

PBK/TOPK overexpression and survival in solid tumors

A PRISMA-compliant meta-analysis

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Abstract

Background: The prognostic significance of PBK/TOPK overexpression in solid tumors remains controversial. Therefore, we carried out a meta-analysis to evaluate the impact of PBK/TOPK overexpression in solid tumors on patients' overall survival (OS) and disease-free survival (DFS).

Methods: Relevant articles were identified through searching the PubMed, Embase and Web of Science up to May 2017. The pooled hazard ratio (HR) with 95% confidence interval (CI) was used to estimate the effects.

Results: In this meta-analysis, 12 studies involving 1571 participants were included, PBK/TOPK overexpression was significantly associated with poor OS (pooled HR=1.91, 95%CI=1.22-3.00, $P=.005$) and short DFS (pooled HR=1.95, 95%CI=1.46-2.58, $P<.001$).

Conclusions: PBK/TOPK overexpression was associated with poor survival in human solid tumors which may be a valuable prognosis biomarker and a potential therapeutic target of solid tumors.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, IHC = immunohistochemistry, OS = overall survival, PBK/TOPK = PDZ-binding kinase/T-LAK cell-originated protein kinase.

Keywords: meta-analysis, PBK/TOPK, prognosis, solid tumors, survival

1. Introduction

PDZ-binding kinase/T-LAK cell-originated protein kinase (PBK/TOPK) is a 322 amino-acid MAPKK-like serine/threonine kinase (mitogen-activated protein kinase kinase-like serine/threonine kinase) that is difficult to detect in normal tissues other than testicular and fetal samples.^[1,2] PBK/TOPK is involved in many cellular functions, such as cell growth, DNA damage repair, apoptosis, immune responses and inflammation.^[3-6] In recent years, it was confirmed that PBK/TOPK is overexpressed in proliferative cells. Expression of PBK/TOPK increased during mitosis.^[7,8] During mitosis, the up-regulated PBK/TOPK directly binds cdk1/cyclin B1 complex and then threonine-9 of PBK/TOPK is phosphorylated by cdk1/cyclin B1 complex^[9] which promotes cytokinesis through phosphorylation of a protein regulator of cytokinesis 1 (PRC1).^[10,11]

A growing number of studies suggested that elevated PBK/TOPK expression in tumor tissue was correlated with poor survival of patients with various solid tumors such as lung adenocarcinoma,^[12-14] colorectal cancer,^[15,16] gastric cancer,^[17] prostate cancer,^[18] gastric carcinoma,^[17] esophageal squamous cell carcinoma,^[19] nasopharyngeal carcinoma,^[20] ovarian cancer,^[21] however, other studies^[22,23] could not confirm this.

Therefore, we conducted this comprehensive meta-analysis, which combined all the published evidence to clarify the prognostic value of PBK/TOPK in solid tumors. The results of this meta-analysis could potentially shed more light on the development of PBK/TOPK -targeted therapy and prognostic prediction in solid tumor.

2. Materials and methods

2.1. Literature search

We conducted a comprehensive literature search of Pubmed, Embase and Web of Science for studies measuring expression of PBK/TOPK and survival in patients with solid tumors from 1993 to May 2017 with the search terms: (PBK/TOPK OR PDZ Binding Kinase OR TOPK OR T-LAK Cell-Originated Protein Kinase) AND (cancer OR carcinoma OR neoplasm OR malignancy OR tumor). All potentially eligible studies were retrieved. The bibliographies in these studies were also carefully scanned to identify other eligible studies and extra studies. When multiple studies of the same patient population were identified, we included the published report with the largest sample size.

2.2. Inclusion criteria

To be eligible for inclusion in this meta-analysis, studies:

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Table 1
Characteristics of studies included in the meta-analysis.

