RESEARCH ARTICLE

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Lack of Association between Red Meat Consumption and a Positive Fecal Immunochemical Colorectal Cancer Screening Test in Khon Kaen, Thailand: a Population- Based Randomized Controlled Trial

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Abstract

Background: There is convincing evidence from epidemiological studies that meat consumption increases colorectal cancer (CRC) risk. However, assessment of any association with a positive fecal immunochemical test (FIT) in CRC screening has been limited. If a link could be shown this might be helpful for establishing a risk group for colonoscopy. **Objective:** This study aimed to assess any association between meat consumption and other lifestyle factors and a positive FIT result in a Thai population. **Methods:** A cross-sectional analytical study was conducted with 1,167 participants in a population-based randomized controlled trial. CRC was screened from May 2016 - February 2017. Subjects aged 45-74 years who met the eligibility criteria were randomly allocated to the study arm. A positive FIT was determined with cut-off 100 ng/mL. Multiple logistic regression was used to analyze any relationship between lifestyle factors and a positive FIT. **Result:** The total number of subjects was 1,060 (90.8% return rate of FIT). With FIT100, FIT150, and FIT200, positive tests were found in 92 (8.68%), 74 (6.98%), and 60 (5.66%), respectively. No significant associations were noted with any of the variables, except for being aged 60-74 years (ORadj = 1.62, 95% CI: 1.03-2.54) Borderline significance was observed for high consumption of vegetables (ORadj = 0.62, 95% CI: 0.36-1.07) and being male (ORadj = 1.39, 95% CI: 0.87-2.22). **Conclusion:** Despite the evidence from the literature, no association was here found between a positive FIT result and meat consumption or other well-established lifestyle parameters. Being aged 60-74 years was a risk factor which should be taken into account in CRC screening strategy in countries like Thailand with limited access to endoscopy.

Keywords: Red meat consumption- fecal immunochemical test- colorectal cancer

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Introduction

Colorectal cancer (CRC) is the fourth major cancer in worldwide. In Thailand, CRC is the third and fourth most common cancer in men and women (age-standardized incidence rate (ASR) = 14.4 per 100,000 population, 11.2 per 100,000 population, respectively). Khon Kaen is a big city in the northeastern region of Thailand with an ASR incidence of CRC in men of 13.1 per 100,000 population and in women of 9.0) (Imsamram et al., 2015). In 1989-2012, the CRC incidence trend in Khon Kaen province gradually increased among both males and females (Sarakarn et al., 2017). This may probably be due to lifestyle changes according to westernization (Suwanrungruang et al., 2006; Sriamporn et al., 2007) and exposure to modifiable risk factors, such as meat products, physical inactivity, obesity, smoking, and alcohol consumption, identified as such in many epidemiological studies (Huxley et al., 2009; Poomphakwaen et al., 2015).

Several investigations have indicated that red and processed meat is a risk factor for CRC (Aykan, 2015; Bernstein et al., 2015). Based on a meta-analysis, dietary hemoglobin and red meat consistently promote aberrant crypt foci (ACF), putative pre-cancer lesions (Bastide et al., 2011). Moreover, the heme iron has a catalytic effect on the endogenous formation of carcinogenic N-nitroso compounds and the generation of cytotoxic and genotoxic aldehydes by lipoperoxidation (Bastide et al., 2011). Red meats can be a source of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) , especially with

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high temperature cooking, these compounds being found to be gastrointestinal carcinogens in animal models (Cross et al., 2010; Chiavarini et al., 2017). Overall, studies have provided evidence that red meat consumption is best described in terms of weak associations with CRC (Alexander et al., 2015).

