

Regional Distribution of Different Types of Human Papillomavirus in Cervixes of Chinese Women: A Meta-analysis

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Abstract: Cervical cancer is a common gynecological malignancy that has shown a gradual increase in morbidity in recent years in China. High-risk human papillomaviruses (HR-HPVs) play a vital role in cervical cancer development and commercial vaccines are available. The overall HPV infection and geographical distribution characteristics of cervical Cancer among Chinese females have not been reported that may guide the application of the vaccines. This study systematically retrieves literature on HPV type and cervical cancer in China published from 2005 to 2017. Data are analyzed according to provinces and administrative areas for the meta-analysis. (1) SPSS17.0 software is used for the statistical data analysis. (2) χ^2 inspection is also employed to analyze the infection rate of different HPV types of different cervical lesion groups in seven regions of China. Results show that China's HR-HPV16, 58, 18, 52, 33, 31, 53, 56, 59, 51, 35, and 68 infection rates are 60.49%, 11.16%, 9.68%, 7.05%, 5.61%, 3.62%, 2.88%, 2.32%, 1.96%, 1.74%, 1.53%, and 1.52%, respectively. Differences in the HR-HPV infection rate of cervical cancer were observed among different areas, especially for HPV 31, 33, 52, and 58. The genotypes of the top five HR-HPV infection rates in cervical cancer also show differences in different regions. The results offer a basis for the prevention and treatment of cervical cancer in different parts of China. HPV type distribution in relation to cervical cancer varies among different regions and parts of China. Therefore, use of available or development of new vaccines suitable for regional types is necessary to improve the efficacy of the vaccines in preventing the primary HPV infection in different areas of China.

Keywords: China, Cervical Cancer, Human Papillomavirus, Meta-analysis

1. Introduction

Cervical cancer is one of the most common gynecologic malignant tumors and has become the most common cause of cancer-related deaths in women in developing countries, where approximately 85% of cases occur. Cervical cancer more frequently occurs in younger women and causes serious harm to women's health [1]. Unlike other tumors, cervical cancer has the characteristics of definite cause and longer

reversing precancerous period. Thus, the early detection and timely treatment of cervical cancer may improve patient prognosis to some extent. Human papillomavirus (HPV) infection is an essential factor of cervical intraepithelial neoplasia (CIN) and cervical cancer. The HPV infection rate and distribution of HPV subtypes vary in different countries and regions. Infection of high-risk HPV (HR-HPV) infection (e.g., HPV 16, 18, 31, and 45) is the main cause of the occurrence and development of cervical cancer. Although the important HR-HPV types (e.g., HPV 16 and 18) show

consistency in the geographic area distribution, the main HPV subtypes differ in different parts of the world [2, 3]. Hence, prevention and control measures with regional specificity to target infection of HPV subtypes are urgently needed.

China is the most populous country in the world with a high prevalence of cervical cancer. However, only a few studies with comprehensive analyses of the latest literature on the HPV infection condition of Chinese women have been conducted. To more comprehensively understand/map the geographic distribution of HPV types in different regions of China and relate the finding with HPV vaccine application. The current study analyzes literature on HR-HPV [4] infection of cervical cancer among Chinese women in different regions published in PubMed from 2005 to 2017. A meta-analysis was conducted to evaluate the status of HPV subtype infection in different Chinese regions. The results will provide evidence for vaccine application and other possible formulations of prevention and control measures that target the HPV subtype infection in various parts of China.

2. Materials and Methods

2.1. Search Strategy and Eligibility Criteria

As the primary data source, literature published from January 2005 to August 2017 were searched with the subject terms of “HPV”, “cervical neoplasms/cervical cancer”, “China” and their entry terms in the PubMed database. Two independent reviewers screened all articles by title and abstract based on the inclusion and exclusion criteria. Duplicate records were automatically removed by a reference management software. Any disagreements between the two reviewers on paper selection were discussed by explicit selection rules, and full texts were reviewed if necessary. Full texts of eligible articles were retrieved and assessed by two reviewers following the set processes.

2.2. Inclusion and Exclusion Criteria for the Literature

Inclusion criteria: (1) The research objects come from China, with clear source areas. The case number in a study includes the general screening patients, which may be suffering from cervical disease, precancerous lesions of the uterine cervix, and patients with cervical cancer. (2) The pathological or cytological classification of cervical lesions is definite, which includes invasive cervical cancer (ICC), high-level cervical intraepithelial neoplasia (HSIL), low-level cervical intraepithelial neoplasia (LSIL), and normal control group (i.e., healthy people and patients with cervicitis). Several studies may contain two or more pathological or cytological classifications. The ICC can be further divided into squamous cell carcinoma (SCC), glandular cell carcinoma or glands squamous cell carcinoma (ADC/ASC), and endometrial carcinoma (EC). HSIL is equivalent to the cervical intraepithelial neoplasia grade 2 (CIN2), cervical intraepithelial neoplasia grade 3 (CIN3), cervical glands intraepithelial neoplasia grade 2 (CGIN2), and cervical glands intraepithelial neoplasia grade 3 (CGIN3). Carcinoma in situ

is classified as CIN3. LSIL is equivalent to the cervical intraepithelial neoplasia grade 1 (CIN1) and cervical glands intraepithelial neoplasia grade 1 (CGIN1). (3) The method for HPV classification is PCR. In this study, the specific case numbers of cervical lesions infection and infection of different HPV subtypes are connected. The essay methods should be sufficiently clear to introduce the HPV DNA detection process. The simple hybridization detection method based on non-amplification has been removed. (4) The minimum case number of each classification is 20. (5) If the article lacks specific information, then the authors were contacted directly for specific details of the HPV classification data. If the data or partial data of the study were reported more than twice, then the largest sample size of the published article was included into the specific article.

Exclusion criteria: (1) A review literature that lacks the original source data. (2) Survey data that may have serious bias. (3) Experiment design in the original literature is not rigorous (e.g., the research data are incomplete). (4) Repeated case reports, vague data description, and investigation methods or data that do not conform to the research requirements.

