Original Article

A real-world research of cervical cancer screening in patients diagnosed with cervical cancer by loop electrosurgical excision procedure

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Background: Cervical cancer is highly prevalent globally, but is effectively prevented or even eliminated through early screening and human papillomavirus (HPV) vaccination. However, overall coverage of cervical cancer screening in developing countries is low.

Methods: A total of 191 patients diagnosed with cervical cancer after loop electrosurgical excision procedure (LEEP) were enrolled in this retrospective study from January 2013 to August 2019 in the West China Second University Hospital. Collected basic clinicopathological information about these patients and all cervical cancer screening results. Chi-square test was used for univariate analysis and Logistic regression was used for multivariate analysis (P<0.05 with meaning).

Results: The standard screening rate was only 20.9% (40/191). The results of univariate analysis showed that: age ≥40 years, number of miscarriages ≥2, mode of delivery as normal, cytological result as high-grade squamous intraepithelial lesion (HSIL), and cervical tissue biopsy result as cervical intraepithelial neoplasia (CIN)III were the high-risk factors for missed diagnosis after standard screening (P<0.05). The results of multivariate analysis showed that only the cytological result as HSIL was an independent risk factor for missed diagnosis of cervical cancer after standard screening (P=0.01). The HPV-negative rate and cervical biopsy negative rate of non-squamous cell carcinoma patients were higher than those of squamous cell carcinoma patients (27.3% *vs.* 1.7%, P=0.01; 33.3% *vs.* 7.5%, P=0.04).

Conclusions: Cytological results showed that HSIL was an independent risk factor for missed diagnosis of cervical cancer after standard screening. The accuracy of HPV detection and cervical biopsy in the diagnosis of non-squamous cell carcinoma is insufficient.

Keywords: Cervical cancer screening; cervical cancer; loop electrosurgical excision procedure (LEEP)

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Introduction

Background

Cervical cancer is the third most common cancer among women in the world, and its incidence is the highest among female genital malignancies. According to the World Health Organization (WHO) in 2019, estimates indicate that every year 569,847 women are diagnosed with cervical cancer and 311,365 die from the disease (1). At present, cervical cancer is one of the few gynecological malignancies that can be effectively prevented or even eliminated through early screening and human papillomavirus (HPV) vaccination. Over the past half century, the incidence and mortality of cervical cancer have been reduced by more than 50% globally through organized population-based screening programmes, as recommended by the International Agency for Research on Cancer (1-3). But the burden of cervical cancer in the developing country remains high.

Rationale and knowledge gap

In China, the total coverage rate of cervical cancer screening is less than 30% (3,4), and many cervical cancer patients are missed due to uneven distribution of medical resources, uneven level of medical staff, and irregular screening. At present, there is no report focusing on the evaluation of the implementation of standardized screening procedures for cervical cancer by medical personnel in China.

Highlight box

Key findings

- High-grade squamous intraepithelial lesion (HSIL) was an independent risk factor for missed diagnosis of cervical cancer after standard screening.

What is known and what is new?

- Screening can reduce cervical cancer incidence and mortality rates.
- This manuscript indicates the HSIL was an independent risk factor for missed diagnosis of cervical cancer after standard screening.

What is the implication, and what should change now?

- The diagnostic accuracy of human papillomavirus detection and cervical biopsy in non-squamous cell carcinoma is inadequate. In cervical cancer screening, we should comprehensively consider patients' own conditions and different screening results, provide personalized diagnosis and treatment for patients, and reduce the missed diagnosis and misdiagnosis of cervical cancer.

Objective

Understanding the challenges and successes in standard screening practices is crucial for addressing the persistently high burden of cervical cancer in China. By offering insights into the nuances of the screening process, this research seeks to enhance clinicians' comprehension and proficiency in standardized cervical cancer screening. Ultimately, the study aspires to contribute to the mitigation of missed diagnoses and the improvement of overall cervical cancer outcomes. It provides some reference for evaluating the master and implementation of standard cervical cancer screening by gynecologists in our province. This study summarized the experience of cervical cancer screening in order to improve clinicians' understanding and level of standardized cervical cancer screening and provide help to minimize the missed diagnosis of cervical cancer. We present this article in accordance with the STROBE reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-23-31/rc).

Methods

We performed a retrospective analysis of all the patients with cervical cancer who were diagnosed by loop electrosurgical excision procedure (LEEP) at the West China Second University Hospital between January 2013 and August 2019. Through case screening, a total of 191 eligible patients were collected. The clinicopathological data included basic clinical characteristics: age, age of first sexual life, menopause, history of pregnancy, the number of abortions, delivery mode, clinical symptoms, and histology. Cervical cancer screening tests performed before LEEP included cytology results, HPV test results, colposcopy results, biopsy results, and the level of hospital in which patients are screened. Combined with cervical cancer screening criteria, the standard screening rate, risk factors for missed diagnosis, and clinicopathological characteristics were analyzed and compared.

