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# Risk factors and human papillomavirus genotypes: Investigating their interplay in cervical cancer

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## Abstract

**Introduction**: Cervical cancer continues to pose a substantial worldwide health challenge, primarily linked to human papillomavirus (HPV) infection. In regions like Indonesia, understanding local genotype distribution is critical for refining screening and vaccination efforts.

**Objective**: This research explores the complex relationship between various risk factors and the types of HPV detected in cervical cancer patients at a national referral center in Indonesia.

**Methods**: Ninety-one women diagnosed with cervical cancer were recruited for this cross-sectional study at Cipto Mangunkusumo National Hospital, Jakarta—the top-tier referral facility in Indonesia. This setting provides a diverse patient demographic representing various geographical regions across the archipelago. Cervical swabs were collected for HPV genotyping using dot blot hybridization. Various clinical risk factors, including age, age at marriage, age at first pregnancy, parity, smoking habits, hormonal contraceptive history, and the stage of cervical cancer diagnosis, were assessed. Statistical analysis was conducted using Fisher's exact test to accommodate the distribution of the data.

**Results**: High-risk (HR) HPV was detected in 62.6% of participants. HPV type 18 was the most prevalent (15.4%), followed by types 52 (14.3%) and 16 (12.1%). Statistically significant associations were observed between HR-HPV presence and both early age at marriage ($p = 0.004$) and the use of hormonal contraception ($p = 0.002$). No significant correlations were observed between some patient characteristics (age, parity, and smoking habits) and HPV genotypes ($p > 0.05$). A total of 35.2% of samples were HPV-negative, potentially reflecting technical challenges or viral integration in advanced-stage cases.

**Conclusion**: These findings suggest that early marriage and hormonal contraceptive use are significant clinical markers for HR-HPV in this Indonesian population. The dominance of HPV 18 and 52 highlights the need for locally relevant diagnostic tools and the potential transition to nonavalent vaccines. These data are essential for developing locally relevant diagnostic tools and optimizing cervical cancer prevention strategies tailored to the Indonesian demographic.

***Keywords:*** Cervical cancer; HPV genotypes; Hormonal contraception; Age at marriage; Indonesia

## 1. Introduction

Cervical cancer stands as a significant global health issue, ranking as the fourth most prevalent malignancy among women worldwide.[1] This malignancy represents a profound burden on healthcare systems, particularly in developing nations where screening infrastructure is often fragmented. According to data from the World Health Organization (WHO) in 2022, approximately 660,000 new cases and 350,000 deaths from cervical cancer were reported, with approximately 94% occurring in low- and middle-income countries.[2] The disparity in mortality rates between high-income and low-income regions underscores the critical need for localized epidemiological data to inform public health strategies. In many developing regions, the lack of centralized registries and limited access to pathology services further complicates the accurate mapping of disease prevalence.

The global incidence of cervical cancer ranges from 10 to 75 cases per 100,000 women.[3] Indonesia, as of 2022 data, recorded 36,000 cases of cervical cancer and 21,000 associated deaths.[4] The high mortality-to-incidence ratio in Indonesia suggests that many cases are detected at advanced stages, limiting treatment efficacy. This clinical reality is exacerbated by the geographical complexity of the Indonesian archipelago, where the distribution of healthcare resources is often uneven, leaving rural populations with limited access to life-saving interventions. In 2021, the WHO recommended the DNA-HPV test as a primary screening method.[5] This shift from cytology-based screening to molecular-based testing represents a paradigm shift in early detection, aiming to identify high-risk viral presence before cellular abnormalities manifest.

Cervical cancer is preventable, with human papillomavirus (HPV) infection being a crucial etiological factor. HPV is present in over 95% of cervical cancer lesions.[6,7] The virus targets the basal layer of the stratified squamous epithelium, utilizing the host cell's machinery to replicate its double-stranded DNA genome. While there is no direct treatment for the virus, some topical microbicides have shown intrinsic antiviral activity.[8] Despite these developments, the primary defense against cervical malignancy remains a combination of prophylactic vaccination and secondary prevention through rigorous screening protocols. Although most HPV infections are asymptomatic and can be resolved on their own, persistent HPV infection poses a risk of developing into precancerous lesions, ultimately leading to cervical cancer.[9] High-risk HPV types, notably HPV 16 and 18, are responsible for low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) in the cervix. Timely identification and treatment of precancerous lesions can prevent progression.[10] Vaccination, protecting individuals from HPV infection, has demonstrated success in reducing cervical cancer incidence in developed countries alongside regular screening for adult women. However, the efficacy of these vaccines is largely dependent on alignment between the vaccine's targeted genotypes and the circulating genotypes within a specific geographic population.