2.3. Data Excerpt

The following key information serves as the excerpt for each paper: (1) The published year and journals name. (2) The specimen source (i.e., fresh or fixed tissue samples, cytology specimens, or their combination). (3) Pathological or cytological classification: the ICC (SCC/ADC/EC), HSIL (CIN 2/3, CGIN2/3), LSIL 1, CGIN1 (CIN), and normal control group (healthy crowd and cervicitis patients). (4) The total case number of each category and HR-HPV infection. 15 types of HR-HPV types were collected, namely, HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, and other probable high-risk types (e.g., HPV 53, 66, and 83). (5) Area: Given the geographical distribution, the areas involved in this study are divided into East China (i.e., Shanghai, Jiangsu, Zhejiang, Anhui, Jiangxi, Shandong, Fujian, and Taiwan province), North China (i.e., Beijing, Tianjin, Shanxi, Hebei, and Central Inner Mongolia Autonomous Region), Central China (i.e., Henan, Hubei, and Hunan province), South China (i.e., Guangdong, Guangxi Zhuang Autonomous Region, Hainan province, the Hong Kong Special Administrative Region, and Macao Special Administrative Region), Southwest China (i.e., Chongqing, Sichuan, Guizhou, Yunnan Province, and the Tibet Autonomous Region), Northwest China (i.e., Shanxi, Gansu, Qinghai, Ningxia Hui Autonomous Region, Xinjiang Uygur Autonomous Region, Inner Mongolia Autonomous Region, and West La Shan Au), and Northeast China (i.e., Heilongjiang, Jilin, Liaoning, and East of Inner Mongolia).

2.4. Statistical Analysis

The general positive rate of HPV is the ratio of the positive numbers of HPV tests and included sample numbers. The different methods and strategies can detect different HPV

types. Therefore, the infection rate of different HPV types were analyzed in the HPV positive samples of cervical cancer. The specific positive ratio of HPV types equals the ratio of HPV positive cases of specific types and sample cases that have the results of this specific type. Therefore, the sample size is different forestimating the diverse types in terms of HPV-positive rates.

SPSS17.0 software is used for the statistical analysis of the data when weighing and combining the infection rates for the different studies. χ^2 inspection is also employed to analyze the infection rate of different HPV types of different cervical lesion groups in seven regions of China to compare the HPV

infection condition of different types.

3. Results

3.1. Included Studies

A total of 316 articles were retrieved from the PubMed database through the keyword search. Approximately 136 articles were initially selected by reviewing their titles and abstracts. Finally, 30 articles were selected after reviewing their full text based on the inclusion criteria (Figure 1, Table1) [5-34].

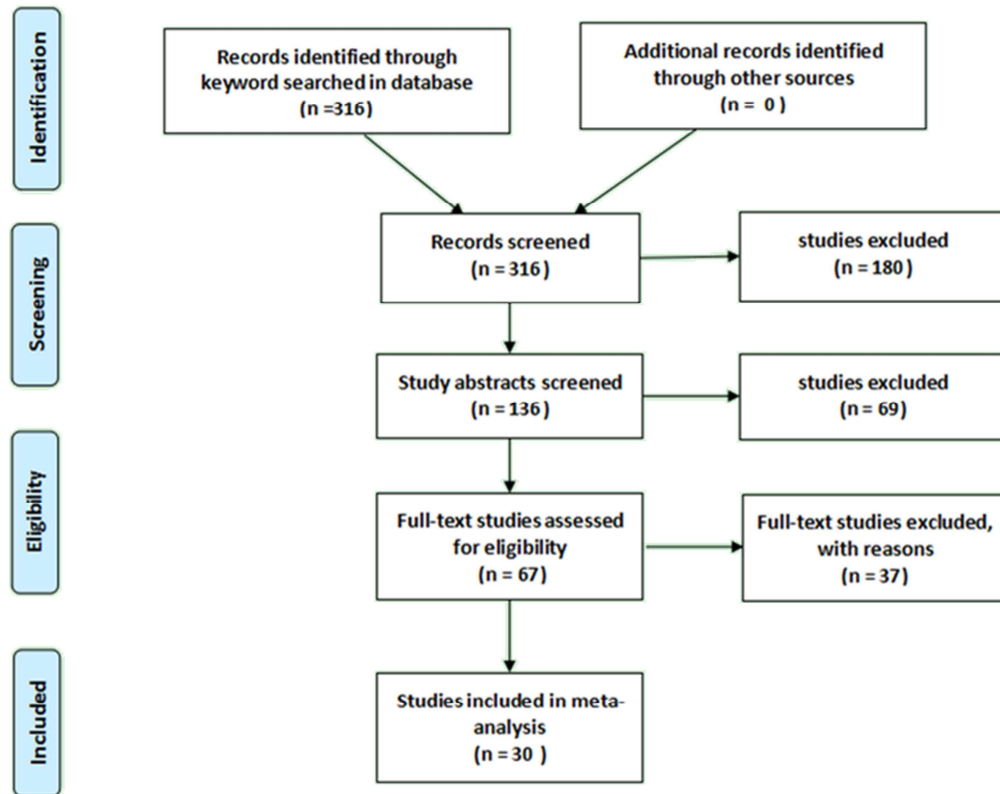


Figure 1. Flowchart showing the selection of articles included in the meta-analysis.

Table 1. The 30 selected studies and the detected HPV genotypes.

Author	Year	Area	No tissue lesions	LSIL	HSIL	ICC	Total number of cases	Detection method	HPV genotypes
Li J et al ⁵ .	2011	Chengdu	-	-	63	144	207	PCR	16,18,31,33,35,45,51,52,58,
Li H et al ⁶ .	2013	Hunan	3115	165	147	78	3505	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68
Zhao Y et al ⁷ .	2008	Yianbian	20	56	146	100	322	PCR	16,18,33,52,58,
Hong D et al ⁸ .	2008	Zhejiang	217	105	345	181	848	PCR	16,18,31,33,39,45,51,52,56,58,59,68,82
Wu EQ et al ⁹ .	2009	Mogolian	-	71	27	77	175	PCR	16,18,31,33,45,52,58,59,
Cai HB et al ¹⁰ .	2009	Hubei	-	-	60	112	172	PCR	16,18,31,33,35,52,58,59,
Li C et al ¹¹ .	2010	Beijing	233	295	-	-	528	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,73
Sun ZR et al ¹² .	2010	Liaoning	165	-	117	154	436	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
Liu X et al ¹³ .	2010	Liaoning	-	180	517	134	831	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
Wu D et al ¹⁴ .	2010	Fujian	314	129	102	96	641	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
Yuan X et al ¹⁵ .	2011	Shandong	471	302	518	198	1489	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
LI J et al ¹⁶ .	2012	Western	-	143	457	-	600	PCR	16,18,31,33,35,39,45,51,52,56,58,59,66,68,
Liu W et al ¹⁷ .	2013	Changchun	40	-	-	65	105	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
Liang LY et al ¹⁸ .	2013	Shenzhen	6866	1457	225	-	8548	PCR	16,18,31,33,39,52,56,58,59,66,
Yang L et al ¹⁹ .	2013	Daqing	1702	24	-	-	1726	PCR	16,18,39,52,58
Liu XX et al ²⁰ .	2014	Zhejiang	13891	260	108	-	14259	PCR	16,18,31,33,39,45,51,52,56,58,59,68,73,82

