RESEARCH ARTICLE

Preliminary Results: Colorectal Cancer Screening Using Fecal Immunochemical Test (FIT) in a Thai Population Aged 45-74 Years: A Population-Based Randomized Controlled Trial

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Abstract

Objective: The aim of this paper is to provide some details and the results to date of a colorectal cancer screening trial using a fecal immunochemical test (FIT). **Methods:** A population-based randomized controlled trial began in May, 2016. All people aged 45 to 74 years living in Nam Phong District, Khon Kaen Province, Thailand, and willing to participate are being recruited using an outreach method. Enrolled participants are randomly allocated by a computer-generated randomization program either to a study arm (receive sample kit for FIT) or to a control arm (no provision of kit). Positive FIT cases are subsequently confirmed by a colonoscopy examination, and negative FIT cases are re-tested with FIT every two years. The preliminary results to date were analysed using descriptive statistics. **Results:** A total of 1,060 enrolled participants provided a complete set of data. Of those randomly assigned to the study arm and tested by FIT, 92 (8.7%) were found to be positive, 39 (11.5%) males and 53 (7.4%) females. The f-Hb concentrations at the 75th, 90th and 95th percentiles for all age groups were higher in males than in females, and the distributions of f-Hb concentration varied with age, especially at the 95th percentile where f-Hb concentrations increased with age. **Conclusion:** The preliminary results of our screening trial have indicated that the prevalence of positive FIT cases is higher than in a similar recent and, at the time unique, previous study in Thailand. This finding is especially the case for males and those in the older age groups.

Keywords: Colorectal cancer screening- randomized controlled trial- fecal immunochemical test (FIT)- Thailand

Introduction

In Thailand, colorectal cancer (CRC) is one of the five most common cancers in both sexes. According to the latest estimated annual incidence rates of CRC in the Thai population (2010-2012), CRC was the third most common cancer in men (age-standardized incidence rate (ASR)=14.4 per 100,000 population) and the fourth most common cancer in women (ASR=11.2 per 100,000 population). Data from the population-based cancer registry of Khon Kaen, a province located in the northeastern region of Thailand, have shown that the incidence of CRC had the same ranking in men (ASR=13.1 per 100,000 population) and women (ASR=9.0 per 100,000 population) as is the case in the country as a whole (Pongnikorn et al., 2012). A recent trend analysis using joinpoint regression showed that the incidence of CRC in Khon Kaen has been gradually increasing over the period 1989 to 2012, especially in women of all age groups (Sarakarn et al., 2017). This may probably be due to detrimental changes in lifestyle and individual behavior such as sedentary habits and insufficient physical activity, smoking and the use of alcohol, and unhealthy diets which include high amounts of red or processed meat and low

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amounts of fiber, fruit and vegetables (Khuhaprema et al., 2014).

According to the natural history of CRC (Bresalier, 2009) and previous RCT studies, CRC screening has the potential to reduce the morbidity and mortality rates of CRC by the removal of polyps and by providing an opportunity to treat CRC in its early stages (Hardcastle et al., 1996; Jørgensen et al., 2002; Faivre et al., 2004). This is especially the case when both a fecal immunochemical test (FIT) and colonoscopy are used together for the purpose of CRC screening (Chen et al., 2007; Chen et al., 2016; Aniwan et al., 2017). Several studies have shown that CRC screening can be cost-effective when FIT is the primary method of screening and colonoscopy is used for confirmation regarding FIT positive cases (Wilschut et al., 2011; Wong et al., 2015; Siripongpreeda et al., 2016). Studies have indicated that the sensitivity and specificity of FIT are higher than guaiac-FOBT (gFOBT) for detecting left-sided CRC (Allison et al., 2007), and FIT has the additional benefits of being inexpensive, non-invasive, very convenient, and associated with lower false-positive test results when compared with gFOBT which, unlike FIT, has the disadvantage of requiring restrictions on diet and medication prior to its use (Inra and Lim, 2016). Even though, as mentioned above, CRC screening is more likely to benefit the entire population, some studies have argued that screening might have no effect on CRC incidence and mortality rates (Welch and Robertson, 2016). A decline in the incidence and mortality of CRC can arise for several reasons, including improved treatment effectiveness and a reduction in risk factors, but about 50% of the decline in incidence and mortality of CRC in the USA over the period 1975-2011 is estimated to have occurred as the result of screening (Zauber, 2015). While a pilot CRC screening project has been conducted in Lampang Province, Thailand (Khuhaprema et al., 2014), in Southeast Asia, and especially in Thailand, there have been no RCT studies to support the implementation of CRC screening in the context and culture of the countries in this region.

