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Epidemiological Investigation and Risk Factors for Cervical Lesions: Cervical Cancer Screening Among Women in Rural Areas of Henan Province China

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Background: This cross-sectional study aimed to investigate the prevalence of cervical lesions and evaluate risk factors for cervical intraepithelial neoplasia (CIN) among women taking part in cervical cancer screening in rural areas of Henan province, China.

Material/Methods: Cervical cancer screening using the ThinPrep cytologic test (TCT) and gynecologic exam was conducted on 1315 women age 20–68 years in rural areas of Henan province, China. Colposcopy and biopsies were carried out for histopathologic diagnosis when indicated. Univariate and multivariate logistic regressions were performed to evaluate risk factors associated with cervical lesions.

Results: Among 1315 women screened, CIN prevalence detected by histopathology was 1.22% (0.38% of CIN 1, 0.76% of CIN 2, and 0.08% of CIN 3). Cervical cancer prevalence was 2.66%. Multivariate analysis confirmed risk factors for cervical lesions included older age (the 21–40 age group *vs.* the 41–66 age group, OR=0.13, 95% CI: 0.03~0.57), postmenopause (OR=0.11, 95% CI: 0.03~0.45), cervical inflammation (OR=0.06, 95% CI: 0.01~0.31), and smoking (OR=6.78, 95% CI: 1.20~38.23).

Conclusions: Older age (41–66 years), presence of HPV infection, postmenopause, cervical inflammation, and smoking are strong risk factors for cervical lesions among women in rural areas of Henan province, China. Particular efforts should be made to provide cervical cancer screening for these women.

MeSH Keywords: **Cervical Intraepithelial Neoplasia • Risk Factors • Uterine Cervical Neoplasms**

Abbreviations: **CCA** – cervical cancer; **CIN** – cervical intraepithelial neoplasia; **HPV** – human papillomavirus; **TCT** – ThinPrep cytology test

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Background

Cervical cancer (CCA), generally presenting malignancies in the uterus, cervix and vagina, is the second most common cancer among women, second only to breast cancer [1,2]. About 135 000 new cases occur each year in China, accounting for a third of the global cases; 73–93% of the female reproductive system tumor incidence, which is 6 times higher than in developed countries, and the cases tend to be younger [3]. Over the past 20 years, incidence and mortality of cervical cancer have been rising in China, with the rise of rural areas obviously higher than in cities.

Compared with other malignancies, CCA has characteristics with clearer pathogenic factors and longer reversible period of precancerous lesions, and often begins with cervical intraepithelial neoplasia (CIN) accompanied by progressive CIN1, 2, and 3. It was reported that at least 25% of women with CIN 2 and 3 progress to carcinoma *in situ* or invasive cancer if lesions are untreated [4].

Previous studies suggested that high-risk human papillomavirus (HR-HPV) infection is a main cause of CIN and invasive cervical cancer [5]. However, only a minority of HPV infections progress to CIN or CCA. Other correlative factors, such as oral contraceptive use and pregnancy frequency, affect HPV persistence and development from CIN to invasive CCA [6–8].

Systematic and effective screening, together with early diagnosis and treatment, can save 99% of the patients with CCA [9]; it is significant to reverse cervical precancerous lesions and block development of CCA by early screening and effective prevention. Due to active CCA prevention and screening in China, the mortality rate of CCA decreased in the 1990s, but had an increasing trend in recent years. The CCA screening work throughout China has not been evenly distributed and various regions have different trends.

There has been no systemic and comprehensive research on risk factors for cervical lesions (including CIN and CCA) among women living in the rural areas of Luohe city, Henan province, central China, which has a high incidence of CCA. In this study, 1315 women were recruited for CCA screening. All women were offered gynecological examinations, HPV test, and ThinPrep cytology test (TCT) to estimate prevalence of cervical lesions and evaluate risk factors for cervical lesions, which provides evidence to nationwide screening strategies of the cervical cancer program.

