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Meta-Analysis

The roles of PTEN expression in gastric cancer: a bibliometric, meta and bioinformatics analysis

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ABSTRACT

PTEN encodes a dual phospholipid phosphatase, and is frequently deleted, mutated or down-regulated in a variety of human malignancies. Here, we performed a systematic bibliometric, meta- and bioinformatics analysis through multiple online databases up to March 14, 2017. The co-citation and co-word analysis showed that the study about PTEN and gastric cancer mainly focused on PTEN discovery, correlation of its genetic and epigenetic alteration with cancers, the effects of PTEN expression on the phenotypes of gastric cancer cells, and the regulatory effects of miRNA on PTEN translation. Meta-analysis indicated that down-regulated PTEN expression was seen in gastric cancer in comparison to normal mucosa and dysplasia ($p < 0.05$), and positively with depth of invasion, lymph node and distant metastasis, TNM staging, dedifferentiation and poor prognosis of gastric cancer ($p < 0.05$). According to bioinformatics databases, *PTEN* mRNA expression was higher in gastric cancer than normal tissues ($p < 0.05$), and positively correlated with depth of invasion and differentiation of gastric cancer ($p < 0.05$). Kaplan-Meier plotter showed that a higher PTEN expression was positively correlated with overall and progression-free survival rates of all cancer patients, even stratified by aggressive parameters ($p < 0.05$). These findings indicated that PTEN expression might be employed as a potential marker to indicate gastric carcinogenesis and subsequent progression, even prognosis.

INTRODUCTION

PTEN (phosphatase and tensin homology deleted from human chromosome 10, also called as MMAC1 or TEP1) encodes a dual phospholipid phosphatase. It specifically dephosphorylates PIP3 to inhibit Akt signaling pathway, and FAK to suppress cell adhesion, spreading and recognition. It also inhibits shc phosphorylation and subsequently Ras/MAP-kinase pathway [1, 2]. PTEN dephosphorylates Akt to suppress membrane GLUT1 expression and glucose consumption in cancer cells [3]. Gu et al. [4] has found that PTEN deficiency resulted in CREB phosphorylation independent of PI3K/Akt pathway. Additionally, Helicobacter pylori might phosphorylate and inactivate PTEN at Ser380/ Thr382/383 to promote gastric epithelial cell survival via PI3K/Akt pathway [5]. CK2 kinase phosphorylates ser/thr residues of PTEN for its stability due to proteasomal degradation resistance [6]. PTENα and PTENβ are N-terminally extended forms of PTEN and initiated from CUG and AUU codons upstream of the coding region of canonical PTEN. PTENα can up-regulate cytochrome c oxidase activity and ATP synthesis, and PTENβ physically associates with and dephosphorylates nucleoli to suppress ribosomal biogenesis [7, 8]. PTEN interacts with DAXX, and subsequently modulateds oncogene expression via diassociation of DAXX-H3.3 on the chromatin [9]. For example, PTEN induces transcriptional activity of HIF-2α by suppressing the expression of Yin Yang 1 via PI3K/Akt pathway [10].

MKRN1 E3 ligase may enhance EGFR/PI3K/Akt-mediated ubiquitination and subsequent degradation of

PTEN protein [11]. PTEN mono-ubiquitination promotes protein stability and nuclear localization [12], where PTEN interferes with interaction of Ku70 with double-strand breaks via post-translational poly (ADP-ribosyl) ation of PARP1 [13]. HECT E3-ligase NEDD4-1 is a proto-oncogenic ubiquitin ligase to mediate proteasomal degradation of PTEN [14, 15]. NEDD4-like protein family, WWP2, physically interacts with PTEN and mediates PTEN degradation through an ubiquitylation-dependent pathway [16]. However, the inhibitory effects of PTEN on NEDD4 expression are diminished by a mutation (C124S) in the catalytic site of PTEN [17]. Deubiquitylation and stabilization of PTEN by USP13 suppresses tumorigenesis and glycolysis in PTEN-positive breast cancer cells [18]. Ret finger protein can promote atypical polyubiquitination of PTEN to inhibit PTEN phosphatase activity [19]. K163 acetylation and activation of PTEN is mediated by HDAC6 inhibition, which suppresses carcinogenesis and subsequent progression [20].

PTEN, as an important tumor suppressor gene, is frequently deleted, mutated or down-regulated in various malignancies [1] and its conditional abrogation of PTEN resulted in organ-specific carcinogenesis, including hepatocellular cancer, urothelial carcinoma, squamous cell carcinoma of vagina and rectum, colonic adenocarcinoma, prostate cancer, papillomas, squamous cell carcinomas and T-cell lymphoma [21]. In the present study, we tried to map the history, emerging trends and research front of PTEN and gastric cancer using CiteSpace II. After that, we investigated the roles of PTEN expression in gastric cancer at both mRNA and protein levels by a meta- and bioinformatics analysis.

RESULTS

The research history, current and future hotspots of PTEN in gastric cancer

CiteSpace II could help us to facilitate the understanding and interpretation of structural and temporal network patterns. Here, we established a network (Figure 1A) using co-citation analysis as shown in Tables 1–3. The highly-cited, centered and burst articles indicated that PTEN discovery, correlation of its genetic and epigenetic alteration with cancers and the regulatory effects of miRNA on PTEN translation would be history, current situation and future hotpots about the roles of PTEN in gastric cancer. Among them, the papers whose titles contain "PTEN" should be read and investigated. On the other hand, we established a network of the key words from 597 articles (Figure 1B). The top frequent key and burst words indicated that investigators mainly explored the relationship between PTEN and gastric carcinogenesis, its effects on phenotypes of gastric cancer cells, and the correlation between PTEN and miRNA (Tables 4 and 5).

Selection and characteristics of preferable studies

We selected 17 articles paper for our meta-analysis as shown in Figure 2 and Table 6. Only 5 articles include gastric normal mucosa and cancer samples [22–26], 3 do gastric dysplasia and cancer samples [23–25], 16 do the relationship between PTEN expression and clinicopathological features of gastric cancer [22–37] and 6 do survival data about PTEN expression [25, 28, 30, 33, 36, 38].

The clinicopathological and prognostic significances of PTEN expression in gastric cancer

In 5 studies, 663 cancers and 361 controls were involved in our analysis. PTEN expression was lower in gastric cancer than normal mucosa epithelium (Figure 3A, $p < 0.00001$). Cancer susceptibility was the same for the PTEN-negative dysplasia using 483 cancers and 103 dysplasia (Figure 3B, $p < 0.00001$). There was a higher PTEN expression in female than male patients with gastric cancer (Figure 3C, $p = 0.03$). PTEN expression was inversely linked to depth of invasion (Figures 3D and 3E, $p < 0.05$), lymph node metastasis (Figure 3F, $p < 0.00001$), distant metastasis (Figure 3G, $p < 0.00001$), TNM staging (Figures 3H and 3I, $p < 0.01$), dedifferentiation (Figure 3J, $p = 0.01$) and un favorable prognosis (Figure 3K, HR = 2.34, 95% CI: 1.85–2.96, $p < 0.00001$) of gastric cancer.

