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Extended HPV typing test performed better predict value for CIN2+ among elderly women in China

Jing Xiao [a], Li Li [a], Liuping Hu [b], Wen Li [c,*], Feng Zou [d,*]

[a] Department of Gynecology and Obstetrics, Shanghai Sixth People's Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai 201306, China
[b] Department of Medical Laboratory, Shanghai Sixth People's Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai 201306, China
[c] Department of Ultrasound in Medicine, Shanghai Sixth People's Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai 201306, China
[d] Department of Anesthesiology, Shanghai Sixth People's Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai 201306, China

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ABSTRACT

Objective: The aim of this study was to examine the cervical cancer screening practices among women residing in Lingang New District of Shanghai. Moreover, the study aimed to delve into the characteristics of HPV infection and cervical lesions in older women (≥60 years old), seeking for more effective method for cervical cancer screening.

Methods: This is a cross-sectional study enrolled women who were referred to colposcopy and cervical histological examination due to abnormal cytology or HPV tests from Shanghai Sixth People's Hospital between January 2018 and December 2022.

Results: A total of 1,931 women (mean age: 41.8 ± 12.5, range: 18–88 years old) were enrolled, 119 individuals aged ≥ 60 and 1732 aged <60. The infection rates of HPV52, 33, 35, 56, 26 and 81 were significantly higher in the elderly group. Multiple HPV infection rates were also higher in this group and were associated with cervical lesions. The probability of LSIL, HSIL and Ca in women over 60 years old was significantly higher compared to women under 60. The top three HPV genotypes in elderly women with CIN2+ were HPV16, 52, and 58. The Yoden index was higher for extended typing for HPV 31/33/45/52/58(0.41) compared to cytology(0.29), high risk HPV without specific typing(0.07), cotest(cytology and high risk HPV, 0.06 or 0.30), or the current shunt strategy(0.07).

Conclusions: Elderly women still need to continue cervical cancer screening, and extended typing test for HPV16/18/31/33/45/52/58 is a more effective method for this age group.

1. Introduction

The World Health Organization defines individuals aged 65 or older as old, while China sets the age at 60. Currently, China has the world's largest population of older adults (individuals ≥ 60 years old), and is experiencing population aging on an unprecedented scale (Chen et al., 2022). In Shanghai, which holds the highest life expectancy in China, the population aged 60 and above has increased by 114,400 individuals or 2.1 % from 2021 to 2022.

It is widely known that many chronic diseases, such as heart and cerebrovascular diseases, are associated with aging, and cancer is no exception (Chen et al., 2024; Ryou et al., 2023; White et al., 2014). Cervical cancer, the fourth most common malignancy in women worldwide, poses a serious threat to women's physical and mental well-being, presenting a major global health challenge (Sung et al., 2021).

Fortunately, the widespread adoption of cervical cancer screening has enabled early detection of this type of cancer (Curry et al., 2018). Effective cervical cancer screening can reduce the incidence rate and mortality of cervical cancer (Vaccarella et al., 2013). The United States and other high income countries had successfully established cervical cancer prevention screening systems, which contributed to decreased mortality for few decades (Cardoso et al., 2021; Xia et al., 2022). China launched the cervical cancer screening program in rural areas in 2009, aming to provide 10 million cervical screenings annually for rural women aged 35 ~ 64 years (Zhang et al., 2022). After more than a decade of effort, the cervical cancer screening rate of women aged 35–64 in China has steadily increased from approximately 25 % in 2010 (Wang et al., 2015), 27 % in 2013 (Bao et al., 2018), 31 % in 2015 (Zhang et al.,

* Corresponding authors.
E-mail addresses: liwen224317@163.com (W. Li), 18964885780@163.com (F. Zou).

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2020), and 37 % in 2019 (14). Although significant progress has been made, there is still a steep road ahead to achieve the goal of 70 % screening coverage for women aged 35–44 by 2030. Furthermore, data from 2018 to 2019 reveals that the cervical cancer screening rate for women aged 60–64 in China was only 18.8 %, significantly lower than the overall target population (Zhang et al., 2022).

Currently, the primary cervical cancer screening tests mainly include HPV (human papilloma virus) test and cervical cytology around the world (Europe; Fontham et al., 2020; Zhu et al., 2023). Organized and planned universal population screening, as well as opportunistic screening for age-appropriate women seeking medical treatment in medical institutions were both effective strategies for cervical cancer screening in China (Commission, 2021).

