衞生防護中心
Centre for Health Protection

Cancer Expert Working Group on Cancer Prevention and Screening (CEWG)

Recommendations on Prevention and Screening for Colorectal Cancer For Health Professionals

Local epidemiology

In Hong Kong, the burden of colorectal cancer (CRC) has been increasing over the past three decades and has become one of the commonest cancers. In 2019, CRC was the second commonest cancer with a total of 5 556 newly diagnosed cases and accounted for 15.8% of all new cancer cases. The median age at diagnosis was 68 for males and 69 for females[1]. In 2020, CRC was the second most common cause of cancer death, resulting in a total of 2 287 registered deaths and accounting for 15.4% of all cancer deaths[2].

2. After adjusting for the effect of population ageing, the age-standardised incidence rates (ASIR) of CRC for both sexes were on a gradual increase over the past decades except for the recent years when the rising trend of ASIR became reversed. The age-standardised mortality rate (ASMR) had shown a decreasing trend for the past two decades[3].

3. In general, the incidence and mortality rates of CRC increased with age in both sexes. In 2019, age-specific incidence rate rose steeply from around age 50-55 and the age-specific mortality rate rose steeply from around age 65. In view of a growing and ageing population, the number of new CRC cases and related healthcare burden are expected to continue to increase.

Risk factors and primary prevention

4. Risk factors for developing CRC may be modifiable or non-modifiable. Non-modifiable risk factors for CRC include aging, male gender, history of familial adenomatous polyposis (FAP) or Lynch Syndrome, positive family history of CRC, colonic polyps and ulcerative colitis.

5. Modifiable risk factors for CRC are those related to lifestyle, such as physical inactivity, low fibre intake, high consumption of red and processed meat, overweight or obesity, smoking and alcohol consumption as reported in the Third Expert Report on Diet, Nutrition, Physical Activity and Cancer as well as the CRC report published by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) in 2018[4].

6. Primary prevention is important in lowering the risk of having CRC. The CEWG recommends the general population to prevent CRC by adopting the following measures:

- 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) and waist circumference (<80cm for women and <90cm for men)
- Avoid or quit tobacco smoking
- Avoid or limit consumption of alcoholic drinks.

Potential role of aspirin for primary prevention of CRC

7. Apart from adopting healthy lifestyle to prevent CRC, many studies have found that people who regularly take aspirin have a lower risk of CRC and colonic polyps[5,6,7,8,9,10,11]. Nevertheless, long term use of aspirin is known to impose potential health risks. According to a systematic review published in 2011[12], aspirin can cause serious or even life-threatening side effects, such as bleeding from gastrointestinal tract (hazards ratio [HR], 1.55; 95% confidence interval [CI], 1.27 - 1.90) and intracranial bleeding (relative risk [RR], 1.43; 95% CI, 0.85 - 2.42) which may outweigh the benefits of using long-term aspirin for members of general public at average risk of developing CRC. Another systematic review published in 2016 to study the bleeding risk associated with long term use of low dose aspirin[13] revealed that the relative risks with low-dose aspirin for upper and lower gastrointestinal bleeding were 2.3 (95% CI, 2.0 - 2.6) and 1.8 (95% CI, 1.1 - 3.0) respectively. The estimated relative risk for intracranial haemorrhage with low-dose aspirin was 1.4 (95% CI, 1.2 - 1.7). Furthermore, a systematic review published by the United States Preventive Services Task Force (USPSTF) in 2016[14] showed that low-dose aspirin (<100mg daily or every other day) increased major gastrointestinal bleeding risk by 58% (odds ratio [OR], 1.58; 95% CI, 1.29 - 1.95) and hemorrhagic stroke risk by 27% (OR, 1.27; 95% CI, 0.96 - 1.68). Therefore, the evidence of long term low-dose use of aspirin leading to increased risk of bleeding is strong.

8. Recommendations on the use of aspirin for prevention of CRC vary among overseas professional bodies and health organisations. They in general recommended 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[15,16,17,18,19,20,21,22].

9. A local cohort study was conducted which included over 200,000 aspirin users under the care of public hospitals with at least 6 months of aspirin use (average 7.7 years) between 2000 and 2004 and with follow up until 2013[23]. The median dose of aspirin used was 80 mg daily. Comparing the 200,000 aspirin users with 400,000 non-aspirin users, the study found significant reduction in multiple cancers including CRC (RR=0.71, 95% CI=0.67-0.75) but the risk of breast cancer was found to be increased (RR=1.14, 95% CI=1.04-1.25). The subjects were mainly local Chinese and results are more generalizable to local population. However, it was not a randomised controlled trial (RCT) and confounding effects might exist.

10. Given (1) the established increased risk of bleeding, (2) the lack of local studies to evaluate the benefits and risks from regular aspirin in CRC prevention (including different age segments and aspirin doses) and (3) varying recommendations by overseas health authorities, the CEWG reaffirms in 2021 the recommendation on adopting healthy lifestyles as a primary preventive measures for CRC, and to keep in view further evidence and practice on the long term use of aspirin prophylaxis for prevention of CRC.

