

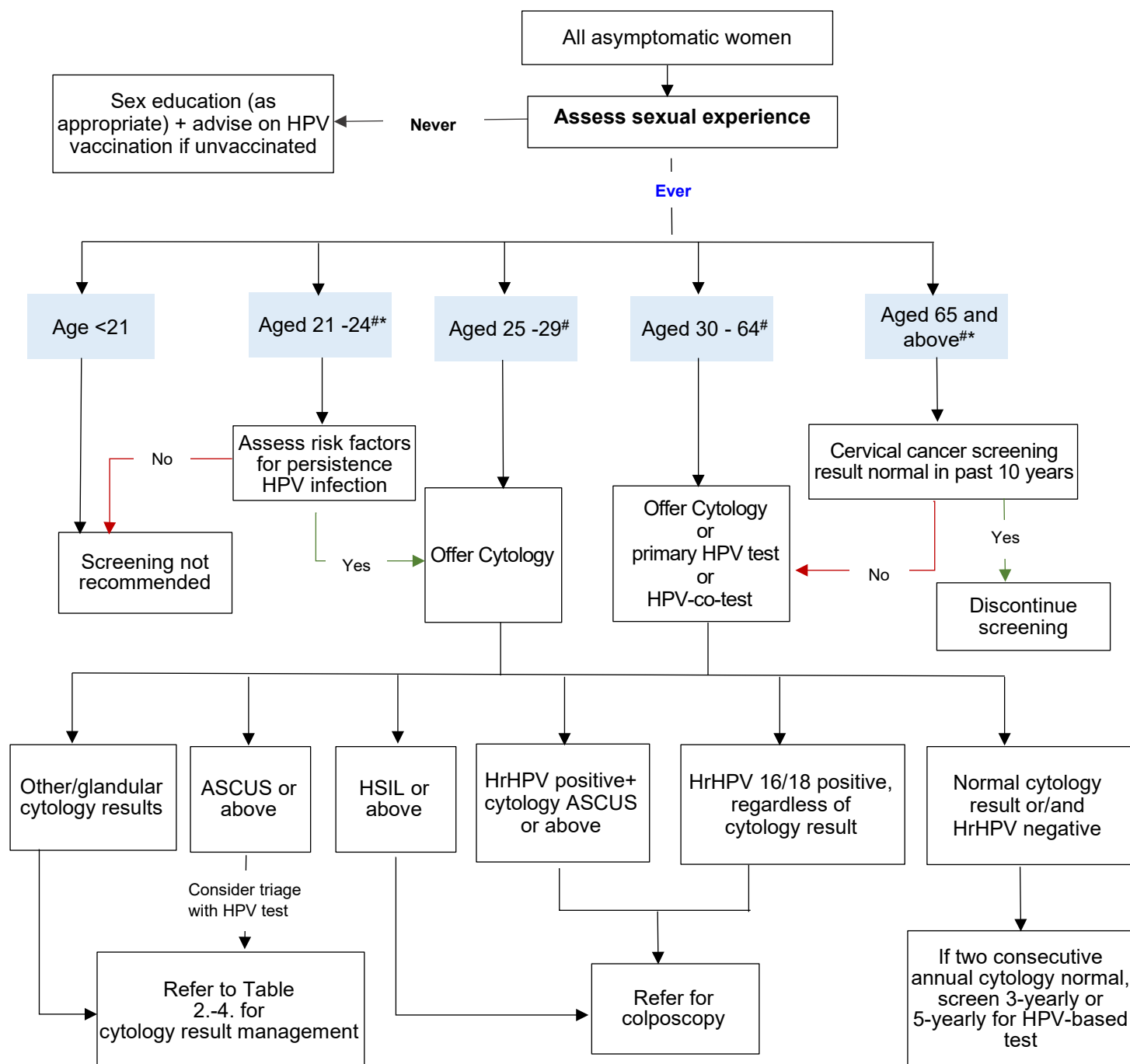
## Cervical Cancer Screening

Recommendations	Grades of Recommendations^
1. Educate all women on symptoms, signs, risk factors and preventive measures for cervical cancer, and the importance of regular cervical cancer screening <sup>1</sup>	A
2. Offer regular cervical cancer screening to women aged 21 or above who ever have sexual experience according to risk profile <sup>2</sup> : <ul style="list-style-type: none"><li>- Aged 21-24 at increased risk</li><li>- Aged 25-64 regardless of risk</li><li>- Aged 65 or above at increased risk, or who never had cervical cancer screening</li></ul>	A

