RESEARCH ARTICLE

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Adult Height as a Risk Factor for Developing Colorectal Cancer: A Population-Based Cohort Study in Thailand

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Abstract

Background: Previous studies have shown that a taller stature has a higher risk of colorectal cancer (CRC) than a shorter stature. However, most prior studies were conducted in the Western region, with few studies and inconsistent results for Asians. To our best knowledge, no previous research has investigated the population of ASEAN countries, which is generally shorter in stature than the Western population. We aimed to examine the association between adult height and CRC risk in a Thai population. **Methods:** This population-based cohort study was conducted in Khon Kaen, Thailand. Overall, 118 patients with CRC were histologically confirmed among 14,418 participants, who were recruited during 1990–2001 and followed up until December 31, 2020. A structured questionnaire was used to obtain baseline data, including demographic and environmental variables. The exposure of interest was measured in height and defined on the basis of the last recorded measurement. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using Cox proportional hazard regression analysis. **Results:** Over a median of 21.7 years of follow-up (interquartile range: 19.9–25.6), 14,418 participants provided a total observation time of 303,899 person-years. The risk of CRC at the highest compared to the lowest height quintile was 1.29 (95% CI, 0.76–2.20; p=0.350). A trend similar to a U shape was observed (HR in Q1 vs. Q2=1.05; 95% CI, 0.62–1.75; Q1 vs. Q3=0.78; 95% CI, 0.43–1.39; Q1 vs. Q4=0.55; 95% CI, 0.29–1.05; and Q1 vs. Q5=1.29; 95% CI, 0.76–2.20). **Conclusions:** Although adult height was not statistically significant, its magnitude still indicated some clues to investigate as evidence, especially for people living in the context of ASEAN countries. Large-scale, comparable studies in such contexts should be considered for confirmation.

Keywords: Colorectal cancer- height- cohort study-Thailand

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Introduction

Colorectal cancer (CRC) constitutes more than 1.9 million new cases worldwide. It remains the third most frequently diagnosed cancer and is the second leading cause of cancer death (Sung et al., 2021). In Asia, CRC had the highest proportions of both incidents and mortality cases (52.3% and 54.2%, respectively) worldwide. There has been a growing trend in this disease across Asia, with some regional geographical variations (Onyoh et al., 2019). In Thailand, CRC is the fourth most common type of cancer (age-standardized incidence rate [ASR]=16.9 per 100,000) (Ferlay et al., 2020). Most patients with CRC in Thailand have adenocarcinomas (67.3%) and present at an advanced stage with a poor prognosis (38.8% with TNM stage 4) (Phiphatpatthamaamphan and Vilaichone, 2016). ASRs for CRC have gradually increased in the northeast region of Thailand. Trends in all age groups were found to be increasing in both sexes (Sarakarn et al., 2017). To spot cancer early, prevention and early detection procedures are needed, especially among populations at higher risk for CRC.

Approximately 70% of CRC cases are influenced by modifiable factors, including dietary habits, exercise, cigarette smoking, and alcohol consumption. Approximately 30% of CRC cases have a genetic predisposition and inherited factors associated with its development (Wong et al., 2019). Risk factor modification may reduce long-term CRC risk, particularly among individuals at higher baseline risk due to non-modifiable factors (Wang et al., 2019). Obesity is a modifiable risk factor that has been linked to the most relevant cancers, including CRC (Xue et al., 2017; Fang et al., 2018; Rim et al., 2019). However, previous studies in Thailand that determined the risk of obesity (measured by body mass index [BMI]) and CRC have inconsistent results with

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studies from other Western countries (Sriamporn et al., 2007; Soonklang et al., 2018). BMI is a well-known anthropomorphic index of weight for height that is commonly used to classify overweight and obesity in adults. Although the association between BMI and cancer has been widely evaluated, the effect of height on cancer risk has received far less attention. Furthermore, because BMI is also correlated with height, there is a need to explore the relationship between adult height and cancer, independent of weight.