Shanghai was one of the cities firstly coordinated cancer screening program in China, which was initiated in 1958 (Kha-Ti et al., 1963). Shanghai Lingang Area commenced development and construction in 2003 and was formally established as Lingang New Area in 2019. In recent years, an increasing number of individuals chosen to reside here. However, data concerning cervical cancer screening among women in this area remains unreported. Being the sole tertiary general hospital in this region, we hace taken on the responsibility to address this tissue. As such, we have gathered pertinent data from women who underwent cervical cancer screening and colposcopy at our hospital in the past 5 years. Through statistical analysis,we aim to comprehend the distribution and demographic characteristics of HPV in this region, as well as the attributes of HPV infection and cervical lesions among elderly women. Additionally, we seek to explore the correlation between these factors and cervical lesions. By doing so, we can develope better-suited cervical cancer prevention, screening, and treatment programs specifically tailored for elderly women in the area.

2. Methods

2.1. Study design and patients

This is a cross-sectional study enrolled women from Shanghai Sixth People's Hospital (Lingang Area) between January 2018 and December 2022. Inclusion criteria: patients who have completed all 4 tests as follows:1) HPV examination, 2) TCT examination, 3) colposcopy examination and 4) cervical biopsy examination. The exclusion criteria were: 1) Incomplete TCT and HPV data or not conducted in our hospital; 2) patients who have undergone surgery because of cervical high-squamous intraepithelial lesion (HSIL) or cervical cancer; 3) patients who have undergone hysterectomy. If there have been repeated screenings in the past 5 years, the worst diagnosis will be retained (Fig. 1).

This study was approved by Institutional Medical Ethics Review Committee of Shanghai Sixth People's Hospital (No: 2023–121). All patients signed the written informed consent forms.

3. Procedures and definition

Basic demographics, HPV, cytology and histology results were collected through an electronic medical record system.

HPV genotyping The HPV genotyping test kit (Jiangsu Shuoshi Biotechnology Co., LTD.) was used to detect 21 HPV genotypes, including 18 high-risk genotypes and 3 low-risk genotypes by using fluorescent PCR. The procedures were carried out by professionals in strict accordance with the instructions of the kit. Multiple infection is identified as sample with two or more HPV genotypes positive.

Cytology testing Cytology testing based on cervical fluid was carried out by experienced experts in gynecological cytology. The microscopic examination results were interpreted according to the definition by the Bethesda system (Wright et al., 2007). Atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells (ASC-H), low-grade squamous intraepithelial lesion (LSIL), HSIL, atypical glandular

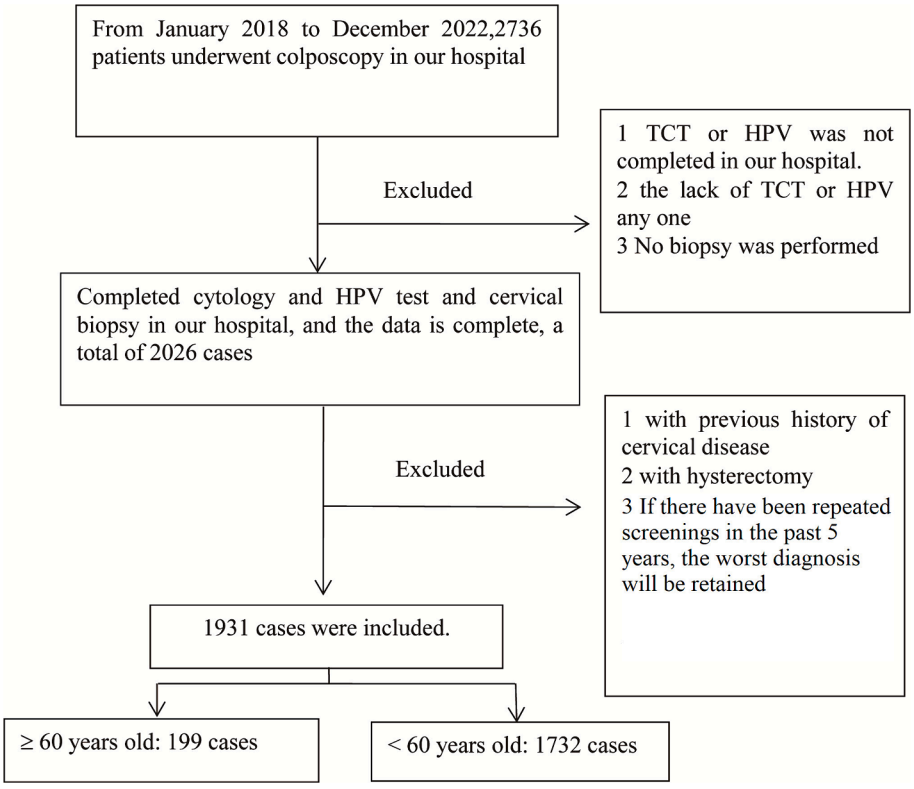

Fig. 1. Flow chart of patients selection who have completed cervical cancer screeing tests in Shanghai LinGang Area, China, 2018 to 2022.

