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Aberrant Methylation of Protocadherin 17 and its Clinical Significance in Patients with Prostate Cancer after Radical Prostatectomy

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Background: Aberrant methylation of protocadherin 17 (PCDH17) has been reported in several human cancers. However, the methylation status of PCDH17 in prostate cancer and its clinical significance remains unclear. The aim of this study was to investigate the methylation status of PCDH17 and its clinical significance in patients with prostate cancer after radical prostatectomy.





Material/Methods: The methylation status of PCDH17 in 152 prostate cancer tissues and 51 non-tumoral prostate tissues was examined by methylation-specific PCR (MSP). Then the association between PCDH17 methylation and clinicopathologic parameters was analyzed. Kaplan-Meier survival analysis, log-rank test and multivariate Cox proportional hazard model analysis were used to analyze the correlation between PCDH17 methylation and prognosis of patients with prostate cancer.

Results: Our data demonstrated that PCDH17 methylation occurred frequently in prostate cancer. PCDH17 methylation was significantly associated with higher pathological Gleason score ($P=0.0315$), advanced pathological stage ($P=0.0260$), higher level of preoperative PSA ($P=0.0354$), positive angiolymphatic invasion ($P=0.0461$), positive lymph node metastasis ($P=0.0362$), and biochemical recurrence (BCR) ($P=0.0018$). In addition, PCDH17 methylation was an independent predictor of poor biochemical recurrence-free (BCR-free) survival and overall survival for patients with prostate cancer.

Conclusions: PCDH17 methylation is a frequent tumor-specific event in prostate cancer, and is significantly correlated with shorter BCR-free survival and overall survival of patients with prostate cancer after radical prostatectomy. PCDH17 methylation in tumor samples after radical prostatectomy may be used as an independent prognostic biomarker.

MeSH Keywords: **Cadherins • DNA Methylation • Urologic Neoplasms**

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Background

Prostate cancer is one of the most commonly diagnosed cancers in men in Western developed countries, and the morbidity is increasing in China with the aging of the population and the advance of diagnostic techniques [1–4]. For patients with localized disease, radical prostatectomy is a potentially curable treatment. Unfortunately, approximately 30% of patients will experience recurrence after the initial therapy and then subsequently developing metastatic disease [5–8]. Currently, the conventional clinicopathological parameters, such as serum prostate-specific antigen (PSA), pathological Gleason score, and tumor stage, are commonly used to predict patient outcome after initial management, but the accuracy of this prediction remains unsatisfactory for many patients [9–11]. Prostate cancer is a heterogeneous, multifocal disease with the outcome difficult to predict, thus new biomarkers are urgently needed to predict the outcome of patients and distinguish which patients need more aggressive adjuvant therapy after initial curative treatment. Like many other human cancers, the initiation and progression of prostate cancer is characterized by gradual accumulation of multiple genetic and epigenetic changes [12–14]. DNA methylation is one of the most studied epigenetic changes in human cancers, which occurs in the CPG islands in the gene promoter regions. Aberrant promoter methylation results in the silencing of tumor suppressor genes and plays an important role in the development and progression of prostate cancer [12–14]. The identification of novel methylated genes may be helpful in the diagnosis, monitoring, prognosis, and individualization of treatment strategy.

In recent years, more and more researchers found that the association between cadherin and tumors is a fascinating field of cancer research. Cadherin is a superfamily, including classical cadherins, protocadherins (PCDHs), and cadherin-related proteins. PCDHs, a subfamily of cadherin superfamily, are divided into 2 groups: clustered PCDHs and non-clustered PCDHs. Studies have demonstrated that promoter methylation and transcriptional silencing of non-clustered PCDHs genes occur frequently in numerous human cancer types. PCDH17 is a member of the non-clustered PCDHs, and the association of PCDH17 with human cancers has been proposed [15]. PCDH17 functions as a tumor suppressor in several human cancers, such as laryngeal squamous cell carcinoma, gastric cancer, colorectal cancer, and bladder cancer [16–21]. Moreover, the PCDH17 gene is located on the chromosome 13q21.2 in humans, and is often inactivated by promoter methylation in human cancers, including prostate cancer [16]. However, the methylation status of PCDH17 in prostate cancer and its clinical significance remain largely unknown.

In the current study, the methylation status of PCDH17 in prostate cancer tissues and non-tumoral prostate tissues was

examined by MSP. Subsequently, we analyzed the potential associations between PCDH17 methylation and clinicopathological characteristics, including patient outcome, to evaluate its clinical significance.

