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Organized colorectal cancer screening in Lampang Province, Thailand: Preliminary results from a pilot implementation programme

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ABSTRACT

Objective: Colorectal cancer (CRC) is the third- and fifth-most common cancer in men and women, in Thailand. The increasing CRC incidence and mortality can be reduced by screening and treating adenomas and early cancers. A pilot CRC screening program using immunochemical focal blood testing (iFOBT) and colonoscopy for test-positives was implemented through the routine Government Health Services in Lampang Province, to inform the acceptability, feasibility and scaling-up of screening in Thailand. This report describes the implementation, coverage and performance indicators of this project.

Design: A target population aged 50-65 years was informed about and invited to undergo CRC screening by community health workers (HWs). The HWs provided fecal sample collection kits and participants brought their samples to one of the primary health units or community hospitals where nurses performed iFOBT. IFOBT-positive persons were referred for colonoscopy at the Lampang cancer hospital and endoscopic polypectomy/biopsies were performed according to colonoscopic findings. Those with confirmed CRC received appropriate treatment.

Results: Of the 127,301 target population 62.9% were screened using iFOBT. Participation was higher among women (67.8%) than men (57.8%) and lower in 50-54 year-old persons than 60-65 year-olds. Of those screened, 873 (1.1%) were found positive; positivity was higher in men (1.2%) than in women (1.0%). To date 627 (72.0%) iFOBT-positive persons have had colonoscopy in which 3.7% had CRC and 30.6% adenomas.

Conclusion: The successful implementation of the pilot CRC screening with satisfactory process measures indicate the feasibility of scaling up organized CRC screening through existing health services in Thailand.

Article focus:

- The article addresses the feasibility of introducing colorectal cancer screening using immunochemical faecal occult blood test (iFPBT) through existing primary health care services and colonoscopy triage and treatment of screen positive subjects in secondary care services in a province in Thailand
- Addresses the performance characteristics of colonoscopy triage in terms of polyp and adenoma detection rates

Key messages:

- Despite the increasing incidence of colorectal cancer (CRC) in middle-income countries, organized colorectal cancer screening programs are yet to evolve in these countries
- This pilot study shows that it is feasible to introduce organized CRC screening with ifOBT and colonoscopy triage with satisfactory input measures and intermediate outcomes, through existing government health services, in middle income country like Thailand
- Experience from this pilot project may pave the way for nationwide scaling-up of organized CRC screening program in Thailand and other middle-income countries with increasing risk of CRC

Strengths and limitations:

- This pilot study will show the efficacy of CRC screening at 5-year intervals on CRC incidence and mortality
- The study reflects the real life conditions and has been conducted using the existing routine health care services allowing a realistic and pragmatic assessment of the feasibility, sustenance and outcomes of colorectal screening in a middle-income country.
- No information is provided on the extent of false negative tests and the impact of the intervention on colorectal cancer incidence and mortality due to lack of long-term

follow-up of the study population at this instance. This information will be eventually generated by both active and passive follow-up the study population in future.

INTRODUCTION

Colorectal cancer (CRC) is a major cancer in Thailand with age-standardized incidence rates of 12.9/100,000 in men and 9.2/100,000 in women in 2005 and an incidence which is steadily increasing over time.[1] Sedentary lifestyle, lack of physical activity, smoking, drinking alcohol, a high consumption of red and processed meats as well as a low consumption of whole grains, fiber, fruits and vegetables are associated with an elevated risk of CRC. Most CRCs occur in pre-existing adenomatous polyps; a small percentage of the colonic polyps may become cancerous and spread elsewhere.[2] This progression takes at least 10 years in most people. Early detection and removal of polyps in the colon and rectum may prevent the development of invasive CRC.[3]

Early detection and prevention of CRC through screening is an effective intervention to reduce the considerable human and financial costs.[4] Tests considered for screening include variants of fecal occult blood tests (FOBT), flexible sigmoidoscopy and colonoscopy. Of these, FOBTs are the most feasible, non-invasive, affordable and acceptable for population screening as they detect intermittent microscopic blood losses from early CRC to advanced adenomas. Chemical FOBT (cFOBT) uses guaiac to detect peroxidase in human blood, but also reacts to the peroxidase present in dietary constituents such as red meat, cruciferous vegetables and some fruits, while the recently developed immunochemical FOBT (iFOBT) uses an antigen-antibody reaction to specifically detect globin which, together with heme, constitutes human hemoglobin. iFOBT is not subject to false-negative results in the presence of high-dose vitamin C supplements, which block the peroxidase reaction; since globin is degraded by digestive enzymes in the upper gastrointestinal tract, iFOBT is more specific for lower gastrointestinal bleeding, thus improving their specificity for colorectal neoplasia.

It has been shown in pooled analysis of four randomized controlled trials that annual or biennial screening with cFOBT reduced overall CRC mortality by 16%, for those allocated to CRC screening, and CRC mortality by 25% for those attending at least one round of screening with cFOBT.[4] The iFOBT provides a suitable and better alternative to cFOBT as a screening test due to its higher sensitivity, simplicity, ease of use and the fact that it does not require any dietary restriction.[5-8]

CRC screening programs are increasingly organized at regional and national levels in many countries. Programs in countries such as Australia, Canada, Finland, France and United

Kingdom use either direct mail invitations or invitations initiated by general practitioners to target populations aged 50-65 or 55-69 or 50-74 years. Programs in Canada and Finland use cFOBT, whereas iFOBT is used in Korea and Japan.[9-12] Although FOBT and colonoscopy are opportunistically provided in urban hospitals, there is no population-based organized CRC program in Thailand. The public health authorities in Thailand, faced with the increasing risk of CRC, due to the transition to westernized lifestyles with socio-economic development, would like to take measures to reduce its incidence and deaths by primary prevention and screening. In this context, a decision was made to implement a pilot CRC screening program with iFOBT followed by full colonoscopy for test positive persons in Lampang Province to inform the feasibility, acceptability, safety in order to guide the subsequent national scaling up of the program through the existing public health services. Lampang Province was chosen to implement the pilot project, due to a relatively high incidence rate of CRC (14.7 per 100,000 in men and 10.1/100,000 in women), the availability of colonoscopy, histopathology and CRC treatment services at the Lampang provincial and cancer hospitals and the existing population-based cancer registry that will help to evaluate the impact of the pilot intervention on CRC incidence and mortality in the province. We report the organization, implementation, coverage and performance of the pilot CRC screening in this manuscript.

MATERIAL AND METHODS

Project proposal development

A detailed project proposal describing the background, project procedures, study questionnaires and forms to capture participant data and details of investigations, the project database, quality assurance methods and means of monitoring and evaluation were jointly developed between June 2010 and March 2011 by the National Cancer Institute (NCI), Bangkok, and the provincial health authorities with technical assistance from the Screening Group of the International Agency for Research on Cancer (IARC) of the World Health Organization, Lyon, France. Following the finalization of the project proposal, its approval by national authorities and completion of training for the providers, screening commenced in April 2011 and recruitment of eligible subjects was closed in November 2012.

Target population and involved healthcare facilities

All apparently healthy, ambulant men and women aged 50 to 65 years with no history of CRC and resident in Lampang Province were the target population for screening in the pilot project, totaling 127,301 eligible subjects. The Government healthcare infrastructure consisting of 154 primary care units (PCUs), 12 community hospitals (CHs), Lampang provincial hospital and Lampang cancer hospital (the Regional Cancer Centre of Lampang) provided the various services for the screening program which was coordinated by the NCI and technically supported by the IARC.

Training for screening and colonoscopy providers

The registered nurses, community health workers (HWs) of the 154 PCUs and 12 CHs of Lampang Province were trained on information dissemination on CRC screening, awareness creation, motivation of the target population and invitation of eligible persons to participate in CRC screening during a one-day session by a faculty from the NCI and provincial health authority. They were trained to explain to the participants how to collect the fecal specimen in the sample collection tube and bring it to the PCU or the CH within 3 hours from collection for occult blood testing. The training also covered the performance and interpretation of the iFOBT test. Attractive pamphlets and posters in Thai language describing the prevention and early detection of CRC, the method of collecting the fecal samples, the iFOBT test procedure, colonoscopy and treatment of CRC were developed and printed by the Thai Health Services with technical support from the NCI and IARC. The posters were

prominently displayed in all health care facilities, educational institutions, public offices and public places and the pamphlets were distributed to all households in the province by the health workers.

Gastroenterologists and surgeons at the Lampang provincial and cancer hospitals were reoriented and re-trained in key aspects of colonoscopy to improve their hands-on colonoscopy/polyp excision/biopsy skills in live sessions during 5 days. They were taught and evaluated by skilled gastroenterologists, with several years of experience in colonoscopy and endoscopic removal of polyps and mucosal resection of small lesions from the NCI and the Thai Association of Gastrointestinal Endoscopy in live sessions under direct observation before the initiation of the program.

Screening invitation and organization

The existing health care infrastructure and personnel in the PCUs and the CHs were used to disseminate information, to invite and provide iFOBT and to refer those testing positive for colonoscopy. The HWs from the PCUs and CHs distributed a fecal sample collection kit to the eligible persons in the households under their jurisdiction as per a regular schedule and explained how to collect the specimen and when to bring the collected specimen to the PCU/CH for testing. The proportion of households visited were much higher in rural than in urban areas, where the sample collection kits were mostly collected by the eligible individuals during their routine visit to the health centers or community hospitals. The colonoscopy, histopathology and treatment services at the Lampang provincial and cancer hospitals were used to diagnose and treat patients in the program.

Screening with iFOBT and referral

All fecal samples were subjected to one-step iFOBT (Hemosure^{TM}, EL Monte, USA) according to the manufacturer's instructions. The test was carried out at the PHU/CH by the nurse in front of the participant. In less than 5 minutes a level of hemoglobin as low as 200 ng/ml can be detected by this test. One pink-rose band appearing in the "C: region and the other "T" region of the test device indicates a positive iFOBT. A negative iFOBT is characterized by only one color band in the "C" region. In this study, fecal material was assessed from one sample taken from each participant (1-day iFOBT). Verbal informed consent was obtained from all participants before analyzing the stool sample. The nurse at the PCU/CH fixed an appointment for colonoscopy at the Lampang cancer hospital for iFOBT positive persons and explained the pre-colonoscopy bowel preparation and the colonoscopy procedure in detail,

provided a prescription for bowel cleansing and encouraged them to comply with the referral.

Colonoscopy

Colonoscopy was provided to iFOBT-positive individuals on scheduled days every week at the Lampang Cancer Hospital. A second informed consent was obtained from people undergoing colonoscopy, biopsy, and treatment. The outcome of colonoscopy was reported as normal, polyps, suspected cancer or invasive cancer. Polyps and small lesions were removed and subjected to histopathology. Large lesions were biopsied for histological assessment. Those diagnosed with CRC received further investigations for clinical staging and treatment as per the standard protocol developed for Thailand. The findings of colonoscopy, histology, stage, treatment and follow-up assessment were recorded in a diagnosis and treatment form and entered into the database.

Data management, monitoring and evaluation

Personal identification (name, age, address, citizen ID number), socio-demographic information, screening test result, results of colonoscopy and other investigations, treatment details and follow-up information were collected in specifically developed forms and entered in a multiuser program database with inbuilt validation checks called CRCreg developed by the IARC. The database was continuously updated as the pilot project progressed. It is possible to link the screening program and the cancer registry databases using the unique citizen ID numbers, which will enable the identification of false-negative cases and interval cancers.

The study database was analyzed to document the participant characteristics, participation rates for screening and test positivity rates by sex, age, the district of residence and the proportion of test-positive individuals complying with referral for colonoscopy, colonoscopy results, final diagnosis, stage of invasive cancer, treatment details and adverse events.

Ethical approval and funding

Ethical approval was obtained from Institutional Review Board and Ethics Committee of NCI and the IARC. The project was funded by the Ministry of Health, Thailand, through the National Cancer Institute, Bangkok.

RESULTS

The flow chart of the program organization and procedures is shown in Figure 1. All 154 PCUs and 12 CHs (100%) in the province participated in the project. Of the 127,301 eligible subjects (63,274 men and 64,027 women), 80,012 (62.9%) (36,601 men and 43,411 women) were enrolled. The distribution of sex, education, occupation and family history of CRC among the participants are given in Table 1. The mean age was 56.6 (SD=4.3) among women and 56.8 (SD=4.3) among men. More than 80% of the subjects had only primary school education; three-fourths were involved in agriculture; 0.7% had family history of CRC.

Table 1. Characteristic of participants in the Lampang pilot colorectal cancer screening project

Characteristics	Number	Percentage
Screened	80,012	
Sex		
Men	36,601	45.7
Women	43,411	54.3
Age (in years)		
50-54	28,956	36.2
55-59	27,825	34.8
60-65	23,231	29.0
Education		
None	6,192	7.7
Primary	66,583	83.2
Secondary	5,208	6.5
College/University	2,028	2.5
Occupation		
Agriculture	57,266	75.8
Managerial/Professional	1,781	2.4
Support/Service	4,718	6.2
Crafts/machinery	371	0.5
Elementary occupations	11,381	15.1
Family income		
<5000	44,940	58.4
5000-10000	26,463	34.4
>10000	5,533	7.2
Family history of colorectal cancer		
Yes	552	0.7
No	72,971	91.2
Unknown	6,489	8.1
Setting		

Rural	58,873	73.6
Urban	21,139	26.4
District		
Mueang (U)	13,016	16.3
Mae Moh (U)	2,772	3.5
Koh Kha (U)	5,351	6.7
Soem Ngam (R)	3,747	4.7
Wang Nua (R)	5,962	7.5
Chae Hom (R)	6,474	8.1
Ngao (R)	7,489	9.4
Thoen (R)	8,486	10.6
Mae Phrik (R)	2,523	3.2
Mae Tha (R)	9,025	11.3
Sop Prap (R)	3,977	5.0
Hang Chat (R)	6,447	8.1
Mueang Pan (R)	4,743	5.9

U: Urban; R: Rural

The overall participation rate for screening (62.9%) was much higher in women (67.8%) than in men (57.8%) (Table 2). Participation in screening varied between the 13 districts in the province: generally being higher in rural than in urban districts (Table 2). The highest iFOBT uptake was in the rural district of Theon (86.0% in women and 73.4% in men) while the lowest participation was in the urban district of Mueang (47.7% in women and 35.1% in men). Screening participation rates increased from 52.9% in those aged 50-54 years to 78.9% among those aged 60-65 years (Table 3).