Screening for CRC

11. Since 2010, the CEWG recommends that average risk people aged 50 to 75 should consult their doctors to consider one of the following screening methods:-

- annual or biennial faecal occult blood test (FOBT);
- sigmoidoscopy every 5 years;
- colonoscopy every 10 years.

12. To reduce burden arising from CRC, the Government's Colorectal Cancer Screening Programme was piloted in 2016, regularised in 2018 and fully implemented in 2020 to subsidise asymptomatic Hong Kong residents aged 50-75 years to undergo screening in private sector. The screening workflow comprises two stages. Participants would first receive subsidised Faecal Immunochemical Test (FIT) from enrolled Primary Care Doctor (PCD). If the FIT result is positive, the participant would receive subsidised colonoscopy examination service from enrolled Colonoscopy Specialist (CS). If the FIT result is negative, the participant would be advised for rescreening two years later.

Latest evidence and overseas' practice of CRC screening for individuals with average risk

13. The NHS Bowel Cancer Screening Programme in United Kingdom recommends people aged between 60-74 to conduct FIT every 2 years[24]. In Canada, its taskforce recommends individuals aged 50 years for screening at interval of every two years for FOBT[25]. In Australia, the National Bowel Cancer Screening Programme invites eligible Australians aged from 50 to 74 years of age to undergo FIT every 2 years[26]. The USPSTF [27], and the American Cancer Society [28] updated the recommendations for CRC screening in 2021 and 2020 which continue to

recommend annual FOBT, sigmoidoscopy every 5 to 10 years or colonoscopy every 10 years to be appropriate screening modalities for average risk individuals.

Potential role of "microbial marker" for CRC screening

14. In a systematic review published in 2018 regarding the use of faecal gut-microbiome for early detection of CRC, several bacteria were reported to differ in abundance between CRC and adenoma cases and healthy controls[29]. Some predictive models used to distinguish CRC patients from healthy controls had reported areas under the receiver operating curve (AUCs) in external validation populations of 0.68–0.77. As for the use of faecal gut-microbiome for detection of colorectal adenomas, several studies in this systematic review have also identified statistically significant differences in the abundance of certain bacteria between people with adenomas compared to healthy controls. Five studies reported AUCs of 0.61–0.90 for their bacteria based model for discerning participants with adenomas from healthy participants.

15. Local study on novel faecal Lachnoclostridium marker for the non-invasive diagnosis of colorectal adenoma and cancer has been conducted locally and was published in 2020[30,31]. According to the study, a new gene marker from a Lachnoclostrium sp. was identified to be enriched in faecal samples of patients with adenoma by metagenomic analysis. The new marker showed the best performance in diagnosing adenoma in two independent Asian groups of 1 012 subjects by quantitative polymerase chain reaction (PCR), which was superior to currently available stool-based tests. Combination of new marker with FIT improved diagnostic sensitivity from 50.8% to 56.8% (specificity 79.6%) for advanced adenoma, while combination of m3 with other bacterial markers (Fn, Ch, Bc) and FIT showed good diagnostic performance for CRC (specificity=81.2% and

sensitivity=93.8%)[32].

16. Although the findings of studies on the use of "microbial marker" suggested the potential for identifying patients with adenoma and CRC, no large scale RCTs has been conducted in demonstrating its diagnostic accuracy, reduction in CRC morbidity and mortality as well as cost-effectiveness in comparison with FIT/colonoscopy. Presently, no national health authority recommends any form of microbial markers in routine CRC screening, either alone or in combination with FIT/colonoscopy.

17. In view of the above, the CEWG reaffirms in 2021 the recommendations on CRC screening for average risk individuals and shall keep in view further evidence and practice on the effectiveness of microbial marker as novel screening tools for CRC.

Latest evidence and overseas' practice of CRC screening for individuals with significant family history

18. Overseas practices on screening for individuals with significant family history of CRC vary. Canada and the UK's population based FIT screening do not specifically exclude increased-risk individuals [33, 34]. Singapore and Taiwan adopt screening by colonoscopy if individuals were at increased risk[35,36]. Australia adopts a mixed approach (screening by FIT biennially from age 35 or 40 depending on risk level for 10 years followed by colonoscopy every 5 years)[37]. According to the European guidelines for quality assurance in CRC screening and diagnosis coordinated by the International Agency for Research on Cancer (IARC), they recommended that in the absence of hereditary bowel syndromes, people with significant family history should not be excluded from FIT based CRC screening programmes[38].

19. There is few high-quality evidence for studying diagnostic accuracy of FIT on persons with significant family history of CRC. However, some studies demonstrated high diagnostic accuracy of FIT for CRC among those with significant family history (quantitative FIT with sensitivity ranged 64-100% and specificity ranged 84-95%) which were comparable with FIT for CRC on averaged risk individuals (quantitative FIT with sensitivity 74% and specificity 94%)[39,40,41,42,43,44,45,46,47].

