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Original Research

Prevalence and risk factors of cervical cancer in the Nanjiang area of the Xinjiang Uyghur Autonomous Region of China: a matched case-control study

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Objective: Nanjiang is the area where cervical cancer has a high incidence in the Xinjiang Uyghur Autonomous Region, China. However, large-scale studies on the risk factors in this area have rarely been reported. This study investigated the prevalence and risk factors of cervical cancer in Nanjiang. *Methods*: A total of 10,038 non-pregnant women with a history of sexual intercourse were screened from five areas of Nanjiang. Their age ranged from 18 years to 64 years. The participants received physical examination, questionnaire surveys, laboratory examinations and cervical cancer screening. A case-control study was designed for 60 women diagnosed with cervical cancer, and uni- and multi-variable logistic regression analyses were performed. *Results*: The prevalence of cervical cancer was 59.77/100,000. The factors associated with cervical cancer included unwilling for physical exercise (Odds Ratio (OR) = 1.96, Confidence interval (95% CI) = 1.02~3.78, $p = 0.043$), the number of sexual partners ≥ 5 (OR = 2.36, 95% CI = 1.15~4.81, $p = 0.019$), high-risk human papilloma virus (HPV) infection (OR = 2.73, 95% CI = 1.35~5.53, $p = 0.005$), herpes simplex virus (HSV) infection (OR = 2.57, 95% CI = 1.33~4.96, $p = 0.005$), and a family history of cervical cancer within three generations (OR = 4.41, 95% CI = 2.21~8.61, $p < 0.001$). High-risk HPV infection and HSV-2 infection interacted with each other among these factors (OR = 3.61, 95% CI = 1.80~7.22, $p < 0.001$). *Conclusions*: HPV infection, sexual behavior, sexually transmitted diseases and heredity are associated with cervical cancer among Uyghur women in Nanjiang. In the prevention and treatment of cervical cancer, biological and behavioral factors should be comprehensively considered.

Keywords

Uyghur ethnicity; Cervical cancer; Prevalence; Risk factor; Cervical intraepithelial neoplasia (CIN)

1. Introduction

Cervical cancer is one of the most common malignancies that greatly threaten women's health globally. It is also the most prevalent genital tract tumor in women in developing countries. It is estimated that the number of new cases of cervical cancer will increase to 850,000 worldwide in 2030 [1]. In China, the increased number in 2014 was 102,000, which accounted nearly for 1/5 of the global number [2, 3]. In China, most cases of cervical cancer occur in the mid-west regions [4]; generally, the mortality in rural areas is slightly higher than that in urban areas, and that in the mid-west regions noticeably higher than that in the east [5]. Globally, the occurrence of cervical cancer has shown a younger trend in recent years [6, 7].

Nanjiang of the Xinjiang Uyghur Autonomous Region, China, is the area where cervical cancer has a high prevalence. Uyghur women in Nanjiang had the highest incidence and mortality of cervical cancer than any other minority in China [8]. Even worse, the incidence among Uyghur women shows a gradual increase trend in recent years. Cervical cancer develops earlier among Uyghur women than other nationalities, which can be as early as 14 years [9]. Therefore, cervical cancer has become a serious public health problem among Uyghur women.

Biological and behavioral factors are the focus of studies on the development of cervical cancer. Numerous studies have shown that the development of cervical cancer and precancerous lesion is associated with human papilloma virus (HPV) infection, particularly HPV-16 and -18 [10–14]. Such an association has also been proved among Uyghur women in Xinjiang [15–19]. Bacterial vaginitis and Trichamonas vaginalis infection contribute to the development of cervical cancer [20, 21]. Oral contraceptives accelerate the progress of cervical lesion development; genital warts, intercourse bleeding, multiple pregnancies and births, multiple sexual partners, and first sexual behavior at an early age are closely associated with cervical cancer and precancerous lesion [22, 23]. Smoking may be another risk factor of cervical cancer and precancerous lesion, no matter active or passive, and the amount and number of years of smoking are two important factors [24, 25]. Cervical cancer has heredofamilial characteristics [26]. Furthermore, it is associated with sociological factors, and population with a lower education level and a lower socioeconomic status has a higher incidence of cervical cancer [27].

