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Prognostic significance of PTK7 in human malignancies

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Summary. Background. Protein tyrosine kinase 7 (PTK7) is a member of receptor protein tyrosine kinase-like molecules, which is involved in tumorigenesis. However, the association between PTK7 expression and its pathological significance in survival prognosis remains under investigation. The purpose of this meta-analysis is to clarify the prognostic value of PTK7 expression in human malignancies. Methods. A comprehensive literature search was performed in databases of PubMed, Embase and Cochrane Library. The statistical procedures were conducted by Stata 14.0 and the effect size was displayed by model of relative risk. Subgroup analyses were additionally implemented to disclose the potential confounding elements. Sensitivity analysis was used for evaluating the outcome stability, both Begg's test and Egger's test were utilized to detect the publication bias across the included studies. Results. We identified 11 studies published with a total sample-size of 2431 participants. Patients with higher PTK7 expression were significantly associated with cancer risk (RR=2.995, 95% CI: 1.048-8.56, p=0.041, random model), and histological grade (RR=0.696, 95% CI: 0.499-0.972, p=0.033, random model). PTK7 was also found to be an unfavorable prognostic marker for overall survival (HR=2.621 95% CI: 1.980-3.468, p=0.000, fixed model) and shorter disease free survival (HR=2.242, 95% CI: 1.112-4.521, p=0.024, random model). Conclusions. Higher expression of PTK7 significantly indicates worse prognosis in human malignancies.

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Introduction

The receptor protein tyrosine kinase 7 (PTK7), also known as colon carcinoma kinase-4 (CCK4), is a transmembrane protein that contains a catalytically inactive tyrosine kinase domain (Park et al., 1996). It consists of seven extracellular immuno-globulin-like domains, a transmembrane region, a juxtamembrane region and a catalytically inert cytoplasmic tyrosine kinase domain (Jung et al., 2002). PTK7 is a versatile regulator, which is involved in embryogenetic tube formation (Xu et al., 2016) and a variety of stem cell functions (Jung et al., 2015; Lhoumeau et al., 2016). In contrast to its important role in embryogenesis and stem cell functions, the functional importance of *PTK7* in malignancy is still a matter of debate.

Some studies revealed that *PTK7* levels are higher in colorectal tumors (Tian et al., 2016), hepatocellular carcinoma (Hishida et al., 2015), prostate cancer (Zhang et al., 2014), gastric cancer (Lin et al., 2012), intrahepatic cholangiocarcinoma (Jin et al., 2014) and so on. Jin et al. reported that ectopic overexpression of PTK7 in intrahepatic cholangiocarcinoma is associated with poor prognosis and higher metastatic potential. Gartner et al. reported that increased expression of PTK7 is correlated with poor clinical outcome for breast cancer (Gartner et al., 2014). Chen et al. used meta-analysis to find that PTK7 is a highly and specifically expressed gene in ADC and a potential therapeutic target in this subset of NSCLC (Chen et al., 2014). All in all, PTK7 levels are higher in such tumors and its high expression show poor prognosis. These studies suggested the

probability of an oncogenic role of PTK7 in such tumors.

However, PTK7 has been reported to be downregulated in clear cell renal cell carcinoma (Behbahani et al., 2012), metastatic melanoma (Easty et al., 1997) and epithelial ovarian cancer (Wang et al., 2014). Su et al. used microarray and northern analysis to verify that PTK7 is downregulated in breast cancer cell lines (Su et al., 2010). Kim et al. reported that *PTK7* plays a tumor suppressor role by inhibiting ERK and AKT phosphorylation in lung cancer (Kim et al., 2014). Wang et al. showed that negative expression of PTK7 had a poorer outcome than those with positive expression, which indicates that *PTK7* may be a tumor suppressor and a potential prognostic marker in ovarian serous carcinomas (Wang et al., 2014). These studies revealed that high expression of PTK7 inhibits cell proliferation, invasion and migration and showed a good prognosis. Taken together, these previous findings suggested that the biological function and expression levels of the PTK7 protein in different cancers is disparate, which depends on specific tissues or tumors.

Although accumulating studies have attempted to associate PTK7 expression with different cancers prognosis, there is no consensus that *PTK7* is an advantageous prognostic marker of cancers since some of the existing studies have drawn controversial and opposing conclusions. To clarify the role of *PTK7* in the prognosis of human malignancies, we conducted this systematic review of the literature and performed a meta-analysis. We sought to determine whether high *PTK7* mRNA levels or elevated/ positive PTK7 protein expression could be a prognostic marker for human malignancies.

