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Original Research

Diagnostic Value of *SMARCE1* and CRISP3 Combined with Tumor Markers in Cervical Cancer

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Abstract

Background: To investigate the diagnostic value of *SMARCE1*, cysteine-rich secreted protein 3 (CRISP3) combined with tumor markers in the diagnosis of cervical cancer. **Methods**: A total of 80 patients with cervical lesions who were diagnosed and treated in our hospital from January 2020 to March 2022 were selected and divided into control group (chronic cervicitis, n = 30) and observation group (cervical cancer, n = 50). Immunohistochemistry was used to detect the expression levels of *SMARCE1* and CRISP3 in cervical tissue of the two groups of subjects, and the relationship between the expression of *SMARCE1* and CRISP3 in cervical cancer tissue and the clinicopathological data of the patients was analyzed. In addition, the serum tumor marker levels of the two groups of subjects were detected, and the diagnostic value of *SMARCE1* and CRISP3 combined with tumor markers in cervical cancer was analyzed. The female sexual function index (FSFI) and the functional assessment of cancer therapy-general (FACT-G) score were used to evaluate female sexual function and quality of life. **Results**: The positive expression rates of *SMARCE1* and CRISP3 in the observation group were significantly higher than those in the control group ($p < 0.05$). There was no significant difference in the positive expression of *SMARCE1* and CRISP3 among cervical cancer patients with age, lymph node metastasis and tumor node metastasis (TNM) classification stage ($p > 0.05$), and the lower the degree of tumor differentiation, the higher the positive expression rate of *SMARCE1* and CRISP3 proteins ($p < 0.05$). The serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125 and CA153 in the observation group were significantly higher than those in the control group ($p < 0.05$). The results of the receiver operating characteristic (ROC) curve analysis showed that the area under curve (AUC) values of *SMARCE1*, *SMARCE1* + tumor markers, CRISP3, CRISP3 + tumor markers, *SMARCE1*, CRISP3 combined with tumor markers for the diagnosis of cervical cancer were 0.760, 0.851, 0.739, 0.810, and 0.944, respectively. **Conclusions**: *SMARCE1* and CRISP3 are expressed in patients with cervical cancer, and CEA, CA125, and CA153 are expressed at high levels in the serum of patients with cervical cancer. The combined detection of *SMARCE1* and CRISP3 combined with tumor markers has high clinical diagnostic value for cervical cancer.

Keywords: *SMARCE1*; CRISP3; tumor markers; cervical cancer; diagnostic value

1. Introduction

Cervical cancer is a common gynecological malignant tumor in clinical practice. As the second most common cancer among female in the world, cervical cancer has become the second leading cause of death of malignant tumors in the female genital system and posing a serious threat to the safety and health of female in China [1]. Cervical cancer is a long-term process and it takes a long time (5 to 10 years) to develop from cervical of precancerous lesions to cervical intraepithelial neoplasia (CIN). Therefore, early diagnosis and treatment of cervical cancer patients is of great significance to improve the prognosis of patients [2]. Patients with early cervical cancer have no conscious symptoms, and their cervical tissues are also lack of special changes with naked-eye, leading to missed diagnosis or misdiagnosis in clinical examination that affects early treatment of patients [3]. Therefore, it is very important to select reasonable and effective detection methods to improve the early diagnosis rate of cervical cancer. The studies found that the expression of *SMARCE1* in cancer tissues of patients with gastric cancer, ovarian carcinoma and liver cancer are closely related to prognosis, and *SMARCE1* is a critical gene to promote the invasion and metastasis of breast carcinoma cells [4–6]. cysteine-rich secretory protein 3 (CRISP3) is the third member of the cysteine-rich secretory protein family that has been confirmed to be low expressed in carcinoma of prostate, breast carcinoma and ovarian carcinoma, and the low expression of CRISP3 is related to the sur the stimulation reaction of malignant tumor cells or the body by tumors, the levels survival rate of breast carcinoma patients [7]. In addition, tumor markers refer to the special biochemical substances that exist in the body fluid, urine or blood of tumor patients and are generated byre higher than those of normal people, the changes can reflect the occurrence and development of tumors and play a role in early screening of cancer [8]. The study is to explore the diagnostic value of *SMARCE1* and CRISP3 combined with tumor markers in cervical cancer, so as to provide reference for clinical diagnosis and treatment.