Material and Methods

Subjects and study design

In rural areas of Henan province, China, 1315 women aged between 21 to 68 years old (mean years=41.84±7.80) attended cervical cancer screening. Inclusion criteria were: (1) current or past sexual activity; (2) not pregnant at the time of enrollment; (3) never been screened or treated for cervical cancer; (4) had not undergone a total uterus or cervix resection. All of the recruited subjects were familiar with the purpose and procedures of the study and signed informed consent forms before the study. Exclusion criteria were: difficulties in obtaining information; unanalyzable samples; pregnant women; history of uterectomy; and refusal to participate. The present study was conducted in accordance with the Declaration of Helsinki. All study protocols were approved by the Ethics Committee of the First Affiliated Hospital of Luohe Medical College.

All the subjects completed the structured case report form (CRF) questionnaires for cervical cancer screening, including socio-demographic information, reproductive history, sexual behavior, birth control measures, medical history, gynecologic examination history, TCT and histologic test results, and demographic data of husbands.

Socio-demographic information collected from each woman included age, education level, occupation, marital status, economic conditions, and living situation. Information was also recorded on reproductive history and sexual characteristics, including menarche age, length of menstrual cycle, menstrual capacity, menopausal age, number of pregnancies, number of abortions, delivery times, birth control measures, sanitary conditions of sexual life, and cervical inflammation. Medical history included any history of gynecological tumors, such as uterine sarcoma, fallopian tube tumors, ovary benign tumors or cancer, and vulvar carcinoma.

Measurements

TCT and histopathologic diagnosis

Exfoliated cervical cells were collected from the ectocervix and endocervix with a plastic Ayres's spatula and cytobrush. The collected cells were analyzed by TCT. Cytological findings were diagnosed according to the Bethesda classification system [10] and were classified as follows: a) negative; b) atypical squamous cells of undetermined significance (ASCUS); c) low-grade squamous intra epithelial lesion (LSIL); d) atypical squamous cells that cannot exclude HSIL (ASC-H); e) high-grade squamous intraepithelial lesion (HSIL). If TCT results were abnormal, participates were referred for colposcopic exams. A histologic test by biopsy was performed to determine

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CIN grade. CIN grades were categorized as CIN1, CIN2, and CIN3 according to Richard's classification [11], in which CIN2 and CIN3 are defined as HSIL.

HPV detection

HPV DNA testing was conducted using polymerase chain reaction (PCR) and HPV types were detected by a commercial HPV genotyping kit (Yaneng Bioscience (Shenzhen) Co., Ltd, China), as previously described [12].

Statistical analysis

Statistical analyses were performed using SPSS software (IBM Corporation, Armonk, New York, USA) (version 19.0). Count data and measurement data of participants' characteristics were examined by χ^2 test and *t* test, respectively. Backward univariate and multivariate logistic regression model was used to assess the relationship between cervical lesions and potential risk factors. *P*-values were two-sided, and statistical significance was defined as $p<0.05$.

Results

A total of 1315 women from the rural areas of Henan province, China, participated in the screening study. Of the subjects, 5 women (0.38%) were identified by pathologic diagnosis as CIN1, 10 (0.76%) as CIN2, 1 (0.076%) as CIN3, and 35 (2.66%) as cervical cancer. The prevalence of cervical lesions in different age groups is shown in Table 1. There were significant differences among the age groups in terms of the prevalence of cervical lesions (χ^2=357.000, p=0.000). The peak age range of onset of CIN was between the ages of 30 and 40 years, and 41–55 years range for the onset of CCA.

The mean age of the subjects with cervical lesions was 41.84±7.80 years, with 36.80±7.19 years for CIN1(range: 30–49 years), 40.10±6.59 years for CIN2 (range: 30–52 years), 41 years for CIN3 (only 1 subject), and 43.09±8.10 for CCA (range: 23–66) (Table 2). The results indicated that with increasing age, the cervical lesions exacerbated. In all subjects, 33 women were positive for HPV infection and the prevalence was 2.51% (Table 3). In detail, the crude prevalence of HPV was 0.4% for the normal or inflammation of the women, 20% for CIN1, 30% for CIN2, and 66.7% for CIN3 and CCA. HPV infection had significant differences between women with the cervical lesions (n=28) and those with normal and inflammatory histology (n=5) (χ^2=33.000, p<0.01). Similarly, there was a significant difference among all the groups (χ^2=132.000, p<0.01).

