·Gynecologic Oncology·

A three-year cervical cancer screening in a rural area of China with acetic acid/Lugol's iodine

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[Abstract] Background and Objective: In China, there has been no established national program for cervical cancer prevention, the screening methods and experiences are especially deficient in the rural areas. The aim of this paper is to evaluate the effects of acetic acid/Lugol's iodine (VIA/VILI) used for screening of cervical cancer and pre-cancerous lesions in a rural area of China by analyzing the large-scale population-based screening data from the demonstration site. **Methods:** Women aged 30–59 years from Xiangyuan County in Shanxi Province were recruited for cervical cancer screening from 2005 to 2007. VIA/VILI was the primary screening method followed by colposcopy if the VIA/VILI was positive. Cervical lesions were diagnosed by directed biopsy under the colposcopy. The VIA/VILI negative women or cervical intraepithelial neoplasia 1 (CIN1) were re-screened using the same procedure in the next year. **Results:** In total, 7145 women received the cervical cancer screening, with a participation rate of 74.75%. Their average age was 42.16 years. A total of 1287 women were consecutively screened for three times from 2005 to 2007. The detection rates of CIN2, CIN3 and cervical cancer were 0.70% (9/1287), 1.01% (13/1287) and 0.23% (3/1287) for the first round screening, and were 0.22% (2/976), 0.11% (1/976) and 0% (0/976) for the second round screening, respectively. Only one CIN2 was found in the third round screening. In the years of 2006–2007, 3490 women were screened consecutively twice. The detection rates of CIN2, CIN3 and cervical cancer were 0.26% (9/3490), 0.52% (18/3490) and 0.15% (5/3490) for the first round screening, and 0.40% (14/2943), 0.40% (14/2943) and 0.03% (1/2943) for the second round screening. Likewise, 2 368 women were screened consecutively twice in the years of 2007–2008. The detection rates of CIN2, CIN3 and cervical cancer were 0.55% (13/2368), 0.25% (6/2368) and 0.12% (3/2368) for the first round screening, and 0.42 (10/2040), 0.04% (1/2040) and 0% for the second round screening. The cumulative detection rates for CIN2, CIN3 and cervical cancer were 0.81% (58/7145), 0.74% (53/7145) and 0.17% (12/7145), respectively. And 53.45% (31/58) of CIN2, 68.81% (37/53) of CIN3 and almost all cervical cancers (11/12) were found during the first round screening, except for an early stage cervical cancer (Ia). Only one CIN2 was detected in the third round screening in the same population. The average age of CIN1, CIN2, CIN3 and cervical cancer were 38.65, 40.61, 44.10 and 46.73 years, respectively. **Conclusions:** VIA/VILI can be used as an alternative screening method for cervical cancer and high-grade pre-cancerous lesions among the women aged 30–59 years in China's rural areas because of its low cost, easy training for the local health providers, and less depending on facilities. One round screening by VIA/VILI can detect more than a half of CIN2, two-thirds of CIN3 and almost all the cervical cancer in the population, and the detection rates of CIN2/3 can be increased by two consecutive rounds of screening.

Key words: Cervical cancer, visual inspection with acetic acid, visual inspection with Lugol's iodine, screening, rural areas

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Cervical cancer is the second leading cause of morbidity in women in the world. There are 500 000 new cases of cervical cancer annually and 83% of them are from developing countries. In the past few decades, the incidence of cervical cancer has been significantly decreased in developed countries because of the application of the Papanicolaou smearing test. However, the

cervical cancer has never been controlled in developing countries because of the lack of screening systems. And it remains to be an important cause of mortality and morbidity in women. Although the total mortality rate of cervical cancer has been lowered in the past two decades in China, the reduction is not universal across the whole country, particularly in some remote areas. Xiangyuan County of Shanxi Province is a region with a high burden of cervical cancer. Statistics from the 1970s showed that the mortality rate of cervical cancer in this region was as high as 54.38/100 000.[1] Cervical cancer screening in the past decade indicated that cervical cancer was still a primary malignant tumor in women from Xiangyuan County.[2,3]