Screening for CRC enables early detection of invasive cancers or precancerous neoplastic lesions, thereby reducing the associated mortality and increasing the likelihood of survival, with treatment usually more successful (Zauber et al., 2012; Winawer, 2015). Screening tests of CRC are categorized into two types, high-risk adenoma screening strategies included flexible sigmoidoscopy or colonoscopy, and measurement of the fecal markers like the fecal occult blood test (FOBT) or DNA tests (Lieberman, 2012; European Colorectal Cancer Screening Guidelines Working et al., 2013). Fecal-base tests are recommended for population screening and fecal immunochemical testing (FIT) can effectively reduce mortality from CRC, so that it has become popular in regions where colonoscopy resources are limited (Benson et al., 2012; Chiu et al., 2015). The fecal immunochemical test is now widely performed for CRC screening and rapidly replacing guaiac fecal occult blood test (gFOBT) because of many advantages (Sung et al., 2015; Mousavinezhad et al., 2016). With good analytical sensitivity with only one sample collection, it has high specificity for colon and rectal tract bleeding with no necessity for dietary restrictions. The result of FIT utilities could improve clinical performance and higher participation rates in screening (Vart et al., 2012; Jensen et al., 2016).

However, the question of whether a positive FIT might be associated with meat consumption has not hitherto attracted much attention. Confirmation of this as a risk factor might be helpful for prompt decision-making in selecting high risk groups for colonoscopy investigation, which could substantially reduce the colonoscopy workload. Here we used a population-based controlled trial with subjects undergoing FIT after random allocation to the study arm for screening in a colorectal cancer screening study in a Thai population aged 45-74 years. The aim was to investigate any association of red meat consumption or other known risk factors with a positive FIT.

Materials and Methods

CRC screening using FIT in a Thai population aged 45-74 years: a population-based randomized controlled trial

This analytical cross-sectional study is a part of the population-based randomized controlled trial of CRC screening program that was launched in May 2016 and is scheduled for completion after six year (Sarakarn et al., 2017). The targets are people aged 45 to 74 years living in Nam Phong District, Khon Kaen Province, Thailand, and willing to participate. Figure 1 shows the flow diagram of identification of subjects which started in the registration and eligibility. Subjects were 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. Recruitment was using an outreach method with the cooperation of health officers, health volunteers, and research staff. All participants sign a consent form for attending the screening program and clustered randomization allocated to the active screening program (ASP or treatment arm) and passive screening program (PSP or control arm). For the treatment arm, subjects received FIT kit (Eiken Chemical Co., Ltd., Tokyo, Japan) and instructions for collecting a stool sample demonstrated by research staff. All FIT kits from participants were sent to the laboratory at Nam Phong Hospital for assessment. For control arm, subjects do not receive FIT kit. All resultant data are stored in the Khon Kaen Community-Based Integrated Screening Program (KKCIS) central database under control of the ASEAN Cancer Epidemiology and Prevention Research Group (ACEP).

Fecal immunochemical test (FIT)

The quantitative human hemoglobin content of each of the collected stool specimens was measured in the laboratory using an OC-SENSOR DIANA analyzer (Eiken Chemical Co., Ltd.). Fecal testing was conducted with 1-day (single sample) sampling, and the haemoglobin cut-offs for the FIT test was established at 100, 150, and 200 ng/mL for positive FIT. In the KKCIS, participants with positive tests (FIT100) were contacted by health officers and referred for colonoscopy by certified endoscopists at a subsequent date. In addition to recording a positive or negative result, numerical data were stored in the database for possible adjustment of the cut-off hemoglobin concentration. This is a cross-sectional study, the positive FIT group by cut-off a hemoglobin concentration ≥100 ng/mL is considered as cases and the negative FIT group (with the hemoglobin concentration less than 100 ng/mL) is considered as controls.

Measurement of variables

Research staff in the CRC screening project interviewed the subjects using a structured questionnaire with third sections. The first covered demographic and socioeconomic status. The second section focused on risk factors of CRC, including a food frequency questionnaire structured by meals per week and methods of cooking, smoking history, alcohol consumption, physical activity, family history of cancer and medical status. The third section concentrated on knowledge of CRC. For the food consumption, an especial focus was on red meat and processed meat intake in four groups as: beef, processed beef, pork and processed pork. Food frequency was categorized into 3 levels as (every day), sometimes (1 or more meal per week) and rarely (not consumed or hardly ever consumed)