cells (AGC), adenocarcinoma in situ (AIS) and squamous cell carcinoma (SCC) and adenocarcinoma were identified as positive. No intraepithelial lesions or malignant tumors (NILM) was identified as negative. (Alrajjal et al., 2021).

Cervical biopsy examination Histological results were sorted into: 1) negative (including normal histopathology and cervicitis), 2) LSIL (cervical intraepithelial neoplasia (CIN 1), 3) HSIL (including CIN2 and CIN3), 4) Ca (including all kinds of invasive cervical cancer and cancer in situ). CIN 2+ included CIN 2, CIN 3,and Ca.

3.1. Statistical analysis

The statistical analysis was performed using SPSS 25.0 (IBM Armonk, NY, USA). All the enrolled patients were divided into two age groups: < 60 years old and ≥ 60 years old. The chi-square test was used for the comparison between them of cytology, HPV, and histology abnormality rate. Two-sided *P*-value < 0.05 was considered statistically significant.

Calculation method of predictive indicators sensitivity = true positive/(true positive + false negative) *100 %, specificity = true negative/(true negative + false positive) *100 %, positive predictive value = true positive/(true positive + false positive) *100 %, negative predictive value = true negative/(true negative + false negative) *100 %, Youden index = sensitivity + specificity −100 %.

4. Results

A total of 2736 patients underwent colposcopy in our hospital were enrolled. Finally, 1931 women (mean age: 41.8 ± 12.5, range: 18–88 years old) were included by inclusion criteria (Fig. 1).

The total abnormal rate of cytology(≥ASCUS) was 15.9 %, and it was sinificantly higher in elderly women than that in women under 60 years old.(21.6 % vs 15.24 %, $X^2 = 5.41$,P = 0.021).

A total of 1750 (90.50 %) cases were detected with HPV infection. In total women, the top three ranked HPV subtypes were HPV52 (22.32 %), HPV16 (15.54 %), and HPV53 (10.56 %). The positive infection rates of HPV33, HPV35, HPV52, HPV56, HPV26 and HPV81 were significantly higher in the ≥ 60 years old group compared with that in the < 60 years old group. (Table 1). A total of 535 (27.7 %) was infected with multiple HPV genotypes. Multiple infection rates were higher in women over 60 years of age(44.22 % vs 25.80 %, $X^2 = 30.212$, $P = 0.001$). Multiple infections were found to be associated with CIN2+ in both women of all age groups ($X^2 = 5.736$, $P = 0.017$) and specifically in elderly women ($X^2 = 8.173$, $P = 0.004$).

Table 1
Prevalence of HPV genotypes among women in Shanghai LinGang Area, China, 2018 to 2022, according to age groups.

HPV genotypes	< 60 years old (n = 1732), n (%)	≥ 60 years old (n = 199), n (%)	Total (n = 1931), n (%)	*P*
HPV	1570 (90.7)	180 (90.5)	1750 (90.6)	0.929
HPV16	266 (15.4)	34 (17.1)	300 (15.5)	0.524
HPV18	103 (6.0)	13 (6.5)	116 (6.0)	0.742
HPV31	90 (5.2)	15 (7.5)	105 (5.4)	0.168
HPV33	68 (3.9)	25 (12.6)	93 (4.8)	<0.001
HPV35	40 (2.3)	11 (5.5)	51 (2.6)	0.007
HPV39	125 (7.2)	16 (8.0)	141 (7.3)	0.673
HPV45	35 (2.0)	3 (1.5)	38 (2.0)	0.823
HPV51	133 (9.23)	18 (9.0)	151 (7.8)	0.497
HPV52	375 (21.7)	56 (28.1)	431 (22.3)	0.037
HPV53	177 (10.2)	27 (13.6)	204 (10.6)	0.146
HPV56	120 (6.9)	23 (11.6)	143 (7.4)	0.018
HPV58	192 (11.1)	25 (12.6)	217 (1.2)	0.532
HPV59	79 (4.6)	4 (2.0)	83 (4.3)	0.093
HPV66	96 (5.5)	13 (6.5)	109 (5.6)	0.567
HPV68	118 (6.8)	19 (9.6)	137 (7.1)	1.155
HPV6	36 (2.1)	6 (3.0)	42 (2.2)	0.548
HPV11	15 (0.9)	1 (0.5)	16 (0.8)	0.902
HPV26	4 (0.2)	3 (1.5)	7 (0.4)	0.028
HPV73	18 (1.0)	2 (1.0)	20 (1.0)	1
HPV81	96 (5.5)	21 (10.6)	117 (6.1)	0.005
HPV82	27 (1.6)	5 (2.5)	32 (1.7)	0.481

