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REVIEW

How significant is the association between metabolic syndrome and prevalence of colorectal neoplasia?

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Abstract

The incidence and prevalence of metabolic syndrome (MS) and colorectal cancer (CRC) has been rising in developed countries. The association between these two diseases has been widely studied and reported. Less evidence is available about the relationship between MS and CRC precancerous lesions (adenomatous polyps, adenomas). The aim of this paper is to present an overview of our scientific understanding of that topic and its implication in clinical practice. One of the principal goals of current CRC secondary prevention efforts is to detect and remove the precancerous lesions in individuals with an average CRC risk to prevent the development of invasive cancer. MS is not currently considered a high-risk CRC factor and is therefore not included in the guidelines of organized screening programs. However, in light of growing scientific evidence, the approach to patients with MS should be changed. Metabolic risk factors for the development of adenomas and cancers are the same - obesity, impaired glucose tolerance, dyslipidemia, hypertension, cardiovascular diseases and diabetes mellitus type 2. Therefore, the key issue in the near future is the development of a simple scoring system, easy to use in clinical practice, which would identify individuals with high metabolic risk of colorectal neoplasia and would be used for individual CRC secondary prevention strategies. Currently, such scoring systems have been published

based on Asian (Asia-Pacific Colorectal Screening Score; APCS) and Polish populations.

Key words: Metabolic syndrome; Diabetes mellitus type 2; Heart ischemic disease; Colorectal neoplasia

Core tip: This article provides a review of our current understanding of the metabolic risk factors in the development of colorectal neoplasia and the scoring systems that may allow tailored secondary screening strategies. In addition, the preliminary results of a Czech multi-center prospective study investigating the relationship between metabolic syndrome and colorectal neoplasia are provided.

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INTRODUCTION

The incidence and prevalence of metabolic syndrome (MS) is rising in developed countries. The prevalence of MS based on National Cholesterol Education Program Adult Treatment Panel Ⅲ criteria (NCEP-ATP Ⅲ 2001) varies from 8% to 43% in men and from 7% to 56% in women worldwide[1]. The Czech Republic is no exception; the prevalence of MS is estimated at 32% in men and 24% in women[2]. MS reflects a combination of risk factors that often occur together and lead to the development of cardiovascular disease, type 2 diabetes mellitus and certain types of cancer, especially tumors of the gastrointestinal and genitourinary tracts[3,4]. These risk factors include abdominal obesity, hyperglycemia, elevated blood pressure, elevated triglycerides and a low high-density lipoprotein (HDL) serum fraction of cholesterol[5].

Colorectal cancer (CRC) with its tremendous population burden represents one of the greatest issues in contemporary health care around the world. The Czech Republic is among the countries with the highest incidence of CRC and related mortality in the world. Each year, there are 8000 new CRC cases and approximately 4000 individuals die from this disease[6]. Central and Western European countries suffer from a long-term worldwide rise in the incidence and mortality of this disease. The Czech Republic currently has the fifth-highest incidence rate in Europe after Slovakia, Hungary, Denmark and the Netherlands[7]. An organized screening program at the population level can successfully reduce the incidence and mortality of CRC[8]. In the Czech Republic, the Czech National CRC Screening Program has been running since the year 2000, focusing on asymptomatic individuals older than 50 years with an average risk of CRC. Immunochemical fecal occult blood test (FOBT) is offered to asymptomatic individuals aged 50-54 years in one-year intervals. In the case of FOBT positivity, colonoscopy is performed. From the age of 55, every individual has the choice of either continuing examinations by FOBT every two years or undergoing a screening colonoscopy, which can be repeated in individuals with negative findings after ten years[9,10]. In 2014, screening invitations addressed to the target population were introduced in the Czech Republic, effecting a transition from an opportunistic screening program to a population-based program. The total screening coverage of the target population in 2014 reached 31.5%, which was 4.6% higher than in 2013. Nevertheless, the total coverage of the Czech population by examination is below the optimum level. According to the European Guidelines, the total screening coverage of the target population should be at least 45% and optimally up to 65%[11]. One of the most important barriers to screening is a lack of perceived risk of CRC among average-risk (AR) patients and primary care providers. New options for screening are therefore sought, such as targeted screening according to metabolic risk[12]. To establish a targeted screening strategy for CRC, it is essential to define high-risk (HR) factors that are associated with colorectal neoplasia.