Heterogeneity analysis

To assess the heterogeneity, we deleted a study to observe the alteration in the pooled results of remaining studies (Figure 4). For example, the pooled OR about relationship between PTEN expression and gender was remarkably decreased if Zheng (2007)'s study was excluded (data not shown).

The clinicopathological and prognostic significances of PTEN mRNA expression in gastric cancer

DErrico's and Wang's datasets were used to perform bioinformatics analysis. PTEN mRNA expression was found to be higher in gastric cancer than normal tissues, even stratified into intestinal-, diffuse- and mixed-type carcinomas (Figure 5A, $p < 0.05$). TCGA data showed that PTEN mRNA expression was positively correlated with depth of invasion (Figure 5B, $p < 0.05$), histological grading (Figure 5B, $p < 0.05$) and dedifferentiation (Figure 5B, $p < 0.05$) of gastric cancers. Kaplan-Meier plotter showed a positive correlation between PTEN mRNA expression and overall or progression-free survival rate of all, T2, T3, N1-3, N1, N2, M0, moderately-differentiated,

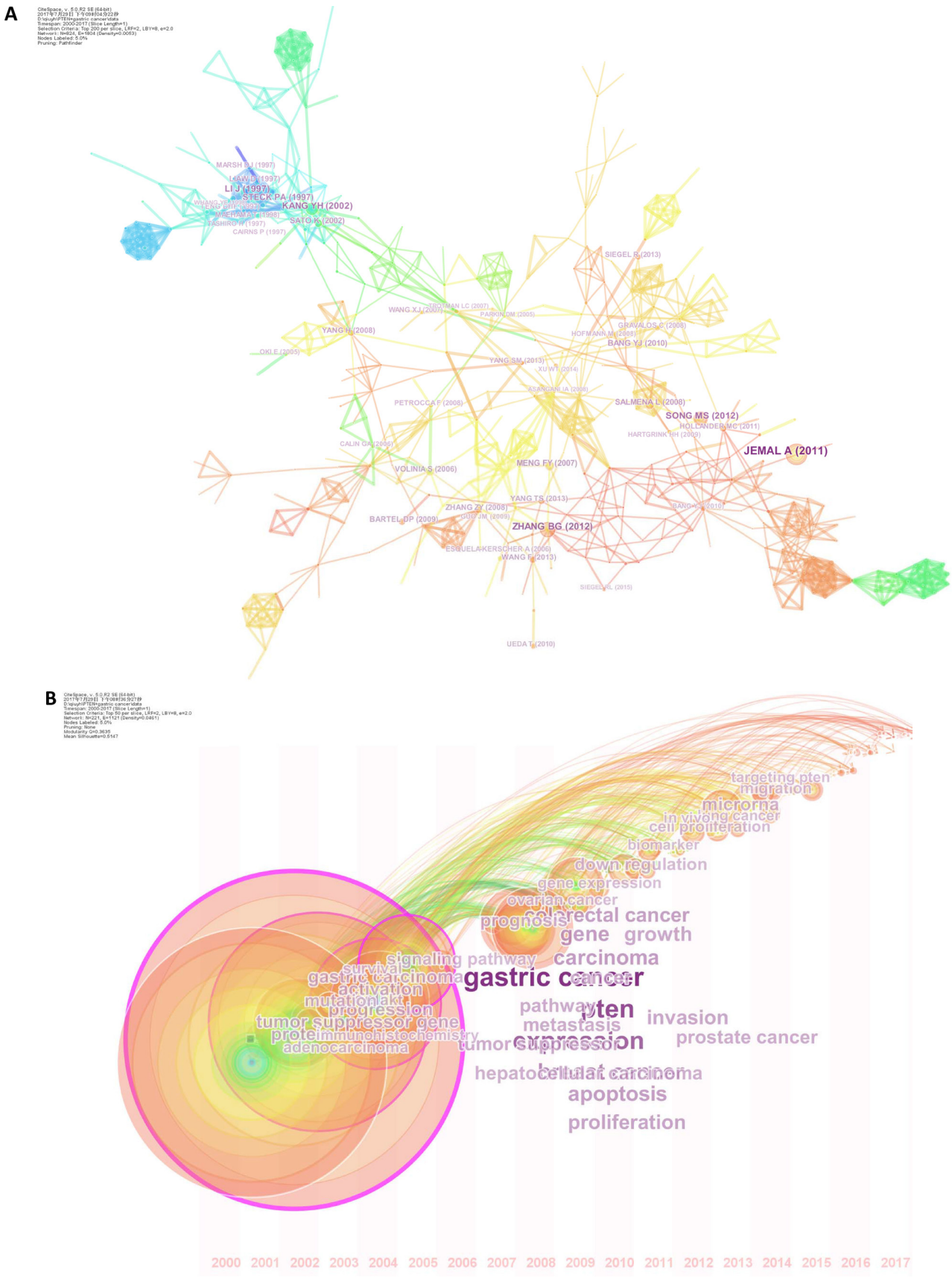


Figure 1: The cluster analysis of co-cited references. (**A**) and highly-frequent key words (**B**).

Table 1: The top 10 highly-cited articles

Rank	Freq	Author	Year	Source	Title
1	41	Jemal A	2011	CA-Cancer J Clin	Global cancer statistics.
2	28	Zhang BG	2012	Oncol Rep	microRNA-21 promotes tumor proliferation and invasion in gastric cancer by targeting PTEN.
3	26	Song MS	2012	Nat Rev Mol Cell Bio	The functions and regulation of the PTEN tumour suppressor.
4	24	Kang YH	2002	Lab Invest	Promoter methylation and silencing of PTEN in gastric carcinoma.
5	23	Li J	1997	Science	PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer.
6	20	Steck PA	1997	Nat Genet	Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers.
7	16	Meng FY	2007	Gastroenterology	MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer.
8	15	Salmena L	2008	Cell	Tenets of PTEN tumor suppression.
9	15	Sato K	2002	Virchows Arch	Analysis of genetic and epigenetic alterations of the PTEN gene in gastric cancer.
10	15	Bang YJ	2010	Lancet	Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial.

stage III, intestinal-type or Her2-positivve cancer patients (Figure 5C and Table 7, $p < 0.05$). Stage I or IV, mixed-type or Her2-negative cancer patients with PTEN mRNA hyperexpression showed a favorable overall prognosis than those with its hypoexpression (Table 7, $p < 0.05$). There was a positive correlation of PTEN expression with a progression-free survival rate of stage II cancer patients (Table 7, $p < 0.05$).