Author	Year	Area	No tissue lesions	LSIL	HSIL	ICC	Total number of cases	Detection method	HPV genotypes
Ding X et al ²¹	2014	Beijing	-	152	256	116	524	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,82
Ma Q et al ²²	2014	Xi'an	-	278	248	130	656	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
Ma L et al ²³	2015	Beijing	379	219	251	20	869	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
Feng Y K et al ²⁴	2015	Sichuan	163	206	518	-	887	PCR	16,18,31,33,35,52,56,58,68
Wang Y et al ²⁵	2016	Guangdong	-	244	308	223	775	PCR	16,18,31,33,35,39,45,51,52,53,56,58,59,66,68,
Li J et al ²⁶	2016	Shanxi	784	353	678	1115	2930	PCR	16,18,31,33,35,39,45,51,52,53,56,58,59,66,68,73,82,83
Xiao M et al ²⁷	2016	Beijing	-	-	1379	828	2207	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68,
Wang L et al ²⁸	2016	Xinjiang	318	42	19	49	428	PCR	16,18,31,33,35,39,45,51,52,53,56,58,59,66,68
Zhang L et al ²⁹	2017	Eastern	-	376	744	544	1664	PCR	16,18,31,33,35,39,45,51,52,53,56,58,59,66,68,73,82,
Baloch et al ³⁰	2016	Yunnan	16968	458	428	44	17898	PCR	16,18,31,33,35,39,45,51,52,53,56,58,59,66,68
Li Y et al ³¹	2016	Beijing	17790	93	176	-	18059	PCR	16,18,31,33,35,39,45,51,52,56,58,59,68
Li K et al ³²	2017	Western	-	1098	2295	-	3393	PCR	16,18,31,33,35,39,45,51,52,53,56,58,59,66,68,73,82
Mai R Q et al ³³	2014	Shantou	-	76	61	2	139	PCR	16,18,31,33,35,39,45,51,52,53,56,58,59,66,68
Han Li-li et al ³⁴	2011	Xinjiang	-	-	-	115	115	PCR	16,18,31,33,39,45,51,52,56,58,59,68,73,

ICC: invasive cervical cancer; HSIL: high grade intraepithelial neoplasia of cervix; LSIL: low-grade intraepithelial neoplasia of the cervix; control group: no lesions in the cervical tissue.

3.2. Meta-analysis of the Total Infection Rate of HPV Genotypes in Cervixes

The meta-analysis includes 84,724 cervical biopsies or specimens of exfoliated cells, namely, 4,525 ICC cases, 10,194 HSIL cases, 6,569 LSIL cases, and 63,436 control subject cases without cervical disease. The most common type is HPV 16. The infection rate of HPV 16 is 60.49% in ICC, 41.77% in HSIL, and 18.75% in LSIL. The infection rate in the normal cervical tissues is 2.39%.

The HPV genotypes in ICC with infection rates of more than 2% are HPV 16, 58, 18, 52, 33, 31, 53, and 56. The infection rates of these genotypes are 60.49%, 11.16%, 9.68%, 7.05%, 5.61%, 3.62%, 2.88%, and 2.32% respectively. The

HPV genotypes in HSIL with infection rates of more than 2% are HPV 16, 58, 52, 33, 31, 53, 18, 56, 66, 51, 39, 59, 68, and 35, with infection rates of 41.77%, 20.29%, 15.31%, 12.04%, 7.98%, 6.65%, 5.94%, 5.59%, 5.58%, 5.35%, 3.22%, 2.12%, 2.11%, and 2.02%, respectively. The HPV genotypes in LSIL with an infection rate of more than 2% are HPV 52, 16, 53, 58, 33, 56, 18, 51, 31, 39, 66, 68, 35, and 59. The infection rates of these genotypes are 19.95%, 18.75%, 16.99%, 12.73%, 8.31%, 7.24%, 6.92%, 6.30%, 5.85%, 5.38%, 5.37%, 4.66%, 3.10%, and 2.63%, respectively. The HPV genotypes in normal cervixes with infection rates of more than 1% are HPV 52, 16, 58, 53, and 83, with infection rates of 2.55%, 2.39%, 2.35%, 1.10%, and 1.02%, respectively (Table 2 and Figure 2).

Table 2. Infection rates of different genotypes in different cervical lesions of the Chinese population.

HPV type	ICC				HSIL				LSIL				control			
	case	all	rate	references	case	all	rate	references	case	all	rate	references	case	all	rate	references
16	2737	4525	60.49%	22	4258	10194	41.77%	26	986	5259	18.75%	24	1514	63436	2.39%	17
58	505	4525	11.16%	22	1517	7477	20.29%	26	647	5081	12.73%	23	1489	63436	2.35%	17
18	438	4525	9.68%	22	511	8600	5.94%	26	265	3827	6.92%	24	570	63436	0.90%	17
52	309	4381	7.05%	20	1122	7330	15.31%	25	1016	5094	19.95%	22	1617	63436	2.55%	17
33	254	4525	5.61%	22	906	7528	12.04%	26	295	3551	8.31%	23	507	61734	0.82%	16
31	160	4425	3.62%	22	593	7430	7.98%	25	209	3563	5.87%	22	388	61714	0.63%	15
53	57	1977	2.88%	6	143	2151	6.65%	7	200	1177	16.99%	7	199	18070	1.10%	3
56	97	4187	2.32%	16	387	6928	5.59%	19	244	3370	7.24%	18	453	54494	0.83%	12
59	84	4281	1.96%	20	146	6900	2.12%	23	128	4868	2.63%	21	421	61551	0.68%	14
51	70	4027	1.74%	18	216	6452	3.35%	20	201	3191	6.30%	19	429	54645	0.79%	12
35	62	4052	1.53%	18	127	6300	2.02%	20	89	2868	3.10%	17	148	40577	0.36%	11
68	62	4092	1.52%	18	148	7010	2.11%	21	160	3432	4.66%	20	391	54848	0.71%	14
66	28	1977	1.42%	6	103	1847	5.58%	9	126	2348	5.37%	9	123	24936	0.49%	4
45	54	4248	1.27%	19	91	6594	1.38%	22	44	3345	1.32%	20	96	54645	0.18%	12
39	51	4092	1.25%	18	208	6459	3.22%	21	252	4684	5.38%	21	588	63253	0.93%	15
83	4	1115	0.36%	1	7	2973	0.24%	1	2	1451	0.14%	1	8	784	1.02%	1
73	6	1890	0.32%	4	9	4081	0.22%	5	10	2534	0.39%	6	17	14908	0.11%	3
82	1	1956	0.05%	4	38	4426	0.86%	6	25	2344	1.07%	6	14	14892	0.09%	3

