Histopathological and epidemiological findings of colonoscopy screening in a population with an average risk of colorectal cancer in Kuwait

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Abstract Background: Colorectal cancer (CRC) is the second most common cancer in women and the third most common in men worldwide, with a significantly rising incidence in the Middle East region over the last few decades. This study investigates the histopathological and epidemiological characteristics of colonoscopic findings in a population with an average risk of CRC in Kuwait.

Methods: In this study, 1,005 asymptomatic average-risk Kuwaiti adults aged over 40 years had their first colonoscopy screening during the 2015–2018 period. Data on lifestyle behaviors (cigarette smoking, alcohol consumption, and physical activity), body mass index (BMI), and comorbidities were routinely collected from these individuals. All colorectal polyps or masses were assessed for their site, size, and number and then resected and sent for histopathological examination.

Results: The mean age of the participants was 54 years, and 52.2% were women. In screened individuals, the polyp detection rate, adenoma detection rate, and carcinoma detection rate were 43.8%, 27.7%, and 1.2%, respectively. Tubular, tubulovillous, and villous types of adenoma constituted 17.3%, 2.8%, and 1.3% of all screened participants. Neoplastic lesions, particularly in the proximal colon, were more common among men aged 40–49 years. Age of 70 years and older (OR: 9.6; 95% Cl: 4.7–19.9; P < 0.001), male gender (OR: 1.6; 95% Cl: 1.1–2.3; P = 0.011), increased BMI (OR: 1.05; 95% Cl: 1.02–1.08; P = 0.001), and smoking (OR: 3.5; 95% Cl: 2.3–5.4; P < 0.001) were the most significant independent risk factors for colorectal neoplasia.

Conclusions: The high adenoma detection rate (ADR) in Kuwaiti population calls for the establishment of a national programe for CRC screening. The higher ADR in those younger than 50 years calls for assessment of the threshold age at which to start screening.

Keywords: Colonoscopy, colorectal cancer, epidemiology, Kuwait, screening

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in women and the third most common in men worldwide, with an estimated 1.8 million new cases and 861,000 deaths in 2018.^[1] In Kuwait, CRC is the second leading cause of cancer-related morbidity and mortality for both genders, with age standardized incidence rates (ASRs) of 16.1 and 13.4 per 100,000 populations for Kuwaiti men and women, respectively.^[2] Furthermore, CRC accounted for 12.7% and 7.7% of all diagnosed cancers among Kuwaiti men and women, respectively, and 7.5 per 100,000 CRC-related mortality in 2018.^[1]

CRC is a multifactorial disease resulting from lifestyle-related risk factors and environmental exposures with a background of genetically determined individual susceptibility.^[3] Epidemiological studies have reported that smoking, alcohol consumption, older age, sedentary lifestyle, obesity, and diabetes were associated with an increased risk of CRC^[4]; some of these risk factors are more prevalent in the Kuwaiti population.^[5]

Over a decade, almost all CRCs develop from colorectal adenomatous polyps.^[6] Therefore, CRC screening is the most effective and efficient method for reducing CRC-related morbidity and mortality, given the limitations of scaling up population-based lifestyle modification measures.^[7,8] Different methods for CRC screening exist, but screening using colonoscopy is the most efficacious one as it allows for the early detection and removal of precancerous polyps and the detection of early-stage CRC.^[9] However, the lack of a comprehensive screening strategy and public acceptance interferes with its wide implementation, particularly in Middle Eastern countries.^[10] Accordingly, CRC screening is widely introduced opportunistically whenever no national policy or program exists. In opportunistic screening, there are many guidelines with some variation regarding the proposed screening procedures, number of repetitive screens, and age where the assessment begins and when it stops.^[7] In Kuwait, only one pilot program for CRC screening targeting asymptomatic average-risk individuals aged 45-75 years has been launched in mid-2015.^[11]

The benefit of a CRC-screening program largely depends on understanding the distribution (i.e., prevalence, incidence, and risk factors) and histopathological features (e.g., distribution, location, and histology type) of CRC, and the adenomas detection rate in the target population.^[12,13] Moreover, detailed risk information has a significant implication for developing national guidelines for CRC screening and effective tailored or risk-based CRC-screening strategies.^[7,14,15] In Kuwait, these data either are limited or do not exist. Therefore, this study determines the prevalence and histopathological characteristics of colorectal precancerous and cancerous lesions and the risk factors among Kuwaiti asymptomatic average-risk individuals who constitute the target population for the national CRC-screening program.