DISCUSSION

PTEN induces cell cycle arrest by inhibition of Notch signaling [39], and suppresses invasion through repression of epithelial-mesenchymal transition [40] and paxillin transcription via PI3K/Akt/NF-κB pathway [41]. PTEN overexpression suppresses adhesion, invasion and metastasis in osteosarcoma and gastric

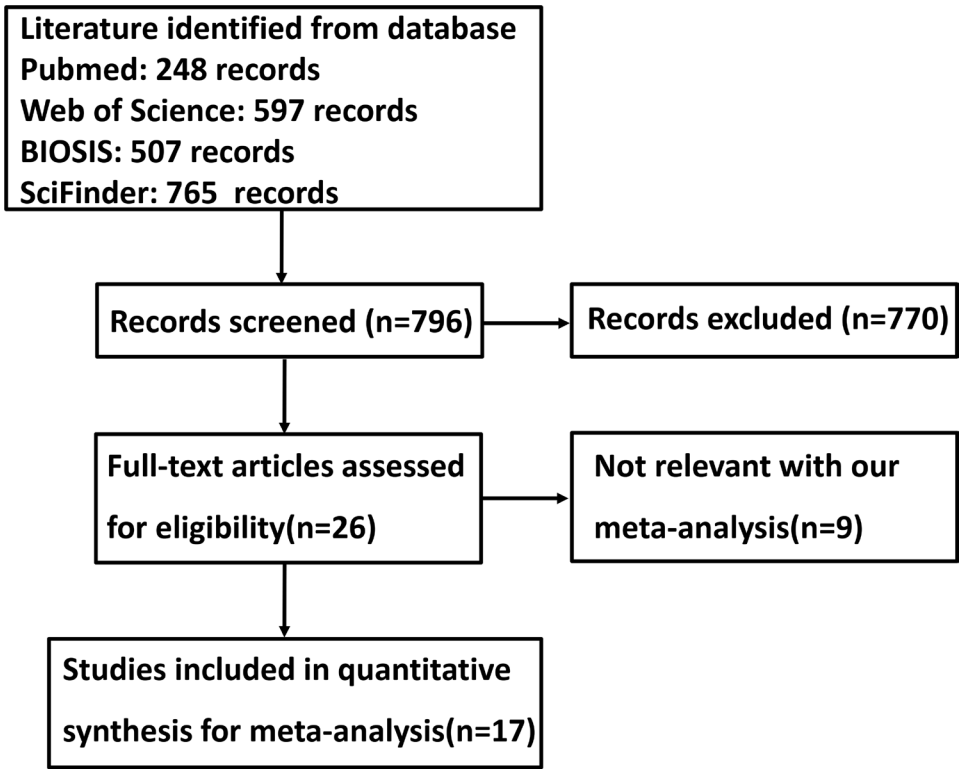
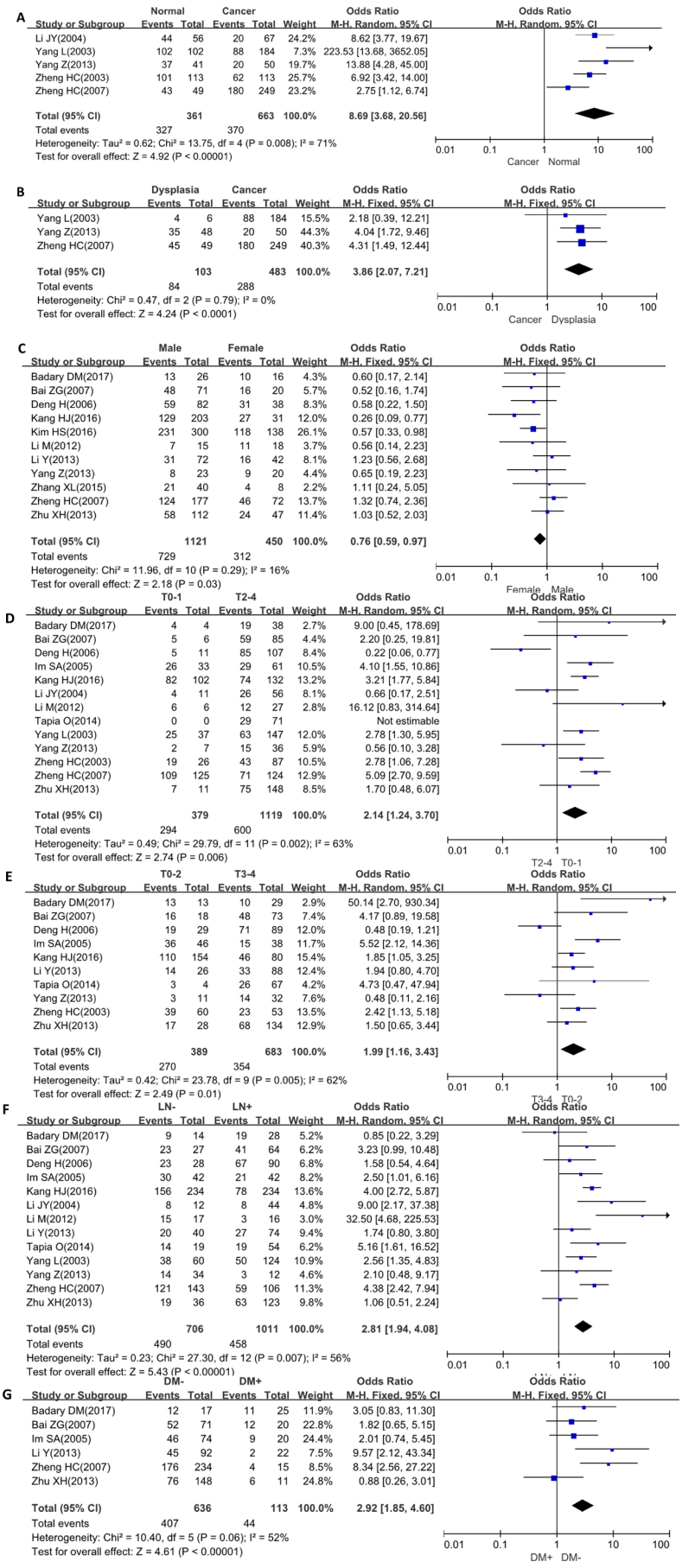


Figure 2: Flow diagram of the selection process in this meta-analysis.