Accordingly, using the most rigorous type of research design, a randomized controlled trial, it was decided to conduct a population-based CRC screening project to assess the effectiveness of FIT as a primary screening tool in Nam Phong District of Khon Kaen Province, Thailand. The purpose of this paper is to provide some details of the trial and the results to date.

Materials and Methods

Study design

The population-based randomized controlled trial began in May, 2016, and will be completed six years after completion of recruitment. Subjects eligible for attending the screening program are allocated to the active screening program (ASP) and passive screening program (PSP) through the mechanism of clustered randomization. The determination of areas of enrollment and interventions for the group of ASP and PSP are provided in the following section. A split screening design for the proposed randomized controlled trial using FIT for the early detection and intervention of CRC is employed.

Setting and location

The setting and location of this study is the Nam Phong District of Khon Kaen Province in Thailand. Nam Phong is one of the northern districts of Khon Kaen which is a province in the northeast region of Thailand. The total population of the district is 113,862 (57,081 males and 56,781 females), and the population density is 138 persons/km2. The district consists of 12 sub-districts, 168 villages, five municipalities and nine sub-district administrative organizations.

Nam Phong Hospital is the main health service facility in the area. The hospital has excellent potential for the introduction of new healthcare initiatives, and it already has a good reputation for health promotion activities. In addition, its laboratory can support a system of screening by FIT. This facility is therefore the center of coordination and screening at an area level. There are 18 sub-district health promotion hospitals, and these are important sub-units for the study and have the roles of making contact with the participants, data collection and follow up during the whole period of the study.

Regarding the economic aspects of Nam Phong District, the majority of the people are rice farmers, and sugar cane and cassava crop growers. There are several important industries in the area so some people also work in factories, but most of them are not included in the target group because they are under 45 years of age. Overall, Nam Phong has a moderately vibrant economy in Thailand. It also near Khon Kaen City so that the people of the district have tended to adopt both urban and rural life-styles. The proximity to Khon Kaen City also means that it is close to the Faculties of Public Health and Medicine at Khon Kaen University and Khon Kaen Regional Hospital, which is the referral hospital for the proposed randomized control trial and the place where the colonoscopies will be performed and confirmed cases referred. For all of the above reasons, Nam Phong District appears to a very suitable location for the proposed study.

Participants

The study participants are being recruited from the electronic database of the data center for Nam Phong District which is located in the Nam Phong District Hospital. Subjects aged between 45 to 74 years, living in Nam Phong District, Khon Kaen Province are the targets for invitation to join the population-based randomized control trial. Subjects who have been examined and diagnosed with cancer during the last two years, or have been examined and diagnosed with inflammatory bowel disease, acute gastritis or a related condition during the last two years are excluded from the trial.

Random allocation

Participants, who meet the eligibility criteria, are randomly allocated by using Stata version 10 to the ASP (study arm) or the PSP (control arm).

Interventions

The interventions for the ASP and PSP are as follows.

Active Screening Program (ASP, Study arm)

Participants, who are randomly allocated to the study arm, are screened by FIT. This test relies on the use of antibodies which are specific to human hemoglobin, making pretest dietary restrictions unnecessary, and it is also more specific for bleeding in the lower parts of the gastrointestinal tract; these factors reduce the false positive rate (Khuhaprema et al., 2014). Studies have confirmed that the test has high sensitivity and specificity (Levi et al., 2006; Lohsiriwat et al., 2007). Lateral flow immunoassays are used to detect the target analyte (Jitthai, 2013), and the test kits are being supplied by the Eiken Chemical Company, Japan. The chosen cut-off is 100 ng/ml, and FIT levels equal to or higher than this are regarded as positive (abnormal) test results (Chen et al., 2007).

Participants, who have positive FIT results, are referred for confirmatory diagnosis by colonoscopy and a subsequent histopathological examination of biopsied tissues (the gold standard) at Khon Kaen Regional Hospital. Those with a confirmed positive finding are divided into adenomatous polyp and malignant neoplasia groups and referred to health service facilities according to the Thai Ministry of Health guidelines. Those with a negative colonoscopy result are advised to have a further FIT every two years. Participants with negative results by FIT are advised to have a further FIT every two years (Figure 1).

