RESEARCH ARTICLE

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Unveiling Optimal Cervical Cancer Screening Age Range: Study of HPV Infection Among 75,719 Women in Indonesia's Metropolitan Regions (2012 – 2022)

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Abstract

Objectives: Human papillomavirus (HPV) is the primary cause of cervical cancer, a global health crisis. Indonesia is placed as having the highest cervical cancer incidence and fatality in Southeast Asia. Currently, under the National Cervical Cancer Elimination (NCCE) plan, Indonesia has extended HPV DNA-based screening from 30–50 to 30–69 years old. However, various factors can lead to inadequate virus clearance in younger populations, and Indonesia has not yet had a large-scale analysis of age-specific HPV infection reports, leaving the ideal screening age uncertain. Therefore, this study aims to investigate age-specific HPV prevalence in Indonesia to inform the optimal age range for cervical cancer screening. **Methods:** In this retrospective cross-sectional study, 75,719 subjects' data were utilized from all metropolitan regions in Indonesia from 2012–2020, who were tested with HPV DNA using PCR (SPF10-DEIA-LiPA25) and hybridization. The data were then analyzed by age and HPV genotype using IBM SPSS 27.0. **Results:** 12.62% of 75,719 women aged 13–75 are HPV-positive. Women aged 30-39 (39.56%) and 40-49 (21.1%) had the highest infection rates, followed by 25-29 (18.9%) and those below 25 years (8.8%). This contrasts with the infection rates of women aged 60-65 (1.5%) and 66-69 (0.6%). Across all age categories, HPV52, HPV16, and HPV58 were the most prevalent high-risk genotypes, with substantial variations in infection rates ($p < 0.001$). High-risk HPV outnumbered low-risk HPV in all age categories. **Conclusion:** HPV-positive prevalence in the younger population, particularly among those aged 25–29, is frequent in Indonesia. After age 65, HPV-positive cases drop significantly. Several variables contribute to this. This study recommends adjusting cervical cancer screening to Indonesian women aged 25–65.

Keywords: Uterine Cervical Neoplasms- Human Papillomavirus Viruses- Early Detection of Cancer- Indonesia

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Introduction

Human Papillomavirus (HPV) is notorious for its involvement in several skin, genital area, and throat cases both in males and females across the world. Even though 90% of cases end up with self-clearance, high-risk HPV can inflict persistent infection, thus inducing abnormal cell development that can lead to precancerous or cancerous lesions [1]. Cervical cancer is one of the tragedies caused by persistent human papillomavirus infections; this condition continues to impose a significant health burden globally, with Indonesia reporting the highest number of cases and deaths annually in Southeast Asia, according to 2022 Globocan data. The country faces 36,964 new cases and 20,708 deaths each year, highlighting the urgent need for effective prevention and control strategies [2].

In order to prevent further calamity, the WHO proposed a global strategy in 2022 to eliminate cervical cancer, which was to receive HPV vaccination, screening with a high-performance test, and proper prompt treatment [3]. As a response, Indonesia has taken steps towards cervical cancer elimination by launching the NCCE Plan in 2023, which includes an extension of the screening age from 30-50 to 30-69 years with HPV DNA-based screening as its primary testing [4]. However, the determination of the appropriate screening age should be customized to the specific target community, as the variations in disease occurrence across different age groups are indicative of disparities among distinct populations. This means strengthening the programs that already exist and developing new ones that would support meeting the WHO global goal [2].

Even though the WHO has recommended 30 as the ideal age due to the increasing prevalence of HPV, early sexual intercourse can pose as a great threat to this standard [5]. Not to mention, other factors that

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contribute to cancer emergence, particularly cervical cancer, are none other than hormone contraception use (with the highest contributing percentage 12.3%), followed by smoking prevalence (2.6%), total fertility rate (2.3%), and last but not least HIV prevalence (0.3%) [1]. Macro- and micronutrient deficiencies, which are influenced by socioeconomic status and low education levels, also contribute to lowered immunity and hinder HPV self-clearance, leading to persistent infections at younger ages than previously recognized [6]. Concerns regarding an increasing trend in young women with cervical cancer cases are supported by an appearing incidence of cervical cancer below the ages of 30 and 40 in Indonesia, as reported by data from the Cancer Registry at Cipto Mangunkusumo Hospital over the past decade [7]. To provide clearer guidance for early screening in Indonesia, this study aims to investigates the age-specific landscape of HPV infection over a 10-year period, using the largest cohort ever reported, and offers evidence-based recommendations for the optimal screening age range.