A
Normal
Cancer
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Li JY(2004) 44 56 20 67 24.2% 8.62 [3.77, 19.67]
Yang L(2003) 102 102 88 184 7.3% 223.53 [13.68, 3652.05]
Yang Z(2013) 37 41 20 50 19.7% 13.88 [4.28, 45.00]
Zheng HC(2003) 101 113 62 113 25.7% 6.92 [3.42, 14.00]
Zheng HC(2007) 43 49 180 249 23.2% 2.75 [1.12, 6.74]
Total (95% CI) 361 663 100.0% 8.69 [3.68, 20.56]
Total events 327 370
Heterogeneity: Tau² = 0.62; Chi² = 13.75, df = 4 (P = 0.008); I² = 71%
Test for overall effect: Z = 4.92 (P < 0.00001)
0.01 0.1 1 10 100
Cancer Normal
B
Dysplasia
Cancer
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Yang L(2003) 4 6 88 184 15.5% 2.18 [0.39, 12.21]
Yang Z(2013) 35 48 20 50 44.3% 4.04 [1.72, 9.46]
Zheng HC(2007) 45 49 180 249 40.3% 4.31 [1.49, 12.44]
Total (95% CI) 103 483 100.0% 3.86 [2.07, 7.21]
Total events 84 288
Heterogeneity: Chi² = 0.47, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.24 (P < 0.0001)
0.01 0.1 1 10 100
Cancer Dysplasia
C
Male
Female
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Badary DM(2017) 13 26 10 16 4.3% 0.60 [0.17, 2.14]
Bai ZG(2007) 48 71 16 20 5.7% 0.52 [0.16, 1.74]
Deng H(2006) 59 82 31 38 8.3% 0.58 [0.22, 1.50]
Kang HJ(2016) 129 203 27 31 12.0% 0.26 [0.09, 0.77]
Kim HS(2016) 231 300 118 138 26.1% 0.57 [0.33, 0.98]
Li M(2012) 7 15 11 18 3.7% 0.56 [0.14, 2.23]
Li Y(2013) 31 72 16 42 8.1% 1.23 [0.56, 2.68]
Yang Z(2013) 8 23 9 20 4.4% 0.65 [0.19, 2.23]
Zhang XL(2015) 21 40 4 8 2.2% 1.11 [0.24, 5.05]
Zheng HC(2007) 124 177 46 72 13.7% 1.32 [0.74, 2.36]
Zhu XH(2013) 58 112 24 47 11.4% 1.03 [0.52, 2.03]
Total (95% CI) 1121 450 100.0% 0.76 [0.59, 0.97]
Total events 729 312
Heterogeneity: Chi² = 11.96, df = 10 (P = 0.29); I² = 16%
Test for overall effect: Z = 2.18 (P = 0.03)
0.01 0.1 1 10 100
Female Male
D
T0-1
T2-4
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Badary DM(2017) 4 4 19 38 2.7% 9.00 [0.45, 178.69]
Bai ZG(2007) 5 6 59 85 4.4% 2.20 [0.25, 19.81]
Deng H(2006) 5 11 85 107 8.4% 0.22 [0.06, 0.77]
Im SA(2005) 26 33 29 61 10.5% 4.10 [1.55, 10.86]
Kang HJ(2016) 82 102 74 132 13.2% 3.21 [1.77, 5.84]
Li JY(2004) 4 11 26 56 8.1% 0.66 [0.17, 2.51]
Li M(2012) 6 6 12 27 2.8% 16.12 [0.83, 314.64]
Tapia O(2014) 0 0 29 71 Not estimable
Yang L(2003) 25 37 63 147 12.0% 2.78 [1.30, 5.95]
Yang Z(2013) 2 7 15 36 5.9% 0.56 [0.10, 3.28]
Zheng HC(2003) 19 26 43 87 10.5% 2.78 [1.06, 7.28]
Zheng HC(2007) 109 125 71 124 12.9% 5.09 [2.70, 9.59]
Zhu XH(2013) 7 11 75 148 8.5% 1.70 [0.48, 6.07]
Total (95% CI) 379 1119 100.0% 2.14 [1.24, 3.70]
Total events 294 600
Heterogeneity: Tau² = 0.49; Chi² = 29.79, df = 11 (P = 0.002); I² = 63%
Test for overall effect: Z = 2.74 (P = 0.006)
0.01 0.1 1 10 100
T2-4 T0-1
E
T0-2
T3-4
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Badary DM(2017) 13 13 10 29 2.9% 50.14 [2.70, 930.34]
Bai ZG(2007) 16 18 48 73 7.4% 4.17 [0.89, 19.58]
Deng H(2006) 19 29 71 89 12.0% 0.48 [0.19, 1.21]
Im SA(2005) 36 46 15 38 11.7% 5.52 [2.12, 14.36]
Kang HJ(2016) 110 154 46 80 15.4% 1.85 [1.05, 3.25]
Li Y(2013) 14 26 33 88 12.4% 1.94 [0.80, 4.70]
Tapia O(2014) 3 4 26 67 4.2% 4.73 [0.47, 47.94]
Yang Z(2013) 3 11 14 32 7.6% 0.48 [0.11, 2.16]
Zheng HC(2003) 39 60 23 53 13.5% 2.42 [1.13, 5.18]
Zhu XH(2013) 17 28 68 134 12.9% 1.50 [0.65, 3.44]
Total (95% CI) 389 683 100.0% 1.99 [1.16, 3.43]
Total events 270 354
Heterogeneity: Tau² = 0.42; Chi² = 23.78, df = 9 (P = 0.005); I² = 62%
Test for overall effect: Z = 2.49 (P = 0.01)
0.01 0.1 1 10 100
T3-4 T0-2
F
LN-
LN+
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Badary DM(2017) 9 14 19 28 5.2% 0.85 [0.22, 3.29]
Bai ZG(2007) 23 27 41 64 6.2% 3.23 [0.99, 10.48]
Deng H(2006) 23 28 67 90 6.8% 1.58 [0.54, 4.64]
Im SA(2005) 30 42 21 42 8.2% 2.50 [1.01, 6.16]
Kang HJ(2016) 156 234 78 234 13.6% 4.00 [2.72, 5.87]
Li JY(2004) 8 12 8 44 4.8% 9.00 [2.17, 37.38]
Li M(2012) 15 17 3 16 3.0% 32.50 [4.68, 225.53]
Li Y(2013) 20 40 27 74 9.4% 1.74 [0.80, 3.80]
Tapia O(2014) 14 19 19 54 6.2% 5.16 [1.61, 16.52]
Yang L(2003) 38 60 50 124 10.9% 2.56 [1.35, 4.83]
Yang Z(2013) 14 34 3 12 4.6% 2.10 [0.48, 9.17]
Zheng HC(2007) 121 143 59 106 11.3% 4.38 [2.42, 7.94]
Zhu XH(2013) 19 36 63 123 9.8% 1.06 [0.51, 2.24]
Total (95% CI) 706 1011 100.0% 2.81 [1.94, 4.08]
Total events 490 458
Heterogeneity: Tau² = 0.23; Chi² = 27.30, df = 12 (P = 0.007); I² = 56%
Test for overall effect: Z = 5.43 (P < 0.00001)
0.01 0.1 1 10 100
G
DM-
DM+
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Badary DM(2017) 12 17 11 25 11.9% 3.05 [0.83, 11.30]
Bai ZG(2007) 52 71 12 20 22.8% 1.82 [0.65, 5.15]
Im SA(2005) 46 74 9 20 24.4% 2.01 [0.74, 5.45]
Li Y(2013) 45 92 2 22 7.5% 9.57 [2.12, 43.34]
Zheng HC(2007) 176 234 4 15 8.5% 8.34 [2.56, 27.22]
Zhu XH(2013) 76 148 6 11 24.8% 0.88 [0.26, 3.01]
Total (95% CI) 636 113 100.0% 2.92 [1.85, 4.60]
Total events 407 44
Heterogeneity: Chi² = 10.40, df = 5 (P = 0.06); I² = 52%
Test for overall effect: Z = 4.61 (P < 0.00001)
0.01 0.1 1 10 100
DM+ DM-

