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Age-specific 3-year risk of cervical precancer among HPV-positive women attending screening: a post hoc analysis from a retrospective cohort

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Abstract

This post hoc analysis explored the age-specific risk of cervical precancer in women infected with human papillomavirus (HPV), using data from a cohort of 7263 participants aged 21-71years undergoing cervical screening. We found a slightly varied prevalence of high-risk HPV (hrHPV) in different age, with highest in women under 30 years old (9.28% for 13 hrHPVs tested by HC2-HPV, 10.82% for 14 hrHPVs tested by DH3-HPV). However, the prevalence of cytology abnormalities peaked in age 30–39 years (~3.6%). A total of 5840 women completed 3-year follow-up. Among them, 558 were positive for HC2 assay and 583 were positive for DH3-HPV at baseline. Of note, the 3-year cumulative risks for cervical intraepithelial neoplasia grade 2+ (CIN2+) or grade 3+ (CIN3+) in women infected with high-risk HPV did not increase with age but declined (e.g., 41.67%, 27.78%, 26.42%, 15.98%, and 18% for CIN2 + risk in HC2-positive women at year 25–29, year 30–39, year 40–49, year 50–59, and year 60–71, respectively). If stratified by the median age, younger women (25–48 years) positive with HC2-HPV at baseline had a higher 3-year CIN2+/CIN3 + risk than older women (49–71 years) [26.55% (95%CI = 21.8-31.92%) vs. 18.28% (95%CI = 14.11-23.34%), $P = 0.019$; 15.52% (95%CI = 11.81-20.14%) vs. 9.7% (95%CI = 6.71-13.83%), $P = 0.039$]. Similarly, for women positive with DH3-HPV at baseline, younger group had a higher 3-year CIN2+/CIN3 + risk than older group [26.44% (95%CI = 21.73-31.75%) vs. 17.01% (95%CI = 13.11-21.78%), $P = 0.006$; 15.25% (95%CI = 11.6-19.8%) vs. 9.03% (95%CI = 6.24-12.9%), $P = 0.021$]. These findings indicate the potential value of age-specific risk assessment in cervical cancer screening.

Keywords Human papillomavirus, Cervical intraepithelial neoplasia, Age, Risk

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Introduction

Persistent infection with high-risk human papillomavirus (HPV) is the necessary cause of cervical cancer [1]. By the principle of "equal management for equal risk", a woman's risk of developing cervical precancer or cancer can be estimated based on current screening results and past history [2]. Personal factors such as age and immunosuppression should also be considered when risk-based management was carried out. However, several previous studies revealed conflicting results in investigating the correlation between the risk of cervical precancer and age [3–8].

Recently, we completed a head-to-head comparison of Hybrid Capture 2 assay (HC2, Qiagen®, Germany) and DH3-HPV (DALTONbio®, China) test, which detects 14 high-risk HPV (hrHPV) with 16/18 genotyping based on hybrid capture technique, in 7263 residual baseline cytology specimens with 3-year follow-up from two screening projects [9]. Using this data, we performed a post hoc analysis to explore the age-specific risk of cervical precancer among women following HPV infection.

Methods

This study is a post hoc analysis using data from a previous retrospective cohort study. Detailed characteristics of the cohort and the study procedures have been described previously [9, 10] and showed in the supplementary file. In brief, the cohort with adjudicated diagnosis consisted of 7263 women, aged 21 to 71 years, from two independent National Medical Products Administration (NMPA) projects of new kits for cervical screening in Zhejiang province, China. 3149 eligible women from Lishui area participated NMPA project 20,160,380 and women with HPV16/18 positive results or cytology≥atypical cells of undetermined significance (ASC-US) were referred to colposcopy. 4132 eligible women from Hangzhou area were enrolled NMPA project 20,160,205 and women with any hrHPV positivity or cytology≥ASC-US were called back for colposcopy. For the two NMPA projects, women exited the screening project once diagnosed with cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+), while those who weren't will continue in the 3-year follow-up phase. Due to the ethical considerations, almost all of the women with negative co-testing results were not referred to colposcopy and regarded as CIN grade 1 (CIN1) or less. After cytological examinations were routinely performed, the residual specimens of cytology in PreservCyt solution (ThinPrep®, Hologic) at baseline were stored in one walk-in refrigerator with 4 °C. Totally, 7263 residual baseline samples were retested with HC2 and DH3-HPV under blinded conditions after 3-year follow-up, because the other 18 residual samples were not sufficient for HPV retesting. Then, the results of HC2 and DH3-HPV from 7263 women were analyzed with the adjudicated diagnosis. Cumulative risks of CIN2+and CIN grade 3 or worse (CIN3+) with 95% confidence intervals (95% CI) were calculated. The chi-square or Fisher exact test was used to compare proportions among different groups. Statistical significance of all two-tailed tests was set at $P \leq 0.05$. The SPSS 21.0 and VassarStats (http://vassarstats.net) were used for the statistical analysis.

