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Original Article

Cribiform and intraductal carcinoma in hereditary prostate cancer: clinical and pathological analysis of 20 cases

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Abstract: Cribiform and intraductal carcinoma are patterns of aggressive prostate carcinoma. This study investigated the clinical and pathological features of hereditary prostate cancer. Twenty cases of hereditary prostate cancer from 11 family lines treated at the First Affiliated Hospital of Zhejiang University School of Medicine between 2016-2022 were included to summarize the clinical and pathological features by analyzing clinical information including follow up the survival of the patients and pathological features. Of the 20 hereditary prostate cancer cases, 19 were radical prostate specimens and 1 was a biopsy specimen. The mean age at diagnosis of the patients was 67.55 years and the mean PSA was 15.44 ng/ml, of which 10 cases had PSA ≥ 10 ng/ml and 5 cases had PSA ≥ 20 ng/ml. Of the 19 radical prostate specimens, Gleason cribriform pattern (Gleason grade 4) of PCa is observed in 15 cases (78.95%), and intraductal carcinoma, usually a rare form, is seen in 9 cases (47.3%). Two cases demonstrated pelvic lymph node metastasis, and 7 cases (35%) belonged to high-risk or very high-risk PCa. One case (5.26%) showed partial deletion of expression of RB1, and 13 cases (68.42%) showed deletion of expression of PTEN. Follow-up was 4-90 months, 2 cases had biochemical recurrence and 1 case died from prostate cancer. The mean age at diagnosis of this group of patients with hereditary prostate cancer was 67.55 years, the mean preoperative PSA was 15.44 ng/ml, and their histomorphology was characterized by a high percentage of intraductal carcinoma and cribriform pattern of the prostate.

Keywords: Prostate cancer, hereditary, cribriform, intraductal carcinoma

Introduction

Prostate cancer (PCa) ranks as one of the most prevalent malignancies globally, standing second in new cancer cases among men and fifth in cancer-related fatalities [1]. Currently, well-defined risk factors for PCa comprise advanced age, African American ethnicity, and a positive family history of the disease [2]. Research suggests that 10%-20% of PCa patients present a positive family history [3-5]. First-degree relatives of PCa patients face a 2-3 times higher likelihood of developing the disease than the general population, with risks escalating with the number of affected relatives [6]. Spangler et al. discovered that individuals with a family history of PCa diagnosed before the age of 60 exhibited a more advanced tumor stage [7].

Hereditary Prostate Cancer (HPCa) refers to patients with PCa meeting one of the Johns Hopkins criteria: (1) three or more first-degree relatives diagnosed with PCa, (2) three consecutive generations affected, or (3) at least two relatives with early-onset PCa (before age 56) [3]. Approximately 1% of PCa patients have been reported to be eligible for HPCa [8, 9].

Little is known about the clinicopathologic features of family history-positive PCa, and several previous studies of family history-positive PCa have reached inconsistent conclusions. Certain studies suggest that individuals with a family history of PCa are diagnosed at a younger age and present unique PSA levels compared to sporadic cases [10, 11]. However, apart from the age of onset, there are no significant differences in other clinical and pathologic features between family history-positive PCa patients and sporadic PCa [9, 12]. Therefore, the clinical and pathological features of family history-positive PCa need to be further explored. At pres-

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Table 1. Relationship of PCa patients in 11 families and the number of included cases

Family Number	Patient relations	Number of cases included in the study
Family 1	Father, 3 sons	1
Family 2	Father, 3 sons	1
Family 3	3 brothers	3
Family 4	3 brothers	3
Family 5	3 brothers	3
Family 6	Father, 2 sons	2
Family 7	Father, 2 sons	2
Family 8	3 brothers	2
Family 9	3 brothers	1
Family 10	Father, 2 sons	1
Family 11	3 brothers	1

ent, very rare relevant studies address the pathologic features of HPCa. Specifically, no studies have investigated intraductal carcinoma (IDC-P) and cribriform patterns (CP) of PCa in HPCa. In our investigation of the clinical and pathological characteristics of HPCa in China, we gathered 20 patients meeting the stringent Johns Hopkins criteria. We analyzed their clinical and pathological characteristics and focused on the distribution of IDC-P and CP components of HPCa, as well as followed up on these patients. Notably, these 20 patients originated from 11 distinct families.

Material and methods

Patient selection

The study was approved by the institutional ethics committee (IIT20240101B-R1). We gathered data on 20 individuals with HPCa who met the Johns Hopkins criteria among patients treated for PCa at the First Hospital of Zhejiang University School of Medicine from 2016 to 2022. Through an investigation of these families, we identified that these 20 HPCa patients originated from 11 distinct family units. The familial connections of the HPCa patients across the 11 families are detailed in **Table 1**. All 20 patients were of Chinese descent, predominantly hailing from southern China. In this study, we excluded individuals lacking a definitive PCa diagnosis, those with insufficient clinical data, and those who declined participation in the research. Family pedigrees for family 2 and family 4 are illustrated in **Figure 1**, while pedigrees for the remaining families can be found in Figure S1.