This table shows the Chinese women infected by different HPV genotypes in ICC, HSIL, LSIL, and cervical tissue without lesions. The cases were sorted according to the ranking of infection rates of different HPV genotypes in ICC.

ICC: invasive cervical cancer; HSIL: high grade intraepithelial neoplasia of cervix; LSIL: low-grade intraepithelial neoplasia of the cervix; control group: no lesions in the cervical tissue.

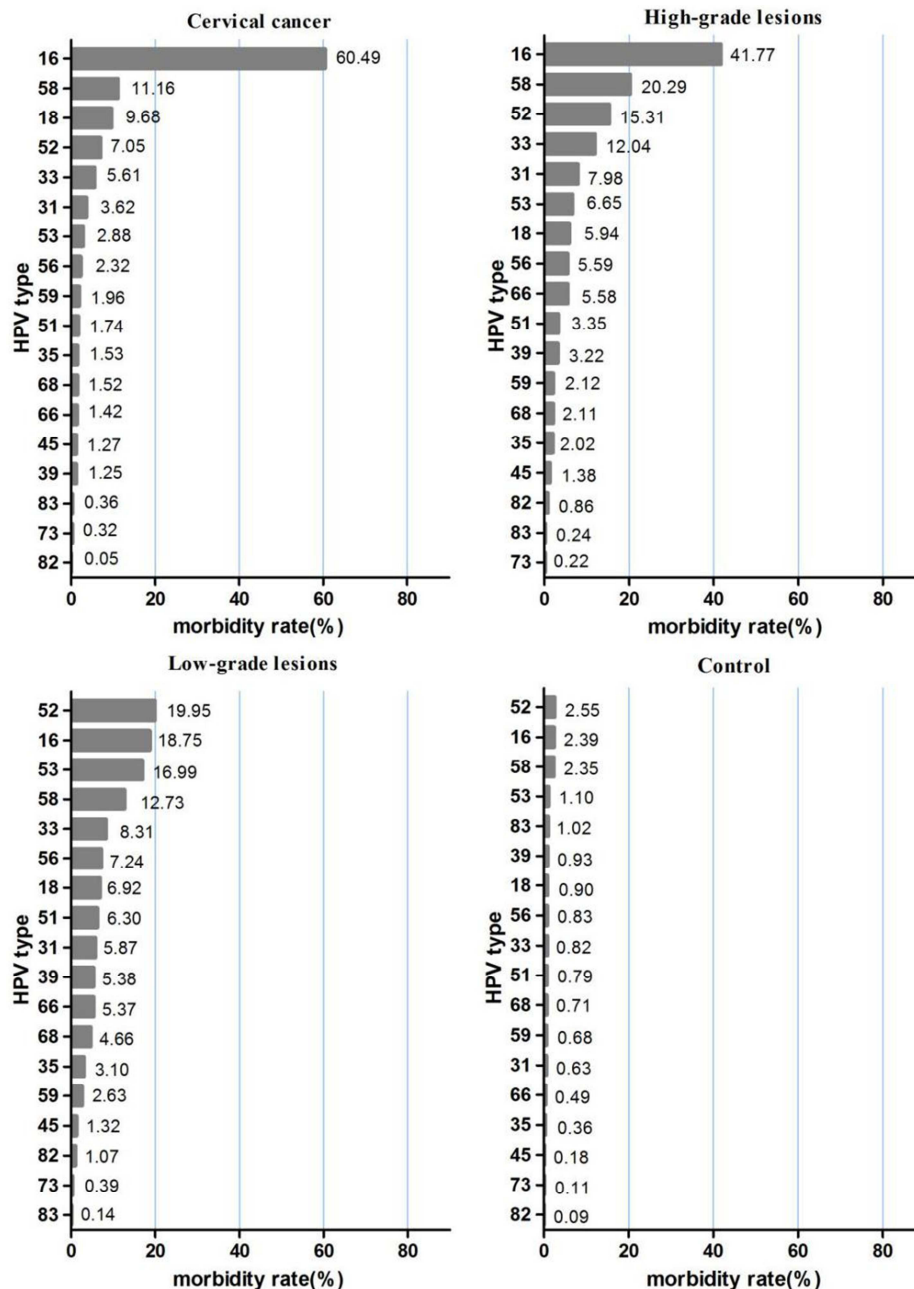


Figure 2. Prevalence of different genotypes in different cervical lesions in the whole China. ICC: invasive cervical cancer; HSIL: high grade intraepithelial neoplasia of cervix; LSIL: low-grade intraepithelial neoplasia of the cervix; control group: no lesions in the cervical tissue. The figure shows the prevalence of different HPV genotypes in ICC, HSIL, LSIL, and the control group in China, where the HPV16 infection rate is the highest.

3.3. Meta-analysis of the Top Five High-Risk Types of Cervical Cancer in Seven Regions of China

Articles for Northeast China, North China, East China, South China, Central China, Northwest China, Southwest China were obtained. A total of eight HR-HPV genotypes (i.e., HPV 16, 18, 31, 33, 52, 58, 59, and 68) of cervical cancer were selected by synthetically analyzing the top five high-risk types of cervical cancer in different regions. Table 3 shows that the top five genotypes of ICC in the seven regions are inconsistent. The top five HPV genotypes in the seven regions of China were generally HPV 16, 18, 31, 33, 52, 58, 59 and 68. A

histogram was made to discuss the distribution of HPV subtypes in the control group (intraepithelial neoplasia) and cervical lesions (cervical cancer) (Table 3 and Figure 3). Figure 2 shows that HPV 16 is the most widely distributed in the seven regions. Its infection rate is 75.56% in South China, 70.12% in North China, 70.00% in Central China, 63.13% in Northeast China, 62.77% in Southwest China, 55.07% in Northwest China, and 51.42% in East China. HPV 16, 18, 52 and 58 were included in the top five HPV genotype infection rates of cervical cancer in the seven regions, which indicates that they were the dominant types. These types were followed by HPV 31, 33, 59, and 68. Figure 3 also shows the top five high-risk infection rates.

