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Original Article

Correlation analysis on risk factors for cervical cancer in perimenopausal women

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Abstract: Objective: To analyze the risk factors for cervical cancer in perimenopausal women. Methods: The data of 380 cervical cancer patients and 380 healthy individuals undergoing physical examinations at the Health Management Center of West China Hospital, Sichuan University, between April 2022 and March 2023, were retrospectively analyzed. The baseline information, genetic characteristics, medical records (both past and present), menstrual cycles, healthy conditions of the reproductive system, and sexual activities of patients in the cervical cancer patient group and healthy control group were compared. Logistic regression analysis was conducted to evaluate the potential risk factors and to comprehensively assess the impact of these factors on the prevention of cervical cancer. Results: Participants in the healthy control group showed a significantly lower age for first intercourse, first marriage and first pregnancy compared to those in the cervical cancer patient group. The proportions of married participants and those with a high school degree or above were higher in the healthy control group than those in the cervical cancer patient group. Additionally, the proportion of participants without a history of genetic diseases or any other diseases was significantly higher in the healthy control group than that in the cervical cancer patient group ($P<0.05$). The number of participants with regular menstrual cycles was significantly higher and the incidence of dysmenorrhea markedly lower in the healthy control group in comparison to the cervical cancer patient group ($P<0.05$). Meanwhile, the number of participants with only one pregnancy experience was higher and those with an abortion history was lower in the healthy control group than those in the cervical cancer patient group ($P<0.05$). Notably, more participants in the healthy control group preferred using contraception, underwent regular gynecological examinations and washed their external genitalia before sexual intercourse when compared to the cervical cancer patient group. Moreover, the healthy control group also had a higher proportion of participants who had sexual intercourses less than 4 times a week and who manually washed their underwear in comparison to the cervical cancer patient group ($P<0.05$). In addition, a total of 11 risk factors were identified to be in association with cervical cancer, which were human papillomavirus (HPV) testing (OR = 30.326), presence of reproductive system symptoms (OR = 27.605), dysmenorrhea (OR = 26.470), washing external genitalia before intercourse (OR = 0.430), passive smoking (OR = 16.119), duration of heating in winter (OR = 0.444), physical exercises (OR = 0.272), consumption of fried foods (OR = 8.240), vegetable intake (OR = 0.933), alcohol consumption (OR = 5.468), and consumption of chili peppers (OR = 4.797), listed in the order of their influential power. Conclusion: Perimenopausal women should have a regular screening for cervical cancer during their hospital visits. More than that, they can seek to avoid risk factors in their daily life to prevent the occurrence of cervical cancer.

Keywords: Perimenopause, screening, cervical cancer, risk factors

Introduction

Cervical cancer is one of the most common gynecological malignancies in China, with an incidence second only to breast cancer, and it has been showing an increasing annual trend. Currently, cervical cancer has become a major threat to women's health worldwide [1, 2]. According to relevant data, approximately 133,100 new cases of cervical cancer occur annually in China, accounting for more than 25.41% of the global cases [3]. Studies have found that HPV infection is an important risk factor for the development of cervical cancer;

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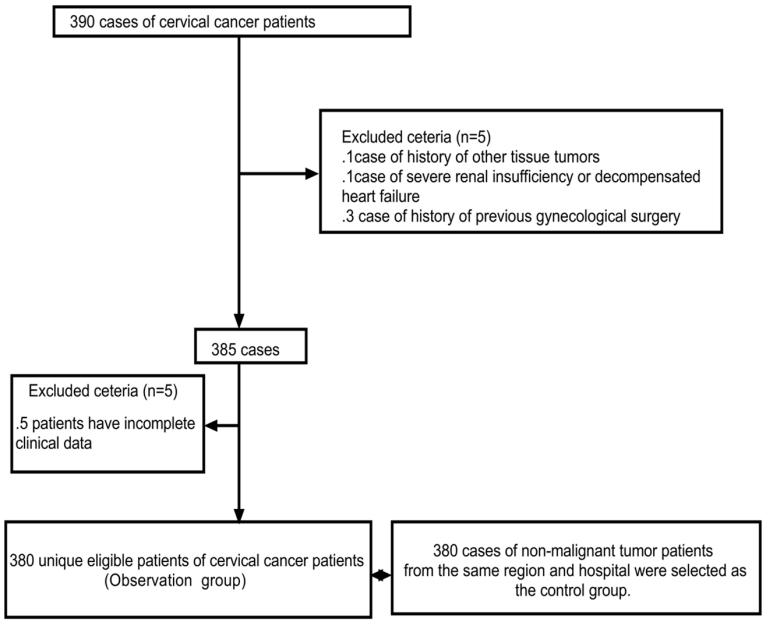

