasis (LNM), differentiation, tumor node metastasis (TNM) stage, and prognosis.[16–26] These results have provided new insights into the role of DANCR in the development of cancers and indicated the potential applications of DANCR as a prognostic marker. However, these studies were limited in their ability to assess the implications of DANCR levels in cancer owing to inconsistent outcomes.[20,21] To date, there has not been a meta-analysis of the published studies available. Therefore, in the pre sent study, we performed a correlation analysis based on meta-analysis and bioinformatics methods to investigate the relationship between DANCR and clinicopathological characteristics and prognosis.

Materials and methods

Literature search and study design

The study was performed according to standard guidelines for the meta-analysis of original studies.[27,28] The PubMed, Medline, Web of Science, EMBASE, Cochrane Library, and Ovid databases were searched. The latest search time was December 30, 2018. The key words for searches were “DANCR” OR “Differentiation antagonizing non-protein coding RNA” OR “Long noncoding RNA DANCR” OR “lncRNA DANCR” and “Cancer” or “Tumor” or “Neoplasia” and “prognos*” or “outcome”.

Inclusion and exclusion criteria

Two researchers assessed all of the included studies and extracted the data independently. In this meta-analysis, the inclusion criteria were as follows: 1) the study reported original data and was published as a full peer-reviewed article; 2) the level of DANCR expression was measured in human tumor tissue by reverse-transcriptase polymerase chain reaction (RT-PCR) and patients were grouped according to different DANCR expression level; 3) the patients had a definitive diagnosis of cancer; 4) studies with sufficient original data for statistical analyses of survival information, namely, overall survival (OS) or clinicopathological features such as LNM, advanced TNM stage, or gender differences with lncRNA DANCR expression.

The exclusion criteria were as follows: 1) cell or animal experiments, letters, case reports, or reviews; 2) cases where the required data could not be extracted from the original article; 3) publications for which a later or more complete version was available for the same data subsets.

Data extraction and quality assessment

Data extraction from the original aritcles was conducted independently by two investigators for each included article. Any disagreements were resolved by discussion and consensus with a third investigator. The extracted data included the first author’s name, year of publication, country, method of DANCR testing, hazard ratio (HR) and the corresponding 95% confidence interval (CI) for lncRNA DANCR for OS (primary outcome) and clinicopathological parameters (gender, age, tumor size, differentiation, LNM, and TNM stage).A database was established after the selected data were arranged and verified. Quality assessment of the included studies was performed according to Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines[28] (Table S1); the study scores ranged from 60% to 75%, and studies with more than 60% scores could be regarded as high quality. The detailed assessment was show in Table S2.

Statistical analysis

Engauge Digitizer 10.0 software was used to extract the survival data from Kaplan–Meier curves. STATA 12.0 software was used to analyze the extracted data. HR and corresponding 95% CI values were used to assess the association between DANCR and OS. Odds ratios (ORs) with 95% CIs were pooled to assess the correlation between DANCR expression and clinicopathological features. The chi-squared Q test and I^2 statistics were used to evaluate the heterogeneity. A fixed-effects model was chosen when there was no severe heterogeneity (I^2<50% or P>0.1). Otherwise, a random-effects model was used. Begg’s test was used to evaluate potential publication bias, and sensitivity analyses were performed to examine the stability of the results.

Bioinformatics analysis

DANCR expression and clinical data of patients with cancer were retrieved from The Cancer Genome Atlas (TCGA) (https://cancergenome.nih.gov/). Htseq-counts data downloaded from TCGA were used to perform differential expression analysis between tumor samples and adjacent normal samples. The analysis was performed using the Edge R package;[29] two-fold changes in expression levels and differences with false discovery rate <0.01 were considered significant. Survival analysis was performed using the median DANCR gene FPKM (fragments per kilobase of transcript per million fragments mapped) as a cutoff value; patients were classified into a DANCR high-expression group and a DANCR low-expression group.[30] Kaplan–Meier survival curves and log-rank tests were used to assess the differences in