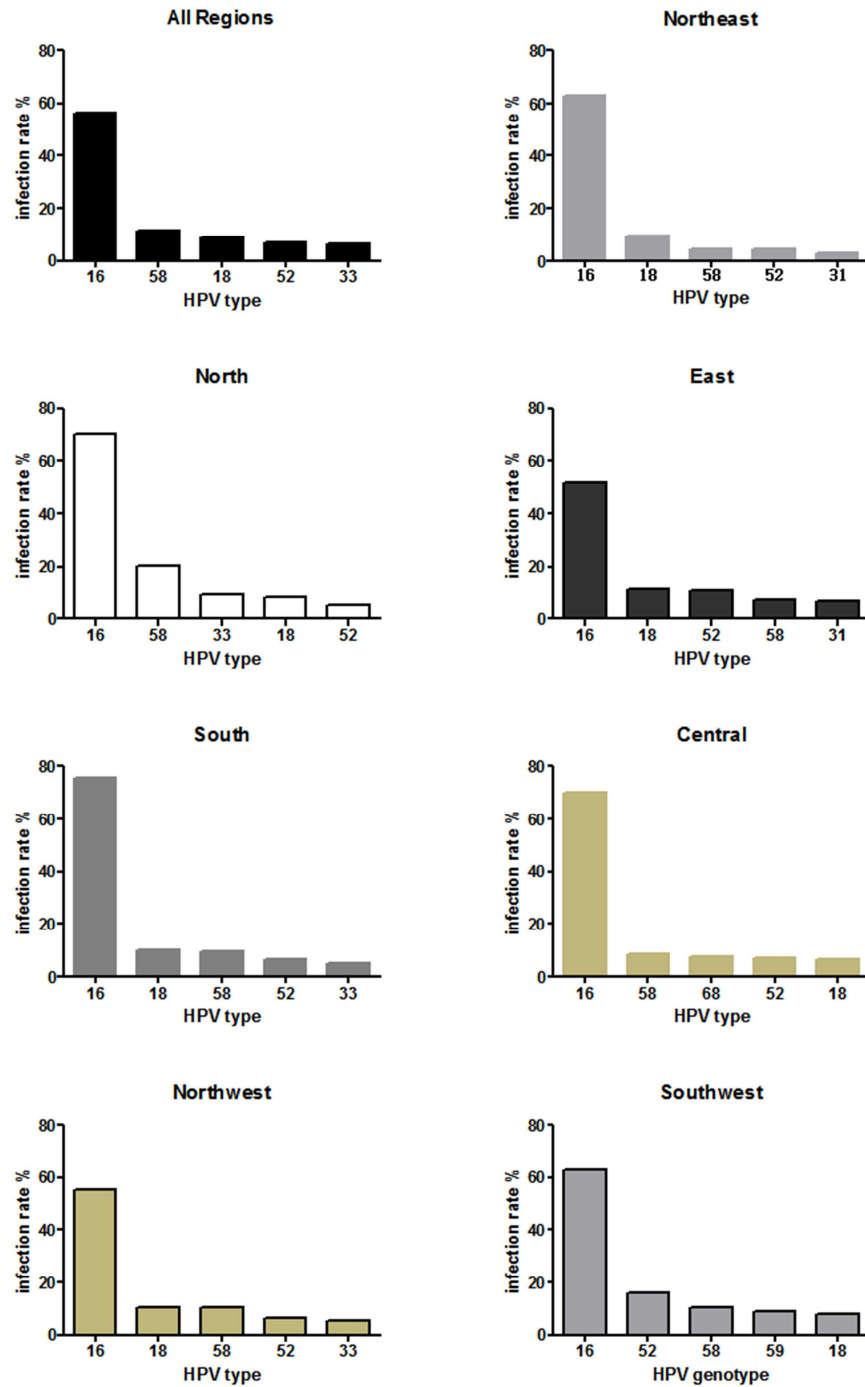


Figure 3. Infection rate of the top five genotypes among the seven regions of China.

Table 3. HPV genotypes of the top five genotypes in the seven regions.

Region	HPV type	CC			HSIL			LSIL			control		
		case	all	rate	case	all	rate	case	all	rate	case	all	rate
Northeast	16	286	453	63.13%	431	780	55.26%	70	260	26.92%	39	1927	2.02%
	18	44	453	9.71%	29	780	3.72%	11	260	4.23%	13	1927	0.67%
	58	21	453	4.64%	94	780	12.05%	37	260	14.23%	15	1927	0.78%
	52	19	453	4.19%	51	780	6.54%	39	260	15.00%	24	1927	1.25%
	31	11	353	3.12%	53	634	8.36%	12	180	6.67%	1	205	0.49%
North	16	730	1041	70.12%	1012	2090	48.42%	110	839	13.11%	382	18402	2.08%
	58	211	1041	20.27%	476	2090	22.78%	58	839	6.91%	425	18402	2.31%
	33	95	1041	9.13%	186	2090	8.90%	27	839	3.22%	82	18402	0.45%
	18	84	1041	8.07%	127	2090	6.08%	18	839	2.15%	162	18402	0.88%