Table 2 Total eligible subjects, screened eligible subjects and test positive frequencies by sex, age and districts in Lampang province, Thailand, 2011-2012

	Men					Women					Overall				
	Eligible persons	Number screened	(%)	Number screen positive	(%)	Eligible persons	Number screened	(%)	Number screen positive	(%)	Eligible persons	Number screened	(%)	Number screen positive	(%)
Overall	63,274	36,601	(57.8)	447	(1.2)	64,027	43,411	(67.8)	426	(1.0)	127,301	80,012	(62.9)	873	(1.1)
Sex															
Men	63,274	36,601	(57.8)	447	(1.2)						63,274	36,601	(57.8)	447	(1.2)
Women						64,027	43,411	(67.8)	426	(1.0)	64,027	43,411	(67.8)	426	(1.0)
Age (in years)															
50-54	27,148	12,927	(47.6)	106	(0.8)	27,597	16,029	(58.1)	131	(0.8)	54,745	28,956	(52.9)	237	(0.8)
55-59	21,328	12,711	(59.6)	146	(1.1)	21,777	15,114	(69.4)	130	(0.9)	43,105	27,825	(64.6)	276	(1.0)
60-65	14,798	10,963	(74.1)	195	(1.8)	14,653	12,268	(83.7)	165	(1.3)	29,451	23,231	(78.9)	360	(1.5)
setting															
Rural	22,985	8,909	(38.8)	130	(1.5)	23,919	12,230	(51.1)	131	(1.1)	46,904	21,139	(45.1)	261	(1.2)
Urban	40,289	27,692	(68.7)	317	(1.1)	40,108	31,181	(77.7)	295	(0.9)	80,397	58,873	(73.2)	612	(1.0)
District															
Mueang (U)	15,188	5,327	(35.1)	60	(1.1)	16,127	7,689	(47.7)	64	(0.8)	31,315	13,016	(41.6)	124	(1.0)
Mae Moh (U)	2,999	1,300	(43.3)	30	(2.3)	2,690	1,472	(54.7)	24	(1.6)	5,689	2,772	(48.7)	54	(1.9)
Koh Kha (U)	4,798	2,282	(47.6)	40	(1.8)	5,102	3,069	(60.2)	43	(1.4)	9,900	5,351	(54.1)	83	(1.6)
Soem Ngam (R)	2,838	1,757	(61.9)	16	(0.9)	2,581	1,990	(77.1)	9	(0.5)	5,419	3,747	(69.1)	25	(0.7)
Wang Nua (R)	4,712	2,988	(63.4)	46	(1.5)	4,429	2,974	(67.1)	51	(1.7)	9,141	5,962	(65.2)	97	(1.6)
Chae Hom (R)	4,324	3,123	(72.2)	42	(1.3)	4,385	3,351	(76.4)	38	(1.1)	8,709	6,474	(74.3)	80	(1.2)
Ngao (R)	5,603	3,642	(65.0)	18	(0.5)	5,289	3,847	(72.7)	22	(0.6)	10,892	7,489	(68.8)	40	(0.5)
Thoen (R)	5,196	3,814	(73.4)	17	(0.4)	5,431	4,672	(86.0)	25	(0.5)	10,627	8,486	(79.9)	42	(0.5)
Mae Phrik (R)	1,490	1,087	(73.0)	11	(1.0)	1,683	1,436	(85.3)	10	(0.7)	3,173	2,523	(79.5)	21	(0.8)
Mae Tha (R)	5,970	4,161	(69.7)	61	(1.5)	6,030	4,864	(80.7)	45	(0.9)	12,000	9,025	(75.2)	106	(1.2)
Sop Prap (R)	2,946	1,876	(63.7)	29	(1.5)	2,993	2,101	(70.2)	16	(0.8)	5,939	3,977	(67.0)	45	(1.1)
Hang Chat (R)	4,009	2,991	(74.6)	41	(1.4)	4,206	3,456	(82.2)	42	(1.2)	8,215	6,447	(78.5)	83	(1.3)
Mueang Pan (R)	3,201	2,253	(70.4)	36	(1.6)	3,081	2,490	(80.8)	37	(1.5)	6,282	4,743	(75.5)	73	(1.5)

U: Urban; R: Rural

Table 3. Colonoscopy attendance, results and final diagnosis by sex

	Men		Women		Total	
Number screened	36,601		43,411		80,012	
Number screen positive (%)	447	(1.2)	426	(1.0)	873	(1.1)
Number attended colonoscopy referral (%)	319	(71.4)	308	(72.3)	627	(71.8)
Colonoscopy result (per 1000 screened)						
Normal	165		215		380	
Polyp	133	(3.6)	73	(1.7)	206	(2.6)
Suspected cancer	16	(0.4)	11	(0.3)	27	(0.3)
Inadequate/Unknown	5		9		14	
Final diagnosis (per 1000 screened)						
Normal	158		206		364	
Inflammatory bowel disease	5	(0.1)	2	(0.0)	7	(0.1)
Adenomatous polyp	12	(0.3)	9	(0.2)	21	(0.3)
Adenomatous polyp with dysplasia	108	(3.0)	51	(1.2)	159	(2.0)
Hyperplastic polyp	4	(0.1)	1	(0.0)	5	(0.1)
Colitis	4	(0.1)	6	(0.1)	10	(0.1)
Adenocarcinoma in-situ	3	(0.1)	4	(0.1)	7	(0.1)
Colorectal cancer	13	(0.4)	10	(0.2)	23	(0.3)
Other	11	(0.3)	18	(0.4)	29	(0.4)
Unknown	1	(0.0)	1	(0.0)	2	(0.0)

Using a cut-off fecal hemoglobin concentration of 200 ng/ml, 873 of 80,012 (1.1%) participants were reported as positive on iFOBT. The iFOBT positivity rate was slightly higher in men (1.2%) than in women (1.0%) (Table 2). Test positivity rate increased from 0.8% in those aged 50-54 years to 1.5% in those aged 60-65 years (Table 2).

To date 627 (71.8%) iFOBT positive persons had colonoscopy; no serious adverse event was reported following colonoscopy. On colonoscopy, 206 were found to have polyps and cancer was suspected in 27 (Table 3). Polyps were excised and biopsies were directed in growths. On histological examination of excised polyps, adenoma was confirmed in 187 persons (Table 3). CRC was histologically confirmed in 23 persons (3.7%). The detection rate of histologically confirmed CRC was 2.9 per 10,000 screened persons and that of adenomatous polyp was 23.4 per 10,000 screened persons. CRC and adenomas were detected in 3.6% and 29.8% respectively of iFOBT-positive individuals who had colonoscopy.

Among the 187 persons with histologically confirmed adenomatous polyps, 75 (40.1%) had advanced adenoma. Advanced adenoma denote adenomatous polyps having one or more of the following features: > 10 mm in diameter, high-grade dysplasia, and significant villous histology (>25%). The stage-distribution of the detected invasive cancers was as follows: 2 stage I, 12 stage II, 7 stage III and 2 missing stage information. Compliance for colonoscopy referral was lower among individuals living in urban compared to rural areas and in those with relatively high compared to those with low monthly family incomes (Table 4).

Table 4. Colonoscopy attendance among screen positives by patient characteristics

Characteristic	Number screen positive	Number attended colonoscopy clinic (%)		Crude OR (95% CI)	p-value
Participants	873	627	(71.8)		
Sex					
Men	447	319	(71.4)	1.0	
Women	426	308	(72.3)	1.0 (0.8 - 1.4)	0.759
Age (in years)					
50-54	237	177	(74.7)	1.0	
55-59	276	196	(71.0)	0.8 (0.6 - 1.2)	0.353
60-65	360	254	(70.6)	0.8 (0.6 - 1.2)	0.271
Education					
None	97	73	(75.3)	1.0	
Primary	704	504	(71.6)	0.8 (0.5 - 1.4)	0.451
Secondary	48	34	(70.8)	0.8 (0.4 - 1.7)	0.569
College/University	24	16	(66.7)	0.7 (0.3 - 1.7)	0.395
Occupation					
Agriculture	632	474	(75.0)	1.0	
Managerial/Professional	22	15	(68.2)	0.7 (0.3 - 1.8)	0.471
Support/Service	54	34	(63.0)	0.6 (0.3 - 1.0)	0.055
Crafts/machinery	4	3	(75.0)	1.0 (0.1 - 9.7)	1.000
Elementary occupations	95	60	(63.2)	0.6 (0.4 - 0.9)	0.016
Family income in Thai Bahts per month (1 US $ = 30 Bahts))					
<5000	531	399	(75.1)	1.0	
5000-10000	254	166	(65.4)	0.6 (0.5 - 0.9)	0.004
>10000	59	42	(71.2)	0.8 (0.5 - 1.5)	0.508
Family history of colorectal cancer					
Yes	19	15	(78.9)	1.0	
No	774	551	(71.2)	0.7 (0.2 - 2.0)	0.463
Unknown	80	61	(76.3)	0.9 (0.3 - 2.9)	0.803
setting					
Rural	612	460	(75.2)	1.0	

Urban	261	167	(64.0)	0.6	(0.4	- 0.8)	0.001
District							
Mueang (U)	124	72	(58.1)	1.0			
Mae Moh (U)	54	39	(72.2)	1.9	(0.9	- 3.8)	0.075
Koh Kha (U)	83	56	(67.5)	1.5	(0.8	- 2.7)	0.173
Soem Ngam (R)	25	21	(84.0)	3.8	(1.2	- 11.7)	0.020
Wang Nua (R)	97	68	(70.1)	1.7	(1.0	- 3.0)	0.066
Chae Hom (R)	80	63	(78.8)	2.7	(1.4	- 5.1)	0.003
Ngao (R)	40	29	(72.5)	1.9	(0.9	- 4.2)	0.106
Thoen (R)	42	30	(71.4)	1.8	(0.8	- 3.9)	0.127
Mae Phrik (R)	21	18	(85.7)	4.3	(1.2	- 15.5)	0.024
Mae Tha (R)	106	84	(79.2)	2.8	(1.5	- 5.0)	0.001
Sop Prap (R)	45	31	(68.9)	1.6	(0.8	- 3.3)	0.204
Hang Chat (R)	83	63	(75.9)	2.3	(1.2	- 4.2)	0.009
Mueang Pan (R)	73	53	(72.6)	1.9	(1.0	- 3.6)	0.042

OR: odds ratio; CI: confidence interval; U: Urban; R: Rural

DISCUSSION

Among the CRC screening approaches in people at average risk (persons aged 50 to 74 years), annual or biennial FOBT followed by colonoscopy triage of screen positive individuals is the most widely used strategy due to its low cost, feasibility, safety and non-invasiveness. Significant reduction in CRC incidence and mortality following cFOBT screening has been shown in four randomized controlled trials.[4] This evidence, the fact that iFOBT is a better alternative to cFOBT and the declines in CRC mortality following widespread CRC screening in Japan, South Korea, Hong Kong and Singapore, despite increasing CRC incidence rates,[13] and in other high income countries[14;15] supported our decision to implement a pilot project based on 1-day iFOBT screening integrated in the routine public health services in Lampang province in Thailand.

Since CRC screening is a major undertaking and integrating a cancer screening program into routine government health services in low-middle income countries has its own complexities and challenges, it was decided to pilot its introduction in one of the provinces of Thailand which already has a population based cancer registry. In high-income countries, large scale population-based organized CRC screening has been preceded by well-planned pilot introductions to evaluate the feasibility, practicality and acceptability of introducing a population screening program with biennial FOBT in government health services.[16-18] For instance, the UK CRC screening pilots were launched in 2000 in England and Scotland, which reported a FOBT uptake rate of 57% and CRC detection rate of 1.62 per 1000 screened, and

the participation rate was 71% in the Finnish pilot introduction.[16;18] The national expansion of CRC screening in UK and Finland following the pilot studies was phased over 6 years.

The preliminary results on participation and detection rates of colorectal neoplasia in our pilot project in Lampang are consistent with findings from pilot and national programs elsewhere. For example, the participation rate of eligible subjects in our Thai study was similar to rates reported from pilot demonstration projects in the United Kingdom (57%), Haut-Rhin, France (55%) and in Finland (71%) and in service programs in UK (54%)[16;18-20] and higher than those reported from a systematic review of participation in CRC screening programs (42%) and from the national CRC screening programs in South Korea (<25%) and Croatia (10%).[11;21;22] These data confirm that the use of primary HWs outreach to promote and provide CRC screening through existing Government health services is feasible in Thailand.

A higher uptake of iFOBT was observed among women and in older age groups in our program. A similar observation has been reported CRC screening programs in other countries.[11;16;18;20;21;23] We observed a higher uptake of iFOBT screening in rural districts than in urban areas of Lampang province. Information on CRC screening and invitations for iFOBT screening in rural districts were mostly delivered to the target population by direct person to person contact and face to face communication, while in urban areas the information on the program was predominantly delivered through poster advertisements due to the challenges in face to face contacts. The higher screening uptake in rural populations than in urban areas indicate that direct person to person contacts and personalized invitations improved participation. A personalized approach to participant recruitment has also been reportedly associated with a higher uptake of CRC screening in other settings.[22] A higher participation in rural populations than in urban and metropolitan populations has been reported from other countries as well.[22;24]

The overall iFOBT positivity rate in our pilot project was in the lower range of test positivity rates reported from high-risk, high-income countries. FOBT test positive rates ranged from 7.9% to 2.1% in high-risk high-income countries.[11;17;18;21;25-27] Our results show that positivity rate in men (1.2%) was slightly higher than in women (1.0%), which is consistent with a higher CRC incidence in men (14.7 per 100 000 men) as compared to that of women (10.1/100,000 women) in Lampang province. A higher test positivity rate in men than in women has also been reported in other settings.[18]

FOBT screening for CRC is effective only when a high proportion of those with a positive result attend further full colonoscopy diagnostic evaluation of the colon. Two-thirds of test positive persons complied with referral for colonoscopy in our program, which is within the range of adherence to colonoscopy referrals in high-income countries. In many national programs, compliance of test-positive subjects to colonoscopy ranged between 38% and 88%.[11;20;21;28;29] There was no serious adverse event following colonoscopy in our program. The risks of serious adverse events such as perforation, hemorrhage, peritonitis and acute diverticulitis following colonoscopy performed as part of CRC screening are low, but increase with age and following polypectomy; the rate of adverse events reportedly varied between 3 to 6 per 1000 colonoscopies performed.[30] The value of short and intensive re-training and re-orientation courses for colonoscopists of varying experience in achieving high standards has been well-established.[31] Teaching practical hands-on skills in short intensive re-orientation sessions to our program gastroenterologists and assessment of their performance and competency in key aspects of colonoscopy by direct observation in live case sessions by experienced colonoscopists was valuable in ensuring the high-quality colonoscopy services in this program.

Test-positive rate, CRC and adenomatous polyp detection rates per 1000 screened persons in our program were lower than those reported from high-risk countries; however the detection frequencies of both CRC and polyps as a proportion of iFOBT positive persons (2.6% for CRC and 21.4% for adenoma) and of those receiving colonoscopy (3.7% for CRC and 29.8% for adenoma)are within the range reported (1.9% - 7.0% for CRC and 20.0% - 43% for adenoma) from high incidence countries, indicating the high quality of interventions in our pilot program.[16-18;27;28] The low test positive and detection rates as a proportion of screened subjects is not surprising given the comparatively low-incidence rates of CRC in Thailand as compared to high-incidence countries.[1;32]

Most CRCs develop from adenomas, among which "advanced" adenomas are considered to be the clinically relevant precursors. Among the adenomatous polyps, advanced adenoma is considered to be the most valid neoplastic surrogate marker for present and future colorectal cancer risk and detecting advanced adenomas is a major focus in CRC screening. A high detection rate of advanced adenoma as compared to the more common, but less clinically significant small adenomas, is an important target of CRC screening and an indicator of high screening efficacy[33]. It has been shown that the cumulative risk of malignancy in advanced polyps range between 25% and 45% in persons aged 55 years and above[34]. Thus, advanced adenomas may be considered as surrogate for CRC. In our pilot

project two-fifths of detected adenomas were advanced adenoma. Two-thirds of CRC detected in our pilot project was in early stages. Both the high detection rate of advanced adenoma and early detection CRC could have a higher impact on future CRC incidence and mortality in this pilot cohort.