Materials and methods

All procedures mentioned below were performed in according with PRISMA Checklist protocol. Two investigators carried out each step independently, while any discrepancy was resolved by mutual discussion.

Search strategy

The systematic literature searches were performed in PubMed, EMBASE and Cochrane Library database. The key words were included in the search: 'protein tyrosine kinase 7'; '*PTK7*'; '*CCK4*'; 'cancer'; 'carcinoma'; 'malignant tumor' and 'malignant neoplasm'. The last literature search was run on 13 November 2016, and the publication language was restricted to English.

Eligibility criteria

The following were criteria for the inclusion: (1) Studies comparing the prognostic value of different *PTK7* expression in human malignancies; (2) Primary cancers; (3) *PTK7* expression defined by IHC and RT-PCR; (4) Inadequate original data of survival analysis were excluded. (5) To avoid overlapping patient samples, only the most complete or the most recent studies were included in our analysis.

Methodological assessment

Since all of the eligible studies were observational cohorts, the Newcastle-Ottawa Scale was therefore utilized for methodological appraisal. There were in total three categories within the scale including selection, comparability and outcome, with a full-mark of nine. Studies were identified as high-quality in methodology with at least six scores.

Data extraction

By using a predefined standardized extraction form, two investigators independently extracted data from each studies, including the details of baseline characteristics and survival data. The original survival data were obtained from the text, tables or Kaplan-Meier curves for both comparative groups. Engauge Digitizer 4.1 helped us to digitize and extract survival information from the Kaplan-Meier curves. Any discrepancies were discussed and reached a consensus for all issues.

Statistical analysis

Stata 14.0 software was adopted for the quantitative calculation in this meta-analysis. Relative ratio (RR) along with 95% confidence interval (CI) was applied to measure the correlation between PTK7 presence and cancer risk and clinicopathological status. Hazard ratio (HR) with 95% CI was calculated for clinical outcome. I^2 was designated as the degree of inconsistency across the included studies, whose value <50% and >50% implied low and severe heterogeneity respectively. Random-effect model was best-fit for severe heterogeneity, while fixed-effect model was the optimal choice for the remaining situations. Moreover, the sensitivity analysis was used for examining the stability of the pooled outcomes. Egger's test and Begg's test were used to investigate the internal publication bias across the included studies. $p<0.05$ denoted statistical significance between the comparison.

Results

Search selection and characteristics

According to the selection criteria, 320 studies were identified by dropping all duplicates. However, due to their irrelevance to topic, 271 studies were excluded. Forty-nine studies were selected as the best candidates and were further reviewed in detail. After 49 studies were further evaluated, 38 studies were removed because their studies did not meet the inclusion criteria.

Eventually, a total of 11 observational studies consisting of 2431 cases were retained for subsequent pooling calculation. Fig. 1 concisely displays the selection workflow of all eligible studies in our meta-analysis.

The number of included studies on PTK7-related expression and certain cancer clinical parameters is summarized in Table 1. Eleven studies were in total summarized for different cancers. Two studies were reported for colorectal cancer (CRC), breast cancer (BC), respectively. Other cancers reported included were only one study.

The majority of included trials were graded as high-quality in methodology, including three 8-score studies, four 7-score studies and three 6-score studies. Only Zhang's study was appraised as low-quality cohorts, with 5 scores by Newcastle-Ottawa Scale (Table 2).

Correlation of PTK7 expression with cancer risk

A meta-analysis shows that high/positive PTK7 expression was significantly correlated to cancer risk (RR =2.995, 95% CI: 1.048-8.56, p=0.041) (Fig. 2A). In all seven included studies, H.Y. Wang et al reported that PTK7 plays a role in suppressing the development of epithelial ovarian carcinomas (Wang et al., 2014). The expression of PTK7 was found in 92.86% (13/14) of normal fallopian tube epithelium. As in other reports with the epithelial ovarian carcinomas, we could not find

Table 1. Baseline characteristics of included studies.