Collection of clinical and pathological characteristics

Among these 20 patients, 19 individuals underwent a prostate biopsy and da Vinci robotic-assisted radical prostatectomy (RP), while one patient solely underwent a prostate biopsy. We gathered data on patients' age, total prostate-specific antigen (tPSA), free prostate-specific antigen (fPSA), serum ferritin levels, magnetic resonance imaging (MRI), and ultrasound reports, along with post-radical surgery treatment modalities, from the medical record system. Following the most recent diagnostic criteria for PCa outlined in the fifth edition of the WHO in 2022 [13], we conducted a reassessment involving the Gleason score, CP, IDC-P, Extraprostatic extension (EPE), seminal vesicle involvement, surgical margins, and lymph node involvement through examination of pathologic sections. Additionally, we performed a detailed evaluation of the proportion of Gleason pattern 4, the proportion of Gleason pattern 4 component accounted for by CP, and the maximum diameters of CP and IDC-P.

During the assessment of IDC-P, we distinguished benign basal cells through immunohistochemical staining utilizing 34βE12 (high molecular weight cytokeratin) and p63, while tumors were identified using (P504S). The latest diagnostic criteria for IDC-P in the fifth edition of WHO PCa in 2022 eliminated the requirement for nuclear size that should be about 6× normal size or larger [13]. Our judgment was aligned with these updated diagnostic criteria.

In addition, we performed immunohistochemical staining for the retinoblastoma susceptibility gene (RB1), protein phosphatase and tensin homolog (PTEN), erythroblast transforming specific-related gene (ERG), p53 (tumor suppressor), and Ki67 (proliferative markers) in 19 RP specimens. We use four grades to document meaningful IHC results. Use grades 1, 2, 3, and 4 to indicate positive or negative 0-25%, 26-50%, 51-75%, and 76-100% of tumor area, respectively. Histologic sections and immunohistochemically stained sections of the prostate were evaluated by 2 senior pathologists, and inconsistencies were judged by a third

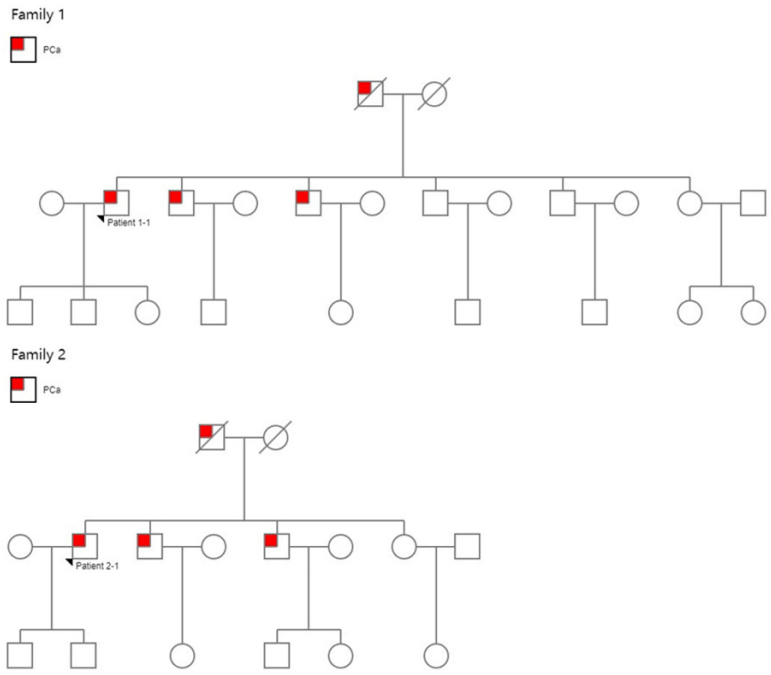

Figure 1. The pedigrees of 2 families with hereditary prostate cancer (1-1 indicates the 1st patient in family 1).

pathologist, with a final discussion leading to consensus.

The time frame of our follow-up was 4-90 months postoperatively. It began with radical PCa surgery and ended on December 31, 2023. BCR was used to assess outcomes after PCa diagnosis and was defined as PSA ≥ 0.2 ng/ml after radical surgery in patients with PCa.

Statistical analysis

Descriptive analysis of clinical parameters was presented as either mean or median values. The data underwent statistical analysis using SPSS 26.0 software. Statistical significance was defined as $P < 0.05$.

