Characteristics of Human Papillomavirus Infection Among Women With Cervical Cytological Abnormalities in the Zhoupu District, Shanghai City, China, 2014–2019

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Abstract

Background: Human papillomavirus (HPV) infection is the main cause of precancerous lesions and cervical cancer in women. To determine the epidemiological characteristics as well as the relationship between the HPV genotype and cytology test results among women, we retrospectively collected and analyzed the data from Zhoupu District hospital in Shanghai, China.

Methods: We made a retrospective analysis of human papillomavirus prevalence rate of 23,724 women between 2014 and 2019 in the District Zhoupu of Shanghai City in China. Their cervical exfoliations were collected. HPV genotype testing was performed using a commercial kit designed to detect 21 HPV subtypes including 15 high-risk HPV subtypes(16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 ,68) and 6 low-risk HPV subtypes(6, 11, 42, 43, 44 and 81). And the thinPrep cytological test (TCT) was also performed at the same time.

Results: Among all 23,724 cases, 3,816 (16.08%) women were infected with HPV. HPV52 (3.19%), HPV58 (2.47%) and HPV16 (2.34%) had higher prevalence. 3,480(91.20%) single-type infections were more common than 336(8.8%) multiple-type infections. Single-type infection was more frequently seen in women aged 50–60 years (16.63%) and <30 years (15.37%), and multiple-type infection was more common in those aged >= 60 (2.67%). Significant differences in secular trends from 2014 to 2019 were observed for subtypes HPV52, 58 and 16.HPV positive rates of women changed significantly along with the time period from 2014 to 2019.

Among 4,502 TCT positive women, 15 (4.04%), 125 (2.64%) ,159 (1.54%), 4,202(17.71%) and 1(0.004%) had atypical squamous cells (ASC), high-grade squamous intraepithelial lesions (HSIL), low-grade squamous intraepithelial lesions (LSIL), atypical glandular cells (AGC) and cervical adenocarcinoma respectively. The HPV infection rates were 66.08%, 63.99%, 115.20%, 119.50%, and 31.72% for NILM, AGCs, HSILs LSILs and ASCs, respectively.

Conclusions: HPV and TCT screening were a key step in the secondary prevention of cervical cancer. Further tracking the results of HPV and TCT was an important clinical strategy for the treatment of cervical precancerous lesions. The widespread use of preventive HPV vaccines can significantly reduce the incidence of pre-neoplastic and neoplastic cervical lesions.

Background

Cervical cancer was the fourth most common cancer among women in the world[1]. China and India together contributed more than a third of the global cervical cancer burden, with 106,000 cases and 48,000 deaths in China[2] , it ranks seventh and ninth in cancer prevalence and mortality in women [3, 4]. Shanghai is the largest metropolis in China, having 16 districts. The resident population of Pudong New District is about 5 million, accounting for 20% of the total population of Shanghai. Zhoupu District is located in the suburb of Pudong New District. During 2002 and 2015 , the incidence of cervical cancer increased by 9.8 and 15.5% annually in urban and rural areas of Pudong New District, respectively [5].

The persistent human papillomavirus (HPV) infection is the main cause of cervical cancer[2]and cervical intraepithelial neoplasia (CIN). According to how much epithelial tissue is affected, CIN can be graded on 1-3 scale, where CIN3 is the most abnormal grade. In our study, CIN1 is equivalent to low-grade squamous intraepithelial neoplasia (LSIL), while ≥CIN2 is called precancerous lesion or high-grade squamous intraepithelial neoplasia (HSIL). High-risk human papilloma virus (HR-HPV) infection due to multiple sexual partners has been positively associated with the occurrence of cervical cancer[6, 7], LSIL and HSIL. In Zhoupu District, our previous research has confirmed that HPV infection rate was 17.92% (10,670 / 59,541) and a HR-HPV positive rate was 15.56% (9263 / 59,541), 86.81% of the HPV infections were caused by HR-HPV and the six most prevalent HR-HPV genotypes were HPV 52, 16, 58, 53, 39, and 51[8]. HPV genotype distribution varies between different regions and countries, causing the incidence and mortality of cervical cancer to change geographically as well[9].

New tools of primary prevention (prophylactic HPV vaccination) and secondary prevention (screening with validated HPV assays and treatment of cervical precancerous lesions) have been shown to be effective[2]. The cervical cancer absence of a further rise in incidence after age 40 years in high-resource countries could reflect cancers prevented by screening [2]. China as

one of the largest developing country in the world, a lot of work has to be done to prevent and screen cervical cancer. Therefore, we underwent the present study to determine the epidemiological characteristics and secular trends of HPV infection subtypes in Zhoupu District of Shanghai. We also analyzed the relationship between HPV genotype and cytology test results. We retrospectively analyzed the data from a tertiary hospital in Shanghai suburb. The results will contribute to the data on HPV genotype-specific prevalence in the Shanghai area in order to encourage implementation of an HPV vaccine program.

Methods

Data Source

We collected the cervical exfoliations data of 23,724 women who visited Shanghai Zhoupu hospital and received both TCT and HPV detection between 2014 and 2019. As a regional medical center, Shanghai Zhoupu hospital provides medical services to 500,000 people nearby around surrounding districts and counties.