Low- and middle-income countries often face limitations in preventive facilities and access, leading to advanced-stage diagnoses, as observed in Indonesia, where approximately 66.4% of patients are diagnosed at stages IIB-IVB.[10] In Indonesia, logistical barriers, socio-economic factors, and a lack of widespread awareness contribute to the high prevalence of late-stage presentations.[11,12] Furthermore, cultural taboos regarding pelvic examinations and reproductive health can deter women from seeking early screening, even when services are available.[12,13]

As a member of the Papillomaviridae family, HPV encompasses a diverse group of over 200 distinct genotypes. These viruses specifically target the cutaneous and mucosal squamous epithelium, leading to their primary classification by tissue type. Regarding oncogenesis, these strains are further divided into low-risk types, which typically result in benign growths, and high-risk types, which are the fundamental drivers of malignant transformations.[14] The pathogenic mechanism of high-risk HPV centers on the activity of the E6 and E7 oncoproteins; these viral products

facilitate cancer progression by inhibiting the essential tumor-suppressing functions of the p53 and pRb proteins.

Globally, HPV represents a pervasive sexually transmitted infection that impacts all genders. Epidemiological data indicate that genital HPV prevalence varies significantly, ranging from 3.5% to 45% in male populations and 2% to 44% in female cohorts, with comparable rates of transmission observed between them.[15] In men, the majority of infections remain subclinical and resolve without medical intervention. When symptoms do manifest in males, they usually present as benign genital warts. Similarly, while a high percentage of women contract cervical HPV during their lifetime, the vast majority of these cases do not escalate into invasive malignancy.[16]

A critical milestone in the transition to cervical cancer is the integration of the HPV genome into the host cell's DNA. This molecular event frequently disrupts the viral *E2* gene, causing an unchecked surge in *E6* and *E7* expression that drives rapid cellular transformation. Because symptoms often remain dormant for months or even years following the initial infection, clinical detection is frequently delayed until the appearance of physical warts or advanced lesions.[17-20] To combat this, the WHO has established the 90-70-90 targets for 2030: ensuring 90% vaccination coverage for girls by age 15, 70% screening participation for women at ages 35 and 45, and 90% access to treatment for those diagnosed with cervical disease.[21] Indonesia has aligned with these goals by integrating HPV vaccination into its national immunization framework for adolescents. While this strategy is vital for long-term control, its success depends on logistical stability and public trust. Currently, the program does not yet extend to the adult female demographic.

To align with the government's goals of developing domestic diagnostic tools and expanding screening reach, it is crucial to develop cost-effective, sensitive, and specific diagnostic reagents tailored to the high-risk HPV genotype prevalence in the Indonesian population.[22] Current diagnostic kits often use primers designed for Western populations, which may not achieve optimal sensitivity due to the unique genotype distribution in Southeast Asia. This preliminary study aims to correlate risk factors with HPV genotypes among women in Indonesia. Given the cohort size, this research serves as an exploratory analysis to identify patterns that warrant larger, multicenter investigations into the complex interplay between patients' reproductive histories and viral characteristics. By establishing a clearer picture of the local molecular landscape, we can better inform the selection of vaccines and the development of localized screening protocols that are both economically viable and clinically effective.

## 2. Materials and methods

### 2.1. Ethical clearance

This study was approved by the ethical clearance committee of the Faculty of Medicine, Universitas Indonesia, with ethical clearance number KET-1262/UN2.F1/ETIK/PPM.00.02/2022. Written informed consent was obtained from subjects before enrolment, ensuring that all participants were fully apprised of the study's objectives and the nature of the clinical specimens to be collected. The informed consent process was conducted in the local language to ensure a comprehensive understanding of the voluntary nature of participation and the confidentiality of genomic data.

