Research Article

Cancer Prevention Research

Risk Prediction of Cervical Cancer and Precancers by Type-Specific Human Papillomavirus: Evidence from a Population-Based Cohort Study in China

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Abstract

Risk stratification of human papillomavirus (HPV)-positive women is needed to avoid excessive colposcopy and overtreatment in cervical cancer screening. We aimed to evaluate the predictive value of type-specific HPV in detecting cervical cancer and precancers in a Chinese population–based cohort and provide evidence of HPV genotyping to triage HPV-positive women. We typed all Hybrid Capture 2–positive cytologic samples of 1,742 women in Shanxi Province Cervical Cancer Screening Study cohort. Cumulative risks of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) among HPV-positive women and cumulative detection rates of CIN2+ among general women by type-specific HPV were estimated during the course of 10-year follow-up. HPV 16 and HPV 52 were most prevalent types among the screening population. Ten-year cumulative risk of CIN2+ was 47.5% [95% confidence interval (CI), 31.6–62.3] for HPV 16–positive women and 46.3% (95% CI, 15.3–75.4) for HPV 31–positive women. Ten-year cumulative risks of CIN2+ among HPV 58, 39, 33, 18, and 52 positive women ranged from 34.3% to 12.0% in a decreasing order. CIN2+ risks were found to be positively associated with infection times of the same genotypes of HPV 16, 31, 33, and 58 (all $P_{trend} < 0.001$). Cumulative detection rates of CIN2+ within 10 years were predominantly contributed by HPV 16, 31, and 58. Our results support the risk-based management of HPV-positive women using HPV genotyping and also indicate the significance of including HPV 31 and 58 apart from commonly acknowledged HPV 16 and HPV 18 in achieving better risk stratification. *Cancer Prev Res; 10(12); 745–51. ©2017 AACR.*

Introduction

Cervical cancer is the second most common cancer in women with an estimated 528,000 new cases and 260,000 deaths per year worldwide. Almost 85% of the global burden occurs in low and middle-income countries (1). Moreover, a substantial increase of cervical cancer incidence was seen in China in contrast to a decreasing trend in some developed countries (2). It is estimated that 98,900 new cases and 30,500 deaths occurred in 2015 in China (3).

High-risk human papillomavirus (hrHPV) infection has been established as a prerequisite for progressing to invasive cervical cancer (4, 5). Growing bodies of biological and epidemiologic studies suggest that different hrHPV genotypes confer different risks of cervical cancer (6, 7). HPV 16 and HPV 18 predict much higher risks of cervical cancer and precancers than other HPV types (8, 9); therefore, HPV 16 or HPV 18–positive women were recommended to triage hrHPV-positive women for further colposcopy (9–11). In addition, HPV 31 infection was reported to cause a distinctive high risk in the Portland Kaiser Cohort Study and in the Denmark cohort study (12, 13). HPV 52 and HPV 58 also attract special attentions, due to their high prevalence and high risk of developing cervical cancer and precancers in East Asian women (9, 10).

What remained unclear, however, was whether additional separation of non-16/18 hrHPV types could better identify Chinese women at particularly high risk of cervical precursors. Therefore, we investigated the association of type-specific HPV infection with subsequent cervical intraepithelial neoplasia grade 2 or worse (CIN2+) risks in a cervical cancer screening cohort among Chinese women to evaluate the feasibility of risk stratification by HPV genotypes. We also evaluated the cumulative detection rate of CIN2+ contributed by hrHPV genotypes.

