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Colorectal cancer screening in Asia

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Introduction: The incidence and mortality of colorectal cancer are rapidly rising in several countries in Asia. However, screening guidelines are lacking.

Sources of data: Review of literature and local data published in peer review journals.

Areas of agreement: The incidence, anatomical distribution and mortality of colorectal cancer among Asian populations are comparable to those in Western countries. Flat and depressed colonic lesions are not uncommon. Male gender, smoking, obesity, metabolic syndrome and family history are risk factors for colorectal cancer. Certain ethnic groups in Asia have increased susceptibility to colorectal cancer. Faecal occult blood test, flexible sigmoidoscopy and colonoscopy are recommended options for colorectal cancer screening in Asia. Regular screening should start at the age of 50 years.

Areas of controversy: The optimal screening method in Asia remains unclear. Faecal immunochemical test has been suggested as the first choice of screening test in countries with limited resources. The role of nurse endoscopists in performing endoscopic procedures for colorectal cancer screening in Asia has not been defined.

Growing points: There is low public awareness and little support by health authorities for screening and prevention of this emerging disease.

Areas timely for developing research: Screening for colorectal cancer should be a national health priority in most Asian countries. Studies on barriers to screening, education of the public and engagement of family physicians are important strategies in promoting colorectal cancer screening. With more health-care support, increased public acceptance and better access to the general population, colorectal cancer screening in Asia can be rewarding.

Keywords: colorectal cancer/screening/Asia

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Introduction

Colorectal cancer is the third most common cancer worldwide with ~1.2 million new cases diagnosed each year and a mortality of over 600 000 per year (accounting for 9% of the total cancer deaths).[1] The highest rates are in developed countries, including the USA, Canada, Australia and Europe. Recent reports from the World Health Organization (WHO) showed that the incidence of colorectal cancer is rapidly rising in many countries in Asia, such as China, Japan, Korea and Singapore.[1] More than 4 billion people live in Asia. The continuous rise of colorectal cancer in this region will have important implications on screening and health-care resources.

Colorectal cancer is an ideal disease for screening. The majority of cancers develop from adenomatous polyps with a long and asymptomatic period during which screening is useful. Screening may identify adenomas or early cancers that are highly treatable, potentially preventing their transformation into late stage diseases with high fatality rates.[2,3] Studies from the West have shown that screening reduces colorectal cancer mortality by up to 53%.[4–6] Despite these benefits, universal screening programme has not been implemented in most parts of the world. This is due to a lack of optimal screening strategy and public acceptance. Traditional methods of faecal occult blood test (FOBT) and sigmoidoscopy have low diagnostic sensitivity and specificity; whereas colonoscopy is associated with a small, but significant risk of perforation. Newer methods, including computed tomography (CT) colonography and faecal DNA test are being developed, but their effects on the incidence and mortality of colorectal cancer in population-based setting are not known. Furthermore, adherence to screening is suboptimal and variable and depends on the screening strategy and population demographics. The aim of this paper is to review the current evidence on colorectal cancer screening in Asia. We will discuss the epidemiology of colorectal cancer in Asia, current recommendations and implications of screening.

Epidemiology of colorectal cancer in Asia

Although colorectal cancer, traditionally, has the highest incidence in western populations, there have been remarkable changes in the incidence of colorectal cancer in Asian countries. The burden of colorectal cancer has increased rapidly in some economically developed countries such as Singapore, Japan and South Korea; with a 2–4-fold increase in incidence over the past few decades.[7] The incidence rate of colorectal

cancer per 100 000 men is 41.6 in Singapore, 41.7 in Japan and 46.9 in South Korea, exceeding that of 36.2 in the UK.[1] In Hong Kong, the age-standardized incidence rate per 100 000 men has increased from 40.8 in 1989 to 47.1 in 2009.[8] A rising incidence of colorectal cancer has also been observed in Taiwan and several regions in mainland China.[9] According to the Chinese National Cancer Database of 2003, colorectal cancer was one of the three cancers with the most rapidly increasing incidence in the country in the past two decades.[10] A comparative study between Japanese and Caucasian populations in the USA showed that the rates of colorectal cancer in these two populations are very similar.[11] However, data regarding the trend of colorectal cancer incidence in countries such as India, Indonesia, Philippines, Vietnam and the Middle East are lacking. Figure 1 shows the age-standardized incidence of colorectal cancer in the countries in Asia-Pacific. The rising incidence of colorectal cancer appeared to be associated with countries with more westernized lifestyle and dietary habits, possibly a result of high fat and protein and lower fibre dietary intake.