Table 1. Comparison of *SMARCE1* and CRISP3 expression between the two groups, cases (%).

Group	Case	*SMARCE1*		CRISP3	
		Positive	Negative	Positive	Negative
Control group	30	14 (46.67)	16 (53.33)	11 (36.67)	19 (63.33)
Observation group	50	38 (76.00)	12 (24.00)	31 (62.00)	19 (38.00)
χ^2		7.092		4.825	
p		0.008		0.028	

CRISP3, cysteine-rich secreted protein 3.

Table 2. The relationship of the expression of *SMARCE1* and CRISP3 in cervical cancer tissues and the clinicopathological characteristics of patients (Cases).

Group	Case	*SMARCE1*			CRISP3		
		Positive	χ^2	p	Positive	χ^2	p
Age							
≥45	35	27	0.005	0.943	21	0.198	0.656
<45	15	11			10		
Lymph node metastasis							
Yes	18	16	1.576	0.209	14	2.972	0.085
No	32	22			17		
Degree of tumor differentiation							
Highly differentiated	20	11	6.255	0.012	9	4.089	0.043
Medium and low differentiation	30	27			22		
TNM staging							
Stage I	36	25	1.882	0.170	23	2.266	0.132
Stage II and III	14	13			8		

CRISP3, cysteine-rich secreted protein 3; TNM, tumor node metastasis.

2. Materials and Methods

2.1 General Materials

80 patients with cervical diseases were diagnosed and treated in Tianjin Fifth Central Hospital from January 2020 to March 2022, and were divided into the control group (with chronic cervicitis, n = 30) and the observation group (with cervical cancer, n = 50) according to the pathological examination results. The observation group was 35~58 years old, with an average age of (47.63 ± 2.75) years. The control group was 35~57 years old, with an average age of (47.34 ± 3.12) years. There was no significant difference in age between the two groups ($p > 0.05$).

2.1.1 Inclusion Criteria

The following inclusion criteria were established for cervical cancer: (1) Meet the diagnostic criteria for cervical cancer in the Expert Consensus On Immunoprophylaxis of Human Papillomavirus-Related Diseases [9]. (2) Patients with available 3-year follow-up data (for non-recurring patients; patients who recurred were included even if they did not complete the three-year follow-up period). (3) It belonged to the early stage of cervical cancer. (4) The clinical data were complete and all patients with cervical cancer were operated on in Tianjin Fifth Central Hospital. (5) Good cognitive function. (6) All subjects signed informed consent and was approved by the ethics committee of Tianjin Fifth Central Hospital.

2.1.2 Exclusion Criteria

Exclusion criteria were the following: (1) Age <18 years. (2) Used immunosuppressants and enhancers in recent one year. (3) Patients with other malignant tumors. (4) Patients with other infectious and immune diseases. (5) Unable to perform surgery. (6) History of human immunodeficiency virus (HIV) and other conditions downregulating the immune system. (7) Ongoing pregnancy; and (8) History of hysterectomy.

2.2 Methods

2.2.1 Instruments and Reagents

Rabbit Anti-Human *SMARCE1* and CRISP3 monoclonal antibodies were purchased from Abcam Corporation, Trading Co., Ltd. (batch number: EPR8848, Shanghai, China) and the immunohistochemistry kits were purchased from ZSGB-BIO Co., Ltd. (batch number: ab105951, Beijing, China).

2.2.2 Detection Method

SP (streptavidin-perosidase) immunohistochemical method was used to detect the immunoreactivity of *SMARCE1* and CRISP3 proteins. Fix the cervical tissues sample with formalin solution (10%) (batch number: RY0380, ZSGB-BIO Co., Ltd., Beijing, China), embed them with paraffin (batch number: 8002-74-2, ZSGB-BIO Co., Ltd., Beijing, China), and cut the samples into 5 μm

Table 3. Comparison of serum tumor markers.