Figure 1. Flow chart of the selection of participants in the two groups.

therefore, HPV vaccination could be an useful approach to reduce the incidence and mortality of cervical cancer [4]. In China, due to its large population and significant urban-rural development disparities, many women in remote areas do not have access to adequate cervical cancer screening and treatment, which severely restricts the maintenance of their reproductive health. This leads to insufficient dissemination of knowledge related to cervical cancer, hindering early prevention, detection, and treatment of the disease [5-7]. Therefore, conducting early screening for cervical cancer and intervening in its risk factors in advance, along with implementing appropriate preventive measures, can significantly reduce the incidence of cervical cancer while increasing awareness about the disease and the importance of HPV vaccination. Although there have been some related studies on the influencing factors of cervical cancer over recent years, the incidence of cervical cancer is associated with a variety of factors and varies in different regions [8, 9]. In addition, no relevant studies have been conducted concerning populations in the Southwest China. Hence, our research team conducted a case-controlled study involving 380 cervical cancer patients and 380 healthy participants from the Health Management Center of West China Hospital, Sichuan University, in Southwest China to analyze risk factors for cervical cancer.

Data and methods

Participants selection

A total of 380 perimenopausal women whose physical examination results were considered questionable by the Health Management Center of West China Hospital, Sichuan University, and were then confirmed as having cervical cancer by clinical and pathological diagnoses between April 2022 to March 2023 were selected as the cervical cancer patient group (initial screening was conducted using liquid-based thin-layer cytology technology, and those whose initial screening results were positive underwent cervical biopsy under colposcopy by harvesting cervical tissues from their squamocolumnar junction. The diagnosis was confirmed in combination with patients' clinical manifestations, cytological examination results and pathological results [10]). This study was approved by the West China Hospital, Sichuan University's medical ethics committee. Based on the 1:1 ratio standard for participant selection in this control study, another 380 participants without malignant tumors from the same region, same hospital, and with an age difference of less than 3 years were selected as the healthy control group. The participant selection process is as follows (**Figure 1**).

Inclusion criteria: participants were eligible for the study if they aged between 40 and 60 years old; already married with pregnancy experiences; had their complete reproductive system intact and no surgical experiences; were identified as CIN1 or above according to their pathological diagnosis; and had complete data.

Exclusion criteria: participants were considered illegible for the study if their liver and kidney functions were impaired; they had gynecological surgery; and they were complicated with other tumors.

Data retrieval method

Patients' medical records were retrieved from the Hospital Information System (HIS), and their general demographic information, such as age, medical payment method, marital status, body mass index (BMI), family history of cancers, reproductive health records (age at menarche, age at first marriage, age at first pregnancy, number of pregnancies, number of deliveries, number of miscarriages, contraceptive experiences, menopausal time, etc.); history of human papillomavirus (HPV) infection, sexual activities, history of reproductive tract infections, and other infections, along with their peripheral blood test results and color Doppler ultrasound results, were collected.

Outcome measures

The baseline data and clinical test results (such as routine blood results, inflammatory markers and Doppler ultrasound results) of the study participants were compared between the cervical cancer patient group and the healthy control group to analyze influencing factors for cervical cancer.

Statistical analysis

SPSS 23.0 software was employed for statistical analysis. The comparability analysis between the cervical cancer patient group and the healthy control group was performed using independent sample t-tests and χ^2 tests. Variables with statistical significance were first screened out, and then further analyzed with the use of a multivariable logistic regression model. Stepwise regression method was utilized for the independent variables entering into the model, with an inclusion criterion of $\alpha \leq 0.05$ and an exclusion criterion of $\alpha \geq 0.10$, at a significance level of $\alpha = 0.05$.

