Asia Pacific consensus recommendations for colorectal cancer screening

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ABSTRACT

Colorectal cancer (CRC) is rapidly increasing in Asia, but screening guidelines are lacking. Through reviewing the literature and regional data, and using the modified Delphi process, the Asia Pacific Working Group on Colorectal Cancer and international experts launch consensus recommendations aiming to improve the awareness of healthcare providers of the changing epidemiology and screening tests available. The incidence, anatomical distribution and mortality of CRC among Asian populations are not different compared with Western countries. There is a trend of proximal migration of colonic polyps. Flat or depressed lesions are not uncommon. Screening for CRC should be started at the age of 50 years. Male gender, smoking, obesity and family history are risk factors for colorectal neoplasia. Faecal occult blood test (FOBT, guaiac-based and immunochemical tests), flexible sigmoidoscopy and colonoscopy are recommended for CRC screening. Double-contrast barium enema and CT colonography are not preferred. In resource-limited countries, FOBT is the first choice for CRC screening. Polyps 5–9 mm in diameter should be removed endoscopically and, following a negative colonoscopy, a repeat examination should be performed in 10 years. Screening for CRC should be a national health priority in most Asian countries. Studies on barriers to CRC screening, education for the public and engagement of primary care physicians should be undertaken. There is no consensus on whether nurses should be trained to perform endoscopic procedures for screening of colorectal neoplasia.

Colorectal cancer (CRC) is one of the most common cancers in Asia and its incidence is rising in a number of Asian countries, yet there are no national or regional guidelines on prevention and screening for early diagnosis of this important disease. The Asia Pacific Working Group on Colorectal Cancer was established in 2004. The group has since conducted several studies and accumulated/published local data on neoplasm of the colon. In 2007, the Working Group members felt that it was time to review regional data on CRC and colorectal neoplasia in Asia in order to draft guidelines and recommendations in the screening and prevention of CRC in Asia.

The aim of this Consensus Conference was to draw up recommendations for CRC screening suitable for Asia.

METHOD

Membership of the consensus group

Members of the Consensus Group were selected using the following criteria: (1) demonstrated knowledge/expertise in CRC by publication/research or participation in national or regional guidelines; (2) geographical representation of the Asia Pacific countries/region; (3) diversity of views and expertise in the healthcare system (including primary care doctor, surgeon, pathologist, health economist, epidemiologist, public health expert, nurse specialists); and (4) stakeholders representing different interest groups (including healthcare policy makers, representatives from patient groups and non-government organisations). Besides members from the Asia Pacific Working Group on Colorectal Cancer, the American Cancer Society (represented by D Brooks) and the Prevent Cancer Foundation of the United States (represented by C Aldige) as well as the International Digestive Cancer Alliance and OMED (represented by G Young) were invited to participate in this conference as overseas experts. D A Lieberman was invited on his personal capacity as an advisor in this conference. The voting members are listed in Appendix A.

Literature search

Comprehensive literature reviews were carried out by the Steering Committee on a number of topics, namely (1) epidemiology of CRC in Asia; (2) colorectal polyps; (3) methods for CRC screening; (4) risk stratification; and (5) policy in CRC screening. We identified relevant articles published in English using MEDLINE, EMBASE and the Cochrane Trials Register in human subjects from 1990 to 2007. National and international guidelines on CRC screening were solicited. Searches on meeting abstracts (Asia Pacific Digestive Week (APDW), American College of Gastroenterology (ACG), American Gastroenterological Association (AGA), American Society of Gastrointestinal Endoscopy (ASGE), British Society of Gastroenterology (BSG), United European Gastroenterology Week (UEGW)) and review articles were limited to the preceding 5 years. The panel members received a copy of the relevant articles before the first iteration. The reviews were presented at the Consensus Conference before the second iteration.

Modified Delphi process

The modified Delphi process was adopted to develop the consensus.[1] The Delphi process is a method for developing consensus using a combination of the principles of evidence-based medicine and anonymous voting. After a systematic literature review, change of views from the Consensus Panel was encouraged. The process was completed by grading of evidence and anonymous voting on a series of iterations of the statements. The Steering Committee (JJYS, JYWL and FKLC) drafted a list of statements and circulated it electronically in advance to panel members. After reading the reviews, each member rated the statements on a Likert scale anchored by 1–5 (1, accept completely; 2, accept with some reservation; 3, accept with major reservation; 4, reject with reservation; 5, reject completely). All votes are anonymous. The first vote was conducted for the entire Consensus Group electronically by e-mail, without explanation or justification of the statement. Feedback of the statements was collated. The results and comments were returned to the Steering Committee before the meeting. Consensus was considered to be achieved when ≥80% of the voting members indicated ''Accept completely'' or ''Accept with some reservation''. A statement was refuted when ≥80% of the voting members indicated ''Reject completely'' or ''Reject with reservation''.

A face-to-face meeting of the entire group was held on 15–16 September 2007 to review the evidence of statements that reached consensus and discuss those statements that did not reach consensus on the first iteration. A series of didactic lectures presented by members reviewed the literature on five topics in colorectal neoplasia, namely (1) Epidemiology of CRC in Asia; (2) Colorectal polyps; (3) Methods for CRC screening; (4) Risk stratification; and (5) Policy in CRC screening. The statements were discussed and debated based on feedback from the first vote. The second vote was held at the end of the talks, using electronic keypads to ensure anonymity.

For statements on which consensus could not be reached, further discussions were conducted. Statements were revised accordingly. Then, the third and last vote was taken electronically using the keypads. Each statement was graded to indicate the level of evidence available and the strength of recommendation by the whole group (table 1).

Funding sources

Some ethnic groups (eg, Japanese, Korean and Chinese) in Asia are more susceptible than others to CRC.

RESULTS

A 2-day Consensus Conference was held on 15–16 September 2007 under the auspices of the Asia Pacific Society of Digestive Endoscopy. Representatives from 14 Asian-Pacific countries/regions participated in the meeting: these included Australia, Brunei, China, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam. A total of 25 statements were presented for the first vote. Fifty members participated in the voting.

