Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: July 10, 2023

Citation: Michel A and Pumpalova, 2023. A Colorectal Cancer Screening Programs in Middle-Income Countries: A Scoping Review, Medical Research Archives, [online] 11(7). https://doi.org/10.18103/mra.v11i7.1.4192

DOI
https://doi.org/10.18103/mra.v11i7.1.4192

ISSN: 2375-1924

REVIEW ARTICLE

A Colorectal Cancer Screening Programs in Middle-Income Countries: A Scoping Review

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ABSTRACT

Background: Colorectal cancer (CRC) is the 3rd most common cancer worldwide, and a major contributor to cancer-related mortality. In contrast to declining CRC incidence and mortality rates across high-income countries, the CRC burden is increasing in low- and middle-income countries. Although CRC screening has been shown to be a cost-effective intervention that decreases CRC incidence and mortality, screening programs remain an unmet need in most low- and middle-income countries. This article reviews evidence on existing CRC screening efforts in middle income countries, where the majority of new CRC cases and deaths are projected to occur over the next decade.

Aims: The aim of this study was to identify and describe opportunistic and organized CRC screening programs in middle income countries and to identify barriers and facilitators of such programs.

Methods: We identified countries defined as middle income countries by the World Bank and conducted a scoping literature review using PubMed, Google Scholar, and ScienceDirect. For each country, we identified whether CRC screening guidelines or programs exist on the national, regional, or local levels, and summarized data on screening methods and uptake, when this information was available. We also summarized published literature describing barriers and facilitators to CRC screening in middle income countries.

Results: Of the 108 countries defined as middle income countries by the World Bank, we identified CRC screening programs in six lower-middle income countries and 23 upper-middle income countries. Most countries have opportunistic CRC screening guidelines/programs. Countries with organized CRC screening programs had higher screening uptake rates, although very few have achieved CRC screening coverage rates of >50% of the eligible population. Most programs were initiated less than 10 years ago, limiting ability to evaluate effect on CRC incidence and mortality. Several barriers to CRC screening were identified, including lack of physician buy in, participant knowledge and resources, and participant fear of screening.

Conclusions: While there has been growth of CRC screening programs in the last decade with the initiation of both opportunistic and organized screening programs in middle income countries, there remain significant barriers to the uptake and implementation of such programs.

Introduction

Colorectal cancer (CRC) is the 3rd most common cancer in the world, with over 1.9 million cases diagnosed and 930,000 CRC-related deaths estimated in 2020.[1] Many CRCs can be prevented through screening (via removal of precancerous lesions and early detection of prevalent cancers) and primary prevention (lifestyle modifications, including decreasing smoking and alcohol use and promoting diets high in fiber and low in red meat).[2–4] Historically CRC incidence rates were highest in Australia, New Zealand and Europe, and lowest in sub-Saharan Africa (SSA) and Southern Asia.[1] However, there is now significant variation in the burden of CRC globally. With the advent of CRC screening programs in the late 1990s, CRC age-standardized death rates have stabilized or declined in many high-income countries, with reductions in CRC mortality ranging between 8 to 52%.[5,6] Meanwhile, CRC burden is increasing in most low- and middle-income countries (LMICs), where CRC screening programs are rare.[7] With a rising burden of CRC, modeling studies have shown that screening in LMICs is cost-effective.[8–10] Due to the reduction in mortality when CRC is prevented or detected early, the International Agency for Cancer Research concludes that there is sufficient evidence to support CRC screening in LMICs.[11]

Middle-income countries (MICs), as defined by the World Bank, consist of countries with a gross national income per capita between $1,086 and $13,205.[12] These counties are diverse in size and population and are further categorized into lower middle- and upper middle-income countries. MICs are home to 75% of the world's population, including 62% of the world's poor.[12] Due to rapid economic and lifestyle changes in these countries, including increases in average life expectancy, a large proportion of global CRC cases over the next several decades are projected to be diagnosed in MICs.[13,14]

In this review article, we aim to summarize the existing published data on opportunistic and organized CRC screening programs in MICs with the goal of highlighting the ongoing challenges to creating, enacting, and sustaining these programs.

Methods

The list of countries currently classified as MICs was obtained from the World Bank website (Supplementary Table 1).[12] We then searched PubMed, Google Scholar and ScienceDirect using the terms "colorectal cancer" and "screening", combined with the name of each MIC country individually and each World Bank Lending Region individually (Supplementary Table 1).[15] Only abstracts written in English were reviewed. Abstracts and publications were reviewed by both authors and included if a CRC guideline or CRC screening program in a MIC was described, discussed, or evaluated. Iterative secondary reference searching was used to find additional sources. We included original research articles, review articles, conference abstracts, and policy/conference briefs that fit the above criteria. Unpublished data were not included.

Colorectal Cancer Screening Modalities Considered

Identified CRC screening guidelines and programs in MICs were classified by the type of initial and follow up testing recommended, as applicable. The most common CRC screening modalities are non-invasive tests (guaiac fecal occult blood tests (gFOBT) and fecal immunochemical tests (FIT)) and lower endoscopic modalities (flexible sigmoidoscopy (FS) and total colonoscopy (TC)).[16] Both gFOBT and FIT detect hemoglobin in the stool, as a proxy for pre-cancerous and cancerous colonic lesions.[16] gFOBT uses the chemical guaiac to detect blood in a stool sample, while FIT detects blood using antibodies specific for human hemoglobin.[16] Two types of FIT exist: quantitative, automated laboratory instrument-based immunoturbidometric FIT and point-of-care qualitative lateral flow immunochromatographic FIT.[16,17] When reported, details on the type of stool test used/recommended (gFOBT, qualitative, or quantitative FIT) was abstracted. We further abstracted data on positivity cutoffs for qualitative and quantitative FIT, when this was available. Newer CRC screening modalities include imaging-based tests (computerized tomography and magnetic resonance imaging colonoscopy), stool-based tests that detect cancer DNA (Cologuard®, Exact Sciences Corporation), and blood-based tests that detect cancer DNA (Galleri®, Grail).[14,16] These CRC screening modalities were not explicitly excluded from our review, but given the high cost of these newer screening modalities, there was a paucity of data on their use in MICs.

Categorization of Colorectal Cancer Screening Guidelines and Programs

Identified CRC guidelines/programs in MICs were categorized as national or local/regional, as organized or opportunistic, and according to whether they were pilot programs or not. Organized CRC screening programs were defined as programs where the government or public health sector issues CRC screening invitations to a pre-specified at-risk population.[18] The same services, information and support are offered to each participant. In contrast, opportunistic CRC screening programs were defined as programs that rely on

the patient to request or clinician to recommend CRC screening for a pre-specified at-risk population.[18]

Colorectal Cancer Screening Uptake Rates and Efficacy Evaluation

When a CRC screening guideline or program was identified in a MIC, we searched for data on CRC screening uptake rates, positivity rates, compliance rates with follow up testing (as applicable), adenoma/advanced adenoma/CRC detection rates, and any reported effects on CRC stage distribution, CRC incidence, or CRC mortality after initiation of screening.

Results

Our main results are summarized in Tables 1 and 2. We also provide a narrative description of all identified CRC screening programs in 30 countries in the Supplementary Materials.

Colorectal Cancer Screening Programs in Middle Income Countries, by Income Level

Our search revealed that only five of the 54 lower-middle income countries have national CRC screening recommendations and/or guidelines in place (Table 1). We also identified two cross-sectional studies that conducted CRC screening at the local level in Indonesia, but were not able to identify a local, regional, or national CRC screening guideline or program that persisted after completion of these studies. Among upper middle-income countries, the prevalence of national, regional, or local CRC screening guidelines and programs is higher, with 24 of 54 countries having existing CRC screening guidelines or programs in place.

