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Colorectal cancer population screening programs worldwide in 2016: An update

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Abstract

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world. The incidence and mortality show wide geographical variations. Screening is recommended to reduce both incidence and mortality. However, there are significant differences among studies in implementation strategies and detection. This review aimed to present the results and strategies of different screening programs worldwide. We reviewed the literature on national and international screening programs published in PubMed, on web pages, and in clinical guidelines. CRC Screening programs are currently underway in most European countries, Canada, specific regions in North and South America, Asia, and Oceania. The most extensive screening strategies were based on fecal occult blood testing, and more recently, the fecal immunochemical test (FIT). Participation in screening has varied greatly among different programs. The Netherlands showed the highest participation rate (68.2%) and some areas of Canada showed the lowest (16%). Participation rates were highest among women and in programs that used the FIT test. Men exhibited the greatest number of positive results. The FIT test has been the most widely used screening program worldwide. The advent of this test has increased participation rates and the detection of positive results.

Key words: Colorectal cancer; Colorectal cancer screening; Fecal occult blood test; Fecal immunochemical test; Colonoscopy

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Core tip: Colorectal cancer is the third most commonly diagnosed cancer worldwide. The incidence and mortality show wide geographical variations across the world. Screening is recommended to reduce both, however, there are significant differences among studies in implementation strategies and detection. This review aimed to present the results and strategies of different screening programs worldwide.

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INTRODUCTION

Colorectal cancer (CRC) is one the most commonly diagnosed cancers worldwide. Among men with cancer, CRC ranked third in prevalence (746000 cases, 10% of the total male population), after lung and prostate cancers. Among women with cancer, CRC ranked second in prevalence (614000 cases, 9.2% of the total female population), after breast cancer. CRC incidence and mortality show wide geographical variations across the world. When comparing age-standardized incidence rates (ASRIs) of CRC in different countries, we found the highest rates in Australia and New Zealand, and the lowest rates in Western Africa^[1].

Nearly 55% of CRC cases occur in developed regions, but CRC-related mortality is highest in less developed countries (including regions of Africa). This poor survival is probably due to the lack of available health resources. However, high- and low-income countries also show large variations in the proportion of the population included in CRC registries. These variations may arise from underdiagnoses, due to local medical and economic situations^[2].

In many regions, the risk of developing CRC is around 5%, and of those patients, 45% will die despite treatment^[3]. According to GLOBOCAN data, 694000 individuals died in 2012 from CRC worldwide (374000 men and 320000 women). Mortality rates show less variability than incidence rates; the highest estimated CRC-related mortality rates in both sexes were found in Central and Eastern Europe, and the lowest were found in Western Africa^[1].

In Europe, there are huge variations in the ASRIs of CRC; the lowest incidences were observed among men and women in Bosnia Herzegovina (30 per 100000 and 19 per 100000, respectively) and in Albania (13 and 11 per 100000 respectively). Among men, the highest incidences were observed in Slovakia, Hungary, and the Czech Republic. Among women, the highest incidences were found in Norway, Denmark, and Holland^[1]. Although mortality rates are generally

geographically similar to incidence rates, mortality is sometimes high in countries with relatively low incidence rates (Moldavia, Russia, Montenegro, Poland, and Lithuania)^[4]. In North America, the ASRi of CRC was estimated to be 26.1 per 100000. In 2016, the American Cancer Society estimated that 134490 new CRC cases would be diagnosed in individuals of both sexes, and that 49190 individuals would die from CRC in the United States^[5]. In the Eastern Mediterranean region, the highest CRC incidence was found in Israel (36 per 100000), followed by Jordan and Kazakhstan (26 and 23 per 100000, respectively). The highest mortality rates were found in Jordan, followed by Kazakhstan, Armenia, and Israel. In the Asian Pacific region, the incidence of CRC varies among regions. The highest incidence was reported in South Korea (ASRi: 45 per 100000). Singapore and Japan also had high incidence rates (ASRIs: 34 and 32 per 100000, respectively). Compared to those regions, other countries, like India, have much lower ASRIs (6 per 100000) and age-standardized mortality rates (ASRm: 5 per 100000)^[4].

CRC qualifies for screening according to the criteria established by Wilson and Jungner as the "gold standard of screening assessment"^[6-8]. The criteria that CRC fulfills include its high incidence rate, its long preclinical phase, its recognizable and tractable precursor, and the correlation between the tumor stage and mortality rate. Although the value of the Wilson and Jungner criteria remains undisputed to this day, newer policy tools are now available (Table 1)^[9].