There are varieties of strategies in the screening of cervical cancer,[4] including the conventional Papanicolaou smearing test and newly developed ThinPrep Cytology Test and HPV DNA detection. However, equipment and technicians required for these techniques are still deficient in the poor rural areas. To address this difficulties, the WHO recommended the use of acetic acid/Lugol's iodine (VIA/VILI) in developing countries, which has been evaluated in some developing countries.[5-8] According to the document "Program for National Cancer Prevention and Control" for the year of 2004–1010 issued by Chinese Ministry of Health, the Ministry of Finance has allocated the special fund to carry out the program of early detection and treatment of cervical cancer in some rural areas. The aim is to explore the mode of cervical prevention and control based on the experience of the local medical units. Xiangyuan County, as the first batch of the demonstration site for early diagnosis and treatment of cervical cancer , has carried out an extensive cervical cancer screening from 2005 to 2008, covering a population of 48 276. The present study aimed to summarize the results of the early detection and treatment of cervical cancer and evaluate the values of VIA/VILI method in the screening of cervical cancer in China's under-developed regions.

Materials and methods

Subjects

The women aged 30–59 years from Xialiang commune, Xiadian Town, Siting Town and Shangma commune of Xiangyuan County, Shangxi Province, who had local household ID, without histories of hysterectomy or surgery of cervix and pelvic radiation therapy, and who were not pregnant at the time of screening with histories of sexual intercourse were recruited for screening for cervical cancer.

Screening methods

VIA The cervix was dipped with 5% acetic acid and then observed after 1 min. The initial diagnosis was made according to the thickness, extension and surface morphology of the opaque acetowhite lesions. The results were classified into negative, positive and suspected conditions.

VILI The cervix was rubbed with 5% iodine solution. The normal cervical epithelium could absorb iodine, turning brown in color. And regions appearing mustard-yellow color were considered the lesions. The initial diagnosis was made according to the extension of mustard-yellow color, surface morphology, appearance of boundary, and the distance to squamo-column boundary. The results were classified into negative, positive and suspected conditions.

Colposcopy Colposcopy was performed in patients with positive result in either VIA or VILI, and biopsy was conducted under the colposcopy. The results were classified into normal/inflammation, low grade CIN, high grade CIN and invasive cancer.

Screening procedures

The subjects were educated and informed consents were obtained. After completing the questionnaire of epidemiological risk factors, the subjects were examined by the experienced gynecologists and the results of VIA and VILI were evaluated. Colposcopy was performed in patients with positive result in either VIA or VILI, and biopsy was taken directed by colposcopy to obtain the pathological diagnosis.

Diagnostic criteria

The pathological results were classified into normal, CIN1, CIN2, CIN3 and cervical cancer, which were finally confirmed by the senior pathologists from hospitals at provincial levels.

Treatment principle and follow-up

The women with negative results of VIA, VILI and colposcopy underwent the same screening procedure in the following years. CIN1 was the reversible lesion, which required follow- up annually and appropriate treatment should be directed by the follow-up outcome. CIN2, CIN3 and cervical cancer were managed with standard strategies and followed up according to the clinical guidelines.

Statistical analysis

Database was established with Foxpro program. Data checking programs were designed, and the data were input to the program twice, followed by checking for duplicated and omitted data, as well as the logical calculation. And finally, SPSS10.0 software was used for statistical analysis.

Results

A total number of 9558 eligible women were registered. Of them, 7165 received risk factor screening and 7145 underwent gynaecological examinations, with a participation rate of 74.75% and the colposcopy referral rate of 4.76% in the three years. The follow-up rates in the second and third years were 84.33% (5959/7066) and 54.64% (688/1259), respectively. The mean age of the screened population was 42.16 years and the menarche age was 15.30 years, and the mean age of their first sexual intercourse was 20.94 years. The median number of pregnancies was 3.00 and the median parity was 2.00. The women with educational level below primary school accounted for 33.90% of the population, those with the level of junior middle school accounted for 56.00%, and those with the level of senior middle school or higher accounted for 10.10%.

The screening of cervical cancer with VIA/VILI by rural gynecologists was first conducted in 2005 in China. A total number of 1287 women were screened with a participation rate of 74.79% . To verify the screening efficacy, the women with

negative results or CIN1 were followed up with the same strategies in 2006 and 2007. There were 10 cases of CIN1, nine cases of CIN2, 13 cases of CIN3, one case of early stage invasive cancer and two cases of invasive squamous carcinoma were detected during the first round screening. The follow-up results of the following two years are shown in Table 1. The rate of the second follow-up was 77.34% (976/1262) and there were four cases of CIN1, two cases of CIN2, one case of CIN3 and no carcinoma. The rate of the third follow-up was 54.65% (688/1259) and there was one case of CIN1, one case of CIN2 and no CIN3 or carcinoma.