Statistical analysis

Clinicopathologic characteristics were evaluated using the basic descriptive statistics. SPSS 26.0 software was used for statistical analysis of the relevant data between different groups. Descriptive statistics, including

Table 1 Demographic characteristics of patients (n=191)

Parameters	N (%)
Age (years)	
21–29	7 (3.7)
30–65	182 (95.3)
>65	2 (1.0)
Residence	
Rural	107 (56.0)
City	84 (44.0)
Age of first sexual life (years)	
<21	77 (40.3)
21–25	104 (54.5)
26–30	9 (4.7)
>30	1 (0.5)
Menopause	
Yes	36 (18.8)
No	155 (81.2)
Gravidity (times)	
0	5 (2.6)
1–2	43 (22.5)
3–4	81 (42.4)
5–6	40 (20.9)
>6	22 (11.5)
The number of abortions (times)	
0	16 (8.4)
1–2	94 (49.2)
3–4	52 (27.2)
5–6	24 (12.6)
>6	5 (2.6)
Delivery way	
Eutocia	137 (71.7)
Caesarean[†]	36 (18.8)
Both	10 (5.2)
Symptoms	
Asymptomatic[‡]	64 (33.5)
Vaginal bleeding after intercourse[§]	97 (50.8)
Irregular vaginal bleeding[¶]	17 (8.9)
Leucorrhea	9 (4.7)
Vaginal discharge	4 (2.1)
Histology	
Squamous cell carcinomas	161 (84.3)
Adenocarcinoma	27 (14.1)
Adenosquamous carcinoma	3 (1.6)
The hospital level	
Third-grade A	104 (54.5)
Second-grade to third-grade B	71 (37.2)
Second-grade hospitals and below	16 (8.4)

[†], there were 183 previous births; [‡], some patients had multiple; [§], clinical symptoms at the same; [¶], time.

number (%) for categorical variables and measures such as mean and standard deviation (SD) for continuous variables, were utilized to summarize the basic clinicopathological characteristics of the study population. The chi-square test was employed for Categorical variables. *T*-test was used to compare the mean of two samples in accordance with normal distribution; non-parametric test was used for univariate analysis when the sample number did not conform to normal distribution; logistic regression analysis was used for multivariable analysis. All the above statistical analyses used α=0.05 as the test level, all analyses had a power >80% with P<0.05 implying statistical significance.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of West China Second Hospital (approved ethics number: 20200076) and individual consent for this retrospective analysis was waived.

Results

Between January 2013 and August 2019, there were 191 patients included in the final analysis. The demographic characteristics of the included patients are shown in *Table 1*. The mean age of all participants was 42.4 years (range, 23–71 years). The mean age of first sexual life was 21.5 years (range, 16–37 years), the mean gravidity was 3.8 times, and the average number of induced abortions was 2.4 times.

The relevant screening indicators were collected,

Table 2 Cervical cancer screening results (n=191)

Parameters	N (%)
Cytology	
Absent	107 (56.0)
Normal	17 (8.9)
ASCUS	15 (7.9)
ASCUS-H	5 (2.6)
LSIL	7 (3.7)
HSIL	36 (18.8)
AGC	4 (2.1)
HPV	
Absent	122 (63.9)
Positive	65 (34.0)
Negative	4 (2.1)
HPV types (n=65)	
16	52 (80.0)
18	5 (7.7)
16+18	2 (3.1)
Non-16/18 high-risk	6 (9.2)
Colposcope	
Absent	132 (69.1)
Had done	59 (30.9)
Biopsy	
Absent	113 (59.2)
Normal	7 (3.7)
CINI	8 (4.2)
CINII	14 (7.3)
CINIII	48 (25.1)
Acuteness wet wart	1 (0.5)

ASCUS, atypical squamous cells of undetermined significance; ASCUS-H, ASCUS: cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cell; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia.

including cytology, HPV examination, colposcopy, biopsy, hospital grade and other specific conditions, as shown in *Tables 2*,*3*.

According to the 2013 guideline for cervical lesion screening of the American Society for Colposcopy and Cervical Pathology (ASCCP), the overall screening status of this study was as follows: only 40 (20.9%) of the 191 patients were screened according to the standard "three-step" method (54.5% of the patients were screened in third-grade A hospitals, 37.2% in second-grade to third-grade B hospitals, and 8.4% in second-grade hospitals and below), as shown in *Table 1*. Among the 151 cases screened not standard, 30.9% (59/191) of the patients did not receive any screening, and 8.9% (17/191) underwent LEEP simply because of irregular vaginal bleeding. In total, 8.9% (17/191) underwent LEEP only after cytology examination, 5.2% (10/191) only after HPV examination, 1.6% (3/191) only after colposcopter examination, and 7.9% (15/191) only after biopsy, more information can be found at Table S1.