Materials and Methods

Study population

In 1999, 1,997 women aged 35 to 45 years were enrolled in Shanxi Province Cervical Cancer Screening Study I (SPOCCS I) study (14–16). They were nonpregnant and had no history of cervical screening or hysterectomy. Three follow-ups were organized in 2005, 2010, and 2014, respectively. Because no cytologic specimens in 1999 remained for HPV genotyping, the final analytic cohort was based on three visits from 2005 to 2014. Finally, a total of 1,742 eligible women were followed up in 2005. Women diagnosed as CIN2+ or receiving hysterectomy due to CIN2+ or noncervical-related diseases during follow-up were

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Table 1. Sociodemographic characteristics for women followed up and lost to follow-up

General characteristics		Analytic women in 2005 $n = 1{,}742$ (%)	Analytic women in 2010[a] Followed up $n = 1{,}435$ (%)	Lost to follow-up $n = 195$ (%)	P	Analytic women in 2014[a] Followed up $n = 1{,}205$ (%)	Lost to follow-up $n = 229$ (%)	P
Median age (years old, IQR)		45 (5)	45 (5)	46 (6)	0.444	45 (5)	46 (7)	0.140
Marital status	Married	1,703 (97.8)	1,408 (98.1)	185 (94.9)	0.004	1,179 (97.8)	226 (98.7)	0.404
	Others[b]	39 (2.2)	27 (1.9)	10 (5.1)		26 (2.2)	3 (1.3)	
Education level[c]	High	969 (55.6)	819 (57.1)	104 (53.3)	0.323	695 (57.7)	128 (55.9)	0.617
	Low	773 (44.4)	616 (42.9)	91 (46.7)		510 (42.3)	101 (44.1)	
Current smoking	Yes	114 (6.5)	92 (6.4)	12 (6.2)	0.890	77 (6.4)	17 (7.4)	0.562
	No	1,628 (93.5)	1,343 (93.6)	183 (93.8)		1,128 (93.6)	212 (92.6)	
Menopause	Yes	255 (14.6)	205 (14.3)	40 (20.5)	0.022	163 (13.3)	41 (17.9)	0.082
	No	1,487 (85.4)	1,230 (85.7)	155 (79.5)		1,042 (86.5)	188 (82.1)	
Age at sexual debut (years old)	>20	888 (51.0)	743 (51.8)	98 (50.3)	0.690	618 (51.3)	127 (55.5)	0.247
	≤20	854 (49.0)	692 (48.2)	97 (49.7)		587 (48.7)	102 (44.5)	
Husband's ESR	Yes	62 (3.6)	47 (3.3)	10 (5.1)	0.186	41 (3.4)	6 (2.6)	0.542
	No	1,680 (96.4)	1,388 (96.7)	185 (94.9)		1,164 (96.6)	223 (97.4)	
Woman's ESR	Yes	179 (10.3)	150 (10.5)	23 (11.8)	0.568	124 (10.3)	22 (9.6)	0.754
	No	1,563 (89.7)	1,285 (89.5)	172 (88.2)		1,081 (89.7)	207 (90.4)	

Abbreviations: ESR, extramarital sexual relationships; IQR, interquartile range.

[a]All comparisons of general characteristics between those followed up and lost to follow-up were based on the information collected in 2005.

[b]Including divorced and widowed.

[c]Junior high school and above was categorized as high level.

excluded from subsequent analysis, as illustrated in Fig. 1. The study protocol was approved by Institutional Ethical and Research Reviews Boards of the Cancer Institute/Hospital, Chinese Academy of Medical Sciences (CICAMS, Beijing, China).

Screening procedures

Detailed screening procedures have been described previously (17). To summarize, participants were screened with liquid-based cytology (LBC), Hybrid Capture 2 (HC2) testing, and visual inspection with acetic acid (VIA) in 1999, 2005, 2010, and 2014 (except for VIA in 2014). Participants positive by any of three tests were referred for colposcopy and biopsy if necessary. Women with histology-confirmed CIN2+ lesions were recommended for treatment according to the local clinical guidelines.

HC2 assay

HC2 assay (Qiagen Inc.) was performed on the remaining cervical cytologic samples by senior technicians. HC2 assay combines antibody capture of HPV DNA and RNA probe hybrids and chemiluminescent signal detection. It can collectively detect 13 hrHPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) but does not discriminate individual genotypes. Samples with 1.0 pg/mL of HPV DNA (approximately 5,000 copies) or greater were considered as HC2 positive.