Study name	Year	Country	Cancer type	Study design	Identification methods
X.Y. TIAN	2016	China	CRC	HB	IHC
A.C. Lhoumeau	2015	France	CRC	HB	IHC
M. Hishida	2015	Japan	HCC	HB	PCR
Z.Q. Ye	2015	China	GAC	HB	IHC
H.T. Zhang	2014	China	PC	HB	IHC
Y. Wang	2014	China	OC	HB	IHC
Jing JIN	2014	Korea	ICC	HB	IHC
S. Gartner	2014	Germany	BC	HB	IHC
B. Ataseven	2014	Germany	BC	HB	IHC
W.S. Shin	2013	korea	ESCC	HB	IHC
Yi LIN	2012	China	GC	HB	IHC

Table 2. Methodological assessment by Newcastle-Ottawa Scale.

Study name	Year	Selection	Comparability	Outcome	Total
X.Y. TIAN	2016	2	1	3	6
A.C. Lhoumeau	2015	3	2	3	8
M. Hishida	2015	3	2	2	7
Z.Q. Ye	2015	3	1	3	7
H.T. Zhang	2014	3	0	2	5
Y. Wang	2014	3	2	3	8
Jing JIN	2014	2	1	3	6
S. Gartner	2014	3	1	3	7
B. Ataseven	2014	2	1	3	6
W.S. Shin	2013	3	2	2	7
Yi LIN	2012	3	2	3	8

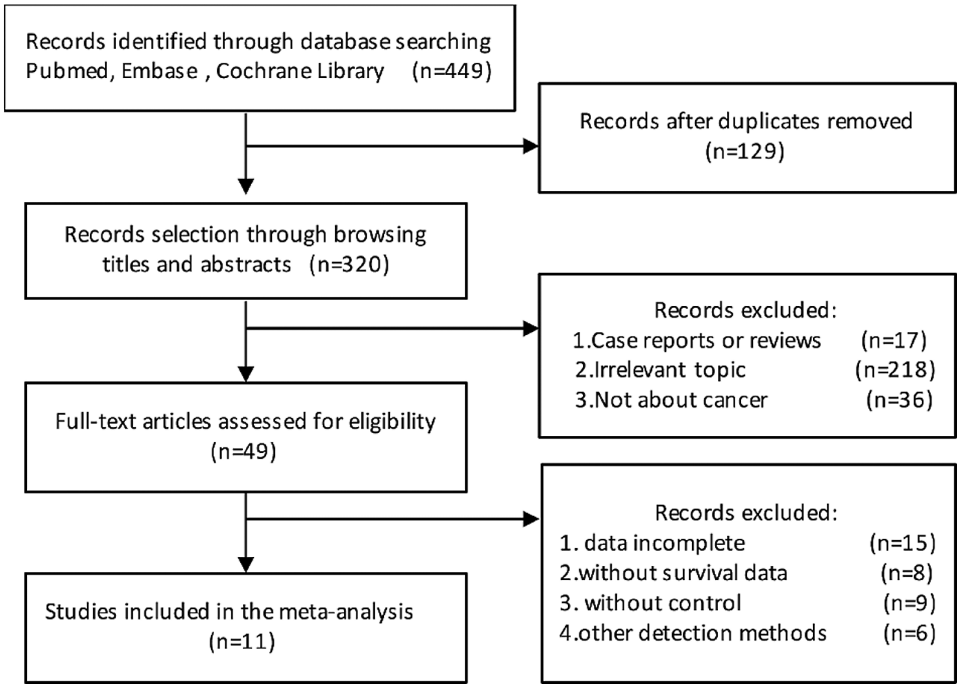


Fig. 1. Search strategy and selection of studies.

such high positive rate of PTK7 in normal fallopian tube epithelium. Subgroup meta-analysis was conducted in order to check for the reason of heterogeneity. The result showed significant correlations of PTK7 to cancer risk (RR=3.507, 95% CI:2.549-4.825, p<0.01 (Fig. 2B).

Correlations of PTK7 expression to cancer clinicopathological status

We conducted meta-analyses to evaluate the correlations of PTK7 expression with cancer clinicopathological status. As for histological grade, high/positive PTK7 expression level was correlated significantly with moderate/poor-differentiation cancers (RR=0.696, 95% CI: 0.499-0.972, p=0.033); For cancer nodal status, only one study reported high PTK7 expression that was significantly correlated to nodal metastasis (p=0.005) (Tian et al., 2016), and no significance was observed from the pooled effect size of studies on PTK7. For metastasis analysis, only two studies reported high PTK7 expression that was significantly correlated to cancer metastasis (p=0.01) (Tian et al., 2016), (p=0.007) (Gartner et al., 2014), and no significance was observed from the pooled effect size of studies on PTK7. For tumor size and TNM stage analyses, no obvious correlations were concluded from statistical analyses on PTK7 (Fig. 3).

