

## Original Article

# PTEN genomic deletion defines favorable prognostic biomarkers in localized prostate cancer: a systematic review and meta-analysis

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**Abstract:** PTEN (10q23.3) is a negative regulator of the phosphatidylinositol 3-kinase (PIK3)/Akt survival pathway and a tumor suppressor frequently deleted in prostate cancer. PTEN genomic deletion is among the most common genetic aberrations in human prostate cancer. At present, the prognostic value of PTEN genomic deletion is unclear. We performed a systematic review and meta-analysis to clarify the association between PTEN genomic deletion and a higher Gleason score or a higher possibility of capsular penetration. A comprehensive, computerized literature search of PubMed was carried out until May 27, 2014. Studies were included according to specific inclusion criteria. Pooled hazard ratio was estimated using the fixed effects model or random effects model according to heterogeneity between studies. Seven eligible studies meeting the specific inclusion criteria were selected for further analysis; all were retrospective studies. Overall meta-analysis demonstrated that PTEN genomic deletion was associated with a higher Gleason score (OR 0.319; 95% confidence interval: 0.153-0.666;  $P = 0.000$ ) and a higher possibility of capsular penetration (OR 0.393; 95% confidence interval: 0.185-0.837;  $P = 0.015$ ). None of the studies materially altered the original results and no evidence of publication bias was found. Conclusion: PTEN genomic deletion in operable localized prostate cancer indicates a higher Gleason score and a higher probability of capsular penetration, indicating a worse prognosis. Further studies should be conducted in order to investigate the effect of PTEN genomic deletion on clinical outcomes in different histological types of prostate cancer or its function in castration-resistant prostate cancer.

**Keywords:** Prostate cancer, PTEN deletion, Gleason score, capsular penetration

## Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer and a leading cause of cancer-related death in American men in addition to strongly affecting men all over the world [1]. With a more comprehensive understanding of PCa and new protocols for treatment, the outcome for PCa patients has improved in the past few decades. However, we are still not completely aware of the factors that affect the prognosis of patients with PCa. Identifying potential biomarkers that could serve as prognostic factors for PCa patients is crucial for individual treatment. Several biomarkers have been demonstrated to affect the survival of PCa patients so far, including androgen receptor variants [2], circulating tumor cells [3], and cysteine-rich secretory protein 3 [4]. PTEN genomic deletion has been detected in human tissues represent-

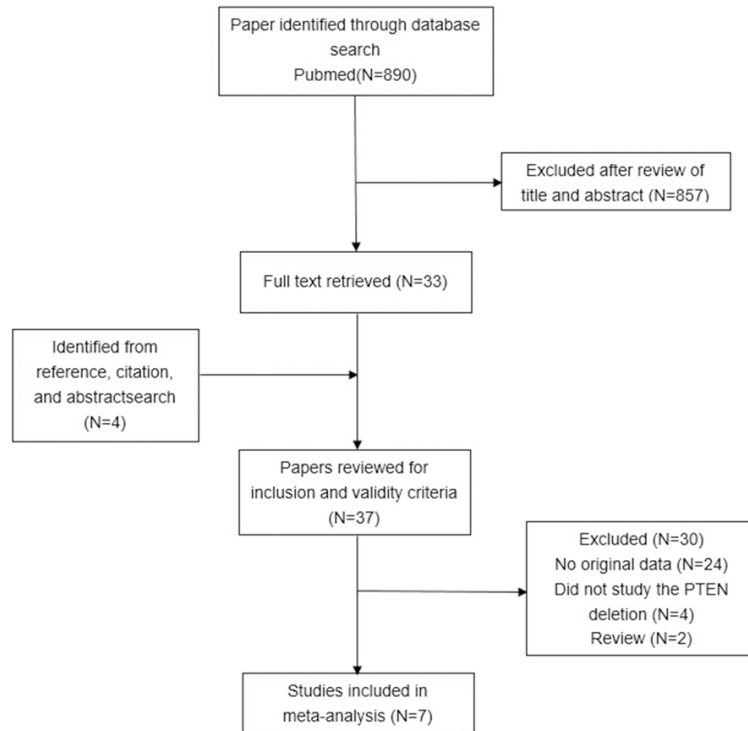
ing all stages of PCa development [5] and progression including high-grade prostatic intraepithelial neoplasia (HGPIN) [6], clinically localized PCa, metastatic PCa, and castration-resistant prostate cancer (CRPC) [7]. To clarify the association of PTEN deletion with the Gleason score and capsular penetration in patients with PCa, we conducted the first comprehensive meta-analysis of the existing published literature on this topic in patients with operable localized PCa.

