Life Course Preventive Care for Women in Primary Healthcare
- Cancer Screening

基層醫療署
PRIMARY HEALTHCARE COMMISSION
香港基層醫療參考概覽
Hong Kong Primary Healthcare Reference Framework

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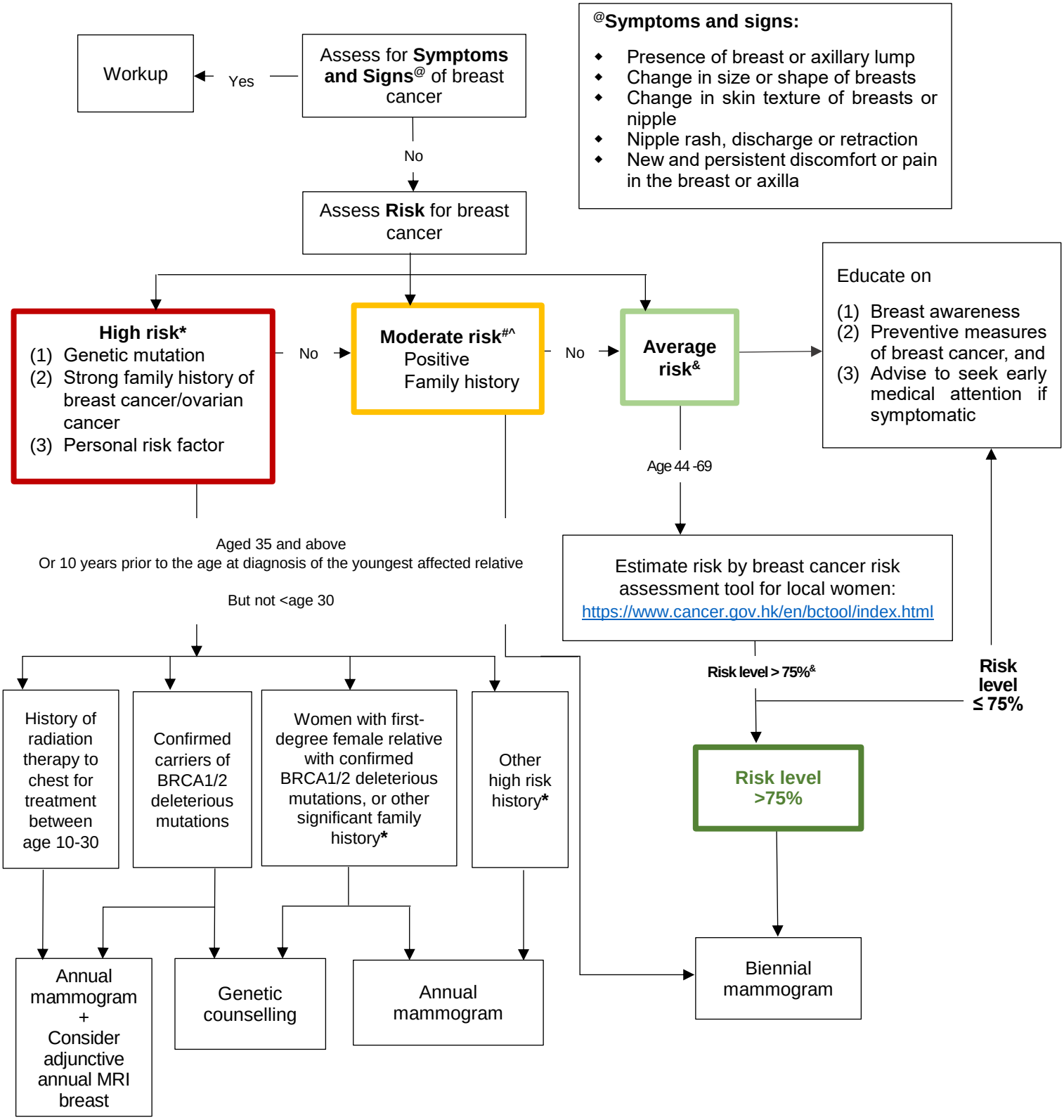
Breast Cancer Screening

Recommendations	Grades of Recommendations^
1. Educate all women on breast awareness, symptoms, signs and risk factors of breast cancer, and importance of regular breast cancer screening[1]	**A**
2. Offer breast cancer screening to asymptomatic women at[2, 3]**:** - **High risk starting at age 35 or 10 years prior to the age at diagnosis of the youngest affected relative (whichever is earlier), but not younger than age 30, annually** - **Moderate risk, biennially** - **Increased risk between age 44-69, biennially**	**A**

^ Scottish Intercollegiate Guidelines Network (SIGN) classification

Figure 1. Breast Cancer Screening Workflow

(For details, refer to the Recommended Care Component)



Adapted from the ***Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) – Recommendations on Prevention and Screening for Breast Cancer***[2]

Risk Groups	Risk Factors
High Risk*	***If any one of the below risk factors:*** **1. Genetic mutation** ◆ Carriers of BRCA1/2 deleterious mutations confirmed by genetic testing **2. Family history of breast cancer/ovarian cancer** ◆ Any first-degree female relative is a confirmed carrier of BRCA1/2 deleterious mutations ◆ Any first- or second-degree female relative with both breast cancer and ovarian cancer ◆ Any first-degree female relative with bilateral breast cancer ◆ Any male relative with a history of breast cancer ◆ 2 first-degree female relatives with breast cancer AND one of them being diagnosed at age ≤50 years ◆ ≥2 first- or second-degree female relatives with ovarian cancer ◆ ≥3 first- or second-degree female relatives with breast cancer OR a combination of breast cancer and ovarian cancer **3. Personal risk factors** ◆ History of radiation therapy to chest for treatment between age 10 and 30 years, e.g. Hodgkin's disease ◆ History of breast cancer, including ductal carcinoma in situ (DCIS); lobular carcinoma ◆ History of atypical ductal hyperplasia or atypical lobular hyperplasia
Moderate Risk#	**1. Family history** ◆ Only one first-degree female relative with breast cancer diagnosed at ≤50 years of age ◆ Two first-degree female relatives diagnosed with breast cancer after the age of 50 years
Increased Risk&	Estimated by **breast cancer risk assessment tool** for local women (www.cancer.gov.hk.hk/bctool) to be at **>75% risk** compared to women of the same age, based on the following personalised risk factors: ◆ Family history of breast cancer among first-degree relative ◆ Prior diagnosis of benign breast disease ◆ Nulliparity ◆ Late age of first live birth ◆ Early age of menarche ◆ High body mass index ◆ Physical inactivity

DCIS = Ductal Carcinoma in Situ

Recommended Care Components

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Empowerment			
Women of all ages	Educate on: ◆ **Breast awareness (Table 1.)** ◆ **Risk factors** of breast cancer ◆ Primary **preventive measures** for breast cancer **(Table 2.)** ◆ Importance of **breast cancer screening** Advise against Clinical breast examination and Self-breast examination for breast cancer screening	Primary Healthcare Providers	Opportunistically
Assessment			
Women of all ages	Assess: **(1) Risk** for breast cancer ◆ BRCA1/2 deleterious mutation ◆ Personal history of breast diseases or radiation therapy to chest for treatment between 10 to 30 years ◆ Family history of breast/ovarian cancer - Number of 1º vs. 2º degree relative and Age at diagnosis - Genetic mutation ◆ Other risk factors by breast cancer risk assessment tool for local women (www.cancer.gov.hk/bctool) - History of benign breast disease - Early age of menarche - Nulliparity - Late age of first live birth - High body mass index - Physical inactivity **(2)** Presence of **symptoms and signs** suggestive of breast cancer[2] ◆ Presence of breast or axillary lump ◆ Change in size or shape of breasts ◆ Change in skin texture of breasts or nipple ◆ Nipple rash, discharge or retraction ◆ New and persistent discomfort or pain in the breast or axilla	Nurses Doctors	Opportunistically
Women with symptoms or signs suggestive of breast cancer	Refer to seek early medical attention *OR* Provide work up assessment	Nurses Doctors	When symptomatic or having signs

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Screening			
Asymptomatic women who are eligible for breast cancer screening	Discuss screening methods, and address misconceptions and concerns	Nurses Doctors	Opportunistically
Women **aged 35 or above** who had **radiation therapy to chest for treatment between age 10 to 30**[2]	Offer screening by **Mammography** + Consider additional **MRI**	Doctors	Annually
Confirmed carriers of BRCA1/2 deleterious mutations[2]	*Starting at age 35 or 10 years prior to the age at diagnosis of the youngest affected relative (whichever is earlier), but not < age 30:* Offer screening by **Mammography** + Consider additional **MRI** Offer referral to **specialist cancer clinic** if wishing to consider prophylactic surgery / chemoprevention for advice and counselling	Doctors	Annually Annually
Women who have any first degree female relative with confirmed BRCA1/2 deleterious mutations	*Starting at age 35 or 10 years prior to the age at diagnosis of the youngest affected relative (whichever is earlier), but not < age 30:* Offer screening by **Mammography** Offer referral to specialist cancer clinic for **genetic counselling and testing***	Doctors	Annually
Women at high risk due to other types of family history	*Starting at age 35 or 10 years prior to the age at diagnosis of the youngest affected relative (whichever is earlier), but not < age 30:* Offer screening by **Mammography** Discuss and consider to offer referral to specialist cancer clinic for **genetic counselling and testing***	Doctors	Annually
Other **women aged 35 or above** with **high risk***	Offer screening by **Mammography**	Doctors	Annually
Women at **moderate risk#**	Offer screening by **Mammography**	Doctors	Biennially
Asymptomatic Women **aged 44 to 69** who are at **increased risk&** according to assessment tool	Offer screening by **Mammography**	Doctors	Biennially

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Management			
Women who underwent mammography screening[4]	Manage result according to the BI-RADS guideline **(Table 3.)**	Doctors	When result available

MRI = Magnetic Resonance Imaging; BI-RADS = Breast Imaging-Reporting and Data System

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a **Grade of recommendation according to colour code**:

Recommended (Strong)	Conditionally recommended	Practice points	Generally not recommended	Not recommended (Strong)

b

Primary Healthcare Providers – All providers of health services in primary healthcare settings

Primary Healthcare Professionals – Includes doctors, dentists, chinese medicine practitioners, nurses, pharmacists, physiotherapist, occupational therapist, dietitians

"Trained" Healthcare Professionals – Additional post-qualification training required to deliver the respective care component(s)