To date, many epidemiological studies have investigated the role of height in the development of many diseases. It has been suggested that environmental factors acting early in life play a vital role in the pathogenesis of diseases in adulthood (Sallout and Walker, 2003). Height is another commonly used proxy for several genetic and environmental exposures in early life, such as socioeconomic status, energy intake, and growth factor levels, which may affect cancer risk later in life (Cecil et al., 2005; Turan et al., 2007). Many studies have reported that height is associated with an increased risk of cancers at various sites, including the breast, lung, colon, and rectum (Jiang et al., 2015; Khankari et al., 2016; Zhao et al., 2019); the results were inconsistent according to sex or smoking (Walter et al., 2013; Abar et al., 2018; Benyi et al., 2019). Although the mechanisms of height in carcinogenesis remain unknown, one possible mechanism might be higher insulin-like growth factor 1 (IGF-1) levels that promote cell proliferation and inhibit apoptosis. Several studies have shown that patients with acromegaly, a chronic disease caused by the excessive secretion of growth hormone and as a result of IGF-1, have a significantly increased risk of CRC (Rokkas et al., 2008; Dworakowska and Grossman, 2019). The IGF-1 concentration is also associated with both growth during childhood and a higher risk for prostate cancer, breast cancer, and CRC (Renehan et al., 2004; Gu et al., 2010; Vigneri et al., 2015).

Recent evidence has shown a positive association between height and risk of CRC (Song et al., 2018). However, most prior studies were conducted in the Western region, with few studies and inconsistent results in Asian people (Shimizu et al., 2003; Otani et al., 2005; Choi et al., 2019). To our best knowledge, no previous research has investigated the population of ASEAN countries, including Thailand, which is generally shorter in stature than the Western population. As risk factors in Asia are slightly different from those in Western countries, targeted screening based on individual risk seems to be a cost-effective approach in our country, where colonoscopy resources are limited. In addition, most researchers have evaluated the overall cancer risk and were thus unable to adjust for CRC-specific risk factors. The results that included a controlled possible confounder were examined in a limited number of studies. Based on this background, the present study is the first of its kind in Thailand with the aim of determining the association between adult height and CRC using Cox proportional hazard regression analysis of the Khon Kaen Cohort Study (KKCS). Our findings may help categorize people with different heights into various screening approaches.

Materials and Methods

Study design

An analytical study of data from a cohort study, the KKCS, was established in 1990–2001. During this period, participants aged 30 to 70 years living in Khon Kaen province were invited to join the KKCS; the study design has been published elsewhere (Sriamporn et al., 2005). From a total of 19,861 participants, we excluded participants who were previous CRC, as were those without documented height at baseline. Within the cohort, there were 14,418 participants with complete data on height, and the analysis was performed based on this number.

Data were collected at baseline using structured questionnaires and medical records. Baseline questionnaires included demographic characteristics, health-related lifestyle habits (e.g., cigarette smoking and alcohol consumption), and family history of cancer. Anthropic variables, including weight and height, were also measured. The exposure of interest was height, measured by a health professional and defined on the basis of the last recorded measurement. The mean body height (standard deviation) of the participants was 155.6 (6.9). The participants were divided into deciles of height for each sex. The deciles from the different sex groups were merged into new quintiles based on height at baseline. All cohort participants were followed up until the end of the study on December 31, 2020. All data of the KKCS participants were linked to the Khon Kaen Cancer Registry using the RECLINK program to identify patients with a diagnosis of CRC. For the outcome, all CRC diagnoses were histologically confirmed, which was defined using the International Classification of Diseases for Oncology codes from C18.0 for the cecum to C20.9 for the rectum, and the date of diagnosis was obtained from medical records. Person-time was computed from the date of recruitment to the database, date of diagnosis, date of loss to follow-up or withdrawal, and date at the end of the study.

Statistical analysis

Demographic characteristics of the participants are described using frequency and percentage for categorical data and mean and standard deviation (SD) for continuous data. Adjusted hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were estimated using Cox proportional hazard regression analysis for the CRC incidence in relation to adult height. The proportional hazards assumption was investigated using double cumulative hazard plots and Schoenfeld residuals (not shown). There was no indication of a violation of the proportional hazard assumption for the height analysis. This analysis was adjusted for baseline variables that were considered biologically and sociologically relevant or showing a univariate relationship with outcomes. Backward elimination was used to develop the final model. The following variables were considered as potential confounders: age, sex, obesity, family history of cancer, smoking status, and drinking status. The linearity of the association between continuous covariates and incident

CRC was also assessed. All test statistics were two-sided, and a p-value <0.05 was considered statistically significant. All analyses were conducted using STATA version 15.0 (StataCorp., 2017).

