Original Article

Distribution of high-risk human papillomavirus genotype prevalence and attribution to cervical precancerous lesions in rural North China

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Abstract

Objective: Precise prevention is more desired for cervical cancer due to the huge population, high prevalence of human papillomavirus (HPV) infection in China and the vision of screen-and-treat strategies in low- and middle-income countries (LMICs). Considerations of combining type-specific prevalence and attribution proportion to high-grade cervical intraepithelial neoplasia are informative to more precise and effective region-specific cervical cancer prevention and control programs. The aim of the current study was to determine the genotype distribution of HPV and attribution to cervical precancerous lesions among women from rural areas in North China.

Methods: A total of 9,526 women participated in the cervical cancer screening project in rural China. The samples of women who tested positive for HPV were retested with a polymerase chain reaction (PCR)-based HPV genotyping test. The attribution proportion of specific high-risk human papillomavirus (HR-HPV) types for different grades of cervical lesions was calculated by using the type contribution weighting method.

Results: A total of 22.2% (2,112/9,526) of women were HR-HPV positive and HPV52 (21.7%) was the most common HR-HPV genotype, followed by HPV58 (18.2%), HPV53 (18.2%) and HPV16 (16.2%). The top three genotypes detected in HR-HPV-positive cervical intraepithelial neoplasia (CIN)1 were HPV16 (36.7%), HPV58 (20.4%), HPV56 (15.3%). Among CIN2+, the most frequent genotypes were HPV16 (75.6%), HPV52 (17.8%), HPV58 (16.7%). HPV16, 56, 58, 53, 52, 59, 68, and 18 combined were attributed to 84.17% of all CIN1 lesions, and HPV16, 58, and 52 combined were attributed to 86.98% of all CIN2+ lesions.

Conclusions: The prevalence of HR-HPV infection among women from rural areas in North China was high and HPV16, HPV58, HPV52 had paramount attributable fraction in CIN2+. Type-specific HPV prevalence and attribution proportion to cervical precancerous lesions should be taken into consideration in the development of vaccines and strategy for screening in this population.

Keywords: Human papillomavirus; cervical intraepithelial neoplasia; genotype distribution; attribution proportion; cervical cancer

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Introduction

Cervical cancer is the 4th most commonly diagnosed cancer in women globally, and it is the 2nd most diagnosed in women living in less-developed regions (1). GLOBOCAN 2018 estimates that there were an estimated 569,847 new cases and approximately 311,365 deaths from cervical cancer worldwide (1). A large majority of the cervical cancer burden occurs in less-developed regions (2). In mainland China, the incidence rate of cervical cancer is estimated to be about 15.4/100,000 and cervical cancer is the 8th leading cause of cancer deaths in Chinese women based on 2018 data, with the mortality rate being as high as 6.9/100,000 (3).

Persistent high-risk human papillomavirus (HR-HPV) infection is the most important cause of the progression of cervical cancer and its precursors. There are more than 150 HPV types being identified and at least 13 of them are regarded as “high risk” contributing to the development of cervical cancer including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 (4); it has been suggested that their

Detection and genotyping of HPV

_Care_HPV testing (Qiagen, Gaithersburg, MD, USA)

_Care_HPV testing is based on nucleic acid hybridization detection, targeting 14 high-risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). However, _care_HPV testing cannot determine the specific HPV genotype. The test measures the ratio of relative light units emitted by microplate reader (RLU) to cutoff (CO). If the RLU/CO value ≥1.0, the participant is considered to be high-risk HPV positive; otherwise, considered to be high-risk HPV negative.

PCR-based HPV testing without genotyping (Sansure, Changsha, China)