METABOLIC RISK AND COLORECTAL NEOPLASIA

Available evidence from epidemiologic investigations and clinical studies supports the hypothesis that MS may be an important etiologic risk factor for the development and progression of certain types of cancer, especially CRC[13]. Studies on the association between MS and the risk of colorectal neoplasia are affected by the methodology (cohort *vs* case-control *vs* cross-sectional studies), cancer site (colon *vs* rectum), territory (United States *vs* Europe *vs* Asia), study quality, and the definition of MS. The main issue in the investigation of this association is the combination of multiple components of the MS. According to a harmonized definition from 2009, MS is present when any three of the following conditions are present: High waist circumference (≥ 102 cm in men, ≥ 88 cm in women), elevated triglycerides ≥ 1.7 mmol/L (≥ 150 mg/dL), reduced HDL cholesterol < 1 mmol/L (< 40 mg/dL) in men; < 1.3 mmol/L (< 50 mg/dL) in women, elevated blood pressure (systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg) or serum glucose level ≥ 5.6 mmol/L (≥ 100 mg/dL)[14].

OBESITY AND COLORECTAL NEOPLASIA

Obesity is associated with chronic low-grade inflammation due to the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, which lead to the secretion of acute phase proteins such as C-reactive protein[15]. This chronic inflammatory process can result in a positive association between obesity and CRC risk. Additionally, a large number of newly discovered adipokines, such as leptin, adiponectin and resistin, are considered to be potential mediators of obesity in cancer development[16].

The most common definition of obesity is a body mass index (BMI) of 30 kg/m^2 or greater. A large number of studies have reported an association between high BMI and CRC. For example, a study conducted by the American Cancer Society[17] demonstrated that the relative risk (RR) of CRC death associated with high BMI (above 30 kg/m^2) was 1.75 for men and 1.25 for women compared to individuals with a BMI below 25 kg/m^2. The association between CRC risk and BMI is stronger for cancers located in the distal colon than in other locations[18]. BMI is also related to a higher risk of colon polyps or adenomas especially in the male population[19]. The results of a large meta-analysis, including 70000 CRC cases, also indicate that obesity is directly and independently associated with CRC[20]. Individuals with a BMI $\geqslant$ 30 kg/m^2 have a approximately 20% greater risk of developing CRC than individuals of normal weight (BMI < 25 kg/m^2). For every 2 kg/m^2 increase in BMI, the risk of developing CRC increased by 7%. Similarly, a 2-cm increase in waist circumference, a measure of central obesity, was associated with a 4% greater risk of CRC. These findings are similar to the results of another prospective meta-analysis conducted by Larsson in 2007[21]. Those data also indicated a sex difference in the strength of the association; the risk of developing CRC was 30% higher in obese men than in obese women. A recent systematic review by Ning *et al*[22]. found predominantly positive associations in the studies with an average RR for CRC of 1.18 (95%CI: 1.14-1.21) with a 5 unit higher BMI. The association was significantly (P = 0.02) stronger for colon cancer (RR = 1.21, 95%CI: 1.17-1.26) than for rectal cancer (RR = 1.11, 95%CI: 1.06-1.16). The association was significantly (P = 0.001) stronger in men (RR = 1.25, 95%CI: 1.2-1.3) than in women (RR = 1.12, 95%CI: 1.06-1.16).

The reason for a sex difference in the association between obesity and CRC may be partly explained by different hormonal levels (especially estrogen) in women. The Women's Health Initiative Estrogen Plus Progestin trial suggested that hormone replacement therapy reduced invasive CRC incidence by 44%[23]. However, a follow-up study of women using estrogen alone did not reveal a reduction in CRC incidence[24].

Another reason for a sex difference may be the differential distribution of adipose tissue. Several studies have demonstrated that central obesity is an independent risk factor of colorectal neoplasia and represents a higher risk factor for CRC than BMI[25]. Adipose tissue distribution can be assessed by the measurement of waist and hip circumferences. Current guidelines suggest a waist circumference of 102 cm in men and 88 cm in women as being the cut-off points for abdominal obesity that is associated with an increased risk of morbidity. Findings from the European Prospective Investigation into Cancer and Nutrition indicated that central (abdominal) obesity is an equally strong risk factor for CRC in both genders, whereas body weight and BMI are associated with CRC risk in men but not in women[26]. The adipose tissue distribution (waist circumference or waist-to-hip ratio) was more associated with CRC risk than BMI[27].

