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 2021, CRC ranked second with a total of 5 899 newly diagnosed cases, accounting for 15.3% of all new cancer cases. The median age at diagnosis in 2021 was 68 years for males and females[1]. In 2022, CRC was the second most common cause of cancer death, resulting in a total of 2 270 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 decrease in the recent few years but reversed in 2021. The age-standardised mortality rate (ASMR) has been on a decreasing trend for the past two decades. When interpreting the data for years 2020 and 2021, the potential impact of COVID-19 pandemic on people's health-seeking

behaviour and related healthcare services may need to be considered. According to GLOBOCAN 2020, the ASIR of CRC in Hong Kong among males (36.5 per 100 000 male standard population) and females (23.4 per 100 000 female standard population) in 2020 were comparable with that in developed countries[3].

3. In general, the incidence and mortality rates of CRC increased with age in both sexes. In 2021, age-specific incidence rate rose steeply from around age 50-55 while the age-specific mortality rate rose steeply from around age 70. In view of a growing and ageing population, the occurrence of new CRC cases and related healthcare burden are expected to remain significant.

4. From 2016 to 2021, more than 5 000 CRC cases were registered per year in Hong Kong. The proportion of CRC cases diagnosed at age 40-49 ranged from only 4.9% - 5.7% while the proportion of CRC cases diagnosed at age 50 or above and at age 70 or above were over 92% and 45% respectively.

Risk factors and primary prevention

5. 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.

6. 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].

7. Primary prevention is important in lowering the risk of having CRC. According to CEWG's current recommendation on primary prevention, the public is advised to prevent CRC by adopting the following primary preventive 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 drinking alcohol.

CEWG recommendations on CRC screening in 2022

8. The latest recommendation on screening for CRC had been discussed in CEWG and updated in June 2022. For asymptomatic population at average risk, individuals aged 50 to 75 years should consider screening by one of the following screening methods - annual or biennial faecal occult blood test; sigmoidoscopy every 5 years; or colonoscopy every 10 years. For individuals at increased risk, the main update involved those with significant family history of CRC (one first degree relative diagnosed with CRC at or below age 60 or more than one first degree relatives with CRC irrespective of age at diagnosis) and without hereditary bowel syndromes, for whom screening by colonoscopy remains to be

recommended in view of their higher risk of developing CRC. Nevertheless, in view of non-invasiveness, potential better compliance and comparable sensitivities of Faecal Immunochemical Test (FIT) for adenocarcinoma, screening by FIT every one or two years can be adopted as an alternative after understanding the pros and cons of FIT as compared with colonoscopy (see **Annex 1**).

The Government subsidised Colorectal Cancer Screening Programme (CRCSP)

9. To reduce burden arising from CRC, the Government's CRCSP was piloted in 2016, regularised in 2018 and fully implemented in 2020 to subsidise average risk Hong Kong residents aged 50-75 years to undergo screening with biennial FIT as primary screening test in private sector under public-private partnership model. The screening workflow comprises two stages. Participants would first receive subsidised 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.

Evaluation study of CRCSP commissioned under the Health and Medical Research Fund (HMRF) of HHB

10. In 2015, the then Food and Health Bureau has commissioned the evaluation study of CRCSP to the University of Hong Kong (HKU) under the HMRF, which has been completed in August 2023. Key findings include –

- The Government's CRCSP is effective in reducing CRC incidence rate.
- The current biennial FIT screening strategy among individuals aged 50-75 was cost-effective when compared with opportunistic

screening.

- The CRCSP improves the equity of screening service utilization and reduces disparities across different education, income and housing status.
- Biennial FIT screening, when compared with opportunistic screening, shifted the demand on cancer treatment to cancer screening related healthcare professionals and has no increase in overall demand for healthcare professional manpower resources.

11. In addition, the report suggests that by simulation model, among other strategies that do not require more colonoscopy examination than the current recommendation, the biennial screening for aged 40-70 may be an efficient alternative to the current recommendation as it would generate more health benefits (in terms of Life-Year gained or QALY gained) but with higher total cost; reduced number of CRC cases averted or CRC deaths averted; larger number needed to screen per CRC case averted or per CRC death averted.

Review of target age group for CRC screening in Hong Kong

12. With reference from statistics of CRCSP data, shifting the screening strategy from aged 50-75 to 40-70 might potentially miss the existing 20% of CRC cases detected among person aged 71-75 under CRCSP. It is also anticipated that the participation rate, FIT positive rate and the CRC detection rate would be lower if the CRCSP recruits population aged 40-49. Based on CRC statistics from the Hong Kong Cancer Registry, the proportion and number of CRC diagnosed before 50 did not show increasing trends from 2016 to 2021. Biennial FIT screening for people starting from aged 50 or 55 and stopping at age of 74 or 75 is the most common screening scenario in countries where population-based CRC

screening have been implemented[5,6,7,8,9,10]. Evidences of effectiveness of CRC screening are in general based on large-scale RCTs and observational studies which showed mortality reduction and were mainly based on target groups of persons aged 50 or above[11].