EPIDEMIOLOGY OF COLORECTAL NEOPLASIA

Statement 1. Colorectal cancer is one of the most common cancers in Asia in both males and females

Level of agreement: a, 90%; b, 10%; c, 0%; d, 0%; e, 0%

Quality of evidence: II-3

Classification of recommendation: A

Reports from the World Health Organization (WHO) data set[2] and individual countries or cities in Asia show that the incidence of CRC is on a rapidly rising trend in regions within countries such as China, Japan, Korea and Singapore.[3–9] The increase in number of new cases of CRC per year is witnessed in both men and women. However, not all countries in Asia witness the same degree of rise in incidence of CRC. For example, in East Asian countries such as Indonesia, Thailand, Vietnam and India, CRC is not the top cancer in either males or females. The group also recognised that there is a lack of adequate cancer registries in many Asian countries. Without such reliable figures, some reservations remain in certain countries in indicating an epidemic of CRC in the Asia Pacific Region.

Statement 2. The incidence of CRC is similar to that of the West

Level of agreement: a, 37%; b, 47%; c, 14%; d, 2%; e, 0%

Quality of evidence: II-3

Classification of recommendation: B

The group considered that in high incidence countries such as Japan, Korea, Singapore and Hong Kong, the incidence of CRC is comparable with or approaching that of Western countries.[10] Direct comparison figures are available from a study comparing Japanese with the white population of the USA which showed that the rates of CRC of these two populations were very similar.[11] However, such direct comparison studies are few. In other countries such as India, Philippines and Vietnam, there is still a gap in the incidence of CRC between these countries and the West. There is a strong feeling that countries with an obviously rising CRC incidence are more ''Westernised'' in lifestyle, especially in dietary habit, with increased consumption of high fat and protein but less fibre in the diet. The change is more evident in urban cities than in rural areas of the same country.[7] Yet, the effects of lifestyle and dietary habit modification on the changing epidemiology of CRC in Asia need to be more adequately studied to confirm this impression.

Statement 3. The incidence of advanced neoplasm in symptomatic and asymptomatic Asians is comparable with the West

Level of agreement: a 37%; b, 43%; c, 16%; d, 4%; e, 0%

Quality of evidence: II-2

Classification of recommendation: B

Advanced neoplasia is defined as adenoma with a diameter of ≥10 mm, a villous adenoma (ie, at least 25% villous), an adenoma with high grade dysplasia or invasive cancer. There are a few studies in Asian populations investigating the incidence of advanced neoplasm in asymptomatic individuals in the Asia Pacific region. A study in Hong Kong which recruited asymptomatic subjects in a Chinese population showed that 4.4% had advanced neoplasia.[12] Similar figures have been reported in a screening colonoscopy study in asymptomatic subjects among Koreans (4.1%)[13] and Chinese (3.0%).[14] Two studies that involved multiple centres in Asia that studied

Table 1 Quality of evidence, classification of recommendation and voting on recommendation

Category and grade	Description
Quality of evidence	
I	Evidence obtained from at least 1 RCT
II-1	Evidence obtained from well-designed control trials without randomisation
II-2	Evidence obtained from well-designed cohort or case–control study
II-3	Evidence obtained from comparison between time or places with or without intervention
III	Opinion of respected authorities, based on clinical experience and expert committees
Classification of recommendation	
A	There is good evidence to support the statement
B	There is fair evidence to support the statement
C	There is poor evidence to support the statement but recommendation made on other grounds
D	There is fair evidence to refute the statement
E	There is good evidence to refute the statement
Voting on recommendation*	
a	Accept completely
b	Accept with some reservation
c	Accept with major reservation
d	Reject with reservation
e	Reject completely

*Statements for which >80% of participants voted a, b or c were accepted.
RCT, randomised controlled trial.

symptomatic and asymptomatic populations have reported the incidence of advanced neoplasm as 7.8%[15] and 4.5%, respectively.[16] These figures are comparable with the larger Western series using colonoscopy as a screening tool for colorectal neoplasm.[17–20] Depending on the method of recruitment, studies enrolling asymptomatic individuals for screening may introduce selection bias by recruiting more health-conscious subjects and hence underestimate the true prevalence of the conditions. This phenomenon may occur in studies from both the East and the West.

Statement 4. While the death rate of CRC is declining in the West, Asia continues to see rising mortality

Level of agreement: a, 78%; b, 20%; c, 0%; d, 2%; e, 0%
   Quality of evidence: III
   Classification of recommendation: C

Reports from the American Cancer Society in 2007 showed that the number of Americans who died of cancer has dropped for a second consecutive year[21] and it was probably caused by "a combination of factors including a decrease in cigarette smoking among men, wider screening for colon cancer…"[22] "By far the greatest decrease in mortality has been in colorectal cancer".[23] A similar decline in CRC mortality has been reported in Europe.[24] On the contrary, according to the WHO mortality database, CRC mortality has doubled in both men and women over the last three decades in Taiwan.[25] In Korea, the National Cancer Center reported a decline in mortality from stomach and liver cancer but an increase in CRC.[26] In China, the National Census Data also demonstrated a decline in mortality related to cancer of the oesophagus, and gastric and liver cancer, but the age-adjusted mortality from CRC has increased in both urban and rural men.[27]

Statement 5. There are some ethnic groups (eg, Japanese, Korean and Chinese) in Asia who are more susceptible to CRC

Level of agreement: a, 49%; b, 43%; c, 6%; d, 0%; e, 2%
   Quality of evidence: II-c
   Classification of recommendation: B

Existing evidence suggests that there are some ethnic difference in susceptibility to CRC. In Singapore, the incidence of CRC is significantly lower among Indians and Malays than among Chinese.[28 29] In Malaysia, the same phenomenon has been reported in a population of mixed ethnic cultures.[30] In the multinational studies conducted by the Asia Pacific Working Group on CRC, Japanese, Korean and Chinese were found to have a higher risk of advanced neoplasia in the colon.[15 16] If advanced neoplasia is considered a premalignant condition, these results will infer that the incidence of CRC is higher in these ethnic groups than in the others (eg, Indians, Thais and Filipinos). The higher incidence among Chinese and the lower incidence among Indians living in the same country mirror the incidence rates in their countries of origin even though both racial groups migrated more than three generations ago. These observations on racial differences suggest that genetic factors have an important aetiological role in CRC development, although differences in dietary habit and lifestyle might also contribute. An interesting study from Israel showed that Arabs born in Israel had a much lower CRC incidence than Israeli-born Jews, and this trend persisted over time.[31] This observation again supports the notion of genetic influence on CRC development. However, the fact that the incidence of CRC among Jews rose concomitantly with Westernisation of their lifestyle hints that environmental influences cannot be neglected.