IMPAIRED GLUCOSE TOLERANCE AND COLORECTAL NEOPLASIA

Glucose intolerance or an elevated serum concentration of insulin is thought to be a risk factor for the development of CRC[28]. This association is based on the hypothesis that hyperinsulinemia promotes colon carcinogenesis. Insulin resistance leads to a compensatory increase in insulin secretion, and this hyperinsulinemia may lead to increased levels of free insulin-like growth factor-1, an antiapoptotic and mitogenic factor that decreases cell death and enhances cell growth[29]. Prospective epidemiological evidence has shown that hyperactivation of the insulin pathway leads to colon cancerogenesis by mitogenic and pro-angiogenic proliferation[30]. According to the Netherland observational population-based cohort study, type 2 diabetes was associated with a moderately increased risk of CRC[4]. Similarly, a large ten-year prospective cohort study in Korea found that serum glucose concentration was strongly associated with colon cancer[31]. Yuhara *et al*[32] reported a significantly higher risk of colon cancer in diabetes patients (RR = 1.38, 95%CI: 1.26-1.51) compared to controls.

A recent Italian meta-analysis shows a 29% increased risk for CRC among individuals with dysglycemia, a condition including states of impaired fasting glucose and impaired glucose tolerance, or overt diabetes mellitus type 2[27]. Another meta-analysis[33] of 29 eligible studies confirmed these estimates indicating an increased risk of CRC in type 2 diabetes (RR = 1.29 for men and 1.34 for women).

DYSLIPIDEMIA AND COLORECTAL NEOPLASIA

The mechanism by which hypertriglyceridemia promotes CRC is unknown. One of the hypotheses cites the effect of secondary bile salts in the colon. Bile salts are increased in patients with high fat intake. An increase of secondary bile salts in the colon may have a carcinogenic effect on the colonocytes[34].

The results of studies that have examined the association between serum triglyceride and HDL-cholesterol, components of MS, and the risk of CRC are inconsistent[35,36]. Some recent prospective studies reported a significant association between high triglyceride levels and colon cancer in men[37] or rectal cancer in both sexes[38]. In a European case-control study, high concentrations of serum HDL were associated with a decreased risk of colon, but not rectal, cancer[39]. The European Prospective case control study with a cohort of more than 520000 participants from 10 western European countries showed that high concentrations of serum HDL are associated with a decreased risk of colon cancer[39]. However, the most recent Italian meta-analysis found nonsignificant or borderline positive associations between higher values of serum triglycerides and lower values of HDL cholesterol and CRC risk[27]. Currently, the finding of an association between colorectal adenoma formation and hypertriacylglyceridemia seems more robust than for CRC[40].

HYPERTENSION AND COLORECTAL NEOPLASIA

Few studies have examined the association between hypertension and the risk of CRC. In some studies, hypertension was found to be a predictor for colorectal adenoma formation[41], but other studies reported conflicting findings[25]. Ahmed *et al*[42] assessed the data from a multi-center prospective cohort study. Hypertensive patients were found to have a 35% greater incidence of CRC compared to normotensive patients. However, these findings were not confirmed by a large Finnish study of male smokers that found no association between hypertension and CRC[43]. A recent retrospective study from Taiwan observed that hypertension was a key predictor for recurrent colorectal adenoma[44]. Interestingly, in a Japanese prospective study, the use of antihypertensive drugs was found to be a potential risk factor for the formation of colorectal polyps[45]. This risk increased with the greater use of antihypertensive drugs. Nevertheless, the current general consensus is that hypertension does not contribute to an increased risk of developing CRC[40].