A positive FIT was determined with cut-off 100 ng/mL. For analysis of associations with a positive FIT, we categorized each variable as follows: occupation activity was categorized into two levels as heavy labor and moderate or light, based on working types. Heavy labor workers are persons who are work in farms. Light workers are persons who mostly work by standing or sitting but move around such as unemployed, government official, state enterprise, own business, salesmen, hair stylists, servants and policeman, managers and clerks. Cigarette smoking was categorized into two groups as smoker and non-smoker. Alcohol drinking was categorized into two groups as drinker and non- drinker. Ever drinkers were defined as having consumed at least one type of all alcoholic beverages (Beer, Sato, white whisky, Maekong and other whisky) within a range of every day to 1-3 time per month. Those who did not drink or consumed all alcoholic beverages less frequently than 3 times per year were categorized as non- drinkers. Dietary intake within the previous year (beef, pork, processed beef and pork, vegetable), were categorized as two levels, low and high. High consumption was defined as who had consumed at least one type of dietary intake (uncooked or raw, boiled or steamed, grilled, fried) every day. Those who did not intake or had consumed all type of dietary intake less than once per day were categorized as low consumption. Body mass index (BMI) was computed as weight (kg) divided by the square of height (m^2) categorized into two levels ; under or normal weight and over weight (BMI < 26 and BMI ≥ 26). Physical activity was categorized into two levels as exerciser and non-exerciser. Exercisers were defined as those who played sports at least 3 times a week and others were considered as non-exercisers. Knowledge of CRC was computed as a total score which are categorized into two levels as poor (<8 scores) and good (≥ 8 scores).

Statistical analysis

The positive FIT proportion with FIT100 cut-off was assessed using percentage in every subgroup in each variable for categorical data. The association between red meat consumption and other variables and positive FIT was assessed using multiple logistic regression. Multivariable analysis used a backward elimination approach to identify a final set of variables independently associated with positive FIT and consider the effect of the factor indicated above, as determined by adjusted odds ratio (ORadj) and their 95% confidence interval (95% CI).

Ethical considerations

This study was given ethical approved by the Khon Kaen University Ethics Committee for Human Research based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines (Reference number: HE602002). The RCT of the CRC screening project 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.

Results

Demographics of study subjects

Of 2,600 subjects who had attended the CRC screening program using outreach method, 266 (10.2%) were excluded due to incomplete information criteria. 1,167 subjects were randomly allocated to the study arm and received a FIT kit. Some 9.2% of these subjects failed to

Table1. Demographic Characteristic of Subjects

Characteristics	Number	Percentage
Gender		
Female	721	68.02
Male	339	31.98
Age		
45 – 49 years	202	19.06
50 – 54 years	198	18.68
55 – 59 years	212	20.00
60 – 64 years	217	20.47
65 - 69 years	160	15.09
70 - 74 years	71	6.70
Mean (standard deviation)	58.14 (7.73)	
Median (Min : Max)	57.77 (45 : 74)	
Highest education level		
Primary and under primary	900	84.91
Secondary and upper	160	15.09
Main occupation		
Unemployed	80	7.55
Farmer /Agriculture	878	82.83
Own business	47	4.43
Labor	27	2.55
Government official/State enter prises	28	2.64
Income per month (Baht)		
≤ 5,000	453	42.82
5,001 – 10,000	497	46.98
>10,000	108	10.20
Mean (standard deviation)	8,652.74 (9,677.75)	
Median (Min : Max)	7500 (500 : 110,000)	
Body mass index (BMI)		
Under and normal (<26)	705	66.51
Over and obese (≥26)	355	33.49
Mean (standard deviation)	24.61(3.95)	
Median (Min : Max)	24.37(13.72 : 38.37)	
Smoking		
Never	802	75.66
Ever	258	24.34
Alcohol consumption		
Non- Drinker	821	77.45
Drinker	239	22.55
Physical activity and exercise		
Exercise	873	82.36
Non-exercise	187	17.64
Family history of cancer		
No	729	68.77
Yes	331	31.23
Diabetes mellitus		
No	923	87.08
Yes	137	12.92
Knowledge of Colorectal cancer (0-11 items)		
Poor (Correct answer < 8 items)	274	25.85
Good (Correct answer ≥8 items)	786	74.15
Mean (standard deviation)	8.36 (1.99)	
Median (Min : Max)	9 (0 : 11)	

Table 2. Crude Odds Ratio for Factor Associations with a Positive Fecal Immunochemical Test (FIT) Using Univariate Analysis