COLORECTAL POLYPS
Statement 6. Distribution of polyps between Asians and Caucasians is similar

Level of agreement: a, 22%; b, 61%; c, 8%; d, 8%; e, 2%
   Quality of evidence: II-2
   Classification of recommendation: B

There are very few direct comparisons of the incidence of CRC or polyps between Asian and Caucasian populations. A study comparing Chinese in Taiwan versus Caucasians in Seattle suggested that Asians are more likely to have distally located colorectal neoplasia.[32] However, the distribution of advanced neoplasia (including advanced adenoma and invasive cancer) is not significantly different between the two studied populations. Comparing three studies from Caucasian populations[17–19] with four studies from Asian populations[12 14 16 33] and one from Australia,[34] there are more distally located polyps in the Asia Pacific studies. In Asia, 30% of polyps are proximal, 57% are distal and 13% are synchronous. In the West, 49% of polyps are proximal, 49% are distal and 2% are synchronous. However, the distribution of advanced neoplasia is not significantly different between the East[12 13 16 34] and the West.[17 18 35] The proximal, distal and synchronous advanced neoplasias are 29%, 52% and 19% in Asia, and 35%, 59% and 6% in the USA (table 2). Studies from Asia showed that 53–68% of proximal advanced neoplasias were found in patients without a distal lesion. This figure is also comparable with that reported in the West. The similar distribution of colorectal polyps implies that arguments used to recommend full colonoscopy instead of flexible sigmoidoscopy in CRC screening can be applied in Asia. However, it is worth pointing out that there are some variations in the definitions of distal colonic disease in the literature. Some use findings in the last 40 cm from the anal verge on

Table 2 Distribution of advanced colorectal neoplasm (ACRN) reported in studies in Asian vs Caucasian populations

		Male (%)	Mean age (years)	ACRN Total (%)	Proximal (%)	Distal (%)	Both (%)
Byeon[16]	Multicentre	860 (54.8)	54.4	39 (4.5)	17 (43.6)	19 (48.7)	3 (7.7)
Chiu[14]	Taiwan, China	1708 (59.8)	52.5	51 (3.0)	10 (19.6)	32 (62.7)	9 (17.6)
Liu[33]	Taiwan, China	5973 (52.3)	56.6	199 (3.3)	56 (28.1)	95 (47.7)	48 (24.1)
Sung[12]	Hong Kong	505 (44.4)	56.5	63 (12.5)	18 (28.6)	37 (58.7)	8 (12.7)
Distribution in Asian studies					19.6–43.6	47.7–62.7	7.7–24.1
Imperiale[18]	USA	1994 (58.9)	59.8	–	50 (45.0)	61 (55.0)	–
Lieberman[17]	USA	3121 (96.8)	62.9	329 (10.5%)	101 (30.7)	201 (61.1)	27 (8.2)
Imperiale[35]	USA	906 (61)	44.8	32 (3.5%)	14 (43.8)	17 (53.1)	1 (3.1)
Distribution of ACRN in Caucasian studies					23.7–45.0	53.1–64.1	3.1–12.2

withdrawal of the colonoscope[12] and others define distal lesions as findings beyond the splenic flexure,[17] or lesions in the descending colon, sigmoid colon and rectum.[14] These discrepant definitions of distal colon limit the interpretation of adenoma distributions reported in the literature.

Statement 7. There is a trend towards proximal migration of polyps in the colon in Asian subjects

Level of agreement: a, 41%; b, 39%; c, 18%; d, 2%; e, 0%

   Quality of evidence: III

   Classification of recommendation: C

Data from the Japan Society for Cancer of the Colon and Rectum from 1974 to 1994 reviewed a right shift of CRC within a period of two decades.[36] The increase in the percentage of right-sided CRC was accompanied by a continuous decline in the percentage of rectal cancer in both males and females in all age groups. A single-centre retrospective cohort study in Hong Kong showed that in the last 10 years there has been an age-adjusted increasing trend of colorectal polyps in the right colon and a decrease in incidence in the left colon.[10] However, this study was limited by its retrospective nature and by not representing a predefined population. In Australia, a study reviewed endoscopy reports on 2578 subjects and found that 51% of polyps are right-sided, 20% are left-sided and 29% are synchronous.[34] The incidence of right-sided adenoma increases with age, and hence evaluation of the proximal bowel is particularly important in older people. In Japan, a cohort study enrolling 23 444 consecutive asymptomatic subjects suggested that the right shift is a phenomenon resulting from ageing.[37] The Japan Polyp Study also reported that more than half of the advanced neoplasias are in the right colon.[38] A contradictory finding was reported from Singapore.[39] This study showed that, from 1968 to 1992, the age-standardised rate of cancer in the distal colon was doubled in the right colon (2–3% annually) but more than doubled in the distal colon (3–4% annually). The incidence of rectal cancer was stable in Singapore. A similar observation was reported in Malaysia.[40] The wider accessibility of screening colonoscopy in some Asian countries together with the ageing population would at least partly account for the apparent increase in proximal CRC. Further studies with a long timeline will be needed to substantiate this change in epidemiology.