CARDIOVASCULAR RISK AND COLORECTAL NEOPLASIA

With regards to the burden of cardiovascular and cancer morbidity, respective mortality, the same risk factors were identified and the same regimen recommendations were formulated, including the principles of healthy nutrition, physical exercise regimen, and quitting smoking and harmful alcohol consumption[46]. Based upon our current knowledge and experience, the assumption may be expressed that the higher risk of cardiovascular mortality also accompanies a higher risk of cancers, particularly CRC[47]. Chan *et al*[48] have shown a strong association between colorectal neoplasia and overt coronary heart disease (CHD). They have found that the prevalence of colorectal neoplasia was greater in patients with CHD in a population undergoing coronary angiography. Yang *et al*[47] have found that the prevalence of colorectal neoplasia was greater in subjects with low-grade coronary atherosclerosis or significant CHD detected by coronary computed tomography angiography. Individuals with overt CHD are burdened with an increased risk of complications in endoscopic examination due to anticoagulation therapy and comorbidities. For targeted screening, it is important to identify individuals who are at high risk of CHD. However, in the literature, there is a lack of information on the risk of colorectal neoplasia in patients who are at a high risk of developing CHD. Lee *et al*[49] have assessed the prevalence of colorectal neoplasia in South Korean patients who are at high risk for CHD by considering their Framingham risk score (FRS). They found an increased prevalence of advanced colorectal neoplasia in subjects with a high FRS $\geqslant$ 10%. Similar results came from a cross-sectional study from Turkey[50], whose authors showed a significantly increased risk for colorectal neoplasia in patients who were at a high risk for CHD determined by ultrasound measurements of carotid intima media thickness ($\geqslant$ 1.0 mm), flow-mediated dilation (< 10%) and calculated FRS (> 20%). According to these results, screening for CRC may be recommended for individuals who are at a high risk of developing CHD.

MS AND COLORECTAL NEOPLASIA

There is epidemiologic evidence to support the claim that subjects with MS are at increased risk of developing CRC. Obesity and hyperglycemia are key components of MS and CRC. According to these results, it appears that MS is also associated with a higher incidence of adenomas. This fact is especially important in CRC screening when identifying individuals at a higher risk for CRC in the general population. However, there are few studies demonstrating any association between MS and the risk of colorectal adenomas in European countries[26,27,51]. In the Portuguese prospective study, MS was associated with an increased prevalence of adenomas (43% *vs* 25%, $P = 0.004$) and CRC (13% *vs* 5%, $P = 0.027$), compared to patients without MS[51]. The literature conclusions suggest that different components of the MS have an additive effect on the development of CRC by acting through a variety of pathophysiologic pathways[41]. However, an Italian meta-analysis that evaluated the influence of individual components of the MS observed that the increased risk of CRC was not greater than the sum of its parts, while the most common risk factors

Table 1 Asia-Pacific Colorectal Screening scoring system (adapted from Wang *et al*[53])

Risk factor	Criterion	Point
Age (yr)	< 50	0
	50-69	1
	⩾ 70	2
Gender	Female	0
	Male	1
Immediate family member with colorectal cancer	No	0
	Yes	1
Smoking status	No smoking history	0
	Current or former smoker	1

Table 2 Risk score for advanced neoplasia (adapted from Segnan *et al*[11])

Risk factor	Category	Point
Age (yr)	40-49	0
	50-54	1
	55-59	2
	60-66	3
	> 66	3
Sex	Female	0
	Male	2
Family history	None	0
	1 first-degree relative ⩾ 60 years old	1
	1 first-degree relative < 60 years old	2
	2 first-degree relatives	2
Smoking, pack years	None	0
	< 10	0
	10-19	1
	⩾ 20	1
Body mass index (kg/m^2)	< 25	0
	25-29	0
	⩾ 30	1 - Female 0 - Male

associated with MS were dysglycemia and/or high waist (⩾ 88 cm in women and ⩾ 102 cm in men)[27].