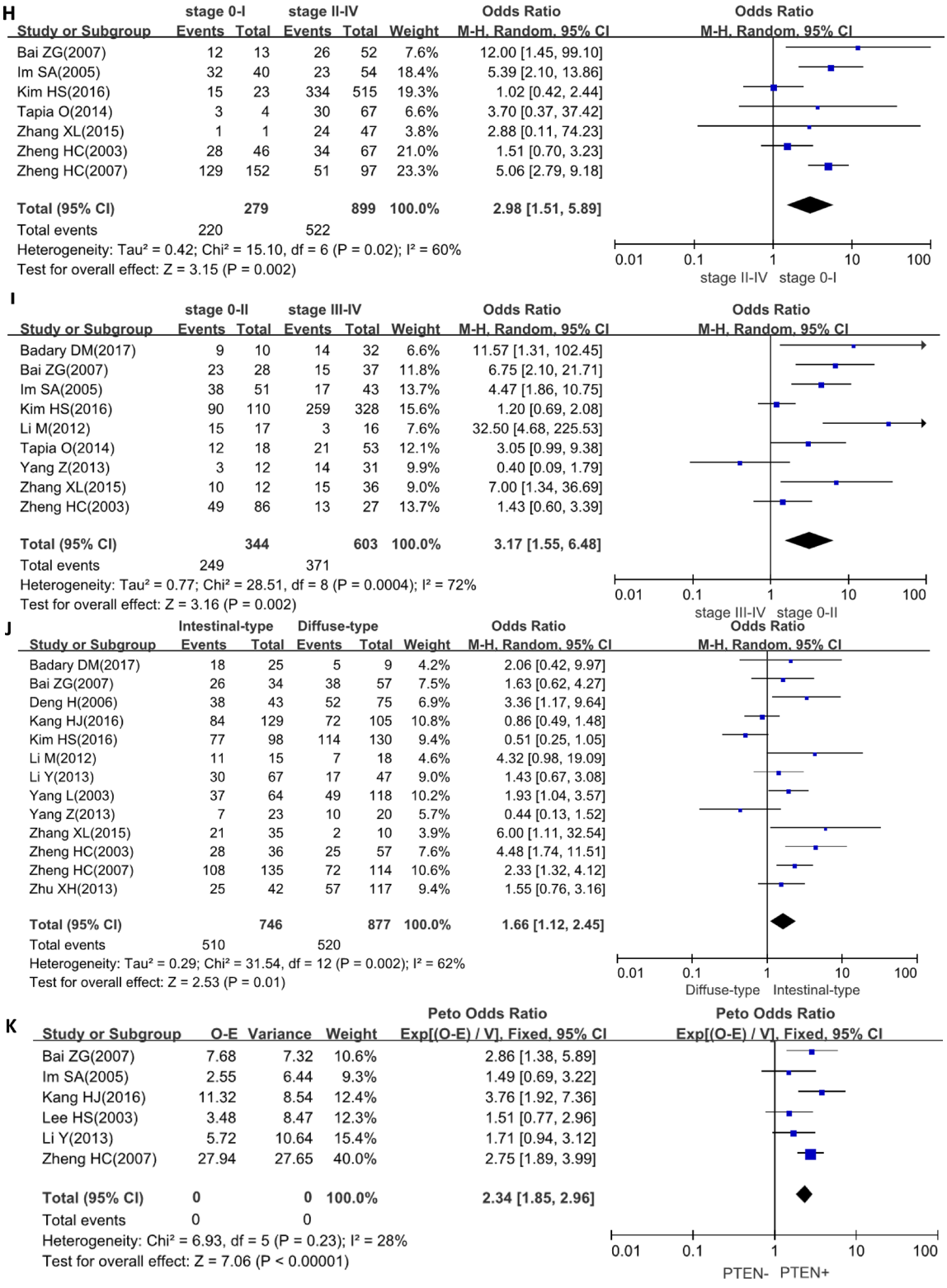


Figure 3: Forest plot for the relationship between PTEN expression and clinicopatholoiocal parameters of gastric cancer. (**A**) gastric carcinogenesis (cancer *vs* normal mucosa); (**B**) gastric carcinogenesis (cancer *vs* dysplasia) ; (**C**) correlation between sex and PTEN expression (male *vs* female); (**D**) correlation between depth of invasion and PTEN expression (T0-1 *vs* T2-4); (**E**) correlation between depth of invasion and PTEN expression (T0-2 *vs* T3-4); (**F**) correlation between lymph node metastasis (LN) and PTEN expression (LN- *vs* LN+); (**G**) correlation between distant metastasis (DM) and PTEN expression (DM- *vs* DM+); (**H**) correlation between TNM staging and PTEN expression (stage 0-I *vs* II-IV); (**I**) correlation between TNM staging and PTEN expression (stage 0-II *vs* III-IV); (**J**) correlation between differentiation and PTEN expression (intestinal-type *vs* diffuse-type); (**K**) correlation between prognosis and PTEN expression (PTEN- *vs* PTEN+).

cancer cells with down-regulation of MMP-9, FAK and p-FAK [42, 43]. PTEN inhibits PI3K/NF-κB pathway and the binding of NF-κB to FAK promoter [43]. Loss of PTEN induces tubulin- based microtentacles for migration and metastasis through PI3K-independent activation of cofilin [44]. PTEN suppresses hyaluronic acid-induced MMP-9 expression in glioblastoma cells via FAK dephosphorylation [45]. Nuclear PTEN arrests cell cycle by suppressing cyclin D1 transcription, which is weakened by ERK1/2 activation [46]. In cancer cells, DNA-damaging agents results in ATM-mediated PTEN phosphorylation and the nuclear translocation PTEN to induce autophagy [47]. PTEN was reported to enhance autophagy by inhibiting ubiquitin-proteasome and PI3K/Akt pathways respectively [48, 49]. Here, our bibliometric analysis indicated that the investigators mainly focused on PTEN discovery, correlation of its genetic and epigenetic alteration with cancers and the regulatory effects of miRNA on PTEN translation in the roles of PTEN expression in gastric cancer. Therefore, we performed a meta- and bioinformatics analysis about PTEN expression in gastric cancer at both mRNA and protein levels in the following work.

Gastric precancerous lesions appear between gastric epithelium and adenocarcinoma, and are divided into adenomatous, regenerative, crysptal and globoid dysplasia [50]. Jang et al. [51] reported that nuclear PTEN expression was gradually down-regulated during colorectal mucosa-adenoma-adenocarcinoma-metastasis sequence. Consistent with the data about