Statement 8. Non-polypoid adenoma is not uncommon among Asians

Level of agreement: a, 82%; b, 16%; c, 0%; d, 0%; e, 2%

   Quality of evidence: II-2

   Classification of recommendation: A

Flat and depressed lesions were first reported by Muto.[41] In Japan, it has been reported that the prevalence of flat depressed and flat elevated lesions constituted around 3% and 18% of neoplastic lesions found on colonoscopy.[42] Submucosal invasion was found much more commonly in flat depressed lesions compared with elevated lesions. Kudo reported that around 1.8–2.3% of colonic neoplasias are depressed lesions.[43] In Japan, de novo cancers—that is, cancers not arising from pre-existing adenomas, are believed to develop from these non-polypoid lesions. It has been estimated that 18.6% of CRC in men and 27.4% of CRC in women are so-called de novo cancers in Japan.[44] Over 80% of de novo cancers were invasive cancers. With the increasing awareness of these lesions, the increasing use of chromoendoscopy and new endoscopic imaging technology, there are increasing reports of flat lesions. In Singapore, 91 flat lesions were found in a cohort of 491 236 patients without using chromoendoscopy or magnifying colonoscopy.[45] In Korea, 18 flat adenomas were identified using chromoendoscopy (indigocarmine) which would have been missed by conventional colonoscopy.[46] In Malaysia, 29 adenomas were identified in 12 patients, of which 14 were flat.[47] The flat adenomas found in this study were <5 mm in size. Despite the advancement in endoscopy imaging technology, the detection of non-polypoid adenoma and de novo cancer remains a challenge. However, the necessity of discovering these small lesions is yet to be determined. Small, polypoid adenomas without villous structure or high grade dysplasia are not associated with an increased risk for CRC. Whether small flat adenomas are of greater significance remains to be determined with certainty.

Statement 9. Certain types of hyperplastic polyps are associated with an increased risk of cancer

Level of agreement: a, 80%; b, 20%; c, 0%; d, 0%; e, 0%

   Quality of evidence: II-3

   Classification of recommendation: A

It is well known that hyperplastic polyposis syndrome is associated with an increased potential for developing into CRC whereas a typical small and distal hyperplastic polyp (with no dysplasia) has little malignant potential. However, subsets of hyperplastic polyps are now being described and the terminology is evolving. The ability to distinguish between hyperplastic polyp, admixed hyperplastic polyp/adenoma and serrated adenoma (a form of hyperplastic polyp with propensity for progression but without distinctive cytological dysplasia) is debated among pathologists. While the majority of CRCs develop through the adenoma–carcinoma sequence with APC, K-Ras, DCC and p53 mutations, it is now clear that an admixed hyperplastic polyp or serrated adenoma may have an alternative pathway for CRC carcinogenesis. Hyperplastic polyps

associated with CRC may be associated with MLH-1 protein, MSI and MLH1 promoter methylation.[48] BRAF mutation and aberrant promoter methylation leading to microsatellite instability and methylation instability are common in serrated adenoma and admixed polyps.[49 50] A large, right-sided, sessile hyperplastic polyp with certain architectural features (eg, branching of crypts, dilation of base of crypts, horizontal extension of crypts, etc.) should be completely removed and carefully monitored.

Statement 10. Polyps 5–9 mm in size should be removed
Level of agreement: a, 75%; b, 20%; c, 2%; d, 3%; e, 0%
   Quality of evidence: III
   Classification of recommendation: C

Reports from the early 1990s showed that screening sigmoidoscopy and removal of the polyp reduced CRC mortality.[51 52] The National Polyp Study which included patients from the USA and the UK,[53] and the Italian Multicenter Study[54] provided the strongest evidence that removal of polyps reduced the risk of subsequent CRC. Recently, long-term follow-up figures from the National Polyp Study showed a reduction in mortality after polyps were removed during screening colonoscopy.[55] The Japan Polyp Study Group conducted a retrospective study of a cohort of 5309 subjects who underwent colonoscopy from 1990 to 1995 and followed-up for >3 years. In this period, polyps larger than 6 mm were removed.[56] The cumulative hazard of developing malignant disease for those who had a polyp <5 mm was comparable with that for those who had no polyp found on index colonoscopy. On the other hand, those with polyps measuring 6–9 mm have a cumulative hazard of developing invasive cancer comparable with those with intramucosal cancer.[38] These are important data from Asia which lend support to the removal of polyps 5–9 mm in size. The Japan Polyp Study Group is now conducting a study randomising polypectomised patients to be followed either at 3 years, or at 1 year and then 3 years to study the outcome of such surveillance intervals in the context of finding new colonic lesions.

SCREENING TESTS FOR COLORECTAL NEOPLASIA
Statement 11. Faecal occult blood test (FOBT; guaiac-based and immunochemical tests), flexible sigmoidoscopy and colonoscopy should be recommended for CRC screening
Level of agreement: a, 74%; b, 18%; c, 6%; d, 2%; e, 0%
   Quality of evidence: I
   Classification of recommendation: A

FOBT, flexible sigmoidoscopy and colonoscopy are recommended options for CRC screening in national guidelines from the USA, the UK and Canada.[57–60] Annual or biennial screening with FOBT using a guaiac-based test or an immunochemical test has been shown to reduce both CRC and CRC-related mortality compared with no screening.[61 62] Although the sensitivity of a single FOBT is low, in the range of 30–50%, repeated annual testing can detect as many as 92% of CRCs. It is perceived that FOBT is a "cancer test" instead of a test for polyps or adenoma. The advantage is that FOBT can be done at home and is non-invasive, but the test needs to be repeated every 1–2 years. Rehydration of the stool sample is not recommended. Although rehydration of the guaiac-based test increases sensitivity, the false-positive rate is also raised, leading to unnecessary anxiety and unnecessary performance of invasive tests. An immunochemical test may obviate the need for dietary restriction.[63 64] Recently, faecal immunochemical

tests for haemoglobin have been shown to be more sensitive than the guaiac test for cancer and adenomas especially in Asian subjects, probably due to lack of dietary interference.[65 66]

Flexible sigmoidoscopy performed every 5 years has been shown in case-controlled studies to reduce mortality from CRC.[51 52] The preliminary findings of a randomised controlled trial of screening flexible sigmoidoscopy have been reported, but the result in terms of effectiveness on an intention-to-screen basis at the population level is not yet available.[67] The recommendation of a 5 year interval was based on a cohort study which showed that 5 years after a negative colonoscopy, new advanced neoplasias are rare.[68] The sensitivity of flexible sigmoidoscopy in detecting advanced neoplasia is reported to be 35–70% and reduced the cancer risk in the rectum and sigmoid by 50–60%.[17–19 69] The recommended interval of screening is shorter than for colonoscopy because flexible sigmoidoscopy is less sensitive than colonoscopy even in the distal colon. This is because of the quality of bowel preparation, the varied experience of the examiners and the discomfort, which leads to colonic spasm which may affect the depth of sigmoidoscope insertion and hence the adequacy of the examination. Since up to two-thirds of proximal advanced lesions in Asians are found in the absence of distal lesions, the disadvantage of creating a false sense of security using flexible sigmoidoscopy for screening is noted.