Variables	N	n	% Positive	n	% Negative	ORc	95% CI	P-value
Red meat								0.7454
Low consume	999	86	8.61	913	91.39	1		
High consume	61	6	9.84	55	90.16	1.16	0.49-2.77	
Processed meat								0.1981
Low consume	1,028	91	8.85	937	91.15	1		
High consume	32	1	3.13	31	96.88	0.33	0.05-2.46	
Vegetables								0.0508
Low consume	763	74	9.7	689	90.3	1		
High consume	297	18	6.06	279	93.94	0.6	0.35-1.02	
Gender								0.0283*
Female	721	53	7.35	668	92.65	1		
Male	339	39	11.5	300	88.5	1.64	1.06-2.53	
Age								0.0418*
45-59 years	612	42	6.86	570	93.14	1		
60-74 years	448	50	11.16	398	88.84	1.7	1.11-2.62	
Education level								0.3655
≤ Primary school	900	81	9	819	91	1		
> Primary school	160	11	6.88	149	93.13	0.75	0.39-1.43	
Occupation								0.4079
Famer	878	79	9	799	91	1		
Light work	182	13	7.14	169	92.86	0.78	0.42-1.43	
Income/month (Baht)								0.6257
≤ 5,000	453	42	9.27	411	90.73	1		
5,001 – 10,000	497	39	7.85	458	92.15	0.83	0.53-1.31	
> 10,000	108	11	10.19	97	89.81	1.11	0.55-2.23	
BMI (kg/m^2)								0.8509
< 26	705	62	8.79	643	91.21	1		
≥ 26	355	30	8.45	325	91.55	0.96	0.61-1.51	
Smoking								0.1635
Never	802	64	7.98	738	92.02	1		
Ever	258	28	10.85	230	89.15	1.4	0.88-2.24	
Alcohol consumption								0.2761
Non-drinker	821	67	8.16	754	91.84	1		
Drinker	239	25	10.46	214	89.54	1.31	0.81-2.13	
Physical activity								0.1114
Exercise	873	70	8.02	803	91.98	1		
Non- Exercise	187	22	11.76	165	88.24	1.53	0.92-2.54	
Family history of cancer								0.5951
No	729	61	8.37	668	91.63	1		
Yes	331	31	9.37	300	90.63	1.13	0.72-1.78	
Diabetes mellitus								0.1988
No	923	76	8.23	847	91.77	1		
Yes	137	16	11.68	121	88.32	1.47	0.83-2.61	
Knowledge of CRC								0.9565
Poor	274	24	8.76	250	91.24	1		
Good	786	68	8.65	718	91.35	0.99	0.61-1.61	

ORc, Crude odds ratio; 95% CI, 95% Confidence interval of crude odds ratio; *, Significant (P-value <0.05)