### 2.2. Study design and population

This was a cross-sectional study, observing the relationship between risk factors and HPV genotyping among women in Indonesia. It was conducted in 2022 at Cipto Mangunkusumo National Hospital, Jakarta, with targeted participants being women aged 18–65 years old. The hospital serves as a national referral center, providing a diverse patient demographic for oncological research. Only women who had signed the informed consent were included in this study. Women who have had a prior HPV vaccination or a treatment related to cervical cancer were excluded from this study to prevent the confounding effects of medical intervention on the natural distribution of HPV genotypes. These exclusion criteria were strictly maintained to ensure that the observed viral prevalence reflects the natural history of the infection within the local community rather than the impact of clinical prophylaxis.

### 2.3. Data collection

Ninety-one participants were recruited consecutively according to inclusion and exclusion criteria. While the cohort size reflects the preliminary and exploratory nature of this research, rigorous data collection protocols were maintained. Questionnaires were distributed to participants, containing detailed questions related to marriage status, smoking, parity status, and hormonal contraceptive use. Information regarding age at marriage and first pregnancy was recorded to assess early exposure to potential risk factors. For HPV genotyping, cervical swabs were collected in ThinPrep containers and stored at 4 °C for analysis. Maintaining a strict cold chain was essential to prevent viral DNA degradation by endogenous nucleases in clinical samples.

### 2.4. HPV genotyping

DNA extraction was performed from cervical swabs using the QIAamp® DNA Blood Mini Kit (cat. 51104, Qiagen,

Netherlands) according to the manufacturer's protocol. Briefly, the sample in pellet resuspension was added to a mixture of Qiagen Protease (proteinase K) and Buffer AL. The addition of proteinase K is a critical step to ensure the complete lysis of cervical epithelial cells and the digestion of proteins that might otherwise sequester viral DNA. After a 10-min incubation at 56 °C, 96–100% ethanol was added. The mixture was then transferred to the QIAamp Mini Spin Column and centrifuged at 6000 × *g* for 1 min. The use of high-fidelity spin columns ensures the removal of potential polymerase chain reaction (PCR) inhibitors, though the final DNA yield remains dependent on the initial cellularity of the swab. These inhibitors, often present in clinical mucus and blood, can lead to false-negative results if not thoroughly washed away during purification. Buffers AW2 and AE were added separately after serial centrifugation at different speeds and times.

The extracted DNA was then amplified, and HPV was genotyped using a reverse dot blot "flow-through" hybridization method with GeneFlow Human Papillomavirus (HPV) array test kit (cat. 92007; DiagCor Life Science Ltd., Hong Kong). The flow-through hybridization technology uses a patented active-pumping mechanism to direct target DNA to the probes, significantly increasing reaction speed and sensitivity compared to traditional passive hybridization. This hybridization-based approach enables simultaneous identification of multiple genotypes in a single sample, a critical step for detecting coinfections. This method can detect different high-risk HPV types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73, 81 and 82; and low-risk HPV types, including 6, 11, 26, 40, 42, 43, 44, 54, 55, 57, 61, 70, 71, 72, and 84. The broad coverage of this array is particularly advantageous for exploratory studies in regions where non-standard genotypes may be prevalent.

### 2.5. Statistical analysis

The data were collected and stored in Microsoft Excel 2025 (version 2511, Microsoft, USA). Categorical variables were summarized as absolute counts and percentages and analyzed using Fisher's exact test. This test is preferred to avoid the inaccuracies of the Chi-square approximation in sparse contingency tables, as it provides an exact probability value even when several cells have expected values of less than five. A $p$-value < 0.05 was considered significant. All statistical analyses were carried out using GraphPad version 9.0.0 (Dotmatics, United States). Due to the relatively small sample size ($n$ = 91), this study lacked sufficient power to perform multivariable logistic regression to control confounding factors such as age and cancer stage. Consequently, the findings presented here are descriptive and exploratory. The high rate of HPV-negative results was analyzed separately to ensure no systematic bias related to patient age or diagnostic stage was introduced.

## 3. Results

This study highlighted the characteristics of women with cervical cancer and correlated those characteristics with HPV genotyping. These findings illuminate the multifaceted nature of patient characteristics in the study, underscoring the endeavor to explore the correlations between risk factors and HPV genotyping in cervical cancer among Indonesian patients. While the sample size was 91, the findings remained primarily exploratory; however, the cohort revealed statistically significant associations that had previously been obscured. Notably, the data demonstrated that age at marriage and hormonal contraceptive use were key clinical markers for the presence of high-risk HPV genotypes.