Colorectal Cancer Screening Programs in Middle Income Countries, by program type (opportunistic vs organized) and testing recommended (one-step vs. two-step)

We identified 18 countries (4 lower MICs and 14 upper MICs) with opportunistic national CRC screening guidelines and/or programs: Philippines,[19] Malaysia,[20] Marshall Islands,[21] Palau,[22] American Samoa,[23] Bosnia and Herzegovina,[24] Georgia,[25] North Macedonia,[26] Brazil,[27] Colombia,[28] Ecuador,[29] Cuba,[30] Jamaica,[31] Jordan,[32] Ghana,[33] Kenya,[34] Nigeria,[35] and South Africa[36] (Table 1). We identified national, regional, or local organized CRC screening programs in 12 MIC countries (1 lower MIC and 11 upper MICs): Thailand,[37] Georgia,[38] Brazil,[27] Mexico,[39,40] China,[41–44] Montenegro,[45] Russian Federation,[46] Serbia,[47] Turkey,[48] Kazakhstan,[49] Argentina,[50,51] and Iran[52] (Table 1).

Out of the 12 MICs with some form of organized CRC screening (local, regional, or national), all except 1 program recommended a two-step approach using a stool-based test for a target population and follow up colonoscopy for those with a positive stool test result only (Table 1). In China, many organized CRC screening programs recommend initial screening with a cancer risk questionnaire, with or without a stool test, and follow up colonoscopy for patients determined to be at high-risk for CRC based on the questionnaire or positive stool test.[42,43] We identified one colonoscopy-based pilot organized CRC screening program for eligible employees of a hospital in Mexico City, but no population-level organized CRC screening programs that recommend screening with colonoscopy upfront.[39] Guidelines in American Samoa,[23] Philippines,[19] Turkey,[48] Argentina,[50,51] Colombia,[28] Jamaica,[31] Jordan,[32] Kenya,[34] Nigeria,[35] and South Africa[36] allow for endoscopy as the initial CRC screening test. However, out of these, only Turkey and Argentina have organized programs, and in Argentina initial screening with colonoscopy is limited to high-risk individuals.[50,51]

Colorectal Cancer Screening Uptake Rates in Middle Income Countries

Of the 18 countries with opportunistic national CRC screening programs/guidelines, 10 countries provided data on screening uptake rates for stool tests: Philippines,[19] Malaysia,[20] Marshall Islands,[21] Palau,[22] Georgia,[25] Brazil,[27] Colombia,[28] Ecuador,[29] Cuba,[30] and Jordan.[32] CRC screening uptake rates for stool tests ranged from <2% (Georgia) to 69% (Philippines) of the eligible population. When only nationally representative data was considered (all except Philippines), CRC screening uptake rates for stool tests ranged from <2% (Georgia) to 27% (Brazil). Among countries with opportunistic national CRC programs/ guidelines, only Malaysia and Brazil had national CRC screening uptake rates >10%. Only Malaysia provided data on colonoscopy completion rates after a positive stool test (52-67% colonoscopy completion rate).

Out of the 16 national, regional, or local organized CRC screening programs in 12 MIC countries, 6 were small-scale pilot regional programs in 4 countries (Lampang province, Thailand;[37] Tbilisi, Georgia;[38] São Paulo and Barretos country, Brazil;[56,57] and Mexico City and Veracruz, Mexico[39,40]) and 10 were large-scale regional or national programs in 9 countries (rural and urban programs in China; national programs in Thailand,[58] Montenegro,[45] Russian Federation,[46] Serbia,[47] Turkey,[48] Kazakhstan,[49] Argentina,[50,51] and Iran[52]) (Table 1).

Table 1: Summary of Existing Colorectal Cancer Screening Programs or Studies within Middle Income Countries, organized by World Bank Lending Region and Income Level

Country	Year	CRC Screening Method	Type of Program	Age (years)	Examination Coverage or Participation rate
EAST ASIA AND PACIFIC					
Lower Middle Income					
Indonesia	2012	Qualitative FIT	Cluster consecutive sampling at a 5 community health centers (Depok district, West Java)[1]	>40	**2012 (Depok district, West Java, N=278)**[1] 100% FIT participation 0% colonoscopy participation
	2021	Quantitative FIT	Random selection at 10 primary health care centers (Semarang city)[2]	>45	**2021 (Semarang city, N=350)**[2] 63% FIT participation 70.3% colonoscopy participation rate
Philippines	2002	gFOBT annually or FS every 3-5 years	Opportunistic (national)[3]	≥ 50	**2007 (Survey, N=343 eligible individuals)** 69% had undergone CRC screening[3]
Upper Middle Income					
China (exluding Tawiwan)	2005	Qualitative FIT	Population-based, organized (local – rural: 234 counties in 31 provinces)	40-74	**2019-2020 (28 communities in Zhejiang Province; N=49,197)**[4] 75.5% participation in qualitative FIT (2 samples) 53.3% colonoscopy participation rate
		Quantitative FIT			70.2% participated in quantitative FIT (1 sample) 56.4% colonoscopy participation rate
	2012	CRC-risk assessment questionnaire or FIT, with colonoscopy for high-risk persons	Population-based, organized (local – urban: 42 cities in 20 provinces)	40-75	**2012-2015 (Entire program; N=1,381,561)**[5] 99.1% participation in cancer risk assessment 14% colonoscopy participation rate for 'high risk' individuals
					2013-2019 (8 cities in Henan province; N=282,377)[6] 99.9% participation in cancer risk assessment 18.71% colonoscopy participation rate for 'high-risk' indivdiuals
					2004 (Hangzhou city; N=38,337)[7] 37.2% participation in FIT; 18.5% colonoscopy participation rate
Malaysia	2014	Qualitative FIT every 2 years	Opportunistic (national)[8]	50-75	**2014-2019 (National)** <1% FIT participation nationally (2018)[8] 10.8% FIT participation nationally (2019)[9] 52-67% Colonscopy Completion Rate (2014-2018)[8]
Marshall Islands	2010/2014	gFOBT	Opportunistic (national)[10]	50-75	**2013 (National)** 6.4% gFOBT participation rate[10]
Palau	2018	gFOBT	Opportunistic (national)[11]	NR	**2018 (National)** 5% gFOBT participation rate[11]
American Samoa	NR	gFOBT or TC	Opportunistic (national)[12]	45-75	NR

Thailand[7/13/2023 10:43:00 AM]	2017	Qualitative FIT	Population-based organized (regional – Lampang province)[13]	50-70	**2012 pilot (Lampang province; n=127,301)** 62.9% FIT participation rate[13] 72% colonoscopy completion rate[13]
		Quantitative FIT	Population-based organized (national)[14]		**2017 (National)** 9% FIT participation[14]
EUROPE AND CENTRAL ASIA					
Upper Middle Income					
Bosnia and Herzegovina	NR	FIT	Opportunistic (national)[15]	>50	NR
Georgia	2011	gFOBT	Organized (regional -Tbilisi)[16]	50-70	NR
			Opportunistic (national)[17]		**2019 (National)** <2% gFOBT participation[17]
Montenegro	2013	gFOBT	Population-based, organized (national)[18]	59-64	**2018 (National)** 42% of target population returned gFOBT to GP[19]
North Macedonia	NR	gFOBT	Opportunistic (national)[20]	50-74	NR
Russian Federation	2013	gFOBT	Organized (national)[21]	NR	NR
Serbia	2013	FIT every 2 years	Organized (national)[22]	50-74	**2014 (National)** 62.5% participation with FIT[22] 41.1% colonoscopy completion rate[22]
Turkey	2013	gFOBT every 2 years or TC every 10 years	Organized (national)[23]	50-70	**2016 (National)** 20-30% of population had undergone CRC screening
Kazakhstan	2011	gFOBT/FIT	Organized (national)[24]	50-70	**2018-2019 (Almaty region, N=202,694)** 53.4-58.2% participation with FIT[25] 17.9-20.2% colonoscopy completion rate[25]
LATIN AMERICA AND CARIBBEAN					
Upper Middle Income					
Argentina	2013	Qualitative FIT every year (avg risk) or TC (high risk)	Population-based, organized (pilot, national)[26,27]	50-75	**2018 (49,170 households in a nationally representative survey)** 30.66% completed CRC screening (FIT or colonoscopy)[28]
Brazil	2006	Colonoscopy	Opportunistic (national)[29]	≥ 50	**2017 (National survey)** 27% participation in CRC screening (any modality)[29]
	2006	Qualitative FIT	Population-based organized (pilot - São Paulo)	>40	**2006 (Hospital Alemão Oswaldo Cruz in São Paulo, N=10,000)** 43.7% FIT participation[30] 86.5% colonoscopy completion rate[30]
	2016	Qualitative FIT every year	Population-based organized (pilot – Barretos county)	50-65	**2017 (Barretos county, N=6,737)** 92.8% FIT participation[31] 84.6% colonoscopy compliance rate[31]