Passive Screening Program (PSP, Control arm)

Participants who are randomly allocated to the control arm, will not be screened by FIT during the six years of the project. After six years, this control group will be invited to attend for an FIT screening test and a colonoscopy if the test is positive (Figure 2).

Data collection and follow-up

All people aged 45 to 74 years living in Nam Phong District, Khon Kaen Province, Thailand, and willing to participate are being recruited using an outreach method (Chou et al., 2016) with the cooperation of health officers, health volunteers, and research staff. There are nine stations used in this method (Figure 2). The functions of each station are as follows: (1) information, (2) registration, (3) eligibility assessment, (4) consent form procedure, (5) interview, (6) randomization, (7) supply of sampling kits for FIT, (8) other health services, and (9) evaluation.

At the first station, all participants are given information about the study. Following this, they move to the registration and eligibility stations. All potential participants are excluded if they have been diagnosed with any cancer during the last two years or with an inflammatory bowel disease, acute gastritis or a related condition during the last two years. Participants who meet the inclusion criteria then sign a consent form before being interviewed by health officers and research staff with a structured questionnaire which has been designed to elicit information about demographic characteristics, food and beverage consumption, risk factors, knowledge about CRC, and address for correspondence.

After this, the participants are randomly allocated by a computer-generated randomization program (Stata10) either to a study arm (receive sample kit for FIT) or to a control arm (no provision of kit). In the study arm, participants receive a sampling bottle (Eiken Chemical Co., Ltd., Tokyo, Japan) and instructions for collecting a stool sample, and the method of sampling is demonstrated by research staff. While participants in the control arm do not receive a sampling kit, they are asked to take part in some other health status measurement program and were given, for example, a container for the collection of a stool sample to be examined for the presence of liver flukes or a kit for the measurement of blood sugar levels. Finally, all participants complete an evaluation form, which is to be used for improving the recruitment processes.

All sampling bottles from participants in the study arm are collected by health volunteers in their villages within two days, and given to health officers at the Tambon (sub-district) Health Promotion Hospital (THPH) for sending to the laboratory at Nam Phong Hospital within one day. The quantitative human hemoglobin content of each of the collected stool specimens is measured in the laboratory using an OC-SENSOR DIANA analyzer (Eiken Chemical Co., Ltd.) (Shin et al., 2016). The results are sent to the principal investigator within two days and to the participants within three weeks. Participants who receive positive results are contacted by health officers, who work in their village, and are prepared for a confirmatory colonoscopy examination at a subsequent date. Participants who receive negative results will be examined for FIT every two years which is the optimal timing for a subsequent FIT (Chiang et al., 2015).

Statistical Methods

Although the main outcomes of the trail are the mortality rate and the incidence of adenomatous polyp and malignant neoplasia, a positive FIT result is the outcome of interest of the present preliminary report and is defined on the basis of the manufacturer's instructions as an Hb concentration greater than 100 ng/mL. The FIT positive rate is defined as the percentage of all participants in the study arm who provided a fecal sample and received a positive FIT result. Another outcome presented in this report is the fecal hemoglobin concentration (f-Hb) level found. These are reported in two ways: (1) for positive FIT results, we categorized the levels into three groups (100-199 ng/mL, 200-449 ng/mL, ≥ 450 ng/mL), (2) for all the participants with f-Hb results, the distributions of f-Hb levels were examined using 75th, 90th and 95th percentiles for males and females in six different age groups (45-49, 50-54, 55-59, 60-64, 65-69 and 70-74 years). All statistical analyses were performed using Stata software version 10.

Ethical Approval and Trial Registration

The trial was given ethical approval by the Khon Kaen University Ethics Committee for Human Research in Thailand (reference number HE571170) and has been registered with the Thai Clinical Trials Registry (TCTR); the trial registration ID is TCTR20160410001.
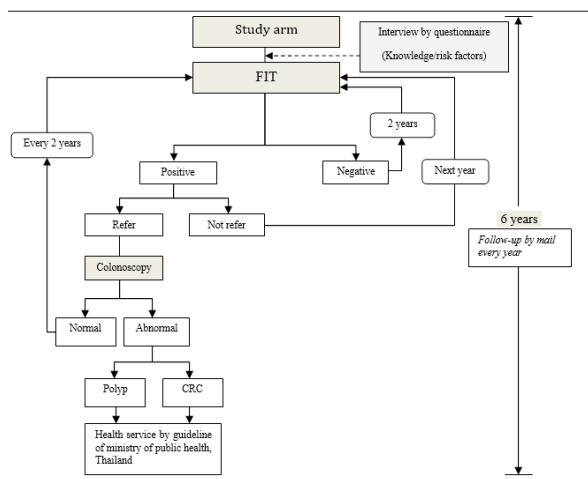
Figure 1. Flow Chart for Implementation in the Study Arm