Results

Basic characteristics

The age of first sexual intercourse in the cervical cancer patient group was significantly lower than that in the healthy control group, while the age at first marriage and age at first pregnancy were significantly younger in the cervical cancer patient group compared to the healthy control group ($P<0.05$). Additionally, the number of family members in the cervical cancer patient group was significantly higher than that in the healthy control group ($P<0.05$). The number of married participants in the healthy control group was significantly higher than that in the cervical cancer patient group, and the overall education level was relatively higher in the healthy control group as well ($P<0.05$). There was also a significant difference in the distribution of different types of insurance between the two groups ($P<0.05$). See **Table 1**.

The impact of genetic disease history and medical records (both past and present) on the incidence of cervical cancer in the two groups

The proportion of participants with a family history of cervical cancer, a family history of other cancers, chronic diseases, gynecological diseases, reproductive system symptoms, and HPV infection in the healthy control group was significantly lower than that in the cervical cancer patient group ($P<0.05$). See **Table 2**.

The impact of menstrual cycles, health conditions of the reproductive system, and sexual activities on the incidence of cervical cancer in the two groups

The number of participants with regular menstrual cycles was significantly higher, and the incidence of dysmenorrhea lower in the healthy control group than those in the cervical cancer patient group ($P<0.05$). Additionally, the number of patients with single pregnancy and without an abortion history was larger in the healthy group in comparison to the cervical cancer patient group ($P<0.05$). The number of participants using contraception, undergoing regular gynecological checks, and washing their external genitalia before intercourse in the healthy control group was higher than that in the cervical cancer patient group. Furthermore, the proportion of participants having intercourse less than 4 times a week and washing their underwear by hand was higher in the healthy control group as well than that in the cervical cancer patient group ($P<0.05$). See **Table 3**.

Peripheral routine blood test results in the two groups

No statistically significant differences in the white blood cell count, the ratios of neutrophils

Table 1. Basic characteristics of participants in the two groups

Items	Healthy control group (n = 380)	Cervical cancer patient group (n = 380)	*t*	*P*
Age at First Intercourse (years)	22.86±2.75	22.25±3.12	2.859	0.004
Age at First Marriage (years)	22.91±2.43	22.54±2.38	2.121	0.034
Age at First Pregnancy (years)	23.61±2.48	23.07±2.79	2.819	0.005
Number of Family Members (persons)	3.36±1.32	3.95±1.44	-5.887	<0.001
Daily Sleep Duration (hours)	7.31±2.43	7.25±2.43	0.34	0.734
Marital Status	318	291	6.025	0.014
Married	62	89		
Others				
Education level			19.552	<0.001
Below High School	87	143		
High School and Above	293	237		
Occupation			5.228	0.073
Employee	152	134		
Farmer	117	147		
Others	111	99		
Insurance type			13.19	0.001
Urban and Rural Residents	197	182		
Employee Medical Insurance	152	134		
Others	31	64		

Table 2. The impact of genetic diseases and medical records (both past and present) on the incidence of cervical cancer in the two groups

Items	Healthy control group	Cervical cancer patient group	X^2	*P*
Family History of Cervical Cancer			50.05	<0.001
No	299	207		
Yes	81	173		
Family History of Other Cancers			20.052	<0.001
No	284	226		
Yes	96	154		
Presence of Chronic Diseases			9.846	0.002
No	271	230		
Yes	109	150		
Presence of Gynecological			3.891	0.049
No	226	199		
Yes	154	181		
Presence of Reproductive System Symptoms			5.79	0.016
No	224	256		
Yes	156	124		
HPV Infection			6.06	0.013
No	294	256		
Yes	96	124		

Note: HPV: human papillomavirus.

Table 3. The impact of menstrual cycles, health conditions of reproductive system, and sexual activities on the incidence of cervical cancer in the two groups

Items	Healthy control group	Cervical cancer patient group	X^2	*P*
Menstrual Cycle			45.351	<0.001
No	107	198		
Yes	273	182		
Dysmenorrhea			96.274	<0.001
No	269	134		
Yes	111	246		
Menopause			1.034	0.309
No	192	206		
Yes	188	174		
Number of Pregnancies			3.882	0.049
Single Pregnancy	224	197		
Multiple Pregnancy	156	183		
Contraception			25.296	<0.001
No	119	187		
Yes	261	193		
Gynecological Check-ups			27.919	<0.001
No	82	149		
Yes	298	231		
Frequency of Sexual Intercourse			43.414	<0.001
<4 times a week	281	193		
≥4 times a week	99	187		
Washing External Genitalia Before Intercourse			12.098	0.001
No	129	176		
Yes	251	204		
Underwear Washing By hand	272	219	16.163	<0.001