Colombia	2013	gFOBT yearly or TC every 10 years	Opportunistic (national)[32]	≥ 50	**2015 (National health survey)** Men: 7.1% (any CRC screening)[32] Women: 8.6% (any CRC screening)[32]
Ecuador	2017	gFOBT/FIT	Opportunistic (national)[33]	50-74	**2018 (National survey, N=4,641)** Men: 22.6% CRC screening with FIT[2034] Women: 25.3% CRC screening with FIT[34]
Mexico	2009	Colonoscopy	Organized (pilot, Mexico City)[35]	40-79	**2010 (Mexico City, N=600)** 20.5% participation with colonoscopy[35]
		Quantitative FIT	Organized (pilot, Veracruz)[36]	≥ 50	**2016 (Veracruz, N=473)** 85.8% FIT participation[36] 87.5% participation with colonoscopy[36]
Cuba	2013	FIT	Opportunistic (national)[37]	≥ 50	**2013 (National)** <3% FIT participation[37]
Jamaica	NR	TC	Opportunistic (national)[38]	NR	NR
MIDDLE EAST AND NORTH AFRICA					
Lower Middle Income					
Iran	2015	FIT every 2 years[39]	Organized (national)[40]	50-70	**National (2018-2019)** 13% of 2.6 million participants invited for screening[40]
Upper Middle Income					
Jordan	NR	gFOBT/FIT annually[41] or FS or TC	Opportunistic (national)[41]	50-75	**2020-2021 Survey (n=861; eligible Jordanians in an nationally-representative survey)** 17% CRC screening uptake (any modality)[41]
SUB-SAHARAN AFRICA					
Lower Middle Income					
Ghana	2011	gFOBT	Opportunistic (national)[42]	50-70	NR
Kenya	2018	gFOBT/TC every 5 years	Opportunistic (national)[43]	≥45	NR
Nigeria	2019	1) Biennial screening with FIT or gFOBT), 2) annual FIT gFOBT with FS every 5 years 3) TC every 10 years 4) CT colonography every 5 years	Opportunistic (national)[44]	≥40	NR
	2021	Qualitative FIT	Cross-sectional (pilot, Osun, Lagos, Kwara states)[45]	45-75	**2021 (Osun, Lagos, Kwara states; N=2330)** 91% returned FIT[45] 66% colonoscopy completion rate[45]
Upper Middle Income					
South Africa	NR	FIT or TC	Opportunistic (national)[46]	50	NR

FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac fecal occult blood test; NR, not reported; TC, total colonoscopy

Table 2: Summary of Test Characteristics and Peformance of Fecal Immunohistochemistry Tests used in Colorectal Cancer Screening Programs/Studies within Middle Income Countries, organized by type of FIT and percent positive FIT

Country (year)	Type of FIT	Brand	ug Hb/g feces cutoff	ng Hb/mL buffer cutoff	%positive test	Detection rates for adenoma, advanced adenoma and/or CRC	N (completed FIT/completed colonoscopy)
Lampang province, Thailand (2012)[13]	Qualitative	Hemosure	NR	200ng Hb/mL	1.1%	Adenoma = 29.8% Avanced adenoma = 11.92% CRC = 3.7%	80,012/627
Hangzhou, China (2003)[7]	Qualitative	NR	NR	NR	3.6%	NR	14,269/94
Indonesia (2012)[1]	Qualitative	FIT OC Light	10ug Hb/g	50ng/mL	4%	NR	278/0
Malaysia (2018)[8]	Qualitative	NR	NR	NR	9.3%	Polyp = 13.9% CRC = 4.1%	127,957/6,548
Cuba (2013)[37]	Qualitative	SUMASOHF, TechnoSuma International	NR	200ng Hb/mL	10.4%	NR	50,756/NR
São Paulo, Brazil (2006)[30]	Qualitative	Hemosure	NR	50ng Hb/mL	10.7%	Polyp or CRC = 32%	3,640/212
Barretos county, Brazil (2016)[31]	Qualitative	Hemosure	50ug Hb/g	50ng Hb/mL	12.7%	Advanced adenoma = 16.5%; CRC = 5.6%	6,253/659
Rural China (2005)[4]	Qualitative	FIT Abon Biopharm	1-5ug Hb/g	100ng Hb/mL	14%	Advanced adenoma = 9.6% CRC = 0.9%	14,437/1,091
Osun, Lagos, Kwara states in Nigeria (2021)[45]	Qualitative	Pinnacle Biolabs	6ug Hb/g feces	50ng Hb/mL	18.5%	Advanced adenoma = 7% CRC = 1.1%	2,109/285
Rural China (2005)[4]	Quantitative	FIT OC-Sensor Eiken Chemical	20ug Hb/g	100ng Hb/mL	5.4%	Advanced adenoma = 15.12% CRC = 2.4%	20,212/619
Thailand (national) (2017)[47]	Quantitative	FIT OC-Sensor Eiken Chemical	NR	150ng Hb/mL	5.9%	Advanced neoplasia = 28.7% CRC = 10.2%	1,479/1,479
Veracruz, Mexico (2009)[36]	Quantitative	OC-FIT check, OC-Sensor Eiken Chemical	20ug Hb/g	100 ng Hb/mL	5.9%	Pre-malignnat lesions (tubular or serrated adenoma) = 33%	406/21
Semarang, Indonesia (2021)[2]	Quantitative	NR	NR	10ng Hb/mL	16.7%	Adenoma = 26.9% CRC = 19%	221/26
Serbia[22]	NR	NR	NR	NR	5.8%	Adenoma = 37.7% CRC = 8.3%	62,252/1,554

NR, not reported; Hb, hemoglobin; FIT, fecal immunohistochemistry test; N, number; Advanced neoplasia, advanced adenoma or CRC

Table 3: Barriers and Facilitators to Colorectal Cancer Screening Programs in Middle Income Countries, organized by population studied.

Reference	Country	# of Participants	Identified Barriers	Identified Facilitators
Patient-Based Studies				
Koo et al[3]	Asian Countries, including Philippines, Malaysia, Thailand	7915 lay people	– Lack of physician endorsement – Lack of knowledge about CRC symptoms, risk factors and tests	– Physician endorsement – Knowledge of CRC tests
Cai et al[7]	China	463 lay people, aged 40-74	– Lack of awareness of CRC and screening programs – Lack of time (46.4%) – Financial burden (20.8%) – Fear of pain (11.1%) and bowel preparation (5.0%)	
Huang et al[48]	China	684 high-risk individuals	– Lack of symptoms or discomfort (71.1%) – Lack of awareness of CRC disease or screening (67.4%) – Lack of physician endorsement (29.8%)	
Taheri-Kharameh et al[49]	Iran	200 lay people	– Lack of awareness of CRC (86.5%)	
Jadallah et al[41]	Jordan	861 lay people, aged 50-75	– Lack of awareness of necessity for CRC screening (41.7% aware of necessity)	– Physician endorsement (82.3%)
Toleutayeva et al[50]	Kazakhstan	486 lay people	– Lack of knowledge about CRC – *50% did not know whether CRC can occur without symptoms* – Fear of getting CRC in future (61.3%) – Fear of receiving unfavorable results (59.9%)	
Ramanathan et al[51]	Malaysia	89 lay people, aged >50	– Lack of awareness of CRC signs/symptoms and screening – Emotional and logistic concerns about sending stool sample to a clinic	
Patient + Provider-Based Studies				
Lussiez et al[52]	Ghana	14 lay people + 14 providers	– Reliance on alternative medicine or religion – Lack of education – Financial burden – Access to FOBT kits	
Unger-Saldaña et al[53]	Mexico	30 lay people at average risk for CRC, 13 health care providers from a public clinic, and 7 endoscopists	– Lack of awareness about CRC risk – Fear of serious disease – Lack of knowledge by primary care providers – Physician work overload – Insufficient hospital infrastructure, personnel, and supplies	– Provider and patient education on CRC screening – Access to screening tests at no cost to the patient
Provider-Based Studies				