Results

The 14,418 participants provided a total observation time of 303,899 person-years; there were 118 cases of histologically confirmed CRC among the 9,715 female and 4,585 male cohort members (Figure 1). The baseline characteristics of the study participants are summarized in Table 1. Most participants were female (67.9%) with a mean (SD) age of 50.9 (8.4) years (range: 30–70). In addition, they were mainly married (81.9%), had a primary education or lower (93.2%), were employed (87.1%), never smoked (73.5%), never consumed alcohol (60.4%), had no family history of cancer (74.8%), and had a normal body mass index (58.5%). According to the height quintile classification, 2,491 participants (17.3%) had the highest height quintile.

Over a median of 21.7 years of follow-up (interquartile range: 19.9–25.6) and a total of 303,899 person-years of follow-up, 118 cases of CRC were identified, including 71 in the colon and 47 in the rectum. Bivariate analysis identified sex, age at enrollment, cigarette smoking, and family history of cancer as significantly associated with CRC risk. The crude HR for CRC associated with every 10-cm increase in height was 1.18 (95% CI, 0.91–1.53; p=0.215). Adult height was found to have a 16% increased risk of CRC in the tallest group, but the difference was not significant (HR=1.16; 95% CI, 0.68–1.97). The demographic variables and adult height associated with CRC at the bivariate level are presented in Table 2.

Multivariate analysis demonstrated the association between height and CRC risk as quintiles (Table 3). The adjusted HR for CRC when comparing the highest height quintile to the lowest height quintile was 1.29 (95% CI, 0.76–2.20; p=0.350). A trend similar to a U shape was observed (HR in Q1 versus [vs.] Q2=1.05; 95% CI, 0.62–1.75; Q1 vs. Q3=0.78; 95% CI, 0.43–1.39; Q1 vs. Q4=0.55; 95% CI, 0.29–1.05; and Q1 vs. Q5=1.29; 95% CI, 0.76–2.20). We further evaluated whether the association between CRC risk and height varied according to sex (Table S1). The association between height and CRC risk in the tallest group was more pronounced among men than among women (adjusted HRs 1.53 and 1.15, respectively), but this was not statistically significant (Figure 2).

Discussion

Based on the KKCS, with a median of 21.7 years of follow-up, the present study is the first population-based cohort study of the association between adult height and CRC risk in Thailand. Our results showed that adult height was associated with a 29% increased risk of CRC in the tallest group compared with the shortest group, but the difference was not statistically significant.

The slightly higher risk in our cohort is similar to findings from other studies (Bowers et al., 2006; Hughes et al., 2011), including those conducted among Asian populations in Japan. In a cohort study of 102,949 middle-aged and elderly Japanese individuals, CRC

Table 1. Demographic Characteristics of the Participants (n=14,418)

Variable	Number	%
Sex		
Female	9,785	67.9
Male	4,633	32.1
Age at enrollment (years)		
30–39	1,451	10
40–49	4,939	34.3
50–59	5,410	37.5
≥60	2,618	18.2
Mean (standard deviation)	50.9 (8.4)	
Median (max:min)	51 (70:30)	
Marital status (missing, 3.1%)		
Married	11,808	81.9
Divorced/Widowed/Separated	1,835	12.7
Single	324	2.3
Education (missing, 2.2%)		
Primary or lower	13,432	93.2
Secondary or higher	660	4.6
Occupation (missing, 8.2%)		
Employed	12,552	87.1
Unemployed	679	4.7
Cigarette smoker		
Never	10,596	73.5
Current or former	3,822	26.5
Alcohol drinker		
Never	8,715	60.4
Current or former	5,703	39.6
Family history of cancer		
No	10,781	74.8
Yes	3,637	25.2
Body mass index (kg/m^2) missing, 0.1%		
Underweight (<18.5)	957	6.7
Normal (18.5–24.9)	8430	58.5
Overweight (25.0–29.9)	4069	28.2
Obese (≥ 30.0)	942	6.5
Mean (standard deviation)	23.8 (3.9)	
Median (max:min)	23.4 (46.4:13.0)	
Height		
1st quintile	3,105	21.5
2nd quintile	3,162	21.9
3rd quintile	2,840	19.7
4th quintile	2,820	19.6
5th quintile	2,491	17.3
Mean (standard deviation)	155.6 (6.9)	
Median (max:min)	155 (178:139)	

Max, maximum; min, minimum.