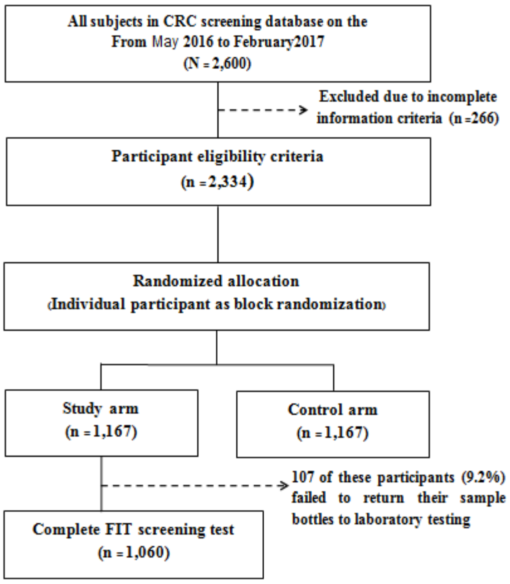

Figure 1. Flow Diagram of Identification of Study Population

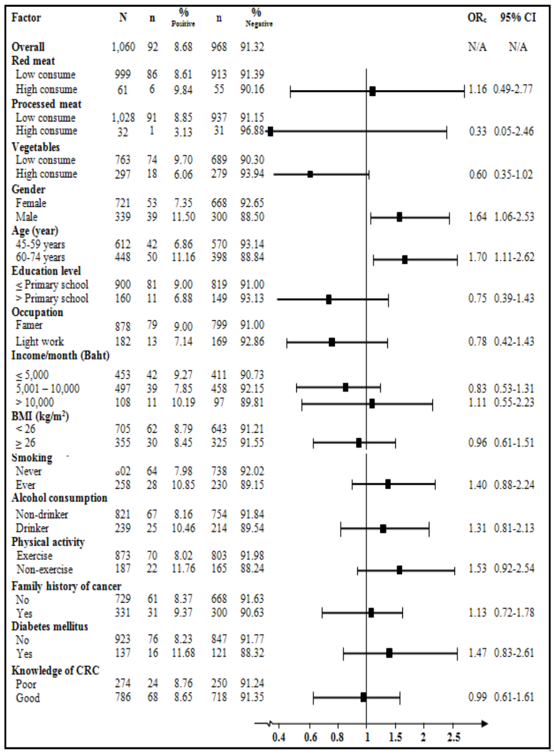

Figure 2. Univariate Analysis of Demographic Factor Associations with a Positive Fecal Immunochemical Test (FIT) Result

return the FIT kit to the laboratory examination, leaving 1,060 subjects with a complete FIT result for the study period. Table 1, shows the baseline characteristic of subjects. Most of the subjects were 721 (68.2%) female, mean age was 58.1 year (SD=7.7) and 448 (42.3%) subjects were age period 60-74 years. The majority were educated lower than high school and 878 (82.8%) were

Table 3. Adjusted Odds Ratio for Factor Associations with a Positive Fecal Immunochemical Test (FIT) Using Multivariable Analysis

Variables	N	n	% Positive	n	% Negative	ORc	ORadj	95% CI	P-value
Red meat									0.6340
Low consume	999	86	8.61	913	91.39	1	1		
High consume	61	6	9.84	55	90.16	1.16	1.25	0.51-3.06	
Vegetables									0.0736
Low consume	763	74	9.7	689	90.3	1	1		
High consume	297	18	6.06	279	93.94	0.6	0.62	0.36-1.07	
Gender									0.1698
Female	721	53	7.35	668	92.65	1	1		
Male	339	39	11.5	300	88.5	1.64	1.39	0.87-2.22	
Age									0.0346*
45-59 years	612	42	6.86	570	93.14	1	1		
60-74 years	448	50	11.16	398	88.84	1.7	1.62	1.03-2.54	
Alcohol consumption									0.6665
Non-drinker	821	67	8.16	754	91.84	1	1		
Drinker	239	25	10.46	214	89.54	1.31	1.22	0.72-2.07	
Physical activity									0.2206
Exercise	873	70	8.02	803	91.98	1	1		
Non- Exercise	187	22	11.76	165	88.24	1.53	1.57	0.93-2.66	
Diabetes mellitus									0.3820
No	923	76	8.23	847	91.77	1	1		
Yes	137	16	11.68	121	88.32	1.47	1.51	0.84-2.73	

ORadj, Adjusted odds ratio; 95% CI, 95% Confidence interval of adjusted odds ratio; *, Significant (P-value <0.05); Adjusted for processed meat and history of smoking farmers.

Positive FIT

Of 1,060 subjects, 92 (8.68%), 74 (6.98%), and 60 (5.66%), respectively were found positive with cut-offs of FIT100, FIT150, and FIT200 .With FIT100, 39 (11.50%) male, 50 (11.16%) in age 60-74 years. Data for univariate associations are shown in Figure 2. With the exception of age 60-74 years and male gender there were no significant associations. A borderline reverse link with vegetable consumption was noted.

Associations with positive FIT using multivariable analysis

The result from the multivariable analysis that found only age of 60-74 years (ORadj= 1.59, 95% CI= 1.03 to 2.46) (Table 3) was a significant risk factor.

Discussion

Thailand is still in the process of pushing for a population-based CRC screening program, which is an important public health policy to provide a basic service for people. Our aim in the present study was to determine whether any of the established risk factors for CRC development might be used to predict a positive FIT result. Unfortunately, we did not find any factors that might be helpful for the prompt decision in selecting the risk group to need to refer for colonoscopy investigation, and thus substantially reduce colonoscopy workload.