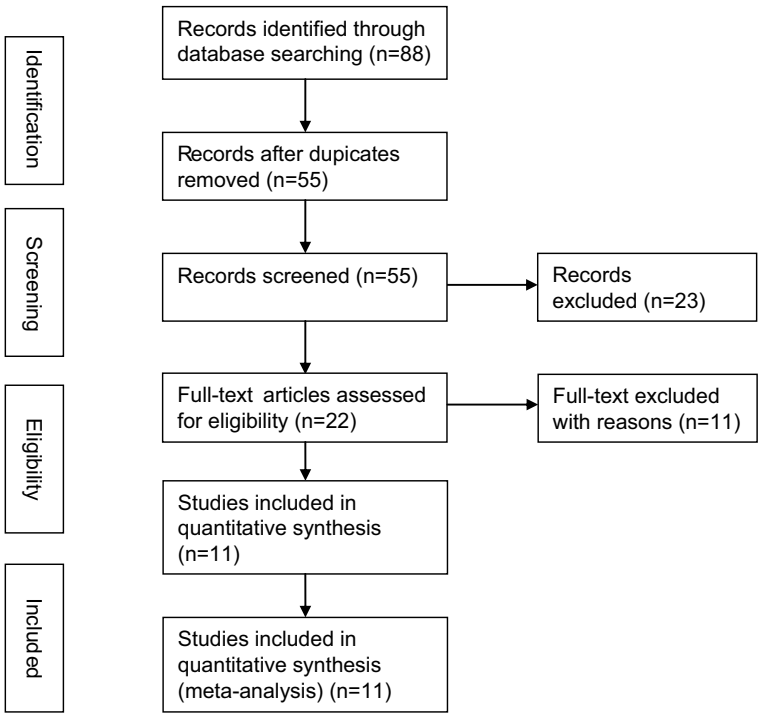


Figure 1 Flow diagram of the study search and selection process in the meta-analysis.

Table 1 Summary of the 11 included articles

Study	Region	Tumor type	Sample size	DANCR expression		Survival information	HR	Laboratory method
				High	Low			
Li et al, 2017[17]	China	glioma	86	43	43	os	0.55(0.27–1.13)(C)	qRT-PCR
Liu et al, 2015[18]	China	CRC	104	52	52	os	0.467(0.141–0.867)(R)	qRT-PCR
Mao et al, 2017[16]	China	GC	60	30	30	NA	NA	qRT-PCR
Hao et al, 2017[19]	China	GC	118	46	72	os	0.52 (0.23–1.17)(C)	qRT-PCR
Pan et al, 2018[20]	China	GC	65	40	25	NA	NA	qRT-PCR
Sha et al, 2017[21]	China	TNBC	63	32	31	os	0.58 (0.32–1.54)(C)	qRT-PCR
Wang et al, 2018[22]	China	NSCLC	128	64	64	os	0.47(024–0.94)(C)	qRT-PCR
Wen et al, 2018[23]	China	NPC	86	43	43	os	0.76(0.42–1.39)(C)	qRT-PCR
Yang et al, 2018[24]	China	glioma	82	41	41	os	0.561(0.287–0.892)(R)	qRT-PCR
Yong et al, 2018[25]	China	CRC	47	26	21	NA	NA	qRT-PCR
Zhan et al, 2018[26]	China	BC	106	70	36	NA	NA	qRT-PCR

Abbreviations: BC, Urothelial carcinoma of the bladder; C, HR was estimated by curve; CRC, colorectal cancer; GC, Gastric cancer; NPC, nasopharyngeal carcinoma; NA, Not available; NSCLC, non-small cell lung cancer; R, HR was reported; TNBC, Triple negative breast cancer.

survival time between the two group, using $P<0.05$ as a threshold. The analysis was performed using survival R packages.

Results

Study identification and characteristics

As shown in Figure 1, a total of 88 potential studies were collected from the database, of which 66 studies were removed as they were found to be non-DANCR-related, duplicated, or did not involve tests in tumor tissues when their titles and abstracts were reviewed; a total of 22 articles were identified for full review. Eleven studies were then excluded owing to lack of specific reporting on the association of DANCR with cancer or insufficient data in the original studies. Finally, the remaining 11 articles were included in the meta-analysis. The assessment for Risk of bias in individual studies is shown in Table S3.

As shown in Table 1, all reports were written in English and were published in China between 2015 and 2018. In these studies, a total of 945 patients were represented, with a mean sample size of 85.9 (range from 47 to 128). There were six types of cancer in this meta-analysis: urothelial carcinoma of the bladder, colorectal cancer, gastric cancer, glioma, nasopharyngeal carcinoma, non-small-cell lung cancer, and triple negative breast cancer. Patients were divided into two groups (high and low expression of DANCR). All the DANCR measurements were performed using RT-PCR. All measurements of pathological parameters were dependent on individual pathology.

