Prognostic significance of long non-coding RNA DANCR expression in human cancers: A systematic review and meta-analysis

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Author’s contribution
Jia Guo and Wei Liu were responsible for study design. Wei Liu and Qin-Peng Wang were responsible for literature search. Wei Liu and Qin-Peng Wang were responsible for data extraction. Wei Liu and Qin-Peng Wang and Jia Guo were responsible for data analysis. Jia Guo and Wei Liu were responsible for drafting the manuscript. All authors approved the final version of the manuscript.

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Abstract

Background: Several studies demonstrated that long non-coding RNA differentiation antagonizing non-protein coding RNA (lncRNA DANCR) expression might have the potential capacity to predict the cancer prognosis, however, definite conclusion has not been obtained. The aim of this meta-analysis was to evaluate the prognostic value of lncRNA DANCR expression in cancers. Methods: PubMed, Web of Science, Scopus and Embase were comprehensively searched for relevant studies. Studies meeting all inclusion standards were included into this meta-analysis. The analysis of overall survival (OS), disease-free survival (DFS) or clinicopathological features was conducted. Results: Eleven studies containing 1,154 cancer patients were analyzed in this meta-analysis. The results showed, compared with low lncRNA DANCR expression, high lncRNA DANCR expression was significantly associated with shorter OS (HR=1.85, 95%CI=1.52-2.26, P<0.01) and DFS (HR=1.82, 95%=1.43-2.32, P<0.01) in cancers. Besides, high lncRNA DANCR expression predicted deeper tumor invasion (P<0.01), earlier lymph node metastasis (P<0.01), earlier distant metastasis (P<0.01) and more advanced clinical stage (P<0.01) compared with low lncRNA DANCR expression in cancer populations. Conclusion: High lncRNA DANCR expression was associated with worse prognosis compared with low lncRNA DANCR expression in cancers. LncRNA DANCR expression could serve as a prognostic factor of human cancers.

Key words: lncRNA DANCR, cancer, prognosis, meta-analysis
Introduction
Cancer has become a crucial public health problem and a leading-cause of death worldwide [1, 2]. Despite of tremendous improvement of diagnosis and treatments, the prognosis of many cancer patients at terminal stage remains disappointing [2, 3]. The lack of efficient biomarkers to serve as treatment targets and predict the prognosis is considered as the main reason for this dilemma. Therefore, a growing number of researchers begin to look for optimal biomarkers of human cancers [4, 5].

With the rapid development of high-throughput sequencing technology, increasing long non-coding RNAs (lncRNAs) are discovered and have become the research hotspots [6]. LncRNA, greater than 200nt in length, is a major type of noncoding RNAs without protein-coding capability [7]. Recently, lncRNAs have been proved to be closely associated with tumorigenesis, differentiation, invasion and metastasis of cancers [8, 9]. LncRNA differentiation antagonizing non-protein coding RNA (lncRNA DANCR), a kind of lncRNA, is located on human chromosome 4 [10]. Recently, accumulating studies have supported a substantial role of lncRNA DANCR expression in the cancer prognosis [11-21]. However, conclusion has not been reached for the contradictory results among different publications [11-21]. Here, we conducted this systematic review and meta-analysis to determine the prognostic value of lncRNA DANCR expression in cancers.

Materials and methods
This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22] (Supplementary Table 1)

Literature search and selection
PubMed, Web of Science, Scopus and Embase were comprehensively searched up to January 15th, 2019. The strategy was as following: (“long non-coding RNA differentiation antagonizing non-protein coding RNA” OR “long non-coding RNA DANCR” OR “lncRNA DANCR” OR “DANCR”) AND (“cancer” OR “tumor” OR “neoplasm” OR “carcinoma”). There was no restriction on the language. References
of retrieved studies were also checked to avoid missing relevant studies. All studies were selected according to inclusion and exclusion criteria.