Results

Among the 7263 women, the overall prevalence of 13 hrHPVs detected by HC2 was 9.12% (663/7263), whereas the overall prevalence of 14 hrHPVs detected by DH3-HPV was 9.51% (691/7263). Patterns of HPV prevalence by age group were showed in Fig. 1A. We found a relatively high HPV prevalence in women under 30 years old (9.28% for 13 hrHPVs, 10.82% for 14 hrHPVs) that slightly decreased thereafter with an upward trend in older women (9.85% for 13 hrHPVs, 10.53% for 14 hrHPVs). The prevalence of abnormal cervical cytology by age group was also showed in Fig. 1A. For any cytology abnormality (≥ASC-US), women aged 21–29 years had the lowest prevalence (1.55%) that increased to 3.6% in women aged 30–39 years, and then gradually declined with age.

A total of 5840 women completed 3-year follow-up. Among them, 558 (aged 25-71years) were positive for HC2 assay and 583 (aged 25-71years) were positive for DH3-HPV at baseline. The age-related cumulative CIN2+and CIN3+risks in this cohort were showed in Table 1. For both CIN2+and CIN3+, the 3-year cumulative risks did not increase with age but declined a certain degree (e.g., 41.67%, 27.78%, 26.42%, 15.98%, and 18% for CIN2+risk in HC2-positive women at year 25–29, year 30–39, year 40–49, year 50–59, and year 60–71, respectively). We found a clear trend that HPV-positive women aged 50 years or older seemed to have a lower risk to develop cervical precancer than younger HPV-positive women.

Furthermore, we compared the cumulative risks for younger (25–48 years) and older (49–71 years) women stratified by the median age (Fig. 1B, C). Younger women positive with HC2-HPV at baseline had a higher 3-year cumulative CIN2+risk than older women [26.55% (95%CI=21.8-31.92%) vs. 18.28% (95%CI=14.11-23.34%), $P=0.019$]. Similarly, younger women positive with DH3-HPV at baseline had a higher 3-year cumulative CIN2+risk than older women [26.44% (95%CI=21.73-31.75%) vs. 17.01% (95%CI=13.11-21.78%), $P=0.006$]. However, by partial genotype of DH3-HPV, the CIN2+risk between the two age groups were significantly different for other hrHPV-positive women only (18.83% vs. 11.45%, $p=0.029$). The difference of CIN2+risk in women infected with HPV16/18 between