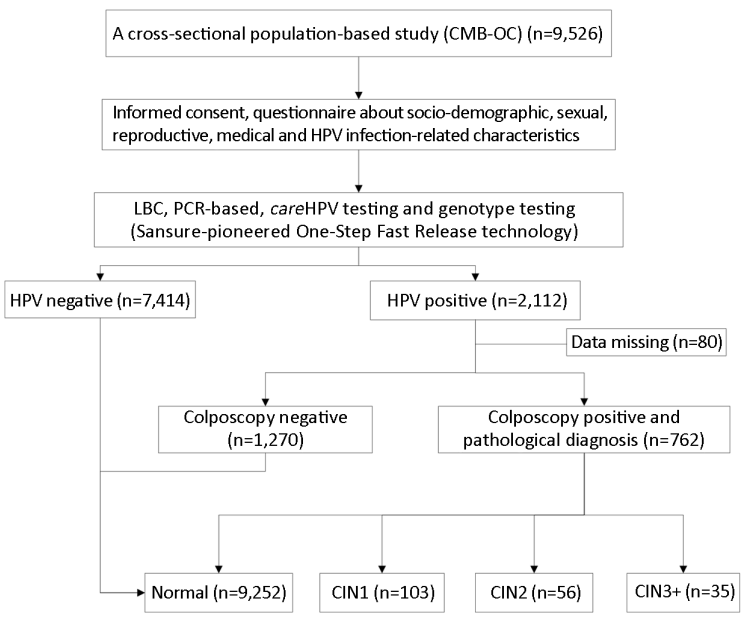
Sansure PCR HPV testing employs the One-Step Fast Release technology, targeting 15 HR-HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68), and has been approved by a European Union Certificate (CE). By applying real-time fluorescent quantitative PCR, the testing utilizes pairs of specific primers and specific probes accompanied with other reagents in the PCR mix to achieve rapid detection of HR-HPV DNA. The manual sample processing requires about 45 min by minimally trained personnel prior to an automated detection procedure, which can be completed within 1 h and 20 min. HPV positivity is measured by the cycle numbers observed (Ct) when the fluorescent signal reaches the set threshold. A Ct ≤39 is considered HPV positive and a Ct >39 is considered negative.

HPV test with genotyping (Sansure, Changsha, China)

Subsequent genotyping for HR-HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68) was performed according to the above-mentioned PCR test principles and workflow but with detection of the exact types.

Confirmation of disease status

Pathology was the gold-standard endpoint measure. Experienced pathologists at CICAMS reviewed every histology slide and classified each finding as negative, CIN grade 1/2/3, squamous cell carcinoma (SCC), adenocarcinoma *in situ* (AIS), or adenocarcinoma (ADC). For women initially without pathological results, final classification was based on the overall combination of testing measures. To exclude verification bias, we applied the following criterion for final analysis: women without biopsies were classified as normal if they either had a negative colposcopy impression or if they had negative results for the HR-HPV test both in _care_HPV and PCR HPV tests (*Figure 1*).



Screening flowchart. CMB-OC, Point of Care (POC) for the Cervical Cancer Screening and Management in Low-resource Settings in China study; HPV, human papillomavirus; LBC, liquid-based cytology; PCR, polymerase chain reaction; CIN1, cervical intraepithelial neoplasia grade 1; CIN2, cervical intraepithelial neoplasia grade 2; CIN3+, cervical intraepithelial neoplasia grade 3 or worse.

It should be noted that local laboratory technicians and physicians involved in this study were trained uniformly by CICAMS and WHO/IARC experts in preparation for this study.

Statistical analysis

Analyses were focused on the description of distribution and attribution of HR-HPV genotypes for cervical precancerous lesions in China. Socio-demographic characteristics of participants were described using means, standard deviations (SD), frequencies, and proportions; comparisons of characteristics of different grades of cervical lesions (normal, CIN1, CIN2 and CIN3+) were conducted by Pearson χ^2 or Fisher's exact tests, as appropriate. The calculations of attributable proportions of lesions caused by specific HPV types have been described in a previous paper (9-11). In short, the proportion of single infection HPV genotype among the population in the same pathological grade was used as the standard for evaluating the contribution ratio of each genotype for individuals with single or multiple infections. If, for example, there are 6 single-type HPV16 incidences and 4 single-type HPV18 for CIN2 cases, the derivation of the attributable portion of each genotype for 2 CIN2 lesions positive for both HPV16 and 18 in a study is as follows: 2×6/(6+4)=1.2 of these 2 multi-type infected lesions would be attributed to HPV16, and 2×4/(6+4)=0.8 would be attributed to HPV18. All analyses were conducted using IBM SPSS Statistics (Version 23.0; IBM Corp., NewYork, USA). We considered P<0.05 to be statistically significant, and all tests performed were two-sided.