HPV genotyping

SPF_{10}-LiPA system was used to discriminate HPV genotypes on all HC2-positive cytologic specimens. Total DNA was isolated with Total Nucleic Acid Isolation Kit (Qiagen) and then amplified with SPF_{10} primers set (DDL Diagnostic Laboratory). PCR-based hybridization line probe assay (LiPA) on auto-LiPA instrument (INNO-LiPA Extra, Innogenetics) was conducted to identify 28 HPV types, including 13 hrHPV types targeted by HC2 assay, three probably carcinogenic HPV types (HPV 26, 53, and 66), and 12 low-risk HPV types (HPV 6, 11, 40, 43, 44, 54, 69, 70, 71, 73, 74, and 82).

Verification of disease status

Cytologic results were interpreted using Bethesda classification system. Pathology diagnoses were interpreted according to the CIN nomenclature. CIN2+ was taken as clinical outcome endpoints. Women lacking of biopsy results but with (i) negative colposcopy impression, or (ii) negative HPV with normal cytology, or (iii) negative HPV with cytologic atypical squamous cells of undetermined significance (ASCUS), or (iv) positive HPV DNA and negative cytology were deemed negative or CIN grade 1 based on previous evidence of low risks among these population (18). Women with unavailable biopsy were reclassified as CIN2 if they had cytologic high-grade squamous intraepithelial lesions or cytologic atypical squamous cells where high-grade squamous intraepithelial lesions could not be excluded. Women with no biopsy results were judged as having incomplete data if they had cytologic low-grade intraepithelial lesions or were hrHPV positive with ASCUS or unsatisfactory cytologic results.

Statistical analysis

Age was presented with median and interquartile range as age was not normally distributed, and the differences of age between women followed up and lost to follow-up were compared using the Wilcoxon rank-sum test. Differences between categorical variables were compared by χ^2 test. Considering the fact that many women with high-grade cervical lesions have prevalent disease at baseline and excluding the subjects with prevalent disease would yield incomplete risk estimates, type-specific cumulative risk and 95% confidence intervals (95% CI) of CIN2+ were estimated using a prevalence–incidence formula based on Kaplan–Meier methods. The cumulative risks of type-specific HPV between two groups were compared using log-rank test. Associations between elevated risk of CIN2+ and increasing times of type-specific HPV infection were presented as ORs without consideration of loss to follow-up for exploratory reasons, and the corresponding trend was calculated using linear χ^2 test. Cumulative detection rates of CIN2+ were defined as number of CIN2+