Screening for CRC appears to be cost-effective compared to no screening^[10]. However, CRC screening programs must be adapted to the risk of each population. An average-risk population is defined as a population of individuals aged 50 years or older, with no additional risk factors. The recommended screening for the average-risk population is one of the following: an annual or biennial fecal immunochemical test (FIT); sigmoidoscopy every 5 years; or colonoscopy every 10 years. When subgroups are identified and characterized with a higher-than-average incidence of colorectal neoplasia, it is necessary to increase the screening frequency to achieve program cost-effectiveness^[11]. Despite recommendations, screening is currently offered to only a small proportion of the population.

In this review, we evaluated the results of 17 screening programs. We obtained ASRIs and ASRms in the different countries reviewed from the website: www.globocan.iarc.fr. A literature search was conducted in PUBMED with the following keywords: Screening, Colorectal Cancer, Bowel cancer, guidelines, programmes, program, results, FIT, guaiac, first round, pilot, rounds, Europe/ United Kingdom/ Ireland/ The Netherlands/ Lithuania/ Italy/ Croatia/ Czech Republic/ Slovenia/ France/ Canada/ California/ USA/ Korea/ Australia/ Thailandia/ Taiwan/ Chile. CRC

Table 1 New screening criteria (Adapted from: Andermann *et al.*^[9])

Emerging screening criteria proposed after Wilson and Junger principles
The screening programme should respond to a recognized need
The objectives of screening should be defined at the outset
There should be a defined target population
There should be scientific evidence of screening programme effectiveness
The programme should integrate education, testing, clinical services and programme management
There should be quality assurance, with mechanisms to minimize potential risks of screening
The programme should ensure informed choice, confidentiality and respect for autonomy
The programme should promote equity and access to screening for the entire target population
Programme evaluation should be planned from the outset
The overall benefits of screening should outweigh the harm

screening program characteristics were also collected from national governmental websites. To evaluate and compare screening programs, we used universally applicable CRC screening indicators.

CRC SCREENING TESTS

Stool tests

It has been established that CRC mortality could be reduced by screening with periodic fecal occult blood tests (FOBTs), followed by colonoscopy when the results were positive. A systematic review published in 2008, which included 4 clinical controlled trials involving over 300000 participants, found that screening with FOBT reduced the relative risk (RR) of CRC mortality by 16%, without adjustment, and by 25% after adjusting for screening attendance^[12]. The follow-up of those patients showed that the effect of screening was reduced CRC-mortality, and this effect persisted for over 30 years^[13]. A reduction in the RR of CRC incidence was also detected in follow-up, mainly due to the removal of adenomatous polyps. This effect was greater among individuals that received annual screenings (20% RR) than among those that received biennial (17%) screenings^[14].

Currently, there are two different tests available: the FIT and the guaiac fecal occult blood test (G-FOBT). The FIT achieved significantly higher detection rates for advanced adenomas and CRC than the G-FOBT. Although the FIT was more sensitive than the G-FOBT (61% vs 23.8%, respectively), its specificity was slightly lower (95.1% vs 97.7%, respectively)^[15,16]. Participation rates appeared to be higher in screening programs that used FIT compared to those that used G-FOBT^[15]. This issue is probably related to the facts that FIT does not require dietary restrictions (due to its specificity to human hemoglobin [Hb]) and that only one sample is needed in most screening programs^[16]. Additionally, FIT offers quantitative results (ng Hb per mL buffer or µg Hb per gram feces) and an automated reading of the results. The cut-off value for the amount of Hb detected can be predetermined by the investigator. Several cut-off values have been used with different sensitivity and specificity rates. The investigator can adjust the

cut-off value to limit the number of colonoscopies required, and thus, avoid overextending the available endoscopic resources. An optimum cut-off value has not been established; therefore, the choice should be based on the availability of endoscopic resources, the epidemiology of CRC in the study population, and the expected participation in the program^[17]. Values between 20 and 30 µg/g are recommended when the Health Care System can accommodate colonoscopies for approximately 5% (expected FIT positivity rate) of the population study (aged 50-74 years)^[18].

Based on current evidence, the FIT has been recommended as the first option for detecting fecal occult blood in CRC screening^[19]. Most European countries with an organized screening program are currently using the FIT. This test has replaced the G-FOBT in screening programs in the United Kingdom since 2014 and in France since 2015^[4].

Other non-invasive techniques are available, such as the fecal DNA analysis. These tests identify molecular alterations in adenomas and CRC cells. However, these tests are currently underused, due to the high cost and relatively low cost-effectiveness^[20].