Whereas FOBT screening is repeated annually or biennially in high-risk countries, we have decided to repeat CRC screening once in 5-years in our pilot project and in Thailand when CRC screening is scaled up nationally, in view of the comparatively low CRC incidence. From a practical and sustainable perspective, particularly from the aspect of providing high quality colonoscopy services, performing iFOBT screening once in 5-years is an attractive option given the level of development of health care infrastructure; however, the performance of screening, particularly false-negative rates and interval cancers, needs to be carefully assessed and the need for appropriate mid-course corrections for this policy should be promptly addressed.

A current limitation of our study is that it describes the process measures and intermediate outcomes such as adenoma detection rates and stage distribution of screen detected colorectal cancers but no information is available on the extent of false negative tests and the impact of the intervention on colorectal cancer incidence and mortality due to lack of long-term follow-up of the study population at this instance. This information will be eventually generated by both active and passive follow-up the study population in future. On the other hand, a major strength is that the study reflects the real life conditions and has been conducted using the existing routine health care services which allows a realistic assessment of the feasibility of colorectal screening in a middle-income country.

In addition to the specific application of these findings to the further development of a CRC screening program in Thailand, the approach taken here illustrates some more general principles of note. First, middle or high human development index countries experiencing the cancer transition[35] may pre-empt projected increases in cancers of certain organs by implementing prevention or early detection before those increases become manifest. Second, the type of implementation research reported here is well-suited to low and middle-income countries given the direct relevance to cancer control and the relatively low additional cost of integrating a research component into national public health programs. Third, the research project converges with capacity building, in this case through training of different categories of health professionals, so that the program once implemented, benefits from the developments required by the research itself.

In conclusion, our results indicate the acceptability, feasibility, organization, and implementation of CRC screening in the general population setting in Thailand and the feasibility of integrating the program within the existing public health services. Although we are encouraged by the high participation rates from rural districts, the participation in urban areas need to be improved by appropriate invitation logistics. It is our belief that no associated financial costs to the eligible individuals and the appropriate organization of services within the program have minimized the barriers to access for socio-economically disadvantaged populations. The implementation of the pilot program has been successful as measured by the process measures of coverage, preliminary performance of the screening test, colonoscopy, removal of colonoscopically detected polyps, provision of histopathology services and detection and treatment of CRC in early clinical stages t which have met the criteria of a successful public health program.

FIGURE LEGEND

Figure 1 A schematic diagram of the pilot colorectal cancer screening program in Lampang province, Thailand

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COMPETING INTERESTS

No author has any potential conflict of interest relevant to these studies and all authors had full rights, access to and management of the data used in this article. There is no additional data other than the study database which are available.

Contributorship statement:

Authors' contributions

• Thiravud Khuhaprema: Conception and design, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published

• Suleeporn Sangrajrang: Conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published

• Somkiat Lalitwongsa: Conception and design, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published

• Vanida Chokvanitphong: Conception and design, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published

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• Eric Lucas: Conception and design, revising the article critically for important intellectual content, and final approval of the version to be published

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• Rengaswamy Sankaranarayanan: Conception, design, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be published.

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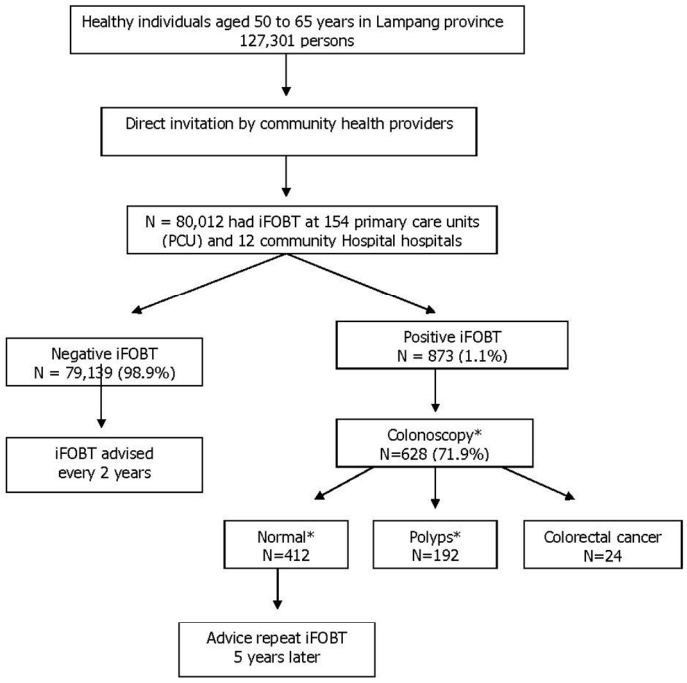
Figure 1



A schematic diagram of the pilot colorectal cancer screening program in Lampang province, Thailand
215x279mm (150 x 150 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**1**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4**
Methods			
Study design	4	Present key elements of study design early in the paper	**6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**6-8**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	**6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**7-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***7-8***
Bias	9	Describe any efforts to address potential sources of bias	**6-7**
Study size	10	Explain how the study size was arrived at	**6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**8**
		(*b*) Describe any methods used to examine subgroups and interactions	**n/a**
		(*c*) Explain how missing data were addressed	**n/a**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	**n/a**
		(*e*) Describe any sensitivity analyses	**n/a**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**9-10**
		(b) Give reasons for non-participation at each stage	**n/a**
		(c) Consider use of a flow diagram	**9**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**10**
		(b) Indicate number of participants with missing data for each variable of interest	**9-10**
Outcome data	15*	Report numbers of outcome events or summary measures	**9-15**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**9-15**

		(*b*) Report category boundaries when continuous variables were categorized	**n/a**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**n/a**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**n/a**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**16-17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**18**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**17-18**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**8-9**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Organized colorectal cancer screening in Lampang Province, Thailand: Preliminary results from a pilot implementation programme

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Keywords:	PRIMARY CARE, Gastrointestinal tumours < ONCOLOGY, Endoscopy < GASTROENTEROLOGY

Organized colorectal cancer screening in Lampang Province, Thailand: Preliminary results from a pilot implementation programme

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ABSTRACT

Objective: Colorectal cancer (CRC) is the third- and fifth-most common cancer in men and women, in Thailand. The increasing CRC incidence and mortality can be reduced by screening and treating adenomas and early cancers. A pilot CRC screening program using immunochemical fecal blood testing (iFOBT) and colonoscopy for test-positives was implemented through the routine Government Health Services in Lampang Province, to inform the acceptability, feasibility and scaling-up of screening in Thailand. This report describes the implementation, coverage and performance indicators of this project.

Design: A target population aged 50-65 years was informed about and invited face to face to undergo CRC screening by community health workers (HWs). The HWs provided fecal sample collection kits and participants brought their samples to one of the primary health units or community hospitals where nurses performed iFOBT. IFOBT-positive persons were referred for colonoscopy at the Lampang cancer hospital and endoscopic polypectomy/biopsies were performed according to colonoscopic findings. Those with confirmed CRC received appropriate treatment.

Results: Of the 127,301 target population 62.9% were screened using iFOBT between April 2011 and November 2012. Participation was higher among women (67.8%) than men (57.8%) and lower in 50-54 year-old persons than 60-65 year-olds. Of those screened, 873 (1.1%) were found positive; positivity was higher in men (1.2%) than in women (1.0%). To date 627 (72.0%) iFOBT-positive persons have had colonoscopy in which 3.7% had CRC and 30.6% adenomas.

Conclusion: The successful implementation of the pilot CRC screening with satisfactory process measures indicate the feasibility of scaling up organized CRC screening through existing health services in Thailand.

Article focus:

- The article addresses the feasibility of introducing colorectal cancer screening using immunochemical fecal occult blood test (iFOBT) through existing primary health care services and colonoscopy triage and treatment of screen positive subjects in secondary/tertiary care services in a province in Thailand.
- Addresses the performance characteristics of colonoscopy triage in terms of polyp and adenoma detection rates and positive predictive values.

Key messages:

- Despite the increasing incidence of colorectal cancer (CRC) in middle-income countries, organized colorectal cancer screening programs are yet to evolve in these countries.
- This pilot study shows that it is feasible to introduce organized CRC screening with iFOBT and colonoscopy triage with satisfactory input measures and intermediate outcomes, through existing government health services, in middle-income country like Thailand
- Experience from this pilot project may pave the way for nationwide scaling-up of organized CRC screening program in Thailand and other middle-income countries with increasing risk of CRC

Strengths and limitations:

- This pilot study documents the feasibility, acceptance and safety of CRC screening in a lower-middle income country.
- The study has been carried out in real life conditions using the existing routine health care services allowing a realistic and pragmatic assessment of the feasibility, sustenance and intermediate outcomes of colorectal screening in a **lower**-middle-income country.

- No information is provided on the extent of false negative tests and the impact of the intervention on colorectal cancer incidence and mortality due to lack of long-term follow-up of the study population at this instance. This information will be eventually generated by both active and passive follow-up the study population in future.

- The study did not include population aged between 66 to 74 years.

INTRODUCTION

Colorectal cancer (CRC) is a major cancer in Thailand with age-standardized incidence rates of 12.9/100,000 in men and 9.2/100,000 in women in 2005 and an incidence which is steadily increasing over time.[1] Sedentary lifestyle, lack of physical activity, smoking, drinking alcohol, a high consumption of red and processed meats as well as a low consumption of whole grains, fiber, fruits and vegetables are associated with an elevated risk of CRC. Most CRCs occur in pre-existing adenomatous polyps; a small percentage of the colonic polyps may become cancerous and spread elsewhere.[2] This progression takes at least 10 years in most people. Early detection and removal of polyps in the colon and rectum may prevent the development of invasive CRC.[3]

Early detection and prevention of CRC through screening is an effective intervention to reduce the considerable human and financial costs.[4] Tests considered for screening include variants of fecal occult blood tests (FOBT), flexible sigmoidoscopy and colonoscopy. Of these, FOBTs are the most feasible, non-invasive, affordable and acceptable for population screening as they detect intermittent microscopic blood losses from early CRC to advanced adenomas. Chemical FOBT (cFOBT) uses guaiac to detect peroxidase in human blood, but also reacts to the peroxidase present in dietary constituents such as red meat, cruciferous vegetables and some fruits, while the recently developed immunochemical FOBT (iFOBT) uses an antigen-antibody reaction to specifically detect globin which, together with heme, constitutes human hemoglobin. iFOBT is not subject to false-negative results in the presence of high-dose vitamin C supplements, which block the peroxidase reaction; since globin is degraded by digestive enzymes in the upper gastrointestinal tract, iFOBT is more specific for lower gastrointestinal bleeding, thus improving their specificity for colorectal neoplasia.

It has been shown in pooled analysis of four randomized controlled trials that annual or biennial screening with cFOBT reduced overall CRC mortality by 16%, for those allocated to CRC screening, and CRC mortality by 25% for those attending at least one round of screening with cFOBT.[4] The iFOBT provides a suitable and better alternative to cFOBT as a screening test due to its higher sensitivity, simplicity, ease of use and the fact that it does not require any dietary restriction.[5-8]

CRC screening programs are increasingly organized at regional and national levels in many countries. Programs in countries such as Australia, Canada, Finland, France and United

Kingdom use either direct mail invitations or invitations initiated by general practitioners to target populations aged 50-65 or 55-69 or 50-74 years. Programs in Canada and Finland use cFOBT, whereas iFOBT is used in Korea and Japan.[9-12] Although FOBT and colonoscopy are opportunistically provided in urban hospitals, there is no population-based organized CRC screening program in Thailand. The public health authorities in Thailand, faced with the increasing risk of CRC, due to the transition to westernized lifestyles with socio-economic development, would like to take measures to reduce its incidence and deaths by primary prevention and screening.

Thailand has a well-developed public health services with an extensive primary care network well integrated with district, provincial hospitals and tertiary care centers such as several comprehensive regional cancer centers and advanced university hospitals. Four decades ago when Thailand was a low-income country, it invested early in health care and transportation infrastructure that has reached most remote rural communities and helped it to achieve health care at low costs, given the fact that 4.1% its gross domestic product (GDP) for health, a figure far lower than the 10% average in high-income countries. Thailand has been successful in training doctors, nurses, auxillary and paramedical health workers and technicians in large numbers for its health system, with innovative distribution of human resources to rural areas. In addition, health volunteers recruited from local communities play important support, prevention and early detection roles, thereby enhancing community involvement. The entire Thai population is covered through a comprehensive health care package through universal health coverage (UHC) for financing an extensive range of preventive, diagnostic, treatment and follow-up care and hospitalisations due to any illness.[13]

In this context, a decision was made to implement a pilot CRC screening program with iFOBT followed by full colonoscopy for test positive persons using existing facilities and personnel in government health services in Lampang Province. This pilot study was implemented to assess the feasibility, acceptability, safety of CRC screening both in urban and rural settings and to inform whether and how to introduce a nationwide, organized CRC screening program through the existing public health services in a phased manner. Lampang Province was chosen to implement the pilot project, due to its representativeness of the wider Thai population in terms of demographic, and socio-economic profiles, a relatively high incidence rate of CRC (18.7 per 100,000 in men and 14.4/100,000 in women),[14] the availability of comprehensive cancer diagnosis, treatment and follow-up care facilities in

general, and colonoscopy, histopathology and CRC treatment services in particular, at the Lampang provincial hospital (803 beds) and the Lampang Cancer Hospital (137 beds) and the existing population-based cancer registry that will help to evaluate the impact of the pilot intervention on CRC incidence and mortality in the province. We report the organization, implementation, coverage and performance of the pilot CRC screening in this manuscript.

MATERIAL AND METHODS

Project proposal development

A detailed project proposal describing the background, project procedures, study questionnaires and forms to capture participant data and details of investigations, the project database, quality assurance methods and means of monitoring and evaluation were jointly developed between June 2010 and March 2011 by the National Cancer Institute (NCI), Bangkok, and the provincial health authorities with technical assistance from the Screening Group of the International Agency for Research on Cancer (IARC) of the World Health Organization, Lyon, France. Following the finalization of the project proposal, its approval by national authorities and completion of training for the providers, screening commenced in April 2011 and recruitment of eligible subjects was closed in November 2012.

Target population and involved healthcare facilities and personnel

All apparently healthy, ambulant men and women aged 50 to 65 years with no past history of CRC and resident in Lampang Province were the target population for screening in the pilot project, totaling 127,301 eligible subjects, as identified from the National Statistics office and from the population registers with the health centers in the province. The Government healthcare infrastructure consisting of 154 primary care units (PCUs), 12 community hospitals (CHs), Lampang provincial hospital and Lampang Cancer Hospital and the doctors, nurses, HWs and technicians in these public facilities provided the various services such as information dissemination, invitation, testing, diagnosis, treatment and follow-up care to the screening project. These tasks were assigned as additional responsibility to these facilities and personnel and no added financial incentives were provided to them for these added tasks. No additional workers were hired for this project.