Association between DANCR and prognosis

The association between DANCR expression level and OS is shown in Figure 2. We performed a cumulative meta-analysis to assess the function of DANCR with respect to OS in cancer patients. Of the 11 included studies, seven studies with 667 patients reported on the relationship between OS and DANCR. A fixed-effects model was used because no obvious heterogeneity was found among those seven studies. The pooled HRs indicated that higher DANCR expression was related to worse survival (low DANCR expression group vs high expression group; pooled HR =0.56, 95% CI=[0.43, 0.72], P=0.000, fixed effect; Figure 2A). The stability of the pooled results was evaluated by sensitivity analysis (Figure 2B), which indicated that the results were reliable. Begg's funnel plot was used to evaluate publication bias, showing that there was no publication bias for OS (P=0.133; Figure 2C).

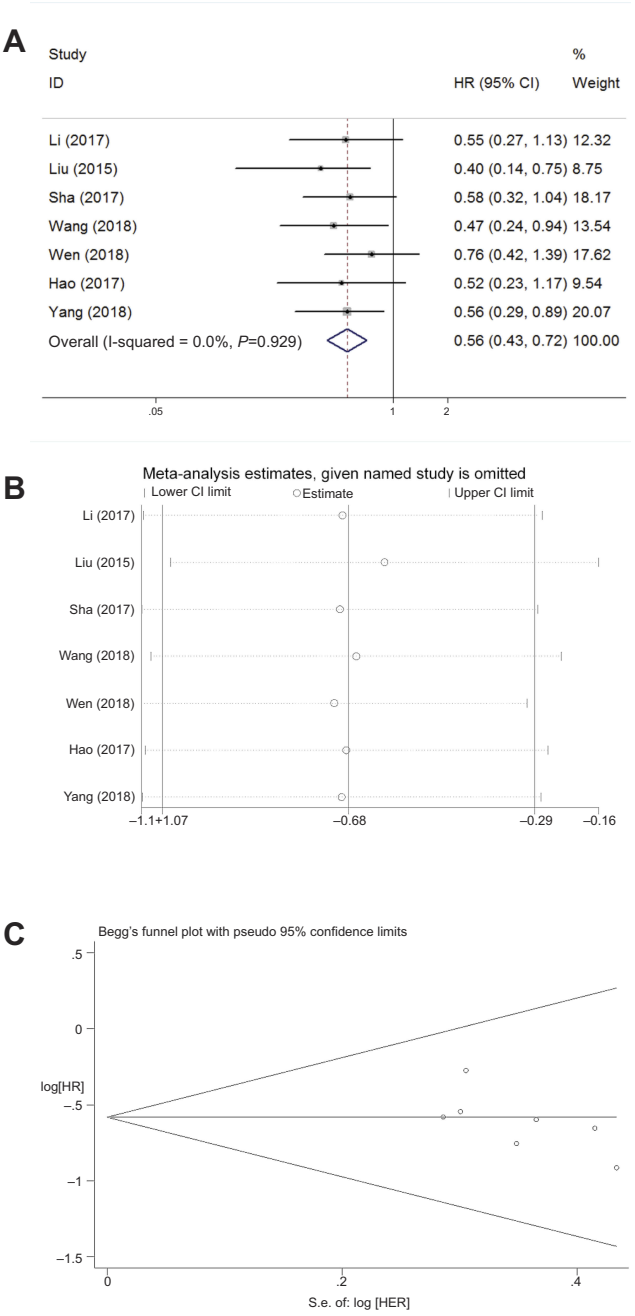


Figure 2 Forest plot of studies evaluating (**A**) the relationship between DANCR expression and overall survival (OS) rate, (**B**) sensitivity analysis for OS, and (**C**) Begg's publication bias plots of OS.

Association between DANCR and clinicopathologic characteristics

In this meta-analysis, four studies reporting on 325 patients with differentiation were included. As shown in Table 2, higher expression of DANCR was related to low differentiation (high + moderate:low, pooled OR=0.36, 95% CI=[0.15, 0.68], P=0.021, random effect). Further, the pooled ORs demonstrated that

Table 2 The association between DANCR expression and clinical features

Clinicopathological parameters	Studies (n)	Patients (n)	OR (95% CI)	*P*-value	Heterogeneity		
					I_2 (%)	P_h	Model
Age	6	484	1.27 (0.87, 1.86)	0.219	0	0.649	Fixed
Gender	5	413	1.29(0.84, 1.96)	0.754	0	0.754	Fixed
Tumor size	5	398	0.72(0.36–1.42)	0.354	61.4	0.035	Random
Differentiation	4	325	0.36, (0.15, 0.68)	0.021	69.2	0.0021	Random
TNM stage	5	378	0.22, (0.14, 0.35)	0.0001	0	0.682	Fixed
LNM	5	398	0.21, (0.13, 0.35)	0.0001	3.3	0.388	Fixed

Note: Bold figures indicate statistically significant $P<0.05$.
Abbreviations: DM, distant metastasis; LNM, lymph node metastasis.