Region	HPV type	CC			HSIL			LSIL			control		
		case	all	rate	case	all	rate	case	all	rate	case	all	rate
East	52	52	1041	5.00%	207	2090	9.90%	52	839	6.20%	564	18402	3.06%
	16	524	1019	51.42%	768	1817	42.27%	222	1172	18.94%	386	14893	2.59%
	18	113	1019	11.09%	53	1817	2.92%	43	1172	3.67%	171	14893	1.15%
	52	112	1019	10.99%	233	1817	12.82%	176	1172	15.02%	296	14893	1.99%
	58	71	1019	6.97%	203	1817	11.17%	117	1172	9.98%	294	14893	1.97%
South	31	69	1019	6.77%	178	1817	9.80%	89	1172	7.59%	160	14893	1.07%
	16	170	225	75.56%	211	594	35.52%	43	245	17.55%	35	6866	0.51%
	18	23	225	10.22%	36	594	6.06%	12	99	12.12%	16	6866	0.23%
	58	22	225	9.78%	98	594	16.50%	127	1555	8.17%	31	6866	0.45%
	52	15	225	6.67%	25	369	6.78%	228	1548	14.73%	78	6866	1.14%
Central	33	11	225	4.89%	57	594	9.60%	23	87	26.44%	31	6866	0.45%
	16	133	190	70.00%	100	207	48.31%	21	165	12.73%	89	3115	2.86%
	58	16	190	8.42%	23	207	11.11%	16	165	9.70%	67	3115	2.15%
	68	6	78	7.69%	1	147	0.68%	2	165	1.21%	25	3115	0.80%
	52	13	190	6.84%	10	207	4.83%	27	165	16.36%	97	3115	3.11%
Northwest	18	12	190	6.32%	12	207	5.80%	4	165	2.42%	36	3115	1.16%
	16	776	1409	55.07%	276	945	29.21%	196	673	29.12%	192	1102	17.42%
	18	147	1409	10.43%	74	945	7.83%	48	673	7.13%	55	1102	4.99%
	58	144	1409	10.22%	132	945	13.97%	101	673	15.01%	113	1102	10.25%
	52	91	1409	6.46%	124	945	13.12%	110	673	16.34%	145	1102	13.16%
Southeast	33	74	1409	5.25%	94	945	9.95%	56	673	8.32%	75	1102	6.81%
	16	118	188	62.77%	1460	3761	38.82%	324	1905	17.01%	391	17131	2.28%
	52	7	44	15.91%	472	1122	42.07%	384	437	87.87%	413	17131	2.41%
	58	20	188	10.64%	491	1044	47.03%	191	417	45.80%	544	17131	3.18%
	59	4	44	9.09%	39	838	4.65%	49	302	16.23%	40	16968	0.24%
	18	15	188	7.98%	180	2167	8.31%	129	619	20.84%	117	17131	0.68%

This table shows the prevalence of the top five HPV genotypes among seven regions of China, namely, include Northeast China, North China, East China, South China, Central China, Northwest China and Southwest China.

3.4. Comparison of the Infection Rate Difference of the Eight Genotypes in the Seven Regions

The chi-square test of $R \times C$ table in the SPSS statistical methods were utilized to compare the multiple sample rates. Finally, the chi-square segmentation method was implemented to readjust the inspection level of the alpha value [35]. The adjusted inspection level alpha was $\alpha' = 0.002273$. The results are listed in Table 4.

The highest infection rate of HPV 16 is 75.56% in South China, which shows significant differences with the infection rates in Northeast China (63.13%, $p = 0.001 < \alpha'$), East China (51.42%, $p = 0.000 < \alpha'$) and Northwest China (55.07%, $p = 0.001 < \alpha'$); the infection rates in North China and Central China are 70.12% and 70.00%, which show significant differences compared with the infection rates of East China (51.42%, $p = 0.000 < \alpha'$) and Northwest China (55.07%, $p = 0.000 < \alpha'$). Moreover, the infection rate in Northeast China is 63.13%, which shows significant difference with the infection rate in East China (51.42%, $p = 0.001 < \alpha'$). The highest infection rate of HPV 31 is 6.77% in East China, which shows significant difference with the infection rates in North China (3.36%, $p = 0.000 < \alpha'$), Northwest China (2.56%, $p = 0.000 < \alpha'$), and Southwest China (0%, $p = 0.000 < \alpha'$). The highest infection rate of HPV33 is 9.13% in North China, which is significantly different from the infection rates of Northeast China (2.87%, $p = 0.000 < \alpha'$), East China (5.59%, $p = 0.002 < \alpha'$), Central China (1.58%, $p = 0.000 < \alpha'$), Northwest China (5.25%, $p = 0.002 < \alpha'$), and Southwest China (0.53%, $p = 0.000 < \alpha'$). The highest infection rate of HPV 52 is 15.91% in Southwest China, which shows significant differences with the infection rates in

Northeast China (4.19%, $p = 0.001 < \alpha'$) and North China (5.00%, $p = 0.002 < \alpha'$); the infection rate in East China is 10.99%, which shows significant differences with the infection rates of Northeast China (4.19%, $p = 0.000 < \alpha'$), North China (5.00%, $p = 0.000 < \alpha'$), and Northwest China (6.49%, $p = 0.001 < \alpha'$). The highest infection rate of HPV 58 is 20.27% in North China, which shows significant differences with the infection rates in Northeast China (4.64%, $p = 0.000 < \alpha'$), East China (6.97%, $p = 0.000 < \alpha'$), South China (9.78%, $p = 0.000 < \alpha'$), Central China (8.42%, $p = 0.000 < \alpha'$), Northwest China (10.22%, $p = 0.000 < \alpha'$), and Southwest China (10.64%, $p = 0.002 < \alpha'$); the infection rate in Northwest China is 10.22%, which also shows significant differences with the infection rate of Northeast China (4.64%, $p = 0.000 < \alpha'$). In addition, the highest infection rate of HPV 59 is 9.09% in Southwest China, which shows significant differences with the infection rates in Northeast China (0.85%, $p = 0.000 < \alpha'$), Central China (1.05%, $p = 0.002 < \alpha'$), and Northwest China (0.92%, $p = 0.000 < \alpha'$); the infection rate in North China is 3.27%, which shows significant differences with the infection rate in Northwest China (0.92%, $p = 0.000 < \alpha'$). The highest infection rate of HPV 68 is 7.69% in Central China, which shows significant differences with the infection rates in Northeast China (1.42%, $p = 0.001 < \alpha'$), North China (1.35%, $p = 0.000 < \alpha'$), East China (0.39%, $p = 0.000 < \alpha'$), and South China (0.89%, $p = 0.001 < \alpha'$); the infection rate in Northwest China is 2.27%, which shows significant differences with the infection rate in East China (0.39%, $p = 0.001 < \alpha'$).

The infection rates of HPV 18 genotype showed no statistical differences among the different regions of China.

Table 4. Comparison of the infection rates of the different genotypes among the seven regions.

