# Comparing the effectiveness and safety of HPV DNA versus cytology-only screening for women aged 18-29 years: a systematic review and meta-analysis

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## Introduction

Cervical cancer is the second most common gynaecological cancer for women aged 30-39 in Singapore. As low grade squamous intraepithelial lesions (LSIL) take approximately 83.5 months to progress to high grade squamous intraepithelial lesions (HSIL) for women with human papillomavirus (HPV) infection, women under 30 remain an important group for screening. Current national guidelines recommend cytology-only screening for women aged 25-29 years and HPV testing above 30. While HPV testing is more sensitive than liquid-based cytology (LBC) in detecting Cervical Intraepithelial Neoplasia 2 and above (CIN2+), it has poor positive predictive value due to high HPV prevalence and clearance, compounded by Singapore's low HPV vaccination coverage. Given high rates of LSIL regression in this age group, treatment may additionally be associated with unnecessary surgical, psychological, fertility, or obstetric implications. We aimed to determine the diagnostic effectiveness and safety of HPV DNA versus LBC screening in this age group.

**Why do we do need an update ?**

Two approaches to primary cervical screening for women aged 25-29 exists, namely cytology-only or HPV DNA testing only. Many national screening programmes, such as that in Singapore, practice cytology-only testing for women aged 25-29 years. There is currently no global consensus on what mode of screening is best for women below 30 years old.

A HPV DNA testing only approach to primary cervical cancer screening for women below 30 years old brings not only a potential increase in detection of cervical abnormalities but also an increase in overtreatment of HPV infection. Overtreatment of cervical lesions can be associated with unnecessary surgical, psychological, and future obstetric complications. This systematic review will provide information important for the updating of cervical cancer screening guidelines in Singapore and guide policymakers on how best to implement an effective and safe national cervical screening programme for Singaporean women below 30 years of age.

This review also aims to determine the effectiveness and safety of HPV DNA testing, as compared with current cytology screening, for primary cervical cancer screening in women aged below 30 years.

**Methodology**

We conducted a systematic review of randomized controlled trials (RCTs) published from 1 January 1992 to December 2022 using PRISMA guidelines. Our protocol is registered with PROSPERO.

| | No. of participants | Screening tests result at the start of the study | Number of referrals to colposcopy | Years between start to end of the study | Screening tests result at the end of the study | Rate of detection | Sensitivity value † | Specificity value |
|---|---|---|---|---|---|---|---|---|
| Leinonnen et al, 2009 | HPV: 1848 | No. of HPV positive in HPV group :425 | HPV: 65 | 12 months | No. of CIN 2 and above: HPV: 21 | HPV: 1.14% | | HPV: 81.9% |
| | CC:1796 | No. of HPV positive in CC group: 1 | CC: 62 | | CC: 14 | CC: 0.78% | | CC: 97.4% |
| Ronco et al, 2008* | HPV: 6937 | No. of HPV positive HPV: 907 | HPV: 850 | 12 months | No. of CIN 2 and above: HPV: 68 | HPV: 0.98% | | HPV: 89.9% |
| | CC: 6788 | CC: not done | CC: 213 | | CC:19 | CC: 0.28% | | CC: 97.2% |
| Canfell et al, 2018** | HPV+Dual staining: 449 | No. of HPV 16/18 positive in HPV+ Dual staining group: 20 | HPV+Dual staining: 40 | 12 months | No. of CIN 2 and above: HPV+Dual staining: 13 | 2.9% | | 94.1% |
| | HPV+CC: 418 | No. of HPV 16/18 positive in HPV+CC group: 21 | HPV+CC: 34 | | HPV+CC: 11 | 2.6% | | 94.7% |
| | CC: 211 | No. of HPV 16/18 positive in CC group: 0 | CC: 10 | | CC: 1 | 0.5% | | 95.9% |
| Porras et al, 2012*** | HPV: 2297 | No. of HPV positive in HPV group: 440 | HPV: 440 CC: 176 | 84 months | No. of CIN 2 and above: HPV: 153 CC: 66 | 1.61% | 60.7% | 84.9% |
| | CC:2297 | No. of HPV positive in CC group: NA | | | | 0.91% | 56.8% | 93.6% |

**Table 1. Eligibility criteria**

| Criteria | Included | Excluded |
|---|---|---|
| Context | • Women 18-29 years old | • Other age group |
| Topic | • Human papillomavirus (HPV) Nucleic Acid Amplification tests (NAAT) screening tests (HPV DNA and RNA tests) **OR** • HPV Cervical cytology (ie, conventional cytology or liquid-based cytology) | • Studies unrelated to these topics. |
| Outcomes | • Progression and regression of cervical intraepithelial neoplasia grade 2+ (CIN2+). | • Other outcomes |
| Source type | • Primary research, systematic review/meta-analysis. | • All other sources |
| Time-period | • 1992-2023 | • Published before 1992 |
| Language | • Published in English | • All other languages |
| Study design | • Randomised controlled trials | • Other study designs |
| Participants | • Female sex | • Male sex |

## Results

Of 24,179 articles screened, 15 were eligible of which 4 provided age-stratified data and were included in meta-analysis. This showed estimated pooled risk ratio as insignificant at 1.05 (95%CI 0.70–1.57; p-value 0.82); meta-analysis $I^2$ statistic of 37.3% (95%CI 0–76.7%), indicating low to moderate heterogeneity; and Cochran's Q test suggested the five comparison groups in the four studies were homogeneous (p-value 0.17). Descriptive synthesis of remaining data showed that HPV testing in this age group had better sensitivity for CIN2+ but poorer specificity and positive predictive value than LBC. Several articles expressed concerns over potential overtreatment and harms, although we found no fertility and obstetric data and general safety data were overly heterogenous.

**Recommendation 1:**

There is insufficient evidence to recommend HPV DNA testing over liquid-based cytology for the purpose of primary cervical cancer screening in women less than 30 years old.

Of the 15 papers chosen from data extraction, only 4 papers had complete data. The remaining 11 papers however provided incomplete data pertaining to our research question, pending authors' reply.

**Recommendation 2:**

Establishing a national database comprising of a systematic collection of relevant cervical cancer screening and preinvasive treatment information for all eligible Singaporean citizens and permanent residents is crucial for the longitudinal analysis of the safety of HPV and cytology as screening strategies for women especially below 30 years of age

**Recommendation 3:**

More high-quality studies using local data looking at safety, cost-effectiveness, and impact of current cervical cancer screening and preinvasive cervical disease management in Singaporean women are required before a further conclusion regarding converting to HPV DNA test as the primary screening strategy for women below 30 years old can be made.

**Conclusion**

Meta-analysis did not show that HPV testing was significantly better than cytology for this age group, and between-study differences were also not significant. Descriptive synthesis also provided mixed results and limited data to inform risks of overtreatment and harm. Thus, there is insufficient evidence to recommend HPV testing over LBC for primary cervical cancer screening for women aged below 30. Establishing a national cervical screening database in Singapore, to include screening, treatment, and long-term follow-up outcomes would help inform screening strategies in this age group.