Invasive techniques

Flexible sigmoidoscopy screening was shown to be effective in reducing the incidence and mortality rates of CRC^[21,22]. It should be taken into account that, when a distal adenomatous polyp is detected in a sigmoidoscopy, a colonoscopy is required. This is necessary, because the characteristics of adenomas found in the rectum and sigma are correlated with the probability of presenting a proximal CRC^[23,24].

Colonoscopy screening is used in several programs. Data are scarce from randomized clinical trials that have attested to its effectiveness. However, several observational studies have reported that colonoscopy screening reduced CRC mortality and incidence, mainly due to its great capacity for detecting neoplasias and adenomas. In a case-control study, performing a colonoscopy, regardless of its indication, was associated with a large reduction in the risk of CRC in the following 10 years after the test. This effect was greater when the colonoscopy had been used as a screening test^[25]. Several cohort studies have

confirmed this finding. One study showed that, in an average-risk population, performing a colonoscopy was associated with a 67% reduction in CRC incidence after an 8-year follow-up^[26]. Another study demonstrated the long-term protective effect of a polypectomy. When a colonoscopy was performed with a polypectomy of at least one adenoma > 5 mm, the CRC incidence was reduced by 80% after a 10-year follow-up^[27].

Colonoscopy quality has varied in reports from different endoscopists. For this reason, over the last decade, a series of quality indicators for colonoscopy have been described. However, application of these indicators has not become well established in endoscopic practice^[28]. Currently, the main quality indicator among endoscopists is the adenoma detection rate (ADR). The ADR is defined as the proportion of screening colonoscopies performed by a physician that detected at least one histologically confirmed colorectal adenoma or adenocarcinoma. The recommended ADR is $\geq 25\%$ (men $\geq 30\%$, women $\geq 20\%$)^[29]. Several studies have demonstrated a strong correlation between the ADR record of an endoscopist and the probability of diagnosing CRC within a given number of months of a colonoscopy (an interval CRC)^[24]. Despite the clinical importance of this measure, large variations remain among endoscopists.

One study analyzed the results of colonoscopies performed in the US through an integrated health services organization, over a 12-year period. The association between the ADR and the risk of diagnosing CRC within 6 mo to 10 years after the first colonoscopy was evaluated, and the risk of death from cancer was calculated. They studied a total of 314872 colonoscopies performed by 136 gastroenterologists, with ADRs that ranged from 7.4% to 52.5%. They identified 712 interval colorectal adenocarcinomas and 147 associated deaths. The gastroenterologists were placed into quintiles, based on their ADRs (lowest ADR quintile $\leq 19.06\%$ and highest ADR quintile $\geq 33.51\%$). They found that patients examined by gastroenterologists in the lowest ADR quintile had almost double the risk of being diagnosed with an interval cancer compared to patients examined by gastroenterologists in the highest quintile. In addition, the risk of a fatal interval cancer was reduced by 62% among patients examined by gastroenterologists in the highest quintile. Each 1% increase in the ADR was associated with a 5% decrease in the risk of a fatal interval colorectal cancer^[30].

Although the colonoscopy is more effective than the FOBT for detecting neoplasias and adenomas, the FOBT is more readily accepted by participants in population screening programs. Thus, the higher FOBT participation rates may counteract its lower detection capacity^[31]. The COLONPREV study hypothesized that biennial FIT screening would be non-inferior to a one-time colonoscopy, for reducing CRC-related mortality among subjects with average risk. They recruited more than 50000 asymptomatic participants between

ages 50 and 69 years, and randomly assigned them to undergo either a one-time colonoscopy or the biennial FIT. After the first round of FIT screening, they confirmed a similar CRC detection rate with both methods. However, advanced adenomas and other adenomas were detected at a higher rate in the colonoscopy than in the FIT groups. This result confirmed, once again, the superiority of the colonoscopy for detecting this type of lesion. Therefore, the colonoscopy has higher potential than the FIT for reducing the CRC incidence. Nevertheless, the higher participation rate in the FIT group (34.2% vs 24.6%), and the biennial periodicity of this test may reduce the apparent advantage of colonoscopy over the long term^[32]. Final results from that study are expected in the next few years.

CRC SCREENING PROGRAMS

CRC screening programs in Europe

In 2003, based on compelling evidence, the Council of the European Union recommended that all Member States should establish early detection programs with CRC screening for men and women aged 50 to 74 years, with annual or biennial FOBTs, followed by colonoscopy, when the results were positive^[33]. Following this recommendation, several CRC screening programs were launched in Europe, with wide variations in screening practices, probably due to different preexisting screening programs (pilots, opportunity-based, or organized) in several countries. Variations among different countries also arose due to differences in financial resources available for research and differences in colonoscopy capacities.