Group	Case	CEA (ng/mL)	CA153 (U/mL)	CA125 (U/mL)
Control group	30	6.24 ± 2.02	15.46 ± 3.46	66.28 ± 8.84
Observation group	50	2.85 ± 0.90	6.84 ± 2.12	41.34 ± 6.76
t		8.673	12.312	13.285
p		0.000	0.000	0.000

CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

Table 4. ROC curve of clinical value of *SMARCE1*, CRISP3 combined with tumor markers in diagnosis of cervical cancer.

Screening method	95% CI	AUC	Specificity (%)	Sensitivity (%)
CRISP3	0.655–0.812	0.739	64.62	75.38
SMARCE1	0.678–0.831	0.760	72.31	70.77
CRISP3 + tumor markers	0.732–0.873	0.810	75.38	70.77
SMARCE1 + tumor markers	0.778–0.908	0.851	89.23	72.31
SMARCE1, CRISP3 Combined tumor markers	0.889–0.977	0.944	95.38	83.08

ROC, receiver operating characteristic; CRISP3, cysteine-rich secreted protein 3; CI, confidence interval; AUC, area under curve.

thin slices after dehydrated. 3% hydrogen peroxide was used to block endogenous peroxidase for 30 minutes after EDTA antigen repair solution (batch number: ab93684, ZSGB-BIO Co., Ltd., Beijing, China) was used to repair under high pressure and Rabbit Anti-Human primary antibody (batch number: Rab125919, ZSGB-BIO Co., Ltd., Beijing, China) of 1:500 concentration was added for overnight with 4 °C. After being taken out overnight, the room temperature was restored and being washed with phosphate buffer solution (PBS) (batch number: FS-B0287, Shanghai MINKE Biotechnology Co., Ltd., Shanghai, China) and the Rabbit Anti-Human second antibody (batch number: 109-005-088, ZSGB-BIO Co., Ltd., Beijing, China) was added and incubated at 37 °C for 30 minutes, and the diaminobenzidine (DAB) chromogenic reagent kit (batch munber: abs9211, ZSGB-BIO Co., Ltd., Beijing, China) was developed and thehematoxylin was stained and then sealed. The whole SP immunohistochemical process was strictly in accordance with the operating procedures of the instructions. During the test, PBS was used as the negative control instead of the primary antibody.

2.2.3 Result Determination

Five visual fields were randomly selected from each section under high power microscope (CX22LED Olympus (China) Co., Ltd., Beijin, China) for observation, and the percentage of positive cells and the staining intensity of cells were judged. The positive signals of *SMARCE1* and CRISP3 proteins were located in the cytoplasm, and the positive cells were brown yellow or brown granules. (I) According to the staining intensity of positive cells, it is judged that: colorless was 0 score, light yellow (weak positive) was 1 score, brown yellow (medium intensity) was 2 score, brown (strong positive) was 3 score. (II) According to the percentage of positive cells, positive cells accounted for 0% was 0 score, positive cells $\leq$10% was 1 score, positive cells accounted for 10%~50% was 2 score, positive cells accounted for 50%~75% was 3 score, positive cells accounted for $>$75% was 4 score. (III) Staining index = staining intensity + proportion of positive cells. Negative expression was staining index was 0 score and positive expression was staining index was $\geq$3 [10].

2.2.4 Detection of Tumor Markers

Took 5 mL of fasting peripheral venous blood from all subjects in the morning, centrifuged for 10 minutes at a rate of 3500 r/min (BY-600A Beijing Baiyang Co., Ltd., Beijing, China), and placed in a refrigerator at –80 °C temperature for testing. The level of serum CEA (batch number: 11731629322), CA125 (batch number: CA125 11776223322) and CA153 (batch number: 03045838122) were measured by electrochemiluminescence immunoassay. The detection instrument was the automatic electrochemiluminescence immunoanalyzer of Roche (Roche cobas 8000, Roche Diagnostics GmbH, Mannheim, Germany). The Kits were purchased from Beijing Lidman Biochemical Co., Ltd., China and operated strictly according to the instructions.

