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Interactive effect of the empirical lifestyle index for insulin resistance with the common genetic susceptibility locus rs2423279 for colorectal cancer

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Abstract

The aim of this study is to examine the empirical insulinemic potential consisting of dietary and lifestyle factors and the interactive effect with the common genetic susceptibility locus rs2423279 on the risk of colorectal cancer (CRC). This case–control study was conducted with 923 CRC patients and 1846 controls. The empirical measures for assessing the insulinemic potential, namely, the empirical dietary index for hyperinsulinemia (EDIH), for insulin resistance (EDIR), the empirical lifestyle index for hyperinsulinemia (ELIH), and for insulin resistance (ELIR), were calculated based on semiquantitative food frequency questionnaire and lifestyle questionnaire. A genetic variant of rs2423279 was genotyped. The CRC patients were more likely to score in the highest quartile for the ELIH (OR 2·90, Q4 *v.* Q1, 95 % CI (2·01, 4·19), $P_{\text{for trend}} < 0{\cdot}001$), EDIR (OR 3·32, Q4 *v.* Q1, 95 % CI (2·32, 4·74), $P < 0{\cdot}001$) and ELIR (OR 2·79, Q4 *v.* Q1, 95 % CI (1·96, 3·97), $P < 0{\cdot}001$) than the controls. The significant effect between the ELIR, which assesses dietary and lifestyle patterns related to insulin resistance, and C allele carriers of rs2423279 was stronger than that for homozygous T allele carriers (OR 2·50, 95 % CI (1·78, 3·51), $P_{\text{for interaction}} = 0{\cdot}034$). The empirical insulinemic potential for insulin resistance might have interactive effects with the rs2423279 polymorphism on the risk of CRC. The results of this study suggest the basis of the metabolic impact of the insulin response on colorectal carcinogenesis.

Key words: Colorectal cancer: Empirical index of insulinemic potential: Insulin resistance: Common variant for colorectal cancer: rs2423279 polymorphism

Colorectal cancer (CRC) ranks among the highest for cancer incidence and mortality worldwide, accounting for over 1·9 million new cases and 935 000 deaths in 2020[1]. According to statistics in South Korea, the mortality and incidence rates of CRC are decreasing due to screening for early detection of CRC and the development of diagnosis and treatment methods[2,3]. However, the incidence of CRC is still ranked high in South Korea, and proactive prevention of risk factors is required. In a systematic literature review by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR), processed meat, alcohol consumption and obesity were listed as convincing factors that directly influenced the increased risk of CRC[4]. On the other hand, physical activity has been noted as a factor that decreases the risk of CRC. Overall, the prevention of CRC is predicted to be possible through the correction of these modifiable risk factors.

A previous study reported that the association between CRC and risk factors, including obesity, physical activity and a Western diet, is linked to the development of colorectal carcinogenesis associated with hyperinsulinemia and insulin

Abbreviations: CRC, colorectal cancer; EDIH, empirical dietary index for hyperinsulinemia; EDIR, empirical dietary index for insulin resistance; ELIH, empirical lifestyle index for hyperinsulinemia; ELIR, empirical lifestyle index for insulin resistance; IGF-1, insulin-like growth factor 1; MET, metabolic equivalent; SQFFQ, semi-quantitative food frequency questionnaire.

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resistance[5,6]. Insulin resistance refers to the reduced sensitivity of insulin-responsive cells, and compensative hyperinsulinemia gives rise to metabolic and energy imbalance. A current study has suggested potential synergistic and cumulative impacts among obesity-related insulin resistance or hyperinsulinemia, non-insulin-dependent diabetes mellitus (type 2 diabetes) and cancer risk[7]. Representing insulin indices derived from the whole diet, Tabung and Wang *et al.* investigated the following four empirical indices in accordance with the insulinemic potential composed of diet and lifestyle: the empirical dietary index for hyperinsulinemia (EDIH), empirical lifestyle index for hyperinsulinemia (ELIH), empirical dietary index for insulin resistance (EDIR) and empirical lifestyle index for insulin resistance (ELIR) to assess insulin resistance and hyperinsulinemia[8]. Given that cumulative evidence has suggested the mechanical linkages among the levels of insulin, obesity, diabetes mellites and colorectal carcinogenesis, it is worthwhile to explore the role of dietary and lifestyle insulinemic potential indices in the risk of CRC.