In 2015, 24 countries in the European Union had established or were preparing to organize country-wide CRC screening programs. For example, Finland, France, Slovenia, and the United Kingdom had completely implemented organized programs. In Belgium, the Netherlands, Denmark, Ireland, Italy, Malta, Poland, and Spain, programs were being launched. Norway, Portugal, and Sweden were in the pilot phase. In contrast, other countries, including Slovakia, with the highest CRC rate in Europe^[1], did not have a national screening program. Similarly, no screening programs existed in Bulgaria, Albania, Bosnia, Herzegovina, Kosovo, Macedonia, Montenegro, Romania, Serbia, and Russia^[4].

An analysis of different programs in several European countries showed that Croatia and the Czech Republic had the lowest participation rates ($< 25\%$), and both countries reported high ASRms (18.7% and 15.4%, respectively), followed by France (participation rate 34.3%). The other countries achieved better participation rates (over 45%); the highest participation was observed in the Netherlands, followed by Slovenia. The Netherlands had the highest positive test rate (test positivity, 12.2%), but the lowest cut-off value for the FIT test: 15 $\mu\text{g/g}$. The

Table 2 Results of European Screening Programs

Country	Netherlands	Italy	Ireland	Lithuania	Croatia	Czech Republic	Slovenia	England	France
ASRi	40.2	33.9	34.9	23.4	32.9	39.9	37	30.2	36.1
ASRm	13.4	10.8	12.2	13.7	18.7	15.4	16.2	10.7	12.9
Period	2014-2015	2007-2009	2008-2009	2009-2012	2007-2011	2000-2011	2009-2014	2006-2010	2008-2009
Age	55-75	50-69	50-74	50-74	50-74	> 50	50-69	60-69	50-74
Test	FIT	FIT	FIT	FIT	gFOBT	gFOBT/FIT	FIT	gFOBT	gFOBT
Participation, n (%)	129395 (68.2)	81619 (54.4)	9993 (51)	271396 (46)	210239 (19.9)	521429 (22.7)	152475 (60.43)	1079293 (52)	2964976 (34.3)
M, n (%)			2126 (42)				55.23%	510864 (49.6)	32.10%
F, n (%)			2937 (42)				65.53%	568429 (54.4)	36.20%
Positive test, n (%)	15802 (12.2)	(5.8)	514 (10)	19455 (7.2)	12477 (6.9)	31794 (6.1)	8108 (5.9)	21106 (2%)	82786 (2.8)
M, n (%)	14.50%		254 (5)				7.60%	12776 (2.5)	3.30%
F, n (%)	10.10%		260 (5)				4.70%	8330 (1.5)	2.40%
Colonoscopies performed	74.30%	92.50%	87%	66.10%	66%	95.70%	98.90%	83%	88.40%
Advanced adenomas, n (%)	3832 (33.5)	702	99 (24)	3.90%	41%	3077	1887 (25.16)	1721 (9.8)	14276
PPV Advanced adenomas	NA	30.20%	5%	NA	NA	16.80%	NA	NA	19.60%
CRC, n (%)	763 (6.7)	70	38 (9)	3.10%	472 (3.6)	829	159 (2.16)	1772 (10.1)	7.50%
PPV CRC	6.70%	3%	4%	NA	NA	4.50%	NA	NA	NA
CRC detection rate per 1000	5.9	1.6	3.3	0.2	NA	1	NA	NA	1.9

NA: Not available.

second highest test positivity was found in Ireland (10% test positivity, with a cut-off value 20 µg/g). In Italy, with the same cut-off value, test positivity was 5.8%, and in Slovenia, it was 5.9%. The lowest test positivity rates were found in England and France (2% and 2.8%, respectively), where the G-FOBT was used. In Croatia, Lithuania, and the Netherlands, the proportion of colonoscopies performed did not exceed 75%; but in the Czech Republic and Slovenia, the proportions were above 95%. In England, a very high CRC percentage was detected (10.1% of patients a with positive G-FOBT result), but only 2% of all patients had a positive G-FOBT. Ireland had a similar CRC percentage (9%), but also a greater number of patients had positive FIT results (10%). The highest detection rate was found in the Netherlands (5.9 per 1000 screenings), followed by Ireland (3.3 per 1000 screenings). More detailed results are described below and in Table 2.