Study	Year	Country	Cancer type	Total number	Follow-up (months)	Detected method	Cut-off value	Outcomes	HRs provided from
Chang CF	2016	China	Oral Cancer	287	Median 47.4 (1-116.4)	IHC	>50% positive cell staining	OS	Directly
Wei DC	2012	China	Lung adenocarcinoma	203	Mean 62.5	IHC	Score>4 (rang of 0-9)	OS,DFS	Directly
Zlobec I	2010	Switzerland	Colorectal cancer	87	Median 60.3	IHC	>90% positive cell staining	OS	Directly
Chen JH	2015	China	Prostate cancer	98	>120	IHC	>50% positive cell staining	DFS	Directly
Lei B	2015	China	Lung adenocarcinoma	127	Mean 36.1 (1-106)	IHC	>13.3% positive cell staining	OS	Directly
Shih MC	2012	China	Lung adenocarcinoma	119	200	IHC	Score≥3 (rang of 0-6)	OS, DFS	Directly
Ohashi T	2017	Japan	Gastric carcinoma	144	Median 80 (0.5-165.9)	IHC	Score ≥5 (rang of 0-6)	OS	Directly
Ohashi T	2016	Japan	Esophageal squamous cell carcinoma	54	Median 59.7 (4.5-156.9)	IHC	Score ≥5 (rang of 0-6)	OS	Directly
Zou J	2017	China	Colorectal cancer	80	60	IHC	At least moderate	OS	Indirectly
Wang MY	2016	China	Casopharyngeal carcinoma	185	>100	IHC	At least moderate	OS, DFS	Indirectly
Ikeda Y	2016	China	Ovarian cancer	163	>60	IHC	At least moderate	OS, DFS	Indirectly
He F	2010	China	Cholangiocarcinoma	24	20	IHC	At least moderate	OS	Indirectly

DFS=disease-free survival, IHC=immunohistochemistry, OS=overall survival.

1. should evaluate PBK/TOPK expression for prognostic value in cancer;
2. should test PBK/TOPK expression by immunohistochemistry (IHC);
3. should have hazard ratios (HRs) with 95% confidence intervals (CIs), or enable estimate these statistics from the data presented;
4. should classify PBK/TOPK expression as “high” and “low” or “positive” and “negative”;
5. should publish in English.

2.3. Exclusion criteria

Exclusion criteria were:

1. literatures published as letters, editorials, abstracts, reviews, case reports and expert opinions;
2. experiments performed in vitro or in vivo, but not associated with patients;
3. articles without the HRs and 95% CI or K-M survival curves dealing with overall survival, disease-free survival;
4. The follow-up duration was less than 3 years.

2.4. Data extraction

Two investigators independently extracted the data from eligible studies using a predefined form. The following data were extracted for each study: the first author’s surname, publication year, country of origin, types of cancer, number of patients analyzed, follow-up time, detected method, cut-off values, outcome endpoint: OS and DFS. For studies that presented only Kaplan-Meier curves, Engauge Digitizer version 4.1 was used to extract the survival data. The estimated HRs and 95% CIs were calculated by Tierney method.^[3] Multivariate HR and 95% CI of high PBK/TOPK expression group versus low were selected if both univariate and multivariate results were reported in an individual study. The main features of these selected studies were summarized in Table 1.

2.5. Statistical analysis

Pooled HRs and 95% CIs for 2 outcome endpoints (OS and DFS) were calculated. Statistical heterogeneity was assessed through the Chi-square test and I-square test, which was checked through

the Q test and a P value >.10 indicated a lack of heterogeneity. We also quantified the effect of heterogeneity via $I^2 = 100\% \times (Q - df) / Q$. I^2 values of <25% could be considered “low”, values of about 50% could be considered “moderate”, and values of over 75% could be considered “high”.^[24] Without statistical heterogeneity, a fixed-effects model was employed to calculate the pooled HRs; otherwise the random-effects model was performed. Funnel plots and the Egger test were utilized to determine the possible publication bias.^[25] If the funnel plot was asymmetric and the Egger test reported a P value of less than .05, publication bias was deemed to probably exist. If publication bias was observed, we adjusted for the effect by the use of the trim-and-fill method. Sensitivity analysis was also conducted to find out if certain single article could influence the overall result. Statistical analyses were performed via the Stata 14.0 (StataCorp, College Station, TX). P values for all comparisons were 2-tailed.

2.6. Ethical approval

All analyses are based on previous published studies. Therefore, there is no need for ethical approval and patient consent.