Results

Clinical information

In family 5, the patient's mother had a history of endometrial cancer, and there was no clear family history of other tumors in the rest of the family. Of the 20 patients with HPCa, 13 were seen for routine physical examinations that revealed an elevated PSA (PSA ≥ 4.0 ng/ml) (**Table 2**); 3 were seen for a family history of PCa and self-consciously examining the PSA revealed an elevated PSA; 2 were seen for urologic symptoms (hematuria, urinary frequency and urgency, etc.); 1 was seen for a persistent elevated PSA on multiple exams; and 1 was seen for low back pain. The mean (range, SD) age at diagnosis of the 20 patients with HPCa was 67.55 years (55-81 years, 5.77), with a median age of 66 years. The mean PSA was 15.44 ng/ml (4.23-45 ng/ml, 10.78), and the median PSA was 12.26 ng/ml. All 20 patients had a PSA greater than 4 ng/ml, with 10 having a PSA of ≥ 10 ng/ml and 5 having a PSA of ≥ 20 ng/ml. The fPSA/tPSA values were tested in 18 patients and were reduced in 16 (fPSA/tPSA < 0.16). 19 patients were tested for serum ferritin, of which 7 were elevated. 11 patients underwent MRI, which suggested the presence of foci of abnormal signals such as hypoechoicity and uneven signals; 15 patients underwent ultrasonography, of which 11 suggested the presence of prostatic hyperplasia (10 with stones or uneven echoes), 1 with post-puncture alterations, 1 with a strong light spot seen in the prostate, 1 with a prostate nodule and cancer were considered, and no abnormality was seen in 1. Of the 20 patients, 6 (30%) had urinary symptoms at the time of initial consultation, 1 had low back pain (later confirmed to be caused by a lumbar disc herniation), and the others had no obvious urinary symptoms. Since bone metastases had already occurred at the time of diagnosis in patient 5-3, RP was not performed, and RP was performed in the remaining 19 patients.

Pathologic characteristics

There was no statistically significant difference between the Gleason grade groups of the 19 RP specimens compared to the biopsy specimens (P=0.441). In biopsy specimens, there were 10 cases with grade group ≤ 2 and 10 cases with grade group > 2 (**Table 3**); in RP specimens, there were 8 cases with grade

Table 2. Clinical characteristics of 20 HPCa cases

Serial No	Cases (n=20)	Age	tPSA (ng/ml)	fPSA (ng/ml)	fPSA/tPSA	Serum ferritin (ng/ml)	Pathological staging
1	1-1	63	5.75	0.79	0.14	203.3	pT2
2	2-1	76	8.51	0.93	0.11	/	pT2
3	3-1	55	6.41	0.78	0.12	290	pT2
4	3-2	70	24.78	2	0.08	226.1	pT3a
5	3-3	64	26.37	3.02	0.11	345.1	pT2
6	4-1	76	5.04	0.89	0.18	93.1	pT2
7	4-2	66	19.38	1.42	0.07	90.6	pT2
8	4-3	67	7.31	1.06	0.15	359.2	pT2
9	5-1	71	26.05	1.49	0.06	121.2	pT3a
10	5-2	70	32.87	2.34	0.07	63	pT3a
11	5-3	65	17	/	/	2426	/
12	6-1	64	13.34	1.09	0.08	176.7	pT3a
13	6-2	66	8.54	1.47	0.17	366.2	pT2
14	7-1	63	7.26	1.36	0.19	171.5	pT2
15	7-2	74	14.92	/	/	412.8	pT2
16	8-1	63	45	1.71	0.04	543.8	pT3a
17	8-2	64	4.23	0.55	0.13	517.7	pT2
18	9-1	81	11.18	1.23	0.1	46	pT2
19	10-1	65	4.36	/	/	113.5	pT2
20	11-1	68	20.51	1.56	0.08	201.5	pT3a

Note: 1-1 indicates the 1st patient in family 1 and 3-3 indicates the 3rd patient in family 3.

Table 3. Pathological features of 20 cases of HPCa

Serial No	Cases (n=20)	Biopsy GS	Percentage of positive core (%)	RP GS	Percentage of GS 4	CP	CP as % of GS 4	IDC-P	EPE	Surgical margin	Lymph node involvement
1	1-1[a]	3+4	50	4+3	70	+	80	+[b]	-	-	-
2	2-1	3+4	/	3+4	40	+	50	-[b]	-	-	-
3	3-1	3+3	30	3+4	40	-	/	-	-	+	/
4	3-2	4+4	11	4+3	80	-	/	-	+	+	-
5	3-3	4+3	10	3+4	30	+	5	-[b]	-	-	-
6	4-1	3+3	20	4+3	80	+	50	+[b]	-	-	/
7	4-2	4+3	/	4+3	70	+	80	+[b]	-	-	-
8	4-3	3+4	20	4+3	60	+	20	-[b]	-	-	/
9	5-1	3+5	/	4+3	60	+	40	+	+	+	-
10	5-2	3+5	/	5+4	30	+	20	+[b]	+	+	-
11	5-3	4+3	70	/	80	-	/	-	-	-	/
12	6-1[a]	4+3	/	4+3	85	+	80	+[b]	+	+	-
13	6-2	3+3	50	3+4	30	-	/	-	-	+	/
14	7-1	4+3	/	4+3	90	+	70	+[b]	-	-	/
15	7-2	3+4	50	3+4	30	+	50	-	-	+	-
16	8-1	4+5	50	4+5	70	+	80	+	+	-	+
17	8-2	3+4	/	3+4	40	+	80	+[b]	-	+	+
18	9-1	4+3	60	4+3	80	+	15	-[b]	-	-	/
19	10-1	3+4	/	3+4	30	-	/	-[b]	-	+	-
20	11-1	3+3	10	3+4	30	+	5	-[b]	+	-	/