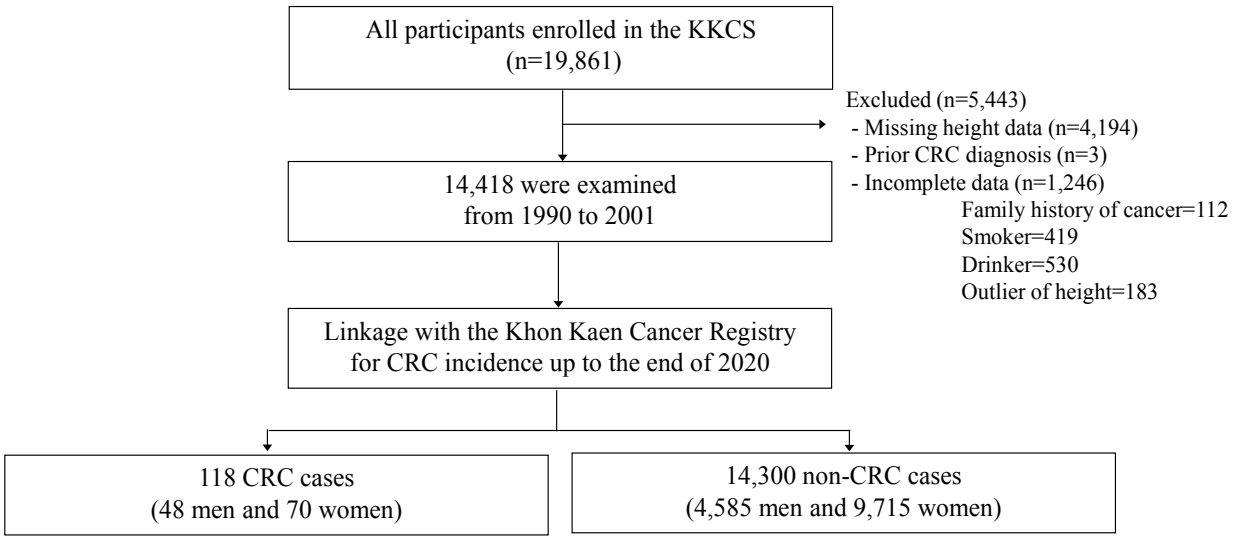

Figure 1. Flow Diagram of the Retrospective Cohort Study and CRC Outcome. CRC, colorectal cancer; KKCS, Khon Kaen Cohort Study.

developed in 986 relatives during the 9.4-year follow-up period. They found no significant association with increased CRC risk in taller stature (men: HR=1.3; 95% CI, 0.8–1.9, women: HR=1.3; 95% CI, 0.7–2.2) (Otani et al., 2005). In contrast, another study reported a positive association between adult height and CRC risk. In an

Table 2. Bivariate Analysis of the Factors Associated with CRC

Factor	No. of participants (n=14,418)	CRC cases	Person-years	IR/1,000	Crude HR	95% CI	p-value
Sex							0.020
Female	9,785	70	209,910	0.33	1		
Male	4,633	48	93,989	0.51	1.55	1.07–2.24	
Age at enrollment (years)							0.003
30–39	1,451	8	36,350	0.22	1		
40–49	4,939	31	110,888	0.28	1.25	0.58–2.73	
50–59	5,410	56	109,177	0.51	2.31	1.10–4.87	
≥60	2,618	23	47,484	0.48	2.23	0.99–5.00	
Cigarette smoker							0.010
Never	10,596	76	226,864	0.34	1		
Current or former	3,822	42	77,035	0.55	1.65	1.13–2.40	
Alcohol drinker							0.887
Never	8,715	71	185,217	0.38	1		
Current or former	5,703	47	118,682	0.4	1.03	0.71–1.49	
Family history of cancer							0.042
No	10,781	77	222,799	0.35	1		
Yes	3,637	41	81,100	0.51	1.48	1.02–2.17	
Body mass index (kg/m^2)							0.880
<25.0	9,387	78	199,114	0.39	1		
≥25.0	5,011	40	104,354	0.38	0.97	0.66–1.42	
Height							0.616
1st quintile	3,106	28	63,961	0.44	1		
2nd quintile	3,163	30	65,670	0.46	1.04	0.62–1.74	
3rd quintile	2,838	19	60,543	0.31	0.72	0.40–1.28	
4th quintile	2,821	14	60,549	0.23	0.53	0.28–1.00	
5th quintile	2,490	27	53,176	0.51	1.16	0.68–1.97	
Each 10-cm increase	14,418	118	303,899	0.39	1.18	0.91–1.53	0.215