Ethics statement

This study was approved by the Institutional Medical Ethics Review Board of Zhoupu Hospital in Shanghai City. Participants have obtained informed consent. For participants under the age of 18, their parents should sign a consent form. Zhoupu Hospital has ensured confidentiality during the data collection process. The data is analyzed anonymously.

Cytology testing

The cervical exfoliations samples were strictly collected during non-menstrual period. Cervical fluid-based cytology was performed by the experienced cytology specialist in gynecology.

According to the definition by the Bethesda system, liquid-based cytological terminality includes intraepithelial lesions or malignant tumors (NILM), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells (ASC-H) which HSIL cannot be excluded, Low-grade squamous intraepithelial lesion (LSIL) and high-squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC) and adenocarcinoma.

HPV genotyping

HPV genotyping was performed on the collected samples by analysis using human papillomavirus (HPV) typing test kit (PCR + membrane hybridization). This assay has been approved by the China Food and Drug Administration (Certificate Number (2014): 3402188).

PCR membrane hybridization is used to detect 21 HPV genotypes (6, 11, 16, 18, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 56, 58, 59, 66, 68 and 81) Hybridization by reverse dot hybridization and envelope specific probe membrane. The experiment conducted internal quality control and external quality assessment, and the results met the requirements.

Statistical analysis

All HPV and TCT data from 2014 to 2019 were merged into one Excel spreadsheet and then analyzed on the R platform (www.r-project.org) (v3.2.0) and R packages.

HPV positive, single-type and multiple-type infection rates were presented in three ways: by the age stratification(<30 years, 30-40years,40-50 years,50-60 years,≥60 years) , by every subtype of all 21 HPV subtypes and secular trend from 2014-2019. TCT positive rates were also presented by the same age stratification.

The secular trends for TCT and HPV positive infection rates as well as their distribution among different age categories were both calculated from 2014-2019.Relationship between TCT test results and HPV subtype infections were calculated. In the

secular trend calculation, student t-test was used and $p<0.05$ was considered statistically significant.

Results

Characteristics of the study participants

In this study, a total of 23,724 women from Shanghai Zhoupu Hospital, underwent outpatient gynecological examinations and received TCT for HPV detection. The ages of participants were between 15 and 94 years. The mean age was 36.76. Among the 23,724 subjects, 3,816 women were positive for HPV infection, with a total HPV infection rate of 16.08% (3,816 / 23,724) and a HR-HPV positive rate of 14.18% (3,363 / 23,724). Therefore, 88.13% of the infections were caused by HR-HPV.

In figure 1, among 3,816 positive HPV infections, there were 31.63% (1,207/3,816) TCT positive rate and 68.37% (2,609/3,816) TCT negative. Whereas, there were 16.55% (3,295/19,908) TCT positive infection and 83.45% (3,295/19,908) TCT negative among 19,908 negative HPV infections.

Single-type and multiple-type HPV infections in women of different ages

Characteristics of HPV infection as well as HPV distribution among different age categories are shown in Table 1. Among 3,816 HPV positive participants, which was more frequently seen in 482 (482/2,513, 19.18%) women aged 50-60 years.

Single-type infection (3,480/3,816, 91.20%) was much more common than multiple-type infection (336/3,816, 8.8%). Single-type HPV infection was more frequently seen in women aged 50-60 years (418/2,513, 16.63%) and <30 years (1,163/7,568, 15.37%), and multiple-type HPV infection was more common in those aged >= 60 years (29/ 10,88, 2.67%) and 50-60 years (64/2,513, 2.55%). And apparently, in our data single-type HPV infection (3480/3,816, 91.19%) was more common than multiple-type infection (336/3,816, 8.80%) ($\chi 2$ test $P < 0.0001$).

Table 1 Single-type and multiple-type infections of HPV of different ages

Age (years)	N	HPV Positive, n(%)	Single-type infection, n(%)	Multiple-type infection,n(%)
<30	7568	1271(16.79)	1163(15.37)	108(1.43)
30-40	7866	1127(14.33)	1043(13.26)	84(1.07)
40-50	4689	741(15.8)	690(14.72)	51(1.09)
50-60	2513	**482(19.18)**	**418(16.63)**	64(2.55)
>60	1088	195(17.92)	166(15.26)	**29(2.67)**
Total	23724	3816	3480	336

Single-type and multiple-type infection rates in every subtype of all 21 HPV subtypes

Among the 21 HPV subtypes (15 HR-HPV and 6 LR-HPV) examined, the top three with the highest prevalence were HPV52, 58 and 16, with infection rates of 3.19%, 2.47% and 2.34%, respectively. These three HPV subtypes were also the most common types of single-type and multiple-type HPV infections. Here, every HPV subtype infection rate was calculated as the ratio of the number of infected women by certain subtype of HPV to the total number of women in this study (N = 23,724) (Table 2).