Collaborative Care

Specialist Referral Recommended
Early Referral to Surgeon: ◆ Clinical features suggestive of breast cancer ◆ BI-RADS Category (4) to (6)
Referral to Specialised Cancer Centres with Expertise in Genetic Counselling*: ◆ **For genetic counselling and testing:** Women who have any **first-degree female relative with confirmed BRCA1/2 deleterious mutations** should be offered genetic testing to confirm or refute their carrier status. ◆ **For advice and counselling on prophylactic surgery / chemoprevention: Confirmed carriers of BRCA1/2 deleterious mutations** who wish to consider prophylactic surgery / chemoprevention ◆ **Discuss and consider referral for genetic testing and counselling:** Women at **high risk due to other types of family history** who wish to clarify their genetic risk or that of their family

BI-RADS = Breast Imaging-Reporting and Data System

*Healthcare professionals should discuss with their clients in detail about the uncertainties and implications of the test results

Table 1. The Breast Awareness 4-point Code[5]

To empower women on their own breast health and facilitate early detection of abnormalities, all women are advised to be "**Breast Aware**", i.e. to familiarize themselves with the normal look and feel of their breasts, and to consult a doctor promptly if they notice any unusual changes.[2, 6]

Breast Awareness 4-Point Code		
	◆ Educate on what is normal	◆ During childbearing years, breasts frequently become larger, tender, and lumpy just before menstruation, but they typically return to their normal state afterwards. ◆ After menopause, breast tissue is often less dense and firm, and becomes fattier, making breasts feel softer.
	◆ Educate on breast changes to look and feel for	◆ The breast - Change in the outline, shape or size - Puckering or dimpling of the skin - Any new discrete lump - Unusual pain or discomfort, particularly if new, persistent and localized ◆ The nipple - Recent inversion or change in shape - Any discharge - Rash around the nipple ◆ The armpit - Swelling under the armpit - Constant pain
	◆ Encourage to look and feel their breasts	◆ Encourage women to examine their breasts by looking in a mirror while changing or to feel them during bathing or while lying down.
	◆ Encourage to seek medical attention if breast abnormalities are noticed	◆ If any breast changes are noticed, advise them to seek medical consultation promptly.

Source: https://www.fhs.gov.hk/english/health_info/woman/12545.html

Table 2. CEWG Recommendation on Primary Preventive Measures for Breast Cancer[2]

Primary Prevention of Breast Cancer
Certain breast cancer risk factors are modifiable and related to personal lifestyle and behaviour. Women can lower their risk of getting breast cancer by pursuing primary preventive measures below: ◆ ***Be physically active:*** Women should do at least 150 minutes of moderate-intensity or equivalent aerobic physical activities per week (e.g. climbing stairs or brisk walking) ◆ ***Do not drink alcohol*** ◆ ***Maintain healthy body weight:*** Asian women should aim for a body mass index (BMI) between 18.5 and 22.9, and a waist circumference of less than 80 cm (~32 inch) ◆ ***Have childbirth at an earlier age and breastfeed each child for a longer duration****

CEWG = Cancer Expert Working Group; BMI = Body Mass Index
*Breast feeding for at least 5-6 months has a protective effect on the risk of developing breast cancer[7]

Table 3. Management of Mammography Results[8]

BI-RADS Categories	Mammographic Abnormality	Likelihood of Malignancy	Recommended Care Explain significance of findings and required next step
0	Incomplete	N/A	• Need additional imaging evaluation and/or prior mammograms for comparison
1	Negative	No evidence of malignancy	• Routine screening as mentioned
2	Benign finding	No evidence of malignancy	• Routine screening as mentioned
3	Probably benign finding	>0% but ≤2%	• Short-interval (6-month) follow-up or continued surveillance mammography
4	Suspicious abnormality	>2 but <95%	• Refer to specialist to consider tissue biopsy
4A	*Low* suspicion for malignancy	>2 to ≤10%	
4B	Moderate suspicion for malignancy	>10 to ≤50%	
4C	*High* suspicion for malignancy	>50 to <95%	
5	Highly suggestive of malignancy	≥ 95%	• Early refer to specialist to consider tissue biopsy
6	Known biopsy proven malignancy	100%	• Refer to specialist to consider surgery

BI-RADS = Breast Imaging-Reporting and Data System

Further Readings

Natural History and Risk Factors for Breast Cancer

- There are 2 types of breast cancer: ductal carcinoma in situ (DCIS) and invasive breast cancer. DCIS consists of presumably malignant cells confined to the mammary ducts and is considered a precursor to invasive breast cancer, with 10-53% of cases progressing to invasive forms.[9-12] Invasive breast cancer consists of cancer cells that have invaded surrounding tissues. It can be further divided into histological subtypes, with invasive ductal carcinoma being the most common, followed by invasive lobular carcinoma.[9, 13] Molecular subtypes include Luminal A, Luminal B, basal-like, and HER2-enriched, each associated with different treatment responses and prognoses. The basal-like and triple-negative subtypes (lacking estrogen receptors, progesterone receptors, and absence of HER2 overexpression) have poorer prognoses; Individuals with BRCA-1 mutations have a higher risk of these subtypes.[14-16] Risk factors for breast cancer were listed in **S Table 1.**

- Breast cancer may not always present as a palpable lump in its early stages, particularly in cases of DCIS. When tumors become large enough to be felt, they often indicate a later stage of the disease. Without breast cancer screening, 83% of breast cancer patients presented with a painless lump, 6.8% presented with nipple abnormalities, 6.4% presented with breast pain, 2% presented with breast skin abnormalities, 1.2% presented with axillary lump, 0.6-0.7% presented with breast contour abnormalities or inflammation.[17] Both screening and early diagnosis facilitated disease detection at earlier stages and improve survival outcomes.[18]

Effectiveness of Breast Cancer Screening[2]

- Mammography (MMG) screening allows disease detection at an asymptomatic stage and improves survival outcomes. For women aged 39-49 at average risk, breast cancer screening is associated with a relative risk (RR) of 0.92 (95% CI 0.75-1.02) in breast cancer mortality compared to those without screening over 10 years of follow-up.[3] For women aged 50-59, the RR was 0.86 (95% CI 0.68-0.97); for those aged 60-69, the RR was 0.67 (95% CI 0.54-0.83); and for ages 70-74, the RR was 0.80 (95% CI 0.51-1.28). Additionally, women aged 50-69 who participated in organised mammography screening

were found to have approximately 40% reduction in the risk of breast cancer mortality.[19] Screening for women under 30 is not recommended due to increased false positive results and risk of over-diagnosis in this younger age group.[20]

- Clinical breast examination is no longer recommended for breast cancer screening due to insufficient evidence regarding its effectiveness in reducing breast cancer mortality,[21] with reported sensitivity of 54.1% (95% CI: 48.3%-59.8%), specificity of 94.0% (95% CI: 90.2%-96.9%), positive predictive value of 14% (95% CI, 2-43%) and negative predictive value 92% (95% CI, 89-94%).[22, 23] Similarly, self-breast examinations are also discouraged because of potential harms related to false positives and unnecessary biopsies.[24, 25] The sensitivity of self-breast examinations ranged from 20% to 30%, while their specificity was 87.4%.[26]

- Risk-based biennial mammography screening was found to be cost-effective in reducing the lifetime risk of breast cancer mortality for women aged 44 to 69 in Hong Kong. A local study estimated that risk-based screening among average-risk women in Hong Kong could yield a health gain of 0.009 quality-adjusted life years (QALY) at a net cost of $159 per woman, resulting in an incremental cost-effectiveness ratio of $18,151 per QALY.[27] Personalized risk-based screening for breast cancer was demonstrated to be more cost-effective than universal age-based screening in Chinese women with average risk. This contrasts with recommendations from other countries, such as the United Kingdom, Australia, and Singapore, which offer universal screening for all women starting at age 50.

- Recommendations for breast cancer screening for high- and moderate-risk women were made by the CEWG based on evidence from international studies and practices. Studies have shown that MRI screening in high-risk women significantly shifted cancer diagnosis from advanced stages to earlier and pre-invasive stages compared to other screening modalities, such as mammography (MMG), and ultrasonography. The International Agency for Research on Cancer (IARC) concluded that MRI, when used as an adjunct to mammography (MMG), could increase sensitivity and decrease specificity in screening women with a high familial risk and BRCA1/2 mutation.[19, 28] Therefore, individual screening strategies for high risk individual should take into consideration the increased

risk of false positive results associated with adjunctive MRI.

- Adjunctive MRI is not recommended for breast cancer screening of women with moderate risk due to risk of false positive results and reduced-cost-effectiveness.[19, 28-31] Adjunctive ultrasound to MMG for breast cancer screening in women with radiologically dense breasts could enhance cancer detection sensitivity.[32] However, the accuracy of breast ultrasound is operator-dependent, and its use alongside MMG has been associated with an increased rate of false positives and unnecessary biopsies compared to MMG alone.[19, 33, 34] Breast cancer screening with ultrasound alone is not recommended due to higher risk of false positive results compared to MMG alone.[35]

- The performances, advantages and limitations of different breast cancer screening methods were summarized in **S Table 2.**

Interventions to Promote Uptake of Breast Cancer Screening

- Despite the benefit of breast cancer screening, the uptake rate of mammography screening is yet to be optimised. Barriers for individuals to undergo mammography included: (1) they do not see the need for screening as they are asymptomatic and healthy; (2) they were never recommended to undergo screening by healthcare professionals; (3) cost for mammography is too high; (4) low health literacy with lack of knowledge on the importance of breast cancer screening.[36, 37] Community-based health education interventions promoting breast cancer screening through newspapers, exhibitions, lectures, information stalls, posters were demonstrated to be effective in encouraging mammography uptake (OR = 3.14, 95% CI 1.98 - 5.01).[38] Campaign on raising medical professional awareness on breast cancer screening may be relevant in near future to encourage referral of eligible individuals to breast cancer screening.