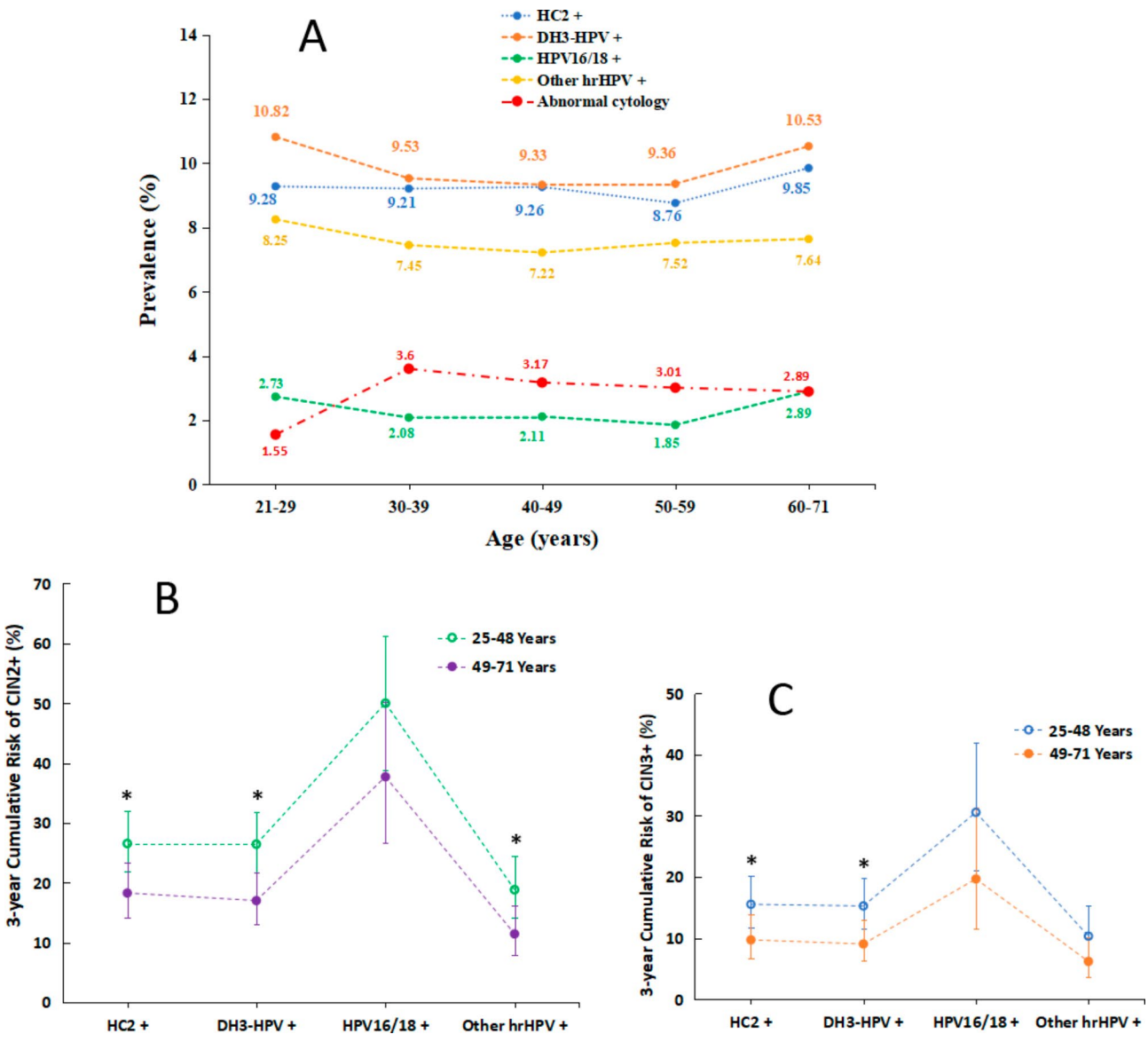

Fig. 1 (**A**) Prevalence of hrHPV and abnormal cytology by age. (**B**) The cumulative 3-year risk of CIN2 + by the HC2 and DH3-HPV test result and age group. (**C**) The cumulative 3-year risk of CIN3 + by the HC2 and DH3-HPV test result and age group.The bars show the 95% confidence interval. * $P < 0.05$. hrHPV, high-risk humanpapillomavirus; CIN, cervical intraepithelial neoplasia; DH3-HPV, tests 14 high-risk HPVs (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) with concurrent 16/18 genotyping

younger and older group was not statistically significant, which may be related to the small sample size. A similar trend was observed for CIN3+. The 3-year cumulative CIN3+risk in younger women positive for HC2-HPV at baseline was higher than that in older group [15.52% (95%CI=11.81-20.14%) vs. 9.7% (95%CI=6.71-13.83%), P=0.039]. Younger group positive for DH3-HPV also had a higher 3-year CIN3+risk than older women [15.25% (95%CI=11.6-19.8%) vs. 9.03% (95%CI=6.24-12.9%), P=0.021].

Discussion

We observed an overall hrHPV prevalence in line with rates previously reported in screening populations from China or Asian [11, 12]. Notably, there was a relatively high prevalence of hrHPV among women under 30 years old, with a slight decrease observed in older age groups. However, unlike the typical U-shaped curve, the age-related variation of HPV prevalence in this cohort was relatively flat. We think it may be related to the conservative sexual attitudes of young women in this area.