Table 2 Single-type and multiple-type infection rates in every subtype of all 21 HPV subtypes

HPV subtype	Positive n(%)	Single-type infection n(%)	Multi-type infection n(%)
HPV16	**555(2.34)**	**363(1.53)**	**192(0.81)**
HPV18	205(0.86)	125(0.53)	80(0.34)
HPV31	171(0.72)	S105(0.44)	66(0.28)
HPV33	255(1.07)	118(0.5)	137(0.58)
HPV35	69(0.29)	43(0.18)	26(0.11)
HPV39	354(1.49)	209(0.88)	145(0.61)
HPV45	53(0.22)	30(0.13)	23(0.1)
HPV51	355(1.5)	228(0.96)	127(0.54)
HPV52	**756(3.19)**	**494(2.08)**	**262(1.1)**
HPV53	373(1.57)	227(0.96)	146(0.62)
HPV56	121(0.51)	65(0.27)	56(0.24)
HPV58	**586(2.47)**	**346(1.46)**	**240(1.01)**
HPV59	70(0.3)	37(0.16)	33(0.14)
HPV66	195(0.82)	108(0.46)	87(0.37)
HPV68	192(0.81)	112(0.47)	80(0.34)
HPV6	147(0.62)	127(0.54)	20(0.08)
HPV11	126(0.53)	108(0.46)	18(0.08)
HPV42	54(0.23)	51(0.21)	3(0.01)
HPV43	26(0.11)	24(0.1)	2(0.01)
HPV44	95(0.4)	88(0.37)	7(0.03)
HPV81	379(1.6)	356(1.5)	23(0.1)

The first 15 was HR-HPV subtypes and the last 6 was LR-HPV subtypes in the table 2

Secular trends of different HPV subtype infection rates from 2014 to 2019

We also investigated the temporal trends of HPV subtype infections during the research period. HPV52, 58 and 16 constantly had the higher infection rates from 2014 to 2019. Significant differences in secular trends between 2014 and 2019 were seen for most of subtypes ($P < 0.05$), except HPV 42 and 43 (Table 3).

In Figure 2, the prevalence of most HR-HPV was higher than that of LR-HPV every year, and the highest prevalence of almost all HPV subtypes occurred in 2018. In Figure 2a, the highest prevalence rate, high-risk HPV subtype HPV52 (238 (3.38%)), occurred in 2018.

Table 3 Secular trends of different HPV subtype infection rates from 2014 to 2019

HPV subtype	2014,n (%)	2015,n (%)	2016,n (%)	2017,n (%)	2018,n (%)	2019,n (%)	P value for trend
HPV16	**28(2.54)**	**105(2.59)**	**106(2.06)**	**161(2.53)**	**154(2.19)**	**1(3.23)**	**0.0179**
HPV18	13(1.18)	40(0.99)	27(0.53)	59(0.93)	66(0.94)	0(0)	0.0229
HPV31	9(0.82)	38(0.94)	39(0.76)	47(0.74)	38(0.54)	0(0)	0.0147
HPV33	23(2.08)	45(1.11)	62(1.21)	67(1.05)	58(0.82)	0(0)	0.0105
HPV35	10(0.91)	9(0.22)	11(0.21)	21(0.33)	18(0.26)	0(0)	0.0125
HPV39	16(1.45)	67(1.65)	77(1.5)	94(1.48)	100(1.42)	0(0)	0.0177
HPV45	7(0.63)	4(0.1)	8(0.16)	21(0.33)	13(0.18)	0(0)	0.0323
HPV51	15(1.36)	64(1.58)	67(1.3)	112(1.76)	97(1.38)	0(0)	0.0219
HPV52	**39(3.53)**	**141(3.48)**	**128(2.49)**	**209(3.29)**	**238(3.38)**	**1(3.23)**	0.0207
HPV53	23(2.08)	73(1.8)	70(1.36)	91(1.43)	116(1.65)	0(0)	0.0167
HPV56	5(0.45)	19(0.47)	11(0.21)	49(0.77)	37(0.53)	0(0)	0.0496
HPV58	**27(2.45)**	**100(2.47)**	**132(2.57)**	**155(2.44)**	**172(2.44)**	**0(0)**	**0.0189**
HPV59	4(0.36)	12(0.3)	13(0.25)	24(0.38)	17(0.24)	0(0)	0.0217
HPV66	8(0.72)	28(0.69)	37(0.72)	54(0.85)	68(0.97)	0(0)	0.0286
HPV68	7(0.63)	32(0.79)	36(0.7)	53(0.83)	64(0.91)	0(0)	0.0259
HPV6	4(0.36)	23(0.57)	35(0.68)	35(0.55)	50(0.71)	0(0)	0.0273
HPV11	4(0.36)	25(0.62)	16(0.31)	43(0.68)	38(0.54)	0(0)	0.0327
HPV42	3(0.27)	1(0.02)	3(0.06)	27(0.42)	20(0.28)	0(0)	0.1135
HPV43	1(0.09)	1(0.02)	5(0.1)	11(0.17)	8(0.11)	0(0)	0.0631
HPV44	8(0.72)	8(0.2)	16(0.31)	31(0.49)	32(0.45)	0(0)	0.0319
HPV81	24(2.17)	89(2.2)	92(1.79)	102(1.6)	71(1.01)	1(3.23)	0.0132
Total	278	924	991	1466	1475	3	

The first 15 was HR-HPV subtypes and the last 6 was LR-HPV subtypes in the table 3