## Materials and methods

### Literature search

A comprehensive, computerized literature search of PubMed was carried out until May 27, 2014. Potentially relevant studies were identified using “prostate cancer” (i.e., “prostate cancer”, “prostate carcinoma”, “prostate neo-

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**Figure 1.** The literature search process. Notes: Eight hundred and ninety studies were identified in the primary literature search. 37 potentially relevant studies were further evaluated and seven studies were finally included in the analysis according to the inclusion criteria.

plasm”) and “PTEN”, “PI3K” and “pAkt” groups of search terms. The references from relevant papers, especially from review articles, were checked to identify studies overlooked in the original search. This systematic review and meta-analysis was planned, conducted, and reported in adherence to the standards of quality for reporting meta-analyses. Studies meeting all of the following inclusion criteria were deemed eligible and included in the analysis: (1) published in English, and (2) explored the relation between PTEN deletion and pathological outcome of operable localized PCa. All studies that did not satisfy the inclusion criteria as well as any data obtained from reviews, animal experiments, or cell line studies were excluded. Study quality was assessed using the Newcastle-Ottawa Scale. A flowchart of the literature search, study selection, and results of each step is presented in **Figure 1**.

### Data extraction and outcomes

In order to ensure homogeneity of the data gathering and to preclude subjectivity in the data collection and entry, two reviewers independently assessed studies for inclusion, and

disagreements were resolved through open discussion. The following information about each study was recorded: first author names, journal and year of publication, patient nationality, total number of patients, median age of patients at diagnosis, the median stage, the median Gleason score, and the number of patients with PTEN deletion.

### Statistical analysis

First, we assessed the heterogeneity between studies using the Q-test and  $I^2$  statistic to measure the proportion of total estimate variation that was attributable to study heterogeneity, and either a  $P$ -value  $< 0.10$  or  $I^2 > 50\%$  was considered statistically significant. The pooled HR was estimated using the fixed effects model unless heterogeneity was found and was unexplainable, in which case, the random effects model was applied. We used the random effects model to analyze the relationship between PTEN deletion and Gleason score as the heterogeneity between studies was statistically significant ( $I^2 = 82.6\%$ ;  $P = 0.000$ ). And the random effects model was also applied to analyze the relationship between PTEN deletion and capsular penetration as the heterogeneity between studies was statistically significant ( $I^2 = 69.7\%$ ;  $P = 0.019$ ). We performed a sensitivity analysis by removing each individual study from the meta-analysis. Several methods were used to assess potential publication bias. Potential bias of publication was examined by using the Begg funnel plot and Egger linear regression test (All reported  $P$  values were two-sided, and  $P$  values  $< 0.05$  were considered statistically significant). All statistical analyses performed in this study were carried out using Stata software (v 12.0; StataCorp LP, College Station, TX, USA).

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### Results

The literature search process and the result of each step are presented in **Figure 1**. Studies

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**Table 1.** Studies included in this meta-analysis