Materials and Methods

The study design was retrospective cross-sectional, and the sample was taken by consecutive sampling from women who were admitted to gynecologic oncology outpatient clinics from metropolitan regions (Jakarta, Bogor, Depok, Tangerang, and Bekasi), which were then sent to the KalGen laboratory. This research utilizes secondary data, specifically the medical records of patients who underwent HPV DNA tests at KalGen Laboratory Jakarta between 2012 and 2022. The procedures for the HPV DNA test were performed after the informed consent to explain the indication, procedure, possible side effects, and follow up. The total subjects are 76,413, obtained by the use of the polymerase chain reaction (PCR; SPF10-DEIA-LiPA25) method for HPV DNA testing and then conducting hybridization. A total of 694 subjects were removed from this research due to incomplete, missing, and illegible subjects, ensuring that duplicate individuals were excluded. A total of 75,719 participants were utilized in this investigation. The data were categorized into age groups as follows: ≤ 25, 25-29, 30-39, 40-49, 50-59, 60-65, 66-69, and ≥70 to assess HPV prevalence and genotype distribution. Statistical analyses were conducted using IBM SPSS 27.0, with chi-square tests ($p<0.05$) for significance and odds ratios (ORs) with 95% confidence intervals (CIs) to evaluate infection risk. The primary endpoint was HPV prevalence across age groups, while secondary endpoints included HPV genotype distribution. Informed consent was waived by the Institutional Review Board (IRB).

Results

The Overall Prevalence of HPV Infection

The age of the women ranged from 13 to 75 years. The most represented age in the study was 37 years. Total 12.62% (9,554/75,719) of subjects tested positive with one or more HPV genotypes.

The Prevalence of HPV Grouped by Age

The prevalence of HPV infection in each age group was calculated, as shown in Table 1. The prevalence initially increased from the age group of below 25 years old and eventually decreased from the peak observed among women under 30 - 39 years old until above 70 years old, as shown in Figure 1. The highest HPV infection rate was observed in those aged 30–39 years old (39.56%), followed by those aged 40–49 years old (21.1%) and below 30 years old, more specifically in the group aged 25–29 years old (18.9%) and below 25 years old (8.8%). Further analysis was done; the age group below 30 years old has a higher risk of developing HPV infection, shown with an OR of age below 25 is 3.76 (3.45 – 4.10) and 25–29 is 1.48 (1.40 – 1.57) (Table 1).

HPV Genotype Distribution by Age

14 high-risk and 6 low-risk HPV genotypes were identified in our population; the value of total HPV-positive is increasing from 9,554 to 12,725 once we analyze deeper into the genotype because of the variety of single and multiple infections among our population. Among the HPV-positive cases, the following HR-HPV genotypes were most common : HPV52 (15.43%), HPV16 (8.26%), HPV58 (7.53%), HPV18 (5.82%), and HPV53 (5.54%). For LR-HPV, the highest is HPV81 (5.58%) and the lowest is HPV11 (2.49%). We observed significant

Table 1. HPV Positive Prevalence by Age

Age Years	HPV +		HPV –		Total	P Value cs*	OR (95%CI)**
	n	%	n	%			
< 25	837	8.8	1,647	2.5	2,484	<0.001	3.76 (3.45 – 4.10)
25 – 29	1,802	18.9	8,968	13.6	10,770	<0.001	1.48 (1.40 – 1.57)
30 – 39	3,780	39.6	27,879	42.1	31,659	<0.001	0.90 (0.86 – 0.94)
40 – 49	2,012	21.1	17,171	26	19,183	<0.001	0.76 (0.72 – 0.80)
50 – 59	703	7.4	6,960	10.5	7,663	<0.001	0.68 (0.62 – 0.73)
60 – 65	142	1.5	1,475	2.2	1,617	<0.001	0.66 (0.56 – 0.79)
66 – 69	57	0.6	468	0.7	525	0.249	0.84 (0.64 – 1.11)
≥ 70	221	2.3	1,597	2.4	1,818	0.573	0.96 (0.83 – 1,10)
Total	9,554	100	66,165	100	75,719		

*cs, chi-square (sig p<0.05); ** OR, odds ratio chi-square test of a series of fourfold (2x2)tables