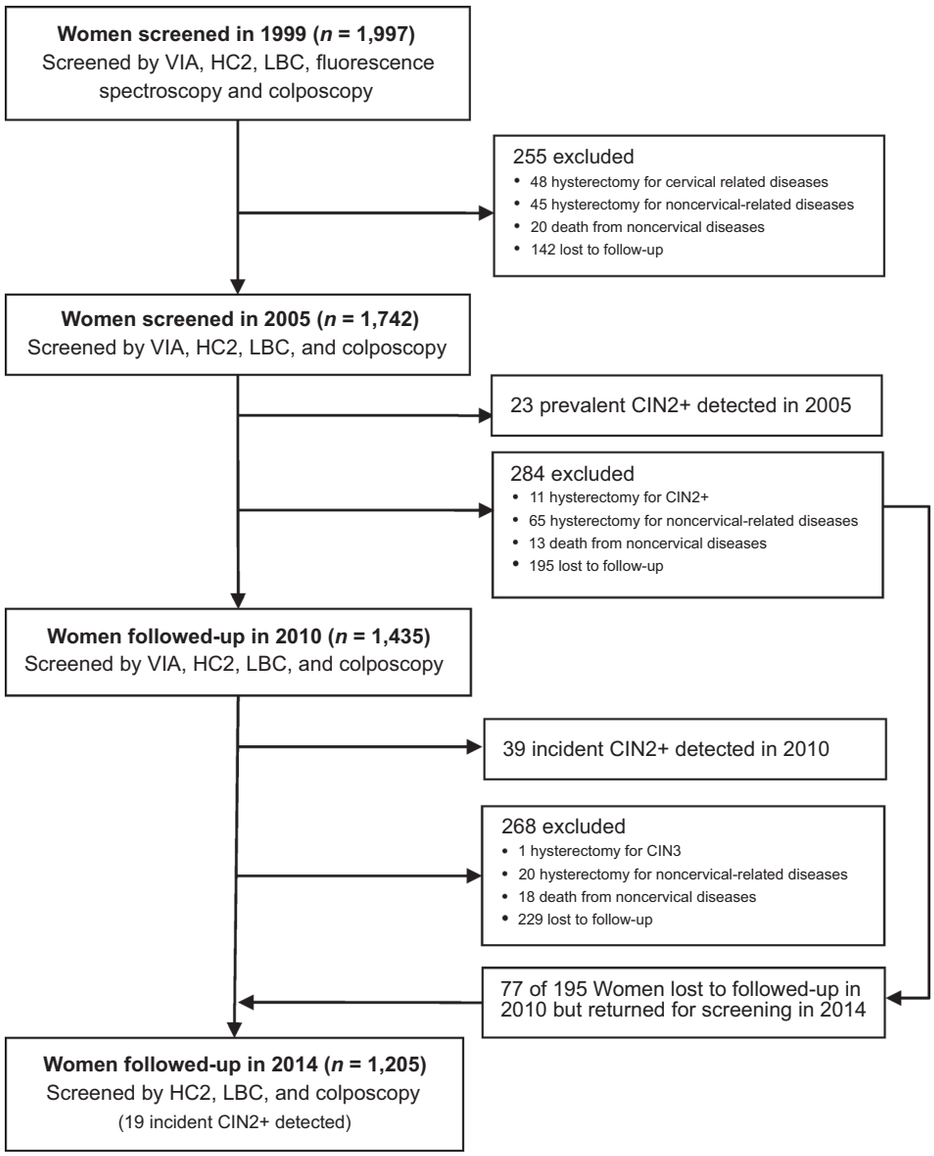

Figure 1.
Flowchart of the Shanxi Province Cervical Cancer Screening Study I (SPOCCS I) study, China, 1999–2014.

cases including both prevalent cases in 2005 and incident cases during follow-ups detected by corresponding HPV types divided by total screening population in 2005. All statistical tests were two tailed with 0.05 as significance level and all analyses were performed using SAS 9.2.

Results

Sociodemographic characteristics

We compared sociodemographic characteristics between women followed up and lost to follow-up. Similar characteristics were observed in 2010 except for marital and menopause status (both $P < 0.05$), and no significant differences were found between groups in 2014, as shown in Table 1.

Type-specific HPV distribution

The proportions of various hrHPV genotypes among hrHPV-positive women differed, as illustrated by Fig. 2. HPV 16 and HPV 52, either in single or multiple infections, were constantly most prevalent during follow-ups. HPV 58, 33, 18, and 31 were also frequently observed, with proportions varied by visits to a moderate extent. Most hrHPV-positive women were infected with single genotype: 58.8% in 2005, 77.6% in 2010, and 59.1% in 2014. Most HPV genotypes were found to only present as single infection except for HPV 56, 59, and 45.

Cumulative risk of CIN2+ after one positive test of type-specific HPV

Cumulative risks of CIN2+ after one positive HPV test differed by HPV genotypes, as shown in Fig. 3. HPV 16 infection (with or without coinfection with other genotypes) had the cumulative risk of CIN2+ of 47.5% (95% CI, 31.6–62.3) during 10-year follow-up, while the majority of CIN2+ occurred within the first 5 years after the infection (42.5%; 95% CI, 31.8–53.8). Considering the strong carcinogenicity of HPV 16, women