Correlations of PTK7 expression with cancer clinical outcomes and predictions

Our quantitative analysis for DFS confirmed that patients with high/positive PTK7 expression possessed rather higher risk (HR=2.242, 95% CI: 1.112-4.521, p=0.024). For OS risk correlations, pooled effect sizes of high/positive PTK7 (HR=2.621 95% CI: 1.980-3.468, p=0.000, fixed model), was significantly related with worse prognosis (Fig. 4). From the statistical analysis of Zhang's report (Zhang et al., 2014), for prostate cancers with high PTK7 expression level have shorter recurrence-free Survival (RR=2.477, 95% CI: 1.432-4.286, p=0.001). According to Lhoumeau's study (Lhoumeau et al., 2015), PTK7 overexpression was significantly associated with a reduced metastasis-free

A

Study	RR	[95% Conf.	Interval]	% Weight
X.Y.TIAN (2016)	3.245	2.481	4.244	14.82
A.C.Lhoumeau (2015)	2.418	1.515	3.861	14.54
M.Hishida (2015)	2.429	1.508	3.912	14.52
H.T.Zhang (2014)	7.533	3.230	17.567	13.64
Y.Wang (2014)	0.486	0.394	0.599	14.88
Jing JIN (2014)	11.126	3.714	33.330	12.87
Yi LIN (2012)	3.562	2.536	5.005	14.74
D+L pooled RR	2.995	1.048	8.560	100.00

Heterogeneity chi-squared = 314.12 (d.f. = 6) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 98.1%
Estimate of between-study variance Tau-squared = 1.9185

Test of RR=1 : z= 2.05 p = 0.041

B

Study	RR	[95% Conf.	Interval]	% Weight
2				
X.Y.TIAN (2016)	3.245	2.481	4.244	14.82
A.C.Lhoumeau (2015)	2.418	1.515	3.861	14.54
M.Hishida (2015)	2.429	1.508	3.912	14.52
H.T.Zhang (2014)	7.533	3.230	17.567	13.64
Jing JIN (2014)	11.126	3.714	33.330	12.87
Yi LIN (2012)	3.562	2.536	5.005	14.74
Sub-total				
D+L pooled RR	3.507	2.549	4.825	85.12
1				
Y.Wang (2014)	0.486	0.394	0.599	14.88
Sub-total				
D+L pooled RR	0.486	0.394	0.599	14.88
Overall				
D+L pooled RR	2.995	1.048	8.560	100.00

Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
2	13.27	5	0.021	62.3%	0.0877
1	0.00	0	.	.%	0.0877
Overall	314.12	6	0.000	98.1%	1.9185

** I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of RR=1

2	z= 7.71	p = 0.000
1	z= 6.75	p = 0.000
Overall	z= 2.05	p = 0.041

Fig. 2. Overall meta-analysis. **A.** Overall meta-analysis of cancer risk. **B.** Subgroup meta-analyses of cancer risk.

survival in non-metastatic colorectal cancer patients.

Sensitivity analysis and Publication bias

The sensitivity analysis was conducted by removing one study each time to test the robustness of the pooled results. The results showed that the summarized RR or HRs and its 95% CIs were not significantly altered. Single study had no significant impact on the combined result and confirmed the stability of the outcome of this

A

Study	RR	[95% Conf.	Interval]	% Weight
A.C.Lhoumeau (2015)	1.349	0.756	2.406	13.15
M.Hishida (2015)	0.832	0.397	1.743	10.52
H.T.Zhang (2014)	0.673	0.537	0.844	19.80
S.Gartner (2014)	0.094	0.032	0.278	6.57
B.Ataseven (2014)	1.021	0.477	2.187	10.20
Z.Q.Ye (2015)	0.856	0.731	1.002	20.77
W.S.Shin (2013)	0.538	0.409	0.707	18.99
D+L pooled RR	0.696	0.499	0.972	100.00

Heterogeneity chi-squared = 33.17 (d.f. = 6) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 81.9%
Estimate of between-study variance Tau-squared = 0.1328