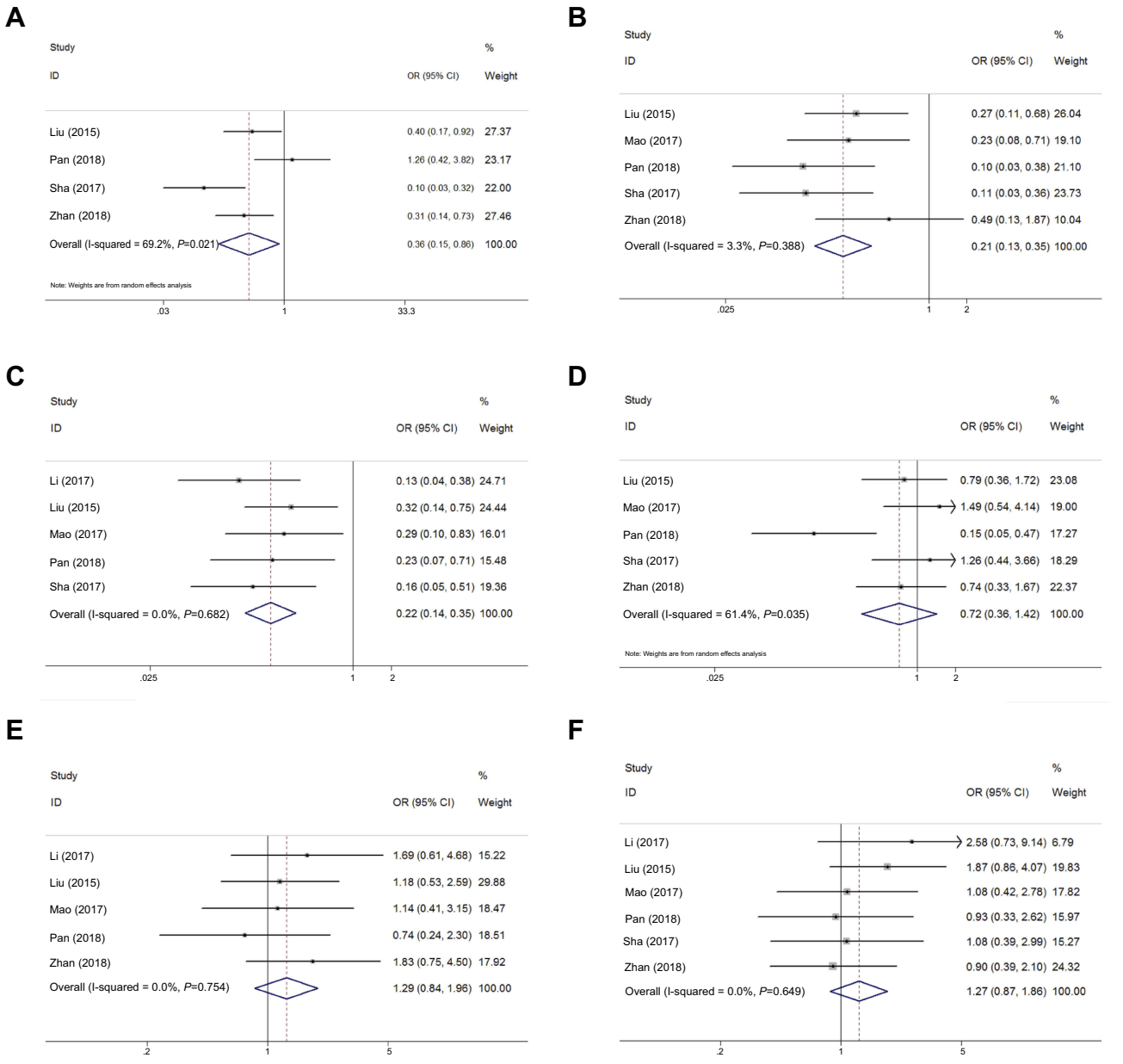


Figure 3 Forest plot of studies evaluating the relationship between DANCR expression and (**A**) differentiation, (**B**) lymph node metastasis, (**C**) stage, (**D**) tumor size, (**E**) gender, and (**F**) age.