CRC, colorectal cancer; No., number; IR, incidence rate; HR, hazard ratio; CI, confidence interval.

Table 3. Adult Height and Risk of Colorectal Cancer

Height	No. of cases	Person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)[a]	p-value
1st quintile	28	63,961	1	1	
2nd quintile	30	65,670	1.05 (0.63–1.76)	1.05 (0.62–1.75)	0.864
3rd quintile	19	60,543	0.78 (0.44–1.40)	0.78 (0.43–1.39)	0.396
4th quintile	14	60,549	0.56 (0.29–1.07)	0.55 (0.29–1.05)	0.070
5th quintile	27	53,176	1.31 (0.77–2.24)	1.29 (0.76–2.20)	0.350

[a] Adjusted for age, sex, family history of cancer, cigarette smoking, and alcohol consumption; No., number; HR, hazard ratio; CI, confidence interval.

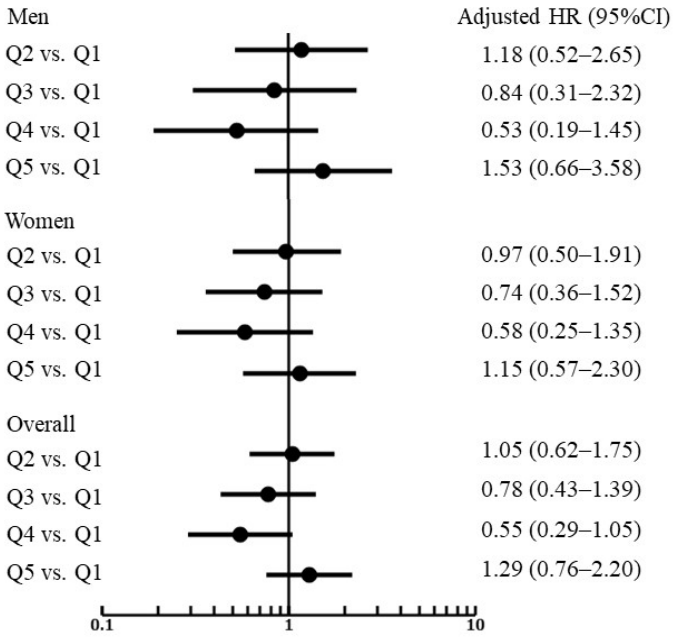

Figure 2. Forest Plot on a Log Scale of the Associations between Adult Height and Colorectal Cancer. HR and 95% CI were derived from Cox regression model adjusting for age, family history of cancer, cigarette smoking, and alcohol consumption. HR, hazard ratio; CI, confidence interval; Q1-Q5, quintile 1 (shortest)-quintile 5 (tallest); vs., versus