The probability of cervical lesions increases with age (Fig. 2). The probability of LSIL, HSIL and Ca in women over 60 years old was significantly higher than that in women under 60(Table 2).There was no significant difference in the incidence of CIN2+ in women aged 60–64 years and women aged 65-plus years(13.33 % vs 14.89 %, $X^2 = 0.1$, $P = 0.752$). In total women, the former 5 HPV genotypes in different histology were shown in Table 3. And the most common HPV genotypes in different age group of women with different cervical lesions were shown in Supplementary Table 1.The predictive efficacy of different strategies for CIN2+ in women over 60 were shown in Table 4.

5. Discussion

It is widely acknowledged that persistent HPV infection is the primary cause of the majority of the cervical cancers (zur Hausen, 2009). HPV 16 and 18 are the most commonly found HPV genotypes in invasive cervical cancer (Fowler et al., 2024), accounting for nearly 70 % cervical cancers (Beavis and Levinson, 2016; Li and Yin, 2023). In addition to these, there are several high-risk HPV genotypes, such as HPV 31, 33, 45, 52, and 58, which are targeted by the 9-valent HPV vaccine , contributed to the most of the remaining 30 % cervical cancers (Beavis and Levinson, 2016).

The distribution of HPV genotypes varies depending on region, race, and age (Hirth, 2019; Li et al., 2019; Trama et al., 2022). In the United States, the top three HPV genotypes are HPV 52, 39, and 51, respectively, with HPV 16 being the fourth common genotype (Trama et al., 2022). Among women with ASC-US cytology in Italy, the top three HPV genotypes were HPV16, HPV31, and HPV66, respectively. (Muresu et al., 2022) Our study discovered that the most prevalent HPV genotypes in the entire cohort were HPV 52, 16 and 53 (Table 3). The result was similar, but not identical to those of other researches. Wang R reported the HPV distribution in 37 cities in China, and the main prevalent HPV genotypes were HPV 16, 52, and 58(Trama et al., 2022). While the top one was HPV 52, followed by HPV 16 and 58 in Beijing, China (Zhang et al., 2023). Moreover, Yang X observed an increasing trend in the prevalence of HPV52 in Guangzhou (Yang et al., 2023). In the 199 elderly women of this study, the most prevalent HPV types were found to be HPV 52, 16, and 53, respectively (Supplementary Table 1). But HPV16, 52, and 58 occupied the top three in both elderly women with cervical cancer and CIN2 +. This pattern remained consistent in women under age of 60 as well. Additionally, a higher rate of infection was observed in elderly women for HPV52, 33, 35, 56, 26 and 81 compared to the women under 60 (Table 1). Moreover, the rate of multiple infection was found to be higher in women over age of 60, which further correlated with the presence of cervical lesions.

Yu YQ discovered that the peak age for HPV16/18 infection was between 56 ~ 65 years old (Yu et al., 2022). Additionally, Wong EL found a second peak of HPV infection in individuals aged 65 and older (Wong et al., 2022). However, we did not find the same prevalance of HPV infection in elderly women. This discrepancy may be attributed to the fact that our study mainly focused on cases and did not include all women who tested negative. Nevertheless, we did observe a significantly higher probability of cervical lesions, particularly cervical cancers, in women over 60 compared to those under 60(Table 2). Furthermore, there was no notable difference in the incidence of CIN2+ between women aged 60–64 years and women aged 65 and above. The findings indicated that there is a serious burden of cervical cancer among elderly women in Lingang New Area. In fact, the burden of cervical cancer among elderly women is also significant in America (Cooley et al., 2023; Qin et al., 2023), Korea (Cho et al., 2022), and other regions in China (Liu et al., 2024).