Lussiez et al[42]	Ghana	39 physicians	– Lack of equipment/facilities (28.1%) – Lack of physician training (18.8%) – Lack of provider awareness of screening/not perceiving CRC as a serious threat (patient-level) – High screening costs/lack of insurance coverage (system-level)
Chandran et al[8]	Malaysia	Implementers + program managers, n= NR	– Hygiene and privacy concerns regarding stool collection – Patient refusal – Lack of awareness of accessibility of CRC testing – Lack of promotion of CRC screening – Limited skilled endoscopists – Financial burden
Sahin et al[54]	Turkey	478 PCPs	– Low level of provider knowledge and awareness of guidelines
Review Articles			
Hatamian et al[55]	Asian countries	36 articles from 13 countries (7 MICs)	– Adequate knowledge and awareness of CRC screening – Physician recommendation
Schliemann et al[56]	MICs	24 studies in 9 MICs	– Face-to-face recruitment – Opportunistic clinic-based CRC screening interventions – Educational interventions combined with CRC screening

N, Not reported

Pilot organized CRC screening programs typically targeted a small population and had high participation rates for both stool tests and colonoscopy completion rates: FIT participation rates ranged from 43.7-92.8% (Sao Paulo, Brazil and Barretos, Brazil) and colonoscopy completion rates ranged from 72-87.5% (Lampang, Thailand and Veracruz, Mexico) (Table 1). A pilot program in Mexico City, Mexico recommended one-step invasive CRC screening with colonoscopy and reported a participation rate of 20.5%. Eight out of the nine countries with national or large-scale regional organized CRC screening programs reported CRC screening rates using a stool test, which ranged from 9% (Thailand, national) to 75.5% (China, rural program) (Table 1). Out of these eight countries, only Thailand had a CRC screening rate of <10% of the eligible population. Four countries reported colonoscopy follow up rates for those with a positive stool test; rates ranged from 14% (China, urban program) to 41.1% (Serbia, national). In China, compliance with CRC screening using a questionnaire was high (>99% in urban populations), but rates of follow up endoscopy for patients identified as being high risk for CRC were low (14-18.7%).

Test Characteristics and Performance of Colorectal Cancer Screening Programs in Middle Income Countries

We found that guidelines/programs in 12 MICs recommended CRC screening using guaiac stool tests (gFOBT): Philippines,[19] Marshall Islands,[21] Palau,[22] American Samoa,[23] Georgia,[25] Montenegro,[45] North Macedonia,[26] Russian Federation,[46] Turkey,[48], Colombia,[28] Ghana,[33] and Kenya,[34] and four recommended gFOBT or FIT: Kazakhstan,[49] Ecuador,[29] Jordan,[32] Nigeria[35] (Table 1). None of the countries that recommend gFOBT for CRC screening reported data on percent positive rates. Among the 16 MICs that recommend CRC screening using FIT, programs in 10 countries did not specify the type of FIT used/recommended: Bosnia and Herzegovina,[24] Serbia,[47] Argentina,[50,51] Cuba,[30] Iran,[52] South Africa,[36] Ecuador (gFOBT or FIT),[29] Kazakhstan (gFOBT or FIT),[49] Jordan (gFOBT or FIT),[32] and Nigeria (national guidelines, gFOBT or FIT)[35] (Table 1).

Table 2 summarizes the data from countries that recommend CRC screening using FIT and reported on test characteristics and performance metrics. Programs in four countries used quantitative FIT: rural Chinese organized screening program,[41] a cross-sectional study in Semarang, Indonesia,[54] the national organized Thai program,[58] and a pilot organized program in Veracruz, Mexico.[40] FIT positivity cutoffs ranged from 10ng Hb/mL – 150ng Hb/mL, with 100 ng Hb/mL being the most common, and FIT positivity rates ranged from 5.4%-16.7%. Adenoma detection rates ranged from 15.12 – 33% and CRC detection rates from 2.4%-19%. The remaining programs/studies in 7 countries used qualitative FIT with positive cutoff ranges of 50ng Hb/mL – 200ng Hb/mL, with 50ng Hb/mL being the most common. The FIT positivity rates ranged from 1.1%-18.5%, the advanced adenoma detection rates ranged from 7%-16.5% and the CRC rates ranged from 0.9%-5.6%. Serbia did not report on the type of FIT used but provided data on percent positive FIT (5.8%) and adenoma/CRC detection rates (37.7% and 8.3% respectively).[47]

Colorectal Cancer Screening Efficacy in Middle Income Countries

Most organized CRC screening programs in MICs have been initiated within the last 10 years, limiting the ability to measure their impact on CRC incidence and mortality – however, it was often unclear from the available literature whether this data is being collected. The effect of CRC screening on CRC stage distribution is evident within a few years of implementing a CRC screening program, but this efficacy outcome was also rarely reported in the identified literature. In Kazakhstan, population-based CRC screening was introduced in 2011; between 2004 and 2018, the incidence of stage I and II CRC increased from 35 to 67.4% and the incidence of stage IV CRC decreased from 19.3% to 13.1%.[59] No other MICs reported on CRC stage migration after initiation of CRC screening programs.

Challenges of Screening Programs in Middle Income Countries

Despite the existence of CRC screening programs in several MICs, uptake in most countries remains low, with many barriers to population-wide, equitable CRC screening. Our search identified patient, provider, and health system level barriers to CRC screening uptake, as summarized below and in Table 3.

Following implementation of CRC screening guidelines and/or programs in MICs, several papers have been published assessing patient's beliefs and attitudes towards screening. At the individual patient level, the most commonly cited barriers to CRC screening were patient lack of knowledge about CRC and how it presents, lack of awareness that CRC screening exists and is available locally, and lack of awareness/knowledge about the benefits of CRC screening. Concerns surrounding stool collection and fear of unfavorable results were the next most identified patient-level barriers. In a systematic

review by Hatamian *et al*, commonly reported barriers for CRC screening among patients in Asia included fear of results, fear of procedure, and fear of pain.[60] This study identified adequate knowledge and awareness of CRC screening as well as physician recommendation as the most frequent facilitators of CRC screening.[60]

In a scoping review of CRC screening interventions in LMICs, Schliemann *et al* identified face-to-face recruitment, opportunistic clinic-based screening interventions, and educational interventions combined with screening as strategies which consistently achieve a CRC screening uptake of >65% in LMICs.[61]

The most commonly cited barrier to CRC screening in MICs at the provider-level was provider knowledge about CRC and CRC screening. A summit focused on CRC in Latin America identified widespread unawareness and misinformation about CRC among primary care providers and policymakers, and in the media.[27] A study by Sahin *et al* revealed that although 86.6% of primary care providers in Turkey performed CRC screening, only 6.9% recommended repeat colonoscopy at the correct interval and only 49.7% knew the guidelines with respect to CRC screening age.[62] A 2021 study surveying 39 physicians working at the Komfo Anokye Teaching Hospital in Kumasi, Ghana found that almost 10% of physicians would not recommend CRC screening for asymptomatic, average risk patients who otherwise met the criteria, 40% would recommend initial screening with colonoscopy, 26.7% would recommend gFOBT in combination with flexible sigmoidoscopy, and only one physician would recommend gFOBT alone as the initial screening test, which is the official national CRC screening recommendation.[33] Reasons for not recommending CRC screening included lack of equipment/facilities for the test (28%) and lack of training (18.8%).[33]

From a health systems perspective, the most commonly cited barrier to CRC screening in MICs was limited infrastructure, including an insufficient number of endoscopists. In Brazil the wait for screening colonoscopy can be up to 7 months, and emergency room presentations for lower gastrointestinal symptoms are common.[27] In addition to the lack of endoscopists, an insufficient number of nurses and technicians is consistently identified as a barrier to the implementation of CRC screening programs.[27] Screening and detection of incident CRCs also leads to the downstream need for surgical and oncological services; such services are generally available in MICs that have CRC screening guidelines and/or programs (with the notable exception of Palau, American Samoa, and the US Marshall Islands, which do not offer chemotherapy or radiation in-country), but high uptake of CRC screening services is likely to increase the demand for sub-specialized care in these countries and may present the next barrier to CRC prevention.