Study	Country	Number of patients	Median patient age, years	Treatment	ethnicity	PTEN positive rate	QUADAS score
Mcmenamin (1999)	USA	39	66	radical prostatectomy	Caucasian	17/39	12
Reid (2010)	UK	322	69	TURPT	Caucasian	266/322	11
Bismar (2010)	USA	659	64	radical prostatectomy	Caucasian	454/659	12
Yoshimoto (2007)	Canada	107	63	radical prostatectomy	Caucasian	60/107	12
Lotan (2011)	USA	397	*	radical prostatectomy	Caucasian	254/397	10
Nagle (2013)	USA	90	63	radical prostatectomy	Caucasian	71/90	12
Tina (2004)	Germany	86	63	radical prostatectomy	Caucasian	48/86	12

were identified in the primary literature, of which 37 potentially relevant studies were further evaluated after review of their titles and abstracts. A total of seven studies meeting the inclusion criteria were finally included in this study. The main characteristics of the eligible studies, all of which were retrospective cohort studies, are shown in **Table 1**. The analyzed studies were published between 1999 and 2013. All seven studies reported the relationship between PTEN deletion and a detailed cancer Gleason score (or sufficient data by which these could be calculated) [8-14], while four of them analyzed the relationship between PTEN deletion and capsular penetration [9, 11-13]. One study defined the PTEN classification as three different types which include positive, negative and mixed [8]. So we excluded the patients who were divided into the group of "mixed". Of all the studies analyzed, six studies presented a less PTEN deletion rate than positive rate while only one study reported the opposite. Data on the percentage of PTEN genomic deletion associated with PCa biochemical recurrence were also recorded. However, we were unable to obtain sufficient data to render any further analysis.

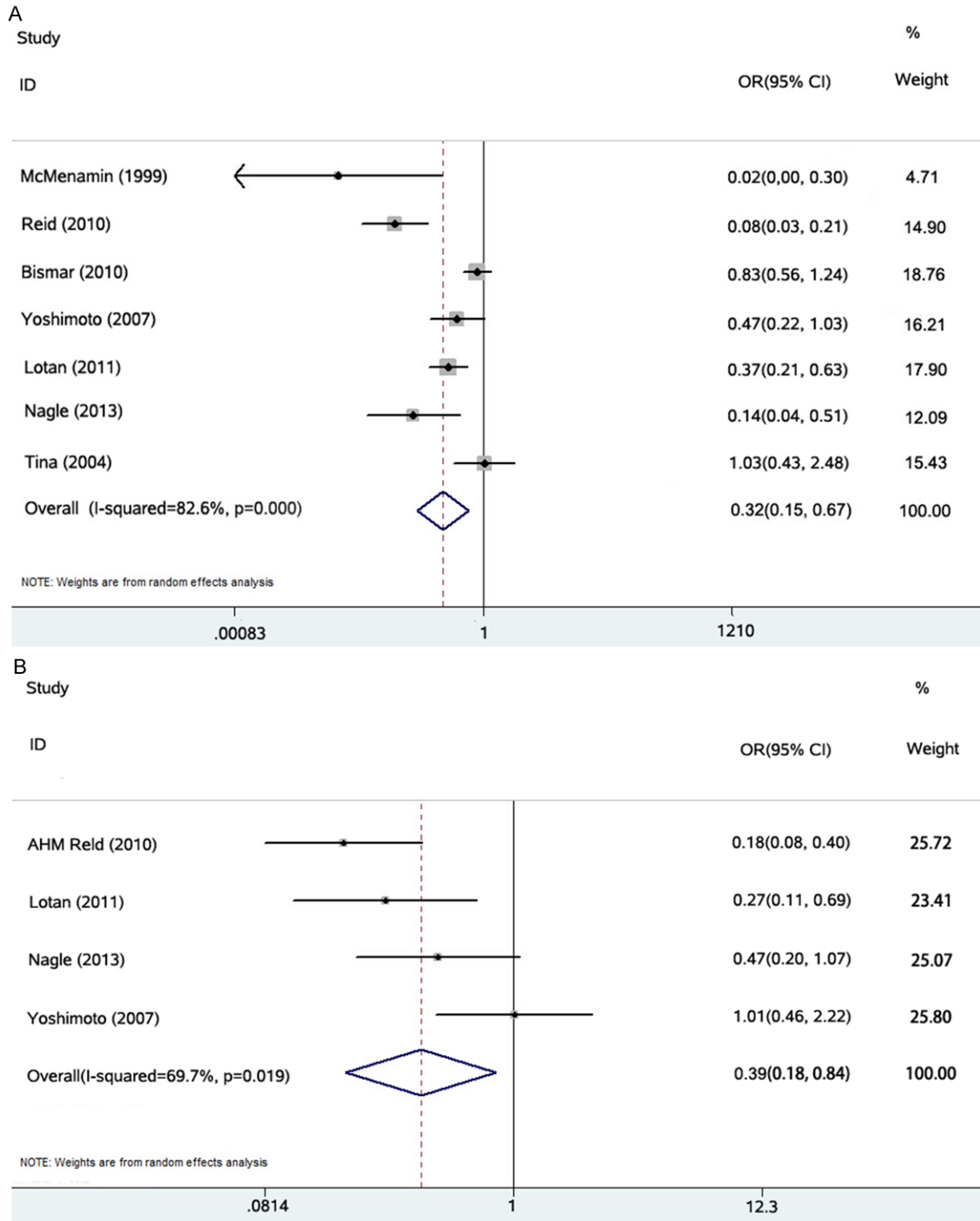
**Figure 2A** presents a forest plot of meta-analysis for the Gleason score, including OR, 95% CIs, and the weight of each study in the analysis. As the heterogeneity between studies was statistically significant ( $I^2 = 82.6\%$ ;  $P = 0.000$ ), the random effects model was applied. The combined OR was 0.319 (95% CI: 0.153-0.666;  $P = 0.000$ ). To further test the robustness of our study, we performed publication bias analysis by Begg's test (**Figure 3A**) and found no evidence of publication bias ( $P = 0.133$ ). The result indicates that loss of PTEN expression in PCa correlates with a higher Gleason score. **Figure 2B** presents the forest plot of meta-analysis for the possibility of capsular penetra-