The strength of our study is that we recruited participants from the population-based randomized controlled trial of CRC screening program and we only included participants from the asymptomatic population. Moreover, we used quantitative FIT which it avoids interpreter error. The finding results, 92 (8.68%) subjects were positive FIT with cut-off FIT 100 ng/mL, and ranged from 6.98% to 10.38%, which is similar to previous studies in high income countries (Kapidzic et al., 2014; Schlichting et al., 2015; Telford et al., 2016). However, it is higher than previous study in Lampang Province, Thailand where only 1.1% of subjects demonstrated a positive FIT (Khuhaprema et al., 2014). Our finding that the positive rate in men (11.5%) was slightly higher than in women (7.35%) is consistent with a CRC incident trend in Khon Kaen province and Thailand, the rates for men being 13.1 and 14.4/100,000 as compared to the 9.0 and 11.2/100,000 women. A higher test positivity rate in men than in women has also been reported in other settings (Imsamram et al., 2015).

Our results are not in line with expectations from previous studies of risk factors for CRC in Thailand (Sriamporn et al., 2007) and other countries in Asia or Europe (Tuan and Chen, 2016; Wada et al., 2017). Because of the cut-off FIT affects its performance and positive rate of FIT. In Thailand, the cut-off FIT150 and FIT200 were recommended in CRC screening (Aniwan et al., 2017).

In our study, the variation of red meat consumptions had not different proportion. Most of the subjects consumed the fiber or vegetables protect against CRC (Tuan and Chen, 2016). However, these associations were not precise because it due to the fact that most of our subjects had similar eating habits, thus limiting the ability to assess even the slightest effects of these variables. In the CRC screening project, health officers and research staff with a structured questionnaire had interviewed the dietary intake. But the dietary intake are depended on individual recall like as a self-report instrument that can be caused measurement error in a major risk factor can affect the association estimate of a suspected risk factor and even slight measurement error (Marshall et al., 1999; Agogo et al., 2016).

Base on the recent systematic review of red meat and CRC, the meta-analysis from cohorts study, a weakly elevated summary relative risk was observed (RR=1.11, 95% CI: 1.03–1.19) (Alexander et al., 2015). The outcome variable of our study is a clue of CRC using FIT test that will be finding to the suspected case of CRC for colonoscopy investigation. Therefore, it may be possible that the relationship between the consumption of red meat, for example, and the positive FIT results is not statistically significant. However, the false-positive results of FIT conducted in colorectal cancer (CRC) screening could lead to incorrect results and unnecessary of colonoscopy. The risk factor of false-positive FIT results is clinically important for the individualization of CRC screening programs such as hemorrhoids (Kim et al., 2017). Meanwhile, the performances of FIT have been reported to show low positive predictive values for advanced colorectal neoplasm (Huang et al., 2016; Jensen et al., 2016; Telford et al., 2016). The previous reported that the FIT had a similar sensitivity for proximal and distal advanced neoplasia at cut-off of FIT 100 ngHb/mL were 33% and 29% (de Wijkerslooth et al., 2012).

Our results found that male gender was slightly associated with a positive test result of FIT but not statistical significant, which is consistent with those of previous studies conducted in Taiwan (Chiang et al., 2015) and the Netherlands (Grobbee et al., 2017). In addition, we found that older age was a positive association with positive FIT which is consistent with those of the previous study conducted in Taiwan (Chiang et al., 2015). However, male gender and older age are well known to be associated with a higher risk for colorectal cancer (Aykan, 2015; Tuan and Chen, 2016).

In conclusion, no significant associations were noted with a positive FIT for consumption of red meat, a high BMI, history of diabetes, smoking, physical activity, gender and income. Further large data needed to confirm these results. However, our study showed that older age were risks factors for participants being more likely to have a positive result in the FIT test. This risk factor might be helpful for the prompt decision in selecting the risk group to need to refer for colonoscopy investigation and design of a tailored screening program for services to detection and treatment in the early stage of colorectal neoplasia.

Conflict of interest

No potential conflict of interest was disclosed.

Acknowledgements

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