Table 3 Statistics of screening results (n=191)

Parameters	Standard screening, n (%)	Non-standard screening, n (%)
21–29 years	1 (0.5)	6 (3.1)
30–65 years	39 (20.4)	73 (38.2)
Total	40 (20.9)	151 (79.1)

In this study, there were seven patients aged 21–29 years old, among whom three patients directly received LEEP treatment due to vaginal bleeding after intercourse without any screening. Two cases underwent cervical biopsy directly. One patient underwent HPV test and cervical biopsy. One case was screened according to the screening standard. Among the 182 patients aged 30–65 years, 56 (29.3%) received LEEP directly only because of vaginal bleeding after intercourse or cervical erosion, among which 34 (18.7%) received LEEP in third-grade A hospitals. There were 17 cases (8.9%) that received LEEP after cytological examination alone, among which three cases were normal cytological results, two cases of low-grade squamous intraepithelial lesion (LSIL), six cases of high-grade squamous intraepithelial lesion (HSIL), four cases of atypical squamous cells of undetermined significance (ASCUS) and two cases of ASCUS: cannot exclude HSIL (ASCUS-H). LEEP was performed in 10 cases (5.2%) after HPV test alone, among which seven cases were HPV16 (+), 1 case was HPV (18+), and two cases were HPV-negative. Three cases underwent LEEP immediately after colposcopy examination. Among the 15 (7.9%) patients who underwent LEEP after biopsy alone, two had normal biopsy results, 1 had biopsy results of condyloma acuminatum, and the

Table 4 Univariate analysis of the influence factors of missed diagnosis after standard screening

Variables	Not misdiagnosis, n (%)	Misdiagnosis, n (%)	χ^2	P
Age (years)			6.373	0.01*
<40 (n=31)	21 (67.7)	10 (32.3)		
≥40 (n=49)	19 (38.8)	30 (61.2)		
Menopause			1.385	0.23
Yes (n=40)	35 (87.5)	5 (12.5)		
No (n=40)	31 (77.5)	9 (22.5)		
Gravidity (times)			2.498	0.11
<4 (n=45)	26 (57.8)	19 (42.2)		
≥4 (n=35)	14 (40.0)	21 (60.0)		
The number of abortions (times)			4.114	0.04*
<2 (n=35)	22 (62.9)	13 (37.1)		
≥2 (n=45)	18 (40.0)	27 (60.0)		
Production method			5.909	0.01*
Caesarean (n=27)	19 (70.4)	8 (29.6)		
Natural birth (n=55)	23 (41.8)	32 (58.2)		
Age of first sexual life (years)			2.581	0.10
<20 (n=18)	6 (33.3)	12 (66.7)		
≥20 (n=62)	34 (54.8)	28 (45.2)		
Cytology result was HSIL			4.650	0.03*
No (n=30)	17 (56.7)	13 (43.3)		
Yes (n=49)	23 (46.9)	26 (53.1)		
Results of biopsy			4.381	0.03*
< CINIII (n=29)	19 (65.5)	10 (34.5)		
CINIII (n=51)	21 (41.2)	30 (58.8)		

*, indicates a significant difference at the 0.05 level (two-tailed). HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; AGC, atypical glandular cell.

remaining 12 had precancerous lesions of cervical cancer. Thirty-nine cases (20.4%) were screened according to the standard screening procedure.

In this study, there were 40 cases of cervical cancer patients who were screened according to the standard screening procedure but still missed diagnosis. The author intended to analyze the related factors of missed diagnosis in screening and compare their clinicopathological data with the clinicopathological data of patients who were not missed diagnosis in the standard screening during the same period. Univariate analysis showed that menopause, number of pregnancies, and age of first sexual activity were not associated with missed cervical cancer diagnosis after standard screening (P>0.05). The rate of missed diagnosis of cervical cancer after standard screening was higher than that of the comparison group with the age ≥40 years old, the number of abortions ≥2 times, the delivery mode was natural, the cytology result was HSIL, and the cervical biopsy result was cervical intraepithelial neoplasia (CIN)III, and the difference was statistically significant (*Table 4*). The results of multivariate analysis showed that cytology result of HSIL was an independent risk factor for missed diagnosis, with statistical significance (P=0.01, *Table 5*).

In this group, 30 cases were non-squamous cell

Table 5 Multivariable logistic regression analysis of the influence factors of missed diagnosis after standard screening

Variables	OR	95% CI	P
Age ≥40 years	1.395	1.636–2.725	0.56
Abortion ≥2 times	0.23	0.011–4.838	0.34
Natural birth	3.834	0.043–2.897	0.79
The cytology was HSIL	17.00	1.964–147.164	0.01*
Biopsy was CINIII	2.61	5.897–23.872	0.65

*, indicates a significant difference at the 0.05 level (two-tailed). OR, odds ratio; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia.

carcinoma, including 27 adenocarcinoma and three adenosquamous cell carcinomas. There was no difference in the distribution of clinical symptoms and cytological results between cervical squamous cell carcinoma and non-squamous cell carcinoma (P>0.05). The negative rate of HPV in non-squamous cell carcinoma patients was higher than that in squamous cell carcinoma patients (27.3% *vs.* 1.7%; 33.3% *vs.* 7.5 %), the difference was statistically significant (P=0.01; P=0.04; Table S2).