In terms of gene–environment interactions for the aetiology of CRC, genome-wide association studies have reported a number of SNP that identify CRC susceptibility loci[9]. Among twenty-six CRC susceptibility loci, SNP rs2423279 located on chromosome 20p12.3 was identified as a novel genetic polymorphism for CRC by genome-wide association studies in an East Asian population[10]. The SNP rs2423279, one of the common risk variants for CRC, is close to the hydroxyacid oxidase 1 (*HAO1*) and phospholipase C β 1 (*PLCB1*) genes, which are both protein-coding genes. Recent studies have reported that glyoxylate could be a marker for diagnosing diabetes[11,12]. Considering the association between diabetes mellitus and the risk of CRC, the SNP rs2423279, which is close to HAO1 and PLCB1, may alter the occurrence of colorectal carcinogenesis through the glyoxylate metabolism in individuals with diabetes. To investigate whether insulinemic resistance composed of modifiable risk factors affects colorectal carcinogenesis associated with the common genetic variant for CRC, it is necessary to demonstrate the effect of integrative linkages between the environmental risk factors related to insulin resistance and the CRC susceptibility locus.

Therefore, we evaluated the interactions between the insulinemic potential indices, which are based on not only dietary patterns but also lifestyle factors, and the rs2423279 SNP, which was identified as a common CRC susceptibility locus for CRC. The purpose of this study was to investigate the association between the empirical indices of insulinemic potential and CRC and whether this association with insulinemic potential, consisting of dietary and lifestyle factors, differs in individuals with the rs2423279 variant.

Materials and methods

Subjects and data collection

The current study is a case–control study initiated in October 2007 at the National Cancer Center. Newly diagnosed CRC patients were recruited at the Center for Colorectal Cancer between August 2010 and August 2013. Accordingly, 1070 patients pathologically confirmed by endoscopic biopsy agreed to participate in this study. As a control, 14 201 individuals were included who were not diagnosed with any types of cancer but who visited the Center for Cancer Prevention and Detection programme to receive health checkups between October 2007 and December 2014. All participants were interviewed to collect demographic and dietary information. Individuals reporting an incomplete semiquantitative food frequency questionnaire (SQFFQ) or general questionnaire with missing data (145 cases and 5044 controls) and those with an implausible energy intake of <500 kcal/day or > 4000 kcal/day (2 cases and 120 controls) were excluded. After frequency-matching of the 5-year age and sex groups (1 case was matched to 2 controls), the data for these analyses ultimately included a total of 2769 subjects (923 cases and 1846 controls) (Fig. 1). For the interaction analyses with a genetic variant, 2095 subjects (695 cases and 1400 controls) were considered due to missing genetic information among the rest of the participants (228 cases and 446 controls). All research participants provided written informed consent, and the Institutional Review Board of the National Cancer Center Korea approved the study (IRB No. NCC2021-0181).

Assessment of diet, anthropometry and physical activity

The dietary information was collected by a validated 106-item SQFFQ comprising the frequency (never or rarely, 1 time/month, 2–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, 1 time/day, 2 times/day and 3 times/day) and amount of food intake based on servings or portion sizes per food item[13]. The daily dietary intake of nutrients and energy were calculated from the SQFFQ data utilising the computer-aided nutritional analysis programme (CAN-PRO 4.0, Korean Nutrition Society). BMI was measured (weight in kilograms/height in square metres) from each participant's current weight and height by standardised equipment. A questionnaire was constructed and used to collect information related to not only sociodemographic factors but also the physical activity levels of the participants. To calculate metabolic equivalent (MET)-h/week of physical activity, the minutes per week spent on a variety of light, moderate and vigorous activities were estimated based on subjects' reports.

Calculation of the empirical indices for assessing insulinemic potential

The recorded food items derived from the SQFFQ were used to estimate four types of empirical indices for insulinemic potential including the EDIH, ELIH, EDIR and ELIR scores. To calculate the empirical indices for insulinemic potential, we used a validated method developed by *Giovannucci et al.* as described elsewhere[8]. Each of the empirical indices is composed of available parameters from the food items and lifestyle factors to calculate the score as follows: (1) the EDIH score includes fifteen parameters with red meat, processed meat, margarine, poultry, butter, fish and other sea food, high-energy beverages, tomatoes, low-fat dairy products and eggs (positive associations), and wine, coffee, whole fruits, high-fat dairy products and green leafy