Results

General characteristics

A total of 9,526 women were included in the final analysis. The mean age of participants was 47.3±7.8 years old, the mean age at menarche was 15.2±2.0 years old, and the mean age of first sexual intercourse was 22.2±2.1 years old. About 1.4% (135/9,516) had more than 2 sexual partners, and 26.4% (2,504/9,469) were post-menopause. Additionally, 70.0% of participants (6,663/9,518) had middle school-level or higher education.

Among the 9,526 women, 2,112 (22.2%) women were positive for either *care*HPV or PCR HPV test without genotyping, in which 88.7% (1,874/2,112) were infected with specific HPV genotypes. All HPV-positive participants had colposcopy except 80 women lost to follow-up. Finally, 9,252 (97.1%) were pathologically normal, 103 (1.1%) had CIN1, and 91 (1.0%) had CIN2+. We set the mean age (47 years old) as the criterion for stratifying the women into subgroups, 15 years old as an early age for menarche, and 22 years old as an early age for first sexual intercourse. The analyses discussed later were performed among the stratified age groups. There was no statistically significant correlation between demographic characteristics and cervical lesion severity (*Table 1*).

Distribution of HR-HPV among different grades of cervical lesions

Among the 1,874 women (19.7%, 1,874/9,526) with HR-HPV positive for any of 15 HR-HPV types, and HPV52 (21.7%) was the most common HR-HPV genotype. This is followed by HPV58 (18.2%), HPV53 (18.2%), HPV16 (16.2%), and HPV68 (14.8%). The prevalence of HPV in normal pathology, CIN1, CIN2, and CIN3+ were 17.4% (1,611/9,252), 95.1% (98/103), 98.2% (55/56), and 100.0% (35/35), respectively. HPV prevalence is positively correlated with cervical lesion severity (χ^2=779.312; P<0.001; P_{trend}<0.001).

Among women with normal pathology results, the 6 most prevalent HR-HPV types were HPV52 (22.3%), HPV53 (18.4%), HPV58 (18.0%), HPV68 (15.1%), HPV51 (12.7%) and HPV16 (11.6%). For women with CIN1, the most prevalent HR-HPV types were HPV16 (36.7%), HPV58 (20.4%), HPV56 (15.3%), HPV52 (14.3%), HPV51 (14.3%), HPV53 (14.3%), and HPV68 (14.3%); for women with CIN2+, the most frequent genotypes were HPV16 (75.6%), HPV52 (17.8%), HPV58 (16.7%), HPV53 (15.6%), HPV33 (10.0%), and HPV31 (8.9%).

The proportions of single and multiple infections among women were 59.0% (951/1,611) and 41.0% (660/1,611) in normal pathology; 51.0% (50/98) and 49.0% (48/98) in CIN1; 50.9% (28/55) and 49.1% (27/55) in CIN2; and 60.0% (21/35) and 40.0% (14/35) in CIN3+, respectively. The trend test showed no significance (χ^2=1.331; P=0.249) (*Figure 2*).

The prevalence of HPV16 was positively correlated with the severity of cervical lesions (11.6% in normal, 36.7% in CIN1, 65.5% in CIN2, 91.4% in CIN3+, Fisher's Exact =546.876; P<0.001) (*Table 2*).

Attributable proportion of HPV in different grades of cervical lesions

The prevalence of specific HPV types in different grades of

Demographic characteristics of study population correlated to cervical lesion severity

Characteristics	Normal	CIN1	CIN2	CIN3+	χ^2	P
Age (ear)						
47	4,885	51	27	14	3.172	0.366
>47	4,367	52	29	21		
Ed cation le. el						
No ed cation	607	12	5	2	4.777*	0.171
Ed cated	8,637	91	51	33		
Age at menarche (ear)						
15	5,475	64	28	20	2.394	0.495
>15	3,769	39	28	15		
Age at first se al interco rse (ear)						
22	5,414	63	33	20	0.326	0.955
>22	3,838	40	23	15		
No. of se al partners						
1	9,112	99	56	34	5.279*	0.109

HR-HPV-positive cervical lesions, along with an estimate of the attributable fraction of HPV (defined as an estimate of the proportion of lesions caused by a given HPV type), was shown in *Table 2*.