3. Results

3.1. Study characteristics

Using the described searching strategy, 256 published studies were initially retrieved after duplicates were removed. Once 242 irrelevant abstracts were excluded, 14 full-text articles were reviewed for a more detailed evaluation. Of these, one article did not have sufficient data to allow for estimation of the HR and one was duplicate report. Finally, 12 studies were enrolled into the meta-analysis.^[12-23] Details of the study selection process are shown in Fig. 1. The characteristics of eligible studies are listed in Table 1. All studies used immunohistochemistry techniques to assess the expression level of PBK/TOPK. A total of 1571 patients from China, Japan and Switzerland were diagnosed with a variety of cancers, including three studies evaluated lung adenocarcinoma,^[12-14] 2 evaluated colorectal cancer,^[15,16] and 1 each evaluated gastric carcinoma,^[17] oral cancer,^[23] prostate cancer,^[18] esophageal squamous cell carcinoma,^[19] nasopharyngeal carcinoma,^[20] ovarian cancer,^[21] cholangiocarcinoma.^[22] The endpoints OS and DFS were addressed in 11

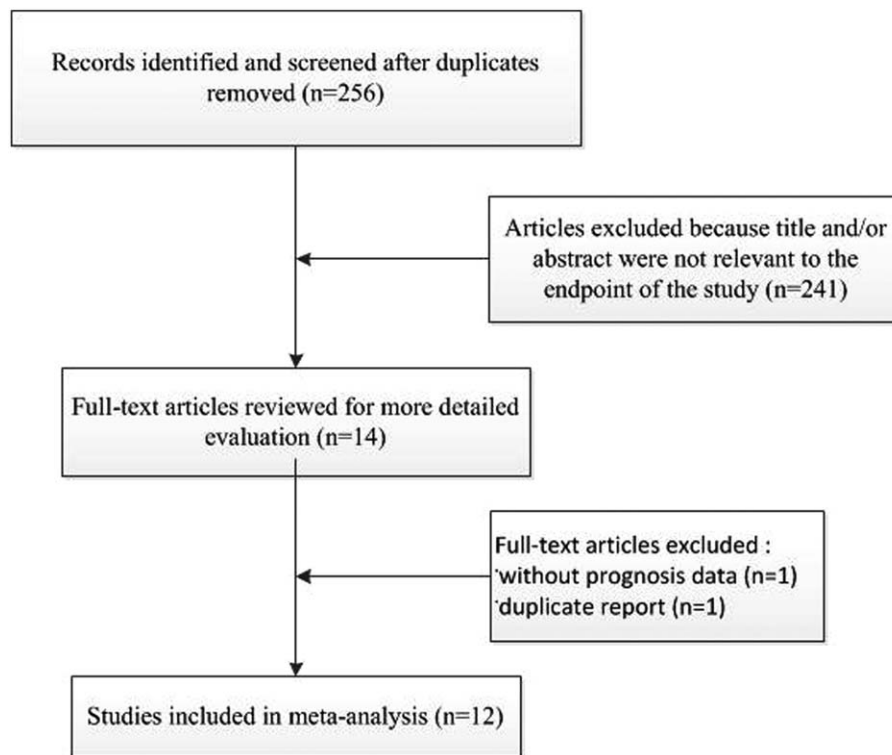


Figure 1. Flow chart depicting the selection of eligible studies.

and 5 studies, respectively. HRs were reported directly in 8 studies and estimated indirectly in the other 4 studies. The cut-off values were different in these studies.

3.2. Meta-analysis

Overall, 11 studies trials offered data on PBK/TOPK over-expression and OS in solid tumors. The synthesis indicated that over-expression of PBK/TOPK was significantly related to a poorer OS (pooled HR=1.91, 95%CI=1.22–3.00, $P=.005$) (Fig. 2). Because there was heterogeneity between studies ($I^2=82.6\%$, $P=.000$), we utilized a random-effects model to determine the pooled HR and 95% CI. In the stratified analysis based on tumor type, high levels of PBK/TOPK was significantly associated with worse OS in lung adenocarcinoma (pooled HR=2.72, 95%CI=1.93–3.83, $P<.001$) with low heterogeneity and colorectal cancer (pooled HR=1.98, 95%CI=1.17–3.37, $P=.011$) without any heterogeneity. There was only 1 study each evaluating the association between PBK/TOPK overexpression and OS in gastric carcinoma,^[17] oral cancer,^[23] prostate cancer,^[18] esophageal squamous cell carcinoma,^[19] nasopharyngeal carcinoma,^[20] ovarian cancer,^[21] cholangiocarcinoma,^[22] and therefore, the results related entirely to these studies; these tumors were defined as “other cancers”. Combined data from these studies showed that PBK/TOPK overexpression has no effect on OS (pooled HR=1.58, 95%CI=0.74–3.36, $P=.239$), along with a high heterogeneity ($I^2=87.3\%$, $P=.000$).