TCT positive infections of different ages

Distribution of TCT test results among different age categories are shown in Table 4. Among all 23,724 participants, 4,502 (18.98%) women were TCT positive, of whom, 15 (4.04%), 125 (2.64%) ,159 (1.54%), 4,202(17.71%) and 1(0.004%) had AGCs, HSILs, LSILs and ASCs, Cervical adenocarcinoma, respectively. The highest TCT positive rate was seen in women aged >=60 years (23.05%), and the lowest rate was found in those women aged <=30 years (17.83%). Additionally, among five cytological subtypes, HSIL and ASC detection increased significantly with age (P < 0.0001, Table 4). Table 4 TCT positive rates of different ages

Age (years)	N	NILM ,n(%)	AGC ,n(%)	HSIL ,n(%)	LSIL ,n(%)	ASC ,n(%)	CERVICAL ADENOCARCINOMA ,n(%)	TCT positive, n (%)
<30	7567	6218(82.17)	4(0.05)	8(0.11)	55(0.73)	1282(16.94)	0(0)	**1349(17.83)**
30-40	7866	6437(81.83)	3(0.04)	34(0.43)	47(0.6)	1345(17.1)	0(0)	1429(18.17)
40-50	4689	3755(80.08)	4(0.09)	38(0.81)	37(0.79)	855(18.23)	0(0)	934(19.92)
50-60	2513	1974(78.55)	3(0.12)	30(1.19)	17(0.68)	489(19.46)	0(0)	539(21.45)
>60	1089	838(76.95)	1(0.09)	15(1.38)	3(0.28)	231(21.21)	1(0.09)	**251(23.05)**
Total	23724	19222	15	125	159	4202	1	4502

Secular trends of HPV and TCT infection rates among different ages from 2014 to 2019

We found that HPV positive rates in all women changed significantly along with the time period (P value for trend< 0.05). whereas, the TCT positive rates among women didn't also showed significant differences from 2014 to 2019 (Table 5).

From figure 3, more TCT infection rates were found than HPV infection. Especially in 2018, 384 women (<30 years) with HPV infection rates occurred, while 1,166 TCT infection of those women in the same age range were found.

Table 5 Secular trends of HPV and TCT infection rates of different ages from 2014 to 2019

Age (years)	2014,n (%)	2015,n (%)	2016,n (%)	2017,n (%)	2018,n (%)	2019,n (%)	P value for trend
HPV positive							
<30	57(27.8)	214(31.56)	234(31.45)	381(35.91)	384(34.13)	1(33.33)	0.0226
30-40	52(25.37)	208(30.68)	220(29.57)	322(30.35)	324(28.8)	1(33.33)	0.0192
40-50	61(29.76)	127(18.73)	149(20.03)	195(18.38)	209(18.58)	0(0)	0.0131
50-60	21(10.24)	104(15.34)	101(13.58)	117(11.03)	138(12.27)	1(33.33)	0.0166
>60	14(6.83)	25(3.69)	40(5.38)	46(4.34)	70(6.22)	0(0)	0.0241
Total	205	678	744	1061	1125	3	-
TCT positive							
<30	14(17.5)	56(23.14)	43(20.38)	70(21.08)	**1166**(32.07)	0(0)	0.2866
30-40	20(25)	73(30.17)	44(20.85)	103(31.02)	1188(32.67)	1(100)	0.2667
40-50	17(21.25)	57(23.55)	58(27.49)	72(21.69)	730(20.08)	0(0)	0.2353
50-60	15(18.75)	46(19.01)	47(22.27)	52(15.66)	379(10.42)	0(0)	0.1849
>60	14(17.5)	10(4.13)	19(9)	35(10.54)	173(4.76)	0(0)	0.1773
Total	80	242	211	332	3636	1	-

Relationship between TCT test results and every HPV subtype infections

The top three highest TCT positive rates were found during HPV16,6 and 42 positive patients, although HPV 52,58 and 16 were in the top three prevalence rate list.

Among five types of cytological lesions, the HPV infection rate was 66.08% (3,495/19,222), 63.99% (5/15), 115.20% (144/125), 119.50% (190/159), and 31.72% (1,333/4,202) for NILM, AGCs, HSILs LSILs and ASCs, respectively. HPV infection rates in both LSILs and ASCs were larger than 100%, which means lots of mixed-multiple subtype HPV infection were found in these two types of cytological lesions.