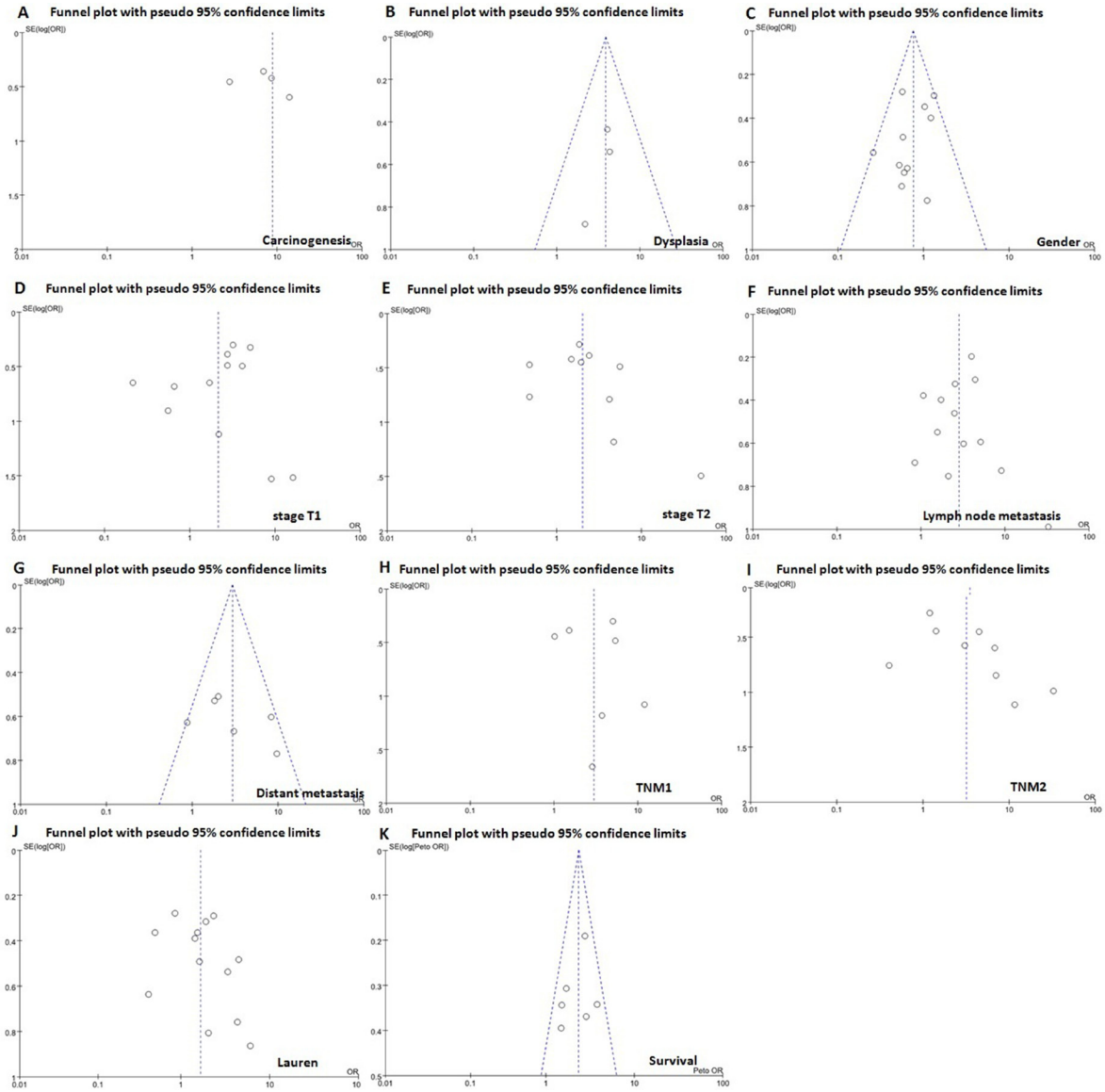


Figure 4: Funnel plot for publication bias test between PTEN expression and gastric carcinogenesis or progression. The bias was analyzed about risk degrees of PTEN expression in gastric mucosa. (**A**) and dysplasia (**B**) for gastric carcinogenesis. Additionally, it was tested between PTEN expression and clinicopathological features of gastric cancer, including age (**C**), depth of invasion (**D**–**E**), lymph node metastasis (**F**), distant metastasis (**G**), TNM staging (**H**–**I**), and differentiation (**J**) and prognosis (**K**).

Table 2: The top 10 centered articles

Rank	Freq	Centrality	Author	Year	Source	Title
1	14	0.13	Yang H	2008	Cancer Res	MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN.
2	8	0.12	Trotman LC	2007	Cell	Ubiquitination regulates PTEN nuclear import and tumor suppression.
3	5	0.12	Barbi S	2010	J Exp Clin Cancer Res	The analysis of PIK3CA mutations in gastric carcinoma and metanalysis of literature suggest that exon-selectivity is a signature of cancer type.
4	24	0.11	Kang YH	2002	Lab Invest	Promoter methylation and silencing of PTEN in gastric carcinoma.
5	12	0.11	Hollander MC	2011	Nat Rev Cancer	PTEN loss in the continuum of common cancers, rare syndromes and mouse models.
6	8	0.11	Asangani IA	2008	Oncogene	MicroRNA-21 (miR-21) post- transcriptionally downregulates tumor suppressor Pdcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer.
7	4	0.09	Lee HS	2003	J Pathol	Tumour suppressor gene expression correlates with gastric cancer prognosis.
8	7	0.08	Tan MH	2012	Clin Cancer Res	Lifetime cancer risks in individuals with germline PTEN mutations.
9	6	0.08	Ambs S	2008	Cancer Res	Genomic profiling of microRNA and messenger RNA reveals deregulated microRNA expression in prostate cancer.
10	5	0.07	Deng NT	2012	Gut	Discovery of potential piRNAs from next generation sequences of the sexually mature porcine testes.

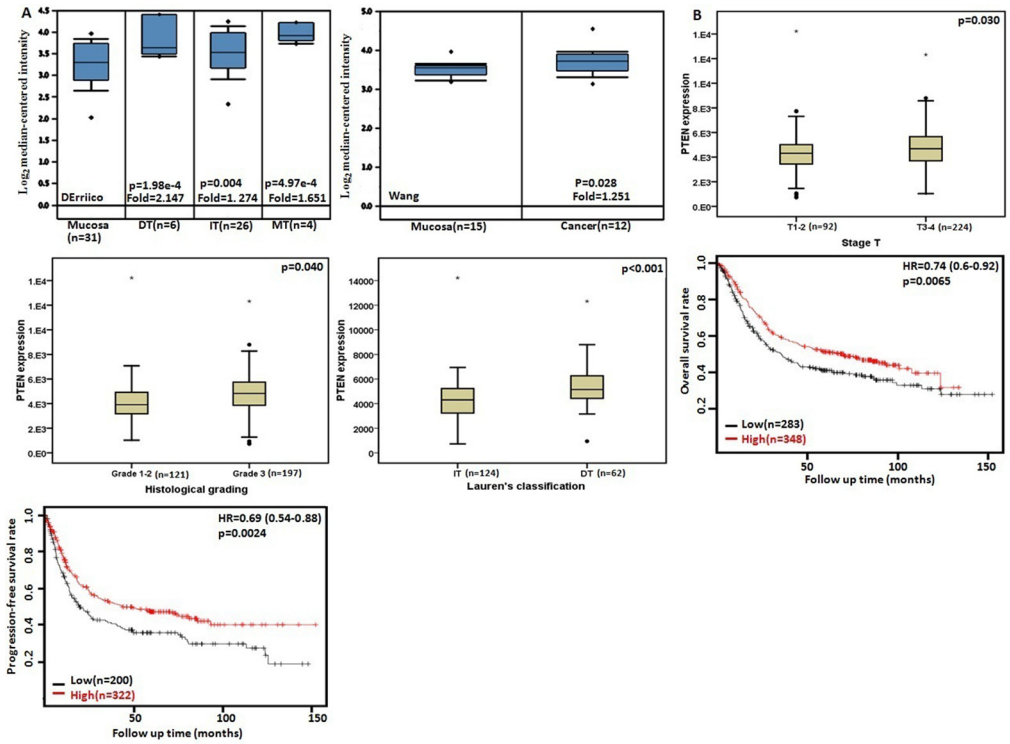


Figure 5: *PTEN* mRNA expression in gastric carcinogenesis and subsequent progression. DErrico's and Wang's datasets were employed for bioinformatics analysis to analyze PTEN expression during gastric carcinogenesis. (**A)** higher *PTEN* expression was detectable in gastric cancer than that in normal gastric mucosa, even stratified into intestinal (IT)-, diffuse-(DT), and mixed-type (MT) carcinomas by Lauren's classification (A, $p < 0.05$). TCGA database shows that *PTEN* was more expressed in T3–T4 than T1-T2 cancers (**B**) ($p < 0.05$). PTEN expression was positively correlated with histological grading and differentiation of gastric cancers (B, $p < 0.05$). According to the data from Kaplan-Meier plotter, *PTEN* expression was positively related to both overall and progression-free survival rates of the patients with gastric cancer (**C**). HR, hazard ratio.