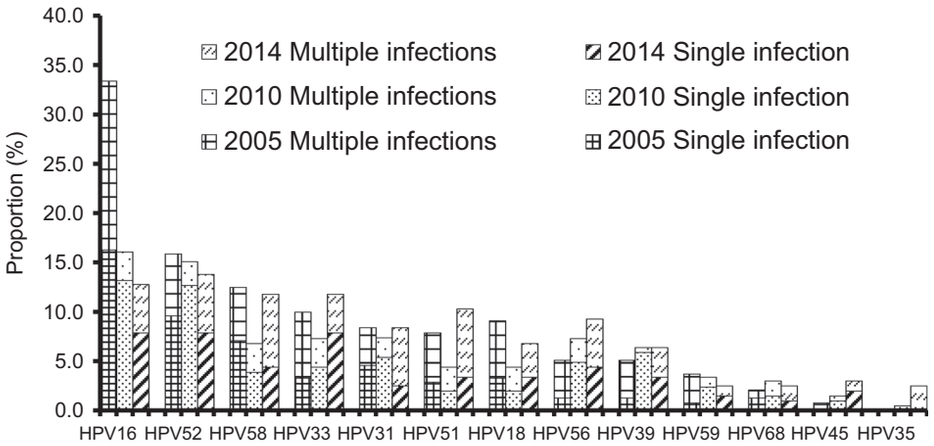

Figure 2.
Type-specific HPV proportions in high-risk HPV positivity by single infection and multiple infections by visits.

coinfected with HPV 16 were excluded from the estimation of CIN2+ cumulative risks for non-16 types of HPV. HPV 31–positive women had a 5-year cumulative risk of 28.4% (95% CI, 6.6–58.8) and 10-year cumulative risk of 46.3% (95% CI, 15.3–75.4), nonsignificantly lower than those of HPV 16 (both $p > 0.05$). HPV 58, 39, 33, 52, and 18 positive women also had high 10-year risk ranging from 34.3% to 12.0% in a decreasing order, respectively. HPV 45, 51, 56, 59, and 68, combined together, generated an extremely low 10-year risk (3.7%; 95% CI, 0.3–15.9), almost close to that of hrHPV-negative women (2.7%; 95% CI, 1.8–4.1; Supplementary Table S1). Further analysis on single infection and multiple infections showed that multiple infections with HPV genotypes did not provide additional risk than single infection (Supplementary Table S2).

CIN3+ cases were observed only in HPV 16, 31, 58, 39, 18, and 52 positive women. Ten-year cumulative risk of CIN3+ was 31.5% (95% CI, 20.6–43.0) for HPV 16, 16.5% (95% CI, 4.0–36.3) for HPV 31, 12.6% (95% CI, 3.1–28.9) for HPV 58, 11.1% (95% CI, 0.6–38.8) for HPV 39, 7.7% (95% CI, 0.5–29.2) for HPV 18, and 3.7% (95% CI, 0.3–15.9) for HPV 52.

Elevated CIN2+ risks by increased positive times of type-specific HPV

CIN2+ risks were elevated with increasing infection times of type-specific HPV during follow-ups, as shown in Fig. 4 (with full details given in Supplementary Table S3). Compared with women never infected with HPV 16 over the 10-year follow-up, one-time HPV 16 infection provided 15-fold (95% CI, 8.7–25.9) higher CIN2+ risk, and HPV 16 infection twice or more provided 58-fold (95% CI, 25.5–132.5) higher CIN2+ risk. Similar trends were found for HPV 31, 33, and 58 (all $P_{trend} < 0.001$).

Incremental cumulative detection rates of CIN2+ by adding more HPV genotypes

Cumulative detection rates of CIN2+ within 10 years were elevated when including more genotypes, as illustrated in Fig. 5, with total detection rate identified by cotesting of cytology, HC2 assay, and VIA as 5.33%. Cumulative detection rate of CIN2+ by HPV 16 was 2.07%, 2.47% by combined HPV 16 and 31, and 2.93% by HPV 16, 31, and 58 in 2005. Other hrHPV types, combined together, contributed a mediocre increase in CIN2+ detection. From another perspective, 42.6% of cumulative CIN2+ cases could be identified by single HPV 16, 51.4% by combined HPV 16 and 31, and 60.8% by combined HPV 16, 31, and 58.