Independent variables and their corresponding encoding number are shown in Table 4. A univariate logistic regression analysis revealed that the age group of 41–66 years (compared with the age group of 21–40 years) (P=0.023), annual income less than 30 000 yuan (P=0.044), HPV infection (P= 0.000), postmenopause (P=0.002), age at first pregnancy below 20 years old (P=0.024), cervical inflammation (P= 0.000), smoking (P=0.000), and breakdown of marital relations (P=0.038) as risk factors significantly associated with presence of the cervical lesions (Table 5). Furthermore, risk factors that remained significant by multivariate logistic regression analysis were being in the age group of 41–66 years (OR=0.131, 95% CI: 0.030–0.573, compared with the age group of 21–40 years), HPV infection (OR=260.630, 95% CI: 19.970–3401.510), postmenopause (OR=0.108, 95% CI: 0.026–0.452), cervical inflammation (OR=0.061, 95% CI: 0.012–0.313), and smoking (OR=6.778, 95% CI: 1.202–38.226) (Table 6).

Discussion

We presented the first large-scale cervical cancer screening study in rural areas of Henan province, China; 1315 women aged 21–68 years were eligible to participate in the study. The prevalence of cervical lesions was 3.88%, among which the prevalence of CIN1, 2, 3, and cervical cancer was 0.38%, 0.76%, 0.076%, and 2.66%, respectively. The prevalence of cervical lesions had a declining trend with age (shown in Table 1). The peak age range of onset of CIN was between the ages of 30 and 40 years, and 41–55 years range for the onset of CCA. With age, cervical lesions became more serious, which is related to the long process of development from CIN to CCA, which takes about 10–15 years. The prevalence of precancerous cervical lesions (CIN1, 2, and 3) in this screening study (1.22%) was higher than the previous report in 2009 (0.20%) [13], as a result of a relatively smaller sample size in the present study. The prevalence of CCA was 2.66%, comparable to rates reported in the China Cancer Registration Annual Report 2014, in which 219 cancer registries were included; the incidence of CCA was 9.84 per 100 000 in China (2.48% in urban and 2.49% in rural areas) [14]. According to a survey of the Cancer Institute and Hospital, Chinese Academy of Medical Sciences, the patients under the age of 35 years accounted for 5.01% of all cervical cancer patients in the 1990s; but, the proportion increased distinctly to 9.88% at the start of this century [15]. Previous reports suggested that the prevalence of CCA was rising in younger women [16,17]. The results of our screening study indicated that cervical cancer screening intervention should be conducted for women from the age of 30.

Consistent with the previous studies [18,19], age 41–66 years was identified as a significant risk factor for cervical lesions in the present study, among which the subjects aged 41–55 years were vulnerable to CCA. Other studies had also revealed that older age and postmenopause were significant risk factors for development of CCA [20,21].

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Table 1. Prevalence of cervical lesions in different age groups.

Age group	CCA (%)	CIN (%)	Normal	Total
20–29	1 (1.49)	0 (0)	66	67
30–35	5 (2.78)	5 (2.78)	170	180
36–40	7 (2.57)	6 (2.21)	259	272
41–45	9 (3.26)	2 (0.72)	265	276
46–50	8 (2.80)	2 (0.70)	276	286
51–55	3 (3)	1 (1)	96	100
56–60	1 (1.06)	0 (0)	93	94
≥61	1 (2.50)	0 (0)	39	40

There were significant differences among the age groups in terms of the prevalence of cervical lesions (χ^2=357.000, p=0.000). CCA – cervical cancer; CIN – cervical intraepithelial neoplasia. Statistical analyses were performed using χ^2 test and *t* test.

Table 2. Distribution of the average age of the subjects with cervical lesions.