Discussion

Colorectal cancer is uniquely well suited to screening – screening tests are safe and can detect both pre-cancerous lesions and early-stage disease, removal of pre-cancerous lesions prevents CRC, and treatment of early-stage CRC is associated with excellent outcomes.[63–65] CRC screening is now well established in many HICs and more recently, several MICs have established national CRC screening guidelines and/or piloted CRC screening programs, which are the focus of this review article.

Colorectal cancer screening can be broadly grouped into one-step testing with invasive, direct-visualization methods such as colonoscopy or flexible sigmoidoscopy and non-invasive, two step methods that require colonoscopy to complete the screening process if the first test is positive. CRC screening tests differ in their sensitivity and specificity for pre-cancerous and cancerous lesions, in their cost, and in the burden that they place on the healthcare system. These factors, in addition to local CRC incidence and local availability of healthcare resources, should be considered when creating CRC screening guidelines in different countries.

In the United States, most individuals undergo one-step CRC screening with colonoscopy, while in most European countries, organized and opportunistic CRC screening guidelines recommend two-step testing, starting with a stool-based test.[66,67] We found that most MICs with organized CRC screening programs recommend a two-step approach with stool-based tests for a target population and follow up colonoscopy for those with a positive stool test result only. The reliance on stool tests for CRC screening in most MICs is likely due to cost and health care resource availability: stool tests are relatively cheap and can be performed at home or in the clinic, while flexible sigmoidoscopy and colonoscopy are expensive and resource intensive, requiring trained endoscopists, endoscopic suites, and appropriate support staff, all of which are often limited in MICs.[51]

We identified 12 MICs with CRC screening guidelines that recommend gFOBT, 12 that recommend FIT, and four that allow for gFOBT or FIT as the initial test. Out of the 16 countries that recommend FIT as a possible initial CRC screening test, 12 programs in 8 countries specified whether a qualitative or quantitative FIT was used (Table 2).

Data from high-income settings suggests that screening with gFOBT reduces CRC mortality by 9-22% while screening with qualitative or quantitative FIT reduces CRC mortality by 10-40%.[68,69] The difference in performance between gFOBT and FIT is attributed to the higher sensitivity and specificity for advanced adenomas and CRC for FIT compared to gFOBT. However, data on sensitivity and specificity for CRC and advanced adenomas using stool tests, as well as impact on CRC incidence and mortality, comes almost exclusively from high-income settings – there is an urgent need to evaluate the performance of CRC screening tests and existing CRC screening programs in MICs. In this review we identified 13 publications that provided data on FIT characteristics and performance in MICs, and none that provided data on gFOBT characteristics and performance (table 2). Data on sensitivity and specificity of FIT for advanced adenoma and CRC was not presented in most of these studies, as only individuals with a positive stool test were recommended for follow up colonoscopy. Furthermore, calculations for FIT adenoma and CRC detection rates and positive predictive values were limited by low colonoscopy completion rates. Nonetheless, we can draw some important conclusions from the available FIT data from MICs. Studies/programs in MICs are more likely to use qualitative FIT for CRC screening instead of quantitative FIT (9 versus 4 studies), most likely because qualitative tests require less upfront investment: they are cheaper and do not require a pathology laboratory or specialized equipment. In 3 out of 4 studies/programs from MICs using quantitative FIT, positivity cutoffs were set at 100–150ng Hb/mL, which is comparable to cutoffs used in the US (100ng Hb/mL), and maximizes specificity and decreases the total number of individuals recommended for endoscopy.[68] The three studies using quantitative FIT with cutoffs 100-150 ng Hb/mL in MICs all had FIT positivity rates of around 5%, and compare favorably to data from high-income countries, where FIT positivity rates consistently range from 5-8% (pooled FIT positivity rate 5.4% for quantitative and qualitative tests).[70,71] In contrast, studies conducted in MICs using qualitative FIT with cut-off ranges from 50-200 ng Hb/mL reported positivity rates ranging from 1.1–18.5%, without a clear correlation between test positivity cut-offs and percent positive rates. The lowest qualitative FIT positivity rate was seen in the pilot organized program in Lampang, Thailand (1.1%, cutoff 200ng Hb/mL) and was much lower compared to nationally representative data using quantitative FIT (5.9%, cutoff 150ng Hb/mL), and may indicate that a cutoff of 200ng Hb/mL for qualitative FIT is too high and would miss too many cancerous and pre-cancerous lesions. The highest FIT positivity rates were seen in studies from Nigeria and Indonesia. In Nigeria, 18.5% of qualitative FITs were positive (cutoff 50ng Hb/mL), with low advanced adenoma and CRC detection rates (7% and 1.1% respectively). This may be due to a cutoff that is too low, a high prevalence of non-malignant occult bleeding in the West African population, or a low prevalence of malignant and pre-malignant lesions. In a small study conducted in Semarang, Indonesia, 16.7% of quantitative FITs were positive (cutoff 10ng Hb/mL), but the adenoma and CRC detection rates were very high (26.9% and 19% respectively); it is hard to draw conclusions from this study given its small size (221 participants total underwent FIT testing and only 26 had a follow up colonoscopy). Overall, the data from studies using qualitative FIT in MICs suggests that these tests produce results that are more variable – this may be because of user error, inappropriate handling of fecal samples, inappropriate handling of point-of-care reagents, or subjectivity in interpretation of point-of-care results. Nonetheless, despite these potential problems, studies from MICs using qualitative FIT to screen for CRC report advanced adenoma and CRC detection rates of 7-16.5% and 0.9-5.6% respectively, which compare favorably to data from high-income countries, where the pooled advanced adenoma detection rate is 25.3% and pooled CRC detection rate is 5.1%.[71] Given the lower CRC incidence rate in most MICs compared to high-income countries, the lower advanced adenoma detection rate may reflect a true lower advanced adenoma incidence in these populations. In addition to providing a comprehensive review of FIT performance for CRC screening in MICs, our study summarizes CRC screening uptake rates in MICs. Although not all countries reported CRC screening uptake rates, there was enough available data to show that organized CRC screening programs achieved higher screening uptake rates, which is consistent with results from a population-based study by Cardoso *et al* of existing CRC screening programs in Europe.[67] Importantly, the Cardoso *et al* study shows consistent decreases in CRC incidence and CRC-associated mortality in European countries that achieve high CRC screening coverage (>50% of the eligible population). In our study, only Serbia and Kazakhstan achieved national CRC screening coverage rates of >50%, both through organized national programs. Montenegro and Argentina have organized national programs with CRC screening coverage rates of >30% and Turkey and Ecuador achieved national CRC screening coverage rates of >20%

with opportunistic programs. In China, the organized Cancer Screening Program in Rural Areas achieved >70% CRC screening coverage in Zhejiang Province. Several organized pilot programs in MICs also achieved high CRC screening coverage rates, but most have not been successfully scaled to the national level.

Implementation of CRC screening programs in the 30 countries included in this review has been quite recent, with nine programs implemented before 2013 and 18 programs implemented after 2013 (Table 1). Given initiation of many of these programs within the last ten years, very little data has been published on changes in national CRC incidence or CRC-associated mortality. However, our study highlights that even within programs with high initial CRC screening rates, colonoscopy completion rates for individuals with positive tests tended to be disappointingly low outside of pilot programs, and thus the positive impacts of CRC screening programs in many MICs may not be observed within 10 years. Notable exceptions were China (organized Cancer Screening Program in Rural Areas, >50% colonoscopy participation rate), Malaysia (national opportunistic CRC screening program, 52-67% colonoscopy participation rate), and Serbia (national organized CRC screening program, 42% colonoscopy participation rate). Low colonoscopy completion rates in other MICs will degrade CRC screening program benefits, even if initial screening rates increase to the target of >50%, thus more resources should be allocated to bridging this implementation gap.