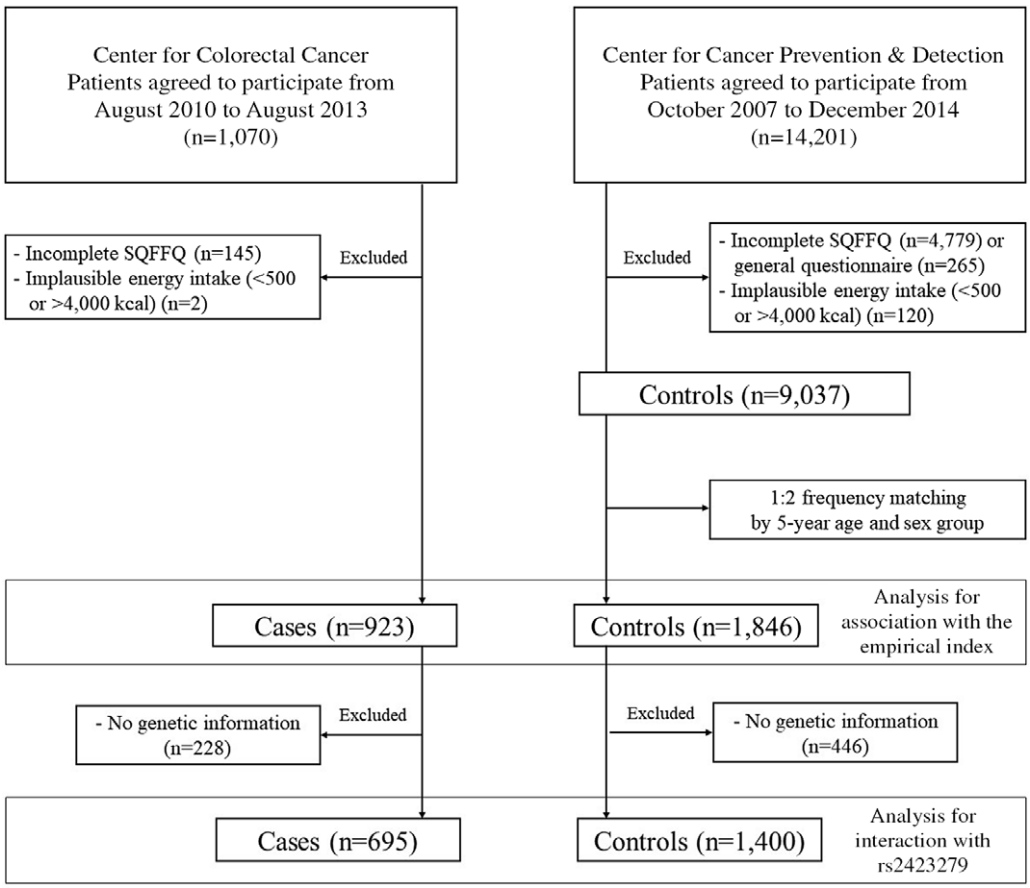

Fig. 1. Flow chart of study subjects. SQFFQ, Semiquantitative Food Frequency Questionnaire.

vegetables (inverse associations); (2) the ELIH score is composed of thirteen parameters, such as BMI (kg/m^2), margarine, liquor, butter, red meat, and fruit juice (positive associations), and coffee, whole fruits, wine, physical activity (MET/week), high-fat dairy products, snacks, and salad dressings (inverse associations); (3) the EDIR score is calculated based on sixteen parameters including margarine, red meat, refined grains, processed meats, tomatoes, other vegetables, fish and other sea food, and fruit juice (positive associations), and coffee, wine, liquor, beer, green leafy vegetables, high-fat dairy products, dark yellow vegetables, and nuts (inverse associations); and (4) the ELIR score is estimated by sixteen parameters, including BMI (kg/m^2), refined grains, red meat, margarine, tomatoes, fruit juice, potatoes, processed meat, other vegetables, and tea (positive associations), and coffee, wine, liquor, high-fat dairy products, physical activity (MET/week), and green leafy vegetables (inverse associations) (online Supplementary Tables S1–S4). Energy adjustment of food intake was performed using a residual method[14]. Each of the parameters was weighted by the regression coefficients and then summed to each of the scores for the empirical indices in accordance with the aforementioned method[8].

Genotyping

Blood samples from the participants were collected for genomic DNA extraction using the MagAttract DNA Blood M48 Kit (Qiagen) and BioRobot M48 automatic extraction equipment (Qiagen). The MassARRAY iPLEX Gold Assay (Agenda Bioscience, Inc.) was used for SNP genotyping. According to the manufacturer's instructions, rs2423279 T > C at the 20p12.3 variant was successfully genotyped from 695 cases and 1400 controls.