**Inclusion and exclusion criteria**

The study was considered to be eligible if it satisfied the following criteria: (1) patients were pathologically diagnosed as cancers; (2) prognostic value of IncRNA DANCR expression in cancers was assessed; (3) overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) or clinicopathological feature was reported; (4) patients were divided into two groups based on the expression level of IncRNA DANCR; (5) full text and sufficient data were provided. The following studies were excluded: reviews, comments, letters, case reports, cell experiments, animal experiments, unpublished studies and duplications.

**Data extraction and quality evaluation**

Data extraction and quality evaluation were independently operated by two authors. Any disagreement would be solved by discussing with the third author. The following items were extracted: first author, publication year, country, sample size, gender, expression level of IncRNA DANCR, cancer type, outcomes and analysis model of OS. As for prognostic variables (e.g. OS, DFS and RFS), hazard ratio (HR) and corresponding 95% confidence interval (CI) were directly extracted from published studies or indirectly calculated from survival curves if only survival curves were available [23]. Moreover, if HR and 95%CI were simultaneously provided in the multivariate analysis and univariate analysis, the former were used. The analysis model of OS was considered as univariate analysis when HR and 95%CI were indirectly calculated from survival curves. Quality of included studies was assessed with Newcastle–Ottawa Scale (NOS). We considered studies with scores no less than 6 as high-quality studies [24].

**Statistical analysis**

For prognostic variables, such as OS, DFS and RFS, HR and 95%CI were pooled to assess the relationship between IncRNA DANCR expression and cancer prognosis. As for dichotomous, such as gender, lymph node metastasis and clinical stage, odds ratio (OR) and 95%CI were applied to detect the overall effects. Heterogeneity was
assessed using Cochran’s Q test and Higgins I-squared statistics. $I^2>50\%$ and/or $P<0.10$ suggested obvious heterogeneity among studies, as a result, a random-effect model was utilized. Alternatively, a fixed-effect model was used. Sensitivity analysis was done by omission of each single study. Publication bias was evaluated using Begg’s test and funnel plots. All analyses were conducted by Reviewer Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 (Stata Corporation, College Station, Texas, USA). All $P$ values were two sides and difference was considered significant when $P$ value was less than 0.05.

Results

Literature search and selection

A total of 118 articles were initially retrieved from four common databases (Figure 1). Thirty-eight articles remained for further evaluation after the removal of duplicates. Then, twenty-three articles were directly excluded by scanning titles or abstracts. Regarding to the remaining fifteen articles, four articles were excluded by evaluating full-texts. Ultimately, eleven studies were included for further analysis [11-21].

Basic information of included studies

The basic information of studies included was listed in Table 1. Eleven studies containing 1,154 cancer patients were included into this research [11-21]. Especially, Yuan et al. study consisted of two cohorts (cohort 1: Chinese population; cohort 2: Korea population) [21], therefore, twelve cohorts were analyzed in this research. Seven studies reported the clinical stage of patients (I/II: 235 patients; III/IV: 317 patients) [11, 13-16, 18, 19]. Besides, IncRNA DANCR expression in cancer tissues was evaluated using quantitative reverse transcription polymerase chain reaction (qRT-PCR) in all studies [11-21]. Three studies used the median value [13, 14, 21] and one study used the normalized value to divide patients into high or low IncRNA DANCR expression groups [16], however, the other studies failed to provide the definite cut-off value [11, 12, 15, 17-20]. Additionally, seven types of cancer were investigated, including gastric cancer [11, 14, 15], osteosarcoma [12, 19], non-small
cell lung cancer[17], colorectal cancer [13, 18], breast cancer [16] and glioma [20] as well as hepatocellular carcinoma [21]. Patients received surgical treatment in eight studies [11-13, 15, 16, 18-20], nevertheless, treatment of patients in the other studies was not available [14, 17, 21]. Regarding to outcomes, nine studies reported clinicopathological parameters [11-16, 18-20], eight studies reported OS [11-13, 16, 17, 19-21], two studies reported DFS [12, 13] and one study reported RFS [21]. Moreover, OS was evaluated using multivariate analysis model in three cohorts [12, 13, 21] and univariate analysis model in six cohorts [11, 16, 17, 19-21]. NOS score was larger than six in all studies, which indicated all studies were with high quality [11-21].