Five studies were included in the meta-analysis of DFS. PBK/TOPK overexpression was significantly associated with poor DFS in all studies (pooled HR=1.95, 95%CI=1.46–2.58, $P<.001$) (Fig. 3). A fixed effects model was used because the heterogeneity test reported a P value of .517.

3.3. Publication bias and sensitivity analysis

The Begg funnel plot shapes for the OS and DFS had no obvious asymmetry (Fig. 4) and Egger test showed there was no publication bias for DFS ($P=.221$). However, publication bias existed for OS ($P=.000$) in the analysis of high versus low PBK/TOPK expression. Therefore, we performed trim and fill method to make pooled HR more reliable, but the P value was not significant (random model: HR=0.442, 95%CI=-0.012–0.896, $P=.010$), and with significant heterogeneity ($P=.001$). Sensitivity analyses were used to evaluate whether individual studies influenced the results of OS and DFS. The results showed that the overall conclusion was not significantly influenced after omitting any single study for the effect of PBK/TOPK expression on OS and DFS (Fig. 5).

4. Discussions

The PBK/TOPK protein, a member of the MAPKK family, is a growth-factor-regulated kinase, which is constitutively high in tumor cells. PBK/TOPK which is phosphorylated by the cdc2/cyclin B complex and activated in a cell cycle-dependent manner during mitosis^[1] may have a role in the regulation of cell proliferation and cell cycle. Growing evidence implicate PBK/TOPK expression in tumor development, cancer growth, and apoptosis.^[6,26–29]

Many clinical studies investigated the prognostic value of PBK/TOPK. Most of these studies, however, include only limited number of patients, and the results remain not comprehensive. PBK/TOPK overexpression often predicts unfavorable outcome in many cancer, such as lung adenocarcinoma,^[12–14] gastric carcinoma,^[17] prostate cancer.^[18] On the other hand, it is a favorable prognostic indicator in oral cancer^[23] and cholangiocarcinoma.^[22]