Although mortality of colorectal cancer is declining in the West (2.7 and 2.5% per year in men and women, respectively),[12] death rates continue to rise in Asia. The WHO mortality database shows that the mortality of colorectal cancer in Taiwan has doubled over the past three decades,[9,13] whereas the National Cancer Centre in Korea reported a

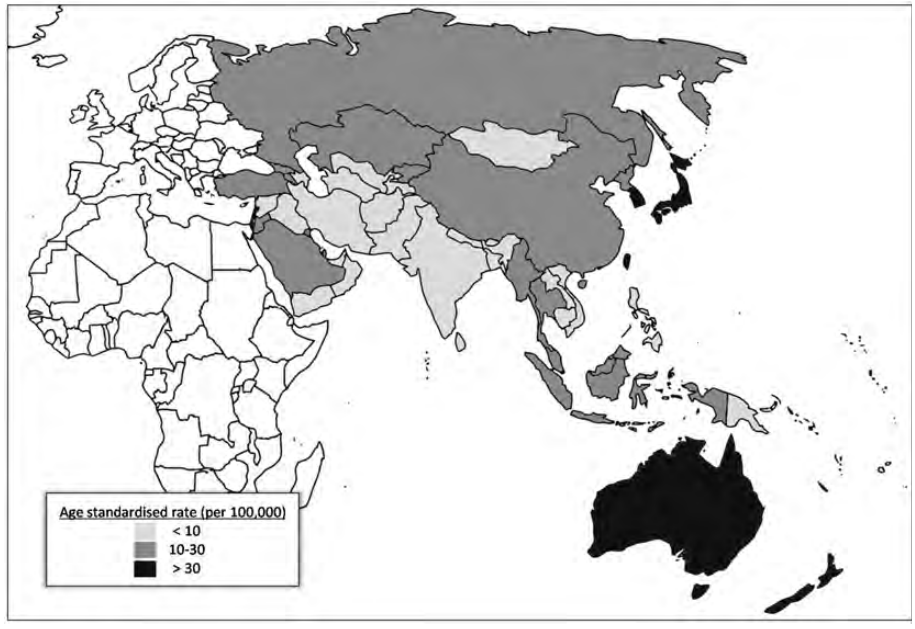

Fig. 1 Age-adjusted incidence of colorectal cancer in Asia-Pacific.[1]

35% increase in colorectal cancer-related mortality in both men and women.[14] A smaller increase in age-adjusted colorectal cancer mortality rate was seen in both urban and rural men in China.[15] There is, however, no consistent time trend for colorectal cancer mortality observed in Japan and Hong Kong.[16]

Certain ethnic groups within Asia (e.g. Japanese, Koreans and Chinese) are more susceptible to colorectal cancer. In countries with multi-ethnic populations such as Malaysia and Singapore, the incidence of colorectal cancer is significantly higher in the Chinese than the Malays or Indians.[17,18] The National Cancer Registry in Malaysia also reported similar discrepancy between different ethnic groups.[19] Moreover, the Asia Pacific Working Group on Colorectal Cancer also found a higher risk of advanced neoplasia among Japanese, Korean and Chinese.[20,21] These observations suggest that genetic factors play an important aetiological role in cancer development.

