

# Cervical Cancer Screening of HPV DNA in Indonesia

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**Abstract:** Cervical cancer is closely related to infection from the Human Papilloma Virus (HPV). Cervical Cancer Screening can reduce the incidence of cervical cancer in almost all over the world. HPV DNA is one of the early detection tests for cervical cancer that has developed in various countries. In Indonesia, this examination is still rarely carried out because it is not widely available and preparation is still needed both in terms of competence to carry out these examinations and the availability of tools.

**Keywords:** HPV DNA, screening, Cervical Cancer, Indonesia

## 1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide with 400,000 cases each year.<sup>1,2</sup> Incidence and mortality from cervical cancer has decreased sharply in the United States since the mid-20th century, influenced by the early detection of cervical cancer screening.<sup>3</sup> In Indonesia, cervical cancer has the highest prevalence of 2013 estimated at 0.8 %. Based on the estimated number of cervical cancer case in Indonesia, the highest number of cases was in East Java Province, with 21,313 people out of 98,692 patients.<sup>4</sup>

Viral infection contributes to 15-20% of all malignancies, which plays an important role in the development of cancer incidence. During the last 20 years, many studies have shown that infection of several viruses is a risk factor for cancer incidence. One of the viruses that give to cancer statistics is human papillomavirus (HPV). HPV is a virus that can be transmitted sexually, and high-risk HPV DNA found in 99.7% of cervical cancer specimens.<sup>2,5</sup>

HPV which has a high risk of causing cervical cancer, namely types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Of all these types, the HPV virus types 16 and 18 are the most common, although the prevalence of HPV types is different in each country. Therefore, the oncogenic type of HPV virus is found in almost all cervical cancers. Most epidemiological studies show more than 90% of cervical cancers are associated with strains of HPV. Some evidence suggests HPV-negative cancers are found in older women and are associated with a poor prognosis. Despite than carcinogenic, namely through mutations of the p53 gene. HPV viruses, including double-stranded DNA viruses (dsDNA), of the Papovavirus family, have a circular genome with a size of 7-8 base pairs (bp), and the genome wrapped in an icosahedral capsid. HPV infection phase consists of a latent phase and a productive phase.<sup>2,6</sup>

Cervical cancer screening has evolved over the years. It influenced a better understanding of how the disease progresses, the role of causes such as high-risk HPV infection, and changes to screening testing technology. For more than half a century, the first cervical cancer cytology test, the Papanicolaou (Pap) test or Pap smear, has been the

basis for cervical cancer screening and is very effective in reducing the rate of this disease worldwide.<sup>1,3,7</sup>

HPV DNA is a screening method using a special instrument where a specimen was taken of the fluid around the cervical os. An indication is a high-risk group for exposure to HPV infection. The technique of examining HPV DNA is to take a sample from the upper part of the vagina and cervical os. Then put the sample into a special container that already contains a liquid preservative. The next process is to carry out non-amplification checks with in situ hybridization methods or amplification checks with polymerase chain reaction (PCR), ligase chain reaction (LCR), and hybrid capture (HC). A program that combines LBC and HPV DNA testing has also been developed (co-testing) for cervical cancer screening in women over 30 years of age.<sup>1,3,5,7</sup>

There is a lot of evidence that shows that screening with cytology and HPV DNA increases the sensitivity of detection of the prevalence of CIN 3 or invasive cancer in terms of frequency range screening compared to the cytological examination of a single. Refers to scientific evidence, there is an increase in sensitivity by the method of this combination and the interval for screening is longer compared to the cytological examination of a single.<sup>1,3</sup>

New guidelines from RANZCOG (Royal Australian and New Zealand College of Obstetricians and Gynaecologists) recommends cervical cancer screening undertaken by HPV testing and DNA test or the Pap smear every 3 years. In Indonesia cancer screening still using the IVA test (visual inspection of acetic acid) and a Pap smear as a diagnostic method in the beginning, especially in the facilities of primary health care. Examination of HPV DNA is still not widely available in Indonesia.<sup>2,8,9</sup>

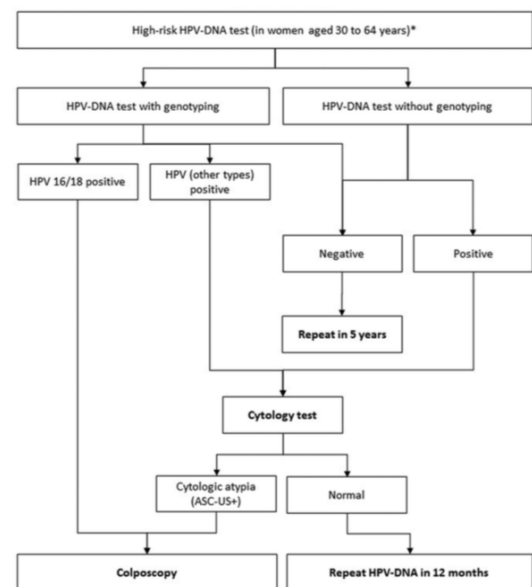
## 2. Literature Review

The latest guidelines from the American Cancer Society 2020 recommend early detection/ screening of cervical cancer using HPV DNA and/or pap cervical smear every 3 or 5 years with the principle screen and treat.<sup>3</sup> Some guidelines to do early detection of cervical cancer :<sup>3,7</sup>