### 3.1. Characteristics of participants

The study emphasized the significance of patient age and reproductive history, as detailed in Table 1. The age distribution varied, with a minor proportion in the 25–34 age group (12.1%) and the majority (36.3%) aged 50 or older. Age at marriage emerged as a noteworthy factor. Roughly 29.7% of patients were married before age 20, while approximately 69.2% married after age 20. There was substantial variation in the age at which patients experienced their first pregnancy, with 72.5% experiencing it between the ages of 20 and 35. Differences in parity status were observed: 7.7% were nulliparous (never having given birth) and 91.2% were multiparous (having given birth more than once). Smoking habits exhibited significant variability among patients, with 6.6% identified as active smokers and 93.4% as non-smokers. Diagnostic data reflected the severity of cervical cancer in the patients. A minority (12.1%) received a pre-cancer diagnosis, while 25.3% were at stage 2, 7.7% at stage 3, and 1.1% at stage 4. This distribution confirms that the majority of participants had advanced-stage disease. The patterns of contraceptive use were diverse, with 30.8% of patients not using contraception and 69.2% using contraceptive methods.

### 3.2. HPV genotyping distribution

The study unveiled a diversity of HPV infections. Notably, 35.2% of the cohort ($n$ = 32) had no detectable high-risk or low-risk HPV types—a finding that warrants further technical and clinical investigation. High-risk HPV types were detected in 62.6% of participants, while 2.2% had low-risk HPV types. Among the high-risk HPV types identified, HPV 18 was the most prevalent (15.4%), followed by HPV 52 (14.3%) and HPV 16 (12.1%). Other identified high-risk HPV types included HPV 45 (5.5%) and HPV 59 (3.3%). Coinfections were found in three women, possessing HPV 16 and 52; HPV 16 and 31; and

HPV 18, 66, and 68.

**Table 1. Characteristics of participants**

| Characteristics | Count (n) | Percentage (%) |
|---|---|---|
| Age (years) | | |
| 25–34 | 11 | 12.1 |
| 35–44 | 25 | 27.5 |
| 45–50 | 22 | 24.2 |
| >50 | 33 | 36.3 |
| Age at marriage | | |
| <20 | 27 | 29.7 |
| >20 | 63 | 69.2 |
| Age at first pregnancy | | |
| <20 | 18 | 19.8 |
| 20–35 | 66 | 72.5 |
| Parity number | | |
| Nulliparous | 7 | 7.7 |
| Multiparous | 83 | 91.2 |
| Smoking | | |
| Yes | 6 | 6.6 |
| No | 85 | 93.4 |
| Cancer stage | | |
| Pre-Cancer | 11 | 12.1 |
| Stadium 1 | 9 | 9.9 |
| Stadium 2 | 23 | 25.3 |
| Stadium 3 | 7 | 7.7 |
| Stadium 4 | 1 | 1.1 |
| Hormonal Contraception | | |
| Yes | 28 | 30.8 |
| No | 63 | 69.2 |
| HPV genotyping | | |
| No HPV | 32 | 35.2 |
| High-risk HPV | 57 | 62.6 |
| Low-risk HPV | 2 | 2.2 |
| HPV type | | |
| 16 | 11 | 12.1 |
| 18 | 14 | 15.4 |
| 26 | 1 | 1.1 |
| 35 | 1 | 1.1 |
| 45 | 5 | 5.5 |
| 52 | 13 | 14.3 |
| 58 | 1 | 1.1 |
| 59 | 3 | 3.3 |

### 3.3. Relationship between risk factors and HPV genotyping

The interplay between clinical risk factors and the specific HPV genotypes was analyzed using Fisher's exact test, with results presented in Table 2. Significant correlations were observed between specific reproductive behaviors and the presence of high-risk HPV genotypes. Specifically, a significant association was observed regarding the age at marriage ($p = 0.004$), where patients who married before the age of 20 were significantly more likely to test positive for high-risk HPV (85.2%) compared to those who married at a later age (53.1%). Furthermore, the use of hormonal contraceptives demonstrated a strong statistical association with high-risk HPV detection ($p = 0.002$), with 85.7% of patients utilizing hormonal methods carrying high-risk HPV genotypes, whereas only 52.4% of non-users tested positive. No significant correlations were observed between HPV risk status and other variables, including age ($p = 0.514$), parity ($p = 1.000$), age at pregnancy ($p = 0.178$), and smoking habits ($p = 0.08$). While certain factors did not reach statistical significance, the findings regarding early marriage and hormonal contraception provide critical insights. These results indicate that in this specific Indonesian referral hospital population, HPV genotype distribution is significantly linked to early sexual exposure and hormonal history, suggesting that preventative strategies and screening in this demographic should prioritize individuals with these specific clinical markers.