Discussion

In this study, we collected 191 patients who were pathologically diagnosed with cervical cancer after LEEP surgery admitted to our hospital, and nearly 64 cases (33.5%) were found to have cervical lesions due to physical examination. We further analyzed their clinicopathological features and summarized our experience, hoping to standardize the screening strategy of doctors, improve the screening level, and reduce the missed diagnosis.

In Europe, the United States, and other developed countries, the incidence and mortality of cervical cancer have been significantly improved after the implementation of the "three-step" screening strategy, especially after the prevention of cervical cancer vaccine (5). However, in developing countries, including China, the incidence of cervical cancer is still high due to economic underdevelopment, weak public awareness, and insufficient medical resources. In addition, many cases of cervical cancer are missed due to irregular screening and inadequate doctors. According to data released by the International Agency for Research on Cancer in 2019, there are about 106,430 new cases of cervical cancer and 47,739 deaths per year in China (5). In recent years, with the popularity of LEEP in the diagnosis and treatment of cervical lesions, many patients were diagnosed as cervical cancer by LEEP without standardized screening. However, up to now, there has been no large sample study on the diagnosis of cervical cancer after LEEP. Early studies showed that 2.5% to 17.93% were diagnosed with cervical cancer after LEEP (6-8). In China, it was reported that 5.98% of patients who received LEEP surgery for cervical lesions were diagnosed with invasive cervical cancer. This study collected 191 patients admitted to our hospital who were pathologically diagnosed as cervical cancer after LEEP surgery, analyzed their clinicopathological characteristics, and summarized their experience, hoping to standardize the screening strategy of physicians, improve the screening level, and reduce the missed diagnosis.

Clinical features

The onset of cervical cancer is insidious, and its early manifestations are vaginal bleeding after intercourse or no obvious clinical symptoms, which is easily ignored by the majority of women (8,9). In this study, 191 patients with cervical cancer were found to have no obvious symptoms, and 64 (33.5%) were found to have cervical lesions only due to physical examination. Therefore, it is necessary to pay attention to patient education and improve women's awareness of cervical cancer screening. Relevant literature indicates that 20% of cervical squamous cell carcinoma patients have smooth cervix and 14% suffer from cervical erosion. The cervix was smooth in 27% of patients with cervical adenocarcinoma and cervical erosion in 16% of patients (10). Cervical erosive changes are similar to the ectopic changes in the physiologic scale columnar epithelium. Cervical cancer screening is needed to determine the presence of cervical lesions and further determine whether follow-up treatment is needed (11). In this study, the cervix of 48 patients (25.1%) was smooth, 108 (56.5%) had cervical erosion changes, and the cervix of the remaining patients was characterized by nazerian cyst

of cervix, cervical hypertrophy, etc. These lesions cannot be diagnosed by the naked eye of the doctor alone. Our results once again suggest that clinicians should screen these lesions according to the guidelines and according to the individual conditions of patients to avoid the occurrence of missed diagnosis and misdiagnosis.

Research by Kassa *et al.* (12) has shown that western women who start having sex before the age of 15 years have a 5.6-fold increased risk of cervical cancer. The average age at which Chinese women have sex for the first time is still lacking in natural population data, and some studies suggest that it is about 17 years later than that of western women. Of the 191 patients with cervical cancer in our study, 181 had their first sex at less than 25 years of age, and 77 of them were less than 20 years of age, which also to some extent demonstrated that early sexual behavior increased the risk of cervical cancer. Women with cervical injuries, including cervical surgery, induced abortion, and natural childbirth with a history of cervical laceration, are at increased risk of cervical cancer (12). Makuza *et al.* (13) have shown that older age at first pregnancy or reduced sexual activity (singledom, divorce, and widowhood) are protective factors for cervical cancer. In this study, only 5 (2.6%) of 191 patients with cervical cancer had no history of pregnancy, which was consistent with the results of previous studies. It is suggested to strengthen publicity through various channels, improve the sexual health education of young people, reduce the sexual behavior in young age, and enhance the awareness of cancer prevention by choosing effective contraceptive measures after adulthood.

Cervical cancer screening

The cervical cancer prevention and screening system in the United States has been established for more than 50 years, and the screening coverage rate has reached more than 85%, reducing the incidence of the disease by more than 50% (14). Nagendiram *et al.* (15) reported that by 2017, the cervical cancer screening coverage rate in Australia reached 54–56%, and the HPV vaccine vaccination reduced the mortality rate of cervical cancer by more than half. Among them, 90% of cervical cancer patients were due to insufficient screening or never screening. Studies have shown that only 20% of Chinese women have ever been screened for cervical cancer. The national average rate of cervical cancer screening in urban areas is 29.1%, of which 31.3% is in eastern cities with a high level of economic development, while only 16.9% is in rural areas (16). Di *et al.* (17) reported that the cervical cancer screening coverage rate in China was only 19% in the 35–65 years age group.