DANCR upregulation was related to LNM (no:yes, OR=0.21, 95% CI=[0.13, 0.35], *P*=0.001, fixed effect) and advanced TNM stage (I+II:III+IV, OR=0.22, 95% CI=[0.14, 0.35], *P*=0.001, fixed effect). However, no significant difference was observed between the two groups for tumor size (OR=0.72, 95% CI:=[0.36–1.42], *P*=0.354, random effect). The pooled results also demonstrated that the expression of DANCR was not related to gender (OR=1.29, 95% CI=[0.84, 1.96], *P*=0.754, fixed effect) or age (OR=1.27, 95% CI=[0.87, 1.86], *P*=0.219, fixed effect). Therefore, our results indicated that high DANCR expression significantly increased the risk of worse clinicopathological features. (Figure 3A–F). Begg's funnel plot was used to evaluate publication bias (Figure 4A–F). There was no publication bias for gender (*P*=0.806), age (*P*=0.707), tumor size (*P*=0.806), differentiation (*P*=0.899), LNM (*P*=0.901), or TNM stage (*P*=0.221).

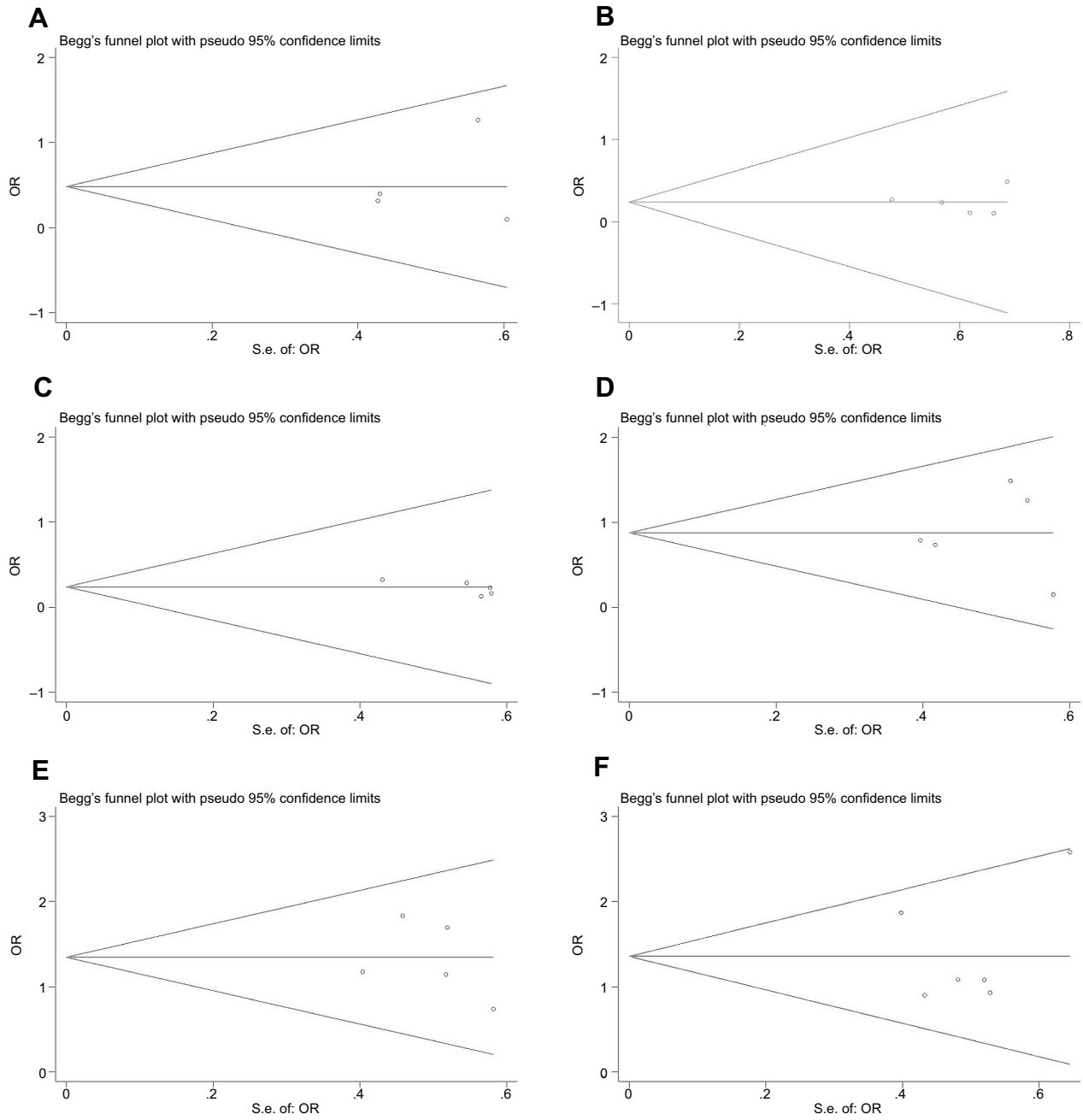


Figure 4 Begg's publication bias plots evaluating the relationship between DANCR expression and (**A**) differentiation (**B**) lymph node metastasis (**C**) Stage (**D**) Tumor size (**E**) Gender (**F**) Age.

Validation of the results in TCGA dataset

Bioinformatics analysis was performed to gain insight into the functional impact of the expression of DANCR on various cancers. We first evaluated the expression of DANCR in six different cancers using data from TCGA. As shown in Figure 5, DANCR was overexpressed in four of these cancers, including brain lower grade glioma, thymoma, diffuse large B-cell lymphoma, and cholangiocarcinoma (|Log_2fold change (FC)| cutoff >1 and P<0.01). Kaplan–Meier curves with log-rank analysis were used to determine the relationships between the expression of DANCR and the OS rates of all patients with various cancers based on the TCGA dataset. Similar to the results of our meta-analysis, we found that higher DANCR expression (n=5021) was correlated with shorter survival time compared with patients with lower DANCR expression (n=5020) (log-rank P<0.05) (Figure 6A). The role of DANCR in different tumor types was then analyzed. Higher expression of DANCR was related to worse OS in adrenocortical carcinoma (ACC), liver hepatocellular carcinoma (LIHC), and sarcoma (SARC) (log-rank P<0.05) (Figure 6B–D). These results suggest that DANCR could function as an independent prognostic biomarker for tumors.