<sup>^</sup> Scottish Intercollegiate Guidelines Network (SIGN) classification

**Figure 1. Cervical Cancer Screening Workflow**

(For details, refer to Recommended Care Components)



HPV = Human Papillomavirus; HrHPV = High-risk HPV; HSIL = High Grade Squamous Intraepithelial Lesion; ASCUS = Atypical Squamous Cells of Undetermined Significance

#Discontinue screening for women with hysterectomy and removal of cervix for benign diseases and without a prior history of cervical dysplasia

\*Offer regular screening for women who are chronically immunosuppressed

Adapted from the **Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) – Recommendations on Prevention and Screening for Cervical Cancer**<sup>3</sup>

## Recommended Care Components

For Who?	Recommended Care Components <sup>a</sup>	By Whom? <sup>b</sup>	How Often?
<b>Empowerment</b>			
Women of all ages	Educate on: <ul style="list-style-type: none"> <li>♦ <b>Risk factors</b>, natural history and, symptoms and signs of cervical cancer</li> <li>♦ Primary <b>preventive measures</b> for cervical cancer (Table 1.)</li> <li>♦ Importance and <b>methods of cervical cancer screening</b></li> </ul>	Primary Healthcare Providers	Opportunistically
<b>Assessment</b>			
<b>For Women Who Ever Have Sexual Experience</b>			
Women of all ages	Assess: <ol style="list-style-type: none"> <li>(1) <b>Risk</b> for persistent Human Papillomavirus (HPV) infection or cervical cancer:               <ul style="list-style-type: none"> <li>- Multiple sexual partner <math>\geq 3^4</math></li> <li>- Early first sexual intercourse</li> <li>- Tobacco use</li> <li>- Chronic immunosuppression</li> <li>- Increasing parity</li> <li>- Younger age at full term pregnancy</li> <li>- Long term use of oral contraceptive pills for more than 5 years (the risk declined after use ceased, and by 10 or more years returned to that of never users)</li> </ul> </li> <li>(2) Presence of <b>symptoms</b> suggestive of cervical cancer: <sup>5</sup> <ul style="list-style-type: none"> <li>- Post-coital or abnormal vaginal bleeding</li> <li>- Foul smelling vaginal discharge</li> <li>- Pelvic pain during intercourse</li> </ul> </li> </ol>	Nurses Doctors	Opportunistically
Women with symptoms suggestive of cervical cancer	Refer to seek early medical attention <b>OR</b> Provide work up assessment	Nurses  Doctors	When symptomatic

For Who?	Recommended Care Components <sup>a</sup>	By Whom? <sup>b</sup>	How Often?
Women indicated for cervical cancer screening	Address misconceptions and concerns about cervical cancer screening	Doctors Nurses	Opportunistically
<b>Screening</b>			
Asymptomatic women aged <b>21 to 24 at increased risk</b>	Offer screening by <b>Cytology</b>	Doctors Trained Nurses	After two consecutive normal annual screening then every 3-year
Asymptomatic women aged <b>25 to 29</b>	Offer screening by <b>Cytology</b>	Doctors Trained Nurses	After two consecutive normal annual screening then every 3-year
Asymptomatic women aged <b>30 to 64</b>	Discuss screening options Offer: ♦ <b>Cytology</b>  OR  ♦ <b>Primary HPV testing</b>  OR  ♦ <b>HPV Co-testing</b>	Doctors, Nurses Doctors Trained Nurses	Opportunistically  After two consecutive normal annual screening then every 3-year  5-yearly
Asymptomatic women aged <b>65 or above with routine screening</b>	Discontinue screening if routine screening within 10 years is normal	Doctors Nurses	
Asymptomatic women aged <b>65 or above who have never been screened</b>	Offer routine screening: ♦ <b>Cytology</b>  OR  ♦ <b>Primary HPV testing</b>  OR  ♦ <b>HPV Co-testing</b>	Doctors Trained Nurses	Opportunistically
Women of all age who are chronically immunosuppressed	Offer: ♦ <b>Cytology</b>  OR  ♦ <b>Primary HPV testing</b>  OR  ♦ <b>HPV Co-testing</b>	Doctors Trained Nurses	After two consecutive normal annual screening then every 3-year  5-yearly
Women with hysterectomy and removal of cervix for benign diseases and without a prior history of cervical dysplasia	Discontinue screening	Doctors Nurses	

