RESEARCH ARTICLE

Risk Factors for Cervical Cancer in Rural Areas of Wuhan China: a Matched Case-control Study

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Abstract

Cervical cancer is a serious public health problem in developing countries. We investigated possible risk factors for cervical cancer in rural areas of Wuhan China using a matched case-control study with 33 women diagnosed with cervical cancer and 132 healthy women selected from the same area as matched controls. A questionnaire, which included questions about general demography conditions, environmental and genetic factors, the first sexual intercourse, first marriage age, age at first pregnancy, pregnancy first child's age, female personal health history, social psychological factors, dietary habits, smoking and alcohol status and other living habits was presented to all participants. At the same time, HPV infection of every participant was examined in laboratory testing. Results showed HPV infection (*P*<0.000, OR=23.4) and pregnancy first child's age (*P*<0.000, OR=13.1) to be risk factors for cervical cancer. Menopause (*P*=0.003, OR=0.073) was a protective factor against cervical cancer. However, there was no indication of associations of environmental (drinking water, insecticide, disinfectant) genetic (cancer family history), or life-style factors (smoking status, alcohol status, physical training, sleep quality), including dietary habits (intake of fruit and vegetable, meat, fried food, bean products and pickled food) or social psychological factors with cervical cancer. The results suggest that the risk of cervical cancer in Chinese rural women may be associated with HPV infection, menopause and the pregnancy first child's age.

Keywords: Cervical cancer - risk factors - matched case control study - rural China

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Introduction

Cervical cancer is the most common malignancies among females worldwide. There are a multitude of risk factors for cervical cancer worldwide (Varghese et al., 1999). Cervical oncogenic risk factors can be divided in two large groups: experimentally documented and clinical or epidemiological factors. Among those classified in the first group, virtually all cases of cervical cancer are attributable to persistent infection by certain strains of Human Papilloma Virus (HPV) especially HPV-16 and HPV-18 (Raychaudhuri et al., 2012). A large body of evidence has suggested that different sexually transmitted infections (STI) may act as cofactors to HPV16 and HPV18 in cervical carcinogenesis. Infection with multiple high-risk HPV types has been suggested to increase the risk for cervical cancer compared with single infections (Kaasila et al., 2009), although there is also evidence that coinfections may act independently of each other in the progression to cervical cancer (Chaturvedi et al., 2011). Regarding clinical or epidemiological risk factors, early age at first sexual intercourse (Munoz, 2000), increased number of sexual partners (Munoz, 2000), long-term use of oral contraceptives, smoking (Giuliano et al., 2002; Parikh et al., 2003), history of infertility (Zhang et al., 1997), intrauterine device (Zhang et al., 1997), high parity (Auvert et al., 2009; Schiff et al., 2000), trauma with pregnancy (Kanato et al., 2006), low education (Shields et al., 2004), and low socioeconomic level. However, there are different risk factors in different countries or areas.

The developing world has carried a disproportionate share of the burden and 80 % of the 250,000 cervical cancer deaths in 2005 occurred there (Uysal et al., 2009). Developed countries have been successful in controlling the incidence of cervix cancer, whereas developing countries have failed dismally in this respect (Uysal et al., 2009). The success of developed countries is largely attributed to the widespread and systematic use of the Papanicolaou (Pap) smear (Cronje, 2005). The population of the People's Republic of China is 1.3 billion, of which 0.9 billion is rural. According to data from a network of 10 Chinese cancer registries, cervical cancer incidence in China is estimated to be below 4/100 000 (Dai et al., 2006). However, nationwide mortality surveys show

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a heterogeneous pattern of cervical cancer risk, with particularly high rates in central rural provinces (Yang et al., 2003a). Furthermore, while cervical cancer mortality appears to have declined considerably in urban China between 1987 and 1999, this is less marked in rural areas (Yang et al., 2003b). A recent study in one such high-risk rural area, Shanxi Province, revealed that 23.6% of women aged 35-50 years were infected with high-risk HPV types (Zhao et al., 2006). The purpose of our study was to examine prevalence rate of cervical cancer and investigate the risk of cervical cancer with menophania age, the first sexual intercourse, first marriage age, age at first pregnancy, pregnant first child's age, female personal health history, social psychological factors, dietary habit, smoking and alcohol status and other living habit, and HPV infection in rural areas of China Wuhan.