Material and Methods

Patients and tissue samples

A total of 152 prostate cancer patients who underwent radical prostatectomy between January 2004 and January 2007 at the Third Hospital of Hebei Medical University were investigated. None of the patients received radiotherapy, chemotherapy, or androgen deprivation therapy prior to surgery. The tumor samples were reviewed on HE-stained tissue sections to confirm diagnosis and tumor content of at least 70% of tumor cells in the tissue samples. This work was performed by 2 senior genitourinary pathologists in our center. The data was collected in a systematic and comprehensive manner. Non-tumoral prostate tissues were obtained from 51 patients with benign prostatic hyperplasia (BPH) who were treated by transurethral resection of the prostate during the same time in the same hospital; these tissues were examined pathologically to exclude the possibility of incidental tumors. The tissue samples were flash-frozen in liquid nitrogen at the time of collection and stored at -80°C until DNA extraction. The clinicopathological parameters of prostate cancer patients, including preoperative serum prostate specific antigen (PSA), pathological stage, pathological Gleason score [22], lymph node status, angiolymphatic invasion, margin status, seminal vesicle invasion, BCR, BCR-free survival, and overall survival, were recorded. The main clinicopathological characteristics of patients with prostate cancer are summarized in Table 1. The pathological parameters were evaluated by 2 senior genitourinary pathologists (Yang SH and Wang LL) in our center. Gleason score no less than 8 was considered as high Gleason score. The BCR was defined as the measurement of 2 successive values of serum PSA level ≥ 0.2 ng/ml. The overall survival time was defined as the period between radical prostatectomy and the death from any cause or the last contact if the patient was still alive, ranging from 20 months to 60 months (median 60 months) [2,9]. Written informed consent was obtained from all participants, and this study was approved by the ethics committee of the Third Hospital of Hebei Medical University (No. HMU20040157E).

DNA extraction, bisulfite modification, and MSP

The genomic DNA was extracted from frozen tissues using the DNeasy Tissue Kit (Qiagen, Valencia, CA) following the manufacturer's instructions. The extracted DNA was modified with bisulfite to convert unmethylated cytosines to uracils prior to

Table 1. Clinicopathological characteristics of patients with prostate cancer (n=152).

Features	Variables	No. (%)
Age (years)	Mean	72.5
	Min. to max.	56–89
	Median	69
Stage	pT1	87
	pT ₂ /pT ₃	65
Preoperative PSA	≤10	58
	>10	94
Pathological Gleason score	<8	104
	≥8	48
Surgical margin status	Presence	11
	Absence	141
Lymph node metastasis	Presence	14
	Absence	138
Angiolymphatic invasion	Presence	29
	Absence	123
Biochemical recurrence	Presence	43
	Absence	109

M – methylation; U – unmethylation.

MSP using the EpiTect Bisulfite Kit (Qiagen, Valencia, CA). The methylation status of PCDH17 was examined using primers specific for PCDH17 unmethylated and methylated sequences, as reported previously [20, 21]. The following primers were used: unmethylated: forward 5'-AGATTATTGGGTGTGTAGTTT-3' and reverse 5'-AACCTAACACAACATACACA-3'; methylated: forward 5'-GATTATCGGGTGTCTAGTTC-3' and reverse 5'-CCCTAACGCAACGTACGCG-3'. The PCR amplification consisted of 1 cycle of 95°C for 10 min, 40 cycles of 94°C for 30 s, 60°C for 30 s, and 72°C for 30 s for the methylated reaction or 42 cycles of 94°C for 30 s, 60°C for 30 s, and 72°C for 30 s for the unmethylated reaction [20,21]. Water blanks were included with each assay. *In vitro* methylated DNA and unmethylated DNA (New England Biolabs, Beverly, MA, USA) were used as methylation and non-methylation positive controls. PCR products were separated in 2% agarose gel, stained with ethidium bromide, and visualized under ultraviolet illumination for analysis. Samples were scored as methylation-positive when methylated alleles were present in the methylated DNA lane and methylation-negative when bands were present only in the unmethylated DNA lane [20,21].

Statistical analysis

Statistical analysis was performed using SAS version 8.0 (SAS Institute, Cary, N.C., USA). Fisher's exact test was used to assess the difference of PCDH17 methylation status between prostate cancer patients and patients with BPH. The chi-square test or Fisher's exact test was used to identify associations between PCDH17 methylation and clinicopathological features. Kaplan-Meier survival analysis and log-rank test were used to assess the differences of BCR-free survival and overall survival between patients with PCDH17 methylated and unmethylated. Multivariate Cox proportional hazard model analysis was used to assess the independent prognostic effect of PCDH17 methylation in prostate cancer. The statistical analysis was performed by Xie PG, who is proficient in biostatistics. A two-sided p value <0.05 was considered statistically significant.