S Table 1. Risk Factors of Breast Cancer

Risk Groups	Risk Factors of Breast Cancer	Relative Risks (RR) (95%C.I)	Level of Evidence
High Risk	Genetic deleterious mutation ◆ BRCA1 ◆ BRCA2	 11 (7.5 – 15) 4.6 (2.7 – 7.8)	2++[39]
	History of receiving radiation therapy at young age (≤30 years) ◆ Dose of 41 to 61Gy ◆ Dose of ≥4 Gy	 8.0 (2.6 – 26.4) 3.2 (1.4 – 8.2)	2++[40]
	Prior history of benign breast diseases ◆ With atypia Proliferative change (e.g. atypical ductal hyperplasia, atypical lobular hyperplasia) ◆ Proliferative changes without atypia ◆ Non proliferative lesion	4.24 (3.26 – 5.41) 1.88 (1.66 – 2.12) 1.27 (1.15 – 1.41)	2++[41]
Moderate Risk	Family history of breast cancer ◆ First-degree relative ◆ Second-degree relative	 1.80 (1.69 – 1.91) 1.5 (1.4 – 1.6)	 2++[42] 2++[43]
Average Risk	Use of hormonal replacement therapy ◆ increase in the relative risk of breast cancer for each year of use ◆ ≥ 5 years of use	 1.023 (1.011 – 1.036) 1.35 (1.21 – 1.49)	2++[44]
	Use of oral contraceptive pills Regardless of duration used ◆ ≥ 10 years of use ◆ ≤ 1 year of use	Pooled OR = 1.19 (1.09 – 1.29) 1.38 (1.26 – 1.51) 1.09 (0.96 – 1.23)	2++[45] 2++[46]
	Alcohol consumption* ◆ Heavy drinking (> 50g) ◆ Moderate drinking(≤ 50g) ◆ Light drinking(≤ 12.5g)	 1.61 (1.33 – 1.94) 1.23 (1.19 – 1.28) 1.04 (1.01 – 1.07)	2++[47]
	Smoking	1.35 (1.13 – 1.63)	2++[48]
	Obesity (BMI ≥ 30) after menopause	OR = 1.26 (1.19 – 1.34)	2++[49]
	Nulliparity	1.27 (1.21 – 1.34)	2++[50]
	Later age of first live birth ◆ Age>35 ◆ Age>30	 1.26 (1.10 – 1.44) 1.07 (1.02 – 1.13)	 2++[51] 2++[52]
	◆ Earlier menarche (age < 12)	1.050 (1.044 – 1.057)	2++[53]
	◆ Later menopause (age >54)	1.029 (1.025 – 1.032)	2++[53]
Protective Factor	Physical activity ◆ ≥ 4 hours of leisure exercise per week	 0.63 (0.42 – 0.95)	2++[54]
	Breast feeding ◆ Ever Breastfed ◆ For every 5 months of breast feeding	 Triple negative breast cancer : RR decrease by 27% ER-PR breast cancer : RR decrease by 16% RR decrease by 2%	 2++[55] 2++[7]

RR = Relative risk; OR = Odd Ratios; ORR = Overall Relative Risk; BMI = Body Mass Index

*10 grams of alcohol = 250 ml of beer with 5% alcohol content, 100 ml of red or white wine with 12% alcohol content.[2]

S Table 2. Method of Breast Cancer Screening

Radiological Screening Methods	Performance			
	Sensitivity	Specificity	PPV	NPV
Mammogram (2-D MMG) ◆ Uses X-Ray to produce clinical images of the compressed breast with cranio-caudal (CC) or medio-lateral oblique (MLO) views	Detecting DCIS or Invasive: 77.0% (70.3% – 83.7%)[32]	Detecting BI-RADS ≥4: 98.5% (97.8% – 99.2%)[31]	Detecting DCIS or Invasive: 25.9% (21.6% – 30.7%)[56]	Detecting DCIS or Invasive: 99.6% (99.4% – 99.7%)[56]
	*Denser breast, age below 50 have lower sensitivity and specificity[57-60] <u>Denser breast</u> Detecting BI-RADS ≥3: Sensitivity = 62.9% Specificity = 89.1%[57] <u>Age below 50</u> Detecting BI-RADS ≥3: Sensitivity = 68.6% – 72.5% Specificity = 90.7%			
Digital breast tomosynthesis (DBT or 3-D MMG) ◆ Creates a three-dimensional image of the breast from X-ray images from different angles	Detecting DCIS or Invasive: 81.1% (74.2% – 86.9%)[56]	Detecting DCIS or Invasive: 97.2% (97.0% – 97.5%)[56]	Detecting DCIS or Invasive: 24.1% (20.5% – 28%)[56]	Detecting DCIS or Invasive: 99.8% (99.7% – 99.9%)[56]
Magnetic resonance imaging (MRI) ◆ Uses magnets and radiofrequency waves to produce a three-dimensional image of the breast	As an adjunct to MMG: Detecting DCIS or Invasive: 71% – 100%[61]	Detecting BI-RADS ≥4: 96.1% (94.8% – 97.4%)[31, 62]		
Ultrasonography (USG) ◆ Use sound waves to produce image of the internal structure of the breast.	As an adjunct to MMG: Detecting DCIS or Invasive: 91.1% (87.2% – 95.0%)[32]	Detecting DCIS or Invasive: 87.7% (87.3% – 88.0%)[32]		

MMG = Mammogram; DBT = Digital Breast Tomosynthesis; MRI = Magnetic Resonance Imaging; USG = Ultrasonography; DCIS = Ductal Carcinoma in Situ; CC = Cranio-caudal; MLO = Medio-Lateral Oblique; PPV = Positive Predictive Value; NPV = Negative Predictive Value; BI-RADS = Breast Imaging-Reporting and Data System

Advantages	Limitations	Remarks
◆ Lower cost ◆ Readily accessible ◆ Simple procedure	Risk of radiation exposure. ◆ MMG and 1-view DBT have similar radiation level despite DBT creates 3-dimensional image of the breast*[63] Pain and discomfort ◆ Compression of the breast during the MMG and DBT may cause pain and discomfort Chance of False-positives ◆ 10-year cumulative rates of false-positive biennial MMG results and biopsies were found to be 42% and 5%[20] ◆ DBT have a lower false positive rate than MMG[64] Chance of False-negatives ◆ It is estimated that 20% of breast cancers are missed at initial MMG screening[65] ◆ False-negatives are less common then false positives in MMG screening	◆ The estimated cumulative risk of breast cancer death due to radiation from mammography screening ranges from 1 to 10 per 100,000 women, depending on age, frequency, and duration of screening. It is at least 100 times smaller than the estimates of breast cancer deaths prevented by mammographic screening across a broad range of ages[19, 66] ◆ False-positives are more common below 50 year old, lower body mass index<25 for age <50, family history of breast cancer, previous benign breast biopsy and high breast density[67] ◆ False-negatives are more common in pre-menopausal age group, higher breast density, family history of breast cancer, previous benign breast biopsy and lower body mass index <25 for age <50[67]
◆ Lower recall rate for false positive results and higher cancer detection rates compared to conventional 2-D MMG due to 3-D image formed by reducing overlapping breast tissue and likelihood of concealed malignancy[68, 69]		◆ Inconclusive evidence on the effectiveness of reducing breast cancer mortality or lowering interval cancer rates[64, 68-74]
◆ Higher sensitivity and favorable stage shifting of cancer diagnosis from advanced to earlier stage in high risk group compared to MMG alone[62, 75-78] ◆ No risk of radiation exposure	◆ Increase false-positive results and biopsy rate	◆ Reduce screening cost-effectiveness in moderate and average-risk individuals[19, 28-31]
◆ Increase sensitivity of cancer detection when used as an adjunct to MMG in women with radiologically dense breasts[32]	◆ Increase false positives and unnecessary biopsies compared to MMG alone[19, 33, 34] ◆ Results are Operator dependent	◆ Insufficient evidence to recommend routine adjunctive ultrasonography screening for reducing mortality rates[79]

******The corresponding list of References is available on HKPRF webpage******

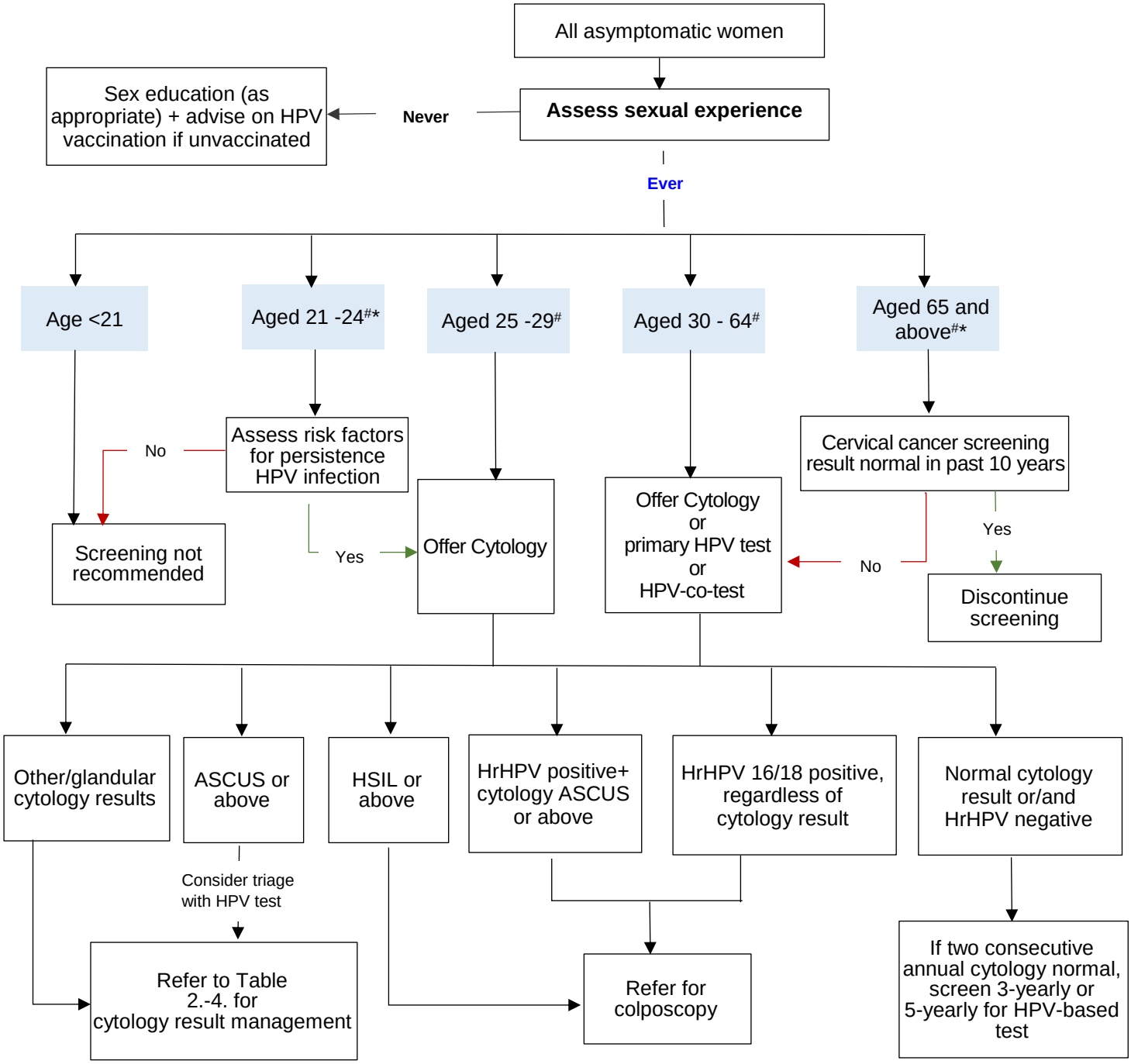
Cervical Cancer Screening

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[1]	**A**
2. Offer regular cervical cancer screening to women aged 21 or above who ever have sexual experience according to risk profile[2]**:** **- Aged 21-24 at increased risk** **- Aged 25-64 regardless of risk** **- Aged 65 or above at increased risk, or who never had cervical cancer screening**	**A**