Disease distribution in Asia

A proper understanding of cancer distribution is essential for designing an optimal population screening strategy. In studies from Asia-Pacific, there are more polyps in the distal colon[22,23] when compared with studies in Caucasian populations.[24,25] However, the distribution of advanced colorectal neoplasm is not significantly different in the East and the West. Proximal, distal and synchronous advanced neoplasm are found in 29 and 35%, 52 and 59%, 19 and 6%, in Asia and the USA, respectively.[26]

A Japanese study has observed a rise in proximal cancers accompanied by a decline in rectal cancer in both male and female in all age groups over a period of two decades.[27] An increasing proportion of proximal adenoma over time was observed in a Hong Kong colorectal polyp registry. More than 5% of asymptomatic individuals were found to have an advanced neoplasm in the proximal colon.[7] The increase in proximal lesions in the right colon may in part be accounted for by the ageing population and wider accessibility of screening colonoscopy in Asia. This observation may argue for the use of colonoscopy, instead of flexible sigmoidoscopy for colorectal cancer screening in this region. Apart from the distribution, studies have suggested that the nature and the phenotype of the tumours may be different in Asian populations.[26] Flat and depressed lesions are not uncommon. Non-polypoid tumour <1 cm in size without adenomatous component has been reported in studies from Japan, Singapore, Malaysia and Korea.[26] It has been estimated that in Japan, 19 and 27% of colorectal cancers in men and

women, respectively, arise from these non-polypoid lesions via a *de novo* pathway.[28] Over 80% of the *de novo* cancers were invasive cancers.

Screening tests for colorectal cancer

There are two main types of screening tests for colorectal cancer. Tests that target colorectal cancer include FOBT and tests that target both colorectal cancers and cancer precursor lesions include flexible sigmoidoscopy, colonoscopy and CT colonography. Each test has its advantages and limitations, in terms of sensitivity and specificity, complexity and risk of procedure and ease of acceptance that ultimately affect the choice of a screening strategy in different populations (Tables 1 and 2). In national guidelines from the USA, the UK and Canada, FOBT, flexible sigmoidoscopy and colonoscopy are recommended options for colorectal cancer screening.[29,30] Considerable variation among screening recommendations exists between countries. FOBT is recommended in Europe and Canada. Sigmoidoscopy is used in the UK and Norway and colonoscopy is the predominant screening tool in Germany, Austria, Poland and Italy. There is currently a lack of Asia-Pacific guideline for colorectal cancer screening, but an Asia-Pacific consensus statement published in 2007 reported that FOBT, flexible sigmoidoscopy and colonoscopy are options for screening in Asia.[26]

Faecal occult blood test

As an inexpensive, non-invasive method, FOBT is the most widely used screening modality for colorectal cancer worldwide. In Europe, this remains the most popular screening tool to date. Since 2007, 12 countries in Europe are using FOBT in population screening programmes;

Table 1 Sensitivity of one-time colorectal cancer screening test.

	Sensitivity (%)	
	Colorectal cancer	Advanced adenoma
gFOBT	50–75	20–25
FIT	60–85	20–50
Barium enema	50	48
CT colonography	Uncertain; >90	>90% (if >10 mm)
Sigmoidoscopy	>95 (in the distal colon)	70
Colonoscopy	>95	88–98

Table 2 Advantages and limitations of current screening tests.

	Advantages	Limitations/uncertainties
Sensitive gFOBT and FIT	Low initial cost Non-invasive Can be performed at home Established benefit of reducing colorectal cancer incidence and mortality	Low sensitivity for adenomas Annual repeat testing recommended Adherence to repeat testing unknown Ideal number of stool samples unclear
Stool DNA	More accurate than detection of blood Non-invasive Can be performed at home	High cost Suitable intervals for testing unclear Low sensitivity for adenomas
Sigmoidoscopy	High sensitivity Office based Full bowel preparation and sedation not required Can take biopsy Established benefit of reducing colorectal cancer incidence and mortality	Does not detect isolated proximal cancer; may be less effective with increasing age and in women because of higher rates of proximal colorectal cancer Requires resources and expertise
Colonoscopy	High sensitivity Can take biopsy Reduce incidence and mortality of colorectal cancer in case control studies	Lack of randomized trials showing reduced incidence and mortality High initial cost Requires resources and expertise Requires bowel preparation and sedationInvasive test with risk of adverse events
CT colonography	Less invasive than colonoscopy High sensitivity for lesions >10 mm Extra colonic findings	Detection of flat lesions unclear Low sensitivity for small lesions Requires resources and expertise Radiation risk
Colon capsule	Minimally invasive Sedation or air insufflations not required	Low sensitivity Requires bowel preparation
Barium enema	Sedation not required Less invasive than colonoscopy	Low sensitivity Radiation risk Requires bowel preparation and patient cooperation