The use of colonoscopy for screening is not supported by a randomised controlled study but by indirect evidence. The National Polyp Study has demonstrated a reduced incidence of CRC[53] and recently a reduced mortality from CRC among those who underwent colonoscopy.[55] Colonoscopy is the only modality that allows removal of the adenoma and prevents CRC. A similar study in Europe has confirmed the benefit of the screening procedure.[54] The effectiveness of colonoscopy is dependent on the quality of the examination (see below).

Statement 12. Double-contrast barium enema (DCBE) is not a preferred CRC screening test
Level of recommendation: a, 78%; b, 20%; c, 0%; d, 2%; e, 0%
   Quality of evidence: III
   Classification of recommendation: C

DCBE every 5 years is listed as one of the options in CRC screening in national guidelines in North America. Like colonoscopy, there is no randomised trial evaluating whether screening DCBE reduces the incidence or mortality of CRC in the average-risk population, and there has been no actual report using barium enema in a true screening environment. The sensitivity of DCBE is lower than that of colonoscopy and it does not permit removal of polyps or biopsy of cancers. In a study comparing DCBE and colonoscopy, the sensitivity of DCBE for lesions >10 mm was 48% and for lesions of 6–9 mm it was 35%.[70] In the National Polyp Study, DCBE detected only 53% of adenomatous polyps 6–10 mm in size and 48% of those >10 mm in size compared with colonoscopy.[71] Because of its lower sensitivity, even for large polyps, the Consensus Group does not recommend DCBE as a first-line option for CRC screening.

Statement 13. CT colonography is not currently a preferred CRC screening test
Level of recommendation: a, 90%; b, 8%; c, 0%; d, 2%; e, 0%
   Quality of evidence: III
   Classification of recommendation: C

Unlike DCBE, there is increasing evidence to suggest that CT colonography is an accurate screening method for the detection of colorectal neoplasia in asymptomatic average-risk adults.[72 73] The sensitivity and specificity of the findings are also dependent on the size of the polyps. Meta-analysis showed that sensitivity is around 85% for polyps >9 mm, 70% for polyps 6–9 mm, and 50% for polyps <6 mm.[74 75] Studies have also shown that large size (≥10 mm in size) is the best prediction of advanced neoplasia.[76] According to this study, high grade dysplasia and invasive cancer is very uncommon in medium sized (6–9 mm) lesions, which justifies the use of size alone as a surrogate measure for predicting advanced histological features. Since it is not clear whether small polyps should be removed by polypectomy, some radiologists recommended that polyps <5 mm in size should not be reported. Patients with polyps of 6–9 mm should have repeat CT at 1–2 yearly intervals.[77] Patients with polyps that are 6–9 mm can have a repeat CT colonography in 3 years, and polyps <6 mm need not be reported. In the literature, however, there is a discrepancy in the results of CT colonography as a result of a difference in CT collimation width, type of scanner and mode of imaging. The use of a multidetector scanner equipped with 3-D flythrough views that simulate colonoscopy may increase the sensitivity of CT colonography. While in the expert centre, a randomised trial of CT colonography compares favourably with conventional colonoscopy,[71] the results in non-expert centres are less promising.[78] Furthermore, acceptability in a true screening population has not been fully explored. High cost, risk associated with radiation and requirement for bowel preparation are the other factors hindering the use of CT colonography as a primary screening method at this stage. In view of the inaccessibility of cutting-edge imaging technology in some Asian countries, the Consensus Group does not recommend CT colonography as a CRC screening tool at this stage. However, the group believes that with increased accessibility, CT colonography may become a recommended tool for CRC screening in the future.

Statement 14. In resource-limited countries, FOBT is the first choice for CRC screening

Level of recommendation: a, 72%; b, 18%; c, 6%; d , 4%; e, 0%
> Quality of evidence: I
> Classification of recommendation: C

FOBTs are used in screening to refine the likelihood of cancer being present and so direct scarce colonoscopy resources to those more likely to have neoplasia.[79] A large-scale case–control study in Japan using immunochemical FOBT has shown a decrease in CRC mortality by 70%.[80] This benefit was witnessed in both men and women in the cohort. Although the overall rate of incidence of CRC has not been significantly reduced, a reduction in advanced CRC was reported. A study from Australia showed that CRC screening by FOBT is cost-effective and comparable with other cancer screening programmes.[81] More cost-effectiveness studies need to be done in Asia. Despite the fact that FOBTs (guaiac or immunochemical tests) are not diagnostically precise, many Western countries consider that they are the best approach to population screening because of their simplicity and high acceptance by asymptomatic subjects even in countries with a well-developed healthcare system. Clearly, in resource-limited countries in Asia, in order to have a population impact, FOBT is the most affordable test.