For Who?	Recommended Care Components <sup>a</sup>	By Whom? <sup>b</sup>	How Often?
<b>Management</b>			
<b>For Women Who Have Undergone Cervical Cancer Screening</b>			
Women who underwent cervical cancer screening	Manage screening tests according to screening strategy <sup>6</sup> : <ul style="list-style-type: none"> <li>- Cytology alone or HPV co-testing (<b>Table 2.-4.</b>)</li> <li>- Primary HPV testing (<b>Table 5.</b>)</li> </ul>	Doctors	As soon as result available

HPV = Human Papillomavirus

<sup>a</sup> **Grade of recommendation according to colour code:**

Recommended (Strong)	Conditionally recommended	Practice points	Generally not recommended	Not recommended (Strong)
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<sup>b</sup>	<p><b>Primary Healthcare Providers</b> – All providers of health services in primary healthcare settings</p> <p><b>Primary Healthcare Professionals</b> – Includes doctors, dentists, chinese medicine practitioners, nurses, pharmacists, physiotherapist, occupational therapist, dietitians</p> <p><b>“Trained” Healthcare Professionals</b> – Additional post-qualification training required to deliver the respective care component(s)</p>
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## Collaborative Care

### Specialist Referral Recommended

**Refer to Gynaecologist:** if clinical features suggestive of cervical cancer

**Early referral to Gynecologist for colposcopy** and further management: if any of the below:

Cytology result showing:

- (i) > 2 Atypical squamous cells of undetermined significance (ASCUS) within 1 year
- (ii) 2 consecutive unsatisfactory cytology
- (iii) Atypical Squamous Cells-Cannot Exclude High Grade SIL (ASC-H)
- (iv) Low Grade Squamous Intraepithelial Lesion (LSIL)
- (v) High Grade Squamous Intraepithelial Lesion (HSIL)
- (vi) Atypical Glandular Cell-Not Otherwise Specified (AGC-NOS) (or atypical endocervical cells)
- (vii) AGC-favor neoplastic (AGC-FN)
- (viii) Atypical endometrial cells
- (ix) Endometrial cells (in a woman  $\geq 45$  years of age)
- (x) Adenocarcinoma in-situ (AIS)
- (xi) Adenocarcinoma
- (xii) Squamous cell carcinoma

HPV-based result showing:

- (xiii) High-risk HPV (HrHPV) positive with ASCUS result
- (xiv) HrHPV positive with unsatisfactory cytology result
- (xv) HrHPV 16/18 positive, regardless of cytology result

ASCUS = Atypical Squamous Cells of Undetermined Significance; ASC-H = Atypical Squamous Cells – Cannot Exclude High Grade SIL; LSIL = Low Grade Squamous Intraepithelial Lesion; HSIL = High Grade Squamous Intraepithelial Lesion; AGC-NOS = Atypical Glandular Cell-Not Otherwise Specified; AGC-FN = AGC-Favor Neoplastic; AIS = Adenocarcinoma in-situ; HrHPV = High-risk HPV

**Table 1. CEWG Recommendation on Primary Preventive Measures for Cervical Cancer<sup>3</sup>**

Primary Prevention of Cervical Cancer	
	<p><b>Certain cervical cancer risk factors are modifiable and related to personal lifestyle and behaviour. Women can lower their risk of getting cervical cancer by pursuing primary preventive measures below:</b></p> <ul style="list-style-type: none"><li>♦ <b><i>HPV vaccination prior to sexual debut</i></b></li><li>♦ <b><i>Practice of safe sex</i></b> (such as avoid having multiple sexual partners and use condoms) to reduce the chance of contracting HPV and other sexually transmitted diseases</li><li>♦ <b><i>Abstinence from tobacco smoking</i></b></li></ul>