Table 2. HPV Genotypes Distribution by Age

HPV Genotype	Age Groups (Years Old)																		P Value cs**
	<25 (n=2,484)		25 – 29 (n=10,770)		30 – 39 (n=31,659)		40 – 49 (n=19,183)		50 – 59 (n=7,663)		60 – 65 (n=1,617)		66 - 69 (n=525)		≥ 70 (n=1,818)		Total (n=75,719)		
HPV 6*	66	4.66%	110	4.23%	176	3.59%	73	2.99%	22	2.62%	2	1.17%	1	1.37%	12	4.18%	462	3.63%	<0.001
HPV 11*	49	3.46%	79	3.04%	115	2.35%	42	1.72%	16	1.90%	2	1.17%	3	4.11%	11	3.83%	317	2.49%	<0.001
HPV 16	110	7.77%	243	9.34%	385	7.86%	211	8.65%	57	6.79%	18	10.53%	5	6.85%	22	7.67%	1,051	8.26%	<0.001
HPV 18	82	5.80%	129	4.96%	280	5.72%	163	6.68%	59	7.02%	6	3.51%	5	6.85%	16	5.57%	740	5.82%	<0.001
HPV 31	27	1.91%	57	2.19%	103	2.10%	39	1.60%	16	1.90%	4	2.34%	1	1.37%	6	2.09%	253	1.99%	<0.001
HPV 33	35	2.47%	61	2.34%	153	3.12%	66	2.70%	31	3.69%	9	5.26%	4	5.48%	15	5.23%	374	2.94%	<0.001
HPV 35	18	1.27%	28	1.08%	38	0.78%	25	1.02%	9	1.07%	2	1.17%	0	0.00%	4	1.39%	124	0.97%	<0.001
HPV 39	56	3.96%	128	4.92%	213	4.35%	98	4.02%	29	3.45%	7	4.09%	3	4.11%	12	4.18%	546	4.29%	<0.001
HPV 42*	52	3.67%	97	3.73%	170	3.47%	73	2.99%	26	3.10%	4	2.34%	2	2.74%	8	2.79%	432	3.39%	<0.001
HPV 43*	69	4.88%	114	4.38%	186	3.80%	86	3.52%	27	3.21%	4	2.34%	2	2.74%	14	4.88%	502	3.94%	<0.001
HPV 44*	31	2.19%	89	3.42%	146	2.98%	109	4.47%	29	3.45%	3	1.75%	2	2.74%	10	3.48%	419	3.29%	<0.001
HPV 45	40	2.83%	68	2.61%	109	2.23%	53	2.17%	13	1.55%	4	2.34%	0	0.00%	3	1.05%	290	2.28%	<0.001
HPV 51	96	6.78%	142	5.46%	277	5.66%	117	4.80%	31	3.69%	9	5.26%	5	6.85%	20	6.97%	697	5.48%	<0.001
HPV 52	164	11.59%	365	14.03%	806	16.46%	374	15.33%	155	18.45%	31	18.13%	17	23.29%	52	18.12%	1,964	15.43%	<0.001
HPV 53	70	4.95%	128	4.92%	273	5.57%	146	5.98%	62	7.38%	9	5.26%	5	6.85%	12	4.18%	705	5.54%	<0.001
HPV 56	73	5.16%	110	4.23%	199	4.06%	103	4.22%	29	3.45%	5	2.92%	2	2.74%	13	4.53%	534	4.20%	<0.001
HPV 58	102	7.21%	192	7.38%	329	6.72%	220	9.02%	70	8.33%	20	11.70%	5	6.85%	20	6.97%	958	7.53%	<0.001
HPV 59	61	4.31%	95	3.65%	161	3.29%	72	2.95%	25	2.98%	3	1.75%	1	1.37%	3	1.05%	421	3.31%	<0.001
HPV 66	71	5.02%	109	4.19%	224	4.57%	100	4.10%	45	5.36%	11	6.43%	3	4.11%	7	2.44%	570	4.48%	<0.001
HPV 68	72	5.09%	136	5.23%	279	5.70%	113	4.63%	37	4.40%	4	2.34%	0	0.00%	15	5.23%	656	5.16%	<0.001
HPV 81*	71	5.02%	122	4.69%	275	5.61%	157	6.43%	52	6.19%	14	8.19%	7	9.59%	12	4.18%	710	5.58%	<0.001
Total	1,415	100%	2,602	100%	4,898	100%	2,440	100%	840	100%	171	100%	73	100%	287	100%	12,725	100%	