Discussion

This population-based, cervical cancer screening cohort study is to date the longest prospective follow-up cohort study to investigate type-specific HPV in association with the risk of cervical cancer and precursors in mainland China. 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, with other hrHPV types presenting low cumulative risk of CIN2+ close to negative HPV results. CIN2+ risks were elevated with increased times of type-specific HPV infection. CIN2+ cases cumulated within 10 years were mainly detected by HPV 16, 31, and 58. Our results indicated the paramount role of HPV 16, 31, and 58.

High prevalence of HPV 16 and 52 observed in our cohort was consistent with other cross-sectional, population-based studies in Chinese women (19, 20) and also coincided with Guan and his colleagues' meta-analysis (21). HPV 58, 31, and 18, commonly seen worldwide (21), were also frequently observed in our study. HPV 35 and 45, highly prevalent worldwide, however, accounted for an extremely low proportions in our cohort. These deviations might result from geographical differences among countries and regions (19, 21) and also different HPV assays used in studies (22).

The paramount carcinogenicity of HPV 16 found in our study was consistent with other studies (9, 23, 24), although the measurement endpoints were different. Nearly one half of HPV 16–infected women would be at risk of developing CIN2+ and one third at risk of developing CIN3+ within 10 years in our study. HPV 31–positive women were at a notably high risk of progressing to CIN2+ in our study, which was also found in the Portland Kaiser Cohort with up to 18-year follow–up for 20,000 participants (13). A well-recognized cross-sectional study about HPV types associated with cervical cancer verified the lower OR of HPV 51, 56, 68 than HPV 16, 18, 31, 33, 52, and 58 (6), which also coincided with their cumulative risk in our study. HPV 58 was a noteworthy type not only for the high prevalence among the general population in Asian areas, but also for high risk of progressing to cervical cancer precursors, as revealed by our cohort and also by a community-based Cancer Screening Program (CBCSP) cohort study in Taiwan (10). The mechanism for the

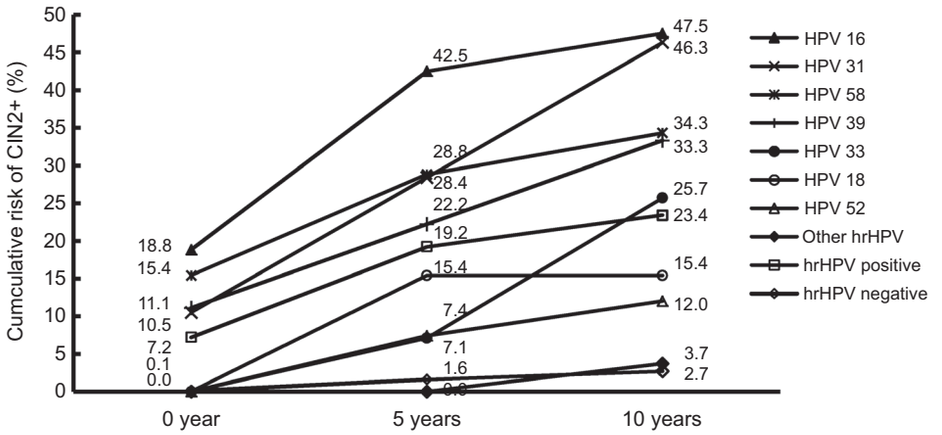

Figure 3.
Ten-year cumulative risk of CIN2+ after one positive test of type-specific HPV.

high carcinogenicity of HPV 58 in East Asia has not been fully understood. It might be related to genetic variability, such as the *HLA-DQB1*06* gene (25), and HPV 58 variants carrying *E7 T20I/G63S*. substitutions (26).

HPV 18 and 45 have an established association with adenocarcinoma (27), but are found less associated with precancers than cancers (28). Among 93 CIN2+ detected in our cohort, only 5 (5.4%) cases were invasive cervical cancer; therefore, risks of HPV 18 and 45 may have been underestimated to some extent when using CIN2+ as the endpoint. The cumulative risk of HPV 35 was not estimated due to its low prevalence in our cohort.