Statement 15. Following a negative colonoscopy, a repeat examination should be performed in 10 years

Level of recommendation: a, 27%; b, 53%; c, 8%; d, 12%; e, 0%
> Quality of evidence: II-3
> Classification of recommendation: C

The choice of a 10-year interval between screening examinations for average-risk subjects after a negative colonoscopy is based on estimates of the sensitivity of colonoscopy and the rate at which advanced neoplasia develops.[53 82] Colonoscopy is not perfect and it can still miss colorectal adenoma or even cancer. The rate of new or missed CRC within 3 years after colonoscopy has been reported as around 5% in the proximal colon and around 2% in the distal colon.[83] The chance of missing a diagnosis is higher in older subjects, those with diverticular disease, right-sided or transverse lesions, suboptimal bowel preparation and when colonoscopy is performed by internists or family doctors in their office. A large series of colonoscopy screening showed that 0.3–0.9% of CRC can be missed.[84–86] These so-called interval cancers after colonoscopy could be due to genuinely new and fast growing lesions,[87] incomplete removal of polyps[85] or missed lesions. Withdrawal time during colonoscopy is found to correlate with adenoma detection during screening colonoscopy.[88 89] In essence, the impact and success of colonoscopy screening depend on the quality of the procedure. The potential benefit and risk of screening change in elderly patients of different life expectancies and the age for stopping screening should be considered.[90] Even though the prevalence of neoplasia increases with age, screening in elderly persons >80 years of age results in only a modest gain in life expectancy and thus may not be desirable.[91]

RISK STRATIFICATION IN CRC SCREENING

Statement 16. The age-adjusted incidence of CRC is higher in men than in women

Level of agreement: a, 82%; b, 16%; c, 0%; d, 0%; e, 2%
> Quality of evidence: II-2
> Classification of recommendation: A

In many Asian countries, the age-adjusted incidence of CRC is found to be higher in men than in women.[3–10] While the exact mechanism of the hormonal effect on colorectal neoplasia is still unclear, in a prospective Japanese study pregnancy was found to be associated with reduced risk of CRC in women.[92] It is postulated that female sex hormones reduce the risk of CRC. Indeed, this observation was also reported in the VA Cooperative Study 380 and suggested that women may start screening at a later age because of their relatively low incidence of colorectal neoplasia at the age of 50–55 years.[19] The fact that the age-adjusted incidence in CRC is lower in women, however, does not imply that screening is less effective in women. In a large population-based Japanese cohort study using FOBT-selected cases for colonoscopy screening, mortality reduction was achieved in both men and women.[80]

Statement 17. CRC screening should begin at the age of 50

Level of agreement: a, 35%; b, 57%; c, 6%; d, 2%; e, 0%
> Quality of evidence: II-2
> Classification of recommendation: B

The prevalence of colorectal neoplasia increases with age. As the risk of CRC starts to escalate at the age of 50 years, most national guidelines recommend that screening programmes should begin by this age.[57–60] Screening colonoscopy studies in Asia also confirm that at the age of 50 the risk of finding advanced neoplasia is significantly increased from around 1% to

>3%.[12–15] Therefore, the Consensus Group showed strong support for starting CRC screening at the age of 50 years. From the large population-based cohort study in Japan using FOBT for CRC screening, the best age to start screening was 50–59 years.[78] The group also noted that in each age group, however, other factors such as gender, family history and race may affect the outcome of CRC screening. Since Asia represents a very heterogeneous population, it is desirable to have a formula stratifying the risk according to age, gender, race and family history to select those who have the highest CRC risk for priority in a screening programme. A risk stratification strategy using colonoscopy and CT colonography has been described in the West.[93 94] This would be a very useful way of making the best use of limited resources in many Asian countries. A two-tier approach has been proposed in Taiwan, which may reduce the workload on colonoscopy without jeopardising the efficacy of screening.[95] This kind of study would need further validation.

Statement 18. First-degree relatives of patients with CRC are at an increased risk and thus should receive screening earlier

Level of agreement: a, 78%; b, 20%; c, 0%; d, 2%; e, 0%

  Quality of evidence: III

  Classification of recommendation: C

A prospective study showed that among first-degree relatives of CRC patients, the age-adjusted risk of CRC was 1.72.[96] With two or more first-degree relatives, the risk is further escalated. For those under the age of 45 who had one or more affected first-degree relatives, the relative risk was increased by more than fivefold. Colonoscopy screening in first-degree relatives of patients with sporadic CRC has been demonstrated to yield a higher rate of finding colorectal neoplasia.[97] The odds ratios (ORs) reported were 1.5 for adenoma, 2.5 for large adenoma and 2.6 for high risk adenoma. A study from Italy also showed that compared with subjects with no family history, asymptomatic patients with one first-degree relative with CRC had nearly double the risk of developing adenomatous polyps.[98] A meta-analysis of pooled data from 27 case–control studies indicates that the first-degree relatives of a patient with CRC have an increased risk of colon cancer of 2.42 and of rectal cancer of 1.89.[99] This applies to both parents and siblings suffering from the disease. This phenomenon is also observed in a study from Taiwan in which 234 immediate family members of 186 CRC patients were screened.[100] The immediate family members were at increased risk for advanced neoplasia, with an OR of 4.5. Individuals with index cancer relatives diagnosed at <50 years or male relatives were found to have an even higher risk of advanced neoplasia.

Statement 19. Smoking increases the risk of CRC

Level of agreement: a, 51%; b, 31%; c, 12%; d, 4%; e, 2%

  Quality of evidence: II-2

  Classification of recommendation: B

There are studies in Asia, especially in Japan, China and Singapore, investigating the effects of cigarette smoking and the risk of CRC. A case–control study in Japan showed smoking in the past 10 years is significantly associated with risk of sigmoid and rectal adenoma.[101] A larger and more recent study from Japan confirms the association of smoking and CRC.[102] The effect of smoking has been observed to be related to the number of cigarettes consumed and the age of starting smoking.[103] Current smokers have a higher risk than ex-smokers, and men and women were equally affected. It has been estimated that approximately half of the CRC cases in Japan can be prevented by tobacco and alcohol control in middle-aged and elderly Japanese men. The relationship of smoking and alcohol consumption to CRC was studied in Chinese living in Singapore.[104] In this population-based study, cigarette smoking was associated with an increased risk of rectal but not colonic cancer. Compared with non-smokers, light smokers have an increased risk of 1.43 and heavy smokers of 2.64 of developing rectal cancers. Smoking appears to interact with alcohol consumption in an additive manner in affecting the risk of rectal cancer.