The above data fully indicates that there is a serious shortage of cervical cancer screening among Chinese women. In addition, there is no relevant research on the proportion of screened women who meet the standard screening. In this study, 151 (79%) cases were screened inappropriately. Only 1 (0.6%) case aged 21–29 years and only 39 (20.4%) cases aged 30–65 years were screened according to the standard screening procedure. The results of this study suggest to some extent that the standard rate of cervical cancer screening methods used by medical personnel in China is low. In order to reduce the incidence of cervical cancer, the first step is to increase women's active participation in cervical cancer screening. Education on cervical cancer and the new national vaccination programme could be strengthened through school advertising campaigns and by general practitioners (15). In addition, the standard services of screening personnel should be strengthened. If necessary, an inspection team and a technical guidance team can be set up to timely correct the problems existing in the screening, so as to provide good technical support for the standard cervical cancer screening and reduce the missed diagnosis of cervical cancer. Since 2003, at least one million women older than 30 years of age have been screened for cervical cancer by a combination of HPV and cytology every 3 years at Kaiser Northern California Health Care Facility, and 907 (0.82%) cases of cervical cancer patients have received standard cervical cancer screening. The incidence of false-negative co-test/sampling errors, false-negative histological diagnosis, and treatment failure was 11.2%, 9.0%, and 4.3%, respectively, in all cancer patients after screening (18). In this study, 12.5% of the standard screening patients were false-negative for cytology and HPV screening, and 15% were false-negative for biopsy histological diagnosis, which was roughly consistent with previous studies. The problems related to missed diagnosis in the specific screening process will be discussed from cytology, HPV test, colposcopy, and biopsy.

Pap smear and liquid-based cytology are the common methods for cervical cancer screening at present, but they have these two characteristics: high specificity and low sensitivity (19). Musa *et al.* (20) pointed out that in the screening of high-grade cervical lesions by cervical cytology, the positive predictive value and negative predictive value of sensitivity and specificity with HSIL as the cut-off point were 30.5%, 96.0%, 78.0%, and 74.8%, respectively. Collected the screening results of 30 patients with accidental cervical cancer, among which the cytological false

negative rate reached 53.33% (6). In this study, 84 patients underwent cytological examination, which contained 17 (20.2%) cases with normal results, 15 (17.9%), 5 (5.9%), 7 (8.3%), 36 (42.9%), 4 (4.8%) cases with results of ASCUS, ASCUS-H, LSIL, HSIL, and atypical glandular cell (AGC), respectively. Other study showed that cytological results ≥ ASCUS-H were risk factors for missed diagnosis of cervical cancer (21). Multivariate analysis in this study showed that HSIL was an independent risk factor for missed diagnosis of cervical cancer after standard screening. It can be seen that the direct diagnostic accuracy of cytology is greatly affected by human factors, such as unsatisfactory specimen sampling by clinicians, failure of brush to reach the lesion site during sampling, insufficient sampling, and missed diagnosis due to lack of experience of pathologists. Therefore, in clinical work, even if the cytological results are normal or suggest low-grade lesions, the next diagnosis and treatment plan should be comprehensively analyzed in combination with the actual situation of patients.

Persistent infection of high-risk HPV viruses is the main cause of cervical prelesions and cervical cancer. HPV 16 and 18 cause 70% of cervical cancer cases worldwide, and about 85% of cervical cancer in China is associated with the infection of these two subtype (22). In China, the proportion of cervical cancer patients infected with high-risk HPV was 90.8%, and the proportion of cervical cancer patients infected with high-risk HPV in the northwest and southwest regions was 89.35% and 81.07%, respectively. The five subtypes with the highest incidence of high-risk HPV infection were 16, 18, 58, 53, and 33, respectively (23). Li *et al.* showed that 9.4% of cervical cancer patients were negative for HPV (22). Rodríguez-Carunchio *et al.* (24) pointed out that 10.2% of cervical cancer patients were negative for HPV by HC2, suggesting that HPV-negative patients are still at risk of cervical cancer. In this study, 69 cases were tested for HPV typing, of which 59 (85.51%) were positive for type 16 or 18, and 6 were positive for non-16/18 high-risk type, which was consistent with the distribution of high-risk HPV infection in China. HPV test was negative in four patients, including three adenocarcinomas and one squamous cell carcinoma. Due to the high sensitivity of HPV detection, but low specificity, it is not only necessary to regulate the shunt of HPV-positive patients in clinical work, but also pay attention to the diagnosis and treatment of negative patients, and be alert to HPV-negative cervical cancer patients.