*low-risk HPV genotype; ** cs, chi-square (sig p<0.05)

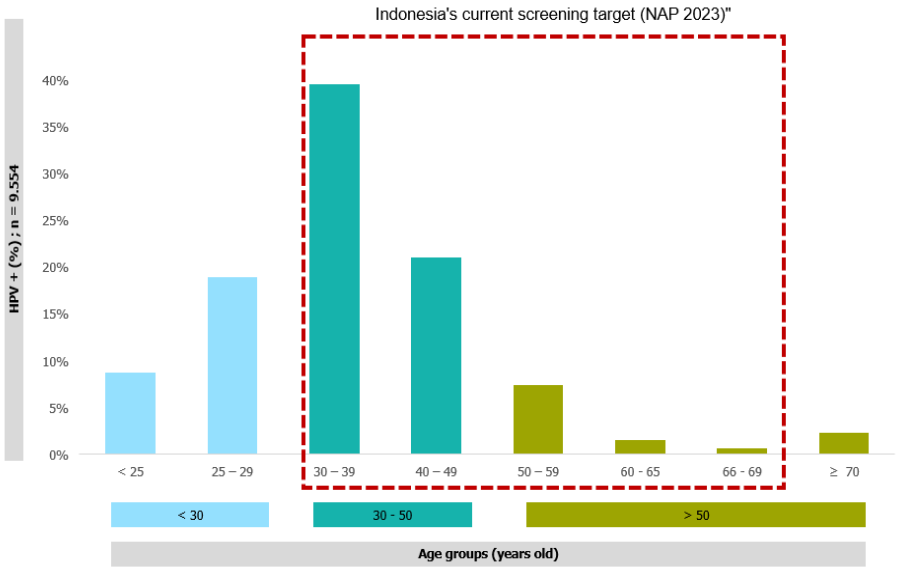

Figure 1. HPV Positive Prevalence by Age

Table 3. Top Five Most Common HPV Genotypes by Age Group

Age Groups (years old)	Top 5 HPV Genotype	Age Groups	Top 5 HPV Genotype
<25	52, 16, 51, 58, 68	50 – 59	52, 58, 53, 18, 16
25 – 29	52, 16, 58, 51, 68	60 – 65	52, 58, 16, 81, 66
30 – 39	52, 16, 58, 18, 68	66 – 69	52, 81, 58, 53, 51
40 – 49	52, 58, 16, 18, 81	≥70	52, 16, 58, 51, 18
Overall top 5 HPV Genotype* = 52, 16, 58, 18, 81			

*Genotypes were written consecutively.

differences (p<0.001) among the different age groups in the HR-HPV infection rates for 14 genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) (Table 2).

Investigation continued into each age group; the data shows HPV 52 is the most common HPV genotype among all, as shown in Figure 2. The top five HPV genotypes by age group are shown in Table 3. Across all age groups, the prevalence of high-risk genotypes is greater than that of low-risk genotypes, as shown in Figure 3.

Discussion

The Overall Prevalence of HPV Infection

In this study, the prevalence of positive HPV infection is 12.62% in 10 years, which is more or less similar to the provided Indonesia GLOBOCAN data of cervical cancer