Statement 20. Obesity increases the risk of CRC

Level of agreement: a, 47%

  Quality of evidence: II-2

  Classification of recommendation: A

Obesity has been found to increase the risk of CRC. A meta-analysis reported a relative risk of CRC of 1.37 for overweight and obese men, and the associated risk appears to be higher for men than for women.[105] Epidemiological studies have also shown in a Korean population that patients with metabolic syndrome had an increased risk of colorectal adenoma (OR 1.51).[106] The association with metabolic syndrome was more evident for proximal, multiple (>3) and advanced adenoma. In Japan, a nationwide prospective study which included >43 000 women and 58 000 women aged 40–70 showed, after adjustment for the lifestyle factors, a significant positive correlation of CRC with baseline body weight.[107] Women with baseline bdoy mass index (BMI) >28 kg/m^2 had a relative risk of 2.4 for CRC compared with those with a BMI of 20–22 kg/m^2. BMI was also found to have a positive correlation with adenoma of the colon in Japan and Korea.[108 109] This trend has not been demonstrated in man. Hyperinsulinaemia may be an important factor, but the role of oxidative stress initiated by hyperglycaemia is another possible mechanism. The lack of physical activity leading to overweight has been identified as a risk factor for CRC in a study from Shanghai.[110] A recent study from Hong Kong also showed that those who underwent investigations for coronary heart disease are more likely to have CRC.[111] Metabolic syndrome among this group of patients is an independent risk factor for the condition.

Statement 21. Screening for CRC should be a national health priority in most Asian countries

Level of agreement: a, 57%; b, 33%; c, 8%; d, 2%; e, 0%

  Quality of evidence: III

  Classification of recommendation: C

In North America and Europe, as well as Australia and New Zealand, there is a widespread scientific agreement on the value of CRC screening. CRC screening is endorsed by the American Cancer Society, the US Preventive Services Task Force, the Multi-Society Taskforce on Colorectal Cancer, the American College of Gastroenterology, the American Gastroenterological Association, the American Society of Gastrointestinal Endoscopy, the American College of Physicians, the British Society of Gastroenterology, the Canadian Task Force on Preventive Health Care and the Royal Colleges of Physicians in the UK, to name just a few.[57–60] Screening is available in different settings, but the vast majority of screening activities are still opportunistic and uncoordinated. In certain localities, large healthcare systems (e.g. Kaiser Permanente of North California and the Veteran's Administration) have developed organised screening for their populations. Local programmes are also found in other regions (eg, the State of Maryland and New

York City). In the USA, Medicare added coverage for CRC screening in 2000. Laws have been enacted in nearly half of the states in the USA requiring private insurers to pay for CRC screening tests. Legislation was introduced in the US Congress in 2007 to create a CRC screening, diagnostic and treatment programme for poor and/or uninsured citizens. In Europe, a public health programme has developed a comprehensive set of recommendations for cancer screening, and CRC screening was added in 2003. In a recent survey conducted by the International Digestive Cancer Alliance (ICDC) across Europe, 21 out of 39 nations have reported national screening guidelines promoted by medical and professional organisations.[112] Fifteen countries are currently performing some form of population screening programmes and seven others have feasibility studies underway. Respondents from 20 countries where screening is not taking place indicated a lack of official recognition of the importance and value of CRC screening. Lack of financial support is identified as the primary barrier to screening. Germany is the European country with the largest screening programme using guaiac-based FOBT. Since 2002, >2.1 million screening colonoscopies have been performed, detecting adenoma in about 20% of subjects and CRC in 0.6–0.8% of subjects.

In Asia, a national guideline is available only in Australia, Japan, Korea, Taiwan and Singapore.[113–117] Despite these guidelines, the uptake of CRC screening is relatively low. In Korea, the government covers 50% of the cost of CRC screening and 100% for low-income individuals. Taiwan is the only country with free mass screening for CRC under the national health insurance scheme. CRC screening is endorsed but not funded in most Asian countries. In countries such as Brunei, China, India, Indonesia, Malaysia, Philippines, Thailand and Vietnam, a national guideline is not available. Government support for CRC screening is very limited. The Consensus Group urges strong support from Asian health authorities to promote CRC screening in the Asia Pacific region.

Statement 22. Research on barriers to CRC screening should be conducted in various Asian countries

Level of agreement: a, 86%, b; 14%; c, 0%; d, 0%; e, 0%
> Quality of evidence: II-3
> Classification of recommendation: B

Adherence to guidelines on screening is low even in Western countries. In Japan, around 17% of the eligible population participates in the immunochemical FOBT.[118] In Canada, 23.5% of eligible respondents received screening.[119] In the USA, the compliance rate was low and has only risen to 40–60% in recent years.[120] Only a limited number of studies have investigated the factors that play a major role in compliance/non-compliance with colon screen advice, and they have yielded somewhat inconsistent findings. A recent study from Hong Kong employed the Health Belief Model to study the knowledge, behavioural and psychological obstacles to CRC screening tests.[121] Knowledge of CRC symptoms and risk factors, recommendation by a doctor and the availability of health insurance are positively associated with uptake of screening tests. On the other hand, health, psychological and access barriers, and perceived negative personal and family consequences of CRC are negatively associated with uptake of the screening test. The Asia Pacific Working Group on CRC is undertaking a similar study to compare the health-seeking behaviour and obstacles to screening tests in different cultures. This kind of study will provide important information for the successful implementation of CRC screening in the region.

Statement 23. Education of the public is essential in promoting CRC screening

Level of agreement: a, 96%; b, 4%; c, 0%; d, 0%; e, 0%
> Quality of evidence: I
> Classification of recommendation: A

In most Asian societies, public knowledge of CRC is poor and uptake of screening tests is expected to be low. Fewer than 10% of the Hong Kong Chinese are aware that CRC is the second most common cancer in their locality.[122] Most Chinese believe that ''screening'' is needed only when they develop symptoms of cancer. Only one-third of the Singaporean Chinese know that they should go for screening even if asymptomatic.[123] Over 70% of individuals cannot name a single screening method for CRC. In both of these studies, there was little recommendation offered to intervene in existing low awareness and willingness to participate in CRC screening. A population survey suggested that male subjects above 50 years of age were significantly deficient in knowledge of CRC symptoms and the perceived benefits of screening.[121] Educating this group would be important as they are the ones who may benefit from CRC screening.