Test of RR=1 : z= 2.13 p = 0.033

B

Study	RR	[95% Conf.	Interval]	% Weight
X.Y.TIAN (2016)	1.268	1.046	1.539	15.74
A.C.Lhoumeau (2015)	0.973	0.704	1.344	11.87
M.Hishida (2015)	0.985	0.626	1.551	8.65
Y.Wang (2014)	0.929	0.358	2.413	3.00
W.S.Shin (2014)	0.875	0.753	1.016	16.96
S.Gartner (2014)	2.500	1.422	4.395	6.65
B.Ataseven (2014)	1.143	0.615	2.124	5.86
Yi LIN (2012)	1.120	0.873	1.436	14.06
Z.Q.Ye (2015)	0.820	0.712	0.944	17.20
D+L pooled RR	1.060	0.886	1.269	100.00

Heterogeneity chi-squared = 28.82 (d.f. = 8) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 72.2%
Estimate of between-study variance Tau-squared = 0.0438

Test of RR=1 : z= 0.64 p = 0.524

C

Study	RR	[95% Conf.	Interval]	% Weight
X.Y.TIAN (2016)	1.310	1.091	1.574	17.21
A.C.Lhoumeau (2015)	1.062	0.831	1.356	15.75
H.T.Zhang (2014)	0.681	0.550	0.844	16.50
Jing JIN (2014)	1.003	0.859	1.172	17.80
S.Gartner (2014)	0.400	0.228	0.703	8.58
B.Ataseven (2014)	0.834	0.497	1.402	9.40
Yi LIN (2012)	0.929	0.699	1.233	14.77
D+L pooled RR	0.893	0.716	1.113	100.00

Heterogeneity chi-squared = 31.40 (d.f. = 6) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 80.9%
Estimate of between-study variance Tau-squared = 0.0650

Test of RR=1 : z= 1.01 p = 0.314

D

Study	RR	[95% Conf.	Interval]	% Weight
X.Y.TIAN (2016)	1.382	1.133	1.686	15.54
A.C.Lhoumeau (2015)	0.926	0.724	1.184	14.96
M.Hishida (2014)	1.179	0.561	2.476	7.98
H.T.Zhang (2014)	0.713	0.580	0.878	15.43
Y.Wang (2014)	1.231	0.646	2.343	9.17
S.Gartner (2014)	4.833	2.297	10.169	7.97
Yi LIN (2012)	1.153	0.758	1.753	12.41
Z.Q.Ye (2015)	0.872	0.803	0.946	16.54
D+L pooled RR	1.149	0.860	1.536	100.00

Heterogeneity chi-squared = 67.59 (d.f. = 7) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 89.6%
Estimate of between-study variance Tau-squared = 0.1305

Test of RR=1 : z= 0.94 p = 0.346

E

Study	RR	[95% Conf.	Interval]	% Weight
X.Y.TIAN (2016)	1.245	1.037	1.495	16.85
M.Hishida (2015)	0.917	0.635	1.323	11.17
H.T.Zhang (2014)	0.684	0.548	0.854	15.63
Y.Wang (2014)	2.281	1.266	4.107	6.55
Jing JIN (2014)	1.041	0.862	1.258	16.68
Yi LIN (2012)	0.912	0.704	1.181	14.42
Z.Q.Ye (2015)	0.884	0.785	0.994	18.69
D+L pooled RR	0.992	0.826	1.192	100.00

Heterogeneity chi-squared = 27.89 (d.f. = 6) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 78.5%
Estimate of between-study variance Tau-squared = 0.0430

Test of RR=1 : z= 0.08 p = 0.934

Fig. 3. A meta-analysis based on cancer clinicopathological status. **A.** Meta-analysis on histological grade. **B.** Meta-analysis on tumor size. **C.** Meta-analysis on cancer nodal status. **D.** Meta-analysis on metastasis. **E.** Meta-analysis on TNM stage.

study (Fig. 5).

After performing Begg's and Egger's test, no publication bias was found among all of the available studies for the correlation of PTK7 expression with cancer risk, clinicopathological status and clinical outcomes, indicating the stability of our results (Tables 3, 4).