Histological grade	Age of patients			
	Number	Min	Max	Average
CIN1	5	30	49	36.80±7.19
CIN2	10	30	52	40.10±6.59
CIN3	1	41	41	41
CCA	35	23	66	43.09±8.10
Total	51	30	66	41.84±7.80

Table 3. HPV infection at all levels of the cervical lesions.

Histological grade	HPV (DNA test)		Totle	Infection rate (%)
	Positive	Negtive		
Normal or inflammation	5	1259	1264	0.40
CIN1	1	4	5	20.00
CIN2	3	7	10	30.00
CIN3	1	0	1	100.00
CCA	23	12	35	65.71
Total	33	1282	1315	2.51

HPV infection had significant differences between women with the cervical lesions (including CIN and CCA) (n=28) and those with normal and inflammatory histology (n=5) (χ^2=33.000, p<0.01). There was a significant difference among all the groups (χ^2=132.000, p<0.01). Statistical analyses were performed using χ^2 test and *t* test.

There was a significant association between abnormal TCT results and gynecologic infections. Cervical inflammation was significantly related to cervical lesions, supporting the previous findings [22,23]. Some epidemiologic evidence suggested that there was a higher incidence of CCA in women with chronic cervicitis than in the general population [24]. If chronic cervicitis cannot be cured as early as possible, inflammation recurs and persists, resulting in atypical squamous epithelial hyperplasia and progression to CCA. Additionally, chronic cervicitis decreases cellular immunity, inducing HPV infection that is not easy cure and persistent infection. Therefore, cervical inflammation can be considered

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Table 4. Independent variables and their corresponding encoding number.

Independent variable	Number	Variable code
Socio-demographic information		
Age	X1	0=41–66; 1=21–40
Education level	X2	0=Illiteracy and primary school; 1=Junior middle school or above
Marital status	X3	0=Married; 1=Single
Occupation	X4	0=House wife; 1=Female professional
Economic conditions	X5	0=Less than or equal to 30000 yuan; 1=More than 30000 yuan
Living situation	X6	0=Living with family; 1=Others
Physical condition and medical history		
HPV infection	X7	1=Yes; 2=No
Medical history	X8	1=Yes; 2=No
Cervical inflammation	X9	1=Yes; 2=No
Menstrual and menopausal history		
Menarche age	X10	0=Less than or equal to 16 years old; 1=More than 16 years old
Length of menstrual cycle	X11	1=Regular; 2=Random
Menstrual capacity	X12	1=Little or much; 2=Modest
Postmenopause	X13	0=No; 1=Yes
Sexual characteristics		
The first sexual behavior	X14	1=Less than or equal to 20 years old; 2=More than 20 years old
Frequency of sex every month	X15	1=Less than or equal to 4 times; 2=More than 4 times
Sexual partners	X16	1=Only one; 2=More than one
Reproductive history		
Age at first pregnancy	X17	1=Less than or equal to 20 years old; 2=More than 20 years old
Age of first delivery	X18	1=Less than or equal to 20 years old; 2=More than 20 years old
Pregnant frequency	X19	1=More than 3 times; 2=Less than or equal to 3 times
Birth control measures	X20	1=Yes; 2=No
Life and behavior way		
Smoking	X21	1=Yes; 2=No
Passive smoking	X22	1=Yes; 2=No
Family status	X23	1=Satisfied; 2=Dissatisfied
Unfortunate events in life	X24	1=Yes; 2=No
Breakdown of marital relations	X25	1=Satisfied; 2=Dissatisfied
Husbands' cases		
Education level	X26	0=Illiteracy and primary school; 1=Junior middle school or above
Living situation	X27	0=Living with family; 1=Others
Occupation	X28	1=Farmer; 2=Others
History of penile carcinoma/prostate cancer	X29	1=Yes; 2=No
Redundant prepuce	X30	1=Yes; 2=No
Sanitary conditions of sexual life	X31	1=Yes; 2=No
History of venereal diseases	X32	1=Yes; 2=No
Cervical lesions (CCA and CIN)	Y1	1=Yes; 2=No

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Table 5. Risk factors for cervical lesions assessed by univariate logistic regression.