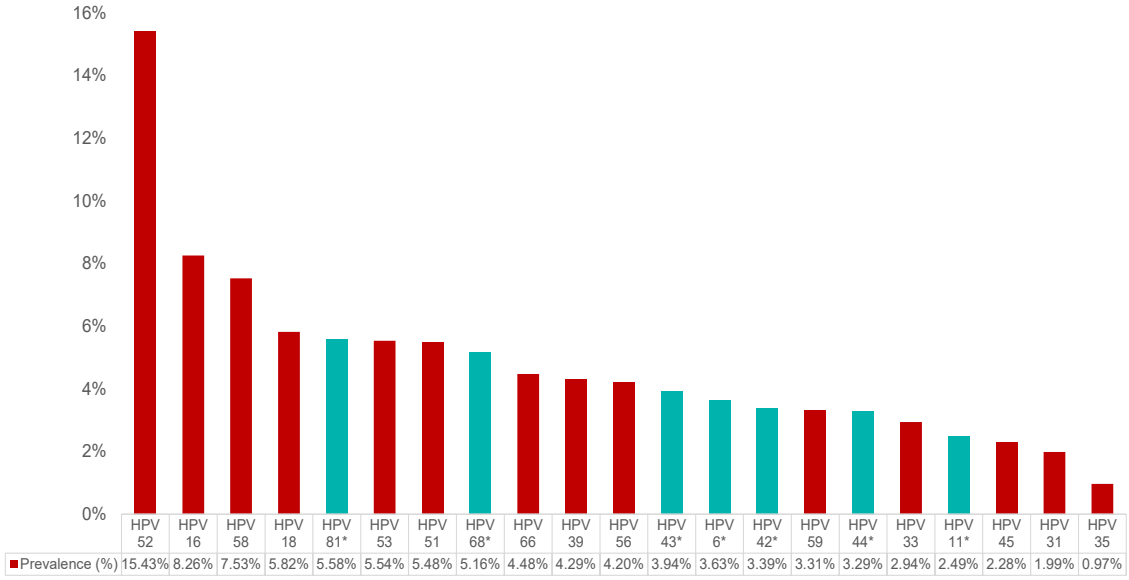

Figure 2. HPV Genotypes Prevalence

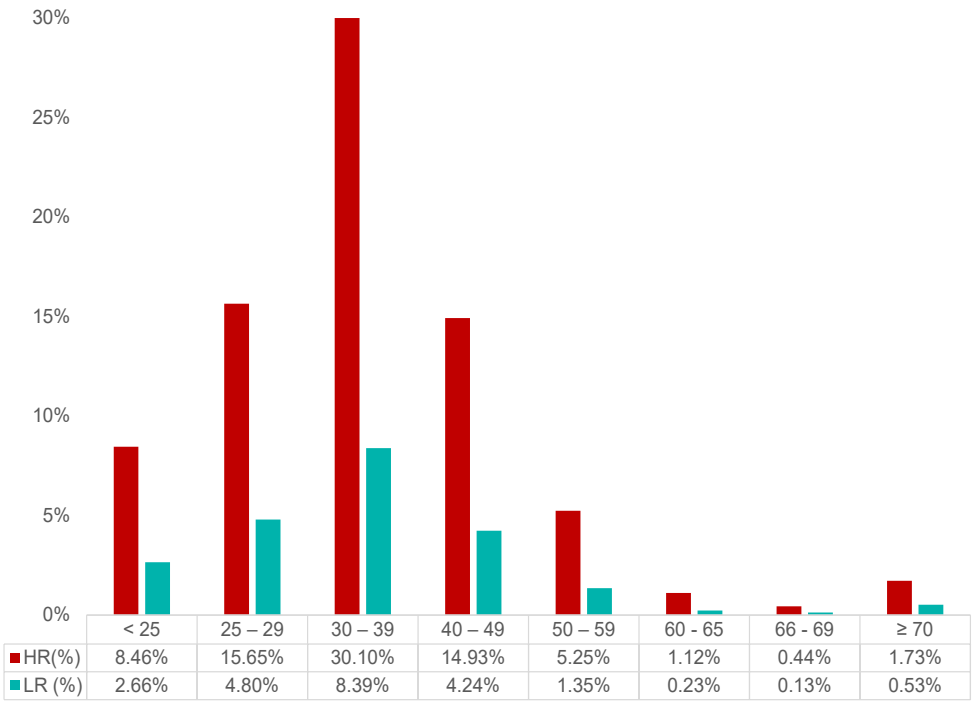

Figure 3. HPV High-Risk and Low-Risk Genotypes Distribution by Age

5-year prevalence (11.9%) [2]. Previous research states that HPV positive rates in Indonesia range from 5.2 to 12% [8]. In Southeast Asia, Indonesia reports the second highest incidence of cervical cancer among women. At the regional level, Indonesia also ranks second in Asia for HPV infection burden. Globally, HPV prevalence varies widely, with the highest rates reported in the Caribbean (35.4%) and East Africa (33.6%), while much lower rates are observed in Western Asia (1.7%) and North America (4.7%) [9]. Cultural variety, the sample plan, the tools and techniques used, and the assays' sensitivity and specificity for detecting HPV were all expected to contribute to the explanation of the difference [10].