Discussion

Accumulating evidence has shown that DANCR is upregulated in various cancers. This meta-analysis was performed to clarify the association between DANCR and clinicopathologic features and prognosis in cancers. The results suggested that the risk of developing LNM, lower differentiation, and advanced TNM stage was higher in the high DANCR expression group compared with the low expression group. The pooled results also showed that high expression of DANCR was related to a worse OS; thus, DANCR could be an independent indicator for the prognosis of cancers. This meta-analysis is the first review to assess the relationship between DANCR and the prognosis of patients in various cancers. We further strengthened the results of our meta-analysis using bioinformatics methods. The Kaplan–Meier curves with log-rank analysis showed that, in ACC, LIHC and SKCM, the OS of patients with high DANCR expression was shorter than that of those with low DANCR expression. These results all illustrate that DANCR could function as a prognostic biomarker, with the potential for new cancer therapies that involve downregulation of DANCR expressions.

Previous studies also investigated the mechanism of DANCR in different cancers, with respect to cell proliferation, invasion, and metastasis. In glioma,[18] DANCR markedly increased migration and proliferation of glioma cells by activating the Wnt/β-catenin signaling pathway. In hepatocellular carcinoma, Yuan et al[15] found that DANCR increased the stemness features of tumor cells to promote tumorigenesis, invasion, and metastasis. In the respiratory system, DANCR contributes to the proliferation, migration, and invasion of lung adenocarcinoma cells by regulating miR-496[31] and miR-758-3p.[22] In bladder cancer, Zhan et al[26] found that knockdown of DANCR inhibited epithelial-mesenchymal transition and malignant phenotypes of bladder cancer cells. DANCR promoted proliferation, migration, and invasion of cells in cervical cancer[32] and osteosarcoma[33] by acting as a competing endogenous RNA, regulating ROCK1 expression through binding to miR-335-5p.In colorectal cancer,