2.3 Statistical Methods

The statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA), and the counting data were chi-square test or rank sum test for comparison. The measurement data were expressed by mean ± standard deviation ($\bar{x}$ ± s) with *t*-test for comparison. The area under the receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of each parameter. The difference was statistically significant. $p \leq 0.05$ was considered statistically significant.

Table 5. The FSFI and FACT-G scores between the two groups ($\bar{x} \pm s$).

Groups	n	FSFI (Score)	FACT-G (Score)
Control group	30	35.69 ± 4.41	89.68 ± 7.98
Cervical cancer group	30	26.35 ± 3.39	64.21 ± 5.68
t		9.197	14.240
p		0.001	0.001

FSFI, female sexual function index; FACT-G, functional assessment of cancer therapy-general.

3. Results

3.1 Comparison of SMARCE1 and CRISP3 Expression

The positive expression rates of *SMARCE1* and CRISP3 in the observation group were significantly higher than the control group ($p < 0.05$). As shown in Table 1.

3.2 The Relationship of the Expression of SMARCE1 and CRISP3 in Cervical Cancer Tissues and the Clinicopathological Characteristics of Patients

There was no significant difference in the positive expression of *SMARCE1* and CRISP3 among the age, lymph node metastasis and tumor node metastasis (TNM) stage of cervical cancer patients ($p > 0.05$). The positive expression rates of *SMARCE1* and CRISP3 were significantly different among different tumor differentiation degrees of cervical cancer patients ($p < 0.05$) and the lower the tumor differentiation degree, the higher the positive expression rates of *SMARCE1* and CRISP3 proteins ($p < 0.05$). As shown in Table 2.

3.3 Comparison of Serum Tumor Markers

The level of the serum CEA, CA125 and CA153 in the control group were significantly higher than observation group ($p < 0.05$). As shown in Table 3.

3.4 ROC Curve of the Clinical Value of SMARCE1, CRISP3 Combined with Tumor Markers in the Diagnosis of Cervical Cancer

The ROC curve results shown that the AUC of *SMARCE1*, *SMARCE1* + tumor marker, CRISP3, CRISP3 + tumor marker, *SMARCE1*, CRISP3 combined with tumor marker for diagnosis of cervical cancer were 0.760, 0.851, 0.739, 0.810 and 0.944 respectively. As shown in Table 4 and Fig. 1.

3.5 The FSFI and FACT-G Scores between the Two Groups

The FSFI and FACT-G scores of cervical cancer group were lower than control group ($p < 0.05$). As shown in Table 5.

3.6 Correlation between the Expression of SMARCE1 CRISP3 and FSFI, FACT-G Scores

The expression of *SMARCE1* CRISP3 were positively correlated with FSFI and FACT-G score ($p < 0.05$), as shown in Table 6.

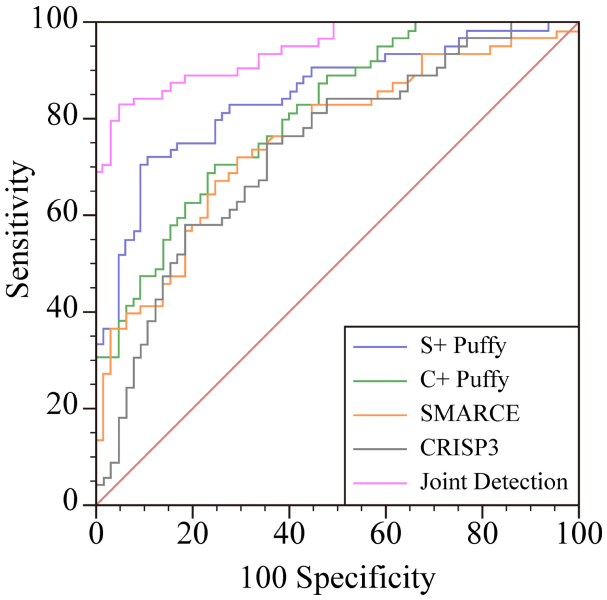

Fig. 1. ROC curve of the clinical value of *SMARCE1*, CRISP3 combined with tumor markers in the diagnosis of cervical cancer. CRISP3, cysteine-rich secreted protein 3.