the majority will arrange colonoscopy for subjects with positive results. The rationale of FOBT relies on the detection of subtle blood loss in the gastrointestinal tract, as a result of cancer bleeding. The traditional guaiac FOBT (gFOBT) detects the peroxidase activity of haeme. Because this guaiac-based test is not specific for human blood, false-positive results may occur, if the patient consumes red meat or peroxidase-containing foods prior to the test. Consumption of vitamin C may result in a false-negative result owing to its reducing property. There have been criticisms about the low sensitivity and specificity of the guaiac-based test. Despite its low diagnostic sensitivity and specificity, randomized studies in the USA, UK and Denmark have shown

that gFOBT reduced colorectal cancer incidence by 20%[31] and mortality by 15–33%.[32,33] In a population-based study in Japan (with a 13-year follow-up involving 42 150 subjects), there was a 60% risk reduction in advanced colorectal cancer and a 30% risk reduction in mortality in subjects who underwent screening with FOBT.[34] Patient compliance remains an important issue, with uptake rates of only 53–69%, compounded by annual or biannual testing in many screening protocols. It would seem that in resource-limited countries in Asia, FOBT is more affordable and is the first choice for screening.

Recently, faecal immunochemical test (FIT), which specifically detects human haemoglobin in stool and without the need for dietary restriction, has been shown to be more sensitive than the guaiac-based test,[35] with a detection rate of 60–85% for colorectal cancer, even in Asian subjects.[36] A study from Spain showed similar cancer detection rate for FIT and colonoscopy; with no significant difference in the stages of tumours detected by the two methods.[37] Nevertheless, the detection rate for advanced adenoma is low at ~20–30%. Both FOBT and FIT are cancer detection tests, rather than tests for adenomas or polyps.

Flexible sigmoidoscopy

Endoscopic screening with sigmoidoscopy can detect adenomatous polyps, the precursor lesions of colorectal cancer. To date, two randomized controlled trials from Europe (UK and Italy) and one from the USA have shown a reduction in colorectal cancer incidence by 18–21% and a reduction in mortality by 22–31%.[6,38] A Norwegian study failed to show any benefit after 7 years of follow-up.[39] Sigmoidoscopy is limited by its inability to visualize the proximal colon. The reduction in incidence and mortality of colorectal cancer in the randomized trials are related to cancers in the distal colon, with no significant benefit for proximal cancers. In the recent study from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, there was a reduction in proximal cancer incidence by 16% with flexible sigmoidoscopy. However, this reduction is largely attributable to the colonoscopy rate of 21.9% as a direct effect of abnormal sigmoidoscopy and out-of-protocol colonoscopy; there was no significant reduction in the proximal cancer mortality.[5]

The inability to examine the proximal colon has aroused concerns about using sigmoidoscopy as a primary screening tool for colorectal cancer. Data from Japan suggested an increase in the proportion of proximal colon cancers over the last few decades,[27] with similar findings seen in other parts of Asia.[40,41] A proximal migration of adenoma

was also noted in a colorectal polyp registry in Hong Kong, which consisted of more than 3000 polyps recorded over 10 years.[42] Given that up to two-thirds of proximal advanced adenomas are identified in the absence of distal lesions in Asian populations,[26] flexible sigmoidoscopy may create a false sense of security and may not be an appropriate first-line screening tool in Asia.

Colonoscopy

Colonoscopy is the endoscopic examination of the entire large bowel. It is the only modality that allows direct visualization of the entire colon and allows removal of precancerous lesions to prevent colorectal cancer. Thus, it is regarded as the gold standard and is often the final assessment tool in every screening programme. However, colonoscopy requires bowel preparation and is associated with a definite procedural risk. To date, no randomized controlled trials have compared the outcomes of colonoscopy with other forms of screening, and efficacy has been based on indirect evidence. Case-control and cohort studies have estimated that colonoscopy has a 53–72% reduction in colorectal cancer incidence and 31% reduction in mortality.[4,43,44] The National Polyp study showed a lower than expected colorectal cancer mortality over more than 15 years in patients with adenoma removed by colonoscopy, with mortality reduction of 53%.[2]