An additional limitation of available data from MICs includes the lack of details surrounding screening invitations for organized programs. While programs are referred to as organized, data regarding invitations to screening were rarely mentioned, limiting our ability to comment on strategies to increase CRC screening rates within organized programs in MICs. Nonetheless, our search identified several actionable barriers to CRC screening in MICs, including lack of physician buy in, lack of participant knowledge and resources, as well as participant fear of screening. Given clear barriers with regards to the public's knowledge of both CRC symptoms and screening, there is room for improvement with regards to educational campaigns in MICs.

Conclusion

In the last decade CRC incidence and mortality continues to increase globally as the adoption of Westernized lifestyles accelerates. Screening remains a key step in effectively reducing incidence and mortality, but population-based CRC screening programs are lacking in most MICs. Our search identified local, regional, or national CRC screening programs in 29 out of 108 MICs. Most countries recommend two-step CRC screening with an initial stool test and follow up colonoscopy for those with positive stool tests only. MICs with organized CRC screening programs had higher CRC screening uptake rates, although most still had low colonoscopy completion rates, and very few have achieved CRC screening coverage of >50% of the eligible population. Significant barriers to CRC screening in MICs included lack of knowledge amongst lay people and providers about CRC symptoms, availability of CRC screening, and screening guidelines. Furthermore, economic constraints and limited infrastructure including colonoscopy devices and trained endoscopists limit the ability of many countries to offer effective screening. While barriers are omnipresent, globally we must strive for the adaption and uptake of feasible and effective CRC screening programs within MICs.

Conflicts of Interest Statement:

Yoanna Pumpalova: Pfizer (Ownership Interest). The other authors indicated no financial relationships.

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SUPPLEMENTARY MATERIAL

Supplemental Table 1: Lower and upper-middle income countries as defined by World Bank, listed alphabetically.

Region	Country
East Asia and Pacific	
Lower Middle Income	Cambodia, **Indonesia**, Kiribati, Laos, Micronesia, Mongolia, Myanmar, Papua New Guinea, **Philippines**, Samoa, Solomon Islands, Timor-Leste, Vanuatu, Vietnam
Upper Middle Income	**American Samoa**, **China**, Fiji, **Malaysia**, **Marshall Islands**, **Palau**, **Thailand**, Tonga, Tuvalu
Europe and Central Asia	
Lower Middle Income	Kyrgyzstan, Tajikistan, Ukraine, Uzbekistan
Upper Middle Income	Albania, Armenia, Azerbaijan, Belarus, **Bosnia and Herzegovina**, Bulgaria, **Georgia**, **Kazakhstan**, Kosovo, Moldova, **Montenegro**, **North Macedonia**, **Russian Federation**, **Serbia**, **Turkey**, Turkmenistan
Latin America & the Caribbean	
Lower Middle Income	Bolivia, El Salvador, Haiti, Honduras, Nicaragua
Upper Middle Income	**Argentina**, Belize, **Brazil**, **Colombia**, Costa Rica, **Cuba**, Dominica, Dominican Republic, **Ecuador**, Grenada, Guatemala, Guyana, **Jamaica**, **Mexico**, Paraguay, Peru, St. Lucia, St Vincent and the Grenadines, Suriname
Middle East and North Africa	
Lower Middle Income	Algeria, Djibouti, Egypt, **Iran**, Lebaon, Morocco, Tunisia, West Bank and Gaza
Upper Middle Income	Iraq, **Jordan**, Libya
South Asia	
Lower Middle Income	Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka
Upper Middle Income	Maldives
Sub-Saharan Africa	
Lower Middle Income	Angola, Benin, Cabo Verde, Cameroon, Comoros, Republic of Congo, Côte d'Ivoire, Eswatini, **Ghana**, **Kenya**, Lesotho, Mauritania, **Nigeria**, São Tomé and Príncipe, Senegal, Tanzania, Zimbabwe
Upper Middle Income	Botswana, Equatorial Guinea, Gabon, Mauritius, Namibia, **South Africa**

Bolded countries included in review.

Supplementary: Narrative Description of CRC Screening Programs in Middle Income Countries, Organized by World Bank Income level and Lending Groups

Lower Middle-Income Countries

East Asia and Pacific

Philippines

Starting in 2002, the Philippines Cancer Control Program recommended opportunistic CRC screening with annual gFOBT or sigmoidoscopy every 3-5 years for people ages 50 years or older.[22] One study evaluating CRC screening participation in Asian countries found very high rates of participation in the Philippines among individuals ages 50 years or older (69% among 343 randomly selected individuals), despite no organized CRC screening program.[7] High uptake may be at least partially attributable to the Philippine Cancer Control Program, enacted in 1988, as an integrated approach to utilizing primary, secondary and tertiary prevention for the six leading cancers, including CRC.[7,8]

Indonesia

According to one published study, the Ministry of Health in Indonesia put out national consensus recommendations for CRC screening in 2017, but implementation has been slow because screening is not covered by the national health insurance.[9] We identified two studies of CRC screening programs in Indonesia using FIT. A study conducted in Depok district, West Java in 2012 evaluated the use of qualitative FIT for CRC screening in a rural population. Using cluster consecutive sampling, 278 patients from five community

health centers in Depok were recruited into the study and all underwent CRC screening using qualitative FIT (positive cutoff: 10µg Hb/g feces;50ng/mL buffer). Eleven patients were found to have a positive FIT (4%), but none underwent follow up colonoscopy.[10] A more recent study recruited 350 average risk patients ages >45 years while they were waiting to be seen across 10 primary health care centers in Semarang, Indonesia from April – October 2021.[9] Screening was completed by 221 participants (63% participation) using a quantitative FIT (Hb 10 ng/mL) and positive tests were followed up by a colonoscopy.[9] The FIT positivity rate was 16.7% and 70.3% of participants underwent follow up colonoscopy.[9] The adenoma detection rate was 26.9% (7/26) and the malignancy detection rate was 19.2%.[9]

Middle East and North Africa

Iran

According to Iran's Package of Essential Non-Communicable Diseases program, the Iranian Ministry of Health piloted an organized CRC screening program for those 50-70 years old using FIT starting in 2015.[11] Individuals in the target population are invited to their local primary health center for registration of cancer-related symptoms and family history. They are then trained on FIT and asked to complete the test at home. Those with negative FIT are asked to repeat the test in 2 years and those with positive FIT are referred for colonoscopy.[12] Adherence to the primary phase of screening with FIT was approximately 13% amongst the over 2.6 million participants who were invited for screening at health centers across Iran between 2018 and 2019.[13]

Sub-Saharan Africa

Ghana

In Ghana, guidelines put out by the National Cancer Steering Committee in 2011 recommend opportunistic CRC screening using gFOBT for individuals ages 50-70 years old.[1] There is limited data on CRC screening uptake in Ghana since the issuance of this screening recommendation, and we did not identify any studies describing any CRC screening programs.

Kenya

The 2017-2022 Kenya National Cancer Screening Guidelines recommend initiation of CRC screening at age 45 years with gFOBT for low/average risk patients and colonoscopy for high-risk patients.[2] Our search did not reveal any publications evaluating pilot CRC screening programs or CRC screening uptake in Kenya since the issuance of these national guidelines. A perspectives piece by Parker *et al* published in December 2018 confirmed that prior to these screening guidelines, essentially all patients diagnosed with CRC at a large referral hospital in southwestern Kenya presented with symptoms, with no cases of CRC detected through routine screening due to lack of availability of screening.[3]

Nigeria

The 2018-2022 Nigeria National Cancer Control Plan states that it aims to make stool testing and colonoscopy for CRC screening available to all Nigerians by 2022.[4] In 2019, Nigerian gastroenterology experts put out CRC screening guidelines, which recommend CRC screening start at age 40 and list the following options for screening: 1) biennial screening with FIT (or gFOBT in absence of FIT), 2) annual FIT (or gFOBT in absence of FIT) with flexible sigmoidoscopy every 5 years and, 3) colonoscopy every 10 years, or 4) CT colonography every 5 years.[5] The authors acknowledged the lack of local data supporting the feasibility or cost-effectiveness of these screening strategies.[6] In 2021, Alatise and colleagues initiated a pilot opportunistic CRC screening program in 3 Nigerian states (Osun, Lagos, and Kwara) using qualitative FIT (50 ng Hb/mL feces). A population-based recruitment strategy was used with print media, radio, television, social media, and community mobilisers to advertise the study in each state. Overall, 2330 participants enrolled in the study and received a FIT KIT and 91% returned it; there were 432 participants with positive tests (18.5%), out of which 285 underwent a colonoscopy (66%).[6] Among those with a positive FIT who completed colonoscopy, the positive predictive value for CRC was 1.1% and 7.0% for advanced adenoma.[6]

Upper Middle-Income Countries

East Asia and the Pacific

Several MICs in East Asia and the Pacific have CRC screening guidelines and/or programs in place, including American Samoa, China, Malaysia, the Marshall Islands, Thailand and Palau.