Spain: Different screening programs have been implemented in all areas of Spain for the population aged 50-69 years. These programs mostly use the FIT. In 2014, participation rates varied among the regions, but the average was 49.2%. More women than men participated (51.41% vs 47.01%). On average, 6.56% of test results were positive, with a higher percentage found in men (8.2%) than in women (5.17%). The positive predictive value (PPV) for cancer was 4.70%. The CRC detection rate was 2.75 per 1000 screenings^[34].

The Netherlands: In 2011, the Netherlands decided to implement a national population screening program

for CRC. The program began in 2014, with the FIT test and a cut-off value of 15 µg/g. This program achieved a 68.2% participation rate. Initially, it was necessary to increase the cut-off value (from 15 µg/g to 47 µg/g), because the proportion of individuals with positive tests was higher than expected (12%). This proportion exceeded the number of false positives, and it surpassed the capacity to perform colonoscopies. With the first cut-off value, test positivity was 10.1% in women and 14.5% in men. Colonoscopies were performed in 74.3% of these patients; among these, CRC was detected in 763 (6.7%) and advanced adenoma was detected in 33.5%. The CRC detection rate was 5.9 per 1000 inhabitants and the PPV was 6.7%^[35].

Ireland: The first pilot program in Ireland was the Adelaide and Meath Hospital/Trinity College Dublin Colorectal Cancer Screening Program (TTC-CRC-SP). It included a population aged 50 to 74 years, and it applied the FIT (OC Sensor, cut-off value 20 µg/g). The participation rate was 51% (58% women and 42% men). The proportion of individuals with positive test results was 10%. Of the colonoscopies performed (87%), advanced adenomas were detected in 99 patients (24%) and CRC was detected in 38 (9%). The PPVs for CRC and advanced adenoma were 4% and 5%, respectively, and the CRC detection rate was 0.33%^[36]. A second round was conducted, where they excluded patients that had changed residence, had been diagnosed with cancer, and had died. The participation rate was 48%, and 375 patients had positive test results (8%). Of the patients with a

Table 3 Results of colorectal cancer screening program time-trend (adapted from Suchanek *et al.*^[43])

	2006	2007	2008	2009	2010	2011	Total
Examined patients (<i>n</i>)	272658	320317	352595	414300	521429	NA	1881299
Positivity rate	3.6%	3.3%	4.1%	5.0%	6.1%	NA	4.6%
PPV for advanced adenoma	14.1%	13.5%	16.2%	16.6%	16.8%	16.7%	16.2%
PPV for CRC	6.3%	5.9%	6.0%	5.1%	4.5%	3.6%	4.8%

CRC: Colorectal cancer; PPV: Positive predictive value.

positive test, 87% underwent a colonoscopy. The PPV for CRC was similar to that of the first round (4%), and the CRC detection rate was 0.12%^[37].

Italy: Lombardy is a densely populated northern region of Italy with the highest incidence of CRC. The screening program began with the population aged 50-69 years, in 2005-2006. They applied the FIT with a cut-off value of 20 µg/g. The second round of the program had been completed in 2009. The PPVs for advanced adenoma were 29% in the first round, and 30.2% in the second round. The PPVs for CRC were 4% and 3%, respectively. The PPVs for advanced adenoma and CRC were higher in people aged 60-69 years and in males. The CRC detection rates in the first and second rounds were 2.5 and 1.6 per 1000 screened, respectively^[38].

Croatia: The Croatian screening program was implemented in 2007 for the population aged 50-74 years. They implemented the G-FOBT. Participation was low, reaching 19.9%. Positive tests were found in 6.9% cases, and of these, only 66% received a colonoscopy. CRC was identified in 472 patients (3.8%)^[39].

Lithuania: The Lithuanian National Screening Program began in 2009, for the population aged 50 to 74 years. The FIT was applied. The participation rate for 3 years was 46% (271396). A positive FIT was observed in 19455 participants (7.2%). Of these, 66.1% underwent a colonoscopy. High-grade neoplasia was detected in 3.9% of cases, and the rate of CRC was 3.1% among all colonoscopies. The rate of CRC detected with the program was 0.2%^[40].

Slovenia: The Slovenian National Screening Program (SVIT program) started in 2009. This program performed a biennial FIT for the population aged 50 to 69 years during 2014. The participation rate was 57.8% (53.2% men, 62.3% women). In this population, 6% had positive test results (7.6% men and 4.7% women). The colonoscopies detected 159 (2.12%) patients with CRC and 1887 (25.16%) patients with advanced adenomas^[41].