However, studies on the risk factors associated with cervical cancer among Uyghur women in Xinjiang, particularly in

Nanjiang, have been rarely reported. Large-scale investigations in Nanjiang are even less. Among the existing literature, most studies in this area only focused on a single county. As the lifestyle, religion, social customs, and genetic background of the Uyghur population are different from those of other ethnic populations, the pathogenetic characteristics of cervical cancer among Uyghur women may be different as well.

In this study, we conducted a large-scale study in Nanjiang to investigate the prevalence of cervical cancer and explored the biological, behavioral and sociological factors associated with this condition. A case-control study was designed. The results of this study may provide a reference for the early prevention, diagnosis and treatment of cervical cancer and prevalence control in Nanjiang, as well as in the regions with similar social, economic and medical conditions.

2. Methods

2.1 Sampling

Between January and December, 2016, five regions were selected from Nanjiang, including the Bayingolin Mongol Autonomous Prefecture, Aksu area, Kizilsu Kirghiz Autonomous Prefecture, Kashgar region, and Hotan region, for sampling using the multi-stage random cluster method. Specifically, in each region, one city/county was selected. In each of the selected cities/counties, two subdistricts/towns were further selected. In each of these subdistricts/towns, three communities/villages were chosen. In these communities/villages, non-pregnant women were contacted door-to-door, and those who had a history of sexual intercourse were randomly selected for physical examination, questionnaire surveys and cervical cancer screening. The age of the recruited women was determined between 18 years (the legal adult age in China) and 64 years based on the high-incidence age of cervical cancer, the guidelines for cervical cancer screening by the American NCCN, and the guidelines for the prevention and treatment of cervical cancer in China. The exclusion criteria included: (1) already confirmed cervical cancer; (2) pregnancy; (3) total hysterectomy; (4) severe internal and surgical diseases; (5) examination intolerance; and (6) unwillingness to participate or to receiving examination.

According to the screening outcomes, the women that had cervical cancer constituted the patient group. The control group was comprised of healthy volunteers that participated in the screening test within the same period. The patient group and the control group were matched in number according to a ratio of 1:2. The participants in the control group were from the same county/district as the patients and at similar age compared with the patients ($\pm$2 years). In the meantime, they had to meet the following criteria: (1) a history of sexual behaviors, hysterectomy, uterine/cervical malignancy, or pelvic irradiation; (2) not pregnant; and (3) willing to participate in the survey.

2.2 Questionnaire

A face-to-face questionnaire interview was performed for each participant, and the investigator filled in the questionnaire form immediately according to the participant's answers. All investigators were experienced gynecologists from the local hospital of the investigated county.

The interview lasted approximately 30 mins. The survey instrument was a self-designed questionnaire of cervical cancer-related risk factors. The content of the questionnaire included more than 30 items, which involved information regarding demography, living environment, sexual behavior characteristics, history of present diseases, menstrual history, history of gestation, and family history.

2.3 Laboratory tests

Each participant satisfying the inclusion criteria received routine examination of vaginal secretions, B-ultrasound, electronic colposcopy, thin-cytologic test (TCT), high-risk HPV detection, and HSV-2 detection.

2.3.1 Electronic colposcopy

The cervix was smeared with cotton balls soaked with 5% glacial acetic acid. After 1 min, the squamo-columnar junctional and transitional zones were checked. When abnormalities were observed, living tissue was taken from the lesion site and near the squamo-columnar junction for biopsy under a colposcope. When the result of colposcopy was unsatisfactory (such as an unclear squamo-columnar junction, the extension of the lesion into the internal cervical canal, biopsy forceps unable to touch the lesion site, and possible grandular lesions), endocervical curettage (ECC) was performed. Before ECC, the glacial acetic acid accumulated at the posterior fornix of the vagina was wiped dry in case of a loss of the scraped tissue. The scraped tissue was immediately immerged in formalin. During colposcopy, the image of the cervix was taken. The examination results were recorded in the questionnaire form.