CEWG = Cancer Expert Working Group

**Table 2. Management of Cytology or Co-Testing Results – Normal and Squamous Lesions<sup>6</sup>**

Screening Result	Recommended Action	
	Cytology Alone	Co-Testing
1. <b>Negative for intraepithelial lesion or malignancy (NILM) (normal cytology)</b>	Repeat every 3 years (after 2 initial annual screen with normal cytology)	<p>If high-risk HPV (<b>hrHPV</b>) <b>negative</b>: Repeat every 5 years</p> <p><i>If hrHPV negative, but history of hrHPV positive or cytology abnormality in the last screening: Repeat screening (co-testing or cytology) in 3 years</i></p> <p>If <b>hrHPV positive</b>, then 3 options:</p> <ul style="list-style-type: none"> <li>♦ Repeat cytology in 6 months for 3 times;</li> <li>♦ Repeat co-testing in 12 months; or</li> <li>♦ Do genotyping for HPV16/18: <ul style="list-style-type: none"> <li>- If <b>HPV 16/18 positive</b>, refer colposcopy</li> <li>- If <b>HPV 16/18 negative</b>, repeat co-testing or cytology in 1 year, then in 3 years, then routine screening</li> </ul> </li> </ul>
2. <b>Normal but transformation zone absent</b>	<p>If <b>age &lt;30 years</b>: manage as normal smears</p> <p>If <b>age ≥30 years</b>: HPV testing (preferred) or manage as normal smears.</p>	
3. <b>Atypical squamous cells of undetermined significance (ASCUS)</b>	<p>Repeat cytology in 6 months and 12 months</p> <p>Or, <b>Triage with HPV testing</b></p>	<p>If <b>hrHPV positive</b>: colposcopy</p> <p>If <b>hrHPV negative</b>: repeat screening in 3 years</p>
4. <b>Low Grade Squamous Intraepithelial Lesion (LSIL)</b>	Refer for colposcopy	<p>If <b>hrHPV positive</b>: colposcopy</p> <p>If <b>hrHPV negative</b>: repeat co-testing or cytology in 12 months</p> <ul style="list-style-type: none"> <li>♦ If either abnormal: refer for colposcopy</li> </ul> <p>If both normal, repeat co-testing or cytology in 3 years, then routine screening</p>
5. <b>ASC-H (including cases with coexisting LSIL)</b>	Refer for colposcopy	
6. <b>High Grade Squamous Intraepithelial Lesion (HSIL)</b>	Refer for colposcopy	
7. <b>Squamous cell carcinoma</b>	<b>Early</b> referral for colposcopy and biopsy	

NILM = Negative for Intraepithelial Lesion or Malignancy; ASCUS = Atypical Squamous Cells of Undetermined Significance; LSIL = Low Grade Squamous Intraepithelial Lesion; ASC-H = Atypical Squamous Cells – Cannot Exclude High Grade SIL; HSIL = High Grade Squamous Intraepithelial Lesion; HPV = Human Papillomavirus; hrHPV = High-risk HPV



**Table 3. Management of Cytology Results – Glandular Lesions<sup>6</sup>**

Screening Result	Recommended Action
1. AGC-NOS (or atypical endocervical cells)	Refer for colposcopy, endometrial and endocervical sampling
2. AGC-favour neoplastic (AGC-FN)	
3. Adenocarcinoma in-situ (AIS)	
4. Atypical endometrial cells	Refer to specialist for endometrial and endocervical sampling
5. Adenocarcinoma	Early referral for colposcopy
6. Endometrial cells (in a woman $\geq 45$ years of age)	<p>If <b>Post-menopausal</b> state, presence of <b>abnormal vaginal bleeding</b> or <b>Obesity</b> (i.e. BMI <math>\geq 25\text{kg/m}^2</math>):</p> <ul style="list-style-type: none"> <li>Refer to specialist for endometrial assessment</li> </ul> <p>Otherwise no further investigation is required</p>

AGC-NOS = Atypical Glandular Cell-Not Otherwise Specified; AGC-FN = AGC-favor Neoplastic; AIS = Adenocarcinoma in-situ; BMI = Body Mass Index

**Table 4. Management of Cytology Results – Others<sup>6</sup>**

Screening Result	Recommended Action	
	Cytology Alone	Co-Testing
Unsatisfactory	<p>Repeat cytology in 2-4 months.</p> <p>If <b>2 consecutive unsatisfactory cytology</b>, refer for colposcopy</p>	<p>If <b>HPV 16/18 positive</b>: refer for colposcopy</p> <p>If <b>non-HrHPV 16/18 positive</b>: repeat cytology in 2-4 months or refer for colposcopy</p> <p>If <b>HPV negative</b>: repeat cytology in 2-4 months.</p> <ul style="list-style-type: none"> <li>If 2 consecutive unsatisfactory cytology, refer for colposcopy</li> </ul>
Other Malignant Neoplasms	Early referral for colposcopy and biopsy	