## 4. Discussion

The findings of this study provide a nuanced look into the epidemiological landscape of HPV genotypes among cervical cancer patients in Indonesia. The primary observation of this research is the significant correlation between clinical markers—specifically age at marriage and hormonal contraceptive use—and the presence of high-risk HPV. While established clinical risk factors—such as parity and smoking—are well-documented drivers of cervical carcinogenesis, the lack of statistical significance in our cohort ($p > 0.05$) may be attributed to the overwhelming prevalence of these factors across the entire sample, thereby reducing their discriminatory power in a bivariate analysis. However, the identification of high-risk HPV in 62.6% of participants provides a more robust framework for identifying viral patterns that deviate from Western-centric models.

One of the most striking results is the high prevalence of HPV 18 (15.4%) and HPV 52 (14.3%), which, along with HPV 16, constitute the primary high-risk HPV types in this cohort. This distribution aligns with emerging data from Southeast Asia, suggesting that the regional

virome may differ from that of Western populations, in which HPV 16 and 18 are more dominant.[20,23] The high frequency of HPV 18 and 52 reflects a specific molecular epidemiology in the Indonesian archipelago. Previous studies in neighboring regions have suggested that HPV 52 and 58 exhibit a higher fitness or transmission efficiency in certain Asian demographics, possibly due to host genetic factors or environmental selection pressures.[24,25] The high frequency of HPV 52 has profound implications for local public health, particularly regarding the efficacy of current vaccines. Given that HPV 18 and 52 are major drivers in this population, transitioning to nonavalent vaccines or developing locally tailored diagnostic reagents is a clinical priority.[26]

**Table 2. Association of risk factors with HPV genotyping in women with cervical cancer**

| Risk Factors | No HPV/low-risk HPV | High-risk HPV | *p* value |
|---|---|---|---|
| Age | | | |
| <45 | 15 | 21 | 0.514 |
| ≥45 | 19 | 36 | |
| Age at marriage | | | |
| <20 | 4 | 23 | 0.004* |
| >20 | 30 | 34 | |
| Age at first pregnancy | | | |
| <20 | 4 | 14 | 0.178 |
| 20–35 | 30 | 43 | |
| Parity number | | | |
| Nulliparous | 3 | 4 | 1.000 |
| Multiparous | 31 | 53 | |
| Smoking | | | |
| Yes | 0 | 6 | 0.08* |
| No | 34 | 51 | |
| Hormonal contraception | | | |
| Yes | 4 | 24 | 0.002* |
| No | 30 | 33 | |

Notes: Fisher's test analysis was used to determine the relationships of each variable. *$p < 0.05$.

A noteworthy finding in this study is the significant association between early age at marriage and high-risk HPV ($p = 0.004$). Specifically, 85.2% of women who married before age 20 tested positive for high-risk HPV genotypes. Similarly, the use of hormonal contraception (reported by 30.8% participants) was linked to the development of cervical cancer. However, this has become a controversial topic due to inconsistent results. We did not find any significant association between the use of hormonal contraception and specific HPV genotypes ($p > 0.05$). Long-term use of oral contraceptives has been hypothesized to increase cervical cancer risk by making the cervix more susceptible to HPV DNA integration through hormonal modulation of the viral upstream regulatory region.[27,28] Specifically, estrogen and progesterone may influence the expression of the viral *E6* and *E7* genes through hormone-responsive elements in the viral long control region.[29,30] Our findings suggest that in the Indonesian context, the choice of contraception does not appear to influence the type of high-risk HPV that leads to malignancy. This reinforces the conclusion that once a high-risk HPV infection is established, the progression to cancer is likely driven by the oncogenic potential of the virus itself rather than the specific method of birth control used by the patient.