Materials and Methods

Participants

A matched case-control comparison (1:4) was designed in this study. Women between 35 and 65 years of age were recruited between June 2011 and June 2012 at Wuhan maternal and child care service centre, Hubei Province. The study comprised 33 cases and 132 controls. The case had a confirmed diagnosis of cervical cancer by pathological examination. Controls were recruited among healthy woman with normal cytology (Pap smear) and histology. Each case was matched to 4 healthy women according to age and residence. The subjects were verbally informed and received documentation explaining the purposes and procedures involved in the study. All of the subjects signed an informed consent form prior to participation in the study. This study was reviewed and approved by the Ethics Committee of both Wuhan Maternal and Child Care Service Centre and Wuhan University of Science and Technology.

Table 1. Association of Cervical Cancer Risk with Environmental and Genetic Factor

	Case group	Control group	*P* value	OR	95%CI
Drinking water			0.042#	1.747	1.021-2.989
Tap water	25	117			
Lake/river	2	2			
Shallow well	6	13			
Insecticide			0.856	1.062	0.554-2.036
Often	2	10			
Rarely	14	57			
Never	17	65			
Disinfectant			0.885	1.046	0.569-1.920
Often	5	15			
Rarely	14	70			
Never	14	47			
Noise			0.112	0.607	0.328-1.124
Often	9	28			
Rarely	21	67			
Never	3	37			
Cancer family history			0.242	1.831	0.665-5.046
Yes	7	15			
No	26	117			

#$P < 0.1$, compared with control group

Questionnaires

The questionnaires were implemented in person by professionally trained investigators. The contents of the questionnaire included questions about general demography conditions, menophania age, the first sexual intercourse, first marriage age, age at first pregnancy, pregnant first child's age, female personal health history, social psychological factors, dietary habit, smoking and alcohol status and other living habit.

HPV infection

The MALDI-TOFMS test is based on PCR amplification and single-base extension. Briefly, according to the manufacturer's instructions, the consensus primers were used to amplify 14 HR-HPV. A thermocycler (Bio-Rad, Hercules, Calif., USA) was used, the initial heating step was at 95°C for 5 min, followed by 35 cycles of 95°C for 15 s, 55°C for 15 s, and 72°C for 30 s. Single-base extension primers are specified for each HR-HPV and can be differentiated by MALDI-TOFMS. The analysis is performed at 94°C for 30 s, primer annealing at 53°C for 40 s, and primer extension at 72°C for 40 s, 50 cycles, and finally at 72°C for 3 min. The β-globin housekeeping gene was used as performance and integrity control. Controls for MALDI-TOFMS included: no template control (water), human control DNA and HPV18 plasmid DNA.

Sample aliquots were deposited onto AnchorChipTM (Bruker Daltonik GmbH, Leipzig, Germany) 400 μm targets prespotted with matrix. The matrix employed was a saturated solution of 3-hydroxypicolinic acid (Sigma-Aldrich Chemie GmbH, Buchs, Switzerland) in acetonitrile/water 1: 1 (Merck, Germany) mixed with 0.4 M dibasic ammonium citrate (Sigma-Aldrich) at a 9: 1 volume ratio. All the solvents utilized were of analytical grade or at least specified for mass spectrometry. Mass spectra were recorded on a Reflex IV MALDI-TOFMS (Bruker Daltonik) that was operated in the linear positive ion mode.

Registration and analysis of spectra were executed using XMASS and FlexAnalysis version 2.4 (Bruker Daltonik). Three times, independent analyses were run to test the detection level.