The screening program was coordinated by the NCI and the provincial health authority and technically supported by the IARC.

Training for screening and colonoscopy providers

The registered nurses, community health workers (HWs) of the 154 PCUs and 12 CHs of Lampang Province were trained on information dissemination on CRC screening, awareness creation, motivation of the target population and invitation of eligible persons to participate in CRC screening during a one-day session by a faculty from the NCI and provincial health authority. They were trained to explain to the participants how to collect the fecal specimen in the sample collection tube and bring it to the PCU or the CH within 3 hours from collection for occult blood testing. The training also covered the performance and interpretation of the iFOBT test. Attractive pamphlets and posters in Thai language describing the prevention and early detection of CRC, the method of collecting the fecal samples, the iFOBT test procedure, colonoscopy and treatment of CRC were developed and printed by the Thai Health Services with technical support from the NCI and IARC. The HWs routinely visit all households under the jurisdiction of each PCU once in 6 months to provide preventive care. The eligible subjects for CRC screening in this study were met, educated, invited and encouraged to participate in screening and the pamphlets and the fecal collection pots were distributed by HWs to eligible subjects during these routine house visits. Family history of CRC among first and second degree relatives was enquired into during the house visits. The posters were prominently displayed in all health care facilities, educational institutions, public offices and public places.

Gastroenterologists and surgeons at the Lampang provincial hospital and the Lampang Cancer Hospital were reoriented and re-trained in key aspects of colonoscopy to improve their hands-on colonoscopy/polyp excision/biopsy skills in live sessions during 5 days. They were taught and evaluated by skilled gastroenterologists, with several years of experience in colonoscopy and endoscopic removal of polyps and mucosal resection of small lesions from the NCI and the Thai Association of Gastrointestinal Endoscopy in live sessions under direct observation before the initiation of the program.

Screening invitation and organization

The existing health care infrastructure and personnel in the PCUs and the CHs were used to disseminate information, to invite and provide iFOBT and to refer those testing positive for

colonoscopy. The HWs from the PCUs and CHs distributed a fecal sample collection kit to the eligible persons in the households under their jurisdiction as per a regular schedule and explained how to collect the specimen and when to bring the collected specimen to the PCU/CH for testing. The colonoscopy, histopathology and treatment services at the Lampang provincial hospital and the Lampang Cancer Hospital were used to diagnose and treat patients in the program.

Screening with iFOBT and referral

All fecal samples were subjected to one-step iFOBT (Hemosure™, EL Monte, USA) according to the manufacturer's instructions. The test was carried out at the PHU/CH by the nurse in front of the participant. In less than 5 minutes a level of hemoglobin as low as 200 ng/ml can be detected by this test. One pink-rose band appearing in the "C: region and the other "T" region of the test device indicates a positive iFOBT. A negative iFOBT is characterized by only one color band in the "C" region. In this study, fecal material was assessed from one sample taken from each participant (1-day iFOBT). Verbal informed consent was obtained from all participants before analyzing the stool sample. The nurse at the PCU/CH fixed an appointment for colonoscopy at the Lampang cancer hospital for iFOBT positive persons and explained the pre-colonoscopy bowel preparation and the colonoscopy procedure in detail, provided a prescription for bowel cleansing and encouraged them to comply with the referral.

Colonoscopy

Colonoscopy was provided to iFOBT-positive individuals on scheduled days every week at the Lampang Regional Cancer Center. A second informed consent was obtained from people undergoing colonoscopy, biopsy, and treatment. The outcome of colonoscopy was reported as normal, polyps, suspected cancer or invasive cancer. Polyps and small lesions were removed and subjected to histopathology. Large lesions were biopsied for histological assessment. Those diagnosed with CRC received further investigations for clinical staging and treatment as per the standard protocol developed for Thailand. The findings of colonoscopy, any severe adverse events within 30 days following colonoscopy (such as bleeding, perforation, administration of blood transfusion, hospitalisations for severe abdominal pain, paralytic ileus, cardiovascular events, hypotension, syncope, shock, dehydration, anaphylactic reactions, cardiorespiratory arrest etc), histology, stage, treatment

and follow-up assessment were recorded in a diagnosis and treatment form and entered into the database.

Data management, monitoring and evaluation

Personal identification (name, age, address, citizen ID number), socio-demographic information, screening test result, results of colonoscopy and other investigations, treatment details and follow-up information were collected in specifically developed forms and entered in a multiuser program database with inbuilt validation checks called CRCreg developed by the IARC. The database was continuously updated as the pilot project progressed. It is possible to link the screening program and the cancer registry databases using the unique citizen ID numbers, which will enable the identification of false-negative cases and interval cancers.

The study database was analyzed to document the participant characteristics, participation rates for screening and test positivity rates by sex, age, the district of residence and the proportion of test-positive individuals complying with referral for colonoscopy, colonoscopy results, final diagnosis, stage of invasive cancer, treatment details and adverse events. Comparison of proportions was done using a two-sided test on the equality of proportions using large-sample statistics, which also gives exact P values. Assessment of the effect of patient characteristics on the attendance for colonoscopy was carried out using logistic regression analysis.

Ethical approval and funding

Ethical approval was obtained from Institutional Review Board and Ethics Committee of NCI and the IARC. The project was funded by the Ministry of Health, Thailand, through the NCI, Bangkok.

RESULTS

The flow chart of the program organization and procedures is shown in Figure 1. All 154 PCUs and 12 CHs (100%) in the province participated in the project. Of the 127,301 eligible subjects (63,274 men and 64,027 women), 80,012 (62.9%) (36,601 men and 43,411 women) were enrolled. The distribution of sex, education, occupation and family history of CRC among the participants are given in Table 1. The mean age was 56.6 (SD=4.3) among women and 56.8 (SD=4.3) among men. More than 80% of the subjects had only primary

school education; three-fourths were involved in agriculture; 0.7% had family history of CRC.

Table 1. Characteristic of participants in the Lampang pilot colorectal cancer screening project

Characteristics	Number	Percentage
Screened	80,012	
Sex		
Men	36,601	45.7
Women	43,411	54.3
Age (in years)		
50-54	28,956	36.2
55-59	27,825	34.8
60-65	23,231	29.0
Education		
None	6,192	7.7
Primary	66,583	83.2
Secondary	5,208	6.5
College/University	2,028	2.5
Occupation		
Agriculture	57,266	75.8
Manual labour	11,381	15.1
Support/Service	4,718	6.2
Crafts/machinery	371	0.5
Family income in Thai Bahts per month (1 USD=30 Bahts)		
<5000	44,940	58.4
5000-10000	26,463	34.4
>10000	5,533	7.2
Colorectal cancer in first and second degree relatives		
Yes	552	0.7
No	72,971	91.2
Unknown	6,489	8.1
Setting		
Rural	58,873	73.6
Urban	21,139	26.4
District		
Mueang (U)	13,016	16.3
Mae Moh (U)	2,772	3.5
Koh Kha (U)	5,351	6.7
Soem Ngam (R)	3,747	4.7

Wang Nua (R)	5,962	7.5
Chae Hom (R)	6,474	8.1
Ngao (R)	7,489	9.4
Thoen (R)	8,486	10.6
Mae Phrik (R)	2,523	3.2
Mae Tha (R)	9,025	11.3
Sop Prap (R)	3,977	5.0
Hang Chat (R)	6,447	8.1
Mueang Pan (R)	4,743	5.9

U: Urban; R: Rural

The overall participation rate for screening (62.9%) was much higher in women (67.8%, 95%CI: 67.4-68.2%) than in men (57.8%, 95%CI: 57.5-58.2%) (Table 2) (p-value<0.001). Participation in screening varied between the 13 districts in the province: generally being higher in rural (73.2%, 95%CI: 72.9-73.5%) than in urban districts (45.1%, 95%CI: 44.6-45.5%) (Table 2) (p-value<0.001), categorized as defined by the National Statistics Office based on demography, economy, educational, occupational and migration criteria. The highest iFOBT uptake was in the rural district of Theon (86.0% in women and 73.4% in men) while the lowest participation was in the urban district of Mueang (47.7% in women and 35.1% in men). Screening participation rates increased from 52.9% in those aged 50-54 years to 78.9% among those aged 60-65 years (Table 3).

Table 2. Total eligible subjects, screened eligible subjects and test positive frequencies by sex, age and districts in Lampang province, Thailand, 2011-2012

	Men					Women					Overall				
	Eligible persons	Number Screened with iFOBT	(%)	Number Screen positive	(%)	Eligible Persons	Number screened with iFOBT	(%)	Number screen positive	(%)	Eligible persons	Number Screened with iFOBT	(%)	Number screen positive	(%)
Overall	63,274	36,601	(57.8)	447	(1.2)	64,027	43,411	(67.8)	426	(1.0)	127,301	80,012	(62.9)	873	(1.1)
Sex															
Men	63,274	36,601	(57.8)	447	(1.2)						63,274	36,601	(57.8)	447	(1.2)
Women						64,027	43,411	(67.8)	426	(1.0)	64,027	43,411	(67.8)	426	(1.0)
p-value													<0.001		0.001
Age (in years)															
50-54	27,148	12,927	(47.6)	106	(0.8)	27,597	16,029	(58.1)	131	(0.8)	54,745	28,956	(52.9)	237	(0.8)
55-59	21,328	12,711	(59.6)	146	(1.1)	21,777	15,114	(69.4)	130	(0.9)	43,105	27,825	(64.6)	276	(1.0)
60-65	14,798	10,963	(74.1)	195	(1.8)	14,653	12,268	(83.7)	165	(1.3)	29,451	23,231	(78.9)	360	(1.5)
Setting															
Rural	40,289	27,692	(68.7)	317	(1.1)	40,108	31,181	(77.7)	295	(0.9)	80,397	58,873	(73.2)	612	(1.0)
Urban	22,985	8,909	(38.8)	130	(1.5)	23,919	12,230	(51.1)	131	(1.1)	46,904	21,139	(45.1)	261	(1.2)
p-value													<0.001		0.019
District															
Mueang (U)	15,188	5,327	(35.1)	60	(1.1)	16,127	7,689	(47.7)	64	(0.8)	31,315	13,016	(41.6)	124	(1.0)
Mae Moh (U)	2,999	1,300	(43.3)	30	(2.3)	2,690	1,472	(54.7)	24	(1.6)	5,689	2,772	(48.7)	54	(1.9)
Koh Kha (U)	4,798	2,282	(47.6)	40	(1.8)	5,102	3,069	(60.2)	43	(1.4)	9,900	5,351	(54.1)	83	(1.6)
Soem Ngam (R)	2,838	1,757	(61.9)	16	(0.9)	2,581	1,990	(77.1)	9	(0.5)	5,419	3,747	(69.1)	25	(0.7)
Wang Nua (R)	4,712	2,988	(63.4)	46	(1.5)	4,429	2,974	(67.1)	51	(1.7)	9,141	5,962	(65.2)	97	(1.6)
Chae Hom (R)	4,324	3,123	(72.2)	42	(1.3)	4,385	3,351	(76.4)	38	(1.1)	8,709	6,474	(74.3)	80	(1.2)
Ngao (R)	5,603	3,642	(65.0)	18	(0.5)	5,289	3,847	(72.7)	22	(0.6)	10,892	7,489	(68.8)	40	(0.5)
Thoen (R)	5,196	3,814	(73.4)	17	(0.4)	5,431	4,672	(86.0)	25	(0.5)	10,627	8,486	(79.9)	42	(0.5)
Mae Phrik (R)	1,490	1,087	(73.0)	11	(1.0)	1,683	1,436	(85.3)	10	(0.7)	3,173	2,523	(79.5)	21	(0.8)
Mae Tha (R)	5,970	4,161	(69.7)	61	(1.5)	6,030	4,864	(80.7)	45	(0.9)	12,000	9,025	(75.2)	106	(1.2)

Sop Prap (R)	2,946	1,876	(63.7)	29	(1.5)	2,993	2,101	(70.2)	16	(0.8)	5,939	3,977	(67.0)	45	(1.1)
Hang Chat (R)	4,009	2,991	(74.6)	41	(1.4)	4,206	3,456	(82.2)	42	(1.2)	8,215	6,447	(78.5)	83	(1.3)
Mueang Pan (R)	3,201	2,253	(70.4)	36	(1.6)	3,081	2,490	(80.8)	37	(1.5)	6,282	4,743	(75.5)	73	(1.5)

U: Urban; R: Rural

Table 3. Colonoscopy attendance, results and final diagnosis by sex

	Men		Women		Total	
Number screened with iFOBT	36,601		43,411		80,012	
Number screen positive (%)	447	(1.2)	426	(1.0)	873	(1.1)
Number attended colonoscopy referral (%)	319	(71.4)	308	(72.3)	627	(71.8)
Colonoscopy result (per 1000 screened)						
Normal	165		215		380	
Polyp	133	(3.6)	73	(1.7)	206	(2.6)
Suspected cancer	16	(0.4)	11	(0.3)	27	(0.3)
Inadequate/Unknown	5		9		14	
Final diagnosis (per 1000 screened)						
Normal	158		206		364	
Inflammatory bowel disease	5	(0.1)	2	(0.0)	7	(0.1)
Adenomatous polyp	12	(0.3)	9	(0.2)	21	(0.3)
Adenomatous polyp with dysplasia	108	(3.0)	51	(1.2)	159	(2.0)
Hyperplastic polyp	4	(0.1)	1	(0.0)	5	(0.1)
Colitis	4	(0.1)	6	(0.1)	10	(0.1)
Adenocarcinoma in-situ	3	(0.1)	4	(0.1)	7	(0.1)
Colorectal cancer	13	(0.4)	10	(0.2)	23	(0.3)
Other	11	(0.3)	18	(0.4)	29	(0.4)
Unknown	1	(0.0)	1	(0.0)	2	(0.0)

Using a cut-off fecal hemoglobin concentration of 200 ng/ml, 873 of 80,012 (1.1%) participants were reported as positive on iFOBT. The iFOBT positivity rate was slightly higher in men (1.2%) than in women (1.0%) (p-value=0.001) (Table 2). Test positivity rate increased from 0.8% in those aged 50-54 years to 1.5% in those aged 60-65 years (Table 2).

As of 21 February 2013, 627 (71.8%) iFOBT positive persons had colonoscopy; no serious adverse event was reported following colonoscopy. On colonoscopy, 206 were found to have polyps and cancer was suspected in 27 (Table 3). Polyps were excised and biopsies were directed in growths. On histological examination of excised polyps, adenoma was confirmed in 187 persons (Table 3). CRC was histologically confirmed in 23 persons (3.7%). The detection rate of histologically confirmed CRC was 2.9 per 10,000 screened persons and that of adenomatous polyp was 23.4 per 10,000 screened persons. CRC and adenomas were

detected in 3.6% and 29.8% respectively of iFOBT-positive individuals who had colonoscopy.

Among the 187 persons with histologically confirmed adenomatous polyps, 75 (40.1%) had advanced adenoma. Advanced adenoma denotes adenomatous polyps having one or more of the following features: > 10 mm in diameter, high-grade dysplasia, and significant villous histology (>25%). The stage-distribution of the detected invasive cancers was as follows: 2 stage I, 12 stage II, 7 stage III and 2 missing stage information. Compliance for colonoscopy referral was lower among individuals living in urban compared to rural areas and in those with relatively high compared to those with low monthly family incomes (Table 4).