**Meta-analysis for the association between lncRNA DANCR expression and prognosis**

Eight studies evaluated the correlation between lncRNA DANCR expression and OS, and all of them were included into the analysis [11-13, 16, 17, 19-21]. As shown in Figure 2, a fixed-effect model was used because there was no obvious heterogeneity among included studies ($I^2=24\%$, $P=0.23$). High lncRNA DANCR expression was significantly correlated with shorter OS compared with low lncRNA DANCR expression in cancers (HR=1.85, 95%CI=1.52-2.26, $P<0.01$).

To further explore the prognostic value of lncRNA DANCR expression in cancers, subgroup analysis was performed (Table 2). Significant relationship between high lncRNA DANCR expression and shorter OS was detected in all subgroup analyses ($P<0.05$).

Two studies reported DFS [12, 13] and one study reported RFS [21], and all of them were included into the analysis for DFS (Figure 3). A fixed-effect model was used because of the moderate heterogeneity ($I^2=43\%$, $P=0.15$). Compared with patients with low lncRNA DANCR expression, patients with high lncRNA DANCR expression tended to have a shorter DFS (HR=1.82, 95%CI=1.43-2.32, $P<0.01$).

**Meta-analysis for the association between lncRNA DANCR expression and clinicopathological parameters**

Meta-analyses for the association between lncRNA DANCR expression and...
clinicopathological parameters were conducted (Table 3). There was no obvious relationship between the expression level of lncRNA DANCR and age (P=0.26), gender (P=0.42), tumor size (P=0.59) or tumor differentiation (P=0.11). However, compared with low expression level of lncRNA DANCR, high expression level of lncRNA DANCR was significantly associated with deeper tumor invasion (P<0.01), earlier lymph node metastasis (P<0.01), earlier distant metastasis (P<0.01) and more advanced clinical stage (P<0.01).

**Publication analysis and sensitivity analysis**

Begg’s test for the meta-analysis of OS showed there was no obvious publication bias among studies (Figure 4). Funnel plots demonstrated there was no distinct publication bias with respect to the meta-analyses of DFS and clinicopathological parameters (Figure 5). Sensitivity analysis indicated the pooled results of OS were not influenced by omitting each single study (Figure 6).

**Discussion**

LncRNAs have been proved to play a vital role in the tumorigenesis, differentiation, invasion and metastasis of cancers [25, 26]. Many lncRNAs have the potential capacity to predict the cancer progression and prognosis [27, 28]. Recently, many studies have found that lncRNA DANCR expression might be involved with the prognosis of cancers, however, dispute remains for conflicting data among different studies [11-21].