The Prevalence of HPV Grouped by Age

Moving on through this study, it was observed that in Indonesia, the age group of 30-39 had the highest prevalence of positive HPV infection, followed by 40-49, 25-29, and below 25. The prevalence then starts to decline as the age group gets older. The age group that showed the highest prevalence in our study (30–39 years old) aligns with the findings of a 13-year meta-analysis conducted by Zare E. et al., which found similar patterns observed in Middle Eastern nations [11]. This peak age group may also be related to the fact that the median age of our sample falls within the range of 30-50 years old, which aligns with the target age group for cervical cancer screening in Indonesia over the past 16 years (prior to the current NAP in 2023). Another factor that could contribute to the variation in HPV case proportions is the geographical region of sample collection and the ethnicity of the respondents [12].

However, the screening strategies of the 2023 Indonesia NAP already cover the age groups of 30-39 years old and 40-49 years old [4]. Therefore, the main concern lies with the age groups below 30 years old, which found to be the third and fourth highest rates of HPV positive in this study, as it is not yet included as the targeted population for screening. Additionally, it is worth noting that individuals in the age group below 30 exhibit a noticeable odds ratio, revealed to be 1.4 to 2 times more likely to have HPV infection. Delayed detection of HPV infection may reduce the effectiveness of screening efforts. Prior research conducted in a specific region has also supported our concern, as most of these studies have indicated that the highest rates of HPV infection occur in the younger age group (25-29 years old) and then stabilize or slightly decrease subsequently [13].

High prevalence of HPV infection in the younger population is also found in some other previous studies. In Congo, a study done by Mutombo et al. showed that infection rates occur the highest among women younger than 30 years old, with the second highest prevalence among women aged 60 years and older [14]. In the United States, a study done by Dunne et al. showed that HPV infections were highest in females aged 20 to 24 years old [15]. This finding is also similar to the previous study conducted by Handayani and Vet in Indonesia, where the age of 25–29 years old held the highest record of positive HPV infection among other age groups [12,16].

With a good immune system, most HPV infections are usually self-cleared by the host within 12-24 months after infection [1]. Yet in some circumstances HPV infection can be latent and reactivation of the virus may occur faster or later according to women's predisposed conditions such as early age of sexual intercourse, menopause, and aging (weaker immune system) and immunosuppressive situations (organ transplants, malnutrition, micronutrient deficiency, autoimmune diseases, uncontrolled HIV), smoking, and oral contraceptive use. The reactivation

may cause the peak in women younger than 30 years old or older women above age 60 [6, 17].

In Indonesia, many of these risk HPV infection and/or reactivation factors are highly prevalent. High rate of early sexual intercourse (before the age of 18) as one in nine Indonesian girls are married before the age of 18 (ranking 8th globally and 2nd in Southeast Asia) [18, 19]. Other factors include micronutrient deficiencies particularly zinc, vitamin A, and iron which strongly associated with persistent HPV infection and cervical neoplasia. Ernawati et al. reported that among 2,456 Indonesian children, the prevalence of zinc, calcium, vitamin A, and vitamin D deficiencies was 19.7%, 4.2%, 3%, and 12.7%, respectively, with girls more affected than boys [6, 20]. Iron-deficiency anemia is also widespread, affecting 21.7% of the population, with the highest burden among women aged 15–34 years. Passive smoke exposure, which affects 75.4% of women; and low adherence to HIV treatment, with only 55.7% of women achieving good compliance despite a prevalence of <0.8% [21-23]. Collectively, these conditions may contribute to the persistence and reactivation of HPV infection observed among younger Indonesian women.

The majority of countries in Asia, such as Malaysia and Singapore, still recommend screening women above 30 to start HPV screening every 5 years. Conversely, countries such as China, Australia, the United States, and the UK recommend screening with HPV testing every 3 or 5 years starting at age 25. This alteration is not novel, as several countries in America, such as Canada, have already considered 25 years as the earliest HPV detection age [24]. However, the necessity to screen HPV younger than 25 years old is contradicted in several studies due to larger harm than good and lack of evidence. Several experts argued due to the potential threat toward obstetric outcomes that can increase the risk of preterm birth. In addition, this test also burdens the suspected individuals financially, psychosocially, and in terms of time. The other supporting reason is the low prevalence of HPV infection discovery in the population younger than age 25 years old [24]. Even in Australia, which has a median age of first sexual intercourse at the age of 16 - 17 years old, according to the MSAC-based evidence recommendation, the country does not emphasize screening in the population younger than 25 years old. However, there is an exception for those who have sexual intercourse before the age of 14 and have not received any HPV vaccination beforehand; they can voluntarily check for HPV infection between the ages of 20 and 24 years old [25]. Indonesia's 2023 NCCE plan notably expands the target screening age from 30-50 to 30-69 years old. While the Indonesian Society of Gynecologic Oncology (INASGO) endorsed an earlier recommendation, setting the screening age at 25-65 years old [26]. Our findings align with the INASGO's recommendation.