Table 6. Correlation between the expression of *SMARCE1* CRISP3 and FSFI, FACT-G scores.

	FSFI	FACT-G
SMARCE1	$r = 0.529$	r = 0.507
	$p = 0.001$	$p = 0.001$
CRISP3	$r = 0.532$	$r = 0.557$
	$p < 0.001$	$p < 0.001$

FSFI, female sexual function index; CRISP3, cysteine-rich secreted protein 3; FACT-G, functional assessment of cancer therapy-general.

4. Discussion

In recent years, with the change of people's life and eating habits, the incidence of cervical cancer has been increasing year by year [11]. Cervical cancer is also known as Invasive Carcinoma of Cervix. Cervical intraepithelial neoplasia is the early stage of cervical cancer, also known as Precancerous Lesion Phase [12]. According to clinical studies, patients with cervical cancer have a long Precancerous Lesion State, and it takes about 5–10 years to develop from cervical intraepithelial neoplasia to cervical cancer [13]. Therefore, early detection and diagnosis of cervical intraepithelial neoplasia and cervical cancer, and active treatment of precancerous lesions can effectively reduce the incidence and mortality of cervical cancer and improve the quality of life of patients with cervical lesions. In clinical screening and diagnosis of cervical cancer with vinegar white test combined with iodine test, colposcopy, human papillo avirus (HPV) screening, cervical smear cytology, cervical and cervical tube biopsy, cervical conization screening [14]. The emergence of various screening tech-

nologies has improved the detection rate of clinical cervical cancer, but the screening costs of various screening methods are different. For cervical cancer, no effective screening methods exist. There is an urgent need to identify novel strategies to detect all gynecologic tumors as early as possible, thus reducing mortality and improving the quality of care [15].

It was found that human SWI/SNF chromatin-remodeling complex consists of 9~12 subunits, and *SMARCE1* was one of the subunits of human SWI/SNF chromatin remodeling complex [16]. The human SWI/SNF chromatin-remodeling complex contains one of the ATPases of the SMARCA4 or SMARCA4 and three major core subunits and other complex specific variant subunits. The subunits together played biological roles in regulating cell cycle progress, differentiation, DNA repair, activation, genomic instability, and programmed cell death [17]. The results of the study shown that the positive expression rates of *SMARCE1* and CRISP3 in the observation group were significantly higher than the control group. It was indicated that SMARCEI was expressed in cervical cancer patients and the abnormal expression of SMARCEI maid participate in the occurrence and development of cervical cancer. The results of the study also found that the positive expression rate of *SMARCE1* was statistically significant in different tumor differentiation degrees of cervical cancer patients, and the lower the tumor differentiation degree, the higher the positive expression rate of *SMARCE1* and CRISP3 proteins. It was indicated that the abnormal expression of SMARCEI may have an impact on the pathological changes of cervical cancer and may play a key role in promoting the carcinogenesis and development of cervical cancer. which were in line with the previous literature reports. Zhang *et al*. [18] found that SMARCEI was a specific and sensitive marker of clear cell meningioma, and SMARCEI mutation could lead to the occurrence of clear cell meningioma. SMARCEI mutation causes the loss of SMARCEI function, leading to the loss of inhibition of SWI/SNF complex on tumor and participating in the occurrence and development of tumor [19].