Table 3: The top 10 burst citation articles

Rank	Freq	Centrality	Author	Year	Source	Title
1	23	11.73	Li J	1997	Science	PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer.
2	24	10.7	Kang YH	2002	Lab Invest	Promoter methylation and silencing of PTEN in gastric carcinoma.
3	20	10.19	Steck PA	1997	Nat Genet	Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers.
4	15	6.65	Sato K	2002	Virchows Arch	Analysis of genetic and epigenetic alterations of the PTEN gene in gastric cancer.
5	13	6.56	Liaw D	1997	Nat Genet	Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome.
6	11	5.93	Maehama T	1998	J Biol Chem	The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5- trisphosphate.
7	11	5.55	Marsh DJ	1997	Nat Genet	Germline mutations in PTEN are present in Bannayan-Zonana syndrome.
8	10	5.26	Teng DHF	1997	Cancer Res	MMAC1/PTEN mutations in primary tumor specimens and tumor cell lines.
9	9	4.73	Cairns P	1997	Cancer Res	Frequent inactivation of PTEN/MMAC1 in primary prostate cancer.
10	9	4.73	Tashiro H	1997	Cancer Res	Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies.

Table 4: The top 20 key words

Rank	Freq	Keyword	Rank	Freq	Keyword
1	256	gastric cancer	11	56	growth
2	209	pten	12	52	prostate cancer
3	168	expression	13	51	pathway
4	104	breast cancer	14	50	tumor suppressor
5	79	carcinoma	15	50	metastasis
6	75	apoptosis	16	46	cancer
7	74	gene	17	44	hepatocellular carcinoma
8	69	colorectal cancer	18	42	cell
9	64	proliferation	19	40	tumor suppressor gene
10	57	invasion	20	40	activation

Table 5: The top 20 burst key words

Rank	Freq	Burst	Keyword	Rank	Freq	Burst	Keyword
1	40	9.65	tumor suppressor gene	11	9	3.83	her2
2	34	7.33	gastric carcinoma	12	37	3.67	prognosis
3	27	5.97	down regulation	13	20	3.65	lung cancer
4	9	4.92	germline mutation	14	34	3.60	microRNA
5	21	4.91	gene expression	15	11	3.36	microRNA expression
6	10	4.80	microsatellite instability	16	5	3.12	pten/mmac1 gene
7	46	4.33	cancer	17	57	3.10	invasion
8	21	4.33	migration	18	74	3.03	gene
9	40	4.18	activation	19	8	3.01	mTOR
10	10	3.90	breast	20	75	2.95	apoptosis

Table 6: Main characteristics of eligible studies

First author	Year	Country	Ethnicity	Antibody Source	Cases	Control	Risk to cancer	Outcome	Quality
Badary DM	2017	Egypt	European	Labvision	42			Pos	7
Kang HJ	2016	Korea	Asian	Cell signal	272			Pos	8
Kim HS	2016	Korea	Asian	Cell signal	438				8
Zhang XL	2015	China	Asian	DAKO	48			Pos	7
Tapia O	2014	Chile	-----	Cell signal	71				7
Li Y	2013	China	Asian	Cell signal	114				8
Zhu XH	2013	China	Asian	Cell signal	159				8
Li M	2012	China	Asian	Cell signal	33				7
Yang Z	2013	China	Asian	Abcam	50	41	Down		8
Bai ZG	2007	China	Asian	Zymed	91			Pos	8
Zheng HC	2006	Japan	Asian	Novocastra	249	49	Down	Pos	9
Deng H	2006	China	Asian	Cell signal	118			Pos	8
Lm SA	2005	Korea	Asian	Neomarker	84			Pos	8
Lee HS	2003	Korea	Asian	Fremont	329			Pos	8
Zheng HC	2003	China	Asian	Zymed	113	113	Down		9
Yang L	2003	China	Asian	Zymed	184	102	Down		9
Li JY	2004	China	Asian	Zymed	67	56	Down		7

Down, down-regulated expression; Pos, positive correlation.

tongue squamous cancer [52], head and neck cancer [53], pancreatic cancer [54], colorectal cancer [55], lung cancer [56], sacral chordoma [57], salivary adenoid cystic carcinoma [58], renal clear cell carcinoma [59], laryngeal and hypopharyngeal squamous cell carcinoma [60], esophageal cancer [61], we found that PTEN underexpression was detected in gastric cancer than mucosa or dysplasia, and negatively with depth of invasion, lymph node and distant metastasis, TNM staging, and dedifferentiation of gastric cancer according to meta-analysis, while versa for its mRNA level according to the bioinformatics analysis. Zhou et al. [62] demonstrated that the expression of *PTEN* mRNA and protein was significantly lower in hepatocellular carcinoma than the paracancerous tissues. The discrepancy might be due to different methodologies, a complex event from mRNA to protein, and a positive feedback overexpression of PTEN mRNA during progression. These results indicate that aberrant PTEN expression promotes gastric carcinogenesis and is considered as a good marker for aggressive behaviors of gastric cancer.

Reportedly, PTEN overexpression was associated with favorable prognosis in breast cancer [63], colorectal cancer [55], triple-negative breast cancer [64], lung cancer [56], ampullary adenocarcinoma [65], pancreatic cancer [66], gastrointestinal stromal tumor [67], oral squamous carcinoma [68], esophageal carcinoma [61], ovarian cancer [69], and hepatocellular carcinoma [70]. It might be also demonstrated to indicate the favorable prognosis of tongue squamous carcinoma [52], colorectal cancer [71], renal cell carcinoma [72], endometrial carcinoma [73], esophageal adenocarcinoma [74], mesothelioma [75], lung cancer [76], and invasive ductal carcinoma of the breast [77] as an independent factor. Our study showed that PTEN expression was positively linked to the favorable prognosis of the gastric cancer patients at either mRNA or protein level. da Costa et al. [78] demonstrated that PTEN hypoexpression was positively associated with a short overall survival of head and neck squamous cell carcinoma patients undergoing chemotherapy and cetuximab. Endoh et al. [79] found that PTEN expression was positively linked to a long survival after in EGFR-mutated lung cancer patients receiving gefitinib ademinstration. These findings suggest that PTEN loss is considered as a potential good marker for unfavorable prognosis of the gastric cancer patients at both mRNA and protein levels.