Table1. Positive FIT Results by Gender

Gender	FIT Result		Total
	Positive (%)	Negative (%)	
Male	39 (11.5%)	300 (88.5%)	339
Female	53 (7.4%)	668 (92.7%)	721
Total	92 (8.7%)	968 (91.3%)	1,060

⁺Cut off ≥ 100 ng/mL

Results

A total of 2,600 potential participants have so far (up to January, 2017) attended sessions of our recruitment process using the outreach method, but 266 (10.2%) were not enrolled in the trial for various reasons: 133 (50%) had a history of acute gastritis or a similar condition in the past two years, 92 (34.6) were outside the eligible age range, 23 (8.6%) were excluded because of incomplete data, 13 (4.9%) were unwilling to participate, and 5 (1.9%) had a history of cancer in the past two years. A total of 1,167 participants were assigned to the study arm which included 368 (31.5%) males, and the same number was assigned to the control arm which included 347 (29.7%) males. Among those 1,167 subjects, there were 1,060
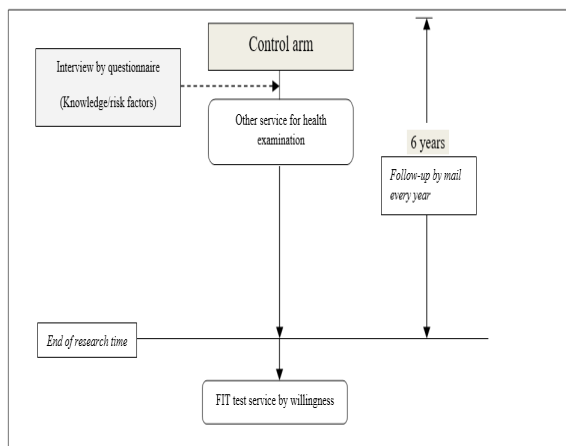

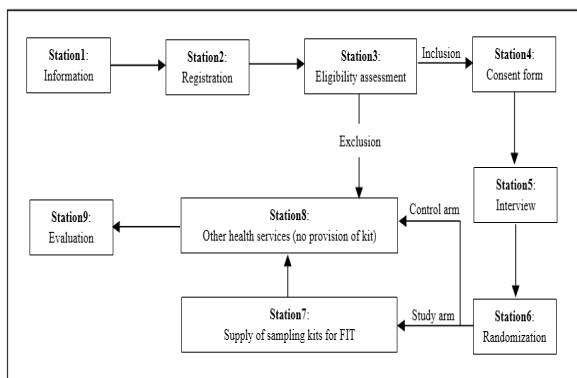Figure 2. Flow Chart for Implementation in the Control Arm

Figure 3. The Nine Stations of the Outreach Method for the Recruitment of Participants into Each Arm

Table 2. Level of f-Hb Concentration in Positive FIT Group (100+ ng/mL) by Gender

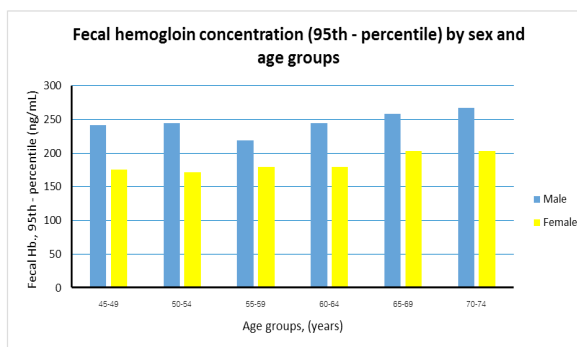| Gender	Level of f-Hb concentration			Total
	100 – 199 ng/mL	200 – 449 ng/mL	≥ 450 ng/mL	
Male	12 (30.8%)	16 (41.0%)	11(28.2%)	39
Female	20 (37.7%)	19 (35.9%)	14 (26.4%)	53
Total	32 (34.8%)	35 (38.0%)	25 (27.2%)	92

Figure 4. Fecal Hemoglobin Concentration at 95th Percentile for Males and Females in Six Age Groups

subjects who completed the FIT screening service, the attendance rate for FIT has so far been 90.8%.