Statement 24. Family doctors should be engaged in promoting CRC screening

Level of agreement: a, 82%; b, 18%; c, 0%; d, 0%; e, 0%
> Quality of evidence: I
> Classification of recommendation: A

Family doctors play a pivotal role in recommending asymptomatic individuals for CRC screening. A study in Iowa in the USA shows that the strongest predictors of patient's compliance with CRC screening, other than symptoms, were patient recollection of a doctor's recommendation and documentation by the doctor of advice to their patients.[124] In two population surveys in Hong Kong, a recommendation from the family doctor was found to have the highest impact on the patients' compliance with CRC screening.[121 122] Recommendation by a doctor increases the likelihood of having a CRC screening test by 21 times.[121] Why are some family doctors not interested in recommending CRC screening? Previous studies have shown that lack of knowledge and training, lack of time and opportunity, lack of financial support for the patients in participating in screening and inconsistency in recommendations are the most important reasons for their reluctance to advise their patients.[125] Education and training for family doctors should be an effective strategy to promote CRC screening.

Statement 25. Nurses in Asia should be trained to perform flexible sigmoidoscopy for CRC screening

Level of agreement: a, 6%; b, 4%; c, 30%; d, 30%; e, 30%
> No consensus reached

The Consensus Group noted that in the UK, the USA and Canada, there are nurse-run flexible sigmoidoscopy programmes.[126–128] There is at least one nurse practitioner-directed colonoscopy programme in the USA (Alaska). The advantages of recruiting nurses to perform endoscopy are to speed up the process of CRC screening and to relieve the endoscopy workload. The enhanced contributions of nurses will also strengthen the nursing profession to become more competent and independent. A stringent training programme and other academic qualifications may ensure the competence of nurse endoscopists. In order to implement nurse-led CRC screening by flexible sigmoidoscopy or colonoscopy, due recognition by the

nursing council and proper licensing criteria will be required. Among the members of the Consensus Group, there was a very divergent view. Issues of liability, third-party reimbursement, lack of medical support, lack of policies and guidelines on this have been discussed. The majority of members have reservations on this issue and a consensus view could not be reached in the meeting. However, despite the hurdles, the Consensus Group believes that other than endoscopy, nurses can play a very important role in patient education, coordination of service and tracking individuals tested positive by FOBT.

CONCLUSION

These are the first Asia Pacific Consensus statements formulated based on evidence in the literature, national registries and local data, input from international experts and thorough discussion among members of the Asia Pacific Working Group for Colorectal Cancer. It provides a basis for further elaboration and modification to suit the needs of each individual Asia Pacific country/region. There are areas which cannot be covered in the present statements. These include the recommendations for hereditary CRC and genetic counselling policy, lifestyle risk factors and intervention, cultural differences in health-seeking behaviour, among others. Future studies in the Asia Pacific region should aim at investigating the effects of culture on compliance with CRC screening, the effects of genetic and environmental factors on CRC development and the practical use of guaiac-based and immunochemical FOBTs in different Asian populations.

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Appendix A

Voting Members of the Consensus Group

Joseph Sung (Chair), Murdani Abdullah, Carolyn Aldige, Edgardo Bondoc, Durado Brooks, Jeong-Sik Byeon, Shan-rong Cai, Annie Chan, Francis Chan, Kelvin Cheng, Jessica Ching, Han-mo Chiu, Vui Heng Chong, Khean-Lee Goh, Lawrence KY Ho, Andrew Ip, Yasuo Kakugawa, Wing-man Ko, Ken Koo, Pinit Kullavanijaya, Philip Kwok, James Lau, Rupert Leong, Suet-yi Leung, Wai-keung Leung, Chu-jun Li, Peng Li, David Lieberman, Su-vui Lo, Vivian Lou, Susie Lum, Govind Makharia, Simon Ng, Yasushi Oda, Fei-chau Pang, Rungsun Rerknimitr, Yasushi Sano, Jose Sollano, Ka-fai To, Kelvin Tsoi, Martin Wong, Mei-Yin Wong, Kai-chun Wu, Deng-chyang Wu, Ming-shiang Wu, Eng-kiong Yeoh, Khay-guan Yeoh, Graeme Young, Siu-tsan Yuen, Shu Zheng

Editor's quiz: GI snapshot

ANSWER

From the question on page 1101

During endoscopy, it was found that a wooden toothpick was embedded in the posterior wall of the distal antrum surrounded by a subtle, rounded bulge seen actively to exude a small amount of pus from its centre (fig 1 of the Question). An overtube was placed and a 33 mm long toothpick was recovered. Figure 1 shows the lesion after removal of the stick. In retrospect, the patient had no recollection of having swallowed a toothpick. There was marked diminution of the patient's pain postprocedure. A follow-up abdominal *x* ray and CT scan to rule out perforation and abscess were unremarkable. The patient was admitted to hospital for 1 day, and subsequently discharged in a stable condition.

Clinicians should include inadvertent foreign body ingestion in the differential diagnosis for abdominal pain and gastrointestinal bleed. Patients should be warned of the potential hazards of toothpicks and cocktails sticks, fragments of which may be left in club sandwiches which have been cut in half.
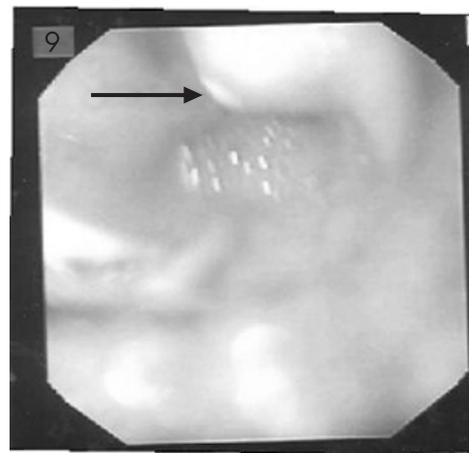

Figure 1 A subtle bulge with pus seen after the removed of the tooth pick from the distal antrum of the stomach.