^ 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***[3]

Recommended Care Components

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Empowerment			
Women of all ages	Educate on: ◆ **Risk factors,** natural history and, symptoms and signs of cervical cancer ◆ Primary **preventive measures** for cervical cancer **(Table 1.)** ◆ Importance and **methods of cervical cancer screening**	Primary Healthcare Providers	Opportunistically
Assessment			
For Women Who Ever **Have Sexual Experience**			
Women of all ages	Assess: (1) **Risk** for persistent Human Papillomavirus (HPV) infection or cervical cancer: - Multiple sexual partner ≥ 3[4] - Early first sexual intercourse - Tobacco use - Chronic immunosuppression - Increasing parity - Younger age at full term pregnancy - 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) (2) Presence of **symptoms** suggestive of cervical cancer: [5] - Post-coital or abnormal vaginal bleeding - Foul smelling vaginal discharge - Pelvic pain during intercourse	Nurses Doctors	Opportunistically
Women with symptoms suggestive of cervical cancer	Refer to seek early medical attention *OR* Provide work up assessment	Nurses Doctors	When symptomatic

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Women indicated for cervical cancer screening	Address misconceptions and concerns about cervical cancer screening	Doctors Nurses	Opportunistically
Screening			
Asymptomatic women aged **21 to 24 at increased risk**	Offer screening by **Cytology**	Doctors Trained Nurses	After two consecutive normal annual screening then every 3-year
Asymptomatic women aged **25 to 29**	Offer screening by **Cytology**	Doctors Trained Nurses	After two consecutive normal annual screening then every 3-year
Asymptomatic women aged **30 to 64**	Discuss screening options Offer: ◆ **Cytology** *OR* ◆ **Primary HPV testing** *OR* ◆ **HPV Co-testing**	Doctors, Nurses Doctors Trained Nurses	Opportunistically After two consecutive normal annual screening then every 3-year 5-yearly
Asymptomatic women aged **65 or above with routine screening**	Discontinue screening if routine screening within 10 years is normal	Doctors Nurses	
Asymptomatic women aged **65 or above who have never been screened**	Offer routine screening: ◆ **Cytology** *OR* ◆ **Primary HPV testing** *OR* ◆ **HPV Co-testing**	Doctors Trained Nurses	Opportunistically
Women of all age who are chronically immunosuppressed	Offer: ◆ **Cytology** *OR* ◆ **Primary HPV testing** *OR* ◆ **HPV Co-testing**	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[a]**	**By Whom?[b]**	**How Often?**
Management			
For Women Who Have **Undergone Cervical Cancer Screening**			
Women who underwent cervical cancer screening	Manage screening tests according to screening strategy[6]: - Cytology alone or HPV co-testing **(Table 2.-4.)** - Primary HPV testing **(Table 5.)**	Doctors	As soon as result available

HPV = Human Papillomavirus

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a **Grade of recommendation according to colour code**:

Recommended (Strong)	Conditionally recommended	Practice points	Generally not recommended	Not recommended (Strong)

b

Primary Healthcare Providers – All providers of health services in primary healthcare settings

Primary Healthcare Professionals – Includes doctors, dentists, chinese medicine practitioners, nurses, pharmacists, physiotherapist, occupational therapist, dietitians

"Trained" Healthcare Professionals – Additional post-qualification training required to deliver the respective care component(s)

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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 ≥ 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[3]

Primary Prevention of Cervical Cancer
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: ◆ ***HPV vaccination prior to sexual debut*** ◆ ***Practice of safe sex*** (such as avoid having multiple sexual partners and use condoms) to reduce the chance of contracting HPV and other sexually transmitted diseases ◆ ***Abstinence from tobacco smoking***

CEWG = Cancer Expert Working Group

Table 2. Management of Cytology or Co-Testing Results – Normal and Squamous Lesions[6]

Screening Result	Recommended Action	
	Cytology Alone	**Co-Testing**
1. Negative for intraepithelial lesion or malignancy (NILM) (normal cytology)	Repeat every 3 years (after 2 initial annual screen with normal cytology)	If high-risk HPV **(hrHPV) negative:** Repeat every 5 years *If hrHPV negative, but history of hrHPV positive or cytology abnormality in the last screening: Repeat screening (co-testing or cytology) in 3 years* If **hrHPV positive**, then 3 options: ◆ Repeat cytology in 6 months for 3 times; ◆ Repeat co-testing in 12 months; or ◆ Do genotyping for HPV16/18: - If **HPV 16/18 positive**, refer colposcopy - If **HPV 16/18 negative**, repeat co-testing or cytology in 1 year, then in 3 years, then routine screening
2. Normal but transformation zone absent	If **age <30 years**: manage as normal smears If **age ≥30 years**: HPV testing (preferred) or manage as normal smears.	
3. Atypical squamous cells of undetermined significance (ASCUS)	Repeat cytology in 6 months and 12 months Or, **Triage with HPV testing**	If **hrHPV positive**: colposcopy If **hrHPV negative**: repeat screening in 3 years
4. Low Grade Squamous Intraepithelial Lesion (LSIL)	Refer for colposcopy	If **hrHPV positive**: colposcopy If **hrHPV negative**: repeat co-testing or cytology in 12 months ◆ If either abnormal: refer for colposcopy If both normal, repeat co-testing or cytology in 3 years , then routine screening
5. ASC-H (including cases with coexisting LSIL)	Refer for colposcopy	
6. High Grade Squamous Intraepithelial Lesion (HSIL)	Refer for colposcopy	
7. Squamous cell carcinoma	**Early** 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[6]

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 ≥ 45 years of age)**	If **Post-menopaus**al state, presence of **abnormal vaginal bleeding** or **Obesity** (i.e. BMI ≥ 25kg/m^2): ◆ Refer to specialist for endometrial assessment Otherwise no further investigation is required

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[6]

Screening Result	Recommended Action	
	Cytology Alone	Co-Testing
Unsatisfactory	Repeat cytology in 2-4 months. If **2 consecutive unsatisfactory cytology**, refer for colposcopy	If **HPV 16/18 positive**: refer for colposcopy If **non-HrHPV 16/18 positive**: repeat cytology in 2-4 months or refer for colposcopy If **HPV negative**: repeat cytology in 2-4 months. ◆ If 2 consecutive unsatisfactory cytology, refer for colposcopy
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[6]

Screening Result	Recommended Action
HrHPV Negative	5 yearly-screening interval with stand-alone HPV testing
HrHPV Positive	**1. Genotyping** if available If **HPV 16/18 positive:** - Refer for reflex cytology if possible - Refer to colposcopy irrespective of cytology result If **HrHPV non-16/18 positive**: - Refer for reflex cytology - if **ASCUS or above**: Refer for colposcopy ◆ If **Normal cytology**: 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)
	2. Reflex / Triage cytology ◆ For all women with positive hrHPV test, regardless of genotype ◆ If **ASCUS or above**: refer for colposcopy ◆ If **Normal cytology**: 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)

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%).[7, 8] 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.[3] 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.[9, 10] 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.[11] 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).[11] 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.[7] 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.[12-15] 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.[16-18] Screening every one to two years offered minimal additional protection compared to screening every three years after two consecutive normal results.[19]

- Cervical cancer screening is not recommended for women under 20 due to the low prevalence of cervical cancer.[20] For women under 25, screening should only be considered if there is a high-risk profile.[3] 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.[21, 22] On the other hand, screening beyond age 65 was found to be not cost-effective.[23]

- HPV testing was introduced to detect high-risk HPV infections and to facilitate earlier detection of cervical precancerous lesions compared to cytology.[24] 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.[25-27] HPV co-testing (i.e., both HPV testing and cytology) was associated with a 40% lower risk of cervical cancer compared to cytology alone.[28]

- 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).[29]

S Table 1. Risk Factors of Cervical Cancer

Risk Factors	Relative Risks (RR) (95%C.I)	Level of Evidence
(1) HPV infection ◆ HPV 16 ◆ HPV 18 ◆ Any type	OR = 434.5 (278.2 – 678.7) OR = 248.1 (138.1 – 445.8) Pooled OR = 158.2 (113.4 – 220.6)	2++[8]
(2) History of sexually transmitted infections (STIs) ◆ Chlamydia trachomatis infection ◆ HSV infection (HSV-2 seropositivity)	Adjusted OR = 6.6 (1.6 – 27.0) Pooled OR = 2.19 (1.41 – 3.40)	2++[30] 2++[31]
(3) Immunosuppression (HIV infection)	2.20 (1.89 – 2.54)	1+[32]
(4) Having multiple sexual partners (≥ 6 versus 1 partner)	2.78 (2.22 – 3.47)	2++[33]
(5) Early age of sexual debut (age < 17 years)	OR = 2.32 (1.89 – 2.85)	2++[34]
(6) Full term Pregnancy at < age 21 ◆ Aged 16 or below ◆ Aged 17 to 20 years	OR = 2.31 (1.85 – 2.87) OR = 1.80 (1.50 – 2.39)	2++[35]
(7) Use of oral contraceptive pills in HPV positive women ◆ ≥10 years ◆ ≥5 years ◆ < 5 years	OR = 4.03 (2.09 – 8.02) OR = 2.82 (1.46 – 5.42) OR = 0.73 (0.52 – 1.03)	2++[36]
(8) Number of full term pregnancy ◆ ≥7 ◆ ≥5 ◆ ≥3 ◆ ≥1	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++[37]
(9) Family history of cervical cancer ◆ First degree relative ◆ Second degree relative	OR = 1.79 (1.71 – 1.88) OR = 1.28 (1.22 – 1.35)	2+[38]
(10) Smoking	1.50 (1.35 – 1.66)	1+[39]