Table 4. Comparison of peripheral blood cell count in participants between the two groups

Items	Healthy control group (n = 380)	Cervical cancer patient group (n = 380)	Statistical value	*P*
WBC ($\times 10^9$)	9.73±1.3	9.71±1.4	0.754	0.664
HB (g/L)	13.8±3.9	13.5±3.8	0.884	0.771
NEU ($\times 10^9$)	5.67±2.36	5.4±2.29	0.769	0.563
LYM ($\times 10^9$)	1.43±0.53	1.5±0.46	0.536	0.438

Note: WBC: white blood cell; HB: hemoglobin; NEU: Neutrophil; LYM: lymphocyte.

and lymphocytes were noticed between the two groups (all P>0.05). See **Table 4**.

Comparison of liver and kidney functions between the two groups

No statistically significant differences were identified in liver enzyme indicators (ALT, AST) and kidney function (creatinine) between the two groups (all P>0.05). See **Table 5**.

Comparison of inflammatory cytokines interleukin-2 (IL-2), interleukin-4 (IL-4), and tumor necrosis factor-alpha (TNF-α) levels between the two groups

The results showed that the IL-2 level in the serum of participants were lower, while the IL-4 and TNF-α levels were higher, in the cervical cancer patient group compared to the healthy control group (all P<0.05). See **Figure 2**.

Table 5. Comparison of liver and kidney functions of patients between the two groups

Items	Healthy control group (n = 380)	Cervical cancer patient group (n = 380)	Statistical value	*P*
Albumin (g/L)	36.0±4.9	35.8±4.5	0.663	0.582
AST (U/L)	20.6±2.3	21.4±2.7	0.574	0.524
ALT (U/L)	22.3±2.5	21.8±2.7	0.793	0.486
Scr (mmol/L)	74.3±4.7	75.0±5.1	0.652	0.697

Note: AST: aspartate transaminase; ALT: alanine aminotransferase; Scr: serum creatinine.

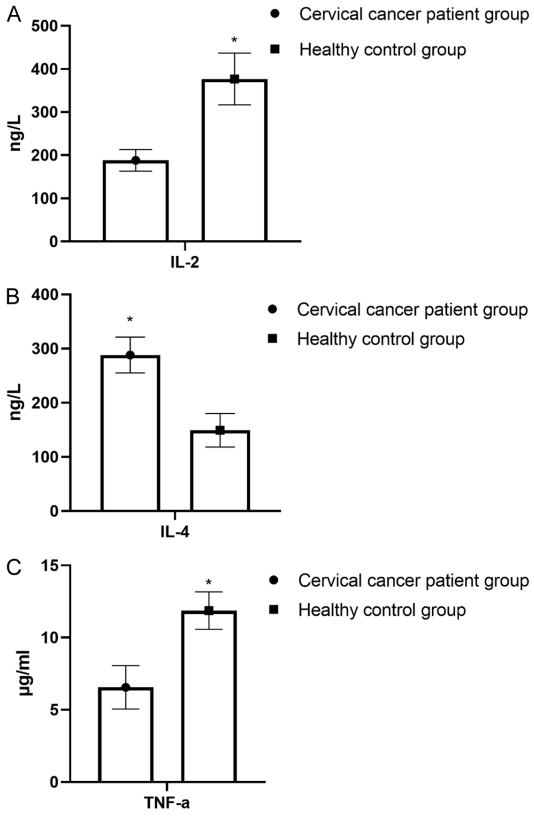

Figure 2. Comparison of peripheral blood inflammatory factors between the two groups. A: Comparison of the IL-2 level between the two groups; B: Comparison of the IL-4 level between the two groups; C: Comparison of the TNF-α level between the two groups. *P<0.05 for comparison between the healthy control group and the cervical cancer patient group. IL: interleukin; TNF-α: tumor necrosis factor-α.