Discussion

PTK7 expression has been studied in different tumors and exhibits no consensus about the indicative role. Some controversial and opposing conclusions have been drawn in different studies, which is similar to BAP1 gene. Luchini et al. found that BAP1 gene

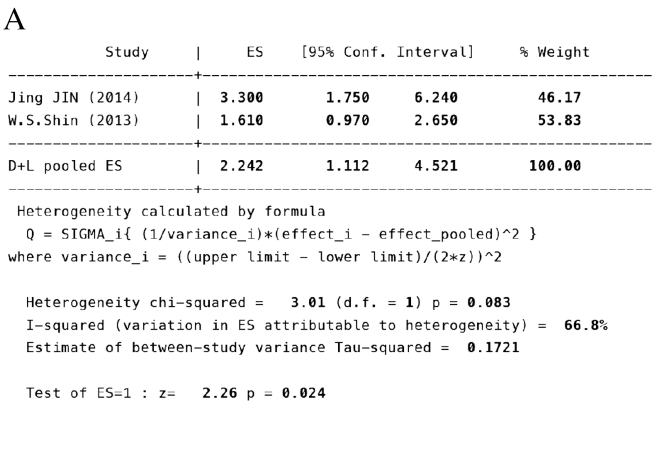
Table 3. Meta-analysis for correlation of PTK7-related expression to cancer clinicopathological status.

n	Heterogeneity analysis		Effect model	RR (95% CI)	*p*	Publication bias	
	I^2 (%)	*p*				Begg's test	Egger's test
For histological grade (well differentiation vs. moderate/poor differentiation)							
7	81.9	0.000	RM	0.696 (0.499-0.972)	0.033	0.368	0.556
For tumor size (T1 + T2 vs. T3 + T4)							
9	72.7	0.000	RM	1.06 (0.886-1.269)	0.524	0.466	0.161
For nodal status (N0 vs. N1+)							
7	80.9	0.000	RM	0.893 (0.716-1.113)	0.314	0.23	0.223
For metastasis (M0 vs. M1)							
8	89.6	0.000	RM	1.149 (0.86-1.536)	0.346	0.266	0.147
TNM stage (I + II vs. III + IV)							
7	78.5	0.000	RM	0.992 (0.826-1.192)	0.934	0.764	0.433

Table 4. Meta-analysis for correlations of PTK7-related expression to cancer clinical outcomes.

n	Heterogeneity analysis		Effect model	HR (95% CI)	*p value*	Publication bias	
	I^2 (%)	*p value*				Begg's test	Egger's test
2	66.8	0.083	RM	2.242 (1.112-4.521)	0.024	-	-
6	48.4	0.085	FM	2.621 (1.980-3.468)	0.000	0.26	0.14

$p < 0.1$ was considered to be statistically significant for the existing of potential publication bias. RM means Random model; FM means Fixed model



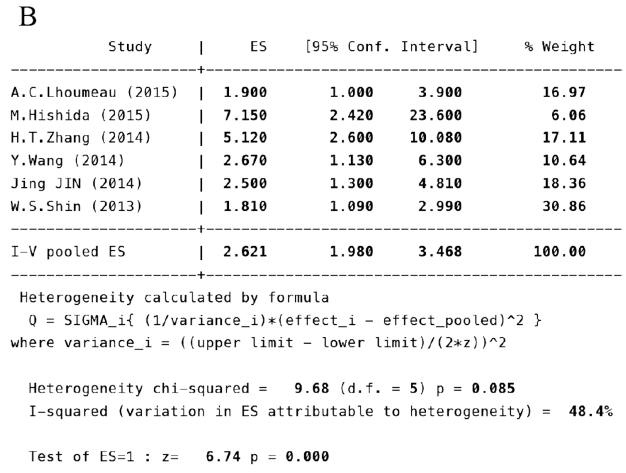


Fig. 4. A meta-analysis based on cancer clinical outcomes and predictions. **A.** Meta-analysis on DFS. **B.** Meta-analysis on OS.