Note: [a]Cases with biochemical relapse, [b]Cases of PTEN IHC expression deficiency.

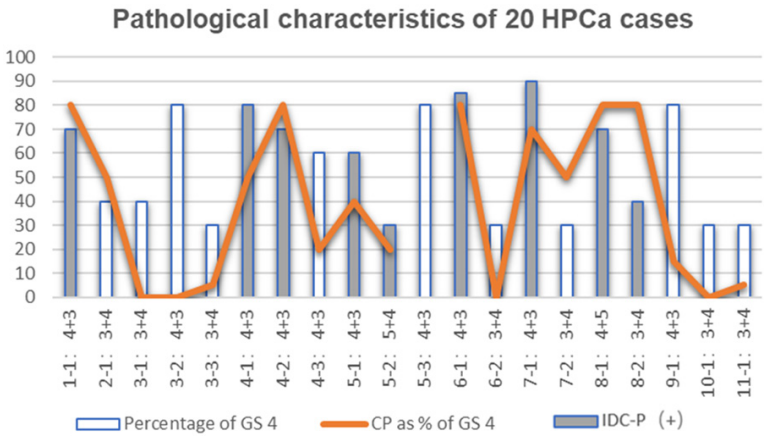

Figure 2. Pathological characteristics of 20 HPCa cases. CP: Cribriform patterns. GS: Gleason score.

group ≤ 2 and 11 cases with grade group > 2. Four of the biopsy specimens in Gleason grade group 1 were upgraded after RP to either grade group 2 or grade group 3. The rate of upgrading of Gleason grade groups was 36.8% (7/19).

All 19 RP specimens had Gleason pattern 4 component, of which cribriform structures of PCa were seen in 15 cases (78.95%), with the maximum diameter of the CP ranging from 0.4 mm to 4.5 mm. The area of the CP in some cases accounted for about 80% of the area of the Gleason pattern 4 component (**Figure 2**).

IDC-P was present in 9 cases (47.3%) of HPCa (**Figure 3**), and the maximum diameter of IDC-P was 2.1 mm; glomeruloid structures were present in 3 cases (15.8%).

EPE of the tumor was seen in 6 cases (31.6%), with a maximum diameter of about 5 mm; positive surgical margins were seen in 9 cases (47.3%), with a maximum extent of about 11 mm. 14 cases (73.7%) showed perineural invasion, 3 cases (15.8%) showed vascular invasion, and 2 cases (10.5%) showed lymph node metastasis. None of the cases showed seminal vesicle gland involvement.

According to the 2021 National Comprehensive Cancer Network (NCCN) guidelines [14], meets pathology staging of T3a, or Gleason score 8/Gleason grade group 4, or Gleason score 9 to 10/Gleason grade group 5, or PSA > 20 ng/ml for high-risk PCa. Pathology stage T3b~T4, or Gleason pattern 5 in the main grading area, or puncture biopsy with 4 or more needle Gleason score 8-10/Gleason grade group 4 or 5 is considered as very high-risk PCa. In this study, 7 cases (35%) were at high or very high risk of PCa.

We performed immunohistochemical staining on RP specimens from 19 patients with HPCa (**Table 4**). 1 of the 19 cases (5.26%) showed partial deletion of expression of RB1, with a negative grade 1. Two cases (10.53%) over expressed ERG, with positive grades of 3 in both cases. 13 cases (68.42%) showed deletion of expression of PTEN, of which one was grade 1, six were grade 2, three were grade 3, and three were grade 4 (**Figure 4**). In addition, 12 of the 15 HPCa (73.33%) with CP showed PTEN expression deficiency. p53 was negative in all cases.