2.3.2 HPV and HSV-2 detection

The kit used for HPV genotyping detection was the product of YanengBio, Shenzhen, China, which was able to detect 23 different HPV genotypes, including 18 high-risk types (16, 18, 3l, 33, 35, 39, 45, 5l, 52, 53, 56, 58, 59, 66, 68, 73, 83, and MM4) and 5 low-risk types (6, 11, 42, 43, and 44). The procedures were performed in strict accordance with the instructions of the kit. HSV-2 detection was performed using the golden-marked immunologic dot method [27], and the reagents were produced by Xunchao Biotech., Yueyang, China.

2.3.3 TCT

Vaginal medicine application and rinsing and sexual intercourse were not allowed within 3 d before the examination to exclude the possibility of infection. The cervix was exposed with a speculum and the secretions at the cervical opening were wiped off. A brush specialized for TCT use was placed

into the cervical canal and rotated five cycles in the same direction. The brush was placed into a container and rinsed 10 times. The cap was tightened, and then sent for examination. Films were prepared with an automatic film maker (ThinPrep 2000; ThinPrep BioTech., Nanjing, China). The films were read under a microscope and diagnosis was made by cycologists from the Xinjiang Uyghur Autonomous Region People's Hospital.

2.3.4 Diagnostic criteria

Diagnosis was formulated based on the following criteria: (1) no intraepithelial lesion or canceration (NILM); (2) atypical squamous cells (ASC), including ASC of undetermined significance (ASCUS), and ASC, including high-grade squamous intraepithelial lesion (ASCH); (3) low-grade squamous intraepithelial lesion (LSIL); (4) high-grade squamous intraepithelial lesion (HSIL); and (5) squamous cell carcinoma (SCC). Pathologically, the diagnostic results were classified into the following grades: (1) normal or inflammatory; (2) mild cervical intraepithelial neoplasia (CIN-I); (3) moderate CIN (CIN-II); and (4) severe CIN (CIN-III).

2.4 Statistical analysis

Data were input into Epidata 3.0 (The Epidata Association, Odense, Denmark) by two data entry clerks. The consistency between the data input by the two clerks was evaluated. For inconsistent data, the questionnaire was re-checked. Statistical analysis was performed with SPSS (version 16.0, IBM Corp., Chicago, IL, USA). The screening outcomes regarding cervical cancer and other diseases of the genital tract were statistically described. With cervical cancer as the dependent variable and other factors as independent variables, univariable logistic regression analysis was performed. The factors of significance were then introduced into multivariable stepwise conditional logistic regression analysis to confirm their potential associations with cervical cancer. A difference of $p < 0.05$ was considered statistically significant.

3. Results

3.1 Screening outcomes

A total of 10,038 women were screened, among whom 60 were diagnosed. Histopathologically, with cervical cancer. Among these 60 patients, 36 were at stage I, 16 were at stage II, 3 were at stage III and 1 was at stage IV, according to the International Federation of Gynecology and Obstetrics (FIGO) staging method. The cases included 17 adenocarcinoma and 43 squamous carcinoma. Precancerous lesions were observed in 389 patients, vaginitis in 1489, fibroids and other benign tumor in 418, condyloma acuminatum in 35, syphilis in 56, and vulvovaginal candidiasis in 230 (Table 1). In addition, 1103 women were detected with high-risk HPV infection and 2368 were detected with HSV-2 infection. A total of 17 HPV genotypes were detected, and the three top genotypes in the constituent proportion were HPV-16 (36.2%), -33 (18.2%), and -58 (10.6%).

Table 1. Screening outcomes.

Disease	Number of the patients	Prevalence (per 10,000)
Cervical cancer	60	59.77
Precancerous lesion	389	387.53
Vaginitis	1489	1483.36
Vulvovaginal candidiasis	230	229.13
Uterine fibroids	418	416.42
Condyloma acuminatum	35	34.87
syphilis	56	55.79
High-risk HPV infection	1103	1098.82
HSV-2 infection	2368	2359.03

3.2 Univariable logistic regression analysis

The patients diagnosed with cervical cancer constituted the patient group (n = 60). The control group was composed of 120 healthy volunteers. The patient group and the control group did not show a significant difference in age (39.1 ± 6.1 vs. 40.2 ± 6.8; $p > 0.05$).