13. Based on local epidemiology, the latest CRCSP participation pattern as well as the latest scientific evidence and overseas practice, CEWG reaffirms the current recommendation on CRC screening age group (i.e. 50-75 years).

Review of evidence on potential use of stool DNA, RNA, "microbial marker" or blood DNA tests for CRC screening

Multitarget stool DNA test (mtsDNA test)

14. The USPSTF includes the mtsDNA test as an acceptable screening modality since 2016. Regarding the accuracy of mtsDNA test for CRC detection, the pooled sensitivity was **0.93** and pooled specificity was **0.84** (Regarding the accuracy of FIT for CRC detection using threshold of 20mcg haemoglobin per gram of stool, the pooled sensitivity was **0.74** and pooled specificity was **0.94**)[16]. The mtsDNA has higher sensitivity but lower specificity for CRC, giving rise to a concern on false-positive results, that is occurrence of positive mtsDNA tests followed by unnecessary colonoscopy examinations. The stool sample for mtsDNA test needs to be delivered to a specific company for analysis and could not be performed in ordinary laboratories. Also, the cost of mtsDNA testing is much higher than that of FIT tests in the US[12].

15. There is also no direct evidence evaluating the effect of mtsDNA test on CRC incidence or mortality reduction[13]. Currently, most overseas national screening programmes and professional organisations still adopt FIT/ colonoscopy as the screening strategy.

16. In recent years, some local and mainland biotechnology companies have developed their own mtsDNA tests for CRC screening. Similar to the overseas mtsDNA test, they reported higher sensitivities and lower specificities than FIT for CRC detection[14,15]. The DNA markers and the algorithm vary among the products and the tests have to be performed and analysed by specific laboratories. Currently, the prices of the local products are also much higher than that of FIT test locally.

Multitarget stool RNA test (mtsRNA test)

17. The mtsRNA test is another modality under development for CRC screening. A phase 3 clinical trial study was conducted in which the participants completed the mtsRNA test, which incorporated FIT with 8 RNA transcripts and participant reported smoking status. The FIT component, the RNA component and smoking status are input in the algorithm to generate results. Regarding the mtsRNA test for CRC detection, the sensitivity was **0.94** and the specificity was **0.88**. The test accuracy was comparable with mtsDNA test and similarly, there remains a concern on implications of false-positive results. The test is still at premarket stage and no information on cost is available. Likewise, the sample should require specific laboratory analysis[16].

18. The mtsRNA platform showed promising results in phase 3 clinical trial. Nonetheless, further studies are required to assess its effectiveness in reducing CRC incidence and mortality.

Stool "microbial marker"

19. The potential role of "microbial marker" for CRC screening had been reviewed in CEWG and it was concluded to keep in view further

evidence on its effectiveness in reducing CRC incidence and mortality.

20. To recap, a systematic review in 2018 suggested use of faecal gut-microbiome for early detection of CRC and several bacteria were reported to differ in abundance between CRC, adenoma cases and healthy controls, with *Fusobacterium* being the most common[17]. Faecal multi-bacterial 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.

21. Local study on novel faecal Lachnoclostridium marker for the non-invasive diagnosis of colorectal adenoma and cancer has been conducted by the Chinese University of Hong Kong (CUHK) published in 2020[18,19]. A new gene marker from a Lachnoclostridium sp., labelled as m3, was identified to be enriched in faecal samples of patients with adenoma by metagenomic analysis. The product involves the combination of m3 with other bacterial markers (Fn, Ch, Bc) and FIT which showed good diagnostic performance for CRC (specificity=81.2% and sensitivity=93.8%).

22. As an update, the CUHK led the team of international experts from Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society of Digestive Endoscopy (APSDE) to develop the recommendations on use of non-invasive biomarkers for diagnosing colorectal neoplasia and published the guideline in British Medical Journal – Gut in April 2023[20]. A systematic review was conducted with analysis of 678 publications and Delphi method involving 16 clinicians was undertaken to develop recommendations of different modalities for detection of CRC and adenoma. Stool microbial markers are sensitive to detect CRC and are superior to tumour based biomarkers for adenomatous polyps. Microbial panel, such as a combination of *Fusobasterium nucleatum*, Lachnoclostridium gene marker (m3) and *Clostridium hathewayi*, has

potential to screen for advanced colorectal neoplasia.