Region		HPV 16%	P	HPV 31%	P	HPV 33%	P	HPV 52%	P	HPV 58%	P	HPV 59%	P	HPV 68%	P
Northeast		63.13		3.12		2.87		4.19		4.64		0.85		1.42	
	North	70.12		3.36		9.13	***	5.00		20.27	***	3.27		1.35	
	East	51.42	***	6.77		5.59		10.99	***	6.97		2.36		0.39	
	South	75.56	**	1.78		4.89		6.67		9.78		1.78		0.89	
	Central	70.00		2.63		1.58		6.84		8.42		1.05		7.69	**
	Northwest	55.07		2.56		5.25		6.46		10.22	***	0.92		2.27	
	Southwest	62.77		0.00		0.53		15.91	**	10.64		9.09	***	0.00	
North		70.12		3.36		9.13		5.00		20.27		3.27		1.35	
	East	51.42	***	6.77	***	5.59	*	10.99	***	6.97	***	2.36		0.39	
	South	75.56		1.78		4.89		6.67		9.78	***	1.78		0.89	
	Central	70.00		2.63		1.58	***	6.84		8.42	***	1.05		7.69	***
	Northwest	55.07	***	2.56		5.25	***	6.46		10.22	***	0.92	***	2.27	
	Southwest	62.77		0.00		0.53	***	15.91	*	10.64	*	9.09		0.00	
East		51.42		6.77		5.59		10.99		6.97		2.36		0.39	
	South	75.56	***	1.78		4.89		6.67		9.78		1.78		0.89	
	Central	70.00	***	2.63		1.58		6.84		8.42		1.05		7.69	***
	Northwest	55.07		2.56	***	5.25		6.46	***	10.22		0.92		2.27	***
	Southwest	62.77		0.00	***	0.53		15.91		10.64		9.09		0.00	
South		75.56		1.78		4.89		6.67		9.78		1.78		0.89	
	Central	70.00		2.63		1.58		6.84		8.42		1.05		7.69	**
	Northwest	55.07	***	2.56		5.25		6.46		10.22		0.92		2.27	
	Southwest	62.77		0.00		0.53		15.91		10.64		9.09		0.00	
Central		70.00		2.63		1.58		6.84		8.42		1.05		7.69	
	Northwest	55.07	***	2.56		5.25		6.46		10.22		0.92		2.27	
	Southwest	62.77		0.00		0.53		15.91		10.64		9.09	*	0.00	
Northwest		55.07		2.56		5.25		6.46		10.22		0.92		2.27	
	Southwest	62.77		0.00		0.53		15.91		10.64		9.09	***	0.00	

This table shows the comparison of infection rates of the different genotypes among the seven regions.

*: $p=0.002$ **: $p=0.001$ ***: $p=0.000$.

4. Discussion

The International Agency for Research on Cancer (IARC) of the World Health Organization has performed meta-analyses of HPV distribution in cervical cancer around the world since 2003 and regularly updates its data [36-38]. Results show that respective preponderant HPV types exist in different populations and regions, which indicate that regional differences existed in HPV prevention and treatment. The latest report concerning HPV distribution in mainland China was published in 2009 [39]. However, the data have not been updated, and the regional differences in the HPV types have not been analyzed in detail. China is the world's most populous country with a population of 1.36 billion, which accounts for approximately 18.84% of the world population. Therefore, determining the HPV infection status of the Chinese population is significant and important. Analysis of the HPV infection status of cervical cancer and associated lesions in Chinese population has also become necessary because of the different geographical types, races, and lifestyles in different regions of China. The latest summary of meta-analyses in existing literature [39] was published in 2009, and the number of people and cases included in this summary is relatively rare. The current study analyzes and summarizes the HPV infection studies in cervical lesions published from 2005 to 2017. A total of 84,414 cervical biopsies or exfoliated cells were included in this study, namely, 4,525 ICC cases,

10,194 HSIL cases, 5,259 LSIL cases, and 63,436 control subject cases without cervical lesions. This meta-analysis has the highest number of samples included to date, which may provide evidence for the prevention and treatment of cervical cancer and precancerous lesions for the Chinese people. In this study, the eight most prevalent of HPV genotypes in ICC and HSIL are HPV 16, 58, 18, 52, 33, 31, 53, and 56, and the second highest infection rate is HPV 58. In the LSIL and control group, the most prevalent is HPV 52 (Figure 2).

This meta-analysis shows that HPV 16 is the most common infection type among Chinese women with different cervical lesions. The HPV16 infection rates in the ICC, HSIL, LSIL, and normal group are 60.49%, 41.77%, 18.75%, and 2.39% respectively, which are higher than the WHO worldwide data, global and Asian meta-analyses [3, 36, 40]. In the study, the five most frequent HR-HPV types with cervical cancer are HPV 16, 58, 18, 52, and 33. Based on WHO worldwide data, the five most frequent HR-HPV types in patients with cervical cancer are HPV 16, 18, 33, 45, and 31. By contrast, WHO data indicate that the five most frequent HPV types in Chinese women cervical cancer are HPV 16, 18, 58, 33, and 52 in 2007 [2]. Clifford et al. determined that the most common genotypes of HPV infection in cervical cancer are HPV 16, 18, 45, 31, and 33 in 2003 [37] (Figure 4). The five most common types of HPV infection in Chinese patients with cervical cancer are HPV 16, 18, 58, 33, and 52 in the study by Bao et al. in 2008 [41]. The infection rate of HPV 16 and 18 accounted

for 70.17% of the total, which is similar to the findings of Bao. Compared with a similar study by Bao et al, changes were also observed in the five most common types of HPV infection in patients with cervical cancer. The results of the study show that HPV 58 and 52 infection rates are higher than Bao's, and HPV18 infection rate has declined. These results are similar to many other studies indicating that HPV 18 is uncommon and that HPV 58 and HPV 52 are more prevalent than HPV 18 in general population and cancer patients in China [42-45].

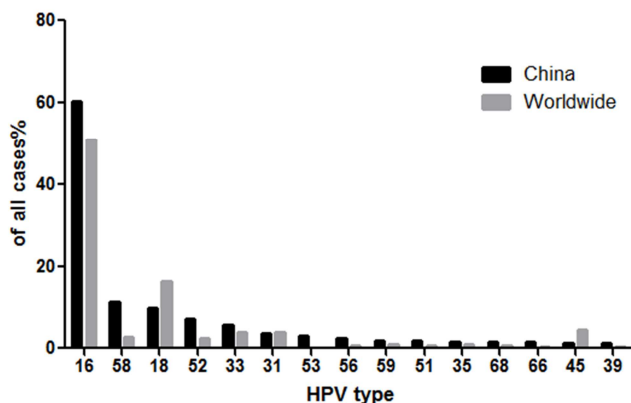


Figure 4. Differences in the HPV infection rates of China and the entire world. This figure shows that the top 10 infection rates of HPV genotypes of China and the entire world are different.