Univariable logistic regression analysis was performed for all investigated factors, and 9, in total, were observed with statistical significance (Table 2), which included occupation, average income per person in family, number of sexual partners, dysmenorrhea, physical exercise, other gynecopathia, family history of cervical cancer within three generations, positive high-risk HPV and HSV-2 infection.

3.3 Multivariable logistic regression analysis

The 9 variables of statistical significance according to the univariable logistic regression analysis were introduced into the multivariable regression analysis, and 5 were finally determined in association with cervical cancer. The factors associated with cervical cancer included unwilling for physical exercise (OR = 1.96, 95% CI = 1.02~3.78, $p = 0.043$), the number of sexual partners $\geq$5 (OR = 2.36, 95% CI = 1.15~4.81, $p = 0.019$), high-risk human papilloma virus (HPV) infection (OR = 2.73, 95% CI = 1.35~5.53, P = 0.005), herpes simplex virus (HSV) infection (OR = 2.57, 95% CI = 1.33~4.96, $p = 0.005$), and a family history of cervical cancer within three generations (OR = 4.41, 95% CI = 2.21~8.61, $p < 0.001$). In addition, the interaction between high-risk HPV infection and HSV infection was also introduced into the equation (OR = 3.61, 95% CI = 1.80~7.22, $p < 0.001$). The results are summarized in Table 3.

4. Discussion

In this study, a total of 10038 women selected from five regions of Nanjiang were investigated and the prevalence and risk factors of cervical cancer were explored. The main findings were as follows: (1) The prevalence of cervical cancer in these five regions was 59.77/10,000, which was lower than that reported by Tao *et al.* [28] (62.2/10,000); more than half of the confirmed cases were at the early stage, and in the meantime, 389 patients were diagnosed with precancerous lesions; (2) Multivariable regression analysis showed that the number of sexual partners, HPV infection, HSV-2 infection, unwillingness for physical exercise, and a family history were

Table 2. Outcomes of the univariable logistic regression analysis.