Table 4. Colonoscopy attendance among screen positives by patient characteristics

Characteristic	Number screen positive	Number attended colonoscopy clinic (%)		Adjusted* OR (95% CI)		p-value
Participants	873	627	(71.8)			
Sex						
Men	447	319	(71.4)	1.0		
Women	426	308	(72.3)	1.1	(0.8 - 1.5)	0.534
Age (in years)						
50-54	237	177	(74.7)	1.0		
55-59	276	196	(71.0)	0.8	(0.5 - 1.3)	0.355
60-65	360	254	(70.6)	0.8	(0.5 - 1.1)	0.186
Education						
None	97	73	(75.3)	1.0		
Primary	704	504	(71.6)	0.7	(0.4 - 1.3)	0.301
Secondary	48	34	(70.8)	0.9	(0.4 - 2.4)	0.881
College/University	24	16	(66.7)	0.6	(0.1 - 2.8)	0.556
Occupation						
Agriculture	632	474	(75.0)	1.0		
Managerial/Professional	22	15	(68.2)	0.8	(0.2 - 3.5)	0.787
Support/Service	54	34	(63.0)	0.7	(0.4 - 1.2)	0.174
Crafts/machinery	4	3	(75.0)	1.0	(0.1 - 10.9)	0.989
Manual labour	95	60	(63.2)	0.7	(0.4 - 1.1)	0.097
Family income						
<5000	531	399	(75.1)	1.0		
5000-10000	254	166	(65.4)	0.6	(0.4 - 0.9)	0.007

>10000	59	42	(71.2)	0.9	(0.4 - 2.1)	0.887
Family history of colorectal cancer						
Yes	19	15	(78.9)	1.0		
No	774	551	(71.2)	0.9	(0.3 - 2.9)	0.827
Unknown	80	61	(76.3)	1.1	(0.3 - 4.4)	0.846
setting						
Rural	612	460	(75.2)	1.0		
Urban	261	167	(64.0)	0.7	(0.5 - 1.0)	0.043
District						
Mueang (U)	124	72	(58.1)	1.0		
Mae Moh (U)	54	39	(72.2)	2.1	(0.9 - 4.6)	0.070
Koh Kha (U)	83	56	(67.5)	1.5	(0.8 - 2.9)	0.225
Soem Ngam (R)	25	21	(84.0)	1.8	(0.4 - 7.7)	0.417
Wang Nua (R)	97	68	(70.1)	1.4	(0.7 - 2.7)	0.296
Chae Hom (R)	80	63	(78.8)	2.0	(1.0 - 4.1)	0.062
Ngao (R)	40	29	(72.5)	1.6	(0.7 - 3.8)	0.267
Thoen (R)	42	30	(71.4)	2.0	(0.8 - 4.6)	0.119
Mae Phrik (R)	21	18	(85.7)	3.2	(0.9 - 12.1)	0.084
Mae Tha (R)	106	84	(79.2)	2.5	(1.3 - 4.8)	0.007
Sop Prap (R)	45	31	(68.9)	1.4	(0.6 - 3.2)	0.462
Hang Chat (R)	83	63	(75.9)	3.2	(1.5 - 6.8)	0.003
Mueang Pan (R)	73	53	(72.6)	1.6	(0.8 - 3.2)	0.185

* Estimates for a characteristic factor adjusted for other characteristics; OR: odds ratio; CI: confidence interval; U: Urban; R: Rural

DISCUSSION

Among the CRC screening approaches in people at average risk (persons aged 50 to 74 years), annual or biennial FOBT followed by colonoscopy triage of screen positive individuals is the most widely used strategy due to its low cost, feasibility, safety and non-invasiveness. Significant reduction in CRC incidence and mortality following cFOBT screening has been shown in four randomized controlled trials.[4] This evidence, the fact that iFOBT is a better alternative to cFOBT and the declines in CRC mortality following widespread CRC screening in Japan, South Korea, Hong Kong and Singapore, despite increasing CRC incidence rates,[15] and in other high income countries[16 17] supported our decision to implement a pilot project based on 1-day iFOBT screening integrated in the routine public health services in Lampang province in Thailand.

Since CRC screening is a major undertaking and integrating a cancer screening program into routine government health services in low-middle income countries has its own complexities

and challenges, it was decided to pilot its introduction in one of the provinces of Thailand which already has a population based cancer registry. In high-income countries, large scale population-based organized CRC screening has been preceded by well-planned pilot introductions to evaluate the feasibility, practicality and acceptability of introducing a population screening program with biennial FOBT in government health services (Table 5).[18-21] The UK CRC screening pilot study was launched in 2000 in England and Scotland, which reported a FOBT uptake rate of 57% and CRC detection rate of 1.62 per 1,000 screened (Table 5).[18 19] In the Australian pilot CRC screening project ,56,907 women aged 55 to 74 years were invited for iFOBT screening during November 2002 to June 2004. Of them 25,840 (45.4%) participated, 25,688 correctly completed iFOBT screening and 2,317 (9.0%) were positive on iFOBT. The pilot project detected 176 persons with advanced adenoma and 67 with suspected cancer yielding a positive predictive value of 19.2% (Table 5); the estimated cost per additional life year saved in the Australian pilot project was 24,000 Australian $.[21] In the Finnish pilot project the participation rate was 71% among 52,994 invited persons and 2.1% of the participants were positive on FOBT and 51.8% of those who underwent colonoscopy were detected with adenomas or suspected cancer.[20] The national expansion of CRC screening in UK, Australia and Finland following the pilot studies was phased over 6 years.

Table 5. Comparison of pilot colorectal cancer screening projects in Thailand, Australia and UK

Criteria	Thailand		Australia[21]		UK[18]	
Period	2011-2012		2002-2004		2000-2003	
Screening test used	iFOBT		iFOBT		gFOBT	
Targeted age group (years)	50-65		55-74		50-69	
Target population, n	127,301		56,907		478,250	
Individuals screened, n (%*)	80,012	(62.9)	25,840	(45.4)	271,646	(56.8)
Individuals screen positive, n (%**)	873	(1.1)	2,308	(8.9)	5,050	(1.9)
Colonoscopy done, n (%†)	627	(71.8)	1,265	(54.8)	4,116	(81.5)
Adenoma detected, n (%‡)	187	(29.8)	251	(19.8)	1,388	(33.7)
Advanced adenoma, n (%‡)	75	(12.0)	176	(13.9)	-	
Colorectal cancer detected, n (%‡)	23	(3.7)	67	(5.3)	552	(13.4)
Stage I and II colorectal cancer, n (%§)	14	(60.9)	-		345	(62.5)
Colorectal cancer detection rate per 100,000 screened		28.7		259.3		203.2

iFOBT: immunochemical fecal blood testing; gFOBT: guaiac fecal blood testing;
* Based on target population; ** Based on individuals screened; † Based on individuals screen positive; ‡ Based on colonoscopy done; § Based on colorectal cancer detected

The results on participation and detection rates of colorectal neoplasia in our pilot project in Lampang are consistent with findings from pilot (Table 5) and national programs elsewhere. For example, the participation rate of eligible subjects in our Thai study was similar to rates reported from pilot demonstration projects in the United Kingdom (57%), Haut-Rhin, France (55%) and in Finland (71%) and in service programs in UK (54%)[18 20 22 23] and higher than those reported from the Australian pilot project (45.4%) (a systematic review of participation in CRC screening programs (42%) and from the national CRC screening programs in Australia (35%),[24] South Korea (<25%) and Croatia (10%).[11 21 25 26] Our results confirm that the use of primary HWs outreach to promote and provide CRC screening through existing Government health services is feasible in Thailand.

A higher uptake of iFOBT was observed among women and in older age groups in our program. A similar observation has been reported CRC screening programs in other countries.[11 18 20 23-25 27] We observed a higher uptake of iFOBT screening in rural populations than in urban populations of Lampang province. Information on CRC screening and invitations for iFOBT screening in rural districts were mostly delivered to the target population by direct person to person contact and face to face communication, while in urban areas the information on the program was predominantly delivered through poster advertisements due to the challenges in face to face contacts. The proportion of households visited were much higher in rural than in urban areas, where the sample collection kits were mostly collected by the eligible individuals during their routine and opportunistic visits to the health centers or community hospitals for routine health checkups for early detection of diabetes, hypertension and helminthiasis and for medical problems. Unfortunately we could not exactly quantify the proportion of participation from home visits or by visits to the PCUs/CHs as this was not documented in the database. The higher screening uptake in rural populations than in urban areas suggests that more direct person to person contacts and personalized invitations and personalized delivery of collection kits improved the participation. A personalized approach to participant recruitment has also been reportedly associated with a higher uptake of CRC screening in other settings.[26] A higher participation in rural populations than in urban and metropolitan populations has been reported from other countries as well.[26 28] Higher participation for colonoscopy among the low-income and

rural population reflects the faith and dependence of the socioeconomically weaker sections on public health services than those with higher incomes and living in urban areas.

The overall iFOBT positivity rate in our pilot project was in the lower range of test positivity rates reported from high-risk, high-income countries. FOBT test positive rates ranged from 2.1% to 9.0% in high-risk high-income countries.[11 19-21 24 25 29-31] Our results show that positivity rate in men (1.2%) was slightly higher than in women (1.0%), which is consistent with a higher CRC incidence in men (14.7 per 100,000 men) as compared to that of women (10.1/100,000 women) in Lampang province. A higher test positivity rate in men than in women has also been reported in other settings.[18-21 24 29 30]

FOBT screening for CRC is effective only when a high proportion of those with a positive result attend further full colonoscopy diagnostic evaluation of the colon. Two-thirds of test positive persons complied with referral for colonoscopy in our program, which is within the range of adherence to colonoscopy referrals in high-income countries. In many national programs, compliance of test-positive subjects to colonoscopy ranged between 38% and 88%.[11 23-25 32 33] There was no serious adverse event following colonoscopy in our program. The risks of serious adverse events such as perforation, hemorrhage, peritonitis and acute diverticulitis following colonoscopy performed as part of CRC screening are low, but increase with age and following polypectomy; the rate of adverse events reportedly varied between 3 to 6 per 1,000 colonoscopies performed.[34] The value of short and intensive re-training and re-orientation courses for colonoscopists of varying experience in achieving high standards has been well-established.[35] Teaching practical hands-on skills in short intensive re-orientation sessions to our program gastroenterologists and assessment of their performance and competency in key aspects of colonoscopy by direct observation in live case sessions by experienced colonoscopists was valuable in ensuring the high-quality colonoscopy services in this program. Based on our experience in this pilot project, we have developed a beginner's manual for colonoscopy for use in low- and middle-income countries.

Test-positive rate, CRC and adenomatous polyp detection rates per 1,000 screened persons in our program were lower than those reported from high-risk countries; however the detection frequencies of both CRC and polyps as a proportion of iFOBT positive persons (2.6% for CRC and 21.4% for adenoma) and of those receiving colonoscopy (3.7% for CRC and 29.8% for adenoma)are within the range reported (1.9% - 7.0% for CRC and 20.0% - 43% for adenoma) from high incidence countries, indicating the high quality of

interventions in our pilot program.[18-21 31 32] The low test positive and detection rates as a proportion of screened subjects is not surprising given the comparatively low-incidence rates of CRC in Thailand as compared to high-incidence countries.[1 14 36]

Most CRCs develop from adenomas, among which "advanced" adenomas are considered to be the clinically relevant precursors. Among the adenomatous polyps, advanced adenoma is considered to be the most valid neoplastic surrogate marker for present and future colorectal cancer risk and detecting advanced adenomas is a major focus in CRC screening. A high detection rate of advanced adenoma as compared to the more common, but less clinically significant small adenomas, is an important target of CRC screening and an indicator of high screening efficacy.[37] It has been shown that the cumulative risk of malignancy in advanced polyps range between 25% and 45% in persons aged 55 years and above. [38] Thus, advanced adenomas may be considered as surrogate for CRC. In our pilot project two-fifths of detected adenomas were advanced adenoma. Two-thirds of CRC detected in our pilot project was in early stages. Both the high detection rate of advanced adenoma and early detection CRC could have a higher impact on future CRC incidence and mortality in this pilot cohort.

Whereas FOBT screening is repeated annually or biennially in high-risk countries, we have decided to repeat CRC screening once in 5-years in our pilot project and in Thailand when CRC screening is scaled up nationally, in view of the comparatively low CRC incidence. From a practical and sustainable perspective, particularly from the aspect of providing high quality colonoscopy services, performing iFOBT screening once in 5-years is an attractive option given the level of development of health care infrastructure. The national scale up of screening following the pilot project in Australia since 2006 occurs in a phased manner.[39] It introduced national bowel cancer screening program (NBCSP) in 2006 as one off test for those turning 55 and 65 years and testing for 50 year-olds was added in 2008 and for 60 year-olds in 2013; 70 year-olds will be added in 2015. It would then progressively shift to 2-yearly screening of all Australians aged 50-74 years from 2017-18. Thus a full scale national scale up in Australia will take 13 years from introduction.[39] In Thailand, as we phase out the scale up over several years, the performance of screening, particularly false-negative rates and interval cancers, needs to be carefully assessed and the need for appropriate mid-course corrections for this policy should be promptly addressed as the program evolves. Based on the preliminary findings from our pilot study, we are conducting a formal cost-effectiveness analysis in collaboration with the Health Intervention and Technology

Assessment Program of the Thailand Government to determine the costs of all services provided along the screening pathway to estimate screening cost-effectiveness and funding required for the national program.

A current limitation of our study is that it describes the process measures and intermediate outcomes such as adenoma detection rates and stage distribution of screen detected colorectal cancers but no information is available on the extent of false negative tests and the impact of the intervention on colorectal cancer incidence and mortality due to lack of long-term follow-up of the study population at this instance. This information will be eventually generated by both active and passive follow-up the study population in future. Another limitation is that people aged 66 to 75 years were not included; however this is unlikely to have a major implication in any future scaling up of screening for this age group. On the other hand, a major strength is that the study reflects the real life conditions and has been conducted using the existing routine health care services which allows a realistic assessment of the feasibility of colorectal screening in a middle-income country. The fact that Thailand has developed an equitably accessible health care system with universal health coverage and has experienced an inclusive socioeconomic progress covering all regions of the country suggests that the pilot experience in Lampang can be translated to the national population in due course. However additional specific measures need to evolve by qualitative studies to ensure adequate participation in urban areas.

In addition to the specific application of these findings to the further development of a CRC screening program in Thailand, the approach taken here illustrates some more general principles of note. First, middle or high human development index countries experiencing the cancer transition[40] may pre-empt projected increases in cancers of certain organs by implementing prevention or early detection before those increases become manifest. Second, the type of implementation research reported here is well-suited to low and middle-income countries given the direct relevance to cancer control and the relatively low additional cost of integrating a research component into national public health programs. Third, the research project converges with capacity building, in this case through training of different categories of health professionals, so that the program once implemented, benefits from the developments required by the research itself.