England: The English National Screening Program began in 2006 for the population aged 60 to 69 years. This program performed a biennial G-FOBT. The

first round was completed in 2010. Of the 2 million invitations sent, 49.6% of men and 54.4% of women responded. The overall participation rate was 52%. Positive test results were found in 2% (2.5% men, 1.5% women). Among the colonoscopies performed (83%), CRC was detected in 10.1% (*n* = 1772; detection rates of 11.6% in men and 7.8% in women). High risk adenomas were detected in 9.8% (*n* = 1721; detection rates of 12.2% in men and 6.2% in women)^[42].

Czech Republic: The Czech National Screening Program started in 2000 for individuals older than 50 years. They applied a biennial G-FOBT. By 2009, the FIT was introduced. The coverage of CRC screening in 2010 was 22.7%^[43]. The results of the program from 2001 to 2011 are shown in Table 3.

France: The French National screening program started in 2008 for the population aged 50-74 years. They applied the G-FOBT. The participation rate was 34.3%. Positive test results were found in 2.8%. Of these, 88% underwent a colonoscopy. CRC was detected in 7.5% (detection was 9% in men and 5.8% in women). The advanced adenoma detection rate was 4.9 per 1000 screened; the CRC detection rate was 1.9%^[44].

CRC screening programs in the Americas

United States: Currently in the US, screening programs have been established on an opportunistic basis. The average-risk population (50-75 years) are encouraged to undergo screening at 50 years of age, and participants choose among several options. The available options are: (1) annual G-FOBT or FIT, according to the manufacturer's recommendations for specimen collection; (2) multi-target stool DNA test every 3 years; (3) flexible sigmoidoscopy every 5 years; (4) colonoscopy every 10 years; (5) double-contrast barium enema every 5 years; or (6) CT colonography every 5 years. In about 90% of cases, colonoscopy is the preferred option^[28].

On the other hand, screening program evaluations have been conducted in several regions of the country. For example, the Kaiser Permanente Northern and Southern California program conducted 4 screening rounds in a population of 50 to 70 years. They used the annual FIT (cut-off value 20 µg/g). They achieved a 48.2% participation rate in the first round. A positive

Table 4 Results of American, Western Pacific and East Asian screening programs

Country	Canada	California (United States)	South Korea	Australia	Thailand	Taiwan	Chile
ASRi	35.5	25 (United States)	45	38	12.4	NA	15
ASRm	10.8	9.2 (United States)	12	9	7.3	NA	8.6
Period	2009-2011	2008	2004-2008	2002-2004	2011-2012	2004-2009	2007-2009
Age range	50-74	50-70	50-75	55-74	50-65	50-69	> 50
Test	G-FOBT/FIT	FIT	FIT	FIT	FIT	FIT	FIT
Participation, <i>n</i> (%)	104750 (16.1)	323349 (48.2)	984915 (21)	25840 (45.4)	80012 (62.9)	1160895 (21.4)	4938
M, <i>n</i> (%)			446590 (20.5)		57.8%	446290 (20.4)	
F, <i>n</i> (%)			538325 (21.9)		67.8%	714605 (25)	
Positive test, <i>n</i> (%)	4661 (4.4)	5%	73568 (7.5)	2308 (8.9)	873 (1.1)	4%	476 (9.6)
M, <i>n</i> (%)	5.9%		39233 (8.8)		1.2%	5%	
F, <i>n</i> (%)	3.4%		34335 (6.4)		1.1%	3.4%	
Colonoscopies performed	80.5%	NA	23117 (31.4)	1265 (54.8)	627 (71.8)	80%	279 (58.6)
Advanced adenoma, <i>n</i> (%)	NA	NA	NA	176 (13.9)	75 (12%)	4284	75 (16)
PPV Advanced adenoma	NA	NA	NA	NA	NA	NA	NA
CRC, <i>n</i> (%)	86		1.2%	67 (5.3)	23 (3.7)	2304	13 (1.1)
PPV CRC	4.4%	3.4%					
CRC Detection rate per 1000	1.8	NA	NA	2.59	0.29	2.5	2

FIT result was found in 5% of participants and the PPVs were 51.5% for adenomas and 3.4% for CRC^[45].

Canada: Canada organized a CRC screening program for average-risk individuals, aged 50-74 years, from January 2009 to December 2011. Five provincial programs were included (British Columbia, Saskatchewan, Manitoba, Nova Scotia, and Prince Edward Island). The results of the first round showed very low participation rates (16.1%)^[46]. The test positivity rate was 4.4% (4.8% with FIT and 3.7% with G-FOBT). Positive test results were more frequent in men (5.9%) than in women (3.4%), and the frequency increased with age: positive tests were found in 5.7% of the 70-74 age group and 3.4% of the 50-54 age group. Compliance with a follow-up colonoscopy was 80.5%. The detection rates were 16.9 per 1000 screened for adenomas, and 1.8 per 1000 screened for CRC. The PPVs for adenoma were 35.9% with the G-FOBT and 50.6% with the FIT. The PPV for CRC was 4.4% in both tests.