In western countries, HPV 45 is one of the five most frequent HR-HPV genotypes in cervical cancer. In China, the infection rate of HPV 45 is very low in patients with cervical cancer. In addition, the infection rates of the HPV 58 and 52 genotypes in China are higher than those in western countries and the world average. Thus, the national difference should be considered in the prevention and control of HPV and vaccine research in China.

These results indicate that the infection spectrum of HR-HPV types in cervical cancer has changed over the past nine years, which may be due to the difference in the experimental method utilized in the included studies. These differences need further research.

These results show that the HPV infection spectra in cervical cancer are relatively different in different countries and parts of China. Given the geography and population distribution, China can be divided into seven regions (i.e., East China, North China, Central China, South China, Southwest China, Northwest China, and Northeast China). The HPV infection spectra in cervical cancer (Figure 3) show that the most common HPV types in Northeast China are HPV 16, 18, 58, 52 and 31; those in North China are HPV 16, 58, 33, 18 and 52; those in East China are HPV 16, 18, 52, 58 and 31; those in South China are HPV 16, 18, 58, 52 and 33; those Central China are HPV 16, 58, 68, 52 and 18; those Northwest China are HPV 16, 18, 58, 52 and 33 and those in Southwest China are HPV 16, 52, 58, 59 and 18.

The most common genotype is HPV 16, whereas the HPV infection genotypes have clear regional differences. The infection rate of HPV 16 in South China is the highest (75.56%), whereas that in Northeast China and East China are lower (55.07% and 51.42%, respectively). The second most

common genotype is HPV 18 in Northeast China, East China, South China, and Northwest China; HPV 58 in North China and Central China; and HPV 52 in Southwest China. The infection rate of the HPV 18 genotype is highest in East China (11.09%). However, its infection rate is not statistically significant compared with that in other regions. The third most common genotype is HPV 58 in Northeast China, South China, Northwest China, and Southwest China; HPV 33 in North China; HPV 52 in East China; and HPV 68 in Central China. The infection rate of HPV 68 in Central China is 7.69%, which is higher than those in Northeast China (1.48%), North China (1.35%), East China (0.39%), and South China (0.89%). Therefore, the HPV 68 genotype should be given particular attention in developing approaches for prevention and control of HPV infection in Central China (Table 4).

These results indicate that the HPV infection spectra in cervical cancer have significant differences in different nations and regions of China. In particular, HPV 68 ranks third in the infection rate in cervical cancer in Central China but shows an extremely low infection rate in other areas. This phenomenon suggests that HPV68 may be the primary infection genotype of Central China, and the regional differences should be considered when performing HPV prevention, control, and vaccine research in China. The current study has certain differences with that of Chen et al in 2009[39], which shows that the HPV 59 infection rate ranks third in North China and Northwest China. By contrast, this study shows that the HPV 59 infection rate is lower. This scenario suggests that the HPV infection spectra in cervical cancer vary in different regions of China, which may be due to the different experimental methods applied in the included studies. This difference requires further research and observation.

The HPV58 infection rate in seven regions are much higher than other types, which need to pay attention to. This result is similar to the result reported by Chan in 2014 [46]. Therefore, HPV58 genotype may be a kind of high-risk genotype with high infection rate besides HPV 18 and HPV16, suggesting that reducing the infection rate of HPV58 plays a significant role in reducing the occurrence of cervical cancer development. The aforementioned results suggest that the corresponding prevention treatment measures should be taken in the progress of HPV prevention or research and application of vaccines in different parts of China according to the primary infection types in these areas. HPV bivalent, tetravalent, or multivalent vaccines should be researched according to the regional differences and economic states.

As the only vaccine that can prevent malignant tumors thus far, the HPV vaccine is a milestone in the prevention and treatment of cervical cancer [47]. Currently, three HPV vaccines are available worldwide. The bivalent HPV vaccine (Cervarix; GlaxoSmithKline, Boronia, VIC, Australia) can protect against HPV 16 and 18, whereas the quadrivalent HPV (4vHPV) vaccine (Gardasil; CSL, Parkville, VIC, and Merck, Macquarie Park, NSW, Australia) can protect against HPV 6, 11, 16, and 18. A nine-valent HPV (9vHPV) vaccine, which includes HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, protecting against the five additional high-risk cancer-causing

HPV types, was approved by the US Food and Drug Administration in 2014 (Gardasil 9) [48]. Studies in Australia [49-51] showed that the prevalence of HPV 6, 11, 16, and 18 declined significantly for the population that had received the 4vHPV vaccine. Given the vast territory and large population of China, the HPV vaccine application is highly significant and has broad prospects. However, many developing countries, including China, have failed to adopt the vaccine largely because of its remarkably high price [47]. The 9vHPV vaccine is more expensive than the bivalent HPV vaccine and 4vHPV. Moreover, HPV 45 infection in Chinese patients, which is included in 9vHPV, has much lower prevalence than that in western countries and worldwide. Accordingly, the 9vHPV vaccine is unsuitable for Chinese women.

The development of a HPV vaccine suitable for Chinese population is significant. Particularly, the development of vaccines with regional advantages according to the primary HPV infection types is necessary to improve the preventive and treatment measures in different areas of China.

5. Conclusion

HPV 16 is the most common infection type in different cervical lesions, however, the infection rate of HPV 16 genotypes has clear regional differences. HPV 58 and HPV 52 are more prevalent than HPV 18 in general population and cancer patients in China, which need to pay more attention to. Compared to Western countries, the infection rate of HPV 45 is very low in patients with cervical cancer in China. Results of the study show that the HPV infection spectra in cervical cancer have significant differences in different nations and regions of China, This conclusion may be equally adapted to other countries and regions in the world. Therefore, the development of a HPV vaccine suitable for Chinese population is significant which could reduce the burden on the country and the government. Developing vaccines with regional advantages and according to the primary HPV infection types is necessary to improve the preventive and treatment measures in different areas of China, it may be suitable for other countries and regions.

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Competing Interests

All authors declare that: there are no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

Conflict of Interest

All authors report no conflicts of interest in this publication.

Authors' Contributions

Yue Wang and Kunpeng Zhang collected all data. Yali Hu participated in the data interpretation. Authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

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