tion, also including OR, 95% CIs, and the weight of each study in the analysis. As the heterogeneity between studies was not statistically significant ( $I^2 = 69.7\%$ ;  $P = 0.019$ ), the random effects model was applied. The combined OR was 0.393 (95% CI: 0.185-0.837;  $P = 0.015$ ). We also performed a publication bias analysis by Begg's test (**Figure 3B**), which showed no evidence of publication bias ( $P = 0.734$ ). Thus, the loss of PTEN expression in PCa correlates with a higher possibility of capsular penetration and a more advanced pathological stage. To further test the robustness of our study, we also performed sensitivity analysis by omitting one study each time. We found that no single study altered the original results significantly.

### Discussion

PTEN loss is proposed to be a critically important and frequently occurring molecular event in prostate carcinogenesis. PTEN targets proteins in signaling pathways that regulate cell growth, survival, and genome stability [15]. PTEN is a phosphoinositide 3-phosphatase located on chromosome 10 and acts as a tumor suppressor gene by negatively regulating the PI3K signaling pathway [16]. It is a negative regulator of the phosphatidylinositol 3-kinase (PIK3)/Akt survival pathway and a tumor suppressor frequently deleted in PCa [17]. The deletion of PTEN has been detected in human tissues representing all stages of PCa development and progression [18], and initiates numerous signaling events involved in oncogenesis including cell proliferation, cell invasion, metastasis, and survival [19-23]. Numerous aberrations of the PI3K-Akt pathway, which contains PTEN deletion has been observed in several human malignancies including PCa, breast cancer, gastric cancer, and colorectal cancer [24-28]. Previous studies using loss of heterozygosity analyses of 10q deletions showed that PTEN