HPV Genotype Distribution by Age

The most frequent high-risk genotype is HPV52, followed by HPV16 and HPV58. While for the most frequent low-risk genotype was HPV 81. The high-risk HPV was found to be more common compared to the low risk. This pattern was similar, with the most common HPV type found in the Asian population. HPV vaccine seems to effectively suppress the population of low-risk HPV and always had a lower amount compared to high-risk in precancerous and cancerous lesions [9].

Our findings indicate that HPV 52 was the predominant genotype, consistent with previous reports from Japan, Korea, and China [13, 27]. Nevertheless, the results published in other investigations contradicted the notion that HPV16 was the most prevalent genotype [13]. HPV 16 is the predominant genotype associated with cancer development. In addition, these findings could also show the impact of the HPV vaccination prevention program, as common high-risk HPV infections by types 16 and 18 should have diminished significantly in vaccinated individuals [27]. Our findings consistently showed that HPV52, HPV16, and HPV58 were the most prevalent high-risk HPV genotypes across all age groups. This suggests that the risk of high-risk HPV infection is similar among all age groups. Therefore, it is recommended to routinely screen individuals in age groups with high prevalence of these genotypes.

This study's strengths include a large sample size and consistent HPV genotyping over a decade, offering a robust foundation for the national cervical cancer screening program's implementation. However, the study has limitations such as limited geographical coverage within Indonesia, a cross-sectional design that does not capture the temporal dynamics of HPV infections, and a lack of consideration for participants HPV vaccination status. Individual HPV vaccination status was not available in the dataset and could not be included in the analysis due to the retrospective nature of the study. Indonesia's HPV vaccination program was implemented in a phased manner with variable provincial coverage during the study period, so vaccination exposure was heterogeneous. While uptake among younger cohorts may partly influence age-specific prevalence estimates, it is unlikely to be the primary driver of the overall patterns observed. Future registry-linked studies integrating vaccination data would allow more refined analyses.

Furthermore, another limitation is the dataset was derived from a large private laboratory network, with most samples originating from metropolitan regions (Jakarta, Bogor, Depok, Tangerang, and Bekasi), since HPV DNA testing was not yet implemented as a national screening method and was mainly accessed through private and referral-based services by the study period. Therefore, the findings primarily represent urban screening populations and may not fully reflect rural communities with different access and risk profiles. Future studies should incorporate broader population coverage to improve generalizability in the current national screening era.

In conclusion, the prevalence of HPV-positive cases among individuals below the age of 30 is notably high in Indonesia, particularly in the age group of 25-29. However, there is a substantial decline in HPV cases after the age of 65. This can be attributed to various factors. Consequently, this study recommends altering cervical cancer screening to a younger and more strategic age group encompass women aged 25 to 65 years in Indonesia.

Author Contribution Statement

Tofan Widya Utami (TWU) : conceptualization, investigation, resources, data curation, writing-original draft, writing-review and editing, visualization, supervision, funding acquisition, data collection, and writing the paper. Laila Nuranna (LN) : data curation, writing-original draft, visualization, data collection, and writing the paper. Gatot Purwoto (GP) : resources, data curation, supervision. Arisda Oktalia (AO) : data curation, writing-review and editing. Raysa Irzami (RI) : data curation, writing-review and editing. Andi Utama (AU) : resources data curation, data collection. Eva Suarthana (ES) : data curation, writing-review and editing, visualization, supervision

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General

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Ethical Declaration

This research has been approved by Institutional Review Board (IRB) in the Faculty of Medicine University of Indonesia, with registration number KET290 / N2.Fl / ETIK / PPM.00.02 / 2022. All authors contributed to editorial changes in the manuscript.

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Data Availability

The datasets generated and/or analysed during the current study are available from corresponding author.

Conflict of Interest

The Author(s) declare(s) that there is no conflict of interest

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