The effectiveness of colonoscopy is dependent on screening uptake and the quality of examination. A Spanish study showed that the benefit of colonoscopy may be reduced due to its lower participation rate.[37] Colonoscopy is also not perfect and can miss cancer or adenomas. There are reports suggesting its limited efficacy in preventing proximal cancers.[44] This may in part relate to a different pathophysiological basis and morphology of proximal cancers, missed lesions during colonoscopy or incomplete polypectomy. Current guidelines recommend a repeat colonoscopy in 10 years after a negative colonoscopy. The rationale for this is based on data showing a low rate of advanced neoplasm up to 10 years after polypectomy.[3]

Other screening tools

Over the past decades, several other tests have been developed for colorectal screening. These include stool-based tests like the stool DNA test and structural evaluation tests such as barium enema, CT colonoscopy or capsule endoscopy. Stool-derived DNA markers have been regarded as a robust screening strategy as the shedding of colonocytes is believed to be a continuous process unlike mucosal bleeding that is generally

intermittent. The test detects somatic mutations associated with colonic neoplasia in stool samples. Despite lower figures in earlier studies,[45] a recent study has shown a satisfactory sensitivity of up to 87% in detecting colorectal cancer and 40% in detecting advanced adenoma.[46] Although stool DNA testing has gained wider acceptance as a screening tool, high cost remains a concern. It is possible that with the development of second-generation stool DNA markers, fewer panels will be required with equal efficacy. Large-scale studies that involve these markers in average-risk individuals in population-based setting are needed.

Barium enema has not been recommended as a first-line screening test by most guidelines because of its lower sensitivity even for large polyps. Unlike barium enema, there is emerging evidence to suggest that CT colonography is an accurate screening method for the detection of colorectal neoplasms in average-risk asymptomatic individuals.[47,48] This test involves a CT scan of the inflated colon after bowel preparation. It can visualize colonic polyps, but not remove them. CT colonoscopy has a sensitivity up to 90% for polyps 10 mm or larger, similar to the detection rate with optical colonoscopy.[47,49] The sensitivity for smaller polyps is lower (50% for polyps <6 mm). There remains controversy surrounding the appropriate reporting and management of small 1–5 mm and 6–9 mm polyps. The Asia-Pacific Working Group on Colorectal Cancer showed that a substantial proportion of polyps <10 mm in size have advanced histological features in Asia, so patients with a polyp of 6 mm or more at CT colonography should be offered colonoscopies with polypectomies, instead of CT colonography surveillance of polyps.[50] Although comparable detection rates between CT colonography and colonoscopy for large polyps have been shown, such accuracy may not be achieved in other centres where radiological expertise is lacking. There have also been concerns about the potential risks of radiation exposure and high cost, and cases of perforation have been reported, despite a lower risk. Acceptability of CT colonography in a true screening population has also not been explored. Most Asian countries do not have easy accessibility to CT colonography; hence, the Asia-Pacific consensus do not recommend using CT colonography as a first-line colorectal cancer screening tool at this stage.[26] Colon capsule has not been recommended as a screening tool, and future studies are required to assess its sensitivity in the screening setting.

Risk stratification in colorectal cancer screening

Current screening recommendations do not differ between age, gender and ethnic groups, but screening outcomes differ according to these

characteristics. Age-adjusted rates for colorectal cancer and advanced adenomas are higher in men than women in studies from the West and Asia.[26] The prevalence of colorectal cancer increases with age. Screening colonoscopy studies in Asia showed that the risk of advanced neoplasm tripled after the age of 50. Most national guidelines recommend screening to start by 50 years of age. Other risk factors for colorectal cancer include family history, smoking, obesity and metabolic syndrome. First-degree relatives of patients with colorectal cancer have a 2-fold increased risk of colorectal cancer.[51] Siblings of subjects with advanced neoplasm also have a 4-fold increased risk of advanced neoplasm, suggesting that screening is strongly indicated in this high-risk groups.