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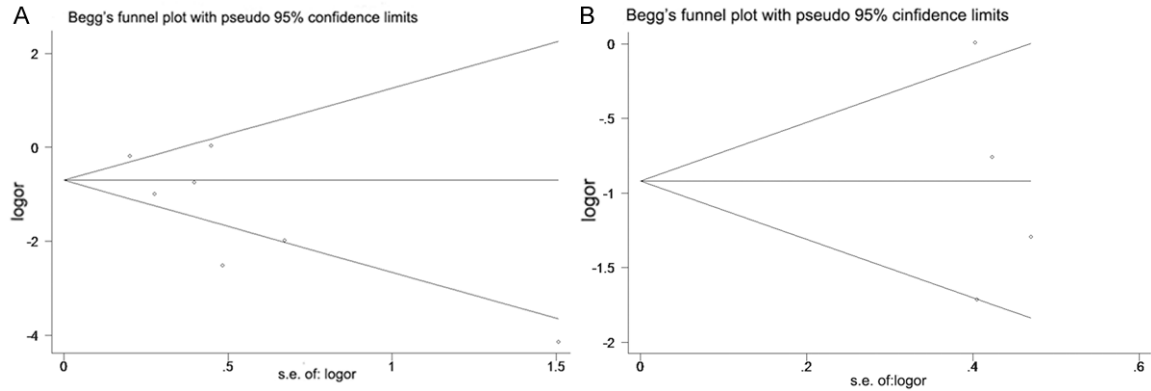


**Figure 2.** A. Individual study and overall ORs of relationships between PTEN deletion and higher Gleason score ( $\geq 7$ ). B. Individual study and overall ORs of relationships between PTEN deletion and capsular penetration.

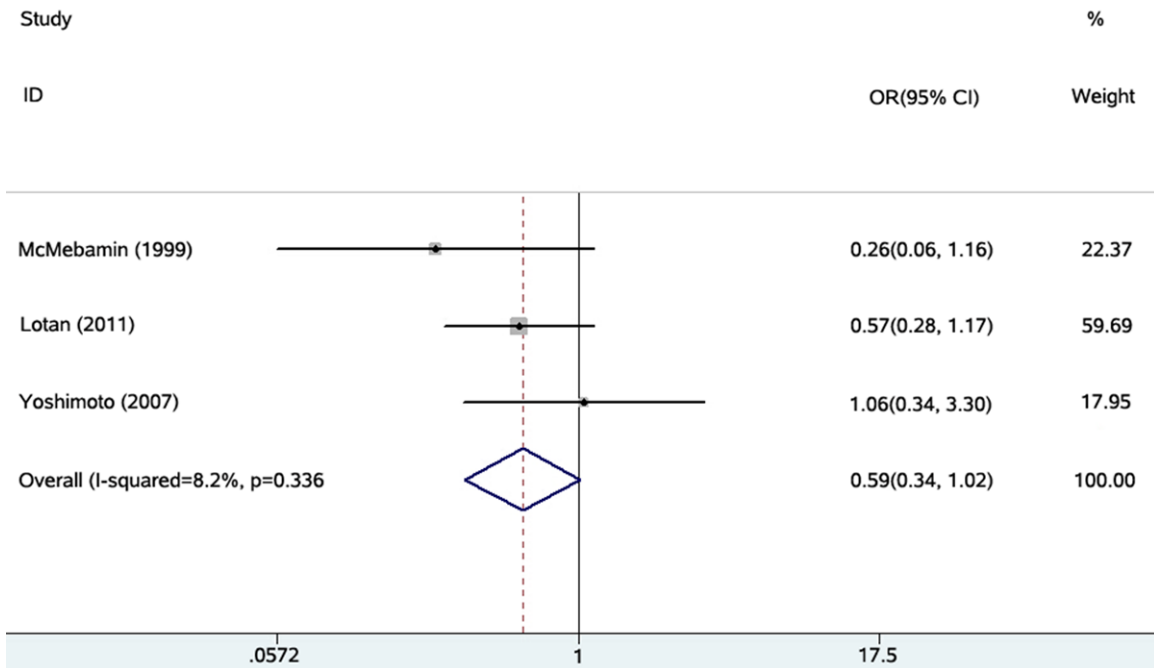
loss is present in nearly 50% cases of advanced PCas [8, 29], and in approximately 40% of localized PCas [30]. In advanced disease, fluorescence in situ hybridization has identified hemizygous and homozygous PTEN deletions, with

the incidence of PTEN deletion approaching 70-80% in CRPC [31]. In particular, recent publications have confirmed the relationship between PTEN deletion and tumor growth in mouse models. Moreover, even though the

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**Figure 3.** A. Test of publication bias of the analysis of PTEN deletion and higher Gleason score ( $\geq 7$ ). B. Test of publication bias of the analysis of PTEN deletion and capsular penetration.