In conclusion, our results indicate the acceptability, feasibility, organization, and implementation of CRC screening in the general population setting in Thailand and the

feasibility of integrating the program within the existing public health services. Although we are encouraged by the high participation rates from rural districts, the participation in urban areas need to be improved by appropriate invitation logistics. It is our belief that no associated direct financial costs to the eligible individuals due to universal health coverage and the appropriate organization, availability and access to services within the program have minimized the barriers to access for socio-economically disadvantaged populations. The implementation of the pilot program has been successful as measured by the process measures of coverage, performance of the screening test, colonoscopy, removal of colonoscopically detected polyps, provision of histopathology services and detection and treatment of CRC in early clinical stages to which have met the criteria of a successful public health program.

FIGURE LEGEND

Figure 1. A schematic diagram of the pilot colorectal cancer screening program in Lampang province, Thailand

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CONTRIBUTORSHIP STATEMENT

• Thiravud Khuhaprema: Conception and design, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published

• Suleeporn Sangrajrang: Conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published

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• Rengaswamy Sankaranarayanan: Conception, design, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be published.

DATA SHARING

No additional data other than the study database are available.

COMPETING INTERESTS

No author has any potential conflict of interest relevant to these studies and all authors had full rights, access to and management of the data used in this article. There is no additional data other than the study database which are available.

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Organized colorectal cancer screening in Lampang Province, Thailand: Preliminary results from a pilot implementation programme

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ABSTRACT

Objective: Colorectal cancer (CRC) is the third- and fifth-most common cancer in men and women, in Thailand. The increasing CRC incidence and mortality can be reduced by screening and treating adenomas and early cancers. A pilot CRC screening program using immunochemical **fecal** blood testing (iFOBT) and colonoscopy for test-positives was implemented through the routine Government Health Services in Lampang Province, to inform the acceptability, feasibility and scaling-up of screening in Thailand. This report describes the implementation, coverage and performance indicators of this project.

Design: A target population aged 50-65 years was informed about and invited **face to face** to undergo CRC screening by community health workers (HWs). The HWs provided fecal sample collection kits and participants brought their samples to one of the primary health units or community hospitals where nurses performed iFOBT. IFOBT-positive persons were referred for colonoscopy at the Lampang cancer hospital and endoscopic polypectomy/biopsies were performed according to colonoscopic findings. Those with confirmed CRC received appropriate treatment.

Results: Of the 127,301 target population 62.9% were screened using iFOBT **between April 2011 and November 2012.** Participation was higher among women (67.8%) than men (57.8%) and lower in 50-54 year-old persons than 60-65 year-olds. Of those screened, 873 (1.1%) were found positive; positivity was higher in men (1.2%) than in women (1.0%). To date 627 (72.0%) iFOBT-positive persons have had colonoscopy in which 3.7% had CRC and 30.6% adenomas.

Conclusion: The successful implementation of the pilot CRC screening with satisfactory process measures indicate the feasibility of scaling up organized CRC screening through existing health services in Thailand.

Article focus:

- The article addresses the feasibility of introducing colorectal cancer screening using immunochemical fecal occult blood test (iFOBT) through existing primary health care services and colonoscopy triage and treatment of screen positive subjects in secondary/tertiary care services in a province in Thailand.
- Addresses the performance characteristics of colonoscopy triage in terms of polyp and adenoma detection rates and positive predictive values.

Key messages:

- Despite the increasing incidence of colorectal cancer (CRC) in middle-income countries, organized colorectal cancer screening programs are yet to evolve in these countries.
- This pilot study shows that it is feasible to introduce organized CRC screening with iFOBT and colonoscopy triage with satisfactory input measures and intermediate outcomes, through existing government health services, in middle-income country like Thailand
- Experience from this pilot project may pave the way for nationwide scaling-up of organized CRC screening program in Thailand and other middle-income countries with increasing risk of CRC

Strengths and limitations:

- This pilot study **documents the feasibility, acceptance and safety of CRC screening in a lower-middle income country.**
- The **study has been carried out in real life conditions** using the existing routine health care services allowing a realistic and pragmatic assessment of the feasibility, sustenance **and intermediate** outcomes of colorectal screening in a **lower**-middle-income country.

- No information is provided on the extent of false negative tests and the impact of the intervention on colorectal cancer incidence and mortality due to lack of long-term follow-up of the study population at this instance. This information will be eventually generated by both active and passive follow-up the study population in future.

- **The study did not include population aged between 66 to 74 years.**

INTRODUCTION

Colorectal cancer (CRC) is a major cancer in Thailand with age-standardized incidence rates of 12.9/100,000 in men and 9.2/100,000 in women in 2005 and an incidence which is steadily increasing over time.[1] Sedentary lifestyle, lack of physical activity, smoking, drinking alcohol, a high consumption of red and processed meats as well as a low consumption of whole grains, fiber, fruits and vegetables are associated with an elevated risk of CRC. Most CRCs occur in pre-existing adenomatous polyps; a small percentage of the colonic polyps may become cancerous and spread elsewhere.[2] This progression takes at least 10 years in most people. Early detection and removal of polyps in the colon and rectum may prevent the development of invasive CRC.[3]

Early detection and prevention of CRC through screening is an effective intervention to reduce the considerable human and financial costs.[4] Tests considered for screening include variants of fecal occult blood tests (FOBT), flexible sigmoidoscopy and colonoscopy. Of these, FOBTs are the most feasible, non-invasive, affordable and acceptable for population screening as they detect intermittent microscopic blood losses from early CRC to advanced adenomas. Chemical FOBT (cFOBT) uses guaiac to detect peroxidase in human blood, but also reacts to the peroxidase present in dietary constituents such as red meat, cruciferous vegetables and some fruits, while the recently developed immunochemical FOBT (iFOBT) uses an antigen-antibody reaction to specifically detect globin which, together with heme, constitutes human hemoglobin. iFOBT is not subject to false-negative results in the presence of high-dose vitamin C supplements, which block the peroxidase reaction; since globin is degraded by digestive enzymes in the upper gastrointestinal tract, iFOBT is more specific for lower gastrointestinal bleeding, thus improving their specificity for colorectal neoplasia.

It has been shown in pooled analysis of four randomized controlled trials that annual or biennial screening with cFOBT reduced overall CRC mortality by 16%, for those allocated to CRC screening, and CRC mortality by 25% for those attending at least one round of screening with cFOBT.[4] The iFOBT provides a suitable and better alternative to cFOBT as a screening test due to its higher sensitivity, simplicity, ease of use and the fact that it does not require any dietary restriction.[5-8]

CRC screening programs are increasingly organized at regional and national levels in many countries. Programs in countries such as Australia, Canada, Finland, France and United

Kingdom use either direct mail invitations or invitations initiated by general practitioners to target populations aged 50-65 or 55-69 or 50-74 years. Programs in Canada and Finland use cFOBT, whereas iFOBT is used in Korea and Japan.[9-12] Although FOBT and colonoscopy are opportunistically provided in urban hospitals, there is no population-based organized CRC **screening** program in Thailand. The public health authorities in Thailand, faced with the increasing risk of CRC, due to the transition to westernized lifestyles with socio-economic development, would like to take measures to reduce its incidence and deaths by primary prevention and screening.

Thailand has a well-developed public health services with an extensive primary care network well integrated with district, provincial hospitals and tertiary care centers such as several comprehensive regional cancer centers and advanced university hospitals. Four decades ago when Thailand was a low-income country, it invested early in health care and transportation infrastructure that has reached most remote rural communities and helped it to achieve health care at low costs, given the fact that 4.1% its gross domestic product (GDP) for health, a figure far lower than the 10% average in high-income countries. Thailand has been successful in training doctors, nurses, auxillary and paramedical health workers and technicians in large numbers for its health system, with innovative distribution of human resources to rural areas. In addition, health volunteers recruited from local communities play important support, prevention and early detection roles, thereby enhancing community involvement. The entire Thai population is covered through a comprehensive health care package through universal health coverage (UHC) for financing an extensive range of preventive, diagnostic, treatment and follow-up care and hospitalisations due to any illness.[13]

In this context, a decision was made to implement a pilot CRC screening program with iFOBT followed by full colonoscopy for test positive persons **using existing facilities and personnel in government health services** in Lampang Province. **This pilot study was implemented to assess the feasibility, acceptability, safety of CRC screening both in urban and rural settings and to inform whether and how to introduce a nationwide, organized CRC screening program through the existing public health services in a phased manner.** Lampang Province was chosen to implement the pilot project, **due to its representativeness of the wider Thai population in terms of**

demographic, and socio-economic profiles, a relatively high incidence rate of CRC (18.7 per 100,000 in men and 14.4/100,000 in women),[14] **the availability of comprehensive cancer diagnosis, treatment and follow-up care facilities in general, and colonoscopy, histopathology and CRC treatment services in particular, at the Lampang provincial hospital (803 beds) and the Lampang Cancer Hospital (137 beds) and the existing population-based cancer registry that will help to evaluate the impact of the pilot intervention on CRC incidence and mortality in the province.** We report the organization, implementation, coverage and performance of the pilot CRC screening in this manuscript.

MATERIAL AND METHODS

Project proposal development

A detailed project proposal describing the background, project procedures, study questionnaires and forms to capture participant data and details of investigations, the project database, quality assurance methods and means of monitoring and evaluation were jointly developed between June 2010 and March 2011 by the National Cancer Institute (NCI), Bangkok, and the provincial health authorities with technical assistance from the Screening Group of the International Agency for Research on Cancer (IARC) of the World Health Organization, Lyon, France. Following the finalization of the project proposal, its approval by national authorities and completion of training for the providers, screening commenced in April 2011 and recruitment of eligible subjects was closed in November 2012.

Target population and involved healthcare facilities and personnel

All apparently healthy, ambulant men and women aged 50 to 65 years with no **past** history of CRC and resident in Lampang Province were the target population for screening in the pilot project, totaling 127,301 eligible subjects, **as identified from the National Statistics office and from the population registers with the health centers in the province.** The Government healthcare infrastructure consisting of 154 primary care units (PCUs), 12 community hospitals (CHs), Lampang provincial hospital and Lampang Cancer Hospital **and the doctors, nurses, HWs and technicians in these public facilities provided the various services such as information dissemination, invitation,**

testing, diagnosis, treatment and follow-up care to the screening project. These tasks were assigned as additional responsibility to these facilities and personnel and no added financial incentives were provided to them for these added tasks. No additional workers were hired for this project. The screening program was coordinated by the NCI and the provincial health authority and technically supported by the IARC.

Training for screening and colonoscopy providers

The registered nurses, community health workers (HWs) of the 154 PCUs and 12 CHs of Lampang Province were trained on information dissemination on CRC screening, awareness creation, motivation of the target population and invitation of eligible persons to participate in CRC screening during a one-day session by a faculty from the NCI and provincial health authority. They were trained to explain to the participants how to collect the fecal specimen in the sample collection tube and bring it to the PCU or the CH within 3 hours from collection for occult blood testing. The training also covered the performance and interpretation of the iFOBT test. Attractive pamphlets and posters in Thai language describing the prevention and early detection of CRC, the method of collecting the fecal samples, the iFOBT test procedure, colonoscopy and treatment of CRC were developed and printed by the Thai Health Services with technical support from the NCI and IARC**. The HWs routinely visit all households under the jurisdiction of each PCU once in 6 months to provide preventive care. The eligible subjects for CRC screening in this study were met, educated, invited and encouraged to participate in screening and the pamphlets and the fecal collection pots were distributed by HWs to eligible subjects during these routine house visits. Family history of CRC among first and second degree relatives was enquired into during the house visits.** The posters were prominently displayed in all health care facilities, educational institutions, public offices and public places.

Gastroenterologists and surgeons at the Lampang provincial hospital and the Lampang Cancer Hospital were reoriented and re-trained in key aspects of colonoscopy to improve their hands-on colonoscopy/polyp excision/biopsy skills in live sessions during 5 days. They were taught and evaluated by skilled gastroenterologists, with several years of experience in colonoscopy and endoscopic removal of polyps and mucosal resection of small lesions from the NCI and the Thai Association of Gastrointestinal Endoscopy in live sessions under direct observation before the initiation of the program.

Screening invitation and organization

The existing health care infrastructure and personnel in the PCUs and the CHs were used to disseminate information, to invite and provide iFOBT and to refer those testing positive for colonoscopy. The HWs from the PCUs and CHs distributed a fecal sample collection kit to the eligible persons in the households under their jurisdiction as per a regular schedule and explained how to collect the specimen and when to bring the collected specimen to the PCU/CH for testing. The colonoscopy, histopathology and treatment services at the Lampang provincial hospital and the Lampang Cancer Hospital were used to diagnose and treat patients in the program.

Screening with iFOBT and referral

All fecal samples were subjected to one-step iFOBT (Hemosure^{TM}, EL Monte, USA) according to the manufacturer's instructions. The test was carried out at the PHU/CH by the nurse in front of the participant. In less than 5 minutes a level of hemoglobin as low as 200 ng/ml can be detected by this test. One pink-rose band appearing in the "C: region and the other "T" region of the test device indicates a positive iFOBT. A negative iFOBT is characterized by only one color band in the "C" region. In this study, fecal material was assessed from one sample taken from each participant (1-day iFOBT). Verbal informed consent was obtained from all participants before analyzing the stool sample. The nurse at the PCU/CH fixed an appointment for colonoscopy at the Lampang cancer hospital for iFOBT positive persons and explained the pre-colonoscopy bowel preparation and the colonoscopy procedure in detail, provided a prescription for bowel cleansing and encouraged them to comply with the referral.

Colonoscopy

Colonoscopy was provided to iFOBT-positive individuals on scheduled days every week at the Lampang Regional Cancer Center. A second informed consent was obtained from people undergoing colonoscopy, biopsy, and treatment. The outcome of colonoscopy was reported as normal, polyps, suspected cancer or invasive cancer. Polyps and small lesions were removed and subjected to histopathology. Large lesions were biopsied for histological assessment. Those diagnosed with CRC received further investigations for clinical staging and treatment as per the standard protocol developed for Thailand. The findings of colonoscopy, **any severe adverse events within 30 days following colonoscopy**

(such as bleeding, perforation, administration of blood transfusion, hospitalisations for severe abdominal pain, paralytic ileus, cardiovascular events, hypotension, syncope, shock, dehydration, anaphylactic reactions, cardiorespiratory arrest etc), histology, stage, treatment and follow-up assessment were recorded in a diagnosis and treatment form and entered into the database.

Data management, monitoring and evaluation

Personal identification (name, age, address, citizen ID number), socio-demographic information, screening test result, results of colonoscopy and other investigations, treatment details and follow-up information were collected in specifically developed forms and entered in a multiuser program database with inbuilt validation checks called CRCreg developed by the IARC. The database was continuously updated as the pilot project progressed. It is possible to link the screening program and the cancer registry databases using the unique citizen ID numbers, which will enable the identification of false-negative cases and interval cancers.

The study database was analyzed to document the participant characteristics, participation rates for screening and test positivity rates by sex, age, the district of residence and the proportion of test-positive individuals complying with referral for colonoscopy, colonoscopy results, final diagnosis, stage of invasive cancer, treatment details and adverse events. Comparison of proportions was done using a two-sided test on the equality of proportions using large-sample statistics, which also gives exact P values. Assessment of the effect of patient characteristics on the attendance for colonoscopy was carried out using logistic regression analysis.