METHODS

This cross-sectional study was conducted at the gastroenterology and endoscopy unit of Al-Sabah Hospital in Kuwait from June 2015 to June 2018. The study participants were Kuwaiti asymptomatic average-risk adults aged 40 years or older who had been referred for their first screening colonoscopy. Participants who have confirmed CRC diagnosis, first-degree family history of CRC, other cancers, inflammatory bowel diseases and a change in bowel habits, rectal bleeding, unintended weight loss over the last 6 months, or iron deficiency anemia were excluded from the study. Ethical approval was obtained from the Standing Committee for Coordination of Medical Research-Kuwait Ministry of Health. Written informed consent was obtained from all eligible participants. Then, the participants were interviewed to determine conventional risk factors such as age, gender, tobacco smoking, alcohol consumption, and comorbidities. Furthermore, they were assessed for physical activity using the Rapid Assessment of Physical Activity questionnaire.^[16] Their body weights (kg) and heights (cm) were recorded for later calculation of body mass index (BMI).

The colonoscopy procedure was performed as described by Lieberman et al.[17] using the EPK-i7000 High definition (HD) colonoscopy system (PENTAX Medical, Alexandra Technopark, Singapore). Senior endoscopists performed the procedures with the participants under conscious sedation. Candidates received a self-administered high volume polyethylene glycol bowel preparation one day before the procedure. Then, the preparation of the bowel was assessed as excellent, good, fair or poor by endoscopists based on Aronchick scale.^[18] Candidates with poor bowel preparation were rescheduled for another appointment. All lesions such as polyps or masses were identified, described according to Paris endoscopic classification^[19] and then either resected or biopsied for histopathological evaluation by senior pathologists. Lesions were assessed for their locations where the rectum, sigmoid, splenic flexure, and descending colon were reported as the distal colon and the transverse colon, hepatic flexure, ascending colon, and cecum were reported as the proximal colon. Lesion sizes were measured using open-biopsy forceps (8 mm). Adenomatous polyps were classified as neoplastic lesions, whereas hyperplastic, hamartomatous, and inflammatory lesions were classified as non-neoplastic.^[20] Sessile serrated lesions (SSLs) were labeled as sessile serrated polyps and adenomas rather than hyperplastic polyps.^[21] Advanced adenomas were defined as adenomas ≥ 10 mm in size and those with villous histology or high-grade dysplasia. Advanced adenomas and adenocarcinomas were combined into advanced neoplastic lesions.^[22] Candidates with multiple lesions were classified according to the most advanced one.

Statistical analysis

The total number available for statistical analysis were 1,005 participants. Using the sample size equation described by Scheaffer,^[23] this number was large enough to detect at least the ealier Adenoma Detection Rate (ADR) among Kuwaiti population of 13% as reported by Alenezi^[24] at 95% level of confidence, and 2% absolute precision level.

All data manipulations and analyses were performed using Statistical Package for Social Sciences, version 25.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were presented as frequency and percentage. Normality of continous data was tested with Kolmogorov-Smirnov test. Continuous variables were summarized as mean, standard deviation, and range (or median and interquartile range if not normally distributed). Participants with non-neoplastic lesions were excluded from the analysis of the associations between risk factors and the presence of neoplastic lesions. Associations were described using crude odds ratio (OR) and 95% confidence interval. Age-standardized rates for non-neoplastic and neoplastic lesions were calculated using the age-specific weights of the world standard population distribution as reported by the World Health Organization (WHO). Multivariable logistic regression was performed to calculate the adjusted OR and 95% confidence interval. Statistical significance was set at P < 0.05 using two-sided tests.