Positive FIT findings
A total of 1,167 participants received sample kits for FIT during the recruitment process, but 107 of these participants (9.2%) failed to return their sample bottles to

Table 3. Level of f-Hb Concentration (ng/mL) by Gender and Age Group (n=1,060)

Age groups (years)	75th Percentile		90th Percentile		95th Percentile	
	Male	Female	Male	Female	Male	Female
45-49	18.0	15.0	108.0	69.0	242.0	176.0
50-54	18.0	14.0	93.0	68.0	245.0	172.0
55-59	18.5	14.0	96.0	69.0	219.0	180.0
60-64	19.0	15.0	93.0	69.0	245.0	180.0
65-69	22.0	15.0	138.0	70.0	258.0	203.0
70-74	22.0	16.0	135.5	82.0	267.0	303.0

the THPHs. Accordingly, FIT results were available for only 1,060 participants (attendance rate=90.8%). Of this group, 92 (8.7%) participants were found to be positive using the 100 ng/mL as cut-off point, 39 (11.5%) males and 53 (7.4%) females (Table 1).

Positive FIT findings categorized into three groups of f-Hb concentration

Among those 92 positive subjects, when those with positive FIT results are categorized into three groups according to their f-Hb concentrations, 32 (34.8%) were found to be in the 100-199 ng/mL range, 35 (38.1%) in the 200-449 ng/mL range, and the remaining 25 (27.1%) were $\geq$ 450 ng/mL (Table 2).

Distribution of f-Hb concentration of FIT

Table 3 shows the f-Hb concentrations at the 75th, 90th and 95th percentiles for males and females in six different age groups. The f-Hb concentrations at the 75th, 90th and 95th percentiles for all age groups were higher in males than in females. It is also the case that the distributions of f-Hb concentration varied with age, especially at 95th percentile where f-Hb concentrations increase with age (Figure 4).

Overall, the positive proportions were greater in males than in females (p-value=0.027, 95%CI of diff=0.002, 0.079), while the differences in positive proportions among aged groups (45-49, 50-54, 55-59, 60-64, 65-69,70-74 years) were statistically significant using the chi-square test (χ^2=13.35, p-value=0.02).

Discussion

The compliance rate in our study (90.8%) is in line with other studies (Wong et al., 2013; Liles et al., 2017) which are about 90% or more.

According to the preliminary results of this study, from the total 1,060 enrolled participants of study arm who provided complete data and returned their sample bottles for FIT, 92 people (8.7%) were positive. This rate is higher than in the previous study in Lampang Province Thailand, in which the target population was aged 50-65 years, and 80,012 participants were screened using FIT. Of those screened, 873 (1.1%) were found positive (Khuhaprema et al., 2014). The age ranges in the two studies are different, 45-74 years in our study compared with 50-65 years in the Lampang's study, but a further analysis of those aged 50-65 years in our study (n=660) has shown that 45 (6.8%) were positive. The results of the present study indicate that the prevalence of positive FIT cases in Thai screening programs may be increasing. This escalation in positive FIT cases could possibly be occurring not only because of lifestyle changes such as increases in lower physical activity, smoking, drinking alcohol, a high consumption of red and processed meats, and a low consumption of whole grains, fibre, fruits and vegetables (Haggar and Boushey, 2009; Khuhaprema et al., 2014; Song et al., 2015), but also because some other risk factors or cofactor-diseases may play a more important role in our study. For example, regarding a family history of any cancer, 10.9% and 8.7% of positive FIT cases were found to have had a father or mother, respectively, who developed some form of cancer.

Several studies have shown that a family history of any cancer, including breast, uterine, and ovarian cancers, is associated with CRC (Nelson et al., 1993; Palmer et al., 2009; Uccella et al., 2011).