Following the work in 2005, the same screening program was conducted in 2006–2007 covering 3490 women and in 2007–2008 covering 2368 women. There were 88 cases of CIN1, 22 cases of CIN2, 24 cases of CIN3, four cases of early stage invasive cancer and four cases of invasive squamous carcinoma were detected during the first round screening. The follow-up rate of the second time was 85.85% (4983/5804) and there were 75 cases of CIN1, 24 cases of CIN2, 15 cases of CIN3, one case of early stage infiltrative cancer (Table 2). Two sessions of screening showed that the incidence of CIN1 as confirmed by pathology was 2.78% (163/5858), CIN2 was 0.79% (46/5858), CIN3 was 0.67% (39/5858) and cervical cancer was 0.15% (9/5858).

Table 1 Detection rates of cervical lesions from the three consecutive screenings in 2005–2007

Screening year	Number of Screened women	CIN1 [patient No. (%)]	CIN2 [patient No. (%)]	CIN3 [patient No. (%)]	Cancer [patient No. (%)]
1st round screening in 2005	1 287	10 (0.78)	9 (0.70)	13 (1.01)	3 (0.23)
2nd round screening in 2006	976	4 (0.44)	2 (0.22)	1 (0.11)	0
3rd round screening in 2007	688	1 (0.18)	1 (0.18)	0	0
Cumulative detection rate	1 287	15 (1.17)	12 (0.93)	14 (1.09)	3 (0.23)

The detection was based on the histopathologic diagnosis.

Table 2 Detection rates of cervical lesions from the two consecutive screenings in 2006–2008

Screening year	Number of Screened women	CIN1 [patient No. (%)]	CIN 2 [patient No. (%)]	CIN3 [patient No. (%)]	Early cancer(Ia) [patient No. (%)]	Invasive cancer(>Ia) [patient No. (%)]
2006						
1st round screening in 2006	3 490	47 (1.35)	9 (0.26)	18 (0.52)	2 (0.06)	3 (0.09)
2nd round screening in 2007	2 943	46 (1.32)	14 (0.40)	14 (0.40)	1 (0.03)	0
Cumulative detection rate	3 490	93 (2.66)	23 (0.66)	32 (0.92)	3 (0.09)	3 (0.09)
2007						
1st round screening in 2007	2 368	41 (1.73)	13 (0.55)	6 (0.25)	2 (0.08)	1 (0.04)
2nd round screening in 2008	2 040	29 (1.22)	10 (0.42)	1 (0.04)	0	0
Cumulative detection rate	2 368	70 (2.96)	23 (0.97)	7 (0.30)	2 (0.08)	1 (0.04)

The detection was based on the histopathologic diagnosis.

The women with the cervical lesions above CIN2 were aged between 30 and 57 years (mean, 42.74). The mean age of the women with CIN1, CIN2 or CIN3 were 38.65, 40.61 and 44.10 years, respectively. It appears that the malignancy of the lesion increased with the aging of these women. The mean age of the patients with cervical cancer was 46.73 (age range: 33–57 years) (Table 3).

Table 3 Age distribution of patients with lesions worse than CIN1 in 2005–2008

Group	Patient No.	Age of patients			
		Min	Max	Average	Standard deviation
CIN 1	177	30	56	38.65	6.14
CIN 2	57	30	54	40.61	6.25
CIN 3/Cancer in situ	53	30	55	44.10	6.85
Cancer	12	33	57	46.73	6.68
Total	299	30	57	40.33	6.74

Min, minimum; Max, maximum.