RESULTS

A total of 1,005 asymptomatic Kuwaiti adults who had their first screening colonoscopy were recruited. The median age of participants was 52 years, with an interquartile range from 48 to 59 years. Approximately two thirds aged 40–59 years. Women constituted 52.2% of all screened individuals. Approximately one-third of the individuals were overweight (35.1%), whereas 54.6% of all screened individuals were obese. Eighty-one participants (8.1%) had morbid obesity (BMI \geq 40 kg/m2). Approximately 20% of the screened individuals were smokers, with an average pack years of 23.2 (\pm 19.9 SD). Only 35 participants (3.5%) were drinking alcohol regularly, but consumed less than 14 units per week. Most of the screened individuals had either sedentary (40.5%) or underactive (38.9%) lifestyles. Approximately 28% of the participants had diabetes mellitus [Table 1].

Cecal intubation was performed in approximately 95% of the participants. Photos were taken during the colonoscopy for documentation. Colonoscopic examination revealed that the overall polyp detection rate (PDR) was 43.8% in the screened population, of them 14.9% had non-neoplastic polyps (hyperplastic, hamartomatous, or inflammatory polyps). Adenoma detection rate (ADR) was 27.7% (including mixed lesions: adenoma/sessile serrated polyps), only 1.2% of the screened individuals had colorectal carcinomas (including mixed lesions: carcinoma/adenoma). Tubular, tubulo-villous, and villous types of adenoma constituted 17.3%, 2.8%, and 1.3% of the screened individuals had SSLs, while 1.7% had mixed lesions (adenoma with either carcinoma or SSLs).

The most frequent site for all adenomas was the sigmoid or descending colon (50%–54%), whereas the cecum or ascending colon was the most common site for SSLs (71.4%). Mixed lesions appeared at multiple sites in 71.4% of all participants. Other histopathological features of colorectal lesions among the screened population are summarized in Table 2 and Figure 1. Distribution of the colorectal lesions by age groups, gender, and

Table 1: Distribution of the screened individuals according to
demographic characteristics and risk factors (N = 1005)

Personal characteristics	No. (%)
Age (years) Mean ± SD	53.8 ± 7.4 (45.0- 75.0)
40-49	351 (34.9%)
50- 59	428 (42.6%)
60- 69	179 (17.8%)
≥70	47 (4.7%)
Gender	
Men	480 (47.8%)
Women	525 (52.2%)
Body mass index (kg/m ²) Mean ± SD	31.2 ± 5.7 (20.0- 57.0)
BMI class	
Normal	103 (10.2%)
Overweight	353 (35.1%)
Obesity class I	312 (31.0%)
Obesity class II	156 (15.5%)
Obesity class III	81 (8.1%)
Smoker	202 (20.1%)
Pack years, n = 202 Mean ± SD(range)	23.2 ± 19.9 (1.75-90.0)
Alcohol intake	35 (3.5%)
Physical activity	
Active	207 (20.6%)
Underactive	391 (38.9%)
Sedentary	407 (40.5%)
Diabetes mellitus	282 (28.1%)

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Histopathological features	Adenomas			Sessile serrated	Mixed (adenoma &	
	Tubular (<i>n</i> = 174)	Tubulo-villous (<i>n</i> = 28)	Villous (<i>n</i> = 13)	(<i>n</i> = 49)	sessile serrated) (n = 14)	
Lesion site, no. (%)						
Rectum	8 (4.6%)	6 (21.4%)	2 (15.4%)	0	0	
Sigmoid/descending colon	88 (50.6%)	14 (50.0%)	7 (53.8%)	0	0	
Transverse colon	14 (8%)	0	0	9 (18.4%)	2 (14.3%)	
Cecum/ascending colon	18 (10.3%)	6 (21.4%)	2 (15.4%)	35 (71.4%)	2 (14.3%)	
Multiple sites	46 (26.4%)	2 (7.1%)	2 (15.4%)	5 (10.2%)	10 (71.4%)	
Number of polyps, no. (%)						
1-2	127 (73%)	24 (85.7%)	13 (100%)	49 (100%)	6 (42.9%)	
3- 5	47 (27%)	4 (14.3%)	0	0	8 (57.1%)	
Size of polyps, no. (%)						
< 10 mm	166 (96%)	10 (35.7%)	0	49 (100%)	14 (100%)	
≥ 10 mm	7 (4%)	18 (64.3%)	13 (100%)	0	0	
Shape of polyps, no. (%)						
Pedunculated	29 (16.7%)	13 (46.4%)	6 (46.2%)	0	0	
Sessile	145 (83.3%)	15 (53.6%)	7 (53.8%)	49 (100%)	14 (100%)	

Table 2: Distribution of significant lesions according to the histopathological features among screened individuals (N = 1005)

locations are further described in Tables 3 and 4. Also, the age-standardized rates (per 1,000) of non-neoplastic and neoplastic lesions were calculated using the WHO's world standard population and presented in Table 3.