Statistical Analysis

The questionnaire answers were recorded twice and verified three times. A conditional logistic regression was performed as both as a univariate and multivariate analysis to identify independent variables. Statistical analysis was performed using the SPSS13.0 software package. All *P* values were derived from two-sided statistical tests, statistical significance of univariate and multivariate analysis was defined as $P<0.10$ and 0.05, respectively.

Results

Study Participants

The mean age was 46.70 ± 8.99 years in the case group, while it was 46.48 ± 8.41 years in the control group. The case and control groups were similar with respect to age, height, family income, and education. There were no significant differences in weight, BMI and marital status between case group and control group ($P>0.05$)

Table 2. Association of Cervical Cancer Risk with Female Personal Health History

	Case group	Control group	*P* value	OR	95%CI
Menophania age (years)	14.45±2.18	14.17±2.02	0.475	0.447	0.199-1.017
≤13	10	60	0.055#		
>14	23	72			
The first sexual intercourse (years)	22.03±2.54	24.33±2.73	0.000#	9.174	2.415-35.714
17-20	9	8	0.001#		
≥21	24	124			
First marriage age (years)	22.73±3.11	24.87±2.53	0.000#	6.25	2.688-14.493
17-20	8	2	0.000#		
21-24	17	60			
≥24	8	70			
Age at first pregnancy (years)	22.85±2.33	25.46±2.68	0.000#	11.111	3.831-32.258
18-21	9	3	0.000#		
22-25	19	67			
≥26	5	62			
Pregnant first child's age (years)	23.33±2.63	25.88±2.73	0.000#	7.353	2.857-18.868
19-22	12	9	0.000#		
23-26	17	74			
≥27	4	49			
Fertility births			0.058#	1.58	0.984-2.538
0	0	0			
1	11	45			
2	10	53			
≥3	12	34			
Vaginal delivery times			0.11	0.643	0.371-1.105
0	0	6			
1	13	45			
2	8	48			
≥3	12	33			
Fornication			0.803	0.75	0.078-7.210
Yes	1	3			
No	32	129			
Menopause			0.002#	0.172	0.057-0.521
Yes	17	38			
No	16	94			
Oral contraceptive			0.259	0.407	0.085-1.937
Yes	3	115			
No	30	17			
HPV infection (Y/N)			0.000#	5.631	2.337-13.570
Positive	15	18			
Negative	18	114			
Gynecological disease			0.207	0.603	0.275-1.322
Yes	19	60			
No	14	72			
Gynecological examination			0.915	1.013	0.803-1.279
Never	9	28			
>2 years	0	8			
1 year to 2 years	1	9			
Half year to 1 year	4	19			
Half year	19	68			

#$P < 0.1$, compared with control group

Environmental and genetic factors

The relationship between environmental and genetic factor (source of drinking water, insecticide, disinfectant and cancer family history) and cervical cancer was concluded from univariate and multivariate analysis. As seen in Table 1, insecticide, disinfectant and cancer family history were not directly associated with the incidence of cervical cancer. There was significant difference in source of drinking water between case group and control group by univariate analysis, but multivariate analysis suggested that drinking water was not directly associated with the incidence of cervical cancer.

Female personal health history

The relationship between female personal health history and cervical cancer was also concluded from both univariate (Table 2) and multivariate analysis (Table 5). At $P<0.10$ level, there was significant difference in menophania age, the first sexual intercourse, age at first pregnancy, pregnant first child's age, fertility births and menopause by univariate analysis, however only pregnant first child's age and menopause were directly associated with cervical cancer by multivariate analysis.

Living habit and social psychological factors

In this study, living habit (smoking, drinking history, physical training) and social psychological factors (adverse event of life, moodiness, emotion regulation capacity) were not directly associated with cervical cancer (Table 3).