HPV = Human Papillomavirus; HrHPV = High-risk HPV

**Table 5. Management of Stand-Alone HPV Test Results<sup>6</sup>**

Screening	Recommended Action
<b>HrHPV Negative</b>	5 yearly-screening interval with stand-alone HPV testing
<b>HrHPV Positive</b>	<p><b>1. Genotyping</b> if available</p> <p>If <b>HPV 16/18 positive</b>:</p> <ul style="list-style-type: none"> <li>- Refer for reflex cytology if possible</li> <li>- Refer to colposcopy irrespective of cytology result</li> </ul> <p>If <b>HrHPV non-16/18 positive</b>:</p> <ul style="list-style-type: none"> <li>- Refer for reflex cytology</li> <li>- if <b>ASCUS or above</b>: Refer for colposcopy</li> </ul> <p>♦ If <b>Normal cytology</b>: Repeat co-testing at 12 months or repeat cytology 6-monthly for 3 times before returning to routine screening (every 5-year for HPV-based testing)</p> <p><b>2. Reflex / Triage cytology</b></p> <ul style="list-style-type: none"> <li>♦ For all women with positive hrHPV test, regardless of genotype</li> <li>♦ If <b>ASCUS or above</b>: refer for colposcopy</li> <li>♦ If <b>Normal cytology</b>: repeat HPV testing or co-testing at 12 months or repeat cytology 6-monthly for 3 times before returning to routine screening (every 5-year for HPV-based testing)</li> </ul>

HPV = Human Papillomavirus; HrHPV = High-risk HPV; ASCUS = Atypical Squamous Cells of Undetermined Significance

## Further Readings

### ***Natural History, Risk Factors and Preventive Measures for Cervical Cancer***

- ♦ Cervical cancers, particularly squamous cell carcinoma and adenocarcinoma, can be classified into HPV-associated and HPV-independent types (approximately 10%).<sup>7, 8</sup> In Hong Kong, 7 types of High risk HPV (i.e. HPV 16, 18, 31, 33, 45, 52 and 58) accounted for approximately 90% of cases of cervical cancer.<sup>3</sup> Risk factors for HPV acquisition and/or persistence or cervical cancer were listed in **S Table 1**. It is estimated that HPV infection takes 10 to 20 years to progress to abnormal cervical cells and then to cancer.<sup>9, 10</sup> Screening allows early identification of pre-cancer lesion and treatment to prevent development of cancer.
- ♦ Human papillomavirus (HPV) vaccination has been promoted as an effective strategy to prevent cervical cancer.<sup>11</sup> In individuals who were offered the 2-valent vaccine at age 12-13 years under a national vaccination programme, the corresponding estimated relative reduction in cervical cancer rates were 87% (72-94) and 97% (96-98) respectively for cervical cancer and cervical intraepithelial neoplasia (CIN3).<sup>11</sup> To align with the World Health Organization's goal of cervical cancer elimination by 2030, 9-valent HPV vaccination has been introduced for Primary 5 and Primary 6 school girls as part of the Hong Kong Childhood Immunization since 2019. However, HPV vaccination does not provide 100% protection against cervical cancer, especially HPV-independent cervical cancer.<sup>7</sup> It remains essential for all sexually active women to continue practising safe sex and to refrain from smoking to prevent cervical cancer. Additionally, regular cervical cancer screening remains crucial for even vaccinated women.

### ***Effectiveness of Cervical Cancer Screening***

- ♦ The incidence and mortality of cervical cancer has been declining since the introduction of cervical cancer screening.<sup>12-15</sup> Compared to no screening, cervical cancer screening every three years using conventional cytology or liquid-based cytology for women aged 25 to 65 could lead to a 90-92% reduction in the cumulative incidence of cervical cancer, with cost-effectiveness ratios of \$9,000 and \$12,300 per year of life saved (US/YLS), respectively.<sup>16-18</sup> Screening every one to two years offered minimal additional protection compared to screening every three years after two consecutive normal results.<sup>19</sup>