HPV 51,39 and16 were frequently determined in NILM. HPV 45,33 and 58 were frequently determined in HSIL. HPV 56,35 and 59 were commonly found in LSIL. HPV 6,42 and 43 were commonly found in ASC. Very few HPV positive were found in AGC. (Table 6)

Table 6 Different HPV subtype infection rates among NILM, AGC, ASC, LSIL, and HSIL, respectively

HPV subtype	N	NILM (%) N=19,222	AGC (%) N=15	HSIL (%) N=125	LSIL (%) N=159	ASC (%) N=4202	CERVICAL ADENOCARCINOMA (%) N=1	TCT positive, n (%)
HPV16	**555**	**319(57.48)**	0(0)	51(9.19)	23(4.14)	162(29.19)	0(0)	**236(42.52)**
HPV18	205	138(67.32)	0(0)	4(1.95)	7(3.41)	56(27.32)	0(0)	67(32.68)
HPV31	171	118(69.01)	0(0)	4(2.34)	6(3.51)	43(25.15)	0(0)	53(30.99)
HPV33	255	161(63.14)	0(0)	**13(5.1)**	10(3.92)	71(27.84)	0(0)	94(36.86)
HPV35	69	45(65.22)	0(0)	2(2.9)	**4(5.8)**	18(26.09)	0(0)	24(34.78)
HPV39	354	**252(71.19)**	**1(0.28)**	3(0.85)	13(3.67)	85(24.01)	0(0)	102(28.81)
HPV45	53	34(64.15)	0(0)	**4(7.55)**	1(1.89)	14(26.42)	0(0)	19(35.85)
HPV51	355	**256(72.11)**	1(0.28)	4(1.13)	11(3.1)	83(23.38)	0(0)	99(27.89)
HPV52	**756**	505(66.8)	1(0.13)	16(2.12)	27(3.57)	207(27.38)	0(0)	251(33.2)
HPV53	373	259(69.44)	0(0)	6(1.61)	18(4.83)	90(24.13)	0(0)	114(30.56)
HPV56	121	77(63.64)	0(0)	1(0.83)	**8(6.61)**	35(28.93)	0(0)	44(36.36)
HPV58	**586**	398(67.92)	1(0.17)	**26(4.44)**	21(3.58)	140(23.89)	0(0)	188(32.08)
HPV59	70	48(68.57)	0(0)	1(1.43)	**4(5.71)**	17(24.29)	0(0)	22(31.43)
HPV66	195	135(69.23)	0(0)	2(1.03)	7(3.59)	51(26.15)	0(0)	60(30.77)
HPV68	192	131(68.23)	0(0)	2(1.04)	5(2.6)	54(28.12)	0(0)	61(31.77)
HPV6	147	89(60.54)	0(0)	1(0.68)	7(4.76)	**50(34.01)**	0(0)	**58(39.46)**
HPV11	126	89(70.63)	0(0)	0(0)	5(3.97)	32(25.4)	0(0)	37(29.37)
HPV42	54	33(61.11)	0(0)	1(1.85)	2(3.7)	**18(33.33)**	0(0)	**21(38.89)**
HPV43	26	16(61.54)	0(0)	1(3.85)	1(3.85)	**8(30.77)**	0(0)	10(38.46)
HPV44	95	67(70.53)	0(0)	0(0)	1(1.05)	27(28.42)	0(0)	28(29.47)
HPV81	379	**295(77.84)**	**1(0.26)**	2(0.53)	9(2.37)	72(19)	0(0)	84(22.16)
Total	5137	3465	5	144	190	1333	0	1672

The first 15 was HR-HPV subtypes and the last 6 was LR-HPV subtypes in the table 6

TCT positive rates distribution between Single and Multiple type HPV infections

Moreover, among single-type and multiple-type HPV infections, the TCT positive rate was 31.61% (1,100/3,480) and 31.84% (107/336), respectively (Figure 4).

Discussion

In our study, HPV prevalence trends of 23,724 women who had received both TCT and HPV detection in Zhoupu district of Shanghai city were analyzed from 2014 to 2019. The overall prevalence of HPV, single-type HPV infection and multiple-type infection was 16.08%, 91.19% and 8.80%, respectively. Our study showed that single-type HPV infection rate was a peak in women aged 50-60 years, second higher in <30 years, multiple-type HPV infection was a peak in those aged >= 60 years ,and second higher in 50-60 years, HR- HPV52, 58 and 16 were the most common types of single-type and multiple-type HPV infections. Our results were different from Xinjiang [10] ,Guizhou[11], which was a less-developed province of China, simple HPV infection and multiple-type was common both in younger women; and different from Beijing[12], in which single-type HPV infection was more frequently seen in women aged 50–60 years, and multiple-type HPV infection was more common in those aged < 30 years but HR-HPV is similar to ours; and different from Suzhou[13], in which HR-HPV infection rate was a peak in women aged <20 years, and second higher in women aged 51-60 years, infection modes were HPV16, 18, 31, 33, 45, 52, 58. One reason for the difference could be the peak or plateau in cervical cancer incidence from ages 35 to 55 years[14], another could be aggravating trend of the aging population in Shanghai.

We found less HPV positive prevalence, but there was a higher overall prevalence of TCT,18.98%. The TCT positive rate of ASCs, AGCs, HSILs, LSILs and Cervical adenocarcinoma were 17.71%, 4.04%, 2.64%,1.54%, and 0.004%, respectively. The highest TCT positive rate was 23.05% in women aged >=60 years, and the lowest rate was 17.83% in those aged <=30 years. Moreover, TCT positive ratio was 16.55% (3,295/19,908) even in the negative HPV infection women. The data from Beijing[15], showed that the TCT positive ratio was 4.04%,2.64%,1.54% for ASC, LSIL, HSIL, respectively. The data from Mongolia[16], a developing country in Asian, presented that HR-HPV 16, 52, 58, and 33 were common. Cytological examination revealed that the positive rate was 12%, 8% 7%,14% for ASC-US, LSIL, HSIL, and squamous cell carcinoma. Moreover, in our study, among single-type and multiple-type HPV infections, the TCT positive rate was an unapparent difference (31.61% vs 31.84%), which suggests that increased numbers of HPV types did not increase the risk for TCT positive.