In addition to the above cofactor-diseases, diabetes mellitus (DM) and particularly type 2 DM may increase the risk of CRC (Berster and Göke, 2008; Guraya, 2015). Research in Thailand has shown that type 2 DM in Thai children and adolescents had increased from 5% during 1986-1995 to 17.9% during 1996-1999 (Likitmaskul et al., 2003). The present study found that 17.4% of positive FIT cases had been diagnosed as suffering from DM. Another factor commonly found together with DM and may in itself increase the risk of CRC is obesity (Frezza et al., 2006; Bardou et al., 2013; Saengboonmee et al., 2015). The results of a relatively recent national Thai food consumption survey found a high prevalence of overweight and obesity in a nationally representative sample of the Thai population. The highest prevalence rates of overweight and obesity were found in the 40-49 year old group in both sexes and were higher in urban areas than in rural communities (Jitnarin et al., 2011). All the associations of these risk factors will be investigated in the present study.

The cut-off for fecal hemoglobin concentrations (f-Hb) is an important issue to consider in terms of the required performance characteristics of FIT. These include a positivity rate appropriate to the available colonoscopy resource, the sensitivity/specificity ratio, and the positive predictive value (Fraser Callum et al., 2014). Our results show that f-Hb concentrations vary with sex and age: the f-Hb concentrations were higher in older than younger participants and higher in males than in females. These findings may be useful in terms of the importance of following up negative FIT cases who are older and male. These matters will be regarded as important issues as the trial proceeds (Chiang et al., 2015). Several studies have highlighted the utility of using f-Hb concentrations to assess CRC screening programs: for example, f-Hbs may not only make a contribution to facilitating individually tailored screening for CRC, but they can also be used as a major predictor of life expectancy (Chen et al., 2013); a f-Hb concentration-based management of screenees may be helpful, and f-Hbs can be applied to adjust screening logistics in order to decrease interval cancers and improve the effectiveness of a CRC screening program (Chiu et al., 2015). A complex analysis of the f-Hb concentrations in our present preliminary report is limited because of the present sample size. More sophisticated analyses of the f-Hb concentrations will be presented as the trial proceeds.

In conclusion, the preliminary results of our screening trial have indicated that the prevalence of positive FIT cases are higher than in a similar a recent and, at the time unique, previous study in Thailand. This finding is especially the case for males and those in the older age groups. As the trial proceeds, we expect to have increasing opportunities for demonstrating that risk factors and f-Hb concentrations are important aspects to assess for the utility of a national CRC population screening program.

Conflict of interest

No potential conflicts of interest were disclosed.

Acknowledgements

References

Allison JE, Sakoda LC, Levin TR, et al (2007). Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *Natl Cancer Inst*, **99**, 1462-70.

Aniwan S, Ratanachu-Ek T, Pongprasobchai S, et al (2017). The optimal cut-off level of the fecal immunochemical test for colorectal cancer screening in a country with limited colonoscopy resources: A multi-center study from Thailand. *Asian Pac J Cancer Prev*, **18**, 405-12.

Bardou M, Barkun AN, Martel M (2013). Obesity and colorectal cancer. *Gut*, **62**, 933-47.

Berster JM, Göke B (2008). Type 2 diabetes mellitus as risk factor for colorectal cancer. *Arch Physiol Biochem*, **114**, 84-98.

Bresalier RS (2009). Early detection of and screening for colorectal neoplasia. *Gut Liver*, **3**, 69-80.

Chen CH, Tsai MK, Wen CP (2016). Extending colorectal cancer screening to persons aged 40 to 49 years with immunochemical fecal occult blood test: A prospective cohort study of 513,283 individuals. *J Clin Gastroenterol*, **50**, 761-8.

Chen L-S, Liao C-S, Chang S-H, et al (2007). Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16). *J Med Screen*, **14**, 191-9.

Chen L-S, Yen AM-F, Fraser CG, et al (2013). Impact of faecal haemoglobin concentration on colorectal cancer mortality and all-cause death. *BMJ Open*, **3**, e003740.

Chiang T-H, Lee Y-C, Liao W-C, et al (2015). Timing and Risk Factors for a Positive Fecal Immunochemical Test in Subsequent Screening for Colorectal Neoplasms. *PLoS One*, **10**, e0136890.

Chiu SY-H, Chuang S-L, Chen SL-S, et al (2015). Faecal haemoglobin concentration influences risk prediction of interval cancers resulting from inadequate colonoscopy quality: analysis of the Taiwanese nationwide colorectal cancer screening program. *Gut*, **0**, 1-8.

Faivre J, Dancourt V, Lejeune C, et al (2004). Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study1. *Gastroenterology*, **126**, 1674-80.