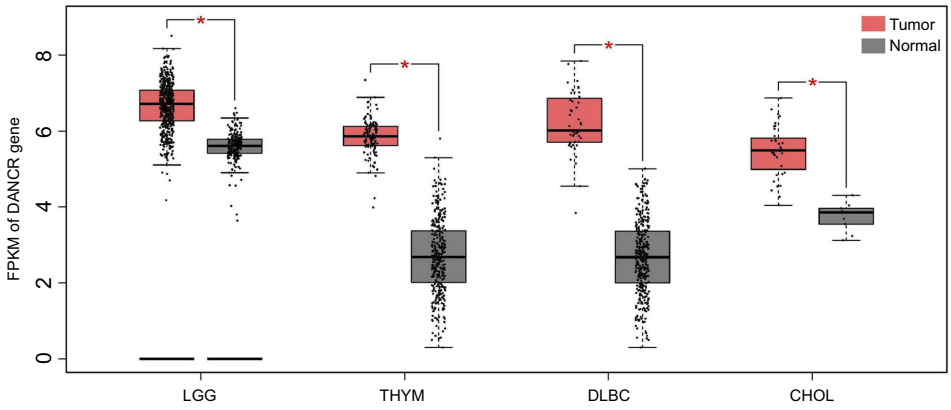


Figure 5 The expression levels of DANCR in four kinds of cancer tissues and normal tissues. "*"|Log_2FC|>1 and P<0.01.
Abbreviations: LGG, brain lower grade glioma; THYM, Thymoma; DLBC, Diffuse Large B-cell Lymphoma; CHOL, Cholangiocarcinoma.