Results

PCDH17 methylation occurs frequently in prostate cancer tissues

In the current study, we first examined the methylation status of PCDH17 in prostate cancer tissues and non-tumoral prostate tissues using MSP. The results showed that PCDH17 methylation occurred in 102 (67.1%) prostate cancer patients, but no PCDH17 methylation was detected in non-tumoral prostate tissues and the difference was significant (P<0.0001). This finding indicated that PCDH17 methylation is a frequent tumor-specific event in prostate cancer. The results are shown in Table 2.

The associations between PCDH17 methylation and clinicopathological parameters

The main purpose of this study was to investigate the clinical significance of PCDH17 methylation in prostate cancer, and then to correlate the methylation status of PCDH17 with clinicopathological parameters. We found that PCDH17 methylation in prostate cancer tissues was associated with higher pathological Gleason score (P=0.0315), advanced pathological stage (P=0.0260), higher level of preoperative PSA (P=0.0354), positive angiolymphatic invasion (P=0.0461), positive lymph node metastasis (P=0.0362), and BCR (P=0.0018). A Gleason score no less than 8 was considered as a high Gleason score. However, PCDH17 methylation was not correlated with age or surgical margin status. These results are summarized in Table 3.

The predictive value of PCDH17 methylation for the outcome of patients with prostate cancer

To determine the prognostic value of PCDH17 for patients with prostate cancer after radical prostatectomy, BCR-free survival

Table 2. The methylation status of PCDH17 in prostate cancer tissues and normal prostate tissues.

Group	M (%)	U (%)	P
PC	102 (67.1)	50 (32.9)	<0.0001
NP	0 (0.0)	51 (100.0)	

M – methylation; U – unmethylation; PC – prostate cancer tissue; NP – normal prostate tissue.

Table 3. Relationship between PCDH17 methylation and clinicopathologic parameters in prostate cancer (n=152).

Features	Variables	No.	M (%)	U (%)	P
Age	<70	81	53 (65.4)	28 (34.6)	0.6391
	≥70	71	49 (69.0)	22 (31.0)	
Stage	pT1	87	52 (59.8)	35 (40.2)	0.0260
	pT ₂ /pT ₃	65	50 (76.9)	15 (23.1)	
Preoperative PSA	≤10	58	33 (56.9)	25 (43.1)	0.0354
	>10	94	69 (73.4)	25 (26.6)	
Pathological Gleason score	<8	104	64 (61.5)	40 (38.5)	0.0315
	≥8	48	38 (79.2)	10 (20.8)	
Surgical margin status	Presence	11	7 (63.6)	4 (36.4)	0.7517
	Absence	141	95 (67.4)	46 (32.6)	
Lymph node metastasis	Presence	14	13 (92.9)	1 (7.1)	0.0362
	Absence	138	89 (64.5)	49 (35.5)	
Angiolymphatic invasion	Presence	29	24 (82.8)	5 (17.2)	0.0461
	Absence	123	78 (63.4)	45 (36.6)	
Biochemical recurrence	Presence	43	37 (86.1)	6 (13.9)	0.0018
	Absence	109	65 (59.6)	44 (40.4)	

M – methylation; U – unmethylation.

and overall survival were analyzed and patients were divided into 2 groups: patients with PCDH17 methylated and PCDH17 unmethylated. Kaplan-Meier survival analysis and log-rank test indicated that patients with PCDH17 methylated had significantly shorter BCR-free survival (Figure 1, P=0.0028) and overall survival (Figure 2, P=0.0187) than patients with PCDH17 unmethylated. To determine if PCDH17 methylation is an independent predictor of BCR-free survival or overall survival after radical prostatectomy, multivariate Cox proportional hazard model analysis was performed. The results suggested the PCDH17 methylation was simultaneously an independent prognostic factor for BCR-free survival and overall survival. The results are presented in Tables 4 and 5.