In our study, we discovered that high lncRNA DANCR expression was significantly associated with shorter OS and DFS in cancers. We also found, compared to patients with low lncRNA DANCR expression, patients with high lncRNA DANCR expression tended to have deeper depth of invasion, earlier lymph node metastasis, earlier distant metastasis and more advanced clinical stage. Unexpectedly, we failed to observe the relationship of lncRNA DANCR expression with tumor size or differentiation, however, it should be noted that the results were not reliable enough because of the distinct heterogeneity among included studies. Overall, high lncRNA DANCR expression was an unfavorable factor in the cancer prognosis. To our
knowledge, this study was the first meta-analysis to explore the prognostic and
clinicopathological value of lncRNA DANCR expression in human cancers.
Many researches have tried to elucidate the prognostic role of lncRNA DANCR
expression in cancers [11-13], however, the underlying mechanism remains unclear.
Yang et al. found that down-expression of lncRNA DANCR could increase the
expression of miR-33a-5p, reduce the EMT and increase the apoptosis of glioma cells
[20]. Differently, Li et al. study demonstrated that high lncRNA DANCR expression
could positively affect the progression of glioma through activating the Wnt/β-catenin
signaling [29]. Besides, lncRNA DANCR could mediate cisplatin resistance in glioma
cells via activating the AXL/PI3K/Akt/NF-κB signaling pathway [30]. Wang et al.
study revealed that lncRNA DNACR facilitated the invasion and metastasis of
osteosarcoma by promoting the ROCK1-mediated progression through decoying both
miR-1972 and miR-335-5p [19]. Besides, lncRNA DANCR could promote the HSP27
expression and its mediation of metastasis via miR-577 sponging in colorectal cancer
[31]. Zhen et al. results showed lncRNA DANCR could promote the progression of
lung cancer by sequestering the miR-216a [32]. Lu et al. study, also focusing on lung
cancer, discovered that lncRNA DANCR expression regulated mTOR expression by
directly binding to miR-496 [33]. In gastric cancer, Pan et al. found SALL4 could
facilitate the lncRNA DANCR expression and exert its oncogenic activities via
activating the β-catenin pathway [15]. As for prostate cancer, Jia et al. study revealed
that lncRNA DANCR promoted the tumor invasion and metastasis through the
down-expression of TIMP2/3 [34].
Several limitations should be considered when interpreting our results. First, only
eleven studies were included into this meta-analysis, which might reduce the
stringency of results. Second, most studies included were conducted in China, which
might result in regional bias. Third, HR and 95%CI were extracted from survival
curves in several studies as described by Tierney et al. [23], which might be affected
by the subjective factors of operators, however, this method has been widely accepted
and used in meta-analyses [35-37]. Forth, the prognostic value of lncRNA DANCR
expression in specific cancer was not determined in this study because of limited
included studies. With a view to these limitations, prospective studies with larger population and longer follow-up time are warranted to clarify this issue.

**Conclusion**

High lncRNA DANCR expression was associated with shorter OS, shorter DFS and worse clinicopathological features compared with low lncRNA DANCR expression in human cancers. LncRNA DANCR expression could serve as a promising prognostic factor of human cancers.

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370 10.2147/ott.s154162.
371
372 Figure legends
373 Figure 1 Flaw chart of literature search and selection
374 Figure 2 Meta-analysis of the association between lncRNA DANCR expression and
375 OS
376 Figure 3 Meta-analysis of the association between lncRNA DANCR expression and
377 DFS
378 Figure 4 Begg’s test for meta-analysis of the association between lncRNA DANCR
379 expression and OS
380 Figure 5 Funnel plots for the meta-analyses of the association between lncRNA
381 DANCR expression and DFS or clinicopathological parameters (a, age; b, gender; c,
382 tumor size; d, tumor differentiation; e, depth of invasion; f, lymph node metastasis; g,
383 distant metastasis; h, clinical stage)
384 Figure 6 Sensitivity analysis for the meta-analysis of the association between lncRNA
385 DANCR expression and OS
386
387 Table legends
388 Table 1 Basic information of included studies
389 Table 2 Subgroup analysis for the association between lncRNA DANCR expression
Table 3 Meta-analysis for the association between lncRNA DANCR expression and clinicopathological parameters

Supplementary Table 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
**PRISMA 2009 Flow Diagram**

**Identification**
- Records identified through database searching
  
  \( n = 118 \)

**Additional records identified through other sources**
  
  \( n = 0 \)

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**Screening**
- Records after duplicates removed
  
  \( n = 38 \)

**Eligibility**
- Records screened
  
  \( n = 38 \)

**Records excluded**
  
  \( n = 23 \)

- Full-text articles assessed for eligibility
  
  \( n = 15 \)

**Studies included in qualitative synthesis**
  
  \( n = 11 \)

**Included**
- Studies included in quantitative synthesis (meta-analysis)
  
  \( n = 11 \)