23. The microbial markers combined with FIT has good sensitivity and specificity compared with FIT alone. It may have the potential for wider application in screening in the future. However, there is still no direct evidence on incidence and mortality reduction for microbial markers on screening persons at average risk.

Blood-based DNA test

24. SEPT9 is a tumour suppressor gene and is mutated early in CRC pathway. The detection of plasma methylated SEPT9 (mSEPT9) gene is currently approved by the US FDA for CRC test in selected individuals.

25. Regarding mSEPT9 test for CRC detection, the sensitivity was **0.68** and specificity was **0.80**. The mSEPT9 assay had comparable sensitivity but lower specificity than FIT for CRC[21]. The lower specificity compared with FIT suggests the assay may lead to false positive results and unnecessary colonoscopies. In U.S., the FDA approved the mSEPT9 test only for persons who have declined recommended screening tests, i.e. colonoscopy, sigmoidoscopy and FOBT. Currently, the cost for mSEPT9 test is much higher than that of FIT[22].

26. There is no research showing a morbidity or mortality benefit from the mSEPT9 test. Currently, most overseas national screening programmes and professional organisations still adopt FIT/ colonosocopy as the screening strategy.

Summary

27. In view of the above, the CEWG shall keep in view further evidence and practice on the effectiveness of stool mtsDNA test and

mtsRNA test, stool microbial marker test and plasma methylated SEPT9 test as CRC screening modalities.

28. The CRCSP was deemed effective in reducing CRC incidence rate as well as cost-effective (compared to opportunistic screening) according to the evaluation study conducted by HKU commissioned under HMRF. While the study provided modelling results that suggested lowering the target screening age to 40-70 years might yield superior outcome in terms of life-years and QALY gained, some other epidemiological parameters and programmatic considerations argue in favor of maintaining the current screening age group of 50-75 years. These include (i) higher cost and more number needed to screen by colonoscopy per CRC case/death averted, (ii) no significant increase in the incidence and proportion of CRC in the age group 40-49 years in recent years, (iii) a low proportion (40%) of people aged 50-75 years who had ever screened for CRC, (iv) increased demand for surveillance colonoscopies for adenomas detected and extra healthcare resources needed, and (v) most overseas health authorities do not include people aged 40-49 years as a recommended target group for CRC screening. On balance, it may be more worthwhile focusing efforts to increase participation and adherence to CRC screening among the existing target population rather than to expand the target age range at this juncture.

29. The CEWG **reaffirms** the current recommendation (**Annex 1**) on adopting healthy lifestyles as a primary preventive measure for CRC and advising average risk people aged 50 to 75 to consider FOBT, sigmoidoscopy or colonoscopy for CRC screening. The reaffirmed recommendation was endorsed by the Cancer Coordinating Committee at its 19th meeting on 28 June 2024. The CEWG shall keep in view the local epidemiology of CRC and further evidence and practice on the CRC screening, including amongst others, the recommended ages for screening and DNA testing.

Annex 1

Current CEWG recommendations on CRC screening

For asymptomatic population at average risk	For asymptomatic 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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References