Our study found that negative hrHPV results ascertained a sustained low risk of CIN2+ even up to 10 years and three consecutive hrHPV-negative results predicted even lower risk. The prospective low risks in individual with negative HPV results ensured an effective long-term protection against cervical cancer and precursors (29, 30). Our study indicated that a 5-year or even longer screening interval could be optional in HPV-based cervical cancer screening programs, especially in low- and middle-income countries.

Cumulative detection rates of CIN2+ take both type-specific HPV prevalence and their subsequent risk of cervical lesions into account. HPV 16, 31, and 58 contributed predominantly to detect CIN2+ cases as observed in our study. In contrast, HPV 39 and 33, albeit at high risk of developing CIN2+, due to low prevalence among population, did not produce great increase in CIN2+ detection rates. HPV 16/18 triage is recommended for women with a normal Pap test or positive hrHPV result according to updated ASCCP guidelines (31). With more commercially available genotyping products, whether additional separation of non-16/18 hrHPV types could better identify women at particularly high risk of cervical cancer and precursors remains controversial. Our findings indicate that for the middle-aged women with unknown cytologic results, in addition to HPV 16, HPV 31 and HPV 58 were correlated with a dramatic increase in the detection of high-grade CIN, which might merit the consideration of referral to colposcopy. Although not very high, CIN2+ risk observed in HPV 18–positive women, considering well-established high carcinogenicity of HPV 18 and our limitation to adopt more advanced end point, there is necessity to still take HPV 18 into triage consideration. Proper management on

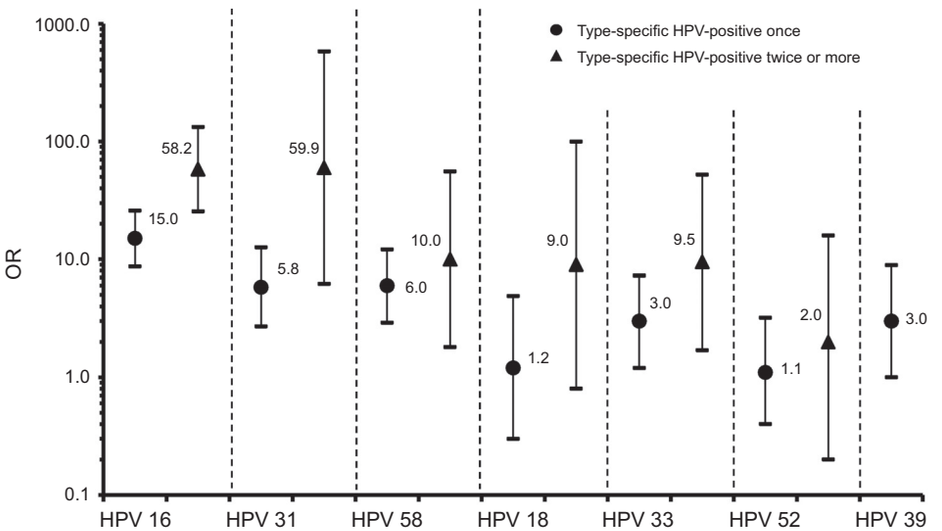

Figure 4.
OR for the risk of CIN2+ after increased positive times of type-specific HPV with continuous negative type-specific HPV as the reference.