Chile: In Chile, an organized screening program was launched between 2007 and 2009 in asymptomatic subjects, aged 50 years or older without risk factors. They applied the FIT test with a cutoff of 20 µg/g. The participation rate was 77%. Of 4938 participants, positive test results were found in 9.6%. Of these, a colonoscopy was performed in 58.6%. CRC detection rates were 2 per 1000 screenings^[47].

CRC screening programs in the western pacific and east asia

The Asian Pacific Colorectal Cancer Working Group has recommended organized screening in regions with the highest CRC incidence (> 30 per 100000)^[48]. The programs target average-risk individuals, aged 50-75 years, and they preferably apply the FIT test. Several studies have investigated the barriers to

CRC detection in different cultural and socio-political contexts in the Asia-Pacific region. These barriers included poor understanding of the characteristics of screening and testing, lack of financial support, and lack of health insurance^[49]. Several countries in East Asia have ongoing organized screening programs, including Japan, Korea, China, Hong Kong, Taiwan, and Bangkok^[50]. The results for several of these CRC Screening Programs are described below and in Table 4.

Japan: In Japan, a CRC screening program has been in place since 1992 for beneficiaries of health insurance, aged 40-69 years. The program applies the FIT. In 2013, participation rates were 41.4% in men and 34.5% in women^[51].

South Korea: The South Korean National Screening Program was introduced in 2004. It targets the National Health Insurance population, aged over 50 years. They employ an annual FIT (qualitative or quantitative). Participation increased from 10.5% in 2004 to 21.1% in 2008 and to 25% in 2012^[52]. In 2008, the FIT positivity rate was 7.5% (8.8% in men and 6.4% in women). A colonoscopy was performed in 31.4% of those with positive test results. The CRC detection rate was 1.2%^[53].

Taiwan: The Taiwanese National program began in 2004. They performed biennial FITs in individuals aged 50 to 69 years. In the first round, 1160895 individuals (21.4%) participated. The test positivity rate was 4%. Subsequent colonoscopies detected 4284 advanced adenomas (detection rate 4.6 per 1000) and 2304 CRCs (detection rate 2.5 per 1000). The PPVs of FITs were 11.7% for advanced adenoma, and 6.1% for CRC^[54].

Thailand: A Thai pilot screening program was implemented in 2011. The FIT was performed in the

population aged 50-65 years in Lampang Province. The participation rate (62.9%) was higher among women (67.8%) than men (57.8%). The test was positive in 1.1% (1.2% men, 1.0% women). Colonoscopy was performed in 72% of those with positive tests. Detection rates were 3.7% for CRC and 30.6% for adenomas^[55].

Australia: An Australian pilot program was conducted from 2002 to 2006 with the biennial FIT in the population aged 55-74 years. The participation rate was 45.4% (women 47.4%, men 43.4%). Positive FIT results were found in 9% of participants. Colonoscopy was performed in 54.8% of the individuals with positive FITs. Adenomas were found in 19.8% (13.9% advanced) and CRC was found in 5.3%^[56]. In 2006, The National Bowel Cancer Screening Program was initiated with a biennial FIT for the population aged 55-65 years. The program will continue to expand until 2020. The program aims to apply biennial screening to the entire population aged 50-74 years^[4].

COMPARISON OF THE RESULTS OF SEVERAL CRC SCREENING PROGRAMS

Most European countries have implemented a national organized screening program. However, some countries have not, despite high CRC incidence and mortality rates, such as Slovakia. Likewise, most countries of Central America, South America, the Middle East, and Africa, do not have organized screening programs. In most cases, the lack of organized programs could be explained by limited resources, including the limited availability of colonoscopy facilities, and the type of organization of the Health Care System. Most organized screening programs use non-invasive tests (FIT or G-FOBT); in contrast, most opportunistic programs rely on endoscopy. Colonoscopy remains the most commonly used screening test in North America, but FIT screening programs are beginning to be implemented in some areas, such as California^[45].