In our study, including 23,724 women, HPV 45, 33 and 58 were frequently determined in HSIL; HPV 56, 35 and 59 were commonly found in LSIL; HPV 51,39 and16 were frequently determined in NILM; which was consistent with the several studies [17-20].One study included 3,143 cases from Beijing[17] showed that HPV16, 58, 52, 31 and 51 were commonly found in HSIL; HPV16, 52, 58, 56 and 51 in the class of LSIL; HPV16, 31, 6,11, 52 and 58 in NILM. Another study involved 18,170 women from Korea reported that HPV 16 was common types in HSIL; HPV 58,53,56,51 in LSIL; HPV 58,52 ,53,16 in ASC. As suggested by the natural history model of Cervical Cancer, the relative significance of HPV16 increased with lesion severity, especially in HSIL[14]. HPV types 6 and 11 are low-risk (LR) genotypes that induce genital warts or condylomas[21], HPV 6 also were commonly found in ASC in our study. Therefore, HPV and TCT screening, as a critical step of secondary prevention for cervical cancer, further tracking of results is an important clinical strategy for the treatment of cervical precancerous lesions.

First-generation vaccines directly protect against oncogenic HPV types 16 and 18 in individuals naive for those types, and these HPV types are responsible for approximately 70% of invasive cervical cancers[22]. Recently, second-generation 9-valent vaccine against the HPV types 6,11,16,18,31,33,45,52,58 which responsible for up to 90% of cervical cancers has been shown either via direct protection against a larger proportion of types[23, 24]. But ,only 14% of low-income and lower-middle-income countries had established vaccination programs in 2016[25].The first HPV vaccine was licensed in China just three years ago, China has not yet decided whether to include HPV vaccines in their routine immunization programs[26]. From our study, the top three with the highest prevalence were HPV52, 58 and 16. The most of CIN 2+ lesions are sustained by HR-HPV genotypes, especially the ones covered by the 9-valent vaccine; therefore, the widespread use of prophylactic HPV vaccines could significantly reduce the incidence of preneoplastic and neoplastic cervical lesions.

Our study also has some limitations. First, although HPV gene subtypes are biologically independent, it is possible that some of these subtypes have common biological characteristics, resulting in similar phenotypes (such as the similarity of the number of infected people). Therefore, further analysis should be made to investigate the similarity of infection for HPV subtypes infection in the cytology test results. Second, although the relationship between HPV and cytology test results was focused on this research, the characteristics of bacterial vaginosis infection were not involved. So, the association among HPV infection, abnormal cervical cytology and bacterial vaginosis should be considered.

Conclusion

The three most common HR-HPVs are ranked in descending order of HPV52, 58, and 16. Single-type infection was more common than multitype infection. The long-term trend in our data from 2014 to 2019 shows that the HPV positive rate had changed significantly. HPV and TCT screening were a key step in the secondary prevention of cervical cancer. Further tracking the results of HPV and TCT was an important clinical strategy for the treatment of cervical precancerous lesions. Our data provides valuable information for Shanghai's HPV-based female screening and prevention strategies. The widespread use of preventive HPV vaccines can significantly reduce the incidence of pre-neoplastic and neoplastic cervical lesions.

Abbreviations

Human papillomavirus: HPV; High-risk HPV: HR-HPV; Intraepithelial lesions or malignancy: NILM; Atypical glandular cells: AGCs; Atypical squamous cells of undetermined significance: ASC-US; Low-grade squamous intraepithelial lesions: LSIL; High-grade squamous intraepithelial lesions: HSIL; ThinPrep cytological test: TCT.

Declarations

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Authors' contributions

HPL and PL designed and supervised the study, having full access to all of the data in the study and taking responsibility for the content of the manuscript. QL, ZL, BLX, SQW, and HPL acquisition of data. WL, HR, LPS, ZL, HFL and PL analyzed and interpreted the data. HPL and PL prepared the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data were collected from Zhoupu Hospital in Shanghai City. We are grateful to their generous help. The data can be free shared. The materials were purchased from Hybribio Biotechnology Limited Corp and
LBP Medicine Science & Technology Co., Ltd.