Ethical approval and funding

Ethical approval was obtained from Institutional Review Board and Ethics Committee of NCI and the IARC. The project was funded by the Ministry of Health, Thailand, through the NCI, Bangkok.

RESULTS

The flow chart of the program organization and procedures is shown in Figure 1. All 154 PCUs and 12 CHs (100%) in the province participated in the project. Of the 127,301 eligible subjects (63,274 men and 64,027 women), 80,012 (62.9%) (36,601 men and 43,411

women) were enrolled. The distribution of sex, education, occupation and family history of CRC among the participants are given in Table 1. The mean age was 56.6 (SD=4.3) among women and 56.8 (SD=4.3) among men. More than 80% of the subjects had only primary school education; three-fourths were involved in agriculture; 0.7% had family history of CRC.

Table 1. Characteristic of participants in the Lampang pilot colorectal cancer screening project

Characteristics	Number	Percentage
Screened	80,012	
Sex		
Men	36,601	45.7
Women	43,411	54.3
Age (in years)		
50-54	28,956	36.2
55-59	27,825	34.8
60-65	23,231	29.0
Education		
None	6,192	7.7
Primary	66,583	83.2
Secondary	5,208	6.5
College/University	2,028	2.5
Occupation		
Agriculture	57,266	75.8
Manual labour	11,381	15.1
Support/Service	4,718	6.2
Crafts/machinery	371	0.5
Family income in Thai Bahts per month (1 USD=30 Bahts)		
<5000	44,940	58.4
5000-10000	26,463	34.4
>10000	5,533	7.2
Colorectal cancer in first and second degree relatives		
Yes	552	0.7
No	72,971	91.2
Unknown	6,489	8.1
Setting		
Rural	58,873	73.6
Urban	21,139	26.4
District		

Mueang (U)	13,016	16.3
Mae Moh (U)	2,772	3.5
Koh Kha (U)	5,351	6.7
Soem Ngam (R)	3,747	4.7
Wang Nua (R)	5,962	7.5
Chae Hom (R)	6,474	8.1
Ngao (R)	7,489	9.4
Thoen (R)	8,486	10.6
Mae Phrik (R)	2,523	3.2
Mae Tha (R)	9,025	11.3
Sop Prap (R)	3,977	5.0
Hang Chat (R)	6,447	8.1
Mueang Pan (R)	4,743	5.9

U: Urban; R: Rural

The overall participation rate for screening (62.9%) was much higher in women (67.8%, 95%CI: 67.4-68.2%) than in men (57.8%, 95%CI: 57.5-58.2%) (Table 2) **(p-value<0.001).** Participation in screening varied between the 13 districts in the province: generally being higher in rural **(73.2%,** 95%CI: 72.9-73.5%**)** than in urban districts **(45.1%,** 95%CI: 44.6-45.5%**)** (Table 2) **(p-value<0.001), categorized as defined by the National Statistics Office based on demography, economy, educational, occupational and migration criteria.** The highest iFOBT uptake was in the rural district of Theon (86.0% in women and 73.4% in men) while the lowest participation was in the urban district of Mueang (47.7% in women and 35.1% in men). Screening participation rates increased from 52.9% in those aged 50-54 years to 78.9% among those aged 60-65 years (Table 3).

Table 2. Total eligible subjects, screened eligible subjects and test positive frequencies by sex, age and districts in Lampang province, Thailand, 2011-2012

	Men					Women					Overall				
	Eligible persons	Number Screened with iFOBT	(%)	Number Screen positive	(%)	Eligible Persons	Number screened with iFOBT	(%)	Number screen positive	(%)	Eligible persons	Number Screened with iFOBT	(%)	Number screen positive	(%)
Overall	63,274	36,601	(57.8)	447	(1.2)	64,027	43,411	(67.8)	426	(1.0)	127,301	80,012	(62.9)	873	(1.1)
Sex															
Men	63,274	36,601	(57.8)	447	(1.2)						63,274	36,601	(57.8)	447	(1.2)
Women						64,027	43,411	(67.8)	426	(1.0)	64,027	43,411	(67.8)	426	(1.0)
p-value													<0.001		0.001
Age (in years)															
50-54	27,148	12,927	(47.6)	106	(0.8)	27,597	16,029	(58.1)	131	(0.8)	54,745	28,956	(52.9)	237	(0.8)
55-59	21,328	12,711	(59.6)	146	(1.1)	21,777	15,114	(69.4)	130	(0.9)	43,105	27,825	(64.6)	276	(1.0)
60-65	14,798	10,963	(74.1)	195	(1.8)	14,653	12,268	(83.7)	165	(1.3)	29,451	23,231	(78.9)	360	(1.5)
Setting															
Rural	40,289	27,692	(68.7)	317	(1.1)	40,108	31,181	(77.7)	295	(0.9)	80,397	58,873	(73.2)	612	(1.0)
Urban	22,985	8,909	(38.8)	130	(1.5)	23,919	12,230	(51.1)	131	(1.1)	46,904	21,139	(45.1)	261	(1.2)
p-value													<0.001		0.019
District															
Mueang (U)	15,188	5,327	(35.1)	60	(1.1)	16,127	7,689	(47.7)	64	(0.8)	31,315	13,016	(41.6)	124	(1.0)
Mae Moh (U)	2,999	1,300	(43.3)	30	(2.3)	2,690	1,472	(54.7)	24	(1.6)	5,689	2,772	(48.7)	54	(1.9)
Koh Kha (U)	4,798	2,282	(47.6)	40	(1.8)	5,102	3,069	(60.2)	43	(1.4)	9,900	5,351	(54.1)	83	(1.6)
Soem Ngam (R)	2,838	1,757	(61.9)	16	(0.9)	2,581	1,990	(77.1)	9	(0.5)	5,419	3,747	(69.1)	25	(0.7)
Wang Nua (R)	4,712	2,988	(63.4)	46	(1.5)	4,429	2,974	(67.1)	51	(1.7)	9,141	5,962	(65.2)	97	(1.6)
Chae Hom (R)	4,324	3,123	(72.2)	42	(1.3)	4,385	3,351	(76.4)	38	(1.1)	8,709	6,474	(74.3)	80	(1.2)
Ngao (R)	5,603	3,642	(65.0)	18	(0.5)	5,289	3,847	(72.7)	22	(0.6)	10,892	7,489	(68.8)	40	(0.5)
Thoen (R)	5,196	3,814	(73.4)	17	(0.4)	5,431	4,672	(86.0)	25	(0.5)	10,627	8,486	(79.9)	42	(0.5)
Mae Phrik (R)	1,490	1,087	(73.0)	11	(1.0)	1,683	1,436	(85.3)	10	(0.7)	3,173	2,523	(79.5)	21	(0.8)
Mae Tha (R)	5,970	4,161	(69.7)	61	(1.5)	6,030	4,864	(80.7)	45	(0.9)	12,000	9,025	(75.2)	106	(1.2)

Sop Prap (R)	2,946	1,876	(63.7)	29	(1.5)	2,993	2,101	(70.2)	16	(0.8)	5,939	3,977	(67.0)	45	(1.1)
Hang Chat (R)	4,009	2,991	(74.6)	41	(1.4)	4,206	3,456	(82.2)	42	(1.2)	8,215	6,447	(78.5)	83	(1.3)
Mueang Pan (R)	3,201	2,253	(70.4)	36	(1.6)	3,081	2,490	(80.8)	37	(1.5)	6,282	4,743	(75.5)	73	(1.5)

U: Urban; R: Rural

Table 3. Colonoscopy attendance, results and final diagnosis by sex

	Men		Women		Total	
Number screened with iFOBT	36,601		43,411		80,012	
Number screen positive (%)	447	(1.2)	426	(1.0)	873	(1.1)
Number attended colonoscopy referral (%)	319	(71.4)	308	(72.3)	627	(71.8)
Colonoscopy result (per 1000 screened)						
Normal	165		215		380	
Polyp	133	(3.6)	73	(1.7)	206	(2.6)
Suspected cancer	16	(0.4)	11	(0.3)	27	(0.3)
Inadequate/Unknown	5		9		14	
Final diagnosis (per 1000 screened)						
Normal	158		206		364	
Inflammatory bowel disease	5	(0.1)	2	(0.0)	7	(0.1)
Adenomatous polyp	12	(0.3)	9	(0.2)	21	(0.3)
Adenomatous polyp with dysplasia	108	(3.0)	51	(1.2)	159	(2.0)
Hyperplastic polyp	4	(0.1)	1	(0.0)	5	(0.1)
Colitis	4	(0.1)	6	(0.1)	10	(0.1)
Adenocarcinoma in-situ	3	(0.1)	4	(0.1)	7	(0.1)
Colorectal cancer	13	(0.4)	10	(0.2)	23	(0.3)
Other	11	(0.3)	18	(0.4)	29	(0.4)
Unknown	1	(0.0)	1	(0.0)	2	(0.0)

Using a cut-off fecal hemoglobin concentration of 200 ng/ml, 873 of 80,012 (1.1%) participants were reported as positive on iFOBT. The iFOBT positivity rate was slightly higher in men (1.2%) than in women (1.0%) (p-value=0.001) (Table 2). Test positivity rate increased from 0.8% in those aged 50-54 years to 1.5% in those aged 60-65 years (Table 2).

As of 21 February 2013, 627 (71.8%) iFOBT positive persons had colonoscopy; no serious adverse event was reported following colonoscopy. On colonoscopy, 206 were found to have polyps and cancer was suspected in 27 (Table 3). Polyps were excised and biopsies were directed in growths. On histological examination of excised polyps, adenoma was confirmed in 187 persons (Table 3). CRC was histologically confirmed in 23 persons (3.7%). The detection rate of histologically confirmed CRC was 2.9 per 10,000 screened persons and that of adenomatous polyp was 23.4 per 10,000 screened persons. CRC and adenomas were

detected in 3.6% and 29.8% respectively of iFOBT-positive individuals who had colonoscopy.

Among the 187 persons with histologically confirmed adenomatous polyps, 75 (40.1%) had advanced adenoma. Advanced adenoma denotes adenomatous polyps having one or more of the following features: > 10 mm in diameter, high-grade dysplasia, and significant villous histology (>25%). The stage-distribution of the detected invasive cancers was as follows: 2 stage I, 12 stage II, 7 stage III and 2 missing stage information. Compliance for colonoscopy referral was lower among individuals living in urban compared to rural areas and in those with relatively high compared to those with low monthly family incomes (Table 4).

Table 4. Colonoscopy attendance among screen positives by patient characteristics

Characteristic	Number screen positive	Number attended colonoscopy clinic (%)		Adjusted* OR (95% CI)				p-value
Participants	873	627	(71.8)					
Sex								
Men	447	319	(71.4)	1.0				
Women	426	308	(72.3)	1.1	(0.8	-	1.5)	0.534
Age (in years)								
50-54	237	177	(74.7)	1.0				
55-59	276	196	(71.0)	0.8	(0.5	-	1.3)	0.355
60-65	360	254	(70.6)	0.8	(0.5	-	1.1)	0.186
Education								
None	97	73	(75.3)	1.0				
Primary	704	504	(71.6)	0.7	(0.4	-	1.3)	0.301
Secondary	48	34	(70.8)	0.9	(0.4	-	2.4)	0.881
College/University	24	16	(66.7)	0.6	(0.1	-	2.8)	0.556
Occupation								
Agriculture	632	474	(75.0)	1.0				
Managerial/Professional	22	15	(68.2)	0.8	(0.2	-	3.5)	0.787
Support/Service	54	34	(63.0)	0.7	(0.4	-	1.2)	0.174
Crafts/machinery	4	3	(75.0)	1.0	(0.1	-	10.9)	0.989
Manual labour	95	60	(63.2)	0.7	(0.4	-	1.1)	0.097
Family income								
<5000	531	399	(75.1)	1.0				
5000-10000	254	166	(65.4)	0.6	(0.4	-	0.9)	0.007

>10000	59	42	(71.2)	0.9	(0.4	-	2.1)	0.887
Family history of colorectal cancer								
Yes	19	15	(78.9)	1.0				
No	774	551	(71.2)	0.9	(0.3	-	2.9)	0.827
Unknown	80	61	(76.3)	1.1	(0.3	-	4.4)	0.846
setting								
Rural	612	460	(75.2)	1.0				
Urban	261	167	(64.0)	0.7	(0.5	-	1.0)	0.043
District								
Mueang (U)	124	72	(58.1)	1.0				
Mae Moh (U)	54	39	(72.2)	2.1	(0.9	-	4.6)	0.070
Koh Kha (U)	83	56	(67.5)	1.5	(0.8	-	2.9)	0.225
Soem Ngam (R)	25	21	(84.0)	1.8	(0.4	-	7.7)	0.417
Wang Nua (R)	97	68	(70.1)	1.4	(0.7	-	2.7)	0.296
Chae Hom (R)	80	63	(78.8)	2.0	(1.0	-	4.1)	0.062
Ngao (R)	40	29	(72.5)	1.6	(0.7	-	3.8)	0.267
Thoen (R)	42	30	(71.4)	2.0	(0.8	-	4.6)	0.119
Mae Phrik (R)	21	18	(85.7)	3.2	(0.9	-	12.1)	0.084
Mae Tha (R)	106	84	(79.2)	2.5	(1.3	-	4.8)	0.007
Sop Prap (R)	45	31	(68.9)	1.4	(0.6	-	3.2)	0.462
Hang Chat (R)	83	63	(75.9)	3.2	(1.5	-	6.8)	0.003
Mueang Pan (R)	73	53	(72.6)	1.6	(0.8	-	3.2)	0.185

* Estimates for a characteristic factor adjusted for other characteristics; OR: odds ratio; CI: confidence interval; U: Urban; R: Rural

DISCUSSION

Among the CRC screening approaches in people at average risk (persons aged 50 to 74 years), annual or biennial FOBT followed by colonoscopy triage of screen positive individuals is the most widely used strategy due to its low cost, feasibility, safety and non-invasiveness. Significant reduction in CRC incidence and mortality following cFOBT screening has been shown in four randomized controlled trials.[4] This evidence, the fact that iFOBT is a better alternative to cFOBT and the declines in CRC mortality following widespread CRC screening in Japan, South Korea, Hong Kong and Singapore, despite increasing CRC incidence rates,[15] and in other high income countries[16 17] supported our decision to implement a pilot project based on 1-day iFOBT screening integrated in the routine public health services in Lampang province in Thailand.