Follow-up results

Patient 5-3 had multiple bone metastases at the time of diagnosis of PCa. He was treated with endocrine therapy without RP and died 24 months after diagnosis. The remaining 19 patients underwent RP, with 2 patients experiencing biochemical recurrence. 4 cases were treated with additional postoperative radiotherapy or endocrine (leuprolide microsphere injection, bicalutamide, etc.) due to the presence of positive surgical margins. Patient 1-1 developed BCR (PSA=0.29 ng/ml) 4 months after RP, which was reduced to 0.00 ng/ml by norethindrone endocrine therapy. Patient 6-1 developed BCR (PSA=0.55 ng/ml) 14 months after RP, which was reduced to less than 0.2 ng/ml by leuprolide microsphere injection, and PSA rose again to 0.36 ng/ml at 23 months after RP.

Discussion

Our study comprised 20 cases of HPCa patients from 11 families who rigorously met the Johns Hopkins criteria for HPCa and represents the inaugural investigation to analyze pathological features like IDC-P and CP. This study encompassed several patients with HPCa originating from the same family, indicating a high degree of genetic relatedness among them. In a Nordic

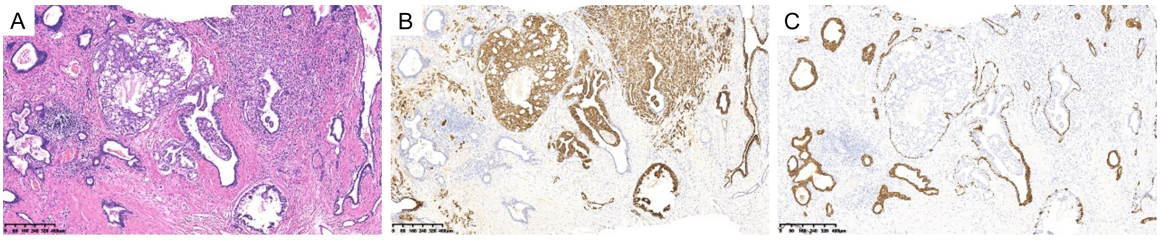

Figure 3. A-C. HE, P504S, 34βE12 staining of intraductal carcinoma.

Table 4. IHC results of 19 RP specimens

	RB1	ERG	PTEN	P53	Ki67	
Negative	1 (5.26%)	17 (89.47%)	13 (68.42%)	19 (100%)	≤ 5%	16 (84.21%)
Positive	18 (94.74%)	2 (10.53%)	6 (31.58%)	0 (0%)	> 5%	3 (15.79%)

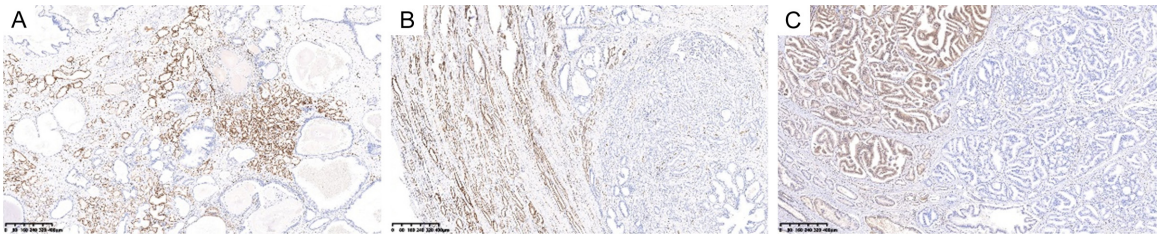

Figure 4. Representative results of immunohistochemical Staining. A, B. IHC staining results for ERG. Positive areas are predominantly structures with a Gleason pattern 3. B. Positivity is observed on the left side of the tumor, while negativity is on the right side. C. PTEN IHC staining shows positivity in the upper left tumor and partial negativity in the lower right.

prospective study involving twins, an estimated AE model heritability of PCa was reported as 57% (95% CI, 51%-63%) [15]. Since the boundary between sporadic and PCa with family history cannot be truly defined, we chose to highlight the influence of genetic factors on the clinical and pathological features of PCa by studying hereditary PCa.

It is widely recognized that the age of onset of HPCa would be lower relative to sporadic PCa. In these 11 HPCa families, the relationship between PCa patients in each family was first-degree relative, and the patients involved 2 generations. The median age at the time of PCa diagnosis for the 20 HPCa patients was 66 years, which was lower than the median age of 68 years in the Chinese PCa cohort [16]. In a German study, the median age at diagnosis in the HPCa group was 63.2 years, significantly lower than the 66.1 years observed in the sporadic PCa group [17]. Similar findings were reported in a large-scale study in the United Kingdom, where the age of diagnosis for family history-positive PCa was just 58 years [18]. According to the current study, the age of onset of PCa is higher in China than in Western countries [16], and the age of onset of HPCa patients in the present study was higher than in the aforementioned studies in Germany and the UK, among others. Therefore, we can draw similar conclusions in the HPCa population. In addition to genetic factors, family history heightens male vigilance for PCa, which may also contribute to the younger age of HPCa patients. Consequently, the characterization of age at diagnosis in HPCa warrants further investigation.