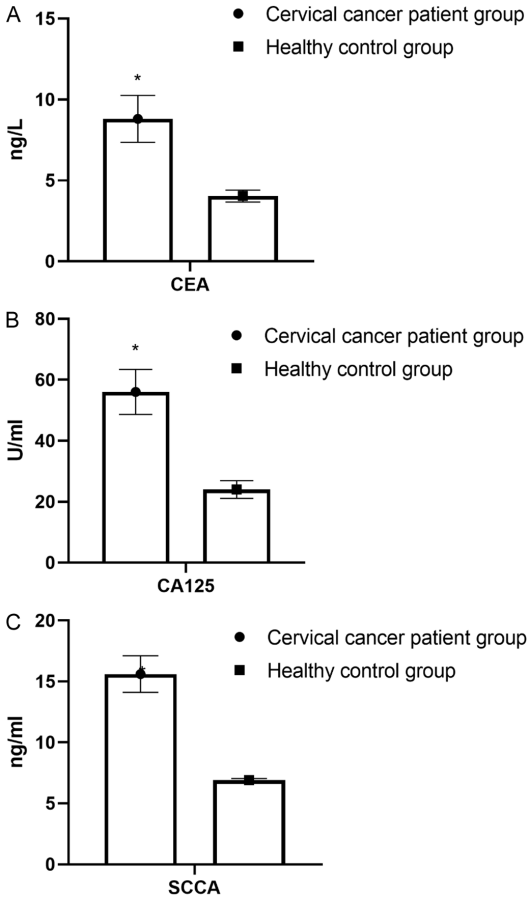

Figure 3. Comparison of peripheral blood tumor markers between the two groups. A: Comparison of the CEA level between the two groups; B: Comparison of the CA125 level between the two groups; C: Comparison of the SCCA level between the two groups. *P<0.05 for comparison between the healthy control group and the cervical cancer patient group. CEA: carcinoembryonic antigen; CA125: Cancer antigen 125; SCCA: squamous cell carcinoma antigen.

Comparisons of tumor markers CEA, CA125, and SCCA levels between the two groups

The study results demonstrated that the levels of tumor markers CEA, CA125, and SCCA in the serum of participants in the cervical cancer patient group were higher when compared to the healthy control group (all P<0.05). See **Figure 3**.

Comparison of Doppler ultrasound blood flow parameters between the two groups

The study results indicated that the peak systolic velocity (PSV) of participants was higher while the resistive index (RI) was lower in the

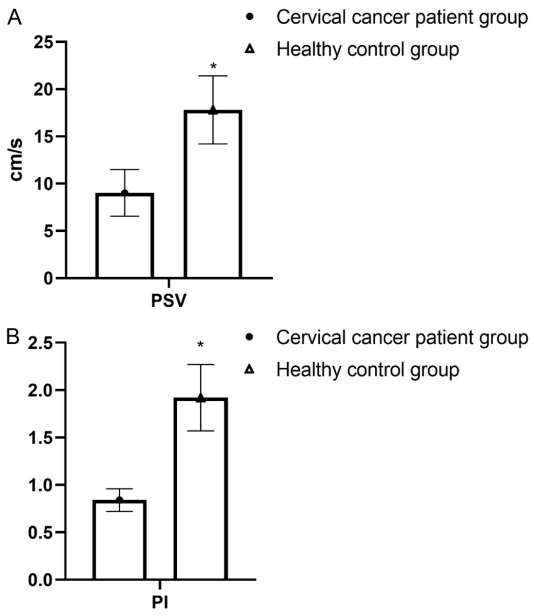

Figure 4. Comparison of blood flow-related indicators of patients between the two groups. A: Comparison of PSV between the two groups; B: Comparison of PI between the two groups. *P<0.05 for comparison between the healthy control group and the cervical cancer patient group. PSV: peak systolic velocity; PI: perfusion index.

cervical cancer patient group than those in the healthy control group (all P<0.05). See **Figure 4**.

Regression analysis of influencing factors for cervical cancer

Using the occurrence of cervical cancer as the dependent variable and differential influencing factors between the two groups as independent variables, a binary logistic regression model was fitted. The results obtained showed statistical significance (χ^2 = 350.117, P<0.05). Ultimately, a total of 20 influencing factors were included in the regression model, which were HPV testing, presence of reproductive system symptoms, dysmenorrhea, washing external genitalia before intercourse, passive smoking, duration of heating in winter, physical exercise, consumption of fried foods, vegetable intake, alcohol consumption, chili pepper consumption, HPV infection, IL-2, IL-4, TNF-α, CEA, CA125, SCCA, PSV and PI levels. See **Table 6**.