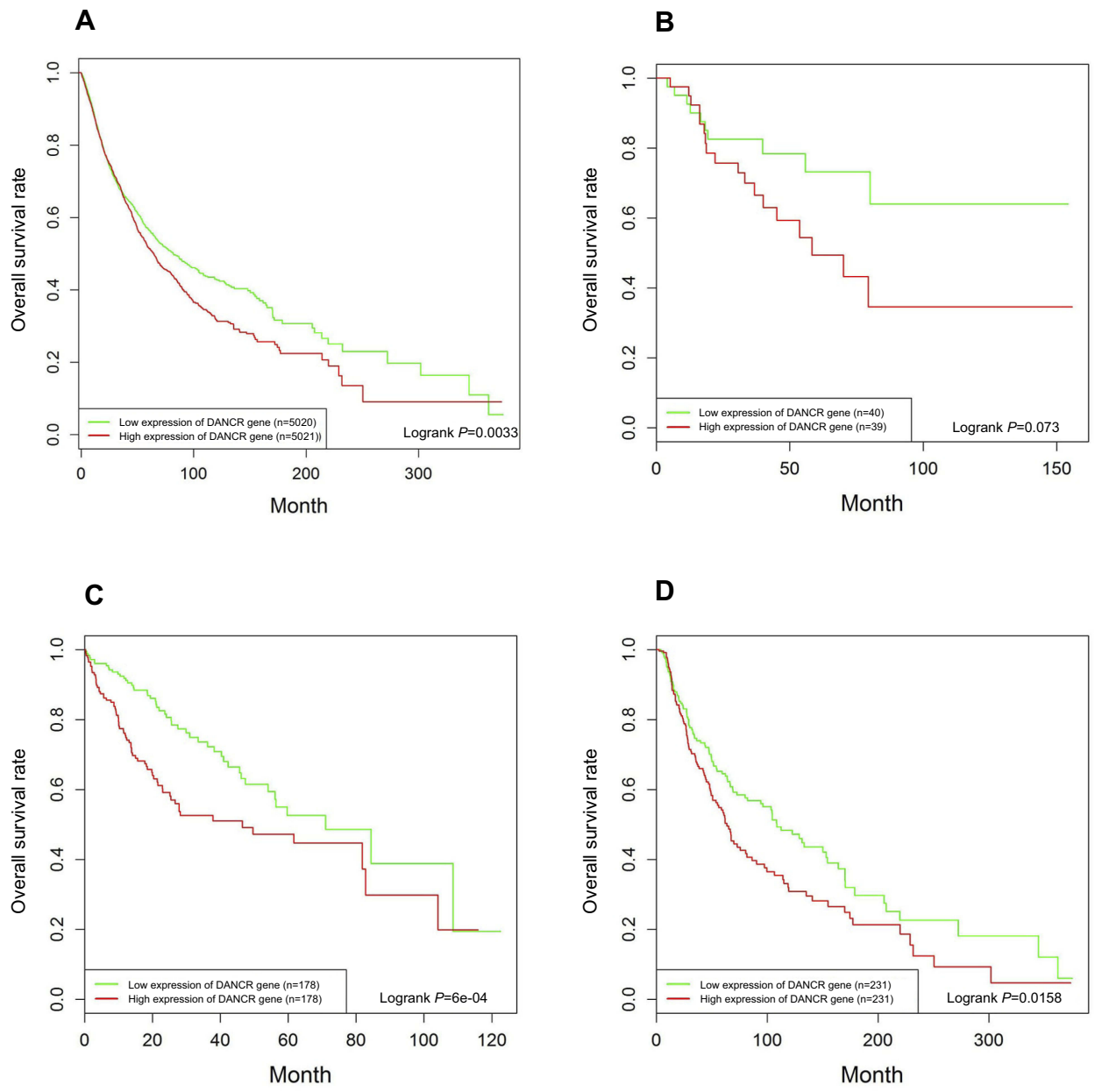


Figure 6 (**A**) Survival curves of DANCR are plotted for all kinds of cancers from TCGA dataset (n=10041). (**B**) The survival curve of patients with ACC. (**C**) The survival curve of patients with LIHC (**D**) the survival curve of patients with SKCM.

Abbreviations: ACC, Adrenocortical carcinoma; LIHC, Liver hepatocellular carcinoma; SKCM, Skin Cutaneous Melanoma; TCGA, The Cancer Genome Atlas.

Wang et al[25] confirmed that overexpression of DANCR promoted proliferation and metastasis of tumor cells via miR-577 binding.

This meta-analysis had some limitations. First, all the studies included were from the People's Republic of China, so our data may not represent global populations. Second, some HRs for OS were extracted from Kaplan–Meier curves, potentially leading to errors. Third, a limited number of tumor types and patients were included. More studies with larger sample sizes and examining various cancers should be included in future analyses.

Conclusions

Our meta-analysis suggested that high expression of DANCR was significantly associated with poor outcomes in various cancers and could serve as a potential prognostic biomarker. However, considering the limitations of the present analysis, more high-quality studies with large sample sizes are needed to confirm the prognostic value of DANCR in cancers.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Reporting recommendations for tumor marker prognostic studies (REMARK) checklist

INTRODUCTION	
1	State the marker examined, the study objectives, and any pre-specified hypotheses.
MATERIALS AND METHODS	
Patients	
2	Describe the characteristics (for example, disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.
3	Describe treatments received and how chosen (for example, randomized or rule-based).
Specimen characteristics	
4	Describe type of biological material used (including control samples) and methods of preservation and storage.
Assay methods	
5	Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.
Study design	
6	State the method of case selection, including whether prospective or retrospective and whether stratification or matching (for example, by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.
7	Precisely define all clinical endpoints examined.
8	List all candidate variables initially examined or considered for inclusion in models.
9	Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.
Statistical analysis methods	
10	Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.
11	Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.
RESULTS	
Data	
12	Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the number of patients and the number of events.
13	Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.
Analysis and presentation	
14	Show the relation of the marker to standard prognostic variables.
15	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect (for example, hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.
16	For key multivariable analyses, report estimated effects (for example, hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.
17	Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.
18	If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.
DISCUSSION	
19	Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.
20	Discuss implications for future research and clinical value.

Table S2 Assessing the quality of included studies based on reporting recommendations for tumor marker prognostic studies (REMARK) guideline

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Tatal (%)
Li et al, 2017[1]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	70
Liu et al, 2015[2]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	70
Mao et al, 2017[3]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	×	×	✓	✓	✓	✓	✓	65
Hao et al, 2017[4]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	70
Pan et al, 2018[5]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	×	×	✓	✓	✓	✓	✓	65
Sha et al, 2017[6]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	70
Wang et al, 2018[7]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	70
Wen et al, 2018[8]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	75
Yang et al, 2018[9]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	75
Yong et al, 2018[10]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	×	×	✓	✓	✓	✓	65
Zhan et al, 2018[11]	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓	✓	✓	×	×	✓	×	✓	✓	60

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Table S3 Risk of bias in individual studies

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Li et al, 2017[1]	H	H	H	L	H
Liu et al, 2015[2]	H	H	H	L	H
Mao et al, 2017[3]	H	L	L	U	H
Hao et al, 2017[4]	H	H	H	L	H
Pan et al, 2018[5]	H	L	L	U	H
Sha et al, 2017[6]	H	H	H	L	H
Wang et al, 2018[7]	H	H	H	L	H
Wen et al, 2018[8]	H	H	H	L	L
Yang et al, 2018[9]	H	L	L	U	L
Yong et al, 2018[10]	H	H	H	L	H
Zhan et al, 2018[11]	H	L	L	U	H

Abbreviations: H, high risk of bias; L, low risk of bias; U, unclear bias.

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