Most of the guidelines around the world currently recommend that women with history of regular screening and negative Pap or HPV tests

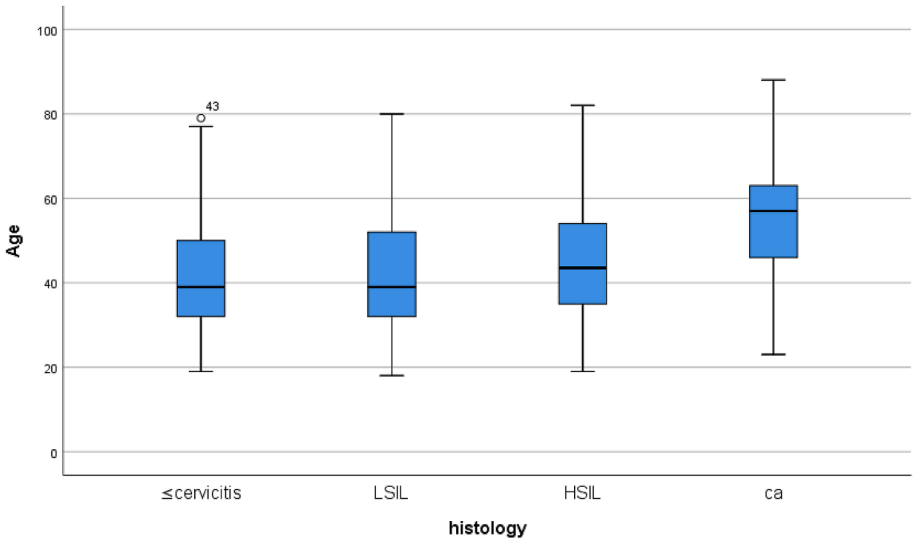

Fig. 2. Relationship between age and cervical lesions among women in Shanghai LinGang Area, China, 2018 to 2022.

Table 2
Cervical histological results among women in Shanghai LinGang Area, China, 2018 to 2022, according to age groups.

histological results	< 60 years old (n = 1732), n (%)	≥60 years old (n = 199), n (%)	Total (n = 1931), n (%)	*P*
≥LSIL	497 (28.7)	72 (36.2)	569 (29.5)	0.025
CIN2+	131(7.6)	28(14.1)	159 (8.2)	0.002
Ca	19 (1.1)	12 (6.0)	31 (1.6)	<0.001

Table 3
The top five hpv genotypes among women in Shanghai LinGang Area, China, 2018 to 2022.

No.	Total, n (%)	Ca, n (%)	HSIL, n (%)	LSIL, n (%)	Cervicitis, n (%)
1	HPV52 (431, 24.6)	HPV16(24, 74.4)	HPV16(68, 53.1)	HPV52 (100, 24.4)	HPV52(300, 22.0)
2	HPV16 (300, 17.1)	HPV52(4, 12.9)	HPV52(27, 21.1)	HPV16(71, 17.3)	HPV53(151, 11.1)
3	HPV58 (217, 12.4)	HPV18(2, 6.5)	HPV58(19, 14.8)	HPV58(53, 12.9)	HPV58(143, 10.5)
4	HPV53 (204, 11.7)	HPV31(2, 6.5)	HPV31(15, 11.7)	HPV53(46, 11.2)	HPV16(137, 10.1)
5	HPV51 (151, 8.6)	HPV45(2, 6.5)	HPV33(14, 10.9)	HPV68(43, 10.5)	HPV39(105, 7.7)

Table 4
Different methods in predicting CIN 2+ among elderly women in Shanghai LinGang Area, China, 2018 to 2022.

predictive factors	sensitivity (%)	specificity (%)	positive predictive value(%)	negative predictive value(%)	Yoden
cytology	46.4	82.5	30.2	90.4	0.29
high risk HPV	92.9	14.0	15.0	92.3	0.07
HPV16	64.3	90.6	52.9	93.9	0.55
HPV16/18	64.3	83.6	39.1	93.5	0.48
HPV16/52	82.1	64.9	27.7	95.7	0.47
HPV16/18/52	82.1	58.5	24.5	95.2	0.41
HPV31/33/45/52/58	95.0	46.4	23.2	98.6	0.41
HPV16/18/31/33/45/52/58	96.4	41.5	21.3	98.6	0.38
cotest 1	100	5.8	14.8	100	0.06
cotest 2	39.3	90.6	40.7	90.1	0.30
Shunt strategy	15.8	91.6	17.6	90.5	0.07