- Full-text articles excluded with reasons
  - Irrelevant to this topic
    
    \( n = 3 \)
  - Review
    
    \( n = 1 \)
| Study or Subgroup | log[Hazard Ratio] | SE    | Weight | IV. Fixed, 95% CI | IV. Fixed, 95% CI |
|-------------------|-------------------|-------|--------|-------------------|-------------------|
| Hao 2017          | 0.3646            | 0.4911| 4.2%   | 1.44 [0.55, 3.77] |                   |
| Jiang 2017        | 1.7317            | 0.6534| 2.4%   | 5.65 [1.57, 20.33]|                   |
| Jiang 2018        | 1.0784            | 0.4658| 4.7%   | 2.94 [1.18, 7.33] |                   |
| Liu 2015          | 0.7566            | 0.3116| 10.5%  | 2.13 [1.16, 3.92] |                   |
| Sha 2017          | 0.6366            | 0.351 | 8.3%   | 1.89 [0.95, 3.76] |                   |
| Wang 2018         | 1.2119            | 0.4467| 5.1%   | 3.36 [1.40, 8.06] |                   |
| Yang 2018         | 0.5783            | 0.2368| 18.2%  | 1.78 [1.12, 2.84] |                   |
| Yuan 2016 (1)     | 1.0141            | 0.3535| 8.2%   | 2.76 [1.38, 5.51] |                   |
| Yuan 2016 (2)     | 0.3293            | 0.1629| 38.4%  | 1.39 [1.01, 1.91] |                   |
| Total (95% CI)    |                   |       | 100.0% | 1.85 [1.52, 2.26] |                   |

Heterogeneity: $\chi^2 = 10.54$, df = 8 ($P = 0.23$); $I^2 = 24\%$

Test for overall effect: $Z = 6.10$ ($P < 0.00001$)
Meta-analysis fixed-effects estimates (exponential form)

Study omitted

Hao 2017

Jiang 2017

Jiang 2018

Liu 2015

Sha 2017

Wang 2018

Yang 2018

Yuan 2016 (1)

Yuan 2016 (2)

1.46| 1.52 | 1.85 | 2.26 | 2.85
| Study     | Country | Sample size (n) | Clinical stage (I+II/III+IV) | Detection methods | Cut-off value | Cancer type       | Treatments | Outcomes | Analysis model | NOS |
|-----------|---------|----------------|-------------------------------|-------------------|---------------|-------------------|------------|----------|----------------|-----|
| Hao 2017  | China   | 118            | 48/70                         | qRT-PCR           | NA            | Gastric cancer    | Surgery    | CP, OS   | U              | 7   |
| Jiang 2017| China   | 34             | NA                            | qRT-PCR           | NA            | Osteosarcoma      | Surgery    | CP, DFS, OS | M              | 8   |
| Jiang 2018| China   | 128            | NA                            | qRT-PCR           | NA            | NSCLC             | NA         | OS       | U              | 6   |
| Liu 2015  | China   | 104            | 37/67                         | qRT-PCR           | Median        | Colorectal cancer | Surgery    | CP, DFS, OS | M              | 8   |
| Mao 2017  | China   | 60             | 33/27                         | qRT-PCR           | Median        | Gastric cancer    | NA         | CP       | NA             | 6   |
| Pan 2018  | China   | 65             | 19/46                         | qRT-PCR           | NA            | Gastric cancer    | Surgery    | CP       | NA             | 6   |
| Sha 2017  | China   | 63             | 37/26                         | qRT-PCR           | ≤0.5 / ≥2.0†  | Breast cancer     | Surgery    | CP, OS   | U              | 7   |
| Wang 2018 | China   | 95             | 42/53                         | qRT-PCR           | NA            | Osteosarcoma      | Surgery    | CP, OS   | U              | 7   |
| Yang 2018 | China   | 82             | NA                            | qRT-PCR           | NA            | Glioma            | Surgery    | CP, OS   | U              | 7   |
| Yuan 2016 | China   | 135            | NA                            | NA                | Median        | Hepatocellular cancer | NA         | RFS, OS  | M              | 7   |
| Yuan 2016 | Korea   | 223            | NA                            | NA                | Median        | Hepatocellular cancer | NA         | RFS, OS  | U              | 6   |
| Zeng 2018 | China   | 47             | 19/28                         | qRT-PCR           | NA            | Colorectal cancer | Surgery    | CP       | NA             | 6   |