It is difficult to distinguish early cervical cancer and high-grade cervical lesions by naked eye alone, but direct biopsy has certain chance and blindness. Through colposcope examination, the cervix can be visually visualized, and the nature, type, location, and scope of cervical lesions can be observed through acetic acid white test and iodine test to guide cervical biopsy and reduce the rate of missed diagnosis of cervical lesions. Therefore, colposcopy has occupied the bridge position of cervical cancer screening. No matter what screening plan is adopted, if the results of screening are abnormal, clinicians should refer to colposcopy for examination according to specific conditions, and biopsy is necessary. However, in different studies, the diagnostic value of colposcopy is not consistent. In recent years, some studies have pointed out that colposcopy has the disadvantages of low specificity and high sensitivity in diagnosing cervical lesions (25). Accurate colposcopy images can accurately diagnose cervical lesions with a rate of 52–66% (26,27). The study (28) found that the accuracy rate of colposcopic biopsy in diagnosing high-grade cervical lesions was 61.6%, while the rate of missed diagnosis of cervical cancer was as high as 10%. Müller *et al.* (26) showed that the accuracy of biopsy results under colposcopy was 90.7% for women under 30 years old, and 72.1% for women over 50 years old.

In this study, 59 patients underwent colposcopy biopsy and 19 patients underwent cervical biopsy with naked eyes. Normal biopsy results were found in seven cases, accounting for 9%. Data from the real world show that colposcopy is affected by many factors. The quality of colposcopy image, the number of biopsy specimens, and the lesion area of the cervix are related factors that affect the accuracy of colposcopy diagnosis. How to improve the level of understanding of colposcope doctors and reduce the missed diagnosis is worthy of further research (29,30). How to improve the understanding of colposcopy doctors and reduce missed diagnosis is worth further study. Clinically, if the results of colposcopy are not satisfactory, patients should have cervical curettage to reduce the rate of missed diagnosis of cervical cancer.

Screening for non-squamous cell carcinoma

Studies have shown that effective screening significantly reduces the incidence of cervical squamous cell carcinoma, not adenocarcinoma (30-32). The incidence of adenocarcinoma is much lower than that of squamous cell carcinoma, accounting for about 7–17% of all cervical malignancies (33,34). The proportion of cervical

adenocarcinoma has increased in recent years, which is associated with a significant decrease in the incidence of cervical squamous cell carcinoma and only a slight decrease, stable, and even increase in the absolute incidence of adenocarcinoma (15,32). Worldwide, data on current cervical adenocarcinoma screening practices are very limited. To date, only a few small retrospective studies have examined cytology, HR-HPV testing, and their combined use in cervical adenocarcinoma screening, but their results have been inconsistent. Pak *et al.* (34) conducted a case-control study of 188 patients with adenocarcinoma and squamous cell carcinoma, and the results showed that cytological results of 5.6% of patients with adenocarcinoma were false negative, higher than those with squamous cell carcinoma (1.3%). In this study, the false negative rate of cytology in non-squamous cell carcinoma patients was 13.3%, which was higher than that in previous studies, which may be related to the small sample size of this study, different hospital grades, and uneven quality of cytology screening. However, the above data still indicate that cytology has certain limitations in screening non-squamous cell carcinoma.

In addition, studies have shown that the correlation between cervical adenocarcinoma and HPV infection is lower than that of cervical squamous cell carcinoma, and the positive rate of HPV in adenocarcinoma screening is 66.7% to 77.8% (35). Adenocarcinoma is a heterogeneous population with different histological subtypes, which have strong, weak, or no correlation with HPV infection. The results showed that the HPV-positive rate of different subtypes of cervical cancer was different: the HPV-positive rate of neuroendocrine carcinoma was 100%, adenosquamous carcinoma was 88.2%, micropartial adenocarcinoma was 51.2%, clear cell adenocarcinoma and serous adenocarcinoma were 50%, and endometrioid adenocarcinoma was 33.3% (35). Li *et al.* (36) showed that the HPV-negative rate was 8.12% in squamous cell carcinoma patients, while the HPV-negative rate was higher in non-squamous cell carcinoma patients: 25% for adenocarcinoma, 15.12% for adenosquamous cell carcinoma, 75% for clear cell carcinoma, 33.33% for micropartial adenocarcinoma and 50% for adenoid basal cell carcinoma. In this study, the negative rate of HPV in non-squamous cell carcinoma patients was 27.3%, higher than that in squamous cell carcinoma patients (1.7%). New kits or second-generation sequencing technology should be developed for in-depth sequencing. Large sample studies are needed to provide a better alternative for screening for non-squamous cell carcinoma.

