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	Cumulative risk of ovarian cancer by age 80	
◆ BRCA1 mutation carrier	44% (36% – 53%)	2++[12]
◆ BRCA2 mutation carrier	17% (11% – 25%)	
Lynch syndrome (HNPCC)	Cumulative risk of ovarian cancer from age 40-70	
◆ MSH2	24% (3% – 52%)	2+[13]
◆ MLH1	20% (1% – 65%)	
◆ MSH 6	1% (0% – 3%)	
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)	HR = 1.46 (1.06 – 1.99)	2++[17]
◆ Each additional year of menstrual lifespan	HR = 1.02 (1.01 – 1.04)	
Menopausal hormonal therapy		
◆ Current use but <5 years	1.43 (1.31 – 1.56)	2++[18]
◆ History of use with cessation < 10 years	1.25 (1.07 – 1.46)	
Endometriosis	Epithelial ovarian cancer: OR = 1.42 (1.28 – 1.57)	2++[19]
Parity		
Risk for nulliparous women:		
◆ Endometrioid ovarian cancer	1.49 (1.18 – 1.89)	2++[20]
◆ Clear cell tumors	1.68 (1.29 – 2.20)	
◆ For all types of ovarian cancer	1.24 (1.16 – 1.33)	
◆ Each additional birth	0.94 (0.92 – 0.96)	
Obesity		
◆ BMI > 30	OR = 1.3 (1.1 – 1.5)	2+[21]
◆ BMI 25-29.9	OR = 1.2 (1.0 – 1.3)	
◆ Per 5 units of Body Mass Index (BMI) increase	1.06 (1.00 – 1.12)	2++[22]
Smoking	All types of ovarian cancer	
◆ Ever smoker	1.07 (1.03 – 1.10)	
	Risk of mucinous ovarian cancer	2++[23]
◆ Current smoker	1.79 (1.60 – 2.00)	
◆ Past smoker	1.28 (1.06 – 1.53)	

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 HKRF webpage******