Table 3. Association of Cervical Cancer Risk with Living Habit and Social Psychological Factors

	Case group	Control group	*P* value	OR	95%CI
Smoking (almost/sometime/hardly)	0/0/33	1/2/129	0.594	12.71	0.001-145.27
Passive smoking (almost/sometime/hardly)	12/12/9	54/44/34	0.801	1.065	0.651-1.744
Drinking (almost/sometime/hardly)	1/6/26	2/28/102	0.946	0.97	0.405-2.327
Physical training (almost/sometime/hardly)	5/10/18	22/53/57	0.653	0.881	0.507-1.529
Stay up late (almost/sometime/hardly)	2/14/17	5/50/77	0.58	1.205	0.624-2.326
Sleep quality (good/common/poor)	9/20/4	28/89/15	0.445	0.76	0.375-1.537
Personality (extroversion/common/introvert)	8/10/5	38/80/14	0.506	1.241	0.657-2.344
Adverse event of life (yes/no)	5/28	17/115	0.669	1.261	0.435-3.663
Moodiness (almost/sometime/hardly)	0/31/2	9/99/24	0.342	1.515	0.643-3.571
Emotion regulation capacity (good/common/poor)	7/24/2	17/104/11	0.354	0.681	0.302-1.535

Table 4. Association of Cervical Cancer Risk with Dietary Habit

	Case group	Control group	*P* value	OR	95%CI
Pickled food(almost/sometime/hardly)	0/29/4	4/114/14	0.731	0.829	0.285-2.410
Fried food(almost/sometime/hardly)	0/26/7	0/107/25	0.747	1.186	0.298-2.380
Meat food (almost/sometime/hardly)	11/17/5	17/114/1	0.385	0.671	0.606-3.663
Vegetable (almost/sometime/hardly)	2025-3-3	97/35/0	0.869	0.935	0.421-2.075
Fruit (almost/sometime/hardly)	4/27/2	15/111/6	0.856	1.094	0.346-0.914
Bean products(almost/sometime/hardly)	3/25/5	9/114/9	0.438	0.687	0.266-1.773
Dairy products(almost/sometime/hardly)	3/26/4	20/99/13	0.464	0.74	0.330-1.658
Tea(almost/sometime/hardly)	2003-11-19	17/50/65	0.488	0.815	0.457-1.453
Health care products(almost/sometime/hardly)	2001-5-27	1/30/101	0.612	0.791	0.319-1.961

Table 5. Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Risk of Cervical Cancer

	B value	SE	Wald	*P* value	ORs	95% CIs
HPV infection	3.155	0.801	15.527	0[#]	23.445	4.882-112.594
Pregnant first child's age	2.575	0.654	15.503	0[#]	13.137	3.654-47.345
Menopause	-2.619	0.87	9.066	0.003[#]	0.073	0.013-0.401

[#]$P < 0.1$, compared with control group

Dietary habit

As indicated in Table 4, univariate analysis showed no significant differences between cervical cancer in relation to dietary habit, such as intake of fruit, meat, bean products, dairy products, fried food or pickled foods and so on.

HPV infection

The relationship between HPV infection and cervical cancer was analyzed by both univariate (Table 2) and multivariate analysis (Table 5). Multivariate analysis suggested that HPV infection could increase significantly the risk of cervical cancer ($P<0.000$, OR=23.445).

Discussion

Although HPV infection is a well-known crucial risk for cervical cancer, other cofactors also have some effects. Studies have shown that some lifestyle, environmental factor, history of previous and present illness, history of personal health, and social psychological factors may promote high-risk HPV carriers to develop cervical cancer (Natphopsuk et al., 2011; Kivistik et al., 2012). In this study, results indicated that HPV infection, menopause, and the pregnant first child's age might influence the incidence of cervical cancer in rural areas of China Wuhan.

In our study, results showed that HPV infection ($P<0.000$, OR=24.335) was identified as a risk factor for cervical cancer. HPV infection is an essential factor in the development of CIN and cervical cancer. When HPV acquisition is followed by HPV persistence instead of clearance, there is a high chance for progression to precancerous lesions and ultimately invasive lesions. HPV is a double stranded closed circular DNA virus with the capacity to incorporate in the human DNA (Hoste et al., 2013). HPV infection is the most common sexual transmitted disease with more than 80% of the population infected at some time in their life. HPV infection was also detected in the controls indicated that not all of the HPV-infected women developed cervical cancer or CIN. Among healthy women, an HPV infection was able to clear within 1-2 years (Schiffman et al., 2007 ; Kapeu et al., 2009) and <1% of HPV-positive women would go on to develop cervical cancer (Nagpal et al., 2002).