PSA is a prostate organ-specific biomarker widely utilized in PCa screening; however, elevated serum PSA levels do not always align with a PCa diagnosis [19]. It has been reported that the positive predictive value of PSA for recognizing PCa during prostate biopsy with PSA ≥ 4 ng/mL is about 30% [20]. All 20 cases of HPCa in this study exhibited PSA values exceeding 4 ng/mL, indicating a potentially enhanced pre-

dictive significance of PSA for HPCa. It is noteworthy that the average PSA level among the 20 patients was 12.26 ng/ml, markedly surpassing the 8.1 ng/ml observed in the German HPCa group and the 7.7 ng/ml in the sporadic cohort [17], as well as exceeding the findings in most recent studies [9, 11, 18]. Racial factors may be an important reason for this distinction. According to Zhao et al., the preoperative PSA levels of PCa patients in the Chinese group were higher than those in the American group [16].

The presence of CP is associated with early biochemical recurrence of PCa and PCa-specific mortality and is an independent factor in the worse prognosis of PCa patients [6, 21]. The 2014 International Society of Urological Pathology (ISUP) Grading Consensus Conference concluded that CP should be counted as a component of a Gleason pattern 4 [22]. The 2021 ISUP has an updated definition of CP for PCa: A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification ×10); there should be no intervening stroma or mucin separating individual or fused glandular structures [23]. All 19 RP specimens contained components with a Gleason score 4. The CP was visible in 15 (78.95%) of them, and the maximum diameter of the CP ranged from 0.4 mm to 4.5 mm. In a study comparing CP and non-CP, Elfandy et al. found that CP have unique molecular phenotypes, such as an increase in mutations in SPOP and ATM [2]. Meanwhile, deletions in PTEN and p27 expression are more common in PCa containing CP [24, 25]. In our study, 13 cases (68.42%) of HPCa showed deletion of PTEN immunohistochemical expression, and CP was seen in 12 of them, which is consistent with the above findings [24, 25]. According to Wyvekens et al., the correlation of dense CP with MMR-deficient PCa suggests that these histologic features may help select MMR IHC cases [26]. In contrast, we observed some consistency in the distribution of CP in the same families. In families 4, 7, and 8, the CP all occupied a relatively large proportion of the Gleason pattern 4 components. In contrast, of the three cases in family 3, only patient 3-3 showed a very small amount (5%) of CP, and no CP was seen in any of the other two cases. This may be related to specific genetic alterations in the family, thus necessitating in-depth studies of PCa-related genetic traits in families.

Both IDC-P and CP are highly malignant PCa components that negatively affect both pathologic and clinical outcomes [27]. The incidence of IDC-P is largely related to the PCa patient cohort. With the advent of updated diagnostic criteria for IDC-P in the fifth edition of WHO PCa in 2022, the proportion of IDC-P diagnoses will change. According to statistics, IDC-P is present in approximately 13-17% of PCa [28]. Miyai et al. revealed that of 901 RP specimens of PCa, 141 showed IDC-P [29]. The presence of IDC-P in 9 (47.3%) HPCa patients in this study suggests that IDC-P structures may be more commonly seen in HPCa. Through follow-up, we found that 2 patients with biochemical recurrence and 2 patients who developed lymph node metastasis were accompanied by IDC-P. These results suggest a relationship between IDC-P and poor prognosis.

We found 13 (68.42%) cases of HPCa with IHC showing PTEN expression deletion, 2 of which were accompanied by ERG IHC positivity. Of the 9 (47.3%) cases with IDC-P, 7 (77.78%) showed PTEN expression deletion. The molecular features of IDC-P usually reveal genetic alterations associated with high-grade PCa, such as PTEN deletion (69-84%) [30]. It has been suggested that large-scale deletion of PTEN may be associated with a more aggressive IDC-P and that IDC-P shows good concordance with ERG and PTEN status of neighboring PCa tissues [31], which is consistent with our findings. It has also been noted that BRCA2 carriers have a higher probability of IDC-P compared with sporadic PCa without a family history, suggesting that BRCA2 may play a role as an inducer in the formation of IDC-P [32]. This shows that there may be a correlation between certain genetic alterations in HPCa and the formation of IDC-P.

P53 is a tumor suppressor gene that undergoes inactivation in more than half of human cancers [33], and pathogenic P53 mutations increase PCa risk [34]. Our results showed that 4 of the 19 HPCa cases showed weak positivity for p53 IHC, and therefore none of the p53 was considered to be abnormally expressed. This may be related to the small number of cases in this study. According to Kim et al., p53 expression was more common in PCa with a family history compared to sporadic PCa (2.1

vs. 0.3%; P=0.059) [9]. ERG is a commonly overexpressed proto-oncogene in PCa, and nearly half of PCa cases will have a gene fusion of ERG, resulting in ERG overexpression [35]. Surprisingly, the ERG rearrangement rate in China was significantly lower than that in Western countries (8% vs. 38%) [36]. We found that 2 cases (10.53%) of HPCa showed positivity of ERG IHC, which is consistent with the report of Kim et al. [16]. The expression intensity of ERG was grade 3 in both cases, and the positive portion was mainly in the region of Gleason pattern 3 or 4, which may be related to the heterogeneity of PCa. Tumor cells in different regions may have different mechanisms of occurrence [37].