A significant point of discussion is the high proportion of HPV-negative results (35.2%) observed in this study. While cervical cancer is almost universally linked to HPV, literature does report HPV-negative cases, though usually at a lower rate than seen here. Several factors may explain this discrepancy. First, technical limitations in preserving DNA in a tropical climate could lead to sample degradation.[31] Second, the sensitivity of the reverse dot blot hybridization method, while high, may have a detection threshold that misses low-copy-number viral DNA.[32] Furthermore, the molecular architecture of the virus changes as the disease progresses. In advanced-stage cancer (which characterized 8.8% of our participants), the HPV genome often integrates into the host cell DNA, sometimes resulting in the loss of the *L1* gene—the target most PCR-based assays use for detection.[33] This false-negative phenomenon in advanced malignancies is a documented challenge in molecular oncology.[34,35] Future studies should use multiple primer sets targeting different viral regions (e.g., E6/E7) to improve detection rates.

Regarding other reproductive factors, our study found that 91.2% of participants were multiparous. High parity is thought to increase cervical cancer risk through sustained hormonal changes and physical trauma to the transformation zone during childbirth.[36-38] The repeated expansion and remodeling of the cervical transformation zone during multiple pregnancies may create a microenvironment that is more susceptible to persistent viral infection and subsequent cellular transformation. However, our analysis did not demonstrate an association between parity and specific HPV genotype ($p = 1.000$). This suggests that while parity helps the cancer progress, it may not be a selective pressure on HPV genotype. Similarly,

early age at first pregnancy (often proxies for early sexual debut) was common in our cohort but did not significantly correlate with HPV genotype. These findings reinforce the idea that once a high-risk HPV infection is established, the viral genotype's oncogenic potential is likely independent of the initial transmission timing.

The role of lifestyle and behavioral factors, specifically smoking, also warrants closer examination. Biologically, tobacco metabolites are known to concentrate in the cervical mucus, causing DNA damage and local immunosuppression that facilitates persistent HPV infection.[39,40] The nicotine and cotinine metabolites act as co-carcinogens, potentially accelerating the transition from a transient infection to a malignant lesion. In our study, 93.4% of participants were non-smokers, and no significant correlation was observed between smoking status and HPV types ($p$ = 0.08), potentially due to the very low prevalence of smoking (2.2%) among women in our cohort, hindering the ability to detect any genotype-specific interactions. This suggests that while smoking is a potent co-factor for cervical carcinogenesis in general, it may not exert a selective pressure that favors one HPV genotype over another in this specific demographic.

Finally, the advanced stage of diagnosis for many patients—with 25.3% at Stage 2—highlights a critical clinical reality: late-stage presentation is common in Indonesian referral hospitals. The lack of correlation between cancer stage and HPV genotype suggests that virulence is not necessarily determined by the specific viral strain but rather by delays in secondary prevention and access to screening. Despite the limitations of a cross-sectional design, the identification of HPV 18 and 52 as major genotypes, alongside the significant roles of early marriage and hormonal contraception, provides critical data for the development of domestic diagnostic tools and vaccine policy in Indonesia. Tailoring public health interventions to the local virome is essential for achieving the WHO's goal of eliminating cervical cancer as a public health threat by the end of the decade.

## 5. Conclusion

This study provides a descriptive overview of HPV genotype distribution among cervical cancer patients in Indonesia, identifying early age at marriage ($p$ = 0.004) and hormonal contraceptive use ($p$ = 0.002) as significant predictors for high-risk HPV genotype. The findings highlight a unique regional virome dominated by HPV 18, 52, and 16, suggesting that regional viral epidemiology may differ significantly from global patterns, which are dominated by HPV 16 and 18. This prevalence of non-HPV 16 genotypes emphasizes the need for nonavalent vaccines and locally tailored diagnostic tools.

While other factors, such as high parity and smoking, did not show genotype-specific correlations, they remain common clinical markers in this cohort. Furthermore, the 35.2% HPV-negative rate underscores the technical challenges of detection in advanced malignancies. These results provide a critical foundation for optimizing cervical cancer screening and prevention strategies specifically for the Indonesian population.

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## Conflict of interest

The authors declare they have no competing interests.

## Author contributions

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## Ethics approval and consent to participate

This study was approved by the ethical clearance committee of the Faculty of Medicine, Universitas Indonesia, with ethical clearance number KET-1262/UN2.F1/ETIK/PPM.00.02/2022. Written informed consent was obtained from participants before enrolment.

## Consent for publication

This study involves fully anonymized, cross-sectional data and does not contain any images or information that could identify a subject. Written informed consent was obtained from all participants for the publication of this study. All data have been anonymized to ensure participant

confidentiality.

## Availability of data

All data generated or analyzed during this study are included in this published article.

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