Recently, a viewpoint published on Lancet Public Health suggested that risk-based strategies appear to be the most effective way for screening services to recover

Table 1 Cumulative risk of CIN2 + and CIN3 + stratified by age or cytology among HPV-positive women at baseline after 3-year follow-up [a]

		Total (N)	CIN2+		CIN3+	
			Cases (n)	Risk (95% CI), %	Cases (n)	Risk (95% CI), %
HC2 positive						
Age (years)	25–29	12	5	41.67 (19.33–68.05)	3	25 (8.89–53.23)
	30–39	90	25	27.78 (19.58–37.8)	16	17.78 (11.25–26.95)
	40–49	212	56	26.42 (20.94–32.74)	30	14.15 (10.09–19.48)
	50–59	194	31	15.98 (11.49–21.79)	16	8.25 (5.14–12.98)
	60–71	50	9	18 (9.77–30.8)	6	12 (5.62–23.8)
Cytology	NILM	406	62	15.27 (12.1-19.09)	33	8.13 (5.85–11.2)
	Low-grade[b]	94	21	22.34 (15.1-31.75)	7	7.45 (3.66–14.59)
	High-grade[c]	58	43	74.14 (61.62–83.66)	31	53.45 (40.8-65.67)
DH3-HPV[d]positive						
Age (years)	25–29	14	5	35.71 (16.34–61.23)	3	21.43 (7.57–47.59)
	30–39	93	25	26.88 (18.92–36.67)	16	17.2 (10.87–26.13)
	40–49	215	57	26.51 (21.06–32.78)	30	13.95 (9.95–19.22)
	50–59	207	31	14.98 (10.76–20.48)	16	7.73 (4.81–12.19)
	60–71	54	9	16.67 (9.03–28.74)	6	11.11 (5.19–22.19)
Cytology	NILM	430	63	14.65 (11.62–18.31)	33	7.67 (5.51–10.58)
	Low-grade[b]	94	21	22.34 (15.1-31.75)	7	7.45 (3.66–14.59)
	High-grade[c]	59	43	72.88 (60.4-82.56)	31	52.54 (40.04–64.73)
HPV16/18 positive						
Age (years)	25–29	5	4	80 (37.5-96.38)	3	60 (23.07–88.24)
	30–39	24	11	45.83 (27.89–64.92)	6	25 (12-44.9)
	40–49	50	26	52 (38.51–65.2)	15	30 (19.1-43.75)
	50–59	39	14	35.9 (2.74–51.58)	8	20.51 (10.78–35.53)
	60–71	15	4	26.67 (10.9-51.95)	2	13.33 (3.73–37.88)
Cytology	NILM	85	26	30.59 (21.81–41.05)	14	16.47)10.07–25.77
	Low-grade[b]	22	11	50 (30.72–69.28)	2	9.09 (2.53–27.81)
	High-grade[c]	26	22	84.62 (66.47–93.85)	18	69.23 (50.01–83.5)
Other hrHPV[e]positive						
Age (years)	25–29	9	1	11.11 (1.99–43.5)	0	0 (0-29.91)
	30–39	69	14	20.29 (12.49–31.22)	10	14.49 (8.07–24.66)
	40–49	165	31	18.79 (13.57–25.43)	15	9.09 (5.59–14.46)
	50–59	168	17	10.12 (6.41–15.61)	8	4.76 (2.43–9.11)
	60–71	39	5	12.82 (5.6-26.71)	4	10.26 (4.06–23.58)
Cytology	NILM	345	37	10.72 (7.88–14.43)	19	5.51 (3.56–8.44)
	Low-grade[b]	72	10	13.89 (7.72–23.71)	5	6.94 (3-15.24)
	High-grade[c]	33	21	63.64 (46.62–77.82)	13	39.39 (24.68–56.31)

CIN, cervical intraepithelial neoplasia; CI, confidence interval; CIN2+, CIN grade 2 or worse; CIN3+, CIN grade 3 or worse; NILM, negative for intraepithelial lesion or malignancy