China

In China, population-based, organized CRC screening programs began in the 1970s in high CRC incidence regions.[14] A population-based study conducted in Jiashan County from 1989 to 1996 randomized residents

ages 30 years and older to CRC screening (using a structured risk-assessment questionnaire and qualitative FIT) or no screening on the township level.[15] Participants categorized as high-risk based on qualitative FIT result and the risk-assessment tool were recommended for flexible sigmoidoscopy. The study found a 31.7% reduction in mortality from rectal cancer in the screening compared to control group during a 5 year-follow up, but no reduction in colon cancer mortality.[15] Additionally, a prospective study of 324 patients recruited from 5 hospitals in Beijing, China between 2003-2004 found that qualitative FIT was cost effective for CRC screening in China compared to gFOBT.[16]

Although there are no nationwide CRC screening programs in China, several organized CRC screening programs are supported by local governments. These programs include the Cancer Screening Program in Rural Areas, which was initiated in 2005 and covers 234 counties in 31 provincial-level administrative divisions (PLADs) as of 2016 and the Cancer Screening Program in Urban Areas, which was initiated in 2012 and covers 42 cities in 20 PLADs as of 2021.[14] CRC screening programs call for screening of average-risk individuals between 50 and 75 years of age using a two-step process of either a risk factor questionnaire alone, or in combination with FIT, as the primary screening test, followed by a full colonoscopy for follow-up of high-risk individuals only.[14,17]

A study by Chen *et al* evaluated participation in the Cancer Screening Program in Urban Areas among over 1 million individuals in 16 provinces in China from 2012 to 2015; this study found a very high rate of participation (99%) for the first CRC screening step (questionnaire only) but only 14% of the 182,927 individuals found to be 'high risk' for CRC completed a colonoscopy.[18] Zhang *et al* evaluated the same CRC screening program after it was adopted in Henan province and found that between 2013-2019, only 18.71% of participants found to be 'high risk' for CRC using a screening questionnaire completed a colonoscopy.[19] In 2004, Cai *et* al evaluated participation in a free community-based CRC screening program in Hangzhou city and found that participation in screening with qualitative FIT was 37.2% among a target population of 38,337 people with a FIT positivity rate of 3.6%; however, the follow up colonoscopy completion rate was only 18.5% (94/509).[20] The Cancer Screening Program in Rural Areas in Zhejian Province was evaluated in 2020 – initial screening was with qualitative or quantitative FIT (cutoff 100 ng Hb/mL buffer), with very high rates of FIT participation (75.5% and 70.2% respectively), FIT positivity rates of 14% and 5.4% respectively, and colonoscopy completion rates of 53.3 and 56.4%.[21] The advanced adenoma detection rates for qualitative versus quantitative FIT were 9.6% and 15.12% and for CRC 0.9% and 2.4%.[21] Detection rates were statistically significantly higher using quantitative FIT.

Malaysia

In Malaysia, the Ministry of Health conducted a CRC screening feasibility study in 2010 using qualitative FIT. Following this study, a pilot implementation program using FIT was rolled out between 2012 and 2013 in six Malaysian states and in 2014 new national guidelines recommended CRC screening using qualitative FIT for all patients ages 50-75 years old. Between 2014 and 2018, 127,957 Malaysians were screened using FIT, with a 9.3% positivity rate, and a 52-67% colonoscopy completion rate among those with a positive FIT.[22] Among those who underwent colonoscopy, 13.9% were diagnosed with colonic polyps and 4.1% with CRC.[22] Between 2018 and 2019, significant gains were made in CRC screening coverage – the percent of eligible Malaysians who had undergone screening with FIT increased from <1% to 10.8%.[23,24]

Marshall Islands

The Marshall Islands National Comprehensive Cancer Control Plan (2017-2022), recommends opportunistic CRC screening for those ages 50-75 years old using gFOBT, with colonoscopy reserved for diagnostic confirmation only.[25] Opportunistic CRC screening began in one of the two hospitals in the country (Ebeye) in 2010, and in the second (Majuro) in 2014. A 2013 chart review by the Ministry of Health showed that just 6.4% of eligible persons had undergone CRC screening. Per the National Comprehensive Cancer Control Plan, the country's goal was to increase the percentage of eligible persons who have undergone CRC screening from 6.4% to 20% by June 2022.[25] No publications were identified during our search regarding whether this goal was met.

Palau

The Pacific Island nation of Palau is supported by the United States and the CDC has funded Comprehensive Cancer Control programs focused on community awareness and screening in Palau since 2004. CRC screening with gFOBT is available in Palau, but the island does not have a formal screening program in place.[26] According to their National Cancer Control Plan for 2018-2023, the country's goal is to increase CRC screening from 5% to 10% by 2023.[2726] Importantly, although cancer is one of the top leading causes of death in Palau, there is no cancer treatment available on the island and patients diagnosed with cancer are referred for treatment in the Philippines, Taiwan or Hawaii.[26]

American Samoa

Similarly, within American Samoa, an unincorporated territory of the United States consisting of seven islands in the southern Pacific Ocean, the Department of Health offers CRC screening with gFOBT.[27] The American Samoa Cancer Control Plan notes a goal of increasing CRC screening to 30% by 2012 without published data to indicate whether this goal has been achieved. Notably, as of 2004, there were only two surgeons in American Samoa trained to perform colonoscopies.[28]

Thailand

In 2017, the Thai government launched a national CRC screening program for asymptomatic people ages 50-70 years old using a two-stepped screening model with a one-time quantitative FIT followed by colonoscopy for positive FIT. The estimated population to be screened was 13.3 million in 2017, and the program covered 1.2 million people that year (9%).[29] Prior to the launch of the national CRC screening program, a pilot implementation program in Lampang Province found that among the target population of 127,301 individuals between 2011 and 2012, uptake of CRC screening using FIT was 62.9%.[30] The FIT positivity rate was 1.1% and of those with a positive FIT, 72% complied with follow-up colonoscopy; adenoma was found in 30.5% of individuals and CRC in 3.7%.[30] Participation was higher among women (67.8%) than men (57.8%).[30]

Europe and Central Asia

Of the upper middle-income countries within Europe, six of ten have CRC screening programs in place: Bosnia and Herzegovina, Georgia, Montenegro, North Macedonia, Russia and Serbia, while two of six Central Asian upper middle-income countries have screening programs: Turkey and Kazakhstan. Most of these eight countries have developed organized CRC screening programs, with the exception of Bosnia and Herzegovina and North Macedonia.