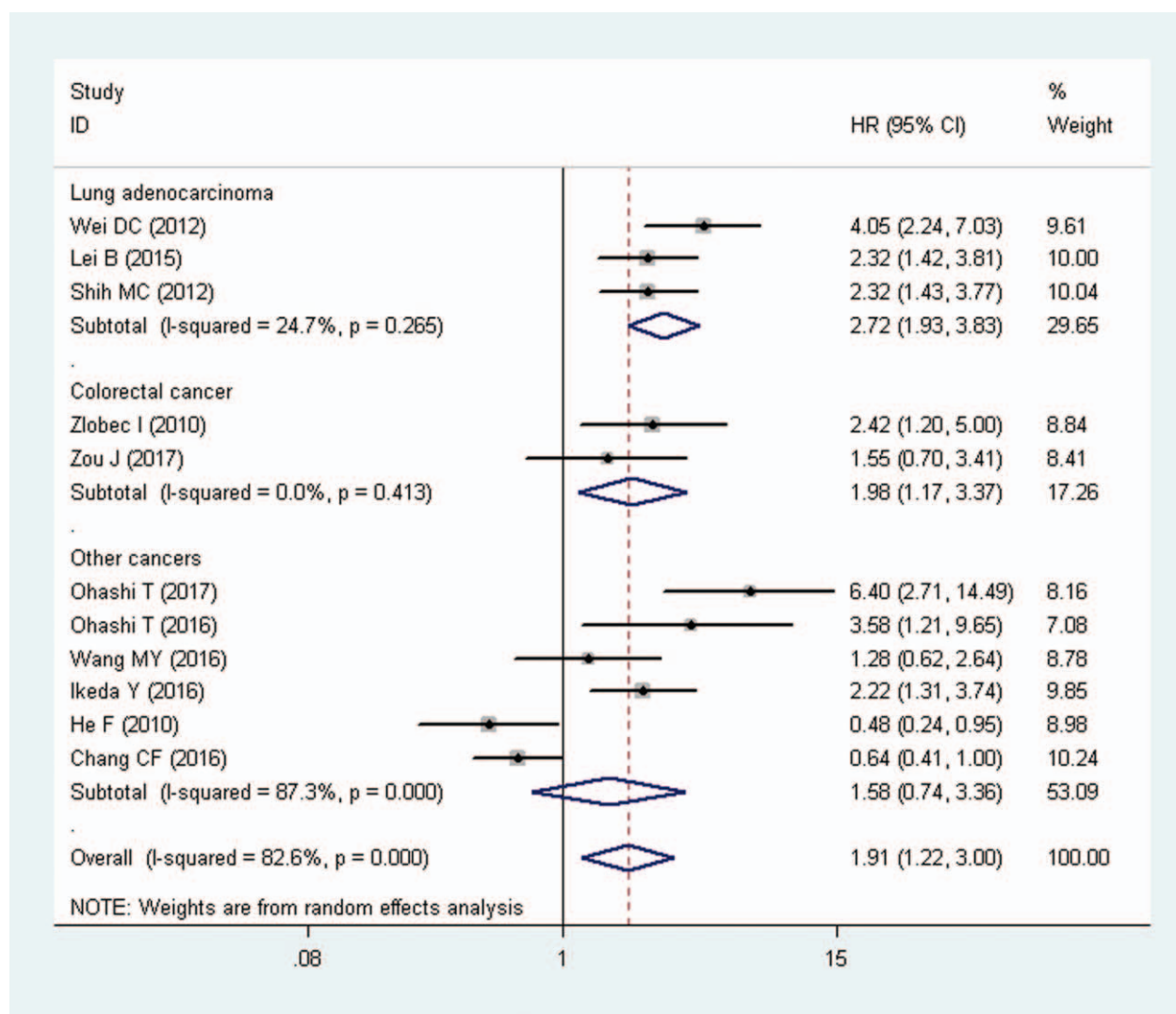


Figure 2. Meta-analysis of the association between PBK/TOPK overexpression and overall survival (OS) stratified by tumor types. Other cancers include gastric carcinoma, oral cancer, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, ovarian cancer and cholangio carcinoma. HR=hazard ratio, CI= confidence intervals.

To our knowledge, the present study is the first complete overview of all reported clinical studies exploring the possible prognostic role of PBK/TOPK up-regulation in solid tumors.

We systematically evaluated survival data of 1571 solid tumor patients included in 12 different studies. Overall, these results clearly show that high PBK/TOPK expression could be a poor prognostic factor of various solid tumors, with both results of poor OS (pooled HR = 1.91, 95%CI = 1.22–3.00, $P = .005$) and poor DFS (pooled HR = 1.95, 95%CI = 1.46–2.58, $P < .001$). Similarly, subgroup analysis based on tumor type, revealing that PBK/TOPK overexpression was significantly associated with worse OS and DFS in lung adenocarcinoma; thus, PBK/TOPK may serve as a novel prognostic marker and therapeutic target for lung adenocarcinoma. Further,

PBK/TOPK overexpression was also significantly related to poor OS in colorectal cancer patients. Apart from being a promising biomarker, PBK/TOPK may also provide a new target for anticancer therapy. HI-TOPK-032, a specific inhibitor for PBK/TOPK, reduces cell viability and colony formation via a

dramatic increase in apoptotic cells in vitro and results in a significant decrease of tumor growth in vivo.^[20,30,31]

This meta-analysis study involves several important implications. First, it reveals that PBK/TOPK overexpression is correlated to unfavorable outcome for a wide range of human cancers, which indicates that PBK/TOPK may be a promising therapeutic target. Second, it identifies a subgroup of tumors with adverse outcome in lung adenocarcinoma and colorectal cancer. Finally, it highlights the potential clinical application of PBK/TOPK as a valuable prognostic biomarker.