[a] A total of 5840 women completed follow-up. Among them, 558 were positive for HC2 assay and 583 were positive for DH3-HPV at baseline

[b] Low-grade includes ASC-US (atypical squamous cells of undetermined significance) and LSIL (low-grade squamous intraepithelial lesions)

[c] High-grade includes ASC-H (atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion), AGC (atypical glandular cells), HSIL (high-grade squamous intraepithelial lesions), and SCC (squamous cell carcinoma)

[d] Includes HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

[e] Includes HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

following disruptions related to the COVID-19 pandemic and the implementation of an age-based risk stratification should be universally feasible [13]. However, the correlation between the risk of cervical precancer following HPV infection and age has not been consistently supported by several previous studies [3–8]. It is reported that the 10-year risk of CIN3+among women with positive HC2 test and a concurrent negative cytology in younger group aged 22–32 was lower than in older group aged 40–50 (13.6% vs. 21.2%) [3]. A cohort study from Taiwan revealed that the cumulative CIN3+risks following persistent HPV infections increased with age (5.5%, 14.4%, and 18.1% for women aged 30–44 years, 45–54 years, and ≥55 years, respectively) [4]. Inconsistently, a

subanalysis of the ATHENA data revealed that The CIN 2+risk was lower in HPV16-positive women aged 40 years or older compared to women under 40 years (16% versus 35%) [5]. Similarly, a large cohort study from Kaiser Permanente Northern California (KPNC) showed that the 5-year CIN 3+risk did not increase with age but decreased slightly for either women with enrollment HPV infections or newly detected HPV infections [6]. Additionally, the 3-year cumulative risk of developing≥HSIL in a cohort of 9434 women varied significantly with age, with the highest risk noted among women aged<40 years [7]. Lately, a real-world data from Norway indicated that the overall CIN3+risk was higher for younger women aged 34–43 compared to older women aged 44–69 (30.6% vs. 18.1%) [8].

In this cohort, the 3-year cumulative risks of CIN2+and CIN3+in women infected with HPV didn't show a significant age-related increase but rather a certain decline. If stratified by median age (48 years) of this cohort, the cumulative risks of high-grade CIN in women positive for hrHPV at baseline were significantly higher in younger age group than in older age group. Our result supports that younger HPV-positive women have a higher risk of developing cervical precancer, which is consistent with several reports [5–8] published in recent years but contrary to the earlier studies [3, 4]. One possible explanation is that women who are genetically susceptible to cervical cancer have developed the precancerous diseases earlier and have been previously identified and treated at their younger ages. While women with low susceptibility to cervical cancer are less likely to develop the disease even years later. It is noteworthy that the incidence of cervical cancer in young women (15–49 years) is increasing globally from 1990 to 2019, especially in areas with high sociodemographic index [14]. Although most cervical cancer burden can be eliminated by HPV-based vaccination and screening, it is urgent to control the younger trend. Noticing the risk of cervical lesions in younger women infected with HPV maybe helpful to control the younger trend of cervical cancer.

There are still some deficiencies in this study. Firstly, the retrospective cohort was consisted of 2 separate screening populations, with several variables that were difficult to control, such as colposcopy referral protocol and screening history. Secondly, due to the ethical considerations, almost all of the women with negative co-testing results were not referred to colposcopy and were all regarded as CIN1 or less. These might result in a lower disease prevalence in this cohort and the risk of CIN2+would be underestimated. Choosing CIN2+as the study endpoint is another limitation. Because CIN2 has appreciable regression rates and the pathological diagnosis of CIN2 is less reproducible. Moreover, the short period of follow-up, as well as the limited number of cases in the youngest and oldest age groups, which may cause some deviation in the research results. Large-scale prospective studies with extended HPV genotyping are needed to validate the findings of the current study.

In summary, our study highlights the potential value of age-specific risk stratification in cervical cancer screening.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13027-024-00614-2.

Supplementary Material 1

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Not applicable.

Author contributions
RC and YL collected and analyzed the data, and were major contributors in writing the original draft. XL, XW and WL interpreted the data, and XL was a major contributor in funding acquisition. YF designed the study, and drafted and reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Women's Hospital, Zhejiang University School of Medicine in accordance with the 2013 Helsinki Declaration (Decision Number: IRB-20200007-R).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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