Distribution and attributable proportion of HR-HPV genotypes among different grades of cervical lesions

HR-HPV genotype	Normal pathology (n=9,252)			CIN1 (n=103)			CIN2+ (n=91)			Total population (n=9,526)***		
	n (%)*	Single infection (n)	Attributable proportion(%)**	n (%)*	Single infection (n)	Attributable proportion (%)**	n (%)*	Single infection (n)	Attributable proportion (%)**	n (%)*	Single infection (n)	Attributable proportion (%)**
Any type	1,611	951	100.00	98	50	100.00	90	49	100.00	1,874	1,089	100.00
16	187 (11.61)	84	8.09	36 (36.73)	13	30.68	68 (75.56)	37	73.53	303 (16.17)	140	12.09
18	83 (5.15)	26	2.27	12 (12.24)	3	5.64	6 (6.67)	0	0.37	105 (5.60)	31	2.41
31	113 (7.01)	45	4.02	8 (8.16)	2	3.40	8 (8.89)	1	1.68	137 (7.31)	49	3.91
33	141 (8.75)	53	5.22	8 (8.16)	1	2.01	9 (10.00)	1	3.42	164 (8.75)	56	4.71
35	66 (4.10)	16	1.45	3 (3.06)	1	1.13	3 (3.33)	1	1.17	75 (4.00)	19	1.45
39	152 (9.44)	27	3.51	6 (6.12)	0	0.00	1 (1.11)	0	0.37	165 (8.80)	28	3.09
45	45 (2.79)	13	0.99	3 (3.06)	2	2.11	1 (1.11)	0	0.00	54 (2.88)	16	1.06
51	204 (12.66)	76	7.86	14 (14.29)	2	5.45	6 (6.67)	2	3.12	229 (12.22)	81	7.20
52	359 (22.28)	155	17.47	14 (14.29)	3	7.29	16 (17.78)	2	5.43	406 (21.66)	164	16.32
53	297 (18.44)	120	13.08	14 (14.29)	4	8.14	14 (15.56)	0	0.56	341 (18.20)	126	12.39
56	176 (10.92)	61	6.31	15 (15.31)	7	10.60	6 (6.67)	0	0.00	211 (11.26)	73	6.49
58	290 (18.00)	124	13.14	20 (20.41)	4	8.62	15 (16.67)	4	8.02	341 (18.20)	140	13.04
59	103 (6.39)	49	4.15	9 (9.18)	5	6.81	2 (2.22)	0	0.56	119 (6.35)	55	4.08
66	146 (9.06)	57	5.33	7 (7.14)	1	1.73	2 (2.22)	0	0.37	158 (8.43)	60	4.83
68	243 (15.08)	45	7.13	14 (14.29)	2	6.39	6 (6.67)	1	1.40	277 (14.78)	51	6.92

HR-HPV, high-risk human papillomaviruses; CIN1, cervical intraepithelial neoplasia grade 1; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; *, The total percentage of each HPV type is not necessarily equal to 100% because a result may be counted more than once in cases where the sampled lesion contained multiple HPV types; **, Proportion of multiple attributable fraction and number of single infection within HR-HPV positive women; ***, Eight women who had no pathological results but had HPV tests results were also included in the total population analysis. A total of 238 women were positive in initial HPV results (*care*HPV or PCR HPV test without genotyping) but failed to be genotyped with specific genotypes, 232 of whom were pathologically normal, 5 of whom had CIN1, and 1 of whom had CIN2+.

HPV16 was attributed to 30.68% of CIN1, 73.53% of CIN2+; it was the genotype with the highest attributable proportion observed in CIN1 and CIN2+ (*Figure 3*).

In total, HPV16, 56, 58, 53, 52, 59, 68, and 18 combined were attributed to 84.17% of all CIN1 lesions, and HPV16, 58, and 52 combined were attributed to 86.98% of all CIN2+ lesions (*Figure 3*).