HPV exposure is critically dependent on risky sexual behavior, such as the age of first sexual intercourse, age at first pregnancy, pregnant first child's age, the selection of contraceptive methods, and most importantly the lifetime number of sexual partners (Appleby et al., 2007). Early age at first sexual intercourse has been associated with an increased risk of high-risk HPV infection that in susceptible women is responsible for virtually all cases of invasive cervical cancer (Bosch et al., 2002). Age at first marriage is often used as a proxy measure for early age at first sexual intercourse, and those who engage in early sexual intercourse may also consequently become pregnant at an early age. Besides early age at first sexual intercourse, early childbearing has also been linked as a

risk factor for cervical carcinogenesis and attributed to the cervical trauma experienced during early age at first pregnancy, or subsequently, by high-parity births (Louie et al., 2009).

The mechanism by which the early experience of first sexual intercourse and first pregnancy could influence the risk of cervical carcinogenesis may be explained by the steroid hormonal influence on HPV infection and on the host's immune response to HPV during pre-adolescence and adolescence. The transformation zone of the cervical epithelium has been recognised as the site in which HPV infection tends to cause cancer, and the susceptibility of this area is believed to be related to its denudation of the stratified epithelium, thus facilitating exposure of the basal layer to HPV with minimal trauma (Louie et al., 2009). During pregnancy, the cervix is exposed to augmented levels of hormonal changes, in which oestrogen stimulation facilitates acidification of the vaginal cavity, a determinant of squamous metaplasia when the endocervical epithelial everts (Elson et al., 2000). When this oestrogen-stimulated metaplastic transformation occurs in the presence of HPV, the probability of cell transformation increases, resulting in neoplastic changes (Elson et al., 2000; Hwang et al., 2009). This phenomenon is dependent primarily on parity, and is more likely to occur during the first pregnancy rather than subsequent pregnancies (Louie et al., 2009). In our study, there was significant difference in the first sexual intercourse, age at first pregnancy, pregnant first child's age and fertility births by univariate analysis, nevertheless, only pregnant first child's age was directly associated with cervical cancer by multivariate analysis. The reason might be because of the difference of the first sexual intercourse. In the present study, the mean age at the first sexual intercourse was 20.85 years compared to 18.0 years in Northern Thailand (Liu et al., 2006) , 14.0 in America (De Genna et al., 2011), 15.7 in Europe (Panatto et al., 2012) and 14.8 in Africa (Dingeta et al., 2012), so, the first sexual intercourse occurs mainly during the adult rather than adolescence.

The uterine cervix is highly responsive to steroidal hormones, such as estrogen. Correspondingly, cervical cancers most commonly arise in the third to fifth decade (i.e., premenopausal period) of life in women. Furthermore, use of oral contraceptives

or high parity has been shown to significantly increase the risk for cervical cancer in HPV-infected women (Chung et al., 2009). These observations raise the possibility that steroidal hormones, such as estrogen, might affect cancers. Therefore, theoretically, the women are more difficult to develop cervical cancers after menopausal period than premenopausal period. Our study also showed that menopause was a protective factor against cervical cancer. A paper reported that menopause showed no significant associations with cervical cancer in Norway (Kvale et al., 1988). The reason of this difference might be environmental and genetic factor in different countries or areas.

In conclusion, our study implies that cervical cancer is the result of multiple factors working together to increase risk. HPV infection and pregnant first child's age are the main risk factors for cervical cancer, and menopause was a protective factor against cervical cancer among females in rural areas of China Wuhan. So, the importance of HPV-vaccination programmes can have a great effect in decreasing the incidence of cervical cancer. Further work is needed to identify potential risk factors for cervical cancer in rural areas of China.

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