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**
1. Cervical Cytology Cells from transformation zone of the cervix are collected for cytological examination for dysplasia, pre-cancerous or cancerous changes	**Conventional Cytology**[40] 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%)[40]	[CIN2+] 96.3% (94.7% – 97.4%)[40]	[CIN2+] 20.4% (18.3% – 22.7%)[41]	
	Liquid-based Cytology[40] Cells collected using an endo-cervical brush and placed in liquid fixative solution			
	[CIN2+] 75.5% (66.6% – 82.7%)[40]	[CIN2+] 91.9% (88.4% – 94.3%)[40]	[CIN2+] 10.1% (8.7% – 11.3%)[42]	[CIN2+] 98.8% (98.3% – 99.2%)[42]
2. HPV Testing 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[43]	**Clinical Sample**[40] 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%)[41]	[CIN2+] 88.7% (88.3% – 89.0%)[41]	[CIN2+] 15.0% (13.9% – 16.1%)[41]	
	Self-sampling HPV Test 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%)[44, 45]	[CIN2+] 85% (75.3% – 92%, 84.4% – 86.3%)[44, 45]		

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**
◆ Simple ◆ Easily available ◆ Low cost	◆ Sampling error (e.g. inadequate sample and/or slide preparation) may result in 20% false negative rate.[46] ◆ Risk of misinterpretation due to presence of obscuring material such as inflammatory cells, blood and overlapped epithelial cells.[47, 48] ◆ Do not allow for additional HPV and/or biomarkers testing using the same sample	◆ Sampling by trained healthcare professionals, may induce bleeding after the procedure ◆ Cervical cytology service should be provided by an accredited laboratory with appropriate quality assurance procedures ◆ Cytology reports should be issued by a qualified anatomical pathologist or (for negative results associated with absence of clinical findings) by a qualified cytotechnologist ◆ Reporting of cervical cytology should be based on the 2014 Bethesda System for Reporting Cervical Cytology
Liquid-Based Cytology		
◆ Lower rate of unsatisfactory sample[6] ◆ Allows for additional HPV and/or biomarkers testing using the same sample	◆ More costly as requires further processing using automated device ◆ Sampling error may result in inadequate sample for HPV testing requiring re-sampling	
Clinical HPV Sample		
◆ Superior sensitivity and slightly lower specificity than cervical cytology in detecting HPV-associated CIN grade 2 or worse (CIN2+), ◆ Earlier detection of cervical precancerous lesions than cytology.[24, 40, 49] ◆ Higher reproducibility, reduced reliance on screener competency, and greater potential for automation[6] ◆ 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[26] ◆ 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.[50] ◆ Potentially more cost-effective	◆ More false-positive results and higher colposcopy rates necessitate triage testing necessary ◆ False-negative as there exists a variety of HPV-independent cervical neoplasm	◆ Only clinically validated HPV tests should be used ◆ Laboratory standard operating procedures and quality assurance programmes should be in place for use of any HPV testing procedures ◆ Reports should be issued by an accredited laboratory with participation in quality assurance programmes[6]
Self-Collected HPV Sample		
◆ Convenient ◆ More comfortable (compared to speculum examination) ◆ Potential to increase cervical cancer uptake by overcoming of barriers such as embarrassment and fear of pain[51]	◆ Education required on proper self-sampling technique ◆ Likely user-dependent, accuracy varies across study[44] ◆ Local data not yet available, study on the validation of HPV self-sampling test is underway	◆ There should be validation of sampling devices for self-collected vaginal specimens, and performance and regulatory approval of HPV tests for self-collected specimen[6]

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)[52]	[CIN2+] 95.1% (94.8 – 95.3)[52]	[CIN2+] 17.8% (15.8 – 19.8)[52]	[CIN2+] 99.4% (99.2 – 99.5)[52]	◆ HPV-based co-test leads to 40% lower risk of invasive cervical carcinoma when compared with cytology alone.[28] ◆ Co-testing led to earlier detection of clinically significant pre-invasive lesions.[53] ◆ 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%).[54]
2. Cytology+ Reflex HPV testing if ASCUS cytology is found	[CIN2+] 40.6% (36.1 – 45.1)[52]	[CIN2+] 97.3% (97.1 – 97.5)[52]	[CIN2+] 24.8% (22.3 – 27.4)[52]	[CIN2+] 98.7% (98.5 – 98.9)[52]	◆ Among women with ASCUS cytology, 50% are high risk HPV carriers[55], who are more likely to have high-grade lesions (CIN2/3).[56] ◆ No role for LSIL or above due to high prevalence of high-risk HPV.[57]
3. Primary HPV testing+ Reflex genotyping+ cytology if high risk HPV is positive	[CIN2+] 64.8% (58.4 – 71.1)[52]	[CIN2+] 95.2% (95 – 95.5)[52]	[CIN2+] 18.5% (16.4 – 20.6)[52]	[CIN2+] 99.4% (99.2 – 99.5)[52]	◆ The lower specificity of a positive HPV test necessitates a triage test by cytology or genotyping to determine referral for colposcopy.[6] ◆ 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 < 30-35 years; from 0.9% to 5.8% with HPV testing versus 1.0% to 2.5% with cytology in > 30-35 years.[6]

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 HKPRF webpage******

Ovarian Cancer Screening

Recommendations	Grades of Recommendations^
1. **Educate all women on risk factors, symptoms and signs of ovarian cancer**[1]	**C**
2. **Do <u>not</u> recommend screening for ovarian cancer for asymptomatic women at average risk**[2, 3]	**B**
3. **Discuss the risk, benefits and approach of screening with women at increased risk for ovarian cancer, such as those with strong family history of ovarian/breast cancer or inherited deleterious gene mutations (e.g. BRCA1/2, Lynch syndrome) when they are seeking medical advice for assessment of their ovarian cancer risk**[4-6]	**A**

^ Scottish Intercollegiate Guidelines Network (SIGN) classification

Recommended Care Components

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Empowerment			
Women of all ages	Educate on: ◆ **Risk factors, symptoms and signs o**f ovarian cancer ◆ Primary **preventive measures** for ovarian cancer **(Table 1.)**	Primary Healthcare Providers	Opportunistically
Assessment			
Women of all ages	Assess: **(1) Risk** for Ovarian cancer **Family history** - Ovarian/breast cancer **Personal history** of genetic mutation - Deleterious gene mutations (e.g. BRCA1/2, Lynch syndrome) (2) Presence of **signs and symptoms** suggestive of Ovarian cancer:[7] ◆ Abdominal mass ◆ Abdominal distention ◆ Abnormal vaginal bleeding ◆ Abdominal or pelvic pain ◆ Abdominal or pelvic bloating	Nurses Doctors	Opportunistically
Women with symptoms suggestive of ovarian cancer	Refer to seek early medical attention OR Provide work up assessment	Nurses Doctors	When symptomatic

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Screening			
Asymptomatic Women at increased risk (i) Strong family history of ovarian/breast cancer (ii) Inherited deleterious gene mutations (e.g. BRCA1/2, Lynch syndrome)	Discuss screening approach of ovarian cancer Refer to specialist as appropriate	Doctors	Opportunistically
Asymptomatic Women of average risk	Screening not recommended		

CA = Cancer Antigen; TVUS = Transvaginal Ultrasound

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[a] **Grade of recommendation according to colour code**:

Recommended (Strong)	Conditionally recommended	Practice points	Generally not recommended	Not recommended (Strong)

[b] **Primary Healthcare Providers** – All providers of health services in primary healthcare settings

Primary Healthcare Professionals – Includes doctors, dentists, chinese medicine practitioners, nurses, pharmacists, physiotherapist, occupational therapist, dietitians

"Trained" Healthcare Professionals – Additional post-qualification training required to deliver the respective care component(s)

Collaborative Care

Specialist Referral Recommended
Early referral to Gynaecologist: ◆ If clinical features are suggestive of ovarian cancer **Consider referral to Gynaecologist:** ◆ Asymptomatic women at increased risk who wish to consider ovarian cancer screening

Table 1. CEWG Recommendation on Primary Preventive Measures for Ovarian Cancer[4]

Primary Prevention of Ovarian Cancer
Certain ovarian cancer risk factors are modifiable and related to personal lifestyle and behaviour. Women can lower their risk of getting ovarian cancer by pursuing primary preventive measures below: ◆ ***Maintaining a healthy body weight*** by having regular physical activities and balanced diet ◆ ***Avoiding or quitting smoking*** ◆ ***Following occupational safety and health rules*** (e.g. proper use of personal protective equipment to reduce exposure to asbestos in the workplace) ◆ ***Breastfeed each child for a longer duration****

CEWG = Cancer Expert Working Group

*Breastfeeding was associated with lower risk of epithelial ovarian cancer, decreasing by 8% for every 5 months increase in breastfeeding duration[8]

Further Readings[4, 9]

Natural History and Risk Factors of Ovarian Cancer

- Early diagnosis of ovarian cancer can be challenging as early-stage ovarian cancer is mostly asymptomatic,[10] but when presented with symptoms (e.g. pelvic or abdominal pain, increased abdominal size or bloating, difficulty eating or feeling full, urinary urgency or frequency), they are non-specific.[4] Education on risk factors **(S Table 1.)** and clinical features of ovarian cancer is essential to encourage women to seek medical attention and facilitate early diagnosis through timely investigation and management of ovarian cancer.