[1] Hong Kong Cancer Registry, Hospital Authority. Colorectal Cancer in 2021. Available from: https://www3.ha.org.hk/cancereg/pdf/factsheet/2021/colorectum_2021.pdf [Accessed 16 November 2023]
[2] Department of Health and Census and Statistics Department, HKSAR. Mortality Statistics, 2022. Available from: https://www.chp.gov.hk/en/healthtopics/content/25/51.html [Accessed 16 November 2023]
[3] The Global Cancer Observatory (GLOBOCAN) 2020. Available from: https://gco.iarc.fr/ [Accessed 16 November 2023]
[4] World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. Available from: https://www.wcrf.org/diet-activity-and-cancer/ [Accessed 16 November 2023]
[5] Australian Government. National Bowel Cancer Screening Program. Available from: https://www.health.gov.au/our-work/national-bowel-cancer-screening-program/about-the-national-bowel-cancer-screening-program [Accessed 16 November 2023]
[6] NHS Bowel Cancer Screening. Available from: https://www.gov.uk/government/publications/bowel-cancer-screening-benefits-and-risks/nhs-bowel-cancer-screening-helping-you-decide [Accessed 16 November 2023]
[7] Screen for Life – National Health Screening Programme (Singapore). Available from: https://www.healthhub.sg/programmes/screen_for_life/sfl-resources#home [Accessed 16 November 2023]
[8] Colorectal Cancer Screening in Canada. Canadian Partnership Against Cancer. Available from: https://www.partnershipagainstcancer.ca/topics/colorectal-cancer-screening-in-canada-2021-2022/programs/guidelines/ [Accessed 16 November 2023]
[9] Barré S, Leleu H, Benamouzig R, Saurin JC, Vimont A, Taleb S, De Bels F. Cost-effectiveness analysis of alternative colon cancer screening strategies in the context of the French national screening program. Therap Adv Gastroenterol. 2020 Sep 20;13:1756284820953364. doi: 10.1177/1756284820953364. PMID: 33014138; PMCID: PMC7509710
[10] Colorectal Cancer Screening Program in the Netherlands. Available from: https://www.rivm.nl/sites/default/files/2020-11/012217-FS-DK-Programme%20Structure%20The%20Netherlands_TG.pdf [Accessed 16 November 2023]
[11] Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2021;325(19):1978–1998. doi:10.1001/jama.2021.4417
[12] Hoffman RM, Levy BT, Allison JE. Rising Use of Multitarget Stool DNA Testing for Colorectal Cancer. JAMA Netw Open. 2021 Sep 1;4(9):e2122328. doi: 10.1001/jamanetworkopen.2021.22328. PMID: 34473264.
[13] Anand S, Liang PS. A Practical Overview of the Stool DNA Test for Colorectal Cancer Screening. Clin Transl Gastroenterol. 2022 Apr 1;13(4):e00464. doi: 10.14309/ctg.0000000000000464. PMID: 35383606; PMCID: PMC9038502.
[14] Xu H, Chen H, Hu J, Xiong Z, Li D, Wang S, Yu J. Feasibility of quantification based on novel evaluation with stool DNA and fecal immunochemical test for colorectal cancer detection. BMC Gastroenterol. 2022 Aug 13;22(1):384. doi: 10.1186/s12876-022-02470-z. PMID: 35963995; PMCID: PMC9375944.
[15] Prenetics Launches ColoClear, a Non-Invasive Stool DNA Test to Detect Early Signs of Colorectal Cancer in Hong Kong. Available from: https://ir.prenetics.com/news-releases/news-release-details/prenetics-launches-coloclear-non-invasive-stool-dna-test-detect. [Accessed 16 November 2023]
[16] Barnell EK, Wurtzler EM, La Rocca J, Fitzgerald T, Petrone J, Hao Y, Kang Y, Holmes FL, Lieberman DA. Multitarget Stool RNA Test for Colorectal Cancer Screening. JAMA. 2023 Oct 23:e2322231. doi: 10.1001/jama.2023.22231. Epub ahead of print. PMID: 37870871; PMCID: PMC10594178.
[17] Amitay EL, Krilaviciute A, Brenner H. Systematic review: Gut microbiota in fecal samples and detection of colorectal neoplasms. Gut Microbes. 2018 Jul 4;9(4):293-307. doi: 10.1080/19490976.2018.1445957. Epub 2018 May 15. PMID: 29543545; PMCID: PMC6219654.
[18] Liang JQ, Li T, Nakatsu G, Chen YX, Yau TO, Chu E, Wong S, Szeto CH, Ng SC, Chan FKL, Fang JY, Sung JJY, Yu J. A novel faecal Lachnoclostridium marker for the non-invasive diagnosis of colorectal adenoma and cancer. Gut. 2020 Jul;69(7):1248-1257. doi: 10.1136/gutjnl-2019-318532. Epub 2019 Nov 27. PMID: 31776231; PMCID: PMC7306980.

[19] CUHK Develops a Novel Faecal Test that can Detect Polyps and Early Colon Cancers with Sensitivity Over 90%. Press release, 28 July 2021. Available from: https://www.med.cuhk.edu.hk/press-releases/cuhk-develops-a-novel-faecal-test-that-can-detect-polyps-and-early-colon-cancers-with-sensitivity-over-90. [Accessed 16 November 2023]

[20] Chan FKL, Wong MCS, Chan AT, East JE, Chiu HM, Makharia GK, Weller D, Ooi CJ, Limsrivilai J, Saito Y, Hang DV, Emery JD, Makmun D, Wu K, Ali RAR, Ng SC. Joint Asian Pacific Association of Gastroenterology (APAGE)-Asian Pacific Society of Digestive Endoscopy (APSDE) clinical practice guidelines on the use of non-invasive biomarkers for diagnosis of colorectal neoplasia. Gut. 2023 Jul;72(7):1240-1254. doi: 10.1136/gutjnl-2023-329429. Epub 2023 Apr 5. PMID: 37019620; PMCID: PMC10314015.

[21] Shaukat, A., Levin, T.R. Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol* **19**, 521–531 (2022). https://doi.org/10.1038/s41575-022-00612-y

[22] Lin KW. mSEPT9 (Epi proColon) Blood Test for Colorectal Cancer Screening. Am Fam Physician. 2019 Jul 1;100(1):10-11. PMID: 31259500.