Discussion

This cross-sectional population-based study describes the distribution of high-risk HPV and their respective attribution proportions to cervical precancerous lesions among women from rural areas in North China. Overall, HR-HPV prevalence was 22.2% (2,112/9,526), which is higher than the pooled analysis from 17 population-based studies throughout China which indicated HR-HPV prevalence was 18.0% in rural women (12); this is attributed to prevalence results arising from positive for *care*HPV or PCR HPV testing without genotyping. In our study, HPV52 was the most commonly detected HR-HPV types in cervical specimens which was consistent with other studies conducted in Jiangsu, Guangdong and other provinces (13,14). However, some other studies found that

knowledge of the distribution of HPV types in different cervical lesions will benefit to estimate the potential protection provided by current HPV vaccines. And the determination of the most common HPV types in cervical lesions can influence the development of new polyvalent HPV vaccines. Our study suggests that HPV16, HPV52, and HPV58 play important roles in the development of cervical lesions in rural North China, and these particular HPV carcinogenic types should be given priority in the development of new polyvalent HPV vaccines. Moreover, based on the ecological principles, there exists competitive restraint between different strains and types, and so also is HPV. Elimination of one strain/type via vaccination may cause an increase in prevalence of other untargeted HPV vaccine genotypes because of reduced competition during natural infection. A study undertaken in US compared the HPV prevalence between HPV-vaccinated and non-vaccinated young adult women (20–26 years old) and reported that compared to the unvaccinated women, vaccinated women had a higher prevalence of nonvaccine high-risk types including HPV39, 52, 53 (20). Therefore, surveillance on the prevalence and attribution of HPV genotypes after wide spread use of vaccines in East Asia is important to identify type replacement early if it ever happens (21,22)

Because of vaccines' high prices, vaccination coverage is still very low in China, especially in low-resource areas. In such regions, screening takes precedence over vaccinations in the prevention of cervical cancer.

In our study, HR-HPV genotype distribution and attribution to cervical precancerous lesions are based on the self-collected cervicovaginal specimens tested for HPV DNA (Self-HPV testing). Self-sampling, as an alternative for the collection of a clinician sample, could become the new paradigm for primary cervical cancer screening in the general population. Most studies made that conclusion based on the evaluating the diagnostic accuracy of self-HPV testing and physician-HPV testing (23). Our results indicated the paramount role of HPV16, 33, 51, 52, 58 attributable to CIN2+, which is consistent with the result of previous study using clinician-collected cervical samples (9). Our study further validates that the identical HR-HPV genotypes need to be focused on using self-HPV testing and physician-HPV testing in terms of the attribution proportion to CIN2+. A population-based cohort study in China using physician-collected samples indicated that HPV 16 and HPV 31 had the highest cumulative risk of CIN2+ within 10-year follow-up, followed by HPV 58, 39, 33, 52, and 18 (24). This was one of the very few studies to evaluate the predictive value of type-specific HPV in detecting cervical cancer and precancers in a Chinese population-based cohort, and it remains a need for more prospective studies with greater sample sizes to identify specific HR-HPV genotype attributable to CIN2+. HPV16, HPV58, and HPV52 combined were attributed to 87.0% of all CIN2+ lesions in our study; HPV52 and HPV58 were attributed to 13.5% of CIN2+ cases. Based on our cross-sectional study, besides HPV16, HPV52, 58 may also deserve special attention if HPV self-sampling rolls out as primary screening in general population. In accordance with updated screening guidelines (25), only HPV 16/18 positive women were recommended for direct referral to colposcopy, and non-16/18 HR-HPV positive women were recommended for triaging with cytology to colposcopy. Our follow-up results will contribute to further clarify whether other HR-HPV genotypes positive women, besides HPV 16/18, should directly be referred to colposcopy. It seems that HPV52 and HPV58 may warrant special attention in screening procedures in these regions. Consideration of combining type-specific HPV prevalence and attribution proportion to high-grade cervical intraepithelial neoplasia could be informative to more precise and effective region-specific cervical cancer screening programs.

Our study does have some limitations. In present study, 238 (11.3%) women with either *care*HPV or PCR HPV positive results failed to be genotyped with specific genotypes, which was also documented in a recent study, presenting a crude agreement of 73.27% between hybrid capture 2 (HC2) test and SPF10-LiPA system in detecting carcinogenic HPV genotypes (26). The potential bias

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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