In conclusion, the study about PTEN and gastric cancer mainly focused on PTEN discovery, correlation of its genetic and epigenetic alteration with cancers, the effects of PTEN expression on the phenotypes of gastric cancer cells, and the regulatory effects of miRNA on PTEN translation. PTEN expression was down-regulated during gastric carcinogenesis as a late event, and was negatively associated with the aggressiveness and poor prognosis of gastric cancer at both mRNA and protein levels. The following disadvantages are mentioned in our study. Firstly, the positive results are published to cause

Table 7: The prognostic significance of PTEN mRNA in gastric cancer

Clinicopathological features	Overall survival		Progression-free survival	
	Hazard ratio	*p*	Hazard ratio	*p*
Sex				
Female	1.26 (0.8–2)	0.32	1.36 (0.87-2.13)	0.18
Male	0.58 (0.43–0.78)	3e–04	0.63 (0.47–0.84)	0.0016
T				
2	0.65 (0.42–1)	0.05	0.66 (0.43–1)	0.047
3	0.59 (0.41–0.84)	0.0037	0.66 (0.47–0.93)	0.017
4	1.76 (0.77–4)	0.17	1.46 (0.68–3.15)	0.33
N				
0	1.49 (0.54–4.1)	0.44	1.59 (0.58–4.35)	0.36
1–3	0.61 (0.47–0.8)	0.00025	0.63 (0.49–0.81)	0.00035
1	0.5 (0.33–0.75)	0.00067	0.52 (0.35–0.77)	0.00081
2	0.46 (0.29–0.72)	0.00059	0.46 (0.3–0.71)	0.00038
3	1.38 (0.81–2.34)	0.23	0.75 (0.41–1.36)	0.34
M				
0	0.67 (0.5–0.88)	0.0046	0.68 (0.52–0.89)	0.0043
1	0.64 (0.36–1.16)	0.14	1.36 (0.7–2.63)	0.36
TNM staging				
I	0.29 (0.08–1.06)	0.047	0.31 (0.09–1.13)	0.062
II	0.52 (0.25–1.08)	0.075	0.5 (0.24–1.01)	0.049
III	0.6 (0.41–0.88)	0.0084	0.61 (0.42–0.88)	0.0084
IV	0.61 (0.41–0.93)	0.019	0.74 (0.5–1.1)	0.14
Differentiation				
Well-differentiated	–	–	–	–
Moderately-differentiated	0.4 (0.19–0.84)	0.012	0.43 (0.21–0.85)	0.013
Poorly-differentiated	1.33 (0.82–2.17)	0.25	1.3 (0.82–2.06)	0.26
Lauren's classification				
Intestinal-type	0.38 (0.26–0.55)	1.2e–07	0.47 (0.33–0.67)	2.4e−05
Diffuse-type	0.72 (0.5–1.02)	0.063	0.75 (0.53–1.06)	0.11
Mixed-type	3.38 (1.13–10.14)	0.021	2.79 (0.94–8.24)	0.054
Her2 positivity				
–	0.75 (0.56–1)	0.047	0.78 (0.58–1.04)	0.094
+	0.57 (0.38–0.84)	0.0046	0.48 (0.31–0.74)	0.00076
Treatment				
Surgery alone	0.75 (0.55–1.02)	0.067	0.8 (0.61–1.06)	0.13
5-FU–based adjuvant	0.44 (0.16–1.26)	0.12	0.63 (0.26–1.55)	0.31
Other adjuvant	1.57 (0.63–3.93)	0.33	0.71 (0.32–1.56)	0.39

publication bias. Secondly, survival data were extracted from published Kaplan-Meier curves using software to cause processing bias. Thirdly, this small sample size influences the association strength between PTEN expression and clinicopathological characteristics to cause subject bias. Fourthly, bibliometric analysis calculates the co-words and co-citation, whose random property influences the final conclusion. Fifthly, bioinformatics analysis used the data of cDNA array and RNA sequencing of tissues, so cell type and proportion of tissues and the disadvantages of both high-throughput methods affect the results' accuracy.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a publication search using PubMed, Web of Science, BIOSIS SciFinder and CNKI

updated on March 14, 2017. The following search terms were used: (PTEN OR MMAC1 OR TEP1) AND (gastric OR stomach) AND (cancer OR carcinoma OR adenocarcinoma). Searching was done without restriction on language or publication years. Inclusion criteria for studies: (1) articles to observe the alteration in PTEN expression in gastric cancer by immunohistochemistry; (2) papers to compare PTEN expression with pathobiological behaviors and prognosis of gastric cancer by immunohistochemistry. Exclusion criteria included: (1) abstract, comment, review and meeting; (2) duplication of the previous publications; (3) Western blot, RT-PCR, cDNA microarray, or transcriptomic sequencing for PTEN expression; (4) lack of sufficient information.

Bibliometric analysis

The downloaded files about PTEN from Web of Science was input into CiteSpace II (http://cluster.cis.drexel.edu/~cchen/citespace/), which is a freely available Java application for visualizing and analyzing trends and patterns in scientific literature. Firstly, we performed a hybrid network and timeline co-citation cluster analysis of the references with term labeled. After that, key terms were determined and subjected to co-word analysis.

Data extraction

Based on the inclusion criteria, two reviewers (HC Zheng and YH Qiu) independently extracted information from all eligible publications. The following information were included in each study: name of first author, year of publication, country, ethnicity, cancer types, source of control, antibody company, numbers of cases and controls, expression alteration, correlation with aggressive features, and follow-up times. Regarding survival analysis, we used Engauge Digitizer software to extract data from Kaplan-Meier curves and calculated the Hazard ratios (HR) and their corresponding 95% confidence intervals (CI). Any disagreement was resolved through discussion until the two reviewers reached a consensus.

Quality score assessment

Two reviewers (HC Zheng and S Zhao) independently assessed the quality of the included studies according to Newcastle Ottawa Scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).
The scale consists of three components related to sample selection, comparability and ascertainment of outcome.

Bioinformatics analysis

PTEN expression was analyzed using Oncomine (www.oncomine.org). We compared the differences in PTEN mRNA level between gastric normal tissue and cancer. The expression data (RNA-seqV2) and clinicopathological data of 392 gastric cancer patients were downloaded from the Cancer Genome Atlas (TCGA, https://cancergenome.nih.gov/) database by TCGA-assembler in R software. We integrated the raw data, analyzed PTEN expression in gastric cancer, and compared it with clinicopathological and prognostic data of the patients with gastric cancer. Additionally, the prognostic significance of PTEN mRNA was also analyzed using Kaplan-Meier plotter (http://kmplot.com).

Statistics analysis

HWE was evaluated using Chi-square test in control groups of each study. Strength of association between PTEN expression and cancer risk was assessed by odds ratios with 95% confidence intervals. Statistical significance of the pooled OR was determined by Z test. If there was no significant heterogeneity, the fixed effect model (Mantel-Haenszel method) would be employed. Otherwise, the random effect model (DerSimonian and Laird method) would be used excluding prognostic analysis. Heterogeneity effect was then quantified by I^2 test, which was subdivided into low, moderate and high degrees of heterogeneity according to the cut-off values of 25%, 50% and 75% respectively. Publication bias was evaluated by funnel plot and quantified by Begg's test and Egger's test to assess funnel plot asymmetry. Meta-analyses were performed with Revman software 5.3 and data from TCGA database was dealt with SPSS 10.0 using student t test. $P < 0.05$ was considered as statistically significant.

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CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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