Discussion

Aberrant DNA methylation is a common event in human cancers and plays important roles in the initiation and progression

of many cancer types, including prostate cancer [12–14]. The identification of DNA methylation involved in the development and progression of prostate cancer can identify novel therapeutic targets as well as being used as diagnostic and prognostic markers [5]. Prostate cancer is one of the most commonly diagnosed cancers in elderly men in the world. Currently, the majority of prostate cancers can be detected at a localized stage, as a result of the widely used PSA-based screening program [12]. Localized prostate cancer is potentially curable by radical prostatectomy. However, a considerable number of the patients will experience biochemical recurrence and many patients inevitably develop metastatic disease [12]. Since prostate cancer is a heterogeneous disease and can present as indolent or aggressive disease, reliable predictive biomarkers are urgently needed to guide individualized therapy strategy, disease monitoring, and adjuvant treatment at the time of diagnosis [5,23–27]. Currently, the only biomarker used for detection and monitoring treatment efficacy of prostate cancer is PSA, but PSA has several limitations. It is not specific for prostate

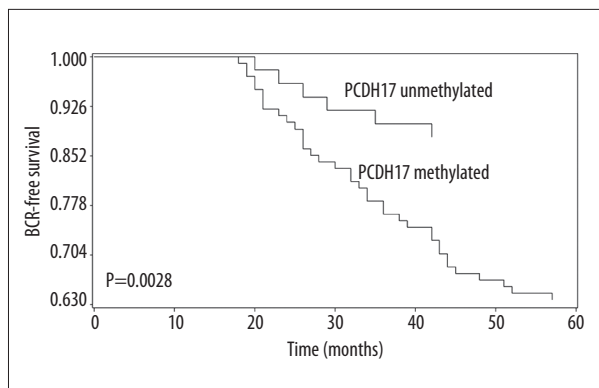


Figure 1. The relationship between PCDH17 methylation and BCR-free survival in patients with prostate cancer. Patients with PCDH17 methylated showed significantly shorter BCR-free survival than patients with PCDH17 unmethylated (P=0.0028, log-rank test).

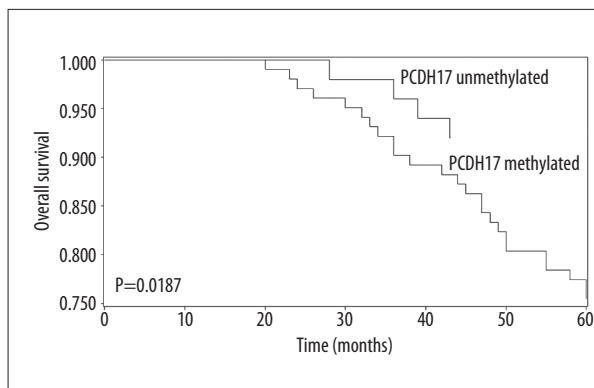


Figure 2. The relationship between PCDH17 methylation and overall survival in patients with prostate cancer. Patients with PCDH17 methylated showed significantly shorter overall survival than patients with PCDH17 unmethylated (P=0.0187, log-rank test).

Table 4. The predictive value of PCDH17 methylation in tumor samples for the BCR-free survival in prostate cancer (n=152).

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
PCDH17 methylation	4.533	1.422–8.501	<0.0001	3.698	1.384–7.417	<0.0001
Pathological Gleason score	3.198	1.176–9.413	0.0006	2.975	1.133–8.531	0.0047
Pathological stage	1.382	0.983–4.653	0.5628			
Surgical margin status	1.563	0.796–10.546	0.4361			
Lymph node metastasis	1.271	0.738–3.546	0.6671			
Angiolymphatic invasion	1.456	0.727–3.967	0.6112			
Preoperative PSA	2.733	1.134–7.985	0.0023	2.115	1.102–6.733	0.0253
Age	1.018	0.782–1.963	0.6972			

HR – hazard ratio.

Table 5. The predictive value of PCDH17 methylation in tumor samples for the overall survival in prostate cancer (n=152).

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
PCDH17 methylation	3.758	1.311–8.977	<0.0001	2.893	1.452–7.926	0.0037
Pathological Gleason score	3.044	1.215–7.413	0.0015	1.964	1.032–9.051	0.0271
Pathological stage	1.541	0.892–3.917	0.7652			
Surgical margin status	1.226	0.753–8.533	0.8587			
Lymph node metastasis	1.451	0.787–7.314	0.8102			
Angiolymphatic invasion	1.106	0.757–4.825	0.8772			
Preoperative PSA	1.336	0.897–6.732	0.8311			
Age	1.033	0.791–2.043	0.8896			

HR – hazard ratio.

cancer, as it is commonly elevated in benign conditions, such as BPH; and it is unable to distinguish indolent disease from aggressive disease at the time of diagnosis. In addition, PSA is not sensitive, as demonstrated by the recent prostate cancer prevention trial, which demonstrated that 15% of men with PSA of 0–4.0 ng/ml have prostate cancer, and with 15% of them having high Gleason grade disease [5,28]. Thus, reliable predictive biomarkers remain to be established.