8-year cohort study of 29,051 Japanese participants, there were 295 cases of CRC, and the findings showed a positive relationship between height and colon cancer in men for the tallest compared with the shortest height tertile (risk ratio [RR]=2.13; 95% CI, 1.26–3.58) but not in women (RR=1.48; 95% CI, 0.81–2.70). This result suggests that the number of cancer cases might be too small to have meaningful analyses (Shimizu et al., 2003). Furthermore, the Netherlands Cohort Study of 120,852 men and women aged 55–69 years found that adult height was unrelated to CRC risk in men (HR=0.80; 95% CI, 0.60–1.08), but it was associated with a significant 32% increased risk of CRC in women (Hughes et al., 2011). However, several previous studies have reported that adult height is associated with the incidence of CRC (Green et al., 2011; Kabat et al., 2013; Boursi et al., 2014; Abar et al., 2018; Benyi et al., 2019). In the most recent large pooled analysis of 31 studies, height comparing the highest versus the lowest category was associated with a significant 18–32% increase in CRC risk (Song et al., 2018). In the Asian region, one study from Korea reported a positive association between height and the risk of CRC (HR=1.26; 95% CI, 1.24–1.28) (Choi et al., 2019). In contrast to recent studies that suggested a positive association between height and CRC, there is inconclusive evidence of a clear effect but possibly important results regarding height and the CRC incidence in Thai adults.

The lack of consistency in the past and present findings is difficult to explain but is probably due to differences between the populations studied, such as the average adult height, family history, and number of cases. This discrepancy might be because only 118 patients developed CRC, leading to the limited power of this study. Differences in the CRC incidence would partly explain this result: the incidence was only 0.4 per 1,000 person-years in our study versus >1.2 in previous studies (Choi et al., 2019). Moreover, body height may exhibit a nonlinear risk trend. Some studies have reported a significant association of a much greater height, over 170 cm (Ahn et al., 2009; Green et al., 2011; Boursi et al., 2014). In these studies, the shortest height category ranged at about 157 cm or less, while in our study, even the highest category was only 158 cm or more in women and 168 cm or more in men. It is also noteworthy that the risk pattern of adult height in terms of CRC risk may be a U-shaped relationship. A previous randomized clinical trial of 695 patients with metastatic CRC reported worse overall survival in patients who were shorter than 165 cm and taller than 179 cm. There was

no linear relationship between height and overall survival (McSkane et al., 2018). In addition, the differences in the magnitude of association in each subsite possibly leads to neutralization of the effect of body height on the colon and rectal cancer incidence (Wei et al., 2004; Demb et al., 2019; Murphy et al., 2019).

The strengths of this study include the cohort design targeting the community-dwelling Thai population, in combination with sufficient follow-up time to allow precise analysis of CRC risk. The study participants were selected from a general population, and the completeness of information on the CRC incidence was confirmed through verification using cancer registration. Additionally, information on height was measured by trained nurses and collected before the diagnosis of CRC, thus avoiding exposure recall bias. Nevertheless, our study had some limitations. First, our study had a small number of CRC cases and subsequently limited statistical power to further stratify data in multivariate analyses. In cases where the etiology or risk factors for CRC may vary by anatomic subsite, we could not explore the effect of adult height on colon and rectal cancer separately. Risk factors and high-risk populations for CRC in each subsite need to be studied further to guide actions to improve the efficacy of screening for CRC. Second, we could not exclude the possibility of other possible confounding factors, such as dietary habits (intake of red meat and fiber) and physical activity. However, we adjusted for generally considered lifestyle-related factors.

In conclusion, the risk of CRC may be associated with adult height. Our current study was based on a Thai population, which usually has a shorter average height than the Western population. Although our findings showed that adult height was not statistically significant, its magnitude still indicated some clues to investigate as evidence, especially for people living in the context of ASEAN countries. Therefore, large-scale, comparable studies in such contexts should be considered for confirmation.

Author Contribution Statement

JB is a principal investigator involved in conceptualization, methodology, formal analysis, writing-original draft preparation, and visualization. JC was involved in conceptualization, methodology, writing-review and editing, and supervision. KS was involved in conceptualization, methodology, resources, and data curation. CS provided resources, data curation, and formal analysis. PS is a supervisor involved in the conceptualization, methodology, statistical analyses, writing-review and editing of the manuscript.

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Ethical Statement

This study was 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 no.: HE641038, date: January 21, 2021).

Data Availability Statement

The datasets that supported the findings of this study are available from the corresponding author on reasonable request. The data are not publicly available since it contains information that can compromise the privacy of research participants.

Supplementary Materials

Supplementary Table S1 Cox proportional HRs and 95% CI for CRC incidence stratified by sex. Supplementary Table S2 STROBE Statement.

Conflicts of interest

The authors declare that there is no conflict of interest.

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