Discussion

In recent years, the cervical cancer reportedly affects the younger population.[9,10] Consequently, the financial burden, morbidity and mortality caused by cervical cancer have become the major causes of the poverty of the rural residents. The early detection and treatment remain to be the primary strategy in the prevention and control of cervical cancer, and in lowering its mortality and morbidity. Papanicolaou smearing has been successful in controlling cervical cancer in developed countries, but it requires the establishment of standard cytological detection

system and the experienced technicians, which are not available currently in the hospitals of the rural areas of China. The state-of-the-art techniques of HPV detection and ThinPrep Cytology Test are even more affordable for the disease screening for the rural women. Obviously, the higher expenses and lack of equipment and experienced technicians all restricted the use of these techniques in developing countries. As a result, many rural women died of cervical cancer because they missed the best treatment opportunity in the early stage.[11]

VIA/VILI is recommended by the WHO to be used in developing countries. The technique can be mastered in a short period of training and its expense is low, the operation is simple and does not need any equipment.[12] And the results can be obtained at that moment. Thus, it is suitable for the wide screening in regions with a high incidence of cervical cancer.12 The sensitivity and specificity of VIA/VILI varied markedly in different studies. Sankaranarayanan *et al*.[7,8] conducted a multi-center screening, showing that the sensitivity and specificity of VILI were 87.2%–91.7% and 84.7%–85.4%, respectively. Qiao *et al*.[3,13] reported that the sensitivity and specificity of VIA were 70.9% and 74.3%, and the sensitivity and specificity of VILI were 53.1% and 82.2% , respectively. The Xiangyuan Women and Children's Hospital in the Shanxi Province was approved by the central government as the "demonstration site of the early detection and treatment of the cervical cancer" in 2004. In 2005, VIA/VILI technique was first used in Chinese rural areas by the local rural gynecologists for the screening of cervical cancer. A three-year screening program from 2005 to 2007 covering 1287 women showed that the initial screening was able to detect all patients with early stage cancers, and no early stage invasive cancer was reported in the second year follow-up, and no CIN3 were detected in the third year (except for one case of CIN2). In the following years between 2006 and 2007, a larger screening program was conducted, which further proved the effectiveness of the VIA/VILI. And this demonstrated that in rural areas lacking of cytologic and other screening techniques, VIA/VILI can be used as an alternative for the screening of cervical cancer.

The five-year work in cervical cancer demonstration site not only proved the feasibility of using VIA/VILI to screen cervical cancer in rural areas, but also obtained the effectiveness of the screening program. The results suggest that, one round of VIA/VILI screening can detect most of the lesions of CIN3 without missing those with early or more advanced cancerous lesions and consecutive screening for two years can detect more lesions of CIN2/3, whereas screening for three years is not recommended because it will marginally increase the number of CIN2. Therefore, the frequency of screening should be determined based on the regional resources, and consecutive two-year screening can detect more early pre-cancerous lesions (CIN2/3), making the treatment more effective. Nevertheless, consecutive screening for three or more times in a population will only result in the waste of the resources. Due to the slow progress of cervical lesions and a long period of time is required for most CIN2/3 lesions to progress into cancer,[14] the interval between the first and second screening can be prolonged to at least three years in the rural areas with shortage of resources. However, this suggestion needs to be validated in the follow-up studies in the future.

In addition, we analyzed the age range of the 299 women detected to have cervical lesions among the 7145 screened women between 2005 and 2008. The 299 cervical lesions included CIN1 (177), CIN2 (57), CIN3 (53) and cervical cancers (12), with mean ages of 38.65, 40.61, 44.10 and 46.73 years, respectively, suggesting that the age range between 30 and 59 years set for the screened women would not miss cervical cancers in young women, which is also in concordance with the cost-effective principle.

The work in the demonstration site of the early detection and treatment of the cervical cancer is being extended. The Bureau of Disease Prevention and Control, Ministry of Health initiated the basic policy to use VIA/VILI strategy[15] for cervical cancer screening in under-developed regions in China, which has achieved a favorable result.[16] The program was extended to 43 counties nationwide in 2008. The Two-Cancer Screening Program of Women in rural areas has been included in the national key issues of public health in 2009 and approximately 10 million women from rural areas will receive cervical cancer screening from 2009 to 2011. The screening techniques can be determined according to the local conditions, which included VIA/VILI. Although the Two-Cancer Screening Program is far from the aim of covering all women in rural areas in China, it is the first step in the long march to screen cervical cancers for women in the rural areas. And the evaluation of the cost-effectiveness of the strategy requires further studies.[17] The results of the present study and the Two-Cancer Screening Program are expected to provide a model and experience to the under-developed areas in China, as well as other moderately developed countries in cervical cancer prevention and control.

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