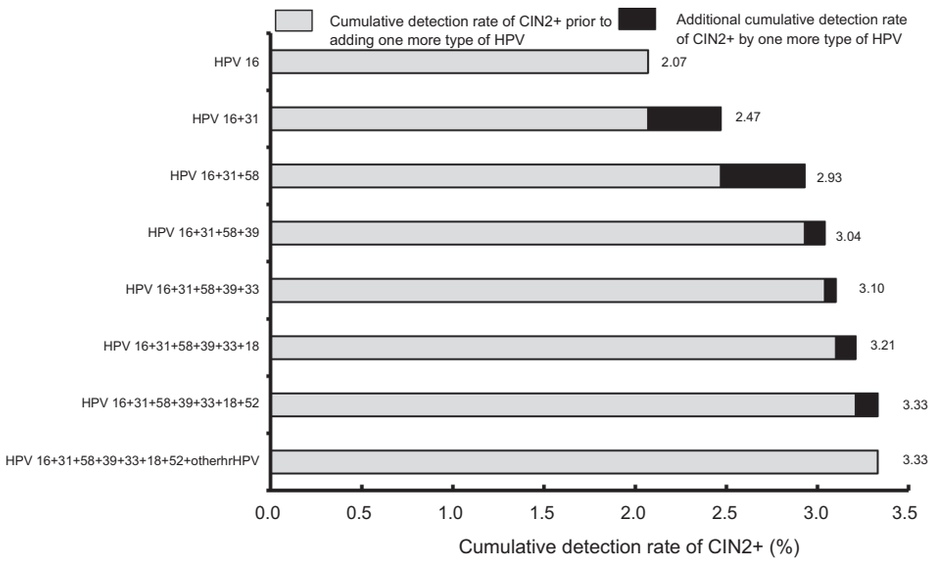

Figure 5.
Cumulative detection rate of CIN2+ in association with increasing hrHPV genotypes.

HPV 39 and 33 needs further data support in a larger sample size due to wide 95% CI observed in our study. Other low-risk HPV types, that is, HPV 56, 59, and 68, might indicate less frequent follow-ups or even routine screening intervals instead of colposcopy examination. Meanwhile, cost-effective analysis with regard to primary screening, colposcopy, and follow-up visits might be helpful to determine the optimal strategies to manage HPV-positive women by separate detection of non-16/18 hrHPV types in cervical cancer screening. Prospective risk assessment for type-specific HPV supported the application of HPV vaccines in preventing high-grade cervical lesions (32, 33). Our data also showed that HPV 16, 31, 58, 33, and 18 were strongly associated with CIN2+ among Chinese women, which were targeted by 9-valent HPV vaccine (32).

There were several limitations in the current study. First, only HC2-positive samples were genotyped and those with lower viral loads than 1 pg/mL of hrHPV were missed by HPV genotyping. This may result in the underestimation of the prevalence of particular genotypes (34). However, considering only a few cases of CIN2+ in all HC2-negative women (2.7% for 10-year cumulative risk of CIN2+ in our study), the conclusions on the risk assessment of type-specific HPV carcinogenicity would not be influenced to some extent. Second, the small sample size of type-specific HPV might resulted in wide CIs for the output measurement, that is, cumulative risk of CIN2+ or CIN3+ for HPV 33 and 39, and in the limited ability to precisely evaluate several uncommon types such as HPV 35. Third, the screening interval was approximately 5 years in our study, whether HPV persistence or clearance was accurately determined remains uncertain. However, based on current evidences that most of HPV infection clears within 2 years and gradually becomes stable after 3 to 5 years (35), we assumed that 5-year intervals at least ruled out most transient infections and so the association between type-specific HPV infection and cumulative risk of progressing to cervical lesions in our analysis was reliable.

In conclusion, our cohort study supported that long-term risk of cervical cancer and precursors for HPV-infected women could be stratified by HPV genotyping. HPV 31 and 58, in addition to HPV 16 and 18, might deserve special attention in the clinical management. Furthermore, consideration of combining type-specific prevalence and their prospective risks could be informative to more precise and effective region-specific cervical cancer screening programs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Dong, S.-Y. Hu, F.-H. Zhao, Y.-L. Qiao
Development of methodology: L. Dong, F.-H. Zhao
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.-Y. Hu, Q. Zhang, L. Zhang, X. Zhang, F.-H. Zhao
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Dong, R.-M. Feng, F.-H. Zhao
Writing, review, and/or revision of the manuscript: L. Dong, S.-Y. Hu, Q. Zhang, R.-M. Feng, L. Zhang, F.-H. Zhao, Y.-L. Qiao
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X.-L. Zhao, X. Zhang, F.-H. Zhao
Study supervision: S.-Y. Hu, F.-H. Zhao, Y.-L. Qiao

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