On the other hand, CRC was detected in 12 patients (nine men and three women) with a mean age of 61 (\pm 7 SD) years. All colorectal carcinomas were solitary mass with an average largest diameter of 2 cm (\pm 0.5 SD). Half of the participants with colorectal carcinomas had lesions located at the sigmoid or descending colon, whereas 33.3% were located at the rectum and 16.7% at the cecum or ascending colon.

Bivariate analyses showed that all measured risk factors (except for alcohol intake) were significantly associated with colorectal neoplasia. However, multivariable regression analysis (as measured by the adjusted odds ratios) revealed that only age, gender, BMI, and smoking contribute independently and significantly, as risk factors, to the likelihood of getting neoplastic colorectal lesions among the screened individuals. Among all other risk factors held constant, age was significantly associated with colorectal neoplasia with a step gradient effect of increasing age [Table 5].

DISCUSSION

Adenoma detection rate has been considered as a predictor key of endoscopic success and is inversely correlated with the diagnosis of colorectal interval carcinoma.^[25] The polyp detection rate (PDR) in our study was 43.8% which is higher than 24.8%, and 23.5% that were reported in Saudi Arabia and Iran, respectively.^[10,26] However, it is still lower than what was found among screened individuals in Spain and Germany (45.8% and 52.4% respectively).^[27,28] The ADR in our study was 27.7%, in similarity to the previous finding in Ohio, USA^[29] and not much lower than previously reported in Spain and Germany (32.7%, 31.7%, respectively).^[27,28] Furthermore, advanced adenomas were detected in 7.8% of our study population which was higher than what was reported in Germany (6%).^[28] This may indicate a delayed detection of simple non-neoplastic adenomas in Kuwaiti population.

Studies from other Gulf Cooperation Council (GCC) states, such as Saudi Arabia and Oman, and regional countries such as Iran, have reported lower adenoma detection rates in comparison to our results (16.8%, 12.1%, and 12.8%, respectively).^[10,11,26] Despite that, Kuwait has a lower adenoma detection rate than Western countries, while a rising trend has occurred in the last two decades. In this study, the ADR (27.7%) was higher than previously reported in Kuwait (4.6% and 13%).^[24,30] This increase in adenoma detection could be attributed to the transition toward a Westernized lifestyle among the Kuwaiti population over the last few decades, in addition to the use of advanced HD scopes.^[31,32] The prevalence of CRC in this study was 1.2%, which is consistent with the earlier studies conducted in Iran, Saudi Arabia^[10,26] and Western countries.[1,33]

Several studies have shown variations in the prevalence of adenomas and advanced neoplasia by age, gender, and ethnicity.^[29,34] In Kuwait, Alenzi *et al.* found that the rise in the prevalence of adenomas and advanced neoplasia was significantly associated with aging.^[24] In this study, most adenomas and advanced neoplasia were detected in individuals aged 50–59 years and 60–69 years with a significant step gradient effect of increasing age and occurrence of colorectal neoplastic lesions. This finding is consistent with studies from the Middle East and Western countries.^[10,26,27,35] However, in our study, a remarkable