Bosnia and Herzegovina

Data from Bosnia and Herzegovina is limited, with one review article reporting a national opportunistic CRC screening program using FIT for those >50 years as well an organized regional program using FIT for the same target population, although no further details are provided for either program.[33] Interestingly, another publication reported the absence of colonoscopy equipment within the General Hospital in Konjic and emphasized the need for proper equipment in order to facilitate CRC screening.[34]

Georgia

In 2011, Georgia adopted opportunistic CRC screening with gFOBT in individuals aged 50-70 years old.[35] At its highest point of uptake in 2019, less than 2% of the targeted population underwent CRC screening.[35,36] While the literature notes a pilot organized screening program within the capital (Tbilisi), according to the National Screening Center, the privatization of health services has prohibited the coordination and quality of screening services, effectively transforming the organized program into an opportunistic type program.[35]

Montenegro

In 2008 the Government of Montenegro developed a National Cancer Control Plan recommending national screening programs for colorectal, breast and cervical cancers.[37] After a pilot initiative, Montenegro initiated an organized national CRC screening invitation program in 2013, which relies on targeted outreach messages via mobile phones encouraging men and women ages 59 – 64 years to undergo free CRC screening.[37] General practitioners (GPs) are also financially incentivized to extend invitations for CRC screening to eligible patients. Screening for CRC is done using gFOBT, with colonoscopy recommended for positive tests.[38] According to reports by the Institute for Public Health in Montenegro, the CRC screening coverage rate in 2018 was 67%, although only 42% of the target population returned the gFOBT to their GP.[38]

North Macedonia

In North Macedonia the CRC Prevention Program is coordinated by the Health Development Strategy and provides evidence and recommendations for the prevention, early detection, and treatment of CRC. The stated objective of the Program for Early Detection of CRC in the Republic of North Macedonia is to reduce mortality by 15% over 5 years and cover 75% of the population at risk by 2015.[39] The opportunistic CRC screening program mandates that primary care physicians inform eligible patients ages 50-74 about CRC screening and advise them to complete 3 consecutive gFOBTs.[39]

Russia

In Russia, CRC screening was not included in the 2010 National Priority Project Health.[40,41] However, a recent article in the ASCO Post states that Russia began an organized national health checkup or "dispensarization" program in 2013, which reportedly includes CRC screening using gFOBT.[42] Data is scarce surrounding details of CRC screening uptake and efficacy.

Serbia

Serbia initiated CRC screening through its National Organized Colorectal Cancer Screening Program in 2013-2014. GPs invite the target population (individuals aged 50-74 years old) by letter and phone to perform FIT every 2 years, with positive tests followed by colonoscopy.[43] Within the first round of invitations, the participation rate was 62.5%, the FIT positivity rate was 5.9% and colonoscopy was performed in 41.1% of those with a positive FIT.[43]

Turkey

Within Central Asia, Turkey initiated an organized CRC screening program in 2013 and recommends either gFOBT every 2 years or colonoscopy every 10 years for individuals ages 50-70 years old.[44] Patients undergo screening at Cancer Early Diagnosis, Screening and Training Centers where personnel are trained in cancer screening.[44] In 2016, 20-30% of the eligible population had undergone CRC screening.[44]

Kazakstan

Kazakstan implemented CRC screening in 2011 with a two-step approach of gFOBT/FIT first, and colonoscopy for positive tests.[45] Studies have shown that after screening implementation, initial incidence of CRC expectedly increased, as did the rates of stage I and II disease.[46] A study from the Almaty region of Kazakhstan showed that among an eligible population of 202,694 people , participation in CRC screening using stool tests was 53.4-58.2% in 2018-2019, but only 17.9-20.2% for follow up colonoscopy among individuals with a positive stool test.[47]

Latin America and the Caribbean

According to the World Health Organization 2013 non-communicable diseases country capacity survey, CRC screening is generally available in most Latin American countries. Nonetheless, organized screening programs remain uncommon across the continent.[48,49] In 2016, the Pan American Health Organization (PAHO) published a report from the CRC screening in the Americas consensus meeting and noted that Argentina and Brazil were the only MICs in the region to offer organized CRC screening programs, largely through pilot programs in urban areas.[48] Colombia, Cuba, Ecuador, Mexico, Suriname, and Jamaica have opportunistic CRC screening clinical guidelines, without organized programs.[48]

Argentina

In Argentina, CRC screening using annual FIT has been shown to be cost-effective compared to no screening or colonoscopy every 10 years.[50] Organized CRC screening began in 2013 and is coordinated through the National Prevention and Early Detection Program for CRC, which recommends yearly qualitative FIT with positives followed up with colonoscopy for average risk individuals and screening colonoscopy for high risk individuals.[51,52] Based on a 2018 nationally representative survey, CRC screening uptake was 30.66% among the target population, increased from 22.26% in 2013.[53]

Brazil

In Brazil, the Ministry of Health has approved opportunistic CRC screening using colonoscopy for those 50 years and older; however, according to a 2014 survey, only 27% of the target population had undergone CRC screening.[54] The Hospital Alemão Oswaldo Cruz in São Paulo initiated a pilot CRC screening program following a prevention campaign in which a large replica of the human colon was exhibited in a local sports gymnasium to educate the population on the organ and the diseases affecting it. Following this campaign, eligible individuals ages greater than 40 years were invited to undergo CRC screening with annual FIT. The FIT uptake rate was 43.7% in 2006 among a target population of approximately 10,000 people who participated in this pilot study.[55] FIT positivity was 10.7%, and colonoscopy follow up rates were high (86.5%).[55] The Barretos Cancer Hospital, one of the largest hospitals caring for underserved patients, implemented a FIT-based organized CRC screening program between 2015 and 2017 and within this program, 92.8% of invited individuals returned the FIT, 12.5% had a positive FIT results, and there were high levels of colonoscopy compliance and completion rates for positive stool tests (84.6% and 98.2% respectively).[56] Analysis of positive FIT showed that 5.6% resulted in a cancer diagnosis, and the stage distribution of screen-detected cancers was earlier compared to clinically diagnosed CRCs.[56]

Colombia

The Colombian public health care system facilitates opportunistic screening with gFOBT, but participation remains low according to the National Demographic and Health Survey, which showed that only 8.6% of women and 7.1% of men aged 50–69 were compliant with CRC screening in 2015.[57]

Ecuador

As part of a new national cancer control strategy put forth in 2017, Ecuador offers opportunistic screening with gFOBT/FIT.[48] A national study conducted in 2018, found that among 4,641 random participants aged 50-69 years, CRC screening rates using gFBOT/FIT were 25.3% and 22.6% among women and men, respectively, and screening rates using colonoscopy were 13.9% and 10.9%.[40]

Mexico

The Mexican national guidelines recommend CRC screening using gFOBT or FIT for those 50 years and older, but organized population-level CRC screening programs do not exist on the national or regional level.[52] Several pilot organized CRC screening programs have emerged at the local level. Medica Sur Hospital in Mexico City conducted a pilot organized CRC screening study among eligible employees from 2009-2010. Six hundred personalized letters were sent to asymptomatic employees 40-79 years of age inviting them to participate in CRC screening via colonoscopy, with a response rate of 20.5% and an adenoma detection rate of 17% among those who completed a colonoscopy.[58] In another pilot program conducted in Veracruz, Mexico from 2015-2016, 473 quantitative FIT kits were distributed to adults aged 50-75 and 85.8% were returned and analyzed; using ≥20 µg Hb/g feces as the positive cutoff, 5.9% of tests were positive (24/406), and twenty-one patients completed a follow-up diagnostic colonoscopy (87.5%).[59]

There are no Caribbean countries with organized screening programs, though opportunistic screening with colonoscopy is available on some islands, including Cuba and Jamaica.

Cuba

In 2013, Cuba began offering opportunistic CRC screening with qualitative FIT (cutoff >0.2 µg Hb/mL feces) as part of the country's cancer control strategy for those over age 50 years.[60] Despite availability of FIT testing in the 116 Cuban municipalities with the highest CRC mortality rates, CRC screening coverage in 2014 was only 2.7%.[60] The FIT percent positive rate was 10.4%, but no data was provided on colonoscopy completion rates.[60]

Jamaica

In Jamaica, a retrospective review of colonoscopies performed at one medical center between 2007 – 2011 revealed that screening colonoscopies accounted for only 11% of the performed colonoscopies, with the main indication for colonoscopy being bleeding.[61]

Middle East and North Africa

Jordan

The healthcare authorities in Jordan endorse and finance opportunistic CRC screening using gFOBT or FIT annually in asymptomatic individuals ages 50-75 years old.[32] The Jordanian Ministry of Health is considering expanding CRC screening to those 45-49 year of age, as has recently been recommended in the United States.[32] A survey study conducted between April 2020 and June 2021 included 861 Jordanians ages 50–75 years old and revealed that only 17.2% of those interviewed had undergone CRC screening, some of whom were prompted to undergo screening due to symptoms suggestive of CRC.[32]

Sub-Saharan Africa

Our search did not identify any organized CRC screening initiatives within the six upper middle-income countries in SSA.

South Africa

South Africa offers opportunistic screening with FIT and colonoscopy in the private and public sectors but has yet to implement a national CRC screening program, and we were unable to find any data on CRC screening uptake rates.[31]

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