- ♦ Cervical cancer screening is not recommended for women under 20 due to the low prevalence of cervical cancer.<sup>20</sup> For women under 25, screening should only be considered if there is a high-risk profile.<sup>3</sup> Routine cervical cancer screening in this age group is generally not recommended because of the high prevalence of HPV infection and cytological abnormalities, which often have a chance of spontaneous regression and pose a risk of unnecessary interventions.<sup>21, 22</sup> On the other hand, screening beyond age 65 was found to be not cost-effective.<sup>23</sup>
- ♦ HPV testing was introduced to detect high-risk HPV infections and to facilitate earlier detection of cervical precancerous lesions compared to cytology.<sup>24</sup> The performance, advantages and limitations of HPV testing compared to cytology were presented in **S Table 2**. Women who tested negative for high-risk HPV were found to have lower cumulative risk of CIN2+/CIN3+ lesion for at least 5 years.<sup>25-27</sup> HPV co-testing (i.e., both HPV testing and cytology) was associated with a 40% lower risk of cervical cancer compared to cytology alone.<sup>28</sup>
- ♦ In Hong Kong, the HPV vaccination program for female adolescents aged 11-12 was implemented in 2019. As the majority of the population has not yet benefited from the vaccination coverage, cost-effectiveness studies indicate that all guideline-based screening strategies utilizing HPV tests are considered cost-effective. Among these strategies, cytology combined with reflex HPV test emerges as the optimal approach for reducing cervical cancer deaths, particularly at a willingness-to-pay threshold of one gross domestic product per capita (US\$47,792).<sup>29</sup>

**S Table 1. Risk Factors of Cervical Cancer**

Risk Factors	Relative Risks (RR) (95%C.I)	Level of Evidence
(1) HPV infection <ul style="list-style-type: none"> <li>♦ HPV 16</li> <li>♦ HPV 18</li> <li>♦ Any type</li> </ul>	OR = 434.5 (278.2 – 678.7) OR = 248.1 (138.1 – 445.8) Pooled OR = 158.2 (113.4 – 220.6)	2++ <sup>8</sup>
(2) History of sexually transmitted infections (STIs) <ul style="list-style-type: none"> <li>♦ Chlamydia trachomatis infection</li> <li>♦ HSV infection (HSV-2 seropositivity)</li> </ul>	Adjusted OR = 6.6 (1.6 – 27.0) Pooled OR = 2.19 (1.41 – 3.40)	2++ <sup>30</sup> 2++ <sup>31</sup>
(3) Immunosuppression (HIV infection)	2.20 (1.89 – 2.54)	1+ <sup>32</sup>
(4) Having multiple sexual partners (≥ 6 versus 1 partner)	2.78 (2.22 – 3.47)	2++ <sup>33</sup>
(5) Early age of sexual debut (age < 17 years)	OR = 2.32 (1.89 – 2.85)	2++ <sup>34</sup>
(6) Full term Pregnancy at < age 21 <ul style="list-style-type: none"> <li>♦ Aged 16 or below</li> <li>♦ Aged 17 to 20 years</li> </ul>	OR = 2.31 (1.85 – 2.87) OR = 1.80 (1.50 – 2.39)	2++ <sup>35</sup>
(7) Use of oral contraceptive pills in HPV positive women <ul style="list-style-type: none"> <li>♦ ≥10 years</li> <li>♦ ≥5 years</li> <li>♦ &lt; 5 years</li> </ul>	OR = 4.03 (2.09 – 8.02) OR = 2.82 (1.46 – 5.42) OR = 0.73 (0.52 – 1.03)	2++ <sup>36</sup>
(8) Number of full term pregnancy <ul style="list-style-type: none"> <li>♦ ≥7</li> <li>♦ ≥5</li> <li>♦ ≥3</li> <li>♦ ≥1</li> </ul>	OR = 3.82 (2.66 – 5.48) OR = 2.83 (2.02 – 3.96) OR = 2.55 (1.95 – 3.34) OR = 1.81 (1.31 – 2.52)	2++ <sup>37</sup>
(9) Family history of cervical cancer <ul style="list-style-type: none"> <li>♦ First degree relative</li> <li>♦ Second degree relative</li> </ul>	OR = 1.79 (1.71 – 1.88) OR = 1.28 (1.22 – 1.35)	2+ <sup>38</sup>
(10) Smoking	1.50 (1.35 – 1.66)	1+ <sup>39</sup>

HPV = Human Papillomavirus; HSV = Herpes Simplex Virus; HIV = Human Immunodeficiency Virus; STI = Sexually Transmitted Infection; RR = Relative Risk; OR = Odd Ratio