Since CRC screening is a major undertaking and integrating a cancer screening program into routine government health services in low-middle income countries has its own complexities

and challenges, it was decided to pilot its introduction in one of the provinces of Thailand which already has a population based cancer registry. In high-income countries, large scale population-based organized CRC screening has been preceded by well-planned pilot introductions to evaluate the feasibility, practicality and acceptability of introducing a population screening program with biennial FOBT in government health services (Table 5).[18-21] The UK CRC screening pilot study was launched in 2000 in England and Scotland, which reported a FOBT uptake rate of 57% and CRC detection rate of 1.62 per 1,000 screened (Table 5).[18 19] **In the Australian pilot CRC screening project ,56,907 women aged 55 to 74 years were invited for iFOBT screening during November 2002 to June 2004. Of them 25,840 (45.4%) participated, 25,688 correctly completed iFOBT screening and 2,317 (9.0%) were positive on iFOBT. The pilot project detected 176 persons with advanced adenoma and 67 with suspected cancer yielding a positive predictive value of 19.2% (Table 5); the estimated cost per additional life year saved in the Australian pilot project was 24,000 Australian $.[21] In the Finnish pilot project the participation rate was 71% among 52,994 invited persons and 2.1% of the participants were positive on FOBT and 51.8% of those who underwent colonoscopy were detected with adenomas or suspected cancer.**[20] The national expansion of CRC screening in UK, Australia and Finland following the pilot studies was phased over 6 years.

Table 5. Comparison of pilot colorectal cancer screening projects in Thailand, Australia and UK

Criteria	Thailand		Australia[21]		UK[18]	
Period	2011-2012		2002-2004		2000-2003	
Screening test used	iFOBT		iFOBT		gFOBT	
Targeted age group (years)	50-65		55-74		50-69	
Target population, n	127,301		56,907		478,250	
Individuals screened, n (%*)	80,012	(62.9)	25,840	(45.4)	271,646	(56.8)
Individuals screen positive, n (%**)	873	(1.1)	2,308	(8.9)	5,050	(1.9)
Colonoscopy done, n (%†)	627	(71.8)	1,265	(54.8)	4,116	(81.5)
Adenoma detected, n (%‡)	187	(29.8)	251	(19.8)	1,388	(33.7)
Advanced adenoma, n (%‡)	75	(12.0)	176	(13.9)	-	
Colorectal cancer detected, n (%‡)	23	(3.7)	67	(5.3)	552	(13.4)
Stage I and II colorectal cancer, n (%§)	14	(60.9)	-		345	(62.5)
Colorectal cancer detection rate per 100,000 screened		28.7		259.3		203.2

iFOBT: immunochemical fecal blood testing; gFOBT: guaiac fecal blood testing;
* Based on target population; ** Based on individuals screened; † Based on individuals screen positive; ‡ Based on colonoscopy done; § Based on colorectal cancer detected

The results on participation and detection rates of colorectal neoplasia in our pilot project in Lampang are consistent with findings from pilot (Table 5) and national programs elsewhere. For example, the participation rate of eligible subjects in our Thai study was similar to rates reported from pilot demonstration projects in the United Kingdom (57%), Haut-Rhin, France (55%) and in Finland (71%) and in service programs in UK (54%)[18 20 22 23] and higher than those **reported from the Australian pilot project (45.4%)** (a systematic review of participation in CRC screening programs (42%) and from the national CRC screening programs in Australia (35%),[24] South Korea (<25%) and Croatia (10%).[11 21 25 26] **Our results** confirm that the use of primary HWs outreach to promote and provide CRC screening through existing Government health services is feasible in Thailand.

A higher uptake of iFOBT was observed among women and in older age groups in our program. A similar observation has been reported CRC screening programs in other countries.[11 18 20 23-25 27] We observed a higher uptake of iFOBT screening in rural populations than in urban populations of Lampang province. Information on CRC screening and invitations for iFOBT screening in rural districts were mostly delivered to the target population by direct person to person contact and face to face communication, while in urban areas the information on the program was predominantly delivered through poster advertisements due to the challenges in face to face contacts. The proportion of households visited were much higher in rural than in urban areas, where the sample collection kits were mostly collected by the eligible individuals during **their routine and opportunistic visits to the health centers or community hospitals for routine health checkups for early detection of diabetes, hypertension and helminthiasis and for medical problems. Unfortunately we could not exactly quantify the proportion of participation from home visits or by visits to the PCUs/CHs as this was not documented in the database.** The higher screening uptake in rural populations than in urban areas **suggests** that **more** direct person to person contacts and personalized invitations and personalized delivery of collection kits improved the participation. A personalized approach to participant recruitment has also been reportedly associated with a higher uptake of CRC screening in other settings.[26] A higher participation in rural populations than in urban and metropolitan populations has been reported from other countries as

well.[26 28] Higher participation for colonoscopy among the low-income and rural population reflects the faith and dependence of the socioeconomically weaker sections on public health services than those with higher incomes and living in urban areas.

The overall iFOBT positivity rate in our pilot project was in the lower range of test positivity rates reported from high-risk, high-income countries. FOBT test positive rates ranged from 2.1% to 9.0% in high-risk high-income countries.[11 19-21 24 25 29-31] Our results show that positivity rate in men (1.2%) was slightly higher than in women (1.0%), which is consistent with a higher CRC incidence in men (14.7 per 100,000 men) as compared to that of women (10.1/100,000 women) in Lampang province. A higher test positivity rate in men than in women has also been reported in other settings.[18-21 24 29 30]

FOBT screening for CRC is effective only when a high proportion of those with a positive result attend further full colonoscopy diagnostic evaluation of the colon. Two-thirds of test positive persons complied with referral for colonoscopy in our program, which is within the range of adherence to colonoscopy referrals in high-income countries. In many national programs, compliance of test-positive subjects to colonoscopy ranged between 38% and 88%.[11 23-25 32 33] There was no serious adverse event following colonoscopy in our program. The risks of serious adverse events such as perforation, hemorrhage, peritonitis and acute diverticulitis following colonoscopy performed as part of CRC screening are low, but increase with age and following polypectomy; the rate of adverse events reportedly varied between 3 to 6 per 1,000 colonoscopies performed.[34] The value of short and intensive re-training and re-orientation courses for colonoscopists of varying experience in achieving high standards has been well-established.[35] Teaching practical hands-on skills in short intensive re-orientation sessions to our program gastroenterologists and assessment of their performance and competency in key aspects of colonoscopy by direct observation in live case sessions by experienced colonoscopists was valuable in ensuring the high-quality colonoscopy services in this program. **Based on our experience in this pilot project, we have developed a beginner's manual for colonoscopy for use in low- and middle-income countries.**

Test-positive rate, CRC and adenomatous polyp detection rates per 1,000 screened persons in our program were lower than those reported from high-risk countries; however the detection frequencies of both CRC and polyps as a proportion of iFOBT positive persons (2.6% for CRC and 21.4% for adenoma) and of those receiving colonoscopy (3.7% for CRC

and 29.8% for adenoma)are within the range reported (1.9% - 7.0% for CRC and 20.0% - 43% for adenoma) from high incidence countries, indicating the high quality of interventions in our pilot program.[18-21 31 32] The low test positive and detection rates as a proportion of screened subjects is not surprising given the comparatively low-incidence rates of CRC in Thailand as compared to high-incidence countries.[1 14 36]

Most CRCs develop from adenomas, among which "advanced" adenomas are considered to be the clinically relevant precursors. Among the adenomatous polyps, advanced adenoma is considered to be the most valid neoplastic surrogate marker for present and future colorectal cancer risk and detecting advanced adenomas is a major focus in CRC screening. A high detection rate of advanced adenoma as compared to the more common, but less clinically significant small adenomas, is an important target of CRC screening and an indicator of high screening efficacy.[37] It has been shown that the cumulative risk of malignancy in advanced polyps range between 25% and 45% in persons aged 55 years and above. [38] Thus, advanced adenomas may be considered as surrogate for CRC. In our pilot project two-fifths of detected adenomas were advanced adenoma. Two-thirds of CRC detected in our pilot project was in early stages. Both the high detection rate of advanced adenoma and early detection CRC could have a higher impact on future CRC incidence and mortality in this pilot cohort.

Whereas FOBT screening is repeated annually or biennially in high-risk countries, we have decided to repeat CRC screening once in 5-years in our pilot project and in Thailand when CRC screening is scaled up nationally, in view of the comparatively low CRC incidence. From a practical and sustainable perspective, particularly from the aspect of providing high quality colonoscopy services, performing iFOBT screening once in 5-years is an attractive option given the level of development of health care infrastructure. **The national scale up of screening following the pilot project in Australia since 2006 occurs in a phased manner.[39] It introduced national bowel cancer screening program (NBCSP) in 2006 as one off test for those turning 55 and 65 years and testing for 50 year-olds was added in 2008 and for 60 year-olds in 2013; 70 year-olds will be added in 2015. It would then progressively shift to 2-yearly screening of all Australians aged 50-74 years from 2017-18. Thus a full scale national scale up in Australia will take 13 years from introduction.[39] In Thailand, as we phase out the scale up over several years,** the performance of screening, particularly false-negative rates and interval cancers, needs to be carefully assessed and the need for appropriate mid-course

corrections for this policy should be promptly addressed as the program evolves. **Based on the preliminary findings from our pilot study, we are conducting a formal cost-effectiveness analysis in collaboration with the Health Intervention and Technology Assessment Program of the Thailand Government to determine the costs of all services provided along the screening pathway to estimate screening cost-effectiveness and funding required for the national program.**

A current limitation of our study is that it describes the process measures and intermediate outcomes such as adenoma detection rates and stage distribution of screen detected colorectal cancers but no information is available on the extent of false negative tests and the impact of the intervention on colorectal cancer incidence and mortality due to lack of long-term follow-up of the study population at this instance. This information will be eventually generated by both active and passive follow-up the study population in future. **Another limitation is that people aged 66 to 75 years were not included; however this is unlikely to have a major implication in any future scaling up of screening for this age group.** On the other hand, a major strength is that the study reflects the real life conditions and has been conducted using the existing routine health care services which allows a realistic assessment of the feasibility of colorectal screening in a middle-income country. **The fact that Thailand has developed an equitably accessible health care system with universal health coverage and has experienced an inclusive socioeconomic progress covering all regions of the country suggests that the pilot experience in Lampang can be translated to the national population in due course. However additional specific measures need to evolve by qualitative studies to ensure adequate participation in urban areas.**

In addition to the specific application of these findings to the further development of a CRC screening program in Thailand, the approach taken here illustrates some more general principles of note. First, middle or high human development index countries experiencing the cancer transition[40] may pre-empt projected increases in cancers of certain organs by implementing prevention or early detection before those increases become manifest. Second, the type of implementation research reported here is well-suited to low and middle-income countries given the direct relevance to cancer control and the relatively low additional cost of integrating a research component into national public health programs. Third, the research project converges with capacity building, in this case through training of

different categories of health professionals, so that the program once implemented, benefits from the developments required by the research itself.

In conclusion, our results indicate the acceptability, feasibility, organization, and implementation of CRC screening in the general population setting in Thailand and the feasibility of integrating the program within the existing public health services. Although we are encouraged by the high participation rates from rural districts, the participation in urban areas need to be improved by appropriate invitation logistics. It is our belief that no associated direct financial costs to the eligible individuals due to universal health coverage and the appropriate organization, availability and access to services within the program have minimized the barriers to access for socio-economically disadvantaged populations. The implementation of the pilot program has been successful as measured by the process measures of coverage, performance of the screening test, colonoscopy, removal of colonoscopically detected polyps, provision of histopathology services and detection and treatment of CRC in early clinical stages to which have met the criteria of a successful public health program.

FIGURE LEGEND

Figure 1. A schematic diagram of the pilot colorectal cancer screening program in Lampang province, Thailand

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COMPETING INTERESTS

No author has any potential conflict of interest relevant to these studies and all authors had full rights, access to and management of the data used in this article. There is no additional data other than the study database which are available.

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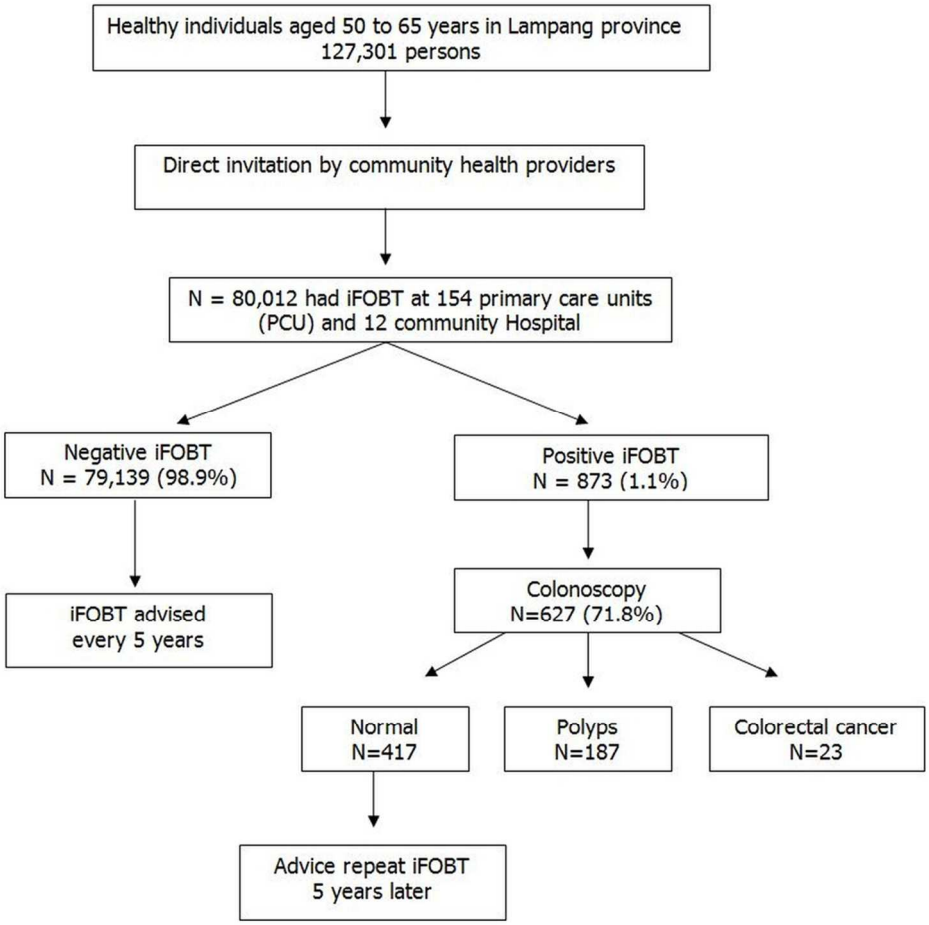

A schematic diagram of the pilot colorectal cancer screening program in Lampang province, Thailand
96x90mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**1**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4**
Methods			
Study design	4	Present key elements of study design early in the paper	**6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**6-8**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	**6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**7-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***7-8***
Bias	9	Describe any efforts to address potential sources of bias	**6-7**
Study size	10	Explain how the study size was arrived at	**6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**8**
		(*b*) Describe any methods used to examine subgroups and interactions	**n/a**
		(*c*) Explain how missing data were addressed	**n/a**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	**n/a**
		(*e*) Describe any sensitivity analyses	**n/a**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**9-10**
		(b) Give reasons for non-participation at each stage	**n/a**
		(c) Consider use of a flow diagram	**9**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**10**
		(b) Indicate number of participants with missing data for each variable of interest	**9-10**
Outcome data	15*	Report numbers of outcome events or summary measures	**9-15**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**9-15**

		(*b*) Report category boundaries when continuous variables were categorized	**n/a**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**n/a**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**n/a**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**16-17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**18**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**17-18**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**8-9**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.