Smoking increases the risk of colorectal cancer. The association of smoking and colorectal cancer has been confirmed in studies from Asia.[26] The risk appeared to be dose related and was stronger for men and for rectal cancers.[52]

The prevalence of non-alcoholic fatty liver disease is increasing in Asia. It affects 20–40% of the general adult population. Epidemiological studies from Asia have shown that metabolic syndrome is associated with an increased risk of colorectal cancer [odds ratio (OR) 1.51]. A recent study from Hong Kong showed that non-alcoholic steatohepatitis was associated with adenomas (OR 4.89) and advanced neoplasms (OR 5.34). Most of the lesions were located in the right side of the colon, suggesting that colonoscopy is the most appropriate screening tool.[53]

Asia consists of a heterogeneous population, and formulating a risk stratification strategy based on age, gender, race and family history to identify those with the highest risk for priority in a screening programme is desirable. In a prospective multi-centre study across 11 Asian cities, a risk score (The Asia-Pacific Colorectal Screening score) based on age, gender, family history and smoking was used to select asymptomatic Asian subjects for priority of colorectal screening. The subjects in the moderate-risk and high-risk tiers had a 2.6-fold and 4.3-fold increased prevalence of advanced neoplasia, respectively, than those in the average-risk tier.[54] This risk score is currently undergoing large-scale validation and may prove to be an important tool to make best use of limited resources in many Asian countries.

Challenges of colorectal cancer screening in Asia

Despite the increase in colorectal cancer incidence, public awareness is low in many Asian countries. Only a minority of population at risk undergoes screening because of perceived health, access and

psychological barriers.[55] A population survey showed that men above 50 years of age were particularly unaware of the symptoms of colorectal cancer and the benefits of screening.[55] Even among primary care physicians, disease awareness is low and insufficient. Emerging data showed that knowledge predicts for greater screening intent. Recommendation for screening by a doctor has been shown to increase the likelihood of screening for 21 times.[55] Resources and culture-specific interventions are recommended to improve overall screening participation.[56] Implementing language- and culture-specific educational programmes involving medical practitioners and media is necessary to improve colorectal cancer screening.[57] In a study in Hong Kong, FOBT and colonoscopy were equally preferable to Chinese. Colonoscopy was preferred among the younger subjects, those with positive family history of colorectal cancer and self-perceived poor health status.[58]

Second, the actual uptake and implementation of screening remain low in many Asian countries due to limited resources. National health-care systems and health insurance are available to only a minority of people. Access to health-care facilities is, therefore, limited in many rural areas and communities of low socioeconomic status.[7] Furthermore, governmental support in Asian countries for colorectal cancer screening is very limited. Lack of financial support has been identified as the primary barrier to screening. Taiwan is the only country with free mass screening for colorectal cancer under the national health insurance scheme. The Korean government covers 50% of the cost of colorectal cancer screening and 100% for low-income persons. The rest of countries in Asia do not have a formal screening programme. In the USA, UK and Canada, nurse-run flexible sigmoidoscopy screening programmes are running to speed up the process of screening and to relieve the endoscopy workload. There are currently no such programme in Asia in part due to lack of medical and nursing council support, third-party reimbursement, issues with liability and lack of policies.[26] With buoyant economies, it is the mindset and the current organizational arrangements as much as lack of resources that predicate against the introduction of screening programmes. The high rates of out-of-pocket payment for health care, and the poorly organized primary care, make population programmes difficult to be organized in the Asia-Pacific region.

Lastly, only few countries or regions have a national colorectal cancer registry. More work is needed to elucidate the magnitude of the problem in Asia.

Summary

With the increasing incidence of colorectal cancer in Asia, it will become a substantial public health burden. However, most Asian populations are not aware of the growing problem of colorectal cancer. FOBT, flexible sigmoidoscopy and colonoscopy are recommended options for colorectal cancer screening. There is low public awareness and little health authority support for colorectal cancer screening in Asia. Screening for colorectal cancer should be a national health priority in countries in Asia. Given the established benefit of colorectal cancer screening, it can be envisioned that much needs to be done to advocate this life-saving public health policy, taking into account, the risk–benefit ratios of the different tools, the local epidemiology and public acceptance.

Conflicts of interest

The authors have no potential conflicts of interest.

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