Ethics approval and consent to participate

This study was approved by the Institutional Medical Ethics Review Board of Zhoupu Hospital in Shanghai City.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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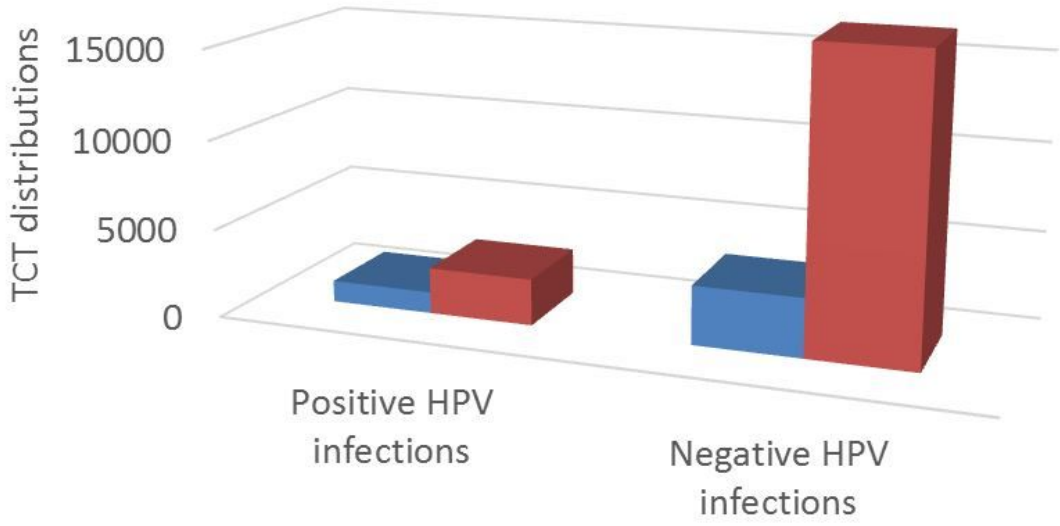
Figures



	Positive HPV infections	Negative HPV infections
TCT positive	1207	3295
TCT negative	2609	16613

Figure 1

TCT cytology test results' distributions between positive and negative HPV infection rates.

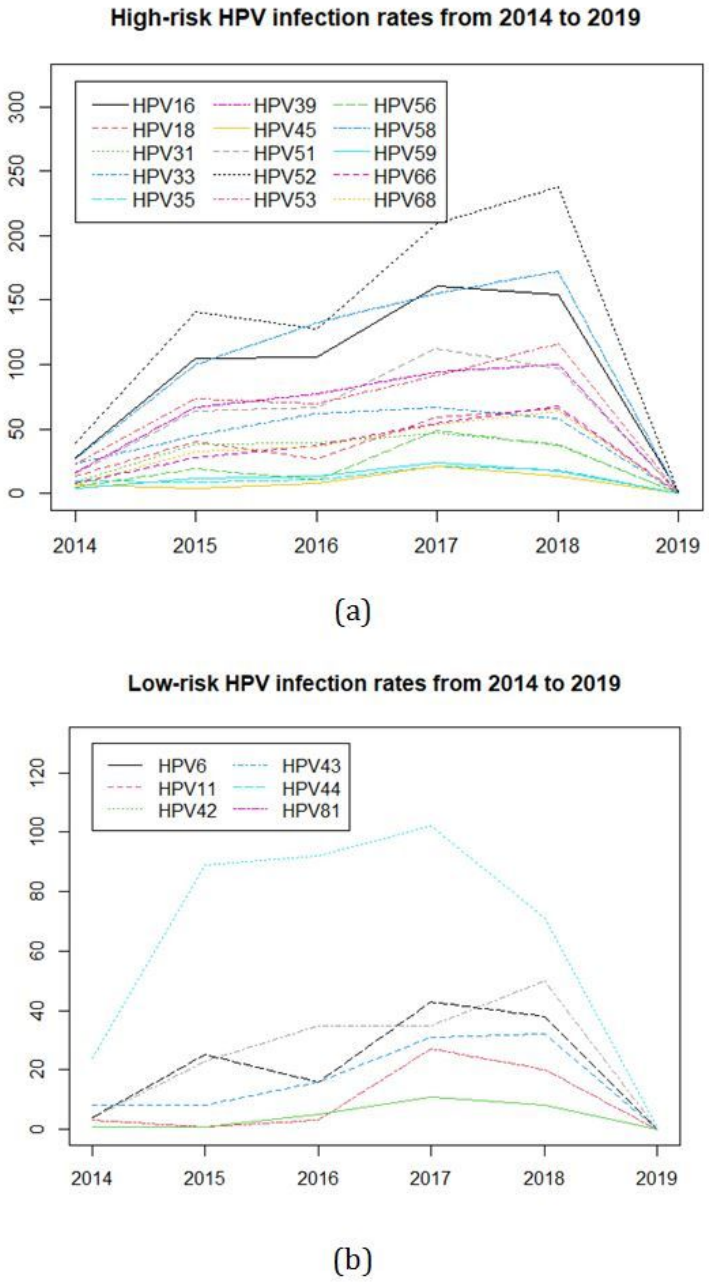


Figure 2

Secular trends of different HPV subtype infection rates from 2014 to 2019. (a)High-risk HPV infection rates. (b) Low-risk HPV infection rates.