Discussion

Cervical cancer, as a malignant tumor that poses a serious threat to women's health, has sparked widespread concern in the medical community and profound reflection in society due to its varying incidence rates worldwide. The occurrence of cervical cancer is not due to a single factor but is the result of a complex interplay of various factors, hence we conducted this research exploring its risk factors [11-13].

Studies have indicated that women with a family history of cervical cancer are at a higher risk of developing the disease. The primary underlying mechanisms are as follows: genetic or epigenetic mutations can increase the risk of developing cervical cancer, primarily through immune surveillance, immune modulation, DNA repair, cellular metabolism, or other mechanisms that enhance the susceptibility to cervical cancer [14-16]. Thus, given the fact that all tumors have their own genetic foundations, researchers suggest that promoting genetic screening is of great importance for the early prediction of cervical cancer [17]. In addition, our research results demonstrated that patients with a family history of cancer had a higher cancer incidence rate as well, which is consistent with previous research conclusions [18].

Additionally, studies have shown that patients who have reproductive system symptoms or who have undergone reproductive system-related surgery or chemotherapy, have a higher incidence of cervical cancer. Among these, HPV infection, one of the reproductive system diseases, is the most significant factor, as it can disturb the stability of genes and promote abnormal proliferation, differentiation, and metastasis of tumor cells, facilitating the progression from low-grade CIN to high-grade CIN and even further development into CSCC. Infections such as bacterial vaginosis, trichomoniasis, and Chlamydia trachomatis may increase the lower reproductive tract's sensitivity to HPV infection. Moreover, individuals with dysmenorrhea often have varying degrees of underlying diseases or local infections [19]. The results of this study indicated that cervical cancer patients had a higher rate of HPV infection and reproductive tract infections than normal participants, corroborating previous research findings [20, 21]. Regarding menstrual cycles, although some studies suggested that a menstrual period exceeding 4 days was strongly associated with the occurrence of cer-

Table 6. Regression analysis of influencing factors for cervical cancer

Variable	*B*	*S.E.*	*Wald*	*P*	*OR*	*95% CI*
HPV Testing	3.412	0.220	240.532	<0.05	30.326	19.704-46.675
Presence of Reproductive System Symptoms	3.318	0.153	470.295	<0.05	27.605	20.453-37.258
Dysmenorrhea	3.276	0.146	503.480	<0.05	26.470	19.883-35.239
Washing External Genitalia Before Intercourse	3.154	0.336	88.114	<0.05	0.430	0.127-0.566
Passive Smoking	2.780	0.319	75.947	<0.05	16.119	8.626-30.122
Duration of Heating in Winter	2.346	0.288	66.355	<0.05	0.444	0.366-0.939
Physical Exercise	2.227	0.165	182.168	<0.05	0.272	0.101-0.812
Consumption of Fried Foods	2.109	0.152	192.516	<0.05	8.240	6.117-11.100
Vegetable Intake	2.071	0.123	283.498	<0.05	7.933	0.233-0.957
Alcohol Consumption	1.699	0.114	222.115	<0.05	5.468	4.373-6.838
Consumption of Chili Peppers	1.568	0.210	55.751	<0.05	4.797	3.178-7.240
HPV Infection	2.390	0.281	40.340	<0.001	38.662	35.334-85.085
IL-2	3.260	0.361	23.621	0.021	4.036	1.484-9.627
IL-4	2.571	0.342	15.830	0.030	2.203	1.036-8.772
TNF-α	1.323	0.428	13.391	0.028	3.003	1.223-4.118
CEA	1.871	0.511	12.634	0.011	5.760	2.104-14.532
CA125	1.324	0.624	4.847	0.019	4.097	1.129-15.476
SCCA	2.153	0.774	15.374	<0.001	5.350	2.454-14.084

Note: HPV: human papillomavirus; IL: interleukin; TNF-α: tumor necrosis factor-α; CEA: carcinoembryonic antigen; CA125: Cancer antigen 125; SCCA: squamous cell carcinoma antigen.

vical cancer, and thus a short menstrual period (<3 days) was a decreased risk factor for cervical cancer, this study did not reveal a potential relationship between menstrual cycle duration and the incidence of cervical cancer, which may be related to the small number of study subjects. Further research is needed to validate this conclusion.