**Figure 4.** Individual study and overall ORs of relationships between PTEN deletion and seminal vesicle invasion.

function and mechanism of PTEN in the human body has not yet been fully elucidated, we can still affirm the value of PTEN from previous studies. For example, some studies have examined the prognostic significance of PTEN deletions by fluorescence in situ hybridization with small patient cohorts and biochemical recurrence as the outcome [32, 33]. Although there is an abundance of information on the association of these genomic changes and clinical outcomes in PCa [34], data on their distribution in individual Gleason grades and capsular penetration are limited. Some studies found that in

PCa, decreased expression of PTEN is associated with high Gleason score and more advanced stage tumors, suggesting that PTEN gene alterations may be associated with tumor progression [10, 11, 35-38]. However, other studies have shown that patients' prognosis cannot be predicted using PTEN loss alone by analysis of the relationship between Gleason score, TNM stage, and PTEN deletion [14]. Since the results from previous studies are inconclusive, we performed a systematic review and meta-analysis to clarify the relationship between PTEN deletion and PCa grade and

stage. In our analysis, we formulated a unified standard where only the patients with operable localized PCa were included. Seven eligible studies with PTEN deletion detected by immunohistochemistry were included in this study. Finally, we concluded that PTEN genomic deletion was associated with a higher Gleason score and a higher possibility of capsular penetration. PTEN is also related to the differentiation and invasion of PCa cells; its deletion indicates a poor prognosis. PTEN deletion can be a good biomarker to judge the prognosis of patients. Moreover, we also analyzed the relationship between PTEN deletion and seminal vesicle invasion, using three studies, which published relevant data and determined that there is no statistical significance between PTEN deletion and seminal vesicle invasion (Figure 4).

In our meta-analysis, even though all studies used IHC staining to assess PTEN expression, seven eligible studies that included the Gleason score analysis showed heterogeneity, and four studies that included the capsular penetration associate analysis were without heterogeneity. Although IHC analysis is simple and cost-effective, tremendous variation exists in the experimental procedures, which may influence the results and may in part be responsible for the observed heterogeneity. For example, when restricted to studies using IHC staining with the same antibody, patients with reduced PTEN expression were related to a higher Gleason score and capsular penetration, and the heterogeneity between studies may reduce. The clinical significance of this study includes the following: First, this analysis solved the contradictory results that exist in previous research, and confirmed that PTEN plays an important role during the development of PCa. PTEN deletion indicates a worse prognosis and results in faster PCa progression. Second, for patients with clinically localized prostate cancer which requires radical surgery, examining the PTEN deletion status should be recommended for providing more information to determine patient prognosis. Third, PTEN and its downstream Akt signaling pathways may become a treatment target in the future.

Our study is not devoid of limitations. First, the number of studies included in our analysis was small, and all of the included studies were retrospective, indicating low levels of evidence in evidence-based medicine. Second, our meta-analysis was based on data only from studies

meeting our inclusion criteria, and there were many other published studies that did not meet these criteria. In addition, we could not obtain updated data on individual patients. The use of individual patient data could further enhance the accuracy and reduce the uncertainty of our estimates. Third, all the tissues in our analysis were from patients with clinically localized PCa who underwent radical prostatectomy; patients with a more advanced stage of PCa and patients with CRPC were not included in our analysis. Finally, publication bias may also be a concern. It was unavoidable that some data would remain unobtainable even after we tried to identify all relevant information. However, after examining the Begg funnel plots and performing the Egger linear regression test, we found that the association between PIK3CA mutation and clinical outcome remained unchanged.

In conclusion, the findings of our meta-analysis support PTEN as a tumor suppressor gene in PCa progression. Indeed, loss of PTEN expression can be an important negative prognostic indicator. Furthermore, the loss of PTEN induced by a majority of the mechanisms through which gene products are inactivated can be detected using immunohistochemistry.

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### Disclosure of conflict of interest

None.

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