**S Table 2. Methods of Cervical Cancer Screening**

Screening Tests	Performance			
	Sensitivity	Specificity	PPV	NPV
<b>1. Cervical Cytology</b> Cells from transformation zone of the cervix are collected for cytological examination for dysplasia, pre-cancerous or cancerous changes	<b>Conventional Cytology<sup>40</sup></b>			
	Cells collected by a spatula or endo-cervical brush, smeared onto a microscope slide and fixed with ethyl alcohol			
	[CIN2+]* 65.9% (54.9% – 75.3%) <sup>40</sup>	[CIN2+] 96.3% (94.7% – 97.4%) <sup>40</sup>	[CIN2+] 20.4% (18.3% – 22.7%) <sup>41</sup>	
	<b>Liquid-based Cytology<sup>40</sup></b>			
<b>2. HPV Testing</b> Cells from the cervix or vagina are tested for the presence of specific DNA or RNA sequences of high-risk human papilloma virus (HPV-16, 18, 31, 33, 45, 52, and 58) <sup>43</sup>	Cells collected using an endo-cervical brush and placed in liquid fixative solution			
	[CIN2+] 75.5% (66.6% – 82.7%) <sup>40</sup>	[CIN2+] 91.9% (88.4% – 94.3%) <sup>40</sup>	[CIN2+] 10.1% (8.7% – 11.3%) <sup>42</sup>	[CIN2+] 98.8% (98.3% – 99.2%) <sup>42</sup>
	<b>Clinical Sample<sup>40</sup></b>			
	Cells from the cervix are collected by healthcare professional using an endo-cervical brush and placed in either in liquid fixative solution or HPV test transport medium			
	[CIN2+] 97.2% (95.6% – 98.4%) <sup>41</sup>	[CIN2+] 88.7% (88.3% – 89.0%) <sup>41</sup>	[CIN2+] 15.0% (13.9% – 16.1%) <sup>41</sup>	
	<b>Self-sampling HPV Test</b>			
	Cells from the vagina are collected by the client using a swab, and sent to the laboratory in HPV test transport medium			
	[CIN2+] 40 – 94.6% (5.3% – 85.3%, 90.7% – 98.5%) <sup>44, 45</sup>	[CIN2+] 85% (75.3% – 92%, 84.4% – 86.3%) <sup>44, 45</sup>		

HPV = Human Papillomavirus; CIN = Cervical Intraepithelial Neoplasia

\*CIN2+ refers to Cervical Intraepithelial neoplasia 2 or above and is equivalent to High-grade Squamous intraepithelial lesion (HSIL)

Advantages	Limitations	Remarks
Conventional Cytology		Cytology
<ul style="list-style-type: none"> <li>Simple</li> <li>Easily available</li> <li>Low cost</li> </ul>	<ul style="list-style-type: none"> <li>Sampling error (e.g. inadequate sample and/or slide preparation) may result in 20% false negative rate.<sup>46</sup></li> <li>Risk of misinterpretation due to presence of obscuring material such as inflammatory cells, blood and overlapped epithelial cells.<sup>47, 48</sup></li> <li>Do not allow for additional HPV and/or biomarkers testing using the same sample</li> </ul>	<ul style="list-style-type: none"> <li>Sampling by trained healthcare professionals, may induce bleeding after the procedure</li> <li>Cervical cytology service should be provided by an accredited laboratory with appropriate quality assurance procedures</li> <li>Cytology reports should be issued by a qualified anatomical pathologist or (for negative results associated with absence of clinical findings) by a qualified cytotechnologist</li> <li>Reporting of cervical cytology should be based on the 2014 Bethesda System for Reporting Cervical Cytology</li> </ul>
Liquid-Based Cytology		
<ul style="list-style-type: none"> <li>Lower rate of unsatisfactory sample<sup>6</sup></li> <li>Allows for additional HPV and/or biomarkers testing using the same sample</li> </ul>	<ul style="list-style-type: none"> <li>More costly as requires further processing using automated device</li> <li>Sampling error may result in inadequate sample for HPV testing requiring re-sampling</li> </ul>	
Clinical HPV Sample		
<ul style="list-style-type: none"> <li>Superior sensitivity and slightly lower specificity than cervical cytology in detecting HPV-associated CIN grade 2 or worse (CIN2+),</li> <li>Earlier detection of cervical precancerous lesions than cytology.<sup>24, 40, 49</sup></li> <li>Higher reproducibility, reduced reliance on screener competency, and greater potential for automation<sup>6</sup></li> <li>HPV-negative status was associated with lower cumulative risk of CIN2+/CIN3+, hence interval of HPV-based screening method can be extended to 5 years<sup>26</sup></li> <li>HPV-based testing starting at age 30 every five years offers the most favorable harm-to-benefit ratio, resulting in increased life years gained and a reduced rate of colposcopies.<sup>50</sup></li> <li>Potentially more cost-effective</li> </ul>	<ul style="list-style-type: none"> <li>More false-positive results and higher colposcopy rates necessitate triage testing necessary</li> <li>False-negative as there exists a variety of HPV-independent cervical neoplasm</li> </ul>	<ul style="list-style-type: none"> <li>Only clinically validated HPV tests should be used</li> <li>Laboratory standard operating procedures and quality assurance programmes should be in place for use of any HPV testing procedures</li> <li>Reports should be issued by an accredited laboratory with participation in quality assurance programmes<sup>6</sup></li> </ul>
Self-Collected HPV Sample		
<ul style="list-style-type: none"> <li>Convenient</li> <li>More comfortable (compared to speculum examination)</li> <li>Potential to increase cervical cancer uptake by overcoming of barriers such as embarrassment and fear of pain<sup>51</sup></li> </ul>	<ul style="list-style-type: none"> <li>Education required on proper self-sampling technique</li> <li>Likely user-dependent, accuracy varies across study<sup>44</sup></li> <li>Local data not yet available, study on the validation of HPV self-sampling test is underway</li> </ul>	<ul style="list-style-type: none"> <li>There should be validation of sampling devices for self-collected vaginal specimens, and performance and regulatory approval of HPV tests for self-collected specimen<sup>6</sup></li> </ul>