- Age < 25 years: Women of < 25 years no need to do screening
- Age 25-65 Years: Women 25 years of age Screening with the HPV test the DNA of every 5 years, or screening with the HPV test DNA and cytological examination every 5 years, or screening with cytological examination every 3 years
- Women > 65 years: No need to do cervical cancer screening when screening adequately before. Screening should be done if there is a high risk of cervical cancer. Besides, it is not necessary to do cervical cancer screening if they have done total hysterectomy and have no history of pre-cancerous lesions or cervical cancer
- Screening sooner than 3 years is considered to have no excess significantly and can increase the risk of danger due to the actions performed

HPV DNA in cervical cancer screening is beneficial because it is more sensitive and can identify more lesions pre-cancer comparing Pap Smear. Specificity is lower than HPV DNA, woman may no need to refer for a colposcopy, which leads to increased cost and morbidity, which is not desirable. One of the advantages of HPV-DNA after an abnormal Pap smear is the high negative predicted value. If HPV-DNA oncogenic cannot be detected, its possibility of the occurrence of lesions or precursors of cervical cancer much less likely. Test HPV DNA assessed as examination gold standard for the detection of HPV infection. When found the results are positive, there is about 70% risk of occurred of cervical cancer. While, if found negative resulted, not required further examination.<sup>3,10</sup>

The HPV DNA test is also easier to perform and less invasive than the Pap test or IVA test, which reduces the risks associated with the procedure. Repeat screening with the HPV DNA test is generally done in a longer interval than other tests, so it is more efficient and can reduce medical costs. A study in the Netherlands stated that the existence of a longer inter-screen interval on the HPV DNA test compared to the cytological test was able to reduce the cost burden by 20-50 thousand euros per quality-adjusted life years and increase the effectiveness in terms of time. However, it should be noted that existing studies suggest that in younger women (32 years and under). HPV is thought to cause regressive cervical intraepithelial neoplasia (CIN) 2 overdiagnosis and cytology may be more cost-effective.<sup>10</sup>



**Figure 1:** Recommendations for testing of HPV-DNA in cervical cancer screening in women aged 30 to 65 years.<sup>10</sup>

### 3. Discussion

Each country has a different screening for cervical cancer. For example, a country uses opportunistic screening, the implementation, which is decided by the individual or at a meeting with a health care provider. In contrast to population-based screening, it is implemented by inviting an individually identified target population and invited to attend the screening. This population method allows screening to be carried out nationally or in specific areas.<sup>11</sup>

The development of cervical cancer screening tests in Indonesia uses 4 methods, namely Pap smear (conventional or liquid-base cytology / LBC), Visual Inspection of Acetic Acid (IVA), Lugoliodin Visual Inspection (VILI), and HPV DNA Test (genotyping/hybrid capture). At the primary care level, a screening method using the IVA test is used. The screening program is carried out through a single visit approach or see and treat program, namely examinations with positive results will be immediately treated with cryotherapy from a trained doctor or midwife. This method is widely used because of the ease in human resources, service facilities, and existing infrastructure.<sup>12</sup>

The HPV DNA method is now more recommended and has been used as first-line screening in countries such as the Netherlands, Australia, New Zealand, Turkey, Argentina, Mexico, and Italy.<sup>1</sup> In Indonesia this method helps in avoiding cervical cancer misdiagnosis. Errors that often arise in the diagnosis include incomplete history taking, the cervical examination that is often ignored, synchronizing the results of the physical examination of the cervix with the results of the pap smear, directly managing the results of the pap smear, and following up on the abnormalities of the incorrect pap smear results. In pap smear examinations, problems often occur in the form of poor specimen collection, so HPV DNA helps as co-testing (additional tests).<sup>13</sup> The use of HPV DNA screening is not used as a first-line in Indonesia due to a lack of competence for such

testing and availability of tools in primary care facilities in Indonesia..<sup>12,14</sup>

#### 4. Conclusion

Cervical cancer is the fourth most common cancer in women in the world and is cancer with the highest prevalence in Indonesia. During its development, there has been a decrease in cases with early detection or screening methods. HPV DNA is one of the early screenings for cervical cancer that has been done in various parts of the world. In Indonesia alone, HPV DNA testing is still rarely carried out, given the limited competence to carry out examinations and provision of tools.

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