Effectiveness of Ovarian Cancer Screening

- Currently, international guidelines do not recommend ovarian cancer screening for asymptomatic women at average risk, as such screening has not demonstrated a mortality benefit. Large randomized controlled trials, including the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), have shown no significant reduction in ovarian cancer mortality among post-menopausal women screened with CA-125, transvaginal ultrasound (TVUS), or a combination of both.[2, 3]

- Research on the effectiveness of ovarian cancer screening for local women at increased risk is lacking. Internationally, there is limited data on the effectiveness of ovarian cancer screening and mortality reduction for women with a family history of ovarian or breast cancer, or genetic mutations such as BRCA1 or BRCA2. Phase I of the United Kingdom Familial Ovarian Cancer Screening Study (UK FOCSS) found that annual screening with CA-125 and transvaginal ultrasound (TVUS) did not significantly change the stage at diagnosis. However, Phase II showed that combining CA-125 screening with the Risk of Ovarian Cancer Algorithm (ROCA) every four months, along with TVUS as determined by ROCA, resulted in a significant stage shift. The impact of ROCA-based screening on survival improvement and the implications of this stage shifting remains unknown.[5, 6]

- Potential harms of ovarian cancer screening include psychological morbidity, false-positive results and subsequent invasive surgeries. Women who underwent recall screening and follow-up investigations had a significantly increased risk of psychological morbidity (OR = 1.28, 95% CI 1.18-1.39).[11]

S Table 1. Risk Factors of Ovarian Cancer

Risk Factors	Relative Risks (RR) (95%C.I)	Level of Evidence
Genetic mutation ◆ BRCA1 mutation carrier ◆ BRCA2 mutation carrier Lynch syndrome (HNPCC) ◆ MSH2 ◆ MLH1 ◆ MSH 6	Cumulative risk of ovarian cancer by age 80 44% (36% – 53%) 17% (11% – 25%) Cumulative risk of ovarian cancer from age 40-70 24% (3% – 52%) 20% (1% – 65%) 1% (0% – 3%)	2++[12] 2+[13]
Family history ◆ Affected first-degree relative	Pooled RR = 3.1 (2.6 – 3.7)	2+[14]
Exposure to Asbestos	Pooled SMR = 1.77 (1.37-2.28)	2++[15]
Diabetes	1.55 (1.11 – 2.19)	2+[16]
◆ Menopause > age 52 (comparing with menopause ⩽45) ◆ Each additional year of menstrual lifespan	HR = 1.46 (1.06 – 1.99) HR = 1.02 (1.01 – 1.04)	2++[17]
Menopausal hormonal therapy ◆ Current use but <5 years ◆ History of use with cessation < 10 years	1.43 (1.31 – 1.56) 1.25 (1.07 – 1.46)	2++[18]
Endometriosis	Epithelial ovarian cancer: OR = 1.42 (1.28 – 1.57)	2++[19]
Parity Risk for nulliparous women: ◆ Endometrioid ovarian cancer ◆ Clear cell tumors ◆ For all types of ovarian cancer ◆ Each additional birth	 1.49 (1.18 – 1.89) 1.68 (1.29 – 2.20) 1.24 (1.16 – 1.33) 0.94 (0.92 – 0.96)	2++[20]
Obesity ◆ BMI > 30 ◆ BMI 25-29.9 ◆ Per 5 units of Body Mass Index (BMI) increase	 OR = 1.3 (1.1 – 1.5) OR = 1.2 (1.0 – 1.3) 1.06 (1.00 – 1.12)	2+[21] 2++[22]
Smoking ◆ Ever smoker ◆ Current smoker ◆ Past smoker	All types of ovarian cancer 1.07 (1.03 – 1.10) Risk of mucinous ovarian cancer 1.79 (1.60 – 2.00) 1.28 (1.06 – 1.53)	 2++[23]

Protective Factors	Relative Risks (RR) (95%C.I)	Level of Evidence
Breast feeding ◆ History of breast feeding regardless of duration Duration: ◆ >12 months ◆ 6 to 12 months ◆ <6 months	Pooled RR = 0.70 (0.64 – 0.76) 0.64 (0.56 – 0.73) 0.73 (0.65 – 0.82) 0.85 (0.77 – 0.93)	2++[24]
Physical activity ◆ Regularly active	RR reduction of 20%	2+[25]
Average Risk Women		
Oral contraceptive pills (OCP) use ◆ OCP use > 10 years ◆ History of OCP use	 OR = 0.43 (0.37 – 0.51) OR = 0.73 (0.66 – 0.81)	2++[26]
Women with BRCA1/ BRCA2 Mutation		
◆ History of OCP use ◆ Each additional 10 years of use	Summary RR = 0.50 (0.33 – 0.75) Summary RR = 0.64 (0.53 – 0.78)	2+[27]

RR = Relative Risk; SMR = Standardized Mortality Ratio; HR = Hazard Ratio; OR = Odd Ratio; OCP = Oral Contraceptive Pill; HNPCC = Lynch Syndrome; BMI = Body Mass Index

S Table 2. Methods of Ovarian Cancer Screening

Screening Tests	Performance			Remarks
	Sensitivity	Specificity	PPV	
Cancer antigen-125 (CA-125) Protein produced by ovary cells as tumor marker		78%[28]	3.7%[29]	◆ CA 125 alone for ovarian cancer screening is not recommended ◆ Elevated CA 125 levels can be found in benign gynecological conditions and malignancies other than ovarian cancer. The level of CA 125 may fluctuate during menstrual cycle and smoking status.[30, 31] ◆ The false positive rate of CA 125 for ovarian cancer screening exceeds 40%.[32]
Transvaginal ultrasound (TVUS) Ultrasound performed by healthcare professional using a transvaginal ultrasound probe	84.9%[33]	98.2%[33]	5.3%[33]	◆ Most adnexal masses detected by TVUS were found to be benign.[33] ◆ The false positive rate was 11.9%, with 3.2% surgeries performed in false positive results of those screened with TVUS alone.[32]
Screening Strategies	**Sensitivity**	**Specificity**	**PPV**	**Remarks**
CA 125 + TVUS	89.4%[33]	99.8%[33]	43.3%[33]	◆ Fewer repeated investigation and unnecessary intervention compared to CA 125 or TVUS alone.[33] ◆ In PLCO Cancer Screening Trial, concurrent testing with CA-125 and TVUS showed no significant difference in the incidence of ovarian cancer between women who were screened and those who were not. Furthermore, there was no notable difference in the proportion of patients diagnosed with advanced disease (stage III or IV), with rates of 77% and 78%, respectively.[29] ◆ The false-positive rate for concurrent CA125 and TVUS screening were approximately 9.7% across all rounds. Nearly one-third of these false positives underwent diagnostic surgery, with major complications occurring in 15% of cases.[3] ◆ In the UKCTOCS trial, elevated CA-125 level with subsequent TVUS screening was associated with stage shifting of ovarian cancer, with 39% increase in stage I and II diagnosis and a 10% decrease in stage III and IV diagnosis compared to individuals without screening, but this did not translate into a reduction in ovarian cancer mortality.[34]
Pelvic Examination Bimanual examination of the uterus and ovaries by healthcare professionals	5.1%[4, 35]	99.0%[4, 35]	0.4%[4, 35]	◆ Not recommended due to low sensitivity

PPV = Positive Predictive Value; CA = Cancer Antigen; TVUS = Transvaginal Ultrasound; UKCTOCS = United Kingdom Collaborative Trial of Ovarian Cancer Screening

******The corresponding list of References is available on HKPRF webpage******

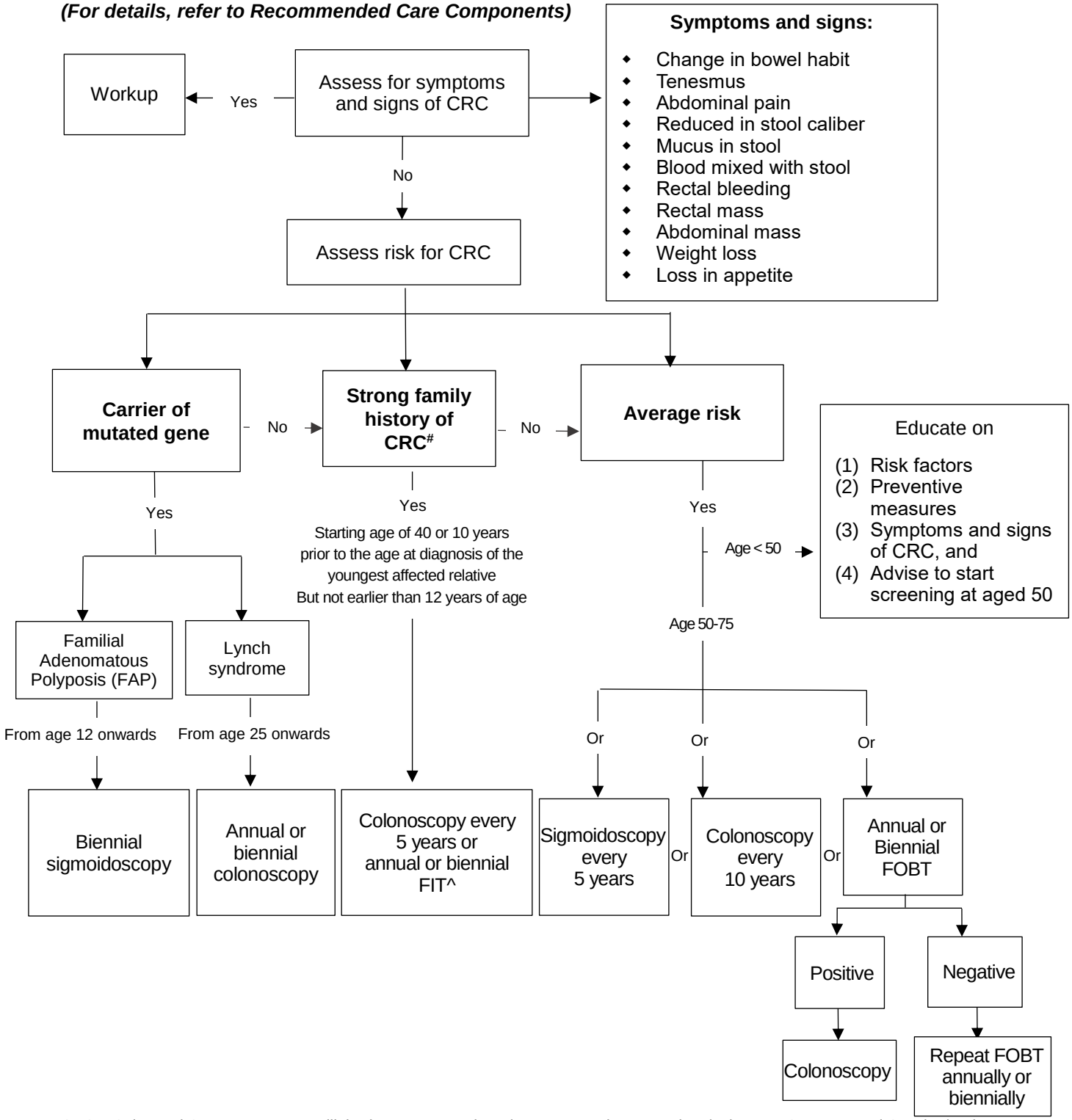
Colorectal Cancer Screening

Recommendations	Grades of Recommendations^
1. Educate all on symptoms, signs, risk factors and preventive measures of colorectal cancer, and the importance of regular colorectal cancer screening[1]	**B**
2. Offer regular colorectal cancer screening to asymptomatic individual according to risk profile:[2] - **Aged 50 to 75 years of average risk** - **Having strong family history of colorectal cancer** - **Carrying mutated gene of Familial Adenomatous Polyposis (FAP) or Lynch Syndrome**	**A**