		Age gro	oups (men), no. (row %)		
	40- 49	50- 59	60- 69	≥ 70	Total
Normal colonoscopy	102 (44.2%)	77 (33.3%)	42 (18.2%)	10 (4.3%)	231
Non-neoplastic lesions	36 (42.4%)	47 (55.3%)	2 (2.4%)	0	85
Neoplastic lesions:					
Non-advanced	24 (20.9%)	54 (47.0%)	27 (23.5%)	10 (8.7%)	115
Advanced	4 (8.2%)	22 (44.9%)	15 (30.6%)	8 (16.3%)	49
		Age grou	ips (women), no. (row %)	
	40- 49	50- 59	60- 69	≥ 70	Total
Normal colonoscopy	141 (42.2%)	146 (43.7%)	39 (11.7%)	8 (2.4%)	334
Non-neoplastic lesions	29 (44.6%)	32 (49.2%)	4 (6.2%)	0	65
Neoplastic lesions:					
Non-advanced	14 (14.6%)	38 (39.6%)	35 (36.5%)	9 (9.4%)	96
Advanced	1 (3.3%)	12 (40.0%)	15 (50.0%)	2 (6.7%)	30
		Age gr	oups (all), no. (row %)		
	40- 49	50- 59	60- 69	≥ 70	Total
Normal colonoscopy	243 (43.0%)	223 (39.5%)	81 (14.3%)	18 (3.2%)	565
Non-neoplastic lesions	65 (43.3%)	79 (52.7%)	6 (4.0%)	0	150
Neoplastic lesions:					
Non-advanced	38 (18.0%)	92 (43.6%)	62 (29.4%)	(9.0%)	211
Advanced	5 (6.3%)	34 (43.0%)	30 (38.0%)	10 (12.7%)	79
		Age-sta	ndardized rate (/1000)		
	40- 49	50- 59	60- 69	≥ 70	Total
Non-neoplastic lesions	23.4	18.3	2.2	0	43.9
Non-advanced neoplastic	13.7	21.3	23.1	21.3	79.5
Advanced neoplastic	1.8	7.9	11.2	11.2	32.1

Table 3: Distribution of colone	scopic findings by gen	ider and age groups ((N = 1005)
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^aBased on the most advanced lesions

proportion of colorectal neoplastic lesions (14.8%) were detected in younger individuals aged 40–49 years, particularly in men. This finding is higher than that reported by Hemmasi *et al.* and Sohrabi *et al.*^[36,37]

In our study, ADR was higher in men than women (34% vs. 24%). This rate is consistent with earlier studies in Saudi Arabia, Iran and USA.^[10,26,29] This variation may be explained by frequent exposure to environmental risk factors (i.e., smoking) among men than in women, in addition to the reported protective role of estrogens against CRC development in women.^[38]

The histopathological features of the resected colorectal polyps during colonoscopic screening are considered important predictors of malignant transformation.^[39] Colorectal adenomas are histopathologically classified into tubular, tubulovillous, and villous patterns based on the classification criteria of the World Health Organization.^[40] In this study, the most frequent pathological finding was tubular adenomas, similar to other studies.^[10,24,41] The large size (≥ 10 mm) of adenomas correlates with the pathological features of advanced neoplasia (villous morphology and high-grade dysplasia) in asymptomatic individuals who underwent colonoscopic screening.^[10] Of the individuals with adenomas, 14.75% had a villous pattern, which was evident in large-sized adenomas and associated with high-grade

dysplasia contributing to the need for colonoscopic removal of advanced adenomas to reduce the incidence of CRC.^[42]

SSLs are substantial precursors for CRCs and constitute a major challenging target of CRC screening and histopathological identification.^[43] Studies observed SSLs in 7–9% of the population who underwent colonoscopic screening, and SSLs were commonly detected at the proximal colon.^[28] In the current study, SSLs were discovered in 6.3% of the study participants coinciding

Table 4: Distribution of colonoscopy findings by gender and lesion site (N = 1005)

	Lesion site (men), no. (row %)			
	Proximal	Distal	Both	Total
Non-neoplastic lesions Neoplastic lesions:	8 (9.4%)	71 (83.5%)	6 (7.1%)	85
Non-advanced Advanced	40 (34.8%) 17 (34.7%)	47 (40.9%) 26 (53.1%)	28 (24.3%) 6 (12.2%)	115 49
	Lesion site (women), no. (row %)			
	Proximal	Distal	Both	Total
Non-neoplastic lesions Neoplastic lesions:	7 (10.8%)	53 (81.5%)	5 (7.7%)	65
Non-advanced Advanced	25 (26.0%) 8 (26.7%)	47 (49.0%) 13 (43.3%)	24 (25.0%) 9 (30.0%)	96 30
	Lesion site (all), no. (row %)			
	Proximal	Distal	Both	Total
Non-neoplastic lesions Neoplastic lesions:	15 (10.0%)	124 (82.7%)	11 (7.3%)	150
Non-advanced Advanced	65 (30.8%) 25 (31.6%)	94 (44.5%) 39 (49.4%)	52 (24.6%) 15 (19.0%)	211 79