However, several limitations also exist in this study. First, most researches included in the meta-analysis were designed as retrospective studies, and such studies are more likely to be published if they have positive results than if they have negative results. Secondly, some of the studies were small sample size; even one study^[22] included only 24 patients. Furthermore, the method for assessing PBK/TOPK expression and definition of PBK/TOPK positivity were inconsistent. Besides, some studies which neither provide complete data nor published in English were excluded in

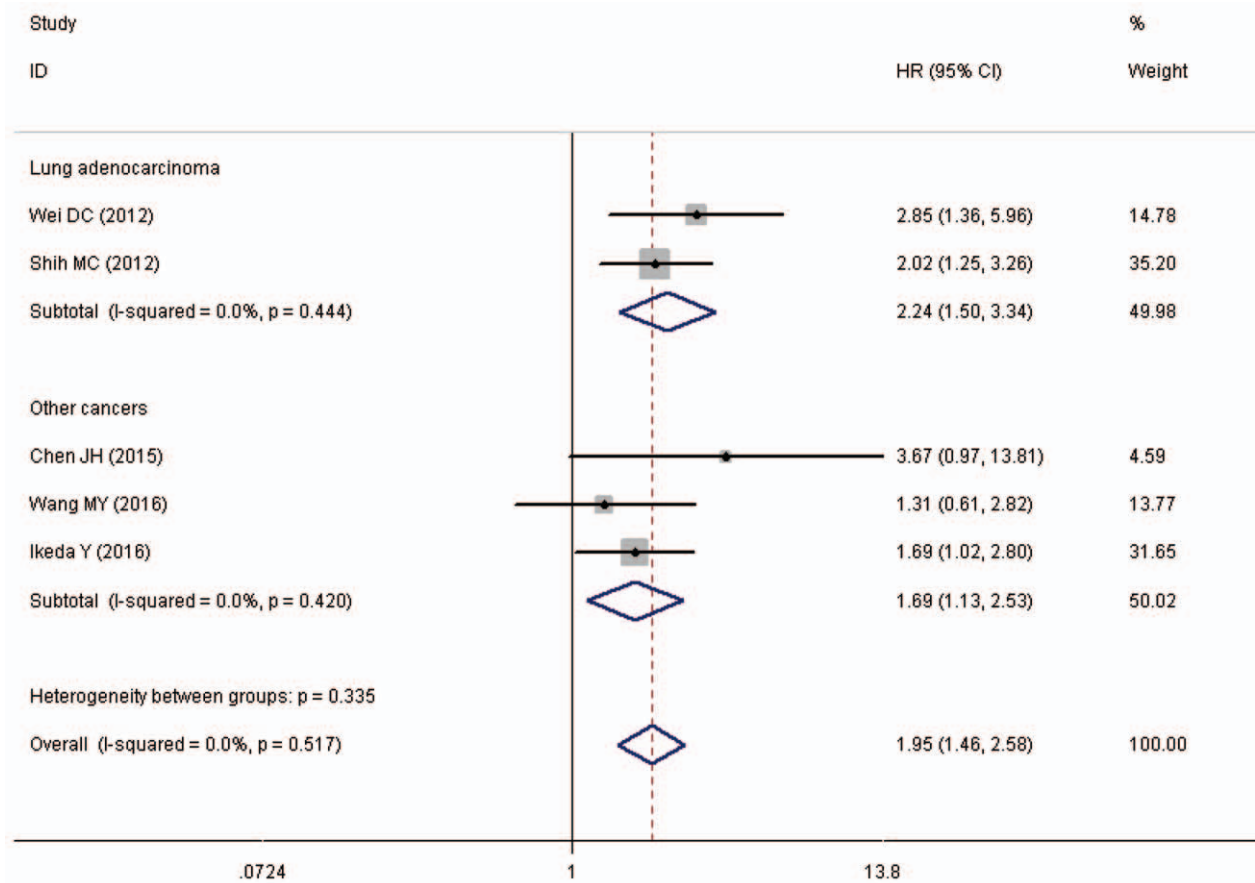


Figure 3. Meta-analysis of the association between PBK/TOPK overexpression and disease-free survival (DFS) stratified by tumor types. Other cancers include prostate cancer, nasopharyngeal carcinoma and ovarian cancer. HR = hazard ratio, CI = confidence intervals.

statistics. Therefore, we detected significant publication bias in the pooled analysis of OS. Lastly, substantial heterogeneity observed among included studies cannot be completely interpreted in spite of the use of appropriate meta-analytic techniques with random-effects models.