ASIA-PACIFIC COLORECTAL SCREENING SCORING SYSTEM

One possibility for improving the effectiveness of screening for CRC can be observed in the scoring of the likelihood of colorectal neoplasia in the target population. In 2011, the Asia-Pacific working group for CRC screening developed the Asia-Pacific colorectal screening scoring system (APCS)[52]. They conducted a prospective, cross-sectional and multi-center study of tertiary hospitals in 11 Asian cities, including 2752 asymptomatic individuals who underwent a screening colonoscopy. The main objective was to determine the clinical risk score predictive of colorectal advanced neoplasia in Asian asymptomatic individuals to prioritize CRC screening. The APCS scoring system uses the age, gender, family history of CRC, and smoking history to calculate the scores (Table 1). Individuals are categorized into three groups according to these scores: The (AR = 0-1), moderate-risk (MR = 2-3), and (HR = 4-7) groups. In this study, patients in the MR and HR groups had a 2.6-fold (95%CI: 1.1-6.0) and 4.3-fold (95%CI: 1.8-10.3) higher rate of advanced neoplasia, respectively, than patients in the AR group. Therefore, a screening colonoscopy is recommended for Asian individuals in the HR group. The use of the APCS scoring system was further modified in the Chinese prospective study[53]. They assessed the utility of the APCS system and the presence of MS components and found that in cases with obesity, the colorectal tumor detection rate significantly increased (59.5% *vs* 19.2% for the MR/HR group without obesity, $P < 0.01$). Utilization of the APCS scoring system in the Western population was examined in an Australian study by Corte *et al*[54]. APCS predicts the colonic findings in a Western population to a greater extent than in Asians, independent of the symptoms.

EUROPEAN COLORECTAL SCREENING SCORING SYSTEM

The risk score for predicting advanced neoplasia in Caucasian individuals developed by Kaminski *et al*[12] was established based upon a cross-sectional analysis of database records for patients aged 40-66 who entered a national primary colonoscopy-based CRC screening program in Poland in the year 2007. Candidate predictors of advanced neoplasia were obtained using a questionnaire and included age, sex, BMI, family history of CRC in first-degree relatives, diabetes, smoking history and aspirin use. The authors showed that independent risk factors for advanced colorectal neoplasia were age, sex, family history of CRC, cigarette smoking ($P < 0.001$ for these four factors), and BMI ($P = 0.033$). Based on these results they developed a scoring system that estimated the probability of detecting advanced neoplasia in the validation set, from 1.32% for patients scoring a 0 to 19.12% for patients scoring a 7-8 (Table 2).

However, a recently published Canadian work showed that the risk index for advanced neoplasia using age, sex, family history of CRC, smoking history and BMI, as derived by Ruco *et al*[55], was less predictive of advanced neoplasia in the population of screening age in North America.

CZECH PILOT STUDY

To study the relationship between metabolic risk and colorectal neoplasia, a multi-center prospective study was performed in the Czech Republic from 2012-2015. Eight endoscopy centers, 32 general practitioners and 24 diabetology practices participated in this project. All data were collected and analyzed by the Institute of Biostatistics and Analyses of Masaryk University in Brno.

Table 3 Comparison of non-advanced adenoma and colorectal neoplasia in the target and control groups

	Target group (n = 726)	Control group (n = 774)	OR, 95%CI (P value)[1]
Adenoma, n	346	270	1.2, 0.9-1.5
(%, 95%CI)	(48%, 44%-51%)	(35%, 32%-38%)	(0.18)
Advanced adenoma, n	131	66	1.8, 1.2-2.5
(%, 95%CI)	(18%, 15%-21%)	(9%, 7%-11%)	(< 0.01)
Cancer, n	11	11	0.7, 0.3-1.6
(%, 95%CI)	(2%, 1%-3%)	(1%, 1%-3%)	(0.35)

[1]Adjusted comparison by logistic regression - including age, sex and previous FIT+ (fecal immunochemical test positivity).

The inclusion criteria were as follows: Asymptomatic individuals aged 45-75 years, individuals with an average risk of colorectal neoplasia (no personal or family medical history of colorectal neoplasia, no CRC symptoms, such as weight loss, enterorrhagia, or anemia), individuals scheduled for preventive (FOBT positive colonoscopy) or individuals aged 55 years or older (screening colonoscopy). The patients with a high risk of colorectal neoplasia (patients with familial hereditary syndromes of CRC or polyposis) were excluded.

Before the colonoscopy, blood samples were taken (complete blood count, coagulation, biochemical analyses including glucose, and lipid profile). After the colonoscopy, the anthropometric (weight, height, and waistline) and blood-pressure measurements were obtained, and the patients filled in a questionnaire about their personal and family medical history, lifestyle, medication and details of their FOBT examination (if performed).