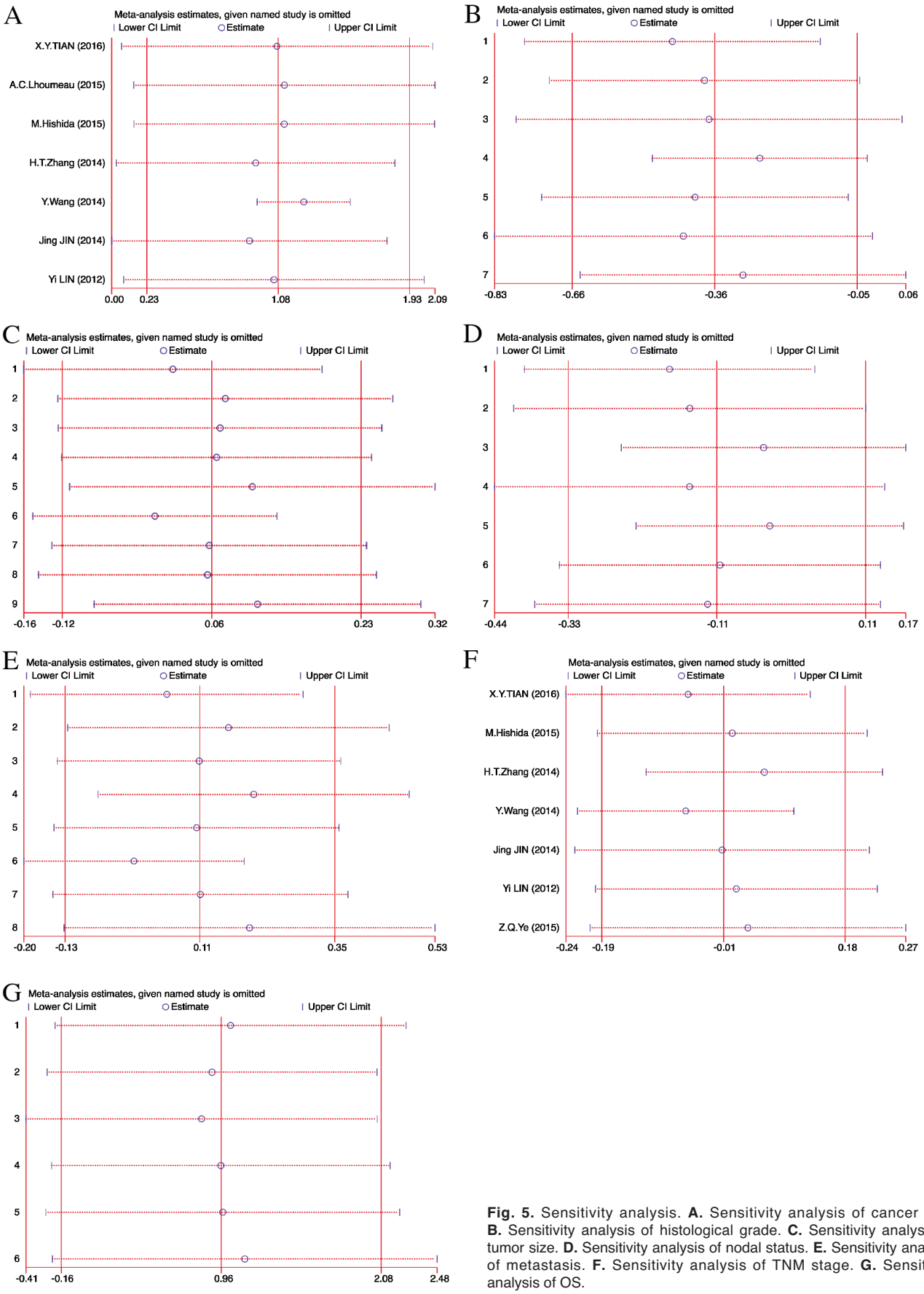


Fig. 5. Sensitivity analysis. **A.** Sensitivity analysis of cancer risk. **B.** Sensitivity analysis of histological grade. **C.** Sensitivity analysis of tumor size. **D.** Sensitivity analysis of nodal status. **E.** Sensitivity analysis of metastasis. **F.** Sensitivity analysis of TNM stage. **G.** Sensitivity analysis of OS.

mutations resulted as predictor of poor prognosis in many cancer types but also protective in mesothelioma patients. Same genes may have a totally different prognostic role (Luchini et al., 2016). This meta-analysis of the pooled data provided evidence about the correlation of PTK7 with cancer risk, cancer clinical parameters, DFS and OS. To our knowledge, the present study is the first meta-analysis systemically exploring the possible role of PTK7 upregulation in human malignancies. The results revealed that the high/positive expression of PTK7 might be a candidate biomarker for cancer risk assessment. Elevated PTK7 expression could distinguish cancer histological grade, which could be used for an indication biomaker. Besides, the high/positive expression of PTK7 was significantly associated with a shorter DFS and a worse OS, which implied the important prognostic value of PTK7 in predicting the outcome of patients.