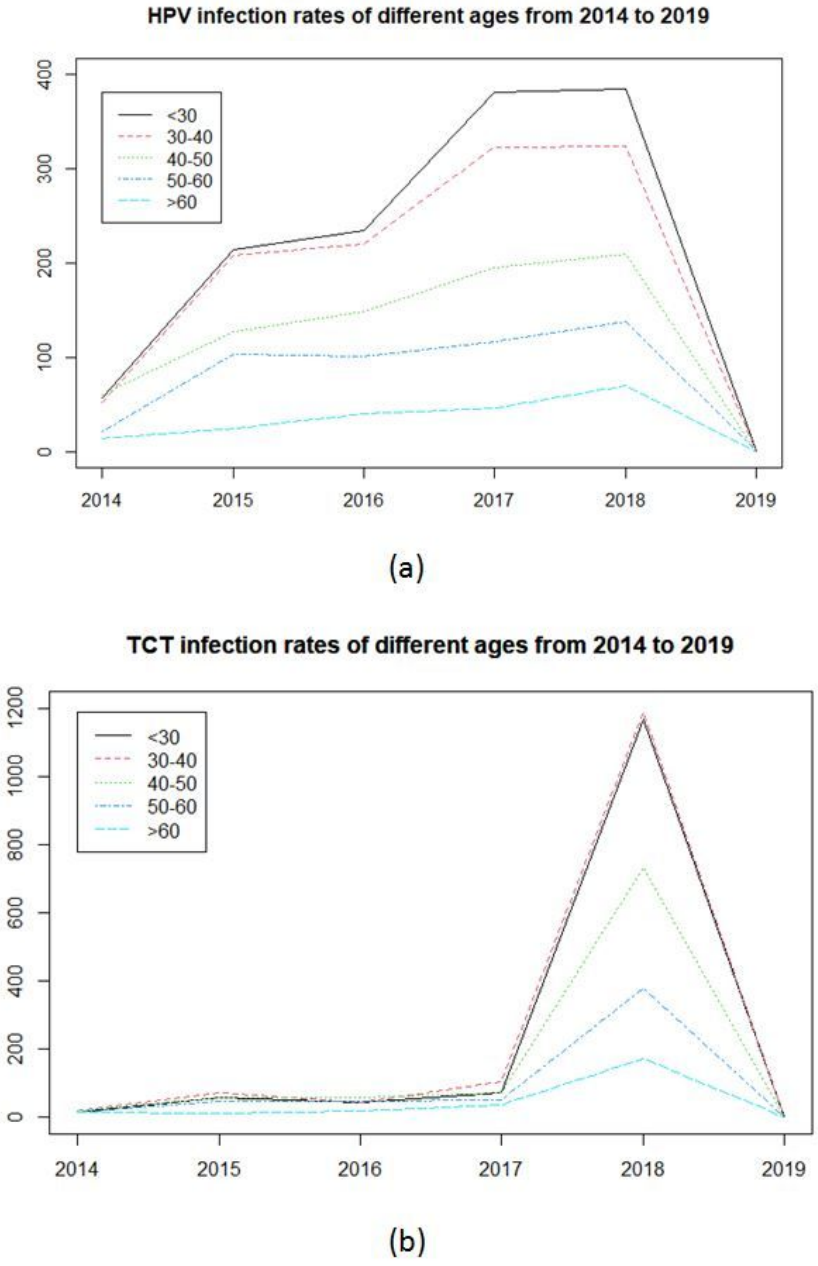
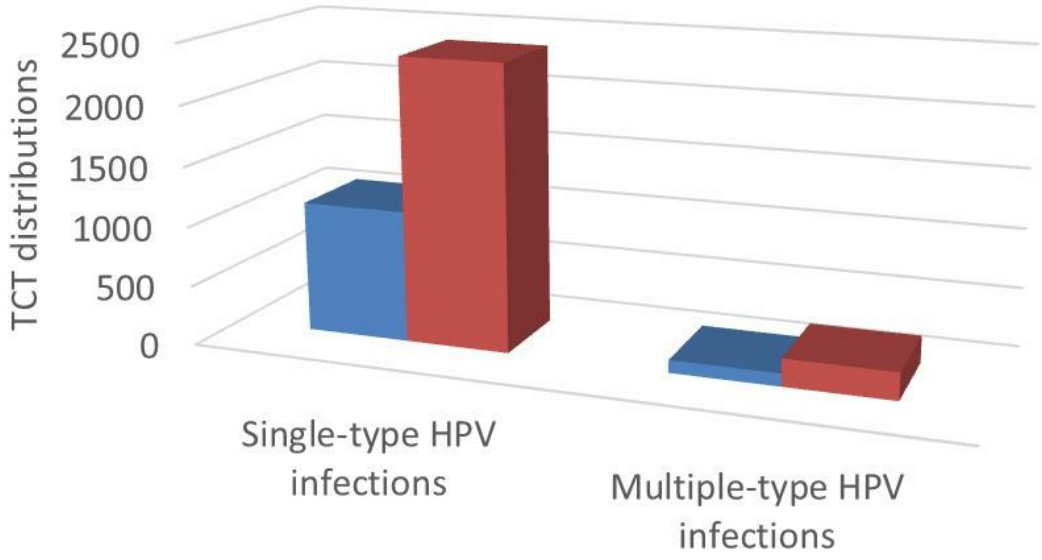


Figure 3

HPV and TCT infection rates among different ages from 2014 to 2019. (a) HPV infection rates distribution (b) TCT infection rates distribution.



	Single-type HPV infections	Multiple-type HPV infections
TCT positive	1100	107
TCT negative	2380	229

Figure 4

TCT positive rates distribution between Single and Multiple type HPV infections.