Figure 1: Distribution of significant colorectal lesions according to dysplasia (N = 1005)

with previous studies, and all lesions were located in the proximal colon. SSLs with cytological dysplasia were identified in 1.9% of the study population, which were carrying a higher risk of malignant transformation.^[44] In this study, 5% of the participants with sessile serrated neoplasia had synchronous conventional adenomas; this is comparable to another study that showed simultaneous presence of adenomatous and serrated pathways in many individuals. In addition, individuals with concurrent sessile serrated and conventional adenomas at baseline colonoscopic screening will have a significantly higher risk of metachronous advanced adenomas.^[45]

Multiple environmental and lifestyle-related risk factors have been involved in increasing the risk of colorectal neoplasia development. In Kuwait, over the last few decades, Westernized lifestyles have emerged, including dietary habits, reduced physical activity, and increasing prevalence of obesity and diabetes.^[5] Smoking has been identified as a risk factor associated with developing colorectal neoplasia and advanced adenomatous lesions.^[46] In our study, the odds of having colorectal neoplasia increased by more than three-folds in smokers compared with nonsmokers. However, a recent study in Kuwait did not find a significant relationship between smoking and CRC risk.^[5] This is probably because of the use of an underpowered sample which lead to a type 2 statistical error. The current study also showed that the odds of having colorectal neoplastic lesions increased by 5% with every unit increase in the BMI, which is consistent with the results of earlier studies describing obesity as a risk factor for colorectal adenomas.^[5,47] Furthermore, our study showed that a sedentary lifestyle and type 2 diabetes mellitus in the presence of other measured risk factors (age, obesity, and smoking) were significantly associated with the risk of colorectal neoplasia, consistent with the protective effect of physical activity against the development of CRC. Alcohol consumption in Muslim countries, particularly in Arab countries, is usually subject to under-reporting because of religious and cultural issues. In our study, the

Table 5: Crude and adjusted odds ratios for the association between patients' risk factors and neoplastic lesions $(N = 855)^a$

	Crude OR (95% CI)	Adjusted OR (95% CI)
Age groups		
50-59	3.193 (2.160- 4.721)	3.469 (2.274- 5.293)
60-69	6.419 (4.130-9.974)	7.128 (4.388- 11.579)
≥ 70	9.105 (4.652-17.821)	9.635 (4.660- 19.923)
Gender	· · · · · ·	· · · · · · · · · · · · · · · · · · ·
Men vs. women	1.882 (1.413-2.506)	1.604 (1.112-2.313)
BMI (kg/m2)	1.037 (1.013- 1.063)	1.050 (1.020- 1.080)
Smoker	2.895 (2.047-4.096)	3.497 (2.270-5.385)
Alcohol intake	1.312 (0.623-2.762)	1.442 (0.617-3.371)
Physical activity		
Underactive	1.381 (0.925-2.061)	1.217 (0.760- 1.951)
Sedentary	1.577 (1.059-2.349)	1.512 (0.964-2.373)
Diabetes mellitus	1.90 (1.399- 2.580)	1.211 (0.856- 1.711)

^aPatients with non-neoplastic lesions were excluded from the analysis

proportion of those consuming alcohol regularly among study participants is very low, and the correlation of exposure with the risk of colorectal neoplasia occurrence was possibly not applicable.

This study has some limitations that should be taken into consideration while interpreting its findings. First, all participants were from one referral center. Second, the dietary pattern was not assessed as an important risk factor for CRC. Third, individuals with lower gastrointestinal symptoms were excluded, which might introduce selection bias to our study. Fourth, the younger age group (40–49 years) was not well represented in our sample, which limited our conclusion about colorectal neoplasia in this group. Finally, other nationalities and ethnic groups were not well represented in our sample, particularly with a substantial proportion of migrant workers residing in Kuwait. However, the selection of the same ethnic group may be important in assessing the risk factors.

In conclusion, the high ADR in our study population calls for the establishment of a national program for colorectal cancer screening. In addition, the higher ADR in the age group younger than 50 years calls for a revision to assess the threshold age at which to start screening colonoscopy in Kuwait. Moreover, male gender, smoking, and obesity should be considered in risk stratification of screened individuals.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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