qRT-PCR, quantitative reverse transcription polymerase chain reaction; NSCLC, non-small cell lung cancer; CP, clinicopathological parameters; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; U, univariate; M, multivariate; NOS, Newcastle-Ottawa Scale; NA, not available; †The normalized values ≤0.5 and ≥2.0 were used to determine low-expression and high-expression of DANC expression, respectively;
Table 2 Subgroup analysis for the association between lncRNA DANCR expression and OS

| Variables          | Cohorts (n) | HR (95% CI)      | P     | Heterogeneity | Model |
|--------------------|-------------|------------------|-------|---------------|-------|
|                    |             |                  |       | I² (%)         | P     |       |
| Analysis model     |             |                  |       |               |       |       |
| Multivariate       | 3           | 2.63 (1.71, 4.05)| <0.01‡| 0             | 0.4   | Fixed |
| Univariate         | 6           | 1.69 (1.35, 2.11)| <0.01‡| 9             | 0.36  | Fixed |
| Sample size (n)    |             |                  |       |               |       |       |
| >100               | 5           | 1.71 (1.34, 2.18)| <0.01‡| 24            | 0.27  | Fixed |
| ≤100               | 4           | 2.16 (1.54, 3.03)| <0.01‡| 26            | 0.25  | Fixed |
| Cut-off value      |             |                  |       |               |       |       |
| Median             | 3           | 1.66 (1.28, 2.15)| <0.01‡| 49            | 0.14  | Fixed |
| Others             | 6           | 2.14 (1.59, 2.90)| <0.01‡| 1             | 0.41  | Fixed |
| Treatments         |             |                  |       |               |       |       |
| Surgery            | 6           | 2.08 (1.56, 2.76)| <0.01‡| 0             | 0.47  | Fixed |
| Others             | 3           | 2.01 (1.17, 3.47)| 0.01‡ | 58            | 0.09  | Random|
| Cancer type        |             |                  |       |               |       |       |
| Gastrointestinal cancers | 4   | 1.64 (1.28, 2.11)| <0.01‡| 24            | 0.27  | Fixed |
| Others             | 5           | 2.24 (1.63, 3.08)| 0.01‡ | 8             | 0.36  | Fixed |

OS, overall survival; HR, hazard ratio; CI, confidence interval; ‡ The association was considered significant when P<0.05.
### Table 3 Meta-analysis for the association between lncRNA DANCR expression and clinicopathological parameters

| Variables                                | Studies (n) | Patients (n) | OR (95% CI)       | P     | Heterogeneity | Model   |
|-------------------------------------------|-------------|--------------|-------------------|-------|---------------|---------|
| Age (old versus young)                    | 7           | 467          | 1.25 (0.85, 1.83) | 0.26  | 0             | Fixed   |
| Gender (male versus female)              | 7           | 523          | 1.16 (0.81, 1.67) | 0.42  | 40            | Fixed   |
| Tumor size (large versus small)           | 7           | 539          | 1.31 (0.50, 3.46) | 0.59  | 84            | Fixed   |
| Tumor differentiation (poor versus well)  | 5           | 394          | 1.99 (0.85, 4.70) | 0.11  | 73            | Random  |
| Invasi0n depth (T3/T4 versus T1/T2)       | 3           | 216          | 2.68 (1.43, 5.04) | <0.01 | 0             | Fixed   |
| Lymph nodes metastasis (yes versus no)    | 5           | 339          | 5.49 (3.29, 9.16) | <0.01 | 0             | Fixed   |
| Distant metastasis (yes versus no)        | 3           | 207          | 4.75 (2.17, 10.41) | <0.01 | 0             | Fixed   |
| Clinical stage (III/IV versus I/II)       | 6           | 435          | 4.11 (2.68, 6.31) | <0.01 | 0             | Fixed   |

OR, odds ratio; CI, confidence interval; ‡ The association was considered significant when P<0.05.