^ Scottish Intercollegiate Guidelines Network (SIGN) classification

Figure 1. Colorectal Cancer Screening Workflow

(For details, refer to Recommended Care Components)



CRC = Colorectal Cancer; FAP = Familial Adenomatous Polyposis; FIT = Fecal Immunochemical Test; FOBT = Faecal Occult Blood Test
#1 First degree relative diagnosed with CRC at or below 60 or >1 First degree relatives with CRC irrespective of age at diagnosis and without hereditary bowel syndromes
^After understanding the pros and cons of FIT compared to colonoscopy

Adapted from the ***Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) – Recommendations on Prevention and Screening for Colorectal Cancer***[3]

Recommended Care Components

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Empowerment			
Individual of all ages	Educate on: ◆ **Risk factors,** symptoms and signs of colorectal cancer (CRC) ◆ **Primary preventive measures** for CRC **(Table 1.)** ◆ Importance and methods of regular CRC screening	Primary Healthcare Providers	Opportunistically
Assessment			
Individuals of all ages	Assess: (1) **Risk** for CRC: **Family history** - 1º vs. 2º degree relative - Age of diagnosis - Total number - Genetic mutation **Personal history** of genetic mutation - Familial Adenomatous Polyposis (FAP) - Lynch syndrome (2) Presence of **symptoms and signs** suggestive of CRC: ◆ Change in bowel habit ◆ Tenesmus ◆ Abdominal pain ◆ Reduced in stool caliber ◆ Mucus in stool ◆ Blood mixed with stool ◆ Rectal bleeding ◆ Rectal mass ◆ Abdominal mass ◆ Weight loss	Nurses Doctors	Opportunistically
Individuals with symptoms or signs suggestive of CRC	Refer to seek early medical attention *OR* Provide work up assessment	Nurses Doctors	When symptomatic

For Who?	Recommended Care Components[a]	By Whom?[b]	How Often?
Screening			
Asymptomatic individuals eligible for colorectal cancer screening	Discuss pros and cons of different screening options, and address misconceptions and concerns	Nurses Doctors	Opportunistically
Asymptomatic Individual **aged 50 to 75 years** of **average risk**	Offer: ◆ **Faecal occult blood test (FOBT)** *OR* ◆ **Sigmoidoscopy** *OR* ◆ **Colonoscopy**	Doctors	Annually or biennially 5-yearly 10-yearly
Asymptomatic individuals with - One 1° relative diagnosed with CRC at or below 60 - More than one 1° relatives with CRC irrespective of age at diagnosis, and without hereditary bowel syndromes	Offer screening by ◆ **Colonoscopy** *OR* ◆ **Faecal Immunochemial Test (FIT)**^ *Starting age of 40 or 10 years prior to the age at diagnosis of the youngest affected relative, but not earlier than 12 years of age*	Doctors Doctors	5-yearly Annually or biennially
Asymptomatic carriers of mutated gene of Familial Adenomatous Polyposis (FAP)	Offer screening by **Sigmoidoscopy** *from age 12 onwards*	Doctors	Biennially
Asymptomatic carriers of mutated gene of Lynch Syndrome	Offer screening by **Colonoscopy** *from age 25 onwards*	Doctors	Annually or biennially
Family members of CRC patients with identifiable genetic mutations	Discuss and consider offering two-tier screening by genetic testing followed by endoscopic examination	Doctors	Opportunistically

CRC = Colorectal Cancer; FAP = Familial Adenomatous Polyposis; FOBT = Faecal Occult Blood Test; FIT = Faecal Immunochemial Test
^After understanding the pros and cons of FIT compared to colonoscopy

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a **Grade of recommendation according to colour code**:

Recommended (Strong)	Conditionally recommended	Practice points	Generally not recommended	Not recommended (Strong)

b

Primary Healthcare Providers – All providers of health services in primary healthcare settings

Primary Healthcare Professionals – Includes doctors, dentists, chinese medicine practitioners, nurses, pharmacists, physiotherapist, occupational therapist, dietitians

"Trained" Healthcare Professionals – Additional post-qualification training required to deliver the respective care component(s)

Collaborative Care

Specialist Referral Recommended
Refer to specialist: if clinical features are suggestive of CRC **Refer to colonoscopy:** if FOBT/ FIT result is positive

CRC = Colorectal Cancer; FOBT = Faecal Occult Blood Test; FIT = Faecal Immunochemial Test

Table 1. CEWG Recommendation on Primary Prevention for Colorectal Cancer (CRC)[3]

Primary Prevention of CRC
Certain CRC risk factors are modifiable and related to personal lifestyle and behavior. Women can lower their risk of getting CRC by pursuing primary preventive measures below: ◆ ***Increase intake of dietary fibre*** (e.g. fibre from at least five servings of fruits and vegetables daily ◆ ***Decrease consumption of red and processed meat*** ◆ ***Increase physical activities:*** by doing at least 150 minutes of moderate-intensity aerobic physical activities per week (e.g. climbing stairs or brisk walking) ◆ ***Maintain healthy body weight:*** (BMI 18.5-22.9 kg/m^2) and waist circumference (<80cm for women and <90cm for men) ◆ ***Avoid or quit tobacco smoking*** ◆ ***Do not drink alcohol***

CEWG = Cancer Expert Working Group; CRC = Colorectal Cancer; BMI = Body Mass Index

Further Readings

Risk Factors of Colorectal Cancer

- Colorectal cancer (CRC) develops from adenomatous polyps over a period of 10 to 15 years.[4] These adenomatous polyps may bleed and present as blood in stool, whereas small amount of bleeding not visible to naked eyes can be detected by fecal occult blood tests. However, polyps that do not bleed may be missed by non-invasive screening tests. Therefore, negative results from fecal occult blood tests do not guarantee the absence of adenomatous polyps.

- Lifestyle factors, which are modifiable, play an important role in the development of colorectal cancer (CRC) and its precursor (i.e. colonic adenoma).[5] Multiple meta-analyses demonstrated that being physically active,[6] and consuming high amount of fruits, vegetables and fibres were associated with lower risk of CRC development,[7, 8] while increased intake of red and processed meat increased the risk of CRC linearly.[9] **S Table 1.** presents the risk factors for developing CRC with their relative risks.

- Apart from adopting a healthy lifestyle to prevent CRC, a large number of studies reported that regular aspirin use was associated with a lower risk of CRC and colonic polyps.[10-20] However, due to strong evidence of long term low-dose use of aspirin leading to increased risk of gastrointestinal bleeding, no consensus has been reached thus far internationally.[12, 21, 22] Most health organisations and professional bodies generally recommend to weigh the potential benefits, including cardiovascular-prevention and cancer risk reduction in individuals with increased CRC risks, as well as harms, including cerebrovascular and gastrointestinal bleeding risks, before recommending decision on long term use of aspirin for CRC prevention.[23-27] Locally, CEWG does not recommend the use of prophylactic low-dose aspirin for CRC prevention.

Effectiveness of Colorectal Cancer Screening

- Options, advantages and limitations of different colorectal cancer screening methods are presented in **S Table 2.** Annual screening using fecal occult blood reduced cumulative colorectal cancer mortality by 33% over 18 years, while biennial screening resulted in a 21% reduction. Both screening strategies significantly decreased the incidence of Dukes'

stage D (Stage 4) cancer, supporting the effectiveness of annual or biennial FIT screening.[28]

- Screening with colonoscopy enables visualization of the lower gastrointestinal tract and removal of precancerous polyps. Colonoscopy screening every 10-year in average risk individuals lead to a 32% reduction in colorectal cancer mortality.[29] This interval is supported by studies on adenoma progression, which have shown that a negative colonoscopy can predict a reduced risk of colorectal cancer (CRC) for over 10 years.[30]

- Screening with sigmoidoscopy every 5 years is associated with a 28% reduction in distal colorectal cancer-related mortality.[31] However, it can only detect adenomatous polyps and colorectal cancer in the left distal colon before the splenic flexure, necessitating follow-up colonoscopy if abnormalities are found.

- In Hong Kong, the Colorectal Cancer Screening Programme (CRCSP) for individuals aged 50 to 75 at average risk has proven to be effective in diagnosing colorectal cancer at earlier stages (i.e. stage shifting), with the potential to reduce colorectal cancer-related mortality in the future.[32]

- Annual or biennial fecal immunochemical test (FIT) screening for individuals aged 50 to 75 was demonstrated to be cost-effective compared to opportunistically screening in local setting. Biennial FIT screening was identified as the most cost-effective option, with an incremental cost-effectiveness ratio (ICER) of HK$43,660 per quality-adjusted life year (QALY).[33] On the other hand, screening with colonoscopy every 10 years is cost-effective compared to no screening, with an incremental cost-effectiveness ratio (ICER) of HK$115,700 per quality-adjusted life year (QALY).[33]

- Novel methods of colorectal cancer screening have been explored, including stool DNA tests, RNA tests, blood-based DNA tests, and stool microbial markers. A study conducted by the Chinese University in 2020 demonstrated good sensitivity and specificity of combining microbial markers with fecal immunochemical tests (FIT) for colorectal cancer screening.[34] A systematic review in 2023 showed that stool microbial markers are sensitive for detecting CRC and superior to tumor-based biomarkers for adenomatous polyps.[35] Microbial panel, such as a combination of *Fusobacterium nucleatum*, the

Lachnoclostridium gene marker (m3), and *Clostridium hathewayi*, has potential to screen for advanced colorectal neoplasia. However, current evidence regarding the direct impact of these novel methods of colorectal cancer screening on incidence and mortality reduction in average-risk individuals, as well as their cost-effectiveness, is insufficient for the recommendation of their application locally.[3]

Target Group for Colorectal Cancer Screening

- The Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) assessed the alternative of earlier biennial colorectal cancer screening for individuals aged 40 to 70, recognizing its potential for increased health benefits (measured in Life Years or QALYs) despite higher costs and fewer cases or deaths averted.[3] However, the review noted that shifting the screening age from 50-75 to 40-70 could overlook 20% of CRC cases detected in those aged 71-75, as data from the Hong Kong Cancer Registry showed no increasing trends in diagnoses before age 50 from 2016 to 2021. Additionally, participation rates, FIT positive rates, and CRC detection rates are likely to decline with the shift of including younger age group, aged 40-49. Current evidence on the effectiveness of colorectal cancer (CRC) screening primarily comes from large-scale randomized controlled trials and observational studies involving individuals aged 50 and older. In countries with population-based screening, common practices include starting biennial fecal immunochemical testing (FIT) at ages 50 or 55 and ending at ages 74 or 75. Therefore, considering local epidemiology, CRCSP participation patterns, and the latest scientific evidence, the CEWG reaffirms the current CRC screening recommendation for the age group of 50-75 years.