Fraser Callum G, Rubeca T, Rapi S, et al (2014). Faecal haemoglobin concentrations vary with sex and age, but data are not transferable across geography for colorectal cancer screening. *Clin Chem Lab Med*, **52**, 1211-16.

Frezza EE, Wachtel MS, Chiriva-Internati M (2006). Influence of obesity on the risk of developing colon cancer. *Gut*, **55**, 285-91.

Guraya SY (2015). Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. *World J Gastroenterol*, **21**, 6026-31.

Haggar FA, Boushey RP (2009). Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg*, **22**, 191-7.

Hardcastle JD, Chamberlain JO, Robinson MHE, et al (1996). Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*, **348**, 1472-7.

Inra JA, Lim R (2016). Colorectal cancer screening. *Am J Hematol Oncol*, **12**, 32-8.

Jitnarin N, Kosulwat V, Rojroongwasinkul N, et al (2011). Prevalence of overweight and obesity in Thai population: results of the national Thai food consumption survey. *Eat Weight Disord*, **16**, 242-9.

Jørgensen OD, Kronborg O, Fenger C (2002). A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut*, **50**, 29-32.

Khuhaprema T, Sangrajrang S, Lalitwongsa S, et al (2014). Organised colorectal cancer screening in Lampang Province, Thailand: preliminary results from a pilot implementation programme. *BMJ Open*, **4**, e003671.

Likitmaskul S, Kiattisathavee P, Chaichanwatanakul K, et al (2003). Increasing prevalence of type 2 diabetes mellitus in Thai children and adolescents associated with increasing prevalence of obesity. *J Pediatr Endocrinol Metab*, **16**, 71-7.

Liles EG, Coronado GD, Perrin N, et al (2017). Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: A randomized trial. *Cancer Treat Commun*, **10**, 27-31.

Nelson CL, Sellers TA, Rich SS, et al (1993). Familial clustering of colon, breast, uterine, and ovarian cancers as assessed by family history. *Genet Epidemiol*, **10**, 235-44.

Palmer JR, Boggs DA, Adams-Campbell LL, Rosenberg L (2009). Family history of cancer and risk of breast cancer in the Black Women's Health Study. Cancer Causes Control **20**, 1733-7.

Pongnikorn D, Suwanrungruang K, Buasom R (2012). Cancer in Thailand volume VIII, 2010–2012. NCIB, VIII, pp 29.

Saengboonmee C, Seubwai W, Wongkham C, Wongkham S (2015). Diabetes mellitus: Possible risk and promoting factors of cholangiocarcinoma. *Cancer Epidemiol*, **39**, 274-8.

Sarakarn P, Suwanrungruang K, Vatanasapt P, et al (2017). Joinpoint analysis trends in the incidence of colorectal cancerin Khon Kaen, Thailand (1989 – 2012). *Asian Pac J Cancer Prev*, **18**, 1039-43.

Siripongpreeda B, Mahidol C, Dusitanond N, et al (2016). High prevalence of advanced colorectal neoplasia in the Thai population: a prospective screening colonoscopy of 1,404 cases. *BMC Gastroenterol*, **16**, 101.

Song Y, Liu M, Yang F, et al (2015). Dietary fibre and the risk of colorectal cancer: a case-control study. *Asian Pac J Cancer Prev*, **16**, 3747-52.

Uccella S, Cha SS, Melton LJ, et al (2011). Risk factors for developing multiple malignancies in endometrial cancer patients. *Int J Gynecol Cancer*, **21**, 896-901.

Welch HG, Robertson DJ (2016). Colorectal cancer on the decline - why screening can't explain it all. *N Engl J Med*, **374**, 1605-7.

Wilschut JA, Hol L, Dekker E, et al (2011). Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. *Gastroenterology*, **141**, 1648-55.

Wong CK, Lam CL, Wan Y, Fong DY (2015). Cost-effectiveness simulation and analysis of colorectal cancer screening in Hong Kong Chinese population: comparison amongst colonoscopy, guaiac and immunologic fecal occult blood testing. *BMC Cancer*, **15**, 705.

Wong MCS, Ching JYL, Lam TYT, et al (2013). Prospective cohort study of compliance with faecal immunochemical tests for colorectal cancer screening in Hong Kong. *Prev*

Med, **57**, 227-31.
Zauber AG (2015). The impact of screening on colorectal cancer
    mortality and incidence - has it really made a difference?.
    Dig Dis Sci, **60**, 681-91.