20. A meta-analysis was published in 2017 which studied the diagnostic accuracy of FIT for CRC or advanced neoplasia among increased risk individuals[48]. The study showed that the average sensitivity of FIT for CRC was 93% (95% CI, 53% - 99%) and average specificity was 91% (95% CI, 89% - 92%), i.e. FIT has high overall diagnostic accuracy for CRC in adults with family history of CRC. On the other hand, the average sensitivity of FIT for advanced neoplasia was 48% (95% CI, 39% - 57%) and the average specificity was 93% (95% CI, 91% - 94%), i.e. FIT only has moderate accuracy for advanced neoplasia in adults with family history of CRC. The subgroup analyses indicated that FIT cut-off values between 15-25 μg Hb/g feces (equivalent to 75-125 ng Hb/mL buffer) provided the best combination of sensitivity and specificity for the diagnosis of CRC (93% and 94% respectively). However, most studies had a small sample size or low prevalence of CRC or advanced neoplasia, limiting the precision of effect estimates. Most analyses had high heterogeneity and wide confidence intervals of pooled estimates, hence raising concerns about the reliability of the findings.

21. A RCT study was published in 2014 to study FIT and colonoscopy in familial CRC screening[41]. The study revealed that no significant difference between direct colonoscopy and repeated FIT screening group in detecting advanced neoplasia or CRC for first degree relatives of CRC patients. In this RCT, 1 918 first-degree relatives of CRC

patients were randomly assigned to receive a single colonoscopy examination or receive annual FIT for 3 years with relatively low FIT cut-off values at 10 μg Hb/g feces (equivalent to 50 ng Hb/ml buffer). Of all eligible asymptomatic first-degree relatives, 782 were in the colonoscopy group and 784 were in the annual FIT group. In the intention-to-screen analysis, advanced neoplasia was detected in 33 (4.2%) and 44 (5.6%) first-degree relatives in the FIT and colonoscopy groups, respectively (OR = 1.41; 95% CI 0.88-2.26; P=0.14). In the per-protocol analysis, 28 first-degree relatives (3.9%) in the FIT group and 43 (5.8%) in the colonoscopy group had advanced neoplasia (OR = 1.56; 95% CI 0.95-2.56, P=0.08). FIT group detected all CRC cases and was shown to be comparable with colonoscopy in detecting advanced neoplasia in first-degree relatives of CRC patients.

22. For individual with family history of CRC, screening by colonoscopy is recommended in view of their higher risk of developing CRC. Nevertheless, colonoscopy is an invasive, expensive procedure with an established risk of complications, while FIT is a safe, simple, low-cost, comfortable, non-invasive and convenient test compared with colonoscopy, and has demonstrated to have high sensitivity for CRC and fair sensitivity for advanced adenoma.

23. After taking into consideration scientific evidence, overseas screening guidelines and practices, the CEWG has revised the recommendation on CRC screening (see Annex) which are highlighted below:-

- For individuals with one first degree relative diagnosed with CRC at or below 60 years of age, or more than one first degree relatives with CRC irrespective of age at diagnosis, and without hereditary bowel syndromes, screening for CRC by colonoscopy every five years

beginning at the age of 40 or ten years prior to the age at diagnosis of the youngest affected relative, but not earlier than 12 years of age continues to be recommended. In view of non-invasiveness, potential better compliance, and comparable sensitivities of **Faecal Immunochemical Test (FIT)** for adenocarcinoma, FIT **every one or two years** can be adopted as **an alternative after understanding the pros and cons of FIT as compared with colonoscopy.**

Annex

Revised CEWG recommendations on colorectal cancer screening

For asymptomatic population at average risk	For persons at increased risk
Individuals aged 50 to 75 years should consider screening by one of the screening methods including: ➢ annual or biennial faecal occult blood test (FOBT); or ➢ sigmoidoscopy every 5 years; or ➢ colonoscopy every 10 years	1. For carriers of mutated gene of Lynch Syndrome, the CEWG recommends screening for colorectal cancer (CRC) by colonoscopy every one to two years from age 25 onwards. 2. For carriers of mutated gene of familial adenomatous polyposis (FAP), the CEWG recommends screening by sigmoidoscopy every two years from age 12. 3. For individuals with one first degree relative diagnosed with CRC at or below 60 years of age, or more than one first degree relatives with CRC irrespective of age at diagnosis, and without hereditary bowel syndromes, screening for CRC by colonoscopy every five years beginning at the age of 40 or ten years prior to the age at diagnosis of the youngest affected relative, but not earlier than 12 years of age is recommended. **As an alternative, the individuals at increased risk may consider Faecal Immunochemical Test (FIT) every one or two years after understanding the pros and cons of FIT as compared with colonoscopy.** Recommendation on genetic testing for CRC: For CRC patients with identifiable genetic mutations, two-tier screening by genetic testing followed by endoscopic examination can be offered to their family members to reduce the number of unnecessary investigations, as well as to reduce the risk of potential complications.

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