This study shows that HSIL is an independent risk factor for missed diagnosis of cervical cancer after standard screening. Physicians are warned that HPV testing and cervical biopsy have insufficient diagnostic accuracy for non-squamous cancers, and that in cervical cancer screening, patients' own conditions and different screening results should be taken into account in order to provide personalized treatment for patients, and to reduce the leakage and misdiagnosis of cervical cancer. However, this study is a retrospective study, the data sources are hospital medical record system and outpatient medical records, telephone follow-up, etc., and the preliminary screening results are from hospitals of different levels, which are deficient in completeness, accuracy, and objectivity to a certain extent. However, the above results can still prompt us that at present, medical staff have a clear lack of knowledge of the standard cervical cancer screening guidelines, which need to strengthen learning and enhance awareness. Meanwhile, this study only collected cases from the same center, which is slightly unrepresentative, but it is important for the development of cervical cancer in local women.

Conclusions

In conclusion, this study once again emphasizes the importance of screening for cervical cancer. Meanwhile, we found that HSIL was an independent risk factor for missed diagnosis of cervical cancer after standard screening. The accuracy of HPV testing and cervical biopsy in the diagnosis of non-squamous cancer was insufficient. Therefore, the results of this study will provide new ideas for the prevention, diagnosis, and treatment of cervical cancer in the near future.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gpm.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm-23-31/coif). R.Y. serves as an unpaid editorial board member of *Gynecology and Pelvic Medicine* from June 2022 to May 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of West China Second Hospital (approved ethics number: 20200076) and individual consent for this retrospective analysis was waived.

References

1. Bedell SL, Goldstein LS, Goldstein AR, et al. Cervical Cancer Screening: Past, Present, and Future. Sex Med Rev 2020;8:28-37.
2. Popadiuk C. Cervical Cancer Screening in Canada. J Obstet Gynaecol Can 2019;41 Suppl 2:S177-80.
3. Vaccarella S, Franceschi S, Engholm G, et al. 50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence. Br J Cancer 2014;111:965-9.
4. Srisomboon S, Tantipalakorn C, Charoenkwan K, et al. Cervical Screening Results Leading to Detection of Adenocarcinoma in Situ of the Uterine Cervix. Asian Pac J Cancer Prev 2019;20:377-82.
5. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
6. Xiang L, Li J, Yang W, et al. Conization Using an Electrosurgical Knife for Cervical Intraepithelial Neoplasia and Microinvasive Carcinoma. PLoS One 2015;10:e0131790.
7. Bonardi R, Cecchini S, Grazzini G, et al. Loop electrosurgical excision procedure of the transformation zone and colposcopically directed punch biopsy in the diagnosis of cervical lesions. Obstet Gynecol 1992;80:1020-2.
8. Gunasekera PC, Phipps JH, Lewis BV. Large loop excision of the transformation zone (LLETZ) compared to carbon dioxide laser in the treatment of CIN: a superior mode of treatment. Br J Obstet Gynaecol 1990;97:995-8.
9. Castillo M, Astudillo A, Clavero O, et al. Poor Cervical Cancer Screening Attendance and False Negatives. A Call for Organized Screening. PLoS One 2016;11:e0161403.
10. Qin WY, Guan CN, Xu ZM, et al. Analysis of clinical characteristics of 854 patients with thyroid cancer. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2019;33:718-21.
11. Lowe B, Kobayashi L, Lorincz A, et al. HPV genotype detection using hybrid capture sample preparation combined with whole genome amplification and multiplex detection with Luminex XMAP. J Mol Diagn 2010;12:847-53.
12. Kassa RT. Risk factors associated with precancerous cervical lesion among women screened at Marie Stops Ethiopia, Adama town, Ethiopia 2017: a case control study. BMC Res Notes 2018;11:145.
13. Makuza JD, Nsanzimana S, Muhimpundu MA, et al. Prevalence and risk factors for cervical cancer and pre-cancerous lesions in Rwanda. Pan Afr Med J 2015;22:26.
14. Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. Minerva Ginecol 2019;71:313-20.
15. Nagendiram A, Bidgood R, Banks J, et al. Knowledge and perspectives of the new National Cervical Screening Program: a qualitative interview study of North Queensland women-'I could be that one percent'. BMJ Open 2020;10:e034483.
16. Wang B, He M, Chao A, et al. Cervical Cancer Screening Among Adult Women in China, 2010. Oncologist 2015;20:627-34.