The size of heterogeneity may be the focus of meta-analysis. In this study, one possible explanation for the heterogeneity is that the source of control group in each article was different. For example, Tian et al. used normal colorectal mucosa and adenoma as control (Tian et al., 2016). Zhang et al. used the benign prostatic hyperplasia as controls (Zhang et al., 2014). Jin et al. used the normal bile duct tissues as controls (Jin et al., 2014). The *PTK7* expression is different in normal tissue and adenoma in certain cancers. Therefore, in order to evaluate the role of PTK7 in tumorigenesis, the control group should choose the normal tissue, rather than tissue obtained from adenoma or hyperplasia, if not, the conclusion may basically extend to other solid cancers. Moreover, Wang et al found PTK7 was expressed in 92.86% (13/14) of normal fallopian tube epithelium and 45.10% (92/204) of epithelial ovarian tumor tissues. This study is the only report that PTK7 highly expressed in the normal tissue, and it differs from other studies. The reason of the higher prevalence in normal ovarian tissue is not known, but this finding suggests *PTK7* could play an important role in sustaining the function of this tissue. Clarifying the role of *PTK7* in normal ovarian tissue is an aim of future studies.

Although our pooled results showed that an undesirable impact of PTK7 redundancy was correlated with cancer risk, histological grade, overall survival and disease-free survival, it is still unclear how PTK7 influences on cancerous cells. Cells with high *PTK7* expression exhibited higher proliferation, DNA synthesis, invasion, and migration abilities than did cells with low PTK7 expression (Shin et al., 2013; Jin et al., 2014). Several reports showed that PTK7 might affect the mobility of cancer cells (Peradziryi et al., 2012; Gartner et al., 2014; Jin et al., 2014). However, Golubkov et al. report that PTK7 inhibited cancer cells mobility (Golubkov and Strongin., 2014). The reasons underlying the diverse functions of PTK7 in different tumors still remain unclear. We think its diverse function might be attributed to different transcriptional variants and proteolytic fragments in cancer cells.

Pseudokinase PTK7 is cracked by membrane type-matrix metalloproteinase (MT1-MMP), members of the Disintegrin Domain and Metalloproteinase (ADAM) family, and γ-secretase. These PTK7 fragments could exert different functions in cancer cells. Currently, we know little about the role that these proteolytic products play in cancer. Golubkov et al found that the full-length membrane PTK7 reduced migration efficiency of fibrosarcoma HT1080 cells through down-regulating the myosin light chain phosphorylation. However, the fragment from MT1-MMP proteolysis promoted cell invasion of HT1080 cells, which reversed the inhibitory effect (Golubkov et al., 2010). This mechanism could partly explain why PTK7 was expressed highly in different tumors, but the prognosis is contrary. PTK7 is cleaved by proteinases in cancer cells, which form various digest fragments. These proteolytic products exert different, sometimes contradictory, functions relative to intact PTK7. Understanding the function of different proteolytic products will deepen our understanding about the role of PTK7 in cancer, which is a target for future research.

PTK7 could regulate both the canonical Wnt and the noncanonical Wnt/planar cell polarity pathways by interacting either directly or indirectly, with plexins, semaphorins, Wnt3a, Wnt8 and β-catenin in different biological systems (Peradziryi et al., 2012; Hayes et al., 2013). However, the exact mechanisms have not been clarified. Recently, several studies have tried to explain the roles played by *PTK7* in cancer types. Shin et al found that *PTK7* upregulates MMP9 through activation of AP-1 and NF-ϰB and, thus increases invasive properties of ESCC cells (Shin et al., 2016). Jiang et al found that PTK7 attenuated cell proliferation, impaired tumorigenic potential, and induced apoptosis in CD44-high glioma cell lines through modulating TGF-b/Smad signaling (Liu et al., 2015). All these reports focused on the full-length PTK7, the study of different proteolytic products was paid little attention. Because PTK7 is a pseudokinase, future studies should focus on the mechanism of exact proteolytic products, rather than simply research *PTK7* as a whole.

Apart from the above outcomes, there are still limitations in this quantitative meta-analysis. First of all, despite the usage of random-effects model and subgroup analysis, the heterogeneity across studies failed to be eliminated completely, which could result in bias of the outcome to a certain extent. Secondly, on account of the lack of effective data, we merely analyzed the correlation between PTK7 redundancy and prognosis in terms of certain clinical elements. Other parameters that may partially contribute to the heterogeneity were not explored, such as pathological grade and body mass index.

To sum up, our findings show that overexpressed PTK7 is associated with cancer risk, poor histological grade, worse overall survival and shorter disease-free survival. *PTK7* could be used for a biomarker for

predicting poor prognosis. However, more well-designed studies, especially focusing on a specific type of cancer, are needed to confirm these conclusions.

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