Extraprostatic extension (EPE) is one of the key factors incorporated into TNM staging and belongs to the pT3 stage. Positive EPE indicates that PCa is in late stage and is associated with a higher risk of biochemical recurrence and metastasis after RP [38]. We found 6 cases (31.6%) of HPCa that showed EPE of the tumor, including 1 case with BCR.

Notably, many studies have shown no significant differences in the clinical and pathologic features of PCa with a family history compared to sporadic PCa, except for the age of onset of the disease [9, 11, 12]. However, because the differences between sporadic, familial, or hereditary PCa cannot be truly resolved, there may be an unavoidable bias in the populations included in the studies. The familial PCa and HPCa criteria have not been fully standardized across studies. With the advancement of next-generation sequencing technology, mutations in DNA damage repair genes (BRCA1, BRCA2, CHEK2, ATM, and PALB2), DNA mismatch repair genes (MSH2, MSH6, MLH1, and PMS2), and HOXB13 have emerged as significant biomarkers for HPCa [39]. However, these genetic alterations have only been detected in a very small percentage of PCa cases, and more in-depth studies are still needed. We expect that some high-risk genetic alterations can be combined to define HPCa in the future.

This study has several limitations. First of all, this is a retrospective study, and only 20 patients with HPCa were collected. Only 1 patient was collected in certain families, which made our analysis of different family characteristics difficult. Secondly, our study was limited to clinical and pathologic information, and we failed to conduct in-depth studies at the genetic level. Furthermore, our follow-up period was relatively short.

Conclusions

Through clinical and pathological analysis of HPCa patients, we added gaps in the distributional characteristics of IDC-P and CP in HPCa and found that IDC-P and CP occurred in a higher proportion in HPCa. Moreover, PTEN IHC deletion predominantly manifested in cases with CP. Patients with HPCa in this study had a later age of onset and higher preoperative PSA levels compared with other areas.

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Disclosure of conflict of interest

None.