17. Di J, Rutherford S, Chu C. Review of the Cervical Cancer Burden and Population-Based Cervical Cancer Screening in China. Asian Pac J Cancer Prev 2015;16:7401-7.
18. Castle PE, Kinney WK, Cheung LC, et al. Why does cervical cancer occur in a state-of-the-art screening program? Gynecol Oncol 2017;146:546-53.
19. Catarino R, Petignat P, Dongui G, et al. Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices. World J Clin Oncol 2015;6:281-90.
20. Musa J, Achenbach CJ, O'Dwyer LC, et al. Effect of cervical cancer education and provider recommendation for screening on screening rates: A systematic review and meta-analysis. PLoS One 2017;12:e0183924.
21. Banila C, Lorincz AT, Scibior-Bentkowska D, et al. Clinical performance of methylation as a biomarker for cervical carcinoma in situ and cancer diagnosis: A worldwide study. Int J Cancer 2022;150:290-302.
22. Li K, Li Q, Song L, et al. The distribution and prevalence of human papillomavirus in women in mainland China. Cancer 2019;125:1030-7.
23. Peng RR, Li HM, Chang H, et al. Prevalence and genotype distribution of cervical human papillomavirus infection among female sex workers in Asia: a systematic literature review and meta-analysis. Sex Health 2012;9:113-9.
24. Rodríguez-Carunchio L, Soveral I, Steenbergen RD, et al. HPV-negative carcinoma of the uterine cervix: a distinct type of cervical cancer with poor prognosis. BJOG 2015;122:119-27.
25. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol 2011;12:663-72.
26. Müller K, Soergel P, Hillemanns P, et al. Accuracy of Colposcopically Guided Diagnostic Methods for the Detection of Cervical Intraepithelial Neoplasia. Geburtshilfe Frauenheilkd 2016;76:182-7.
27. Kyrgiou M, Mitra A, Arbyn M, et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database Syst Rev 2015;2015:CD008478.
28. Li H, Li L, Sun J, et al. Value of TCT combined with serum CA153 and CA50 in early diagnosis of cervical cancer and precancerous lesions. Pak J Med Sci 2022;38:1471-6.
29. Fan A, Zhang L, Wang C, et al. Analysis of clinical factors correlated with the accuracy of colposcopically directed biopsy. Arch Gynecol Obstet 2017;296:965-72.
30. Manley KM, Simms RA, Platt S, et al. Unsatisfactory colposcopy: clinical decision-making in conditions of uncertainty. BMC Med Inform Decis Mak 2017;17:125.
31. Pirog EC. Cervical Adenocarcinoma: Diagnosis of Human Papillomavirus-Positive and Human Papillomavirus-Negative Tumors. Arch Pathol Lab Med 2017;141:1653-67.
32. Xie F, Zhang L, Zhao D, et al. Prior cervical cytology and high-risk HPV testing results for 311 patients with invasive cervical adenocarcinoma: a multicenter retrospective study from China's largest independent operator of pathology laboratories. BMC Infect Dis 2019;19:962.
33. Chen W, Sun H, Molijn A, et al. The Variable Characteristics of Human Papillomavirus in Squamous Cell Carcinoma and Adenocarcinoma of Cervix in China. J Low Genit Tract Dis 2018;22:355-61.
34. Pak SC, Martens M, Bekkers R, et al. Pap smear screening history of women with squamous cell carcinoma and adenocarcinoma of the cervix. Aust N Z J Obstet Gynaecol 2007;47:504-7.
35. Pirog EC, Lloveras B, Molijn A, et al. HPV prevalence and genotypes in different histological subtypes of cervical adenocarcinoma, a worldwide analysis of 760 cases. Mod Pathol 2014;27:1559-67.
36. Li K, Yin R, Wang D, et al. Human papillomavirus subtypes distribution among 2309 cervical cancer patients in West China. Oncotarget 2017;8:28502-9.

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Supplementary

Table S1 Statistics of screening results (n=191)

Parameters	N (%)
Standard screening	
21–29 years	
Cytology +HPV test + colposcopy + biopsy	1 (0.5)
30–65 years	
Cytology + colposcopy + biopsy	12 (6.3)
HPV test + colposcopy + biopsy	5 (2.6)
Cytology + HPV test + colposcopy + biopsy	22 (11.5)
Total	40 (20.9)
Non-standard screening	
21–29 years	
No screening was performed	3 (1.6)
Only biopsy	2 (1.1)
HPV test + biopsy	1 (0.5)
30–65 years	
No screening was performed	56 (29.3)
Only cytology	17 (8.9)
Only HPV test	10 (5.2)
Only colposcopy	3 (1.6)
Only biopsy	15 (7.9)
The rest non-standard screenings	42 (22.0)
>65 years	
Only biopsy	2 (1.0)
Total	151 (79.1)

HPV, human papillomavirus.

Table S2 Comparison between squamous cell carcinoma and non-squamous cell carcinoma cases

Parameters	Squamous carcinoma, n (%)	Non-squamous carcinoma, n (%)	χ^2	P
Symptoms	n=161	n=30	0.197	0.65
Present	106 (65.8)	21 (70.0)		
Absent	55 (34.2)	9 (30.0)		
Cytological results (n=84)	n=70	n=10	0.015	>0.99
< HSIL	38 (54.3)	6 (60.0)		
HSIL	32 (45.7)	4 (40.0)		
HPV result (n=69)	n=58	n=11	2.134	0.01*
Positive	57 (98.3)	8 (72.7)		
Negative	1 (1.7)	3 (27.3)		
Biopsy (n=78)	n=67	n=9	3.241	0.04*
Negative	5 (7.5)	3 (33.3)		
Positive	62 (92.5)	6 (66.7)		

*, indicates a significant difference at the 0.05 level (two-tailed). HPV, human papillomavirus.

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