Variable (N:M, non-cervical cancer:cervical cancer)		OR	95% CI		Wald χ^2	p
			Lower	Upper		
Ethnic group	Minority (115:57) vs. Han (5:3)	1.21	0.28	5.25	0.065	0.798
Place of residence	Rural (82:37) vs. urban (10:6)	1.01	0.31	3.29	0	0.984
	Suburb (28:17) vs. urban (10:6)	0.75	0.25	2.22	0.265	0.606
Occupation	Manual (115:53) vs. non-manual (5:7)	0.28	0.09	0.91	4.525	0.033
Education level	Middle school (51:22) vs. primary school and below (35:20)	1.08	0.49	2.38	0.036	0.85
	College and above (34:18) vs. primary school and below (35:20)	0.82	0.38	1.74	0.28	0.597
Average income per person in family	Below 1000 yuan (28:23) vs. above 3000 yuan (23:6)	3.15	1.10	9.04	4.547	0.033
	1000–3000 yuan (69:31) vs. above 3000 yuan (23:6)	1.72	0.64	4.65	1.15	0.283
Alcohol consumption	Sometimes (57:26) vs. often (28:18)	1.41	0.61	3.25	0.637	0.425
	Never (35:16) vs. often (28:18)	1.00	0.47	2.12	0	0.995
Smoking	Sometimes (2:2) vs. often (6:3)	2.04	0.28	14.84	0.492	0.483
	Never (112:55) vs. often (6:3)	1.02	0.25	4.23	0.001	0.98
Age of the first sexual intercourse	<16 years (14:6) vs. 16–35 years (94:50)	1.60	0.49	5.21	0.6	0.439
	>35 years (12:4) vs. 16–35 years (94:50)	1.29	0.29	5.66	0.111	0.74
Number of sexual partners	3–5 (15:13) vs. 2 and less (105:47)	1.79	0.71	4.48	1.526	0.217
	5 (80:40) and more (25:7) vs. 2 and less (80:40)	3.10	1.01	9.49	3.911	0.048
Divorce	Yes (17:8) vs. no (103:52)	0.93	0.38	2.30	0.023	0.879
Use of condoms	Yes (32:15) vs. no (88:45)	1.09	0.54	2.22	0.058	0.81
Dysmenorrhea	Often (12:14) vs. no (108:46)	2.74	1.18	6.38	5.466	0.019
Age of pregnancy	<20 years or >30 years (36:20) vs. 20 30 years (84:40)	1.17	0.60	2.27	0.207	0.649
Number of childbirths	One (22:11) vs. three and more (18:7)	1.35	0.52	3.49	0.384	0.536
	Two (80:42) vs. three and more (18:7)	1.29	0.41	4.00	0.189	0.664
Self-perceived pressure	Light (26:13) vs. heavy (12:8)	0.75	0.25	2.29	0.256	0.613
	Moderate (82:39) vs. heavy (12:8)	0.71	0.27	1.89	0.463	0.496
Frequency of couple quarrels	>5/w (29:16) vs. 5 and less/w (91:44)	0.88	0.43	1.78	0.133	0.715
Physical status	General (96:51) vs. good (17:7)	1.44	0.24	8.73	0.158	0.691
	Poor (7:2) vs. good (17:7)	1.86	0.37	9.28	0.572	0.45
Physical exercise	Often (27:15) vs. not often (93:45)	0.87	0.42	1.80	0.14	0.709
Other gynecopathia	Yes (21:26) vs. no (99:34)	3.61	1.80	7.22	13.09	0
Venereal disease	Yes (4:1) vs. no (116:59)	2.03	0.22	18.61	0.395	0.529
History of other severe diseases	Yes (7:5) vs. no (113:55)	1.47	0.45	4.83	0.398	0.528
Long-term use of hormone or contraceptives	Yes (21:7) vs. no (99:53)	0.62	0.25	1.56	1.023	0.312
Mother's gestational age	37 42 w (105:47) vs. <37 w or >42 w (15:13)	2.13	0.95	4.77	3.378	0.066
Maternal long-term use of hormone or contraceptives	Yes (7:3) vs. no or unknown (113:57)	0.85	0.21	3.41	0.053	0.818
Maternal smoking	Yes (25:12) vs. no (95:48)	0.95	0.44	2.05	0.017	0.896
Family history within three generations	Yes (4:7) vs. no (116:53)	3.83	1.08	13.65	4.29	0.038
Positive high-risk HPV	Yes (11:15) vs. no (109:45)	3.30	1.41	7.74	7.555	0.006
HSV-2 infection	Yes (29:27) vs. no (91:33)	2.57	1.33	4.96	7.881	0.005
BMI (kg/m^2)	<18.5 (20:9) vs. 18.5–24 (54:28)	1.15	0.46	2.86	0.093	0.76
	>24 (46:23) vs. 18.5–24 (54:28)	1.11	0.44	2.82	0.049	0.825

Table 3. Outcomes of the multivariable logistic regression analysis.

Variable		OR	95% CI		Wald χ^2	p
			Lower	Upper		
Willingness for physical exercise	Yes vs. no	1.96	1.02	3.78	4.099	0.043
Number of sexual partners	≥5 vs. ≤2	2.36	1.15	4.81	5.540	0.019
High-risk HPV infection	Yes vs. no	2.73	1.35	5.53	7.785	0.005
HSV infection	Yes vs. no	2.57	1.33	4.96	7.881	0.005
Family history of cervical cancer within three generations	Yes vs. no	4.41	2.21	8.81	17.692	<0.001
High-risk HPV infection & HSV infection	Interactive	3.61	1.80	7.22	13.093	<0.001

associated with cervical cancer, which cover the factors from biology, daily life behaviors, sexual behaviors and genetics; and (3) High-risk HPV infection and HSV-2 infection have an interactive effect on the development of cervical cancer.