Human CRISP3 is located on human chromosome 6 and is the third member of the cysteine rich secretory protein family and is widely distributed in human tissues. It is detected in human body fluid secretion including sweat, plasma, prostate, pancreas and salivary glands [20]. The study found that CRISP3 is low expressed in colon, thymus, ovary and epididymis tissues, but its specific function has not been clearly studied [21]. CRISP3 is also low expressed in various tumor tissues that Henriksen *et al*. [22] found that CRISP3 is low expressed in malignant ovarian epithelial cells. Volpert *et al*. [23] found that CRISP3 can be used as a prognostic marker of prostate cancer. The higher the expression level of CRISP3 in prostate tissue, the higher the risk of recurrence of prostate cancer patients. Wang *et al*. [24] found that the detection of CRISP3 level may be a new method to predict breast cancer. The low expression of CRISP3 in breast cancer patients is related to the overall survival rate and disease-free survival rate. The results of the study shown that the positive expression rate of CRISP3 in the observation group was significantly higher than the control group. It is indicated that CRISP3 is expressed in patients with cervical cancer and the abnormal expression of CRISP3 may participate in the occurrence and development of cervical cancer. The results of the study also shown that the positive expression rate of CRISP3 was statistically significant in different tumor differentiation degrees of cervical cancer patients, and the lower the tumor differentiation degree, the higher the positive expression rate of *SMARCE1* and CRISP3 proteins. The abnormal expression of CRISP3 may have an impact on the pathological changes of cervical cancer, and may play a key role in promoting the carcinogenesis and development of cervical cancer which were in line with the previous literature reports.

Tumor markers refer to proteins, peptides or other biological substances are produced by the body in the process of tumor occurrence, development, invasion and metastasis of tumor cells which are synthesized, secreted or shed into body fluids or tissues by the tumor cells or the body in response to tumor cells [25]. The content of tumor markers in normal healthy people is extremely low, but it is obviously expressed at a high level in tumor tissues. Therefore, the determination of tumor markers presence or content could be used to diagnose the generation of malignant tumors, analyze the patient's condition, monitor metastasis, and judge the prognosis of patients [26]. CEA is an acid glycoprotein isolated from embryonic colon mucosa and colon adenocarcinoma which is expressed on the surface of tissue cell membrane and is widely used in the differential diagnosis of malignant tumors [27]. CA125 is a mucin-like glycoprotein with high molecular weight which can promote cell metastasis and infiltration by influencing mutual recognition and adhesion among cells [28]. CA153 is a polymorphic epithelial mucin secreted by glands and exists in many kinds of adenocarcinoma. Studies have found that the increase rate of CA153 can reach about 70% when tumor cells metastasize so that it has good diagnostic value for the development and prognosis of the disease [29]. The results of the study shown that the level of the serum CEA, CA125, CA153 in the observation group were significantly higher than the control group. It is indicated that CEA, CA125 and CA153 are highly expressed in cervical cancer patients, and the changes are related to the occurrence and development of cervical cancer.

In addition, the study results also found that the ROC curve analysis showed that the AUC values of *SMARCE1*, *SMARCE1* + tumor markers, CRISP3, CRISP3 + tumor markers, *SMARCE1* and CRISP3 combined tumor markers in the diagnosis of cervical cancer were 0.760, 0.851, 0.739, 0.810, 0.944, respectively. It is indicated that the combined detection of *SMARCE1* and CRISP3 combined

tumor markers has high clinical diagnostic value for cervical cancer. The study has the following deficiencies including only a small sample, single center study, and does not clarify how *SMARCE1* and CRISP3 participate in the occurrence and development of cervical cancer. Large sample, multi-center studies are still needed in the future, and more in-depth biological research is needed to further clarify the relevant pathways.

5. Conclusions

To sum up, *SMARCE1* and CRISP3 are expressed in cervical cancer patients, These data may serve as the basis for clinical counselling and future discussions on this relevant topic.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

Author Contributions

Conception and design—LH; Administrative support—HZ; Provision of study materials or patients—LH; Data analysis and interpretation—JW; Manuscript writing—All authors. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Tianjin Fifth Central Hospital Ethics Committee (approval number: 20221120). We confirmed that informed consent was obtained from all patients and their families. We confirmed all methods were carried out in accordance with Helsinki declaration.

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Conflict of Interest

The authors declare no conflict of interest.

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