Protocadherins are a subfamily of the cadherin superfamily, and some protocadherins act as tumor suppressors, such as PCDH8, PCDH10, PCDH17, and PCDH20 [29–32]. Recent studies demonstrated that PCDH8 is frequently inactivated by promoter methylation in several human cancers, and functions as a tumor suppressor. Moreover, PCDH8 methylation is a common event in bladder cancer, and is associated with worse outcomes of patients with bladder cancer [33–35]. PCDH10 and PCDH20 are also frequently downregulated by promoter methylation and may serve as tumor suppressors in several human cancers [36–39]. PCDH-PC is another member of the non-clustered PCDHs, and recent studies demonstrated that it is enriched in advanced castration-resistant prostate cancers and their metastases. In addition, ectopic expression of PCDH-PC in human prostate cancer cells induces cell growth and survival *in vitro*, and causes tumorigenesis in castrated mice. These findings indicate that not all non-clustered PCDHs function as tumor suppressors in human cancer [15]. However, a recent study found that PCDH17 occurred in urothelial carcinomas [16]. In addition, our previous study found that PCDH17 methylation is associated with the development and poor prognosis of bladder cancer [20,21]. These findings prompted us to investigate the clinical significance of PCDH17 methylation in prostate cancer.

In the present study, we firstly investigated the methylation status of PCDH17 in prostate cancer tissues and non-tumoral prostate tissues. The results suggested that PCDH17 is a frequent tumor-specific event in prostate cancer, and may be used as potential biomarker. Subsequently, we examined the relationship between PCDH17 methylation status and clinicopathologic parameters. To the best of our knowledge, this is the first report to describe the associations between PCDH17 methylation and clinicopathologic features. Interestingly, PCDH17 methylation significantly correlated with higher pathological Gleason score, advanced stage, higher level of preoperative PSA, positive angiolymphatic invasion, positive lymph node metastasis, and biochemical recurrence, which are all risk factors for prostate cancer progression and poor outcome [23,24]. These findings suggest that PCDH17 methylation may be a potential prognostic factor for the outcome of

prostate cancer patients. We then analyzed the BCR-free survival and overall survival according to the methylation status of PCDH17 in tumor samples. Kaplan-Meier survival analysis and log-rank test indicated that patients with PCDH17 methylated had significantly shorter BCR-free survival and overall survival, respectively; indicating that PCDH17 methylation in tumor samples is a potential prognostic biomarker for predicting worse outcome after radical prostatectomy. The multivariate analysis showed that PCDH17 methylation was an independent predictor of shorter BCR-free survival and overall survival in prostate cancer patients after radical prostatectomy. Taken together, these findings indicate that PCDH17 methylation may play crucial roles in the pathogenesis and aggressiveness of prostate cancer, and correlate with worse outcome in prostate cancer.

Furthermore, DNA methylation can be reversed by demethylating agents and the crucial role of PCDH17 methylation in human cancer, suggesting the possibility of making it a potential therapeutic target for anticancer treatment. Haruki et al. reported that the methylation status of PCDH17 in esophageal squamous cell carcinoma cells can be reversed by 5-aza-2'-deoxycytidine, and reduced cell proliferation, migration, and invasion *in vitro* [40]. To the best of our knowledge, there has been no published report about using PCDH17 as anticancer therapy target in prostate cancer. In the future, we will focus on investigating the possibility of using PCDH17 methylation as a therapeutic target *in vitro* and *in vivo*. In addition, the precise cause and mechanism of PCDH17 methylation in prostate cancer remains unclear, and additional studies are needed to elucidate it in the future.

Conclusions

Our current data demonstrated that PCDH17 methylation in tumor samples is a frequent tumor-specific event in prostate cancer, and is significantly correlated with higher pathological Gleason score, advanced stage, higher level of preoperative PSA, positive angiolymphatic invasion, positive lymph node metastasis, and biochemical recurrence. In addition, patients with PCDH17 methylated had significantly shorter BCR-free survival and overall survival. PCDH17 methylation is a potential prognostic biomarker for predicting worse outcome after radical prostatectomy. For patients with PCDH17 methylated in tumor samples, more aggressive adjuvant therapy should be performed after radical prostatectomy in order to achieve better outcome. However, our findings need to be verified in future multi-center studies with larger sample sizes of patients with prostate cancer.

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