The efficacy of CRC screening is determined by the degree of participation and the diagnostic yield of the test. Studies have shown that FIT screening is superior to G-FOBT in both aspects^[20,47]. The overall results showed that the highest participation rates were obtained in programs using FIT. In fact, in programs that used both tests (FIT and G-FOBT), participation rates increased after FIT was introduced, as observed in the Czech Republic^[43].

FIT screening also produced more positive tests than G-FOBT screening. Therefore, the lowest rates of test positivity in Europe were obtained in England and France, where screening was performed with the G-FOBT^[42,44]. As mentioned, in the Czech Republic program, after the G-FOBT was replaced with the FIT, the PPV for advanced adenoma increased, and the PPV for CRC decreased^[43]. This result implied

that, compared to the G-FOBT, the FIT had a higher sensitivity and PPV for advanced adenomas, but a lower PPV for CRC.

Among all the programs reviewed, only Korea used a qualitative FIT. Studies worldwide using different Hb thresholds have shown that defining a positive FIT result with a cut-off value of 100 ng/mL Hb (20 µg/g) provided high sensitivity, specificity, and PPV for detecting neoplasia^[49,53,54]. Other studies reported a decline in specificity with cut-off values below 100 ng/mL Hb^[5,45,46,48,53]. According to this information, a cutoff value between 75 and 100 ng/mL Hb might represent an optimum in most European populations, depending on the resources and availability of colonoscopy.

Some countries had to modify the cut-off value to align the need for colonoscopies with the limited capacity of endoscopic resources. For example, in the Netherlands, which had the highest rates of positivity among all international and European programs, the cutoff value was raised from 88 to 275 ng/mL Hb (15 µg/g to 47 µg/g) at the beginning of their program^[35]. In addition, the Netherlands had the highest CRC detection rate in Europe; the detection rates were double those of several European and other countries. The program in Ireland also had a high percentage of positive tests (10%). In comparison, with the same cut-off value, Italy had almost half (5.8%) the proportion of positive tests. This suggested that there might be a relatively high incidence of adenomas in Ireland, and that lower cut-off values would be very difficult to manage with the current availability of colonoscopy resources in the country.

Another problem to consider is the low acceptance of colonoscopy in some countries. In South Korea, only 31.4% of individuals with a positive FIT had undergone a colonoscopy after. This reluctance could result in low detection rates^[53]. In other European countries, like Croatia, Lithuania, and The Netherlands, the proportion of colonoscopies among individuals with positive test results did not exceed 75%^[35,39,40].

Participation rates in the screening programs were higher among women than men. This difference probably occurred because women had a greater awareness of preventive programs; in particular, women were likely to have had experience in breast and cervix screening. In addition, positive FIT rates were significantly higher in men than in women (except in Ireland and Thailand, where rates were similar between the sexes). The CRC detection rates were also higher in men than in women; in some programs, detection rates in men were double the rates in women. Special efforts should be made in all screening programs to increase both the overall participation and male participation rates.

The lowest participation rates were found in Canada, possibly because the data were published recently after the programs had been started.

In general, participation rates in the different

programs currently exceed the acceptable minimum of 45%, but they have not reached the desired target (> 65%). Screening programs must employ specific strategies to attract the target population and encourage participation in screening programs. A better understanding of the barriers and facilitators to participation is needed to design strategies that promote equity of access. It is important to monitor, record, and evaluate the minimum indicators and requirements of CRC Population Screening Programs, to ensure they meet the standards of the European Quality Control Guide.

CONCLUSION

This review highlighted the large variations in CRC incidence and mortality around the world. Some regions with high CRC rates do not have screening programs, and other regions, like Europe, have widespread organized screening programs. Additionally, participation rates vary greatly between programs around the world. The highest rates were found in the Netherlands and the lowest were found in Canada. The most common test used as a screening tool in organized screening programs was the fecal occult blood test. In countries with screening programs that arose opportunistically, colonoscopy was most commonly used for screening. Between the two types of fecal occult blood tests, the most commonly used test was the FIT. Use of the FIT has increased participation rates, because it is user friendly; a single sample suffices, and no dietary restrictions are imposed prior to the test. Because the FIT is more sensitive than the G-FOBT, the number of false positives and the demand for invasive tests has increased. Consequently, the cut-off value of the test must be adapted to each region, taking into account the availability of endoscopic resources. The FIT also exhibited superior detection of advanced adenomas compared to the G-FOBT. This feature promotes treatment in early stages and prevents the formation of cancer. Participation rates were higher among women, possibly due to their increased awareness of the importance of other screening programs, such as breast cancer screening. Positive test results and CRC detection rates were higher in men than in women; therefore, men's awareness should be increased to encourage participation in screening programs.

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