**S Table 3. Screening Strategies for Cervical Cancer Screening**

Strategies	Performance				Considerations
	Sensitivity	Specificity	PPV	NPV	
1. Cytology+ HPV testing Co-test on the same LBC sample	[CIN2+] 63.4% (56.7 – 70.1) <sup>52</sup>	[CIN2+] 95.1% (94.8 – 95.3) <sup>52</sup>	[CIN2+] 17.8% (15.8 – 19.8) <sup>52</sup>	[CIN2+] 99.4% (99.2 – 99.5) <sup>52</sup>	<ul style="list-style-type: none"> <li>♦ HPV-based co-test leads to 40% lower risk of invasive cervical carcinoma when compared with cytology alone.<sup>28</sup></li> <li>♦ Co-testing led to earlier detection of clinically significant pre-invasive lesions.<sup>53</sup></li> <li>♦ Women who are co-test negative have a lower 5-year risk of CIN3+ (0.12%) compared to following a negative cytology alone (ranged from 0.33-0.52%).<sup>54</sup></li> </ul>
2. Cytology+ Reflex HPV testing if ASCUS cytology is found	[CIN2+] 40.6% (36.1 – 45.1) <sup>52</sup>	[CIN2+] 97.3% (97.1 – 97.5) <sup>52</sup>	[CIN2+] 24.8% (22.3 – 27.4) <sup>52</sup>	[CIN2+] 98.7% (98.5 – 98.9) <sup>52</sup>	<ul style="list-style-type: none"> <li>♦ Among women with ASCUS cytology, 50% are high risk HPV carriers<sup>55</sup>, who are more likely to have high-grade lesions (CIN2/3).<sup>56</sup></li> <li>♦ No role for LSIL or above due to high prevalence of high-risk HPV.<sup>57</sup></li> </ul>
3. Primary HPV testing+ Reflex genotyping+ cytology if high risk HPV is positive	[CIN2+] 64.8% (58.4 – 71.1) <sup>52</sup>	[CIN2+] 95.2% (95 – 95.5) <sup>52</sup>	[CIN2+] 18.5% (16.4 – 20.6) <sup>52</sup>	[CIN2+] 99.4% (99.2 – 99.5) <sup>52</sup>	<ul style="list-style-type: none"> <li>♦ The lower specificity of a positive HPV test necessitates a triage test by cytology or genotyping to determine referral for colposcopy.<sup>6</sup></li> <li>♦ HPV stand-alone test led to a significantly increased colposcopy rate: from 2.3% to 13.1% with HPV testing versus 1.9% to 4.7% with cytology in &lt; 30-35 years; from 0.9% to 5.8% with HPV testing versus 1.0% to 2.5% with cytology in &gt; 30-35 years.<sup>6</sup></li> </ul>

HPV = Human Papillomavirus; CIN = Cervical Intraepithelial Neoplasia; ASCUS = Atypical Squamous Cells of Undetermined Significance; LBC = Liquid Based Cytology; PPV = Positive Predictive Value; NPV = Negative Predictive Value

\*\*\*The corresponding list of References is available on HKRF webpage\*\*\*