Based on the collected data, the individuals were divided into a target group (patients with diabetes mellitus type 2 and/or cardiovascular risk) and a control group. The diagnosis of diabetes mellitus type 2 was assessed by glucose and glycated hemoglobin serum levels and confirmed by the oral glucose tolerance test. Cardiovascular risk was determined according to the SCORE project (Systematic COronary Risk Evaluation)[56], based on four criteria: Sex, smoking habits, systolic blood pressure and serum cholesterol level. Patients with a SCORE level > 10 were included in the target group.

Colonoscopy examinations were performed mainly under conscious sedation after regular bowel cleansing. Colorectal neoplasia was defined based upon the presence of advanced adenomatous polyps (size > 10 mm and/or presence of villous component and/or high grade dysplasia) or cancer.

In this study, 2071 individuals were enrolled, and the first statistical analysis of 1500 records has already been completed. The main aim of the analyses was to compare the prevalence of colorectal neoplasia and non-advanced adenomatous polyps (adenomas) in both groups.

As the main finding, a significantly higher prevalence of advanced adenomas was observed in the target group (18%, 95%CI: 15%-21%) compared to the control group (9%, 95%CI: 7%-11%); the OR was 1.8, and P = 0.002.

Similarly, the prevalence of all adenomas was higher in the target group (48%, 95%CI: 44%-51%) than in the control group (35%, 95%CI: 32%-38%); the OR was 1.2, but the difference was not statistically significant (P = 0.179). The prevalence of cancer was the same in both groups. Complete results are stated in Table 3.

Another aim of this study was to identify individuals who are considered to be at an average risk of developing colorectal neoplasia according to the current Czech guidelines, but because of their metabolic risk, should be managed similarly to patients at high risk of colorectal neoplasia (patients with a personal history of colonic neoplasia, *etc.*). A more comprehensive multivariate analysis, similar to that in the Polish study[12], is planned once the data from all individuals are available.

As a first step towards this goal, a more detailed evaluation of the target group has already been performed by dividing the target group into three groups: Diabetes mellitus type 2 only; cardiovascular risk only; and a combination of these two risk factors. It appears that the individuals with cardiovascular risk only had a higher prevalence of both non-advanced adenomas (51%, 95%CI: 46%-56%, P = 0.327) and advanced adenomas (22%, 95%CI: 18%-26%, P = 0.049), compared to the other two groups (Table 4). Advanced adenomas were more likely in patients aged 65-75 years. This finding is in agreement with results of the work of Brenner *et al*[57], which has shown that age is the most important risk factor for CRC.

As a conclusion of these preliminary results, individualized CRC screening should be considered in individuals aged 65-75 years with a SCORE $\geqslant$ 10.

CONCLUSION

The MS shows increasing prevalence worldwide. It has been shown that the strongest risk factors are central obesity and hyperglycemia in relation to CRC. Furthermore, cardiovascular risk is directly associated with the risk of colorectal neoplasia.

These observations should be reflected in future

Table 4 Prevalence of non-advanced adenoma and colorectal neoplasia within the target group

	Combination of DM2 and SCORE ⩾ 10 (n = 157)	SCORE ⩾ 10 (n = 413)	DM2 (n = 156)	P value[1]
Adenoma, n	69	211	66	0.33
(%, 95%CI)	(44%, 36%-52%)	(51%, 46%-56%)	(42%, 34%-50%)	
Advanced adenoma, n	25	89	17	< 0.05
(%, 95%CI)	(16%, 11%-23%)	(22%, 18%-26%)	(11%, 6%-17%)	
Cancer, n	3	5	3	0.56
(%, 95%CI)	(2%, 0%-5%)	(1%, 0%-3%)	(2%, 0%-6%)	

[1]P value was obtained using a likelihood ratio test. The comparison models were adjusted for age, sex and previous FIT+ (fecal immunochemical test positivity). DM2: Type 2 diabetes mellitus; SCORE: Systematic COronary Risk Evaluation.

preventive strategies. While preventing and controlling the components of the MS could be important for the prevention of CRC, patients with the MS (including high cardiovascular risk) would probably benefit from tailored CRC screening.

A modified APCS scoring system and Risk Score for advanced neoplasia formulated by the Polish group can aid in identifying CRC HR subgroups in the general population.

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