S Table 1. Risk Factors of Colorectal Cancer

Risk Factors	Relative Risks (RR) (95%C.I)	Level of Evidence
Non Modifiable Risk Factors		
Hereditary CRC syndromes Familial adenomatous polyposis (FAP)	*Cumulative lifetime risk:* 100% HR = 4.61 (2.58 – 8.22)	1-[36-38] 2+[39-41]
Lynch syndrome ◆ Men ◆ Women	*Cumulative lifetime risk by age 70:* 66.08% (59.47% – 76.17%) 42.71% (36.57% – 52.83%)	2+[42]
Family history of CRC ◆ First degree relative of young-onset CRC (<40 years old) ◆ 2 or more First degree Relatives with CRC ◆ 2º Relatives of young-onset CRC (<40 years old) ◆ 1 First degree relative with CRC	 HR = 2.53 (1.7 – 3.79) 2.40 (1.76 – 3.28) HR = 1.47 (1.14 – 1.9) 1.37 (0.76 – 2.46)	 2++[43] 2++[44] 2++[43] 2++[44]
Age *(compared to individuals aged <50)* ◆ Aged >69 ◆ Aged 60 to 69 ◆ Aged 50 to 59	*Presence of adenocarcinoma:* OR = 4.02 (2.99 – 5.40) OR = 2.73 (1.99 – 3.73) OR = 1.56 (1.50 – 1.99)	2++[45]
Male gender (compared to female)	*Presence of adenocarcinoma:* OR = 1.43 (1.22 – 1.68)	2++[45]
History of Colonic polyps	Pooled OR = 1.76 (1.48 – 2.09)	2++[46]
Ulcerative colitis	*Overall risk of CRC*: 3.7% (3.2% – 4.2%)	2++[47]
Modifiable Risk Factors		
Obesity, BMI ≥ 30 kg/m^2 BMI per 5kg/m^2 increment	1.33 (1.25 – 1.42) Risk estimate = 1.05 (1.03 – 1.07)	2++[48] 2++[49]
Alcohol consumption ◆ Heavy drinker in Asia (≥4 drinks/ 50 g alcohol/day) ◆ Moderate drinker (2–3 drinks/day) ◆ Light drinker (≤1 drink/12.5g alcohol/day)	 1.81 (1.33 – 2.46) 1.21 (1.13 – 1.28) 1.07 (1.04 – 1.10)	2++[50]
Smoking ◆ Former smokers ◆ Current smokers	 1.17 (1.15 – 1.20) 1.14 (1.10 – 1.18)	2++[51]
Consumption of: ◆ Processed meat, for 50 g/day increase ◆ Fresh red meat, for 100 g/day increase ◆ Red and processed meat, for every 100 g/day increase	 1.18 (1.10 – 1.28) 1.17 (1.05 – 1.31) 1.14 (1.04 – 1.24)	2++[9]
Protective Factors		
Physical activity: ◆ Regular physical exercise for people without 1º family history of colorectal cancer ◆ Regular physical exercise for people with 1º family history of colorectal cancer	 0.56 (0.39 – 0.80) 0.72 (0.39 – 1.32)	2++[52]
Intake of whole grain ◆ >3 Servings (90g) / day	 0.83 (0.78 – 0.89)	2++[53]

RR = Relative Risk; HR = Hazard Ratio; OR = Odd Ratio; CRC = Colorectal Cancer; FAP = Familial Adenomatous Polyposis; BMI = Body Mass Index

S Table 2. Methods of Colorectal Cancer Screening

Colorectal Cancer Screening Tests	Performance			
	Sensitivity	Specificity	PPV	NPV
Fecal Occult Blood Test: Test for hidden blood in stool	**Guaiac FOBT (gFOBT)** Detects fecal occult blood by placing fecal sample on guaiac paper			
	Detect CRC: 50% – 75%[54]	Detect CRC: 96% – 98%[54]	Detect CRC: 3.45%[55]	Detect CRC: 98.99%[55]
	Fecal Immunochemical Test (FIT) Detects human hemoglobin protein using antibodies, specific for low gastrointestinal lesions[56]			
	Detect CRC: 79% (69% – 86%)[57]	Detect CRC: 94% (92% – 95%)[57]	Detect CRC: 2.0% (1.0% – 3.6%)[58]	Detect CRC: 99.8% (99.6% – 99.9%)[58]
Colonoscopy: Endoscopy performed to visualize lower Gastrointestinal tract	Detect adenomas ≥1 cm: 89% – 95% (70% – 99%)[54]	Detect adenomas ≥1 cm: 89% (86% – 91%)[54]		
Flexible Sigmoidoscopy: Endoscopy performed to visualize lower Gastrointestinal tract up to splenic flexure	Detect advanced lesion[#]: 77.8%[59]	Detect advanced lesion[#]: 83.9%[59]		
Computed Tomography Colonography (CTC)*: Uses multiple thin-slice CT scans to create two- and three-dimensional images of the bowel mucosa for polyp detection	Detect adenomas ≥1 cm: 89% (83% – 96%)[54] Detect lesions ≥6 mm[@]: 86% (78% – 95%)[54]	Detect adenomas ≥1 cm: 94% (89% – 100%)[54] Detect lesions ≥6 mm[@]: 88% (83% – 95%)[54]		

CRC = Colorectal Cancer; Gfobt = Guaiac Fecal Occult Blood Test; FIT = Fecal Immunochemical Test; CTC = Computed Tomography Colonography; PPV = Positive Predictive Value; NPV = Negative Predictive Value

[#]Advanced colonic lesion is defined as adenoma ≥10 mm, villous adenoma, adenoma with moderate or severe dysplasia, or invasive cancer

*Accuracy varies by polyp size and type, sensitivity decreasing for smaller or flat lesions

[@]Using a 6 mm CTC size cut-off

Advantages	Limitations	Remarks
◆ Non-invasive ◆ Allows self-collection ◆ Does not require bowel preparation or sedation	◆ Requires collection of three samples ◆ Requires dietary and medication restrictions before sample collection ◆ Risk of false positives from upper gastrointestinal tract bleeding	◆ Clinical trials indicate that gFOBT can reduce CRC mortality by 15-33%[60-62] ◆ A large prospective cohort study showed that a 21.4% coverage of the population receiving FIT reduced CRC mortality by 10%[63]
◆ Non-invasive ◆ Allows self-collection ◆ Does not require dietary or medication restrictions, bowel preparation or sedation ◆ Requires one sample only, improving compliance	◆ Risk of false positives if excessive upper gastrointestinal tract bleeding[56, 64]	
◆ Allows direct visualization of the lower gastrointestinal tract, removal and biopsy of detected lesions/ polyps	◆ Inconvenience of bowel preparation ◆ Risk of major bleeding (14.6/10 000 procedures) and perforation (3.1/10 000 procedures)[54]	◆ Colonoscopy can reduce colorectal cancer mortality by 32%.[29] ◆ The screening interval for average-risk individuals every 10 years is supported by studies on adenoma progression which have shown that a negative colonoscopy can predict a reduced risk of colorectal cancer for over 10 years[30]
◆ Allows direct visualization of the lower gastrointestinal tract **up to the splenic flexure**, removal and biopsy of the detected lesions/polyps of lesions in the rectum up to the splenic flexure ◆ No need for sedation ◆ Shorter procedure time	◆ Focuses on the distal colon may miss proximal and right-sided CRC ◆ Follow-up colonoscopy is required if polyps are detected ◆ Inconvenience of bowel preparation ◆ Risk of major bleeding 0.5 per 10 000 procedures (95% CI, 0-1.3) and perforation 0.2 per 10 000 procedures (95% CI, 0.1-0.4)[54]	◆ Reduce distal CRC-related mortality risk by 28%[31, 65]
◆ Non-invasive	◆ Inconvenience of bowel preparation ◆ Carbon dioxide insufflation may cause cramping ◆ Multiple sessions of Breath-holding (up to 20s) during the examination ◆ Follow-up colonoscopy is required if abnormalities are detected	◆ Accuracy of colorectal polyp detection varies by size and type, with decreasing sensitivity for smaller or flat lesions[54]

S Table 3. Other Methods of Colorectal Cancer Screening

Tests	Performance		Remarks[3]
	Sensitivity	Specificity	
Multitarget Stool DNA Test (mtsDNA test) Test for DNA molecular markers using stool sample	Detect CRC: 93%[66]	Detect CRC: 84%[66]	◆ Much higher cost than FIT tests locally ◆ No direct evidence on CRC incidence or mortality reduction ◆ Risk of false-positive results ◆ Stool sample requires specific laboratory analysis ◆ DNA markers and the algorithm vary among the products
Multitarget Stool RNA Test (mtsRNA test) Test for RNA molecular markers using stool sample	Detect CRC: 94%[66]	Detect CRC: 88%[66]	◆ Still at premarket stage ◆ No direct evidence on CRC incidence or mortality reduction ◆ Risk of false-positive results ◆ Stool sample requires specific laboratory analysis
Stool "Microbial Marker" Test for faecal gut-microbiome and bacteria for early detection of CRC	Detect CRC: 94%[35]	Detect CRC: 81%[35]	◆ Presence of supportive evidence on its performance but lack direct evidence on CRC incidence or mortality reduction
Blood-based DNA Test Blood test for plasma methylated SEPT9 (mSEPT9) gene	Detect CRC: 68%[67]	Detect CRC: 80%[67]	◆ Much higher cost than FIT[68] ◆ Risk of false-positive results ◆ No direct evidence on CRC incidence or mortality reduction

mtsDNA test = Multitarget Stool DNA Test; Mtsrna Test = Multitarget Stool RNA Test; Msept9 = Methylated SEPT9; CRC = Colorectal Cancer; FIT = Fecal Immunochemical Test
*SEPT9 is a tumour suppressor gene and is mutated early in CRC pathway

******The corresponding list of References is available on HKPRF webpage******