In conclusion, this meta-analysis indicates that PBK/TOPK expression is associated with unfavorable outcome in most solid tumors, suggesting that PBK/TOPK is a useful prognostic biomarker and a promising therapeutic target for solid tumors. Nevertheless, more clinical studies related to specific tumor types

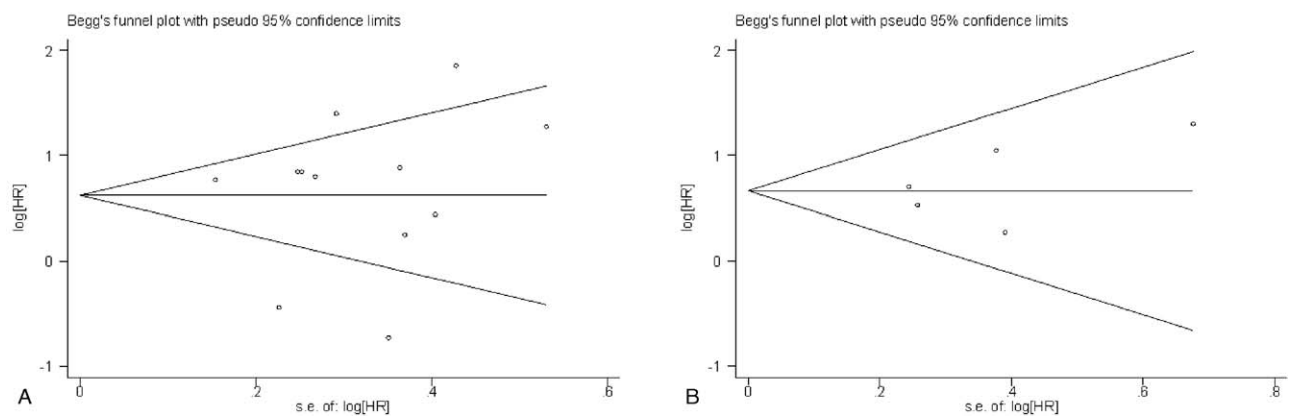


Figure 4. Begg funnel plots for the studies involved in the meta-analysis. (a) Overall survival. (b) disease free survival (DFS). log₁₀HR = logarithm of hazard ratios, s.e. = standard error.

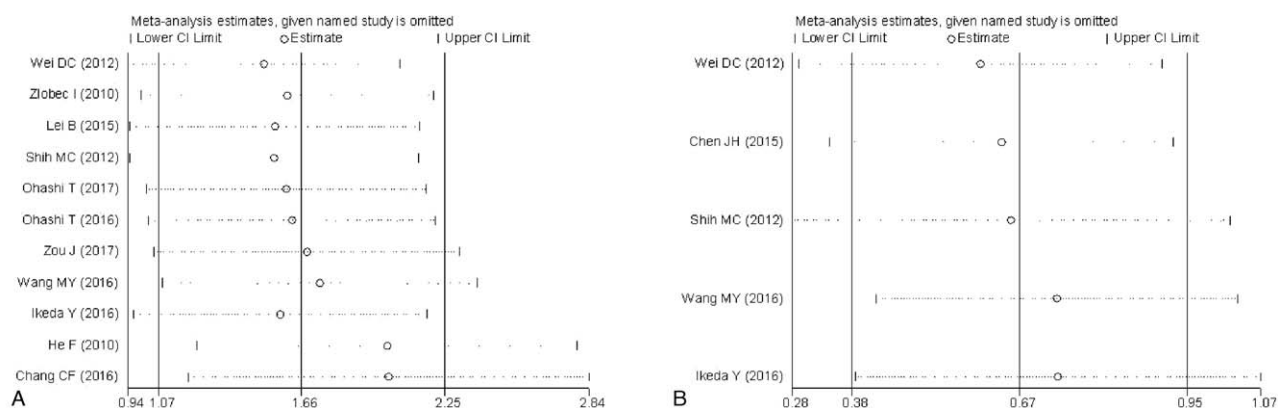


Figure 5. Sensitivity analysis of the meta-analysis. (A) Overall survival. (B) disease-free survival (DFS).

and perspectives are required to corroborate the clinical utility of PBK/TOPK expression in solid tumors.

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Author contributions

Data curation: Ming Xu, Song Xu.

Formal analysis: Ming Xu.

Project administration: Song Xu.

Software: Song Xu.

Writing – original draft: Ming Xu.

Writing – review and editing: Song Xu

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