Cotest 1:cytology ≥ ASCUS or hr HPV positve individuals were classified as cotest positive.
Cotest 2:cytology ≥ ASCUS, while hr HPV positve at the same time, was considered as cotest positive.
Shunt strategy: cytology = ASCUS while hr HPV positive (cytology ≥ LSIL was excluded).

could stop screening at 65. However, the reality in China is the cervical screening rate for the women aged 60 ~ 64 years is significantly lower than that for women under 60 (Zhang et al., 2022). The current strategies for cervical cancer screening in China include cytology, HPV testing, or cotesting (combining cytology with HPV testing). Cytology can be utilized as a shunt for non-HPV16/18 infection, while hr-HPV test can be choosed as the shunt when cytology is ASCUS. Cotesting is recommended for opportunistic cervical caner screening in hospital settings, and the guidelines apply to individuals aged 35 ~ 64 years.

However, we have found that the likelihood of abnormal cytological screening results is much higher in elderly women compared to those under 60 years old. HPV 16 and 52 were the most prevalent HPV genotypes in women agde over 60 with CIN 2 +. We employed several strategies to screen for CIN 2 + in elderly women aged over 60, as outlined in Table 4. HPV16, which is the primary cause of CIN2+, had the best predicting value when detected positive. HPV16/52 positive showed a similar Yoden Index to HPV 16/18, which will be referred to coposcopy immediately in all cervical cancer screening guidelines. The sensitivity of HPV16/18/52 was 82.1 %, the same as HPV16/52, and notably higher than that of HPV16 alone or HPV16/18. HPV16/18/31/33/52/58 exhibited the same sensitivity(92.9 %) as high risk HPV, but with significantly better specificity.

The cytology screening program for cervical cancer has played a significant role in reducing the incidence and mortality rates associated with the disease (Whitlock et al., 2011). However, the high demands placed on cytology in terms of sampling and pathologist expertise result in its lead to limited sensitivity and high specificity (Moy et al., 2010). Consequently, oue findings regarding the cytological Yoden index, which was 0.29, were not surprising and were considerably lower than those observed with extended HPV typing. Moreover, we also assessed the predictive indicators of cotesting. When considering cytology ≥ ASCUS or hr HPV positve as a positive cotesting result, we achieved the highest sensitivity (100 %), but the worst specificity (5.8 %). On the

other hand, when considering cytology ≥ ASCUS and hr HPV positve simutaneously as a positve cotesting result, the Yoden index was 0.3, which was wtill lower than that of extended HPV typing. Currently the shunt strategy (cytology result is ASCUS while hr-HPV positive) demonstrated good specificity but bad sensitivity. The Yoden index for this shunt strategy was 0.07, significantly lower than that of HPV typing. In summary, all of our results suggest that HPV typing provides a much stronger predictive value for CIN2+ in elderly women compared to other methods, including cytology, cotesting, and shunt strategy.

Therefore, the conclusion of this study was extended HPV typing wolud be a preferable option for cervical cancer screening among elderly women aged 60 and above. It is recommended that patients infected with HPV16/18 should be referred to colposcopy (Fontham et al., 2020; Kyrgiou et al., 2020; Perkins et al., 2020). Additionally, elderly women with HPV31/33/45/52/58 should also undergo coposcopy in order to detect CIN2+.

However, there were still several limitations to this study. Firstly, the sample size was deemed insufficient, consisting of only 199 women aged 60 and above, which accounted for 10.3 % of the study population. This could potentially be attributed to inadequate coverage of cervical cancer screening. Secondly, as this was a single-center study, its findings cannot be generalized to reflect the overall prevalence in China. Thirdly, this study did not include women who were negative for cervical cancer screening, so the overall abnormal rate of cytological screening and HPV infection rate in the elderly female population remains unclear.

6. Ethics approval and consent to participate

This study was approved by Institutional Medical Ethics Review Committee of Shanghai Sixth People's Hospital (No: 2023-121). All patients signed the written informed consent forms.

7. Consent for publication

Not applicable.

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9. Authors' contributions

Li Li and Liuping Hu carried out the studies, participated in collecting data, and drafted the manuscript. Jing Xiao and Wen Li performed the statistical analysis and participated in its design. Feng Zou and Jing Xiao participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Jing Xiao: Writing – original draft, Formal analysis, Conceptualization. **Li Li:** Investigation. **Liuping Hu:** Formal analysis. **Wen Li:** Writing – review & editing, Writing – original draft, Resources. **Feng Zou:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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