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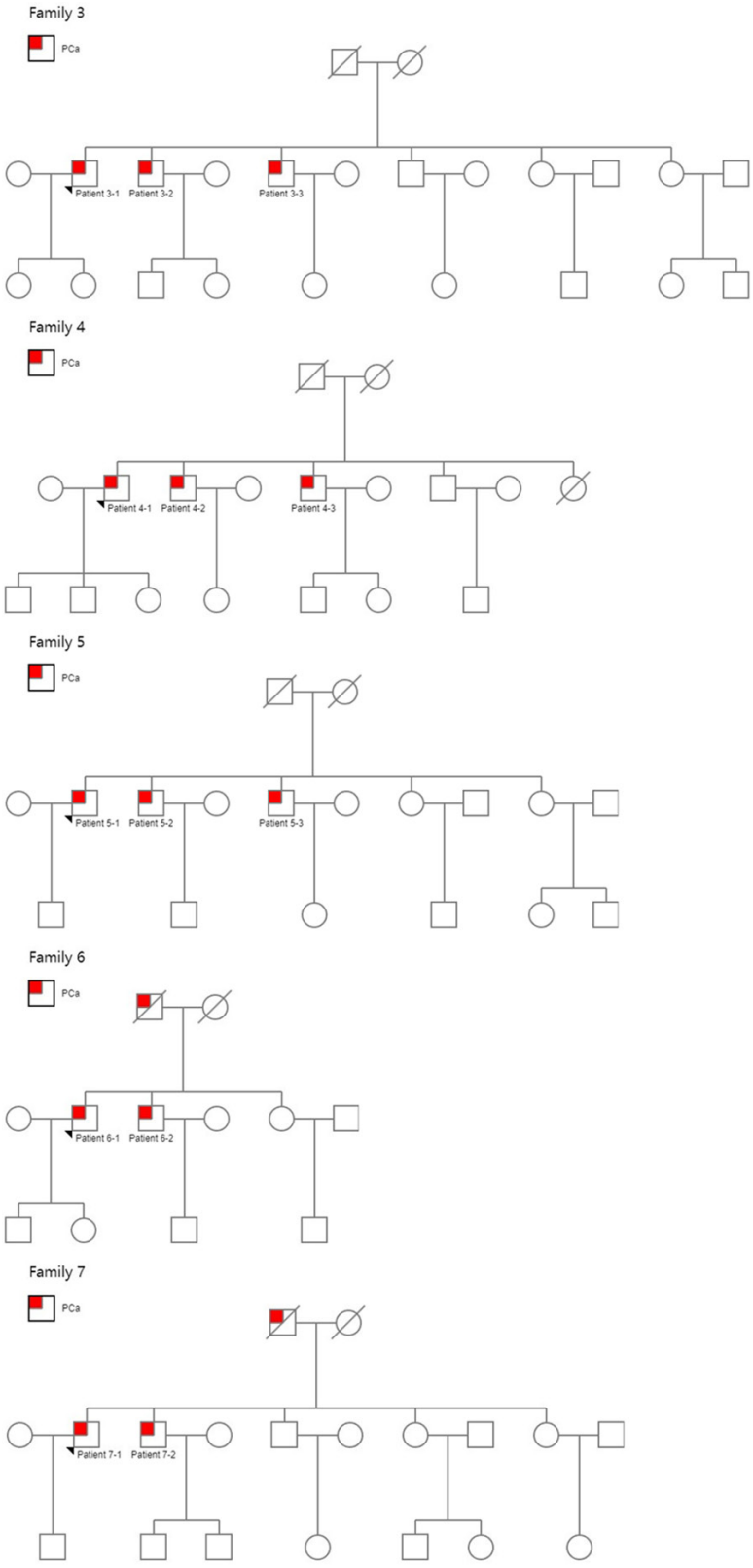
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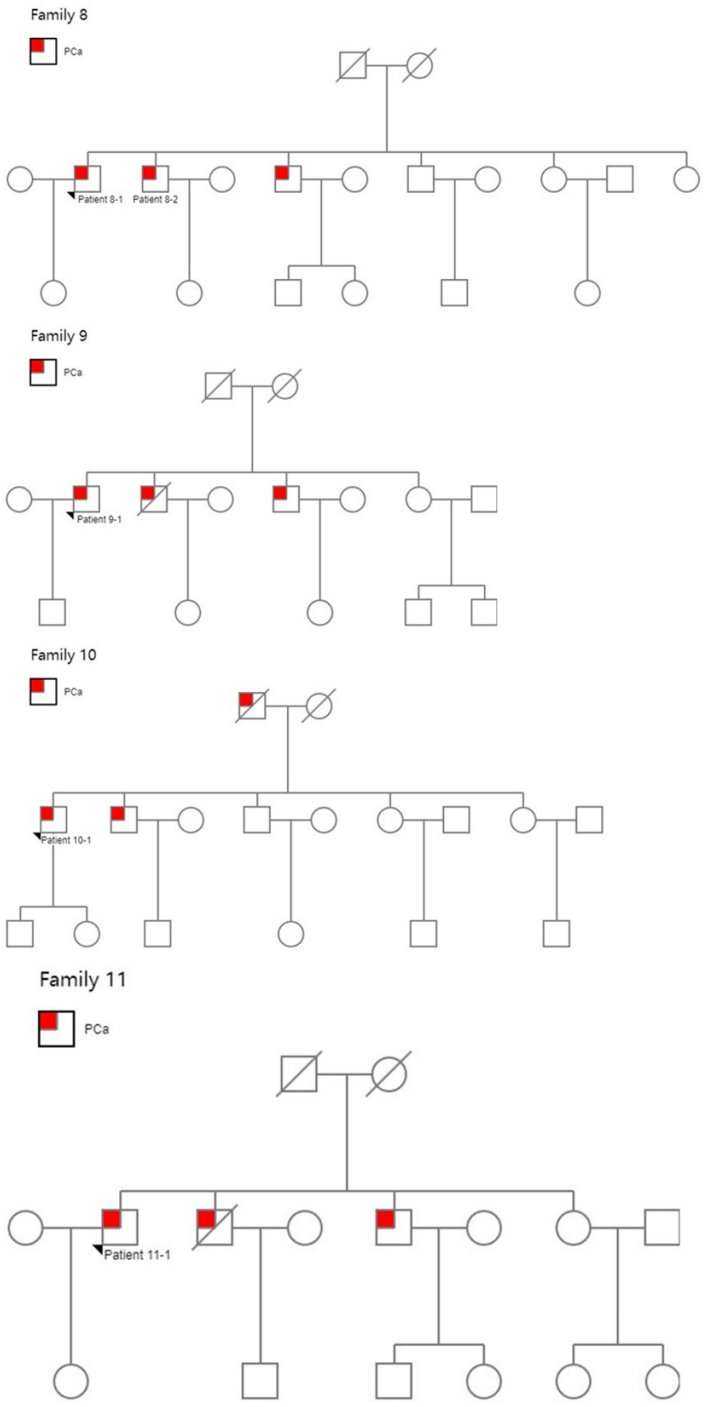

Figure S1. The pedigrees of family 3-11 with hereditary prostate cancer.