Estrogen and progesterone receptors have been found in the cervical cancer tumor tissues, and due to the relative hormonal imbalance in menopausal women, along with the fact that menopausal women are generally older than non-menopausal women, their risk of developing cancers in their reproductive systems increases. Women with dysmenorrhea are at a higher risk of developing cervical cancer because their epithelial cells have shown increased sensitivity to various carcinogenic factors. Combined with dysmenorrhea-related cervical damage, this leads to abnormal changes in cervical epithelial cells (such as atypical hyperplasia or epithelial cell metaplasia), ultimately increasing the incidence of cervical cancer [22, 23].

Literature indicates that menopause may serve as a protective factor against cervical cancer. Research suggests that estrogen can influence the development of cervical cancer, and after menopause, the estrogen levels in the body decrease rapidly, thereby offering a protective effect. The potential correlation between pregnancy experiences and cervical cancer might be related to direct damage to the endometrium by surgical instruments during procedures [24, 25]. Previous studies have shown that cytokines are related to the occurrence and development of tumors. For example, the IL-2 levels in the serum of tumor patients are lower than healthy controls, and the IL-4 and TNF-α levels are lower as well than in healthy participants, which may be related to the imbalance between Th1 and Th2 homeostasis. Compared with healthy individuals, the homeostasis between Th1 and Th2 cytokines is disrupted in the tumorigenic microenvironment within tumor patients. Th1 cells produce TNF-α, IL-2, and IFN-γ, promoting cellular immunity and inflammation primarily mediated by phagocytes. Th2 cells produce IL-4, IL-6, and IL-10, leading to significant antibody effects and the accumulation of a large number of eosinophils, resulting in a decrease in phagocytic activities. These two indicators change when tumors occur. The results of this study showed chang-

es in these indicators as well in cervical cancer patients, which has been confirmed by similar studies. At the same time, previous studies have shown that CEA, CA125, and SCCA are of great significance in the early diagnosis of cervical cancer and may be related to the following mechanisms: CA125 is distributed in the endometrium and fallopian tubes. It is a high molecular-weight glycoprotein with antigenicity, positively correlated with the severity of cervical cancer in patients. SCCA belongs to a class of serine protease inhibitors that help diagnose and reflect the levels of cancer cells, which is closely associated with cervical cancer, with higher levels indicating a larger tumor cell area. CEA is a differentiation antigen, and the higher its differentiation level, the higher the carcinoembryonic antigen positivity rate. The results of this study also showed that the levels of CEA, CA125, and SCCA in the serum of cervical cancer patients were higher than those in healthy controls, further solidifying previous research conclusions. Finally, previous literature has confirmed that changes occur in the arterial blood flow of cervical cancer patients. This may be related to the fact that blood supply in the cervix comes from the cervical-vaginal vessels. However, the arterial diameter is relatively small, when the cervix undergoes cancerous changes, tumor cells stimulate the body to secrete a large number of angiogenic factors, generating a new vascular network to grow and metabolize. At this time, the vascular bed changes from a capillary bed with a small caliber and uniform distribution to a dilated, sinusoidal, immature, and disorderly distributed vessels, forming arteriovenous fistulas lacking a complete basement membrane, leading to a significant increase in blood flow and a noticeable acceleration of blood flow speed in the lesion tissue. Meanwhile, the results of this study showed that when examining the changes in cervical blood flow within the participants in both groups, the PSV from the Doppler ultrasound in cervical cancer patients was higher and the RI lower than those in the healthy controls, which are consistent with the results from previous research.

In summary, many factors are correlated with the occurrence and development of cervical cancer. In clinical practice, attention should be paid to the dissemination of related knowledge, in combination with various early detection methods, for diagnosing cervical cancer at the earliest time, thereby improving the treatment of this disease. However, this study has its limitations. It is a single-center study with only a small number of participants, thus larger sample sizes from multiple centers are necessary to further validate the conclusions of this study. Secondly, this study is a regional study, which may lead to certain biases in the results, and therefore subsequent multi-regional studies are needed to further refine the findings of this paper.

Disclosure of conflict of interest

None.

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