High-risk HPV infection serves as an independent risk factor of cervical cancer, particularly infection of HPV 16, 18, 31, 33, 52, and 58 [29]. HPV belongs to a special DNA virus type. It is able to immortalize normal cells and possesses highly generic specificity and special epitheliotropic feature, causing benign and malignant lesions at the infected site. To date, numerous studies have confirmed the association of HPV infection with the development of cervical cancer [30–32]. HPV load was positively correlated with cervical lesions [33]. Even more, even when the HPV loads were equivalent, Uyghur women were more likely to suffer from cervical lesions and the lesions were more possible to be more severe, compared to the Han population [33]. HPV infection is subject to a sexually transmitted disease. Vaginal epithelium is easily damaged, which caused high sensitivity to HPV. Sexual behavior characteristics are also associated with HPV infection. Frequent use of condoms is a protective factor of HPV infection, whereas multiple number of sexual partners increases the possibility of exposure to HPV, thereby increasing the risk of HPV infection (as sexual intercourse without use of condoms tend to occur in this condition). Singlehood is another protective factor of HPV infection. Women of child-bearing age should pay much attention to personal life behaviors and avoid unsafe sexual behaviors.

The role of HSV-2 infection in pathogenesis of cervical cancer remains controversial. According to a meta analysis based on multiple independent epidemiologic studies, HSV-2 might contribute to the development of cervical cancer [34]. In this study, the results evidenced the significant association of HSV-2 infection with the development of cervical cancer. In addition, this study showed that HSV-2 infection and high-risk HPV infection had a synergistic effect on the development of cervical cancer, that is, the co-infection of HSV-2 and high-risk HPV increased the risk of the malignancy. HSV-2 is transmitted via sexual behavior, a way similar to HPV. Although HSV-2 has a synergistic effect with HPV-16 and -18 on the pathogenesis of genital tumor, the underlying mechanisms remain unclear. Some gene fragments of HSV-2 can induce the transformation of HPV immortalized epithelial cells into tumor [35]. HSV-2 promotes the synthesis of HPV DNA in a variety of cells [36, 37]. HSV-2 infection can stimulate the amplification of HPV-18 DNA in Hela cells; it stimulates HPV regulation and the overexpression of carcinogenes, thereby increasing the possibility of the development of cervical cancer [38, 39]. The result of our study was consistent with those reported in these studies.

The number of sexual partners, the age of first sexual behavior and the sexual behavior characteristics of the sexual partner are the high-risk factors of cervical cancer in women [40, 41]. Marriage status, in essence, is an indirect manifestation pattern of sexual behavior characteristics. Married women are more likely to suffer cervical cancer and CIN II/III, compared to the unmarried, divorced, and those in widowhood [42]. The conditions of the male sexual partner are an influential factor of female sexual hygiene. Therefore, investigations among the male sexual partners of the interviewed women should be strengthened in the future.

Cervical cancer also possesses the characteristic of a family history [43]. In a family, if a direct relative, such as the mother and sisters, has cervical cancer, regular screening tests, including cervical scraping smear, TCT, and cytological DNA test, should be received to ensure early detection and treatment of this condition.

This study had some limitations. First, although this study found that multiple factors were associated with the development of cervical cancer, the causal relationship between them needs to be validated in the future. Second, this study was retrospective, and therefore, recall and information biases might be caused during questionnaire form filling.

5. Conclusions

To draw a conclusion, the prevalence of cervical cancer among Uyghur women in Nanjiang is associated with HPV infection, sexual behavior characteristics, sexually transmitted diseases, and genetic factors. For the sake of the prevention and control of cervical cancer, both biological and behavior factors should be taken into consideration.

Author contributions

LLH and SH devised the study plan and led the writing of the article. XLW and HR collected the data and conducted the experiments. MN performed and explained the analysis, supervised the whole process and gave constructive advice and acquired funding. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Xinjiang Uyghur Municipal People's Hospital (approval number: KY20180118164).

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Conflict of interest

The authors declare no conflict of interest.

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