Variables	OR	95% CI		*P*
		Lower	Upper	
X1	3.426	1.183	9.917	0.023
X2	3.210	0.422	24.425	0.260
X3	0.000	0.000	–	0.998
X4	21082869.07	0.000	–	0.997
X5	2.778	1.027	7.511	0.044
X6	0.000	0.000	–	0.998
X7	20.633	6.722	63.332	<0.001
X8	20272625.47	0.000	–	0.998
X9	26.095	8.893	76.570	<0.001
X10	1.144	0.323	4.050	0.834
X11	1.154	0.398	3.345	0.792
X12	1.258	0.273	5.796	0.768
X13	4.832	1.783	13.092	0.002
X14	2.598	0.968	6.975	0.058
X15	1.960	0.725	5.302	0.185
X16	1.202	0.340	4.246	0.776
X17	3.752	1.189	11.835	0.024
X18	1.816	0.235	14.043	0.568
X19	1.482	0.420	5.323	0.541
X20	1.053	0.390	2,844	0.920
X21	29.838	10.479	84.965	<0.001
X22	1.100	0.352	3.437	0.869
X23	3.474	0.985	12.249	0.053
X24	2.730	0.359	20.781	0.332
X25	8.590	1.131	65.232	0.038
X26	21485949.69	0.000	–	0.997
X27	20513966.25	0.000	–	0.998
X28	1.167	0.422	3.233	0.766
X29	20612119.20	0.000	–	0.998
X30	1.896	0.424	8.472	0.402
X31	1.529	0.343	6.813	0.578
X32	20005880.40	0.000	–	0.999

Statistical analyses were performed using backward univariate and multivariate logistic regression.

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Table 6. Risk factors for cervical lesions assessed by multiple logistic regression.

Variables	OR	95% CI		*P*
		Lower	Upper	
X1	0.131	0.030	0.573	0.007
X5	0.758	0.188	3.059	0.697
X7	260.630	19.970	3401.510	<0.001
X9	0.061	0.012	0.313	0.001
X13	0.108	0.026	.452	0.002
X17	0.616	0.084	4.543	0.635
X21	6.778	1.202	38.226	0.030
X22	4.980	0.556	44.639	0.151

Statistical analyses were performed using backward univariate and multivariate logistic regression.

as a cofactor contributing to HPV infection development to high-grade CIN and CCA [25].

Our results showed that the postmenopausal women were inclined to have CCA. Although the postmenopausal women with cervical lesions had no obvious symptoms, the incidence of abnormal cervical cytology was higher than the non-menopausal group in our study. Due to estrogen decrease, the vaginal wall beginning to thin, and glycogen in the epithelial cells decline, the postmenopausal women were susceptible to senile vaginitis, which further induced abnormal cervical cytology. Furthermore, Ter Harmsel's et al. findings indicated that postmenopausal women tended to develop persistent HPV infection and develop high-grade CIN and CCA [26]. Consequently, it is of great significance for prevention of cervical lesions that postmenopausal women with reproductive tract HPV infection get early treatment.

Additionally, a significant association between smoking and cervical lesions was identified in the present study, as multiple studies have already demonstrated [27,28]. Chemical carcinogens in tobacco, such as cotinine and nicotine, were found to exist in cervix mucosae of smoking women [29], probably exerting a series of carcinogenic effects by activating nitrosamines and causing DNA damage, and may destroy the local immune defense in the cervical epithelium [30]. Thus, smoking has a serious impact on the development of cervical lesions, consistent with findings indicating that smoking cessation benefits CIN regression [31]. However, the biological mechanism by which smoking facilitates development of cervical cancer needs further study.

Conclusions

We presented the first large-scale cervical cancer screening study in rural areas of Henan province, China. The prevalence of cervical lesions was relatively high (3.88%). Women aged 41–66 years, with HPV infection, cervical inflammation, smoking, and those reporting postmenopause have strong risk for cervical lesions in this study. Particular efforts should be taken for cervical cancer screening in these women. Moreover, our data provide evidence for the primary screening of cervical cancer in rural areas.

Competing interests

The authors declare no competing financial interests.

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