Statistical analysis

Comparisons between two groups were assessed with the χ^2 test for categorical variables reporting numbers with percentages and the *t* test for continuous variables presented as the means and standard deviations. The Wilcoxon signed-rank test was used to assess the non-normality of continuous variables. The associations between the empirical indices and CRC were estimated using OR and 95 % CI through unconditional logistic regression according to quartiles of the empirical index scores. The multivariable model was adjusted for age (<50 years or ≥50 years), sex (male or female), BMI (<25 kg/m^2 or ≥25 kg/m^2), prior BMI (<25 kg/m^2 or ≥25 kg/m^2), education level, occupation, income, smoking status (never or ever), alcohol drinking status (never or ever), regular physical activity status (yes or no), first-degree family history of CRC (yes or no), diabetes mellitus status (yes or no) and total energy intake. The diabetes mellitus status was defined based on either diabetes history from a self-report or fasting blood glucose level ≥126 mg/dl. For the

anatomic subsites of CRC (proximal colon, distal colon and rectum), a multinomial logistic regression model was used. The rs2423279 variant testing for Hardy–Weinberg equilibrium was combined into genetic dominant and recessive effect models. To assess the gene–diet interaction, the scores of the empirical indices for assessing insulinemic potential were divided into low and high groups based on the median levels of the control intake, and multivariable logistic regression was performed after adjusting for the same covariates. In terms of power analyses for the gene–diet interaction, this study had sufficient power to detect the gene–diet interaction effect of rs2423279 (OR = 2·0) according to the assumption of genetic effects (OR = 1·6) and environmental effects (OR = 2·5) using Quanto version 1.2.4 (http://hydra.usc.edu/gxe) with 80 % power at an α level of 0·05. Analyses were conducted using SAS version 9.4 software (SAS Institute Inc.), and statistical significance was set at $P < 0·05$ for two-tailed tests.

Results

Participant characteristics

The general characteristics of the participants (923 cases and 1846 controls) are shown in Table 1. The mean (± SD) age was 56·1 (± 9·1) years for the controls and 56·6 (± 9·7) years for the patients. The mean (± SD) BMI was 24·26 (± 2·86) kg/m^2 for the controls and 24·03 (± 3·35) for the cases, but the prior BMI was 24·24 (± 2·79) kg/m^2 for the controls and 24·53 (± 3·12) kg/m^2 for the patients 2 years before measuring the current BMI. CRC patients had a higher prior BMI, prevalence of diabetes mellites, first-degree family history of CRC, pack-years of smoking and alcohol consumption than the controls. The patients were less likely to have a lower education level, to be involved in an occupation, to have a lower income and to participate in regular physical activity than the controls. Regarding the level of physical activity, the mean (± SD) MET-min/week was 2731·01 (± 2945·47) in the controls and 2236·69 (± 2025·33) in the cases.

Comparison of the empirical indices of insulinemic potential

The differences in the empirical indices of insulinemic potential between the cases and the controls are presented in Table 2. When comparing the daily dietary intake, the total energy intake among the cases was 2026·34 (± 533·96) kcal/d, and the mean intake among the controls was 1689·60 (± 560·43) kcal/d. For the mean scores of the four empirical indices, the CRC patients had lower EDIH (17·49 ± 194·91 *v.* 14·37 ± 24·98, $P = 0·001$) and higher ELIH (−25·47 ± 262·57 *v.* −4·49 ± 56·78, $P < 0·001$), EDIR (63·73 ± 307·74 *v.* 79·08 ± 46·95, $P < 0·001$), and ELIR scores (45·22 ± 303·91 *v.* 58·23 ± 70·19, $P = 0·002$) than the controls.

Association between the empirical indices for assessing insulinemic potential and colorectal cancer risk

The associations between the quartiles of the empirical indices for assessing insulinemic potential and CRC are shown in Table 3. The highest quartiles of ELIH, EDIR and ELIR were significantly associated with the risk of CRC compared with the lowest quartiles in multivariable models (OR Q4 *v.* Q1, $P_{\text{for trend}}$: ELIH = 2·90, 95 % CI (2·01, 4·19), $P_{\text{for trend}} < 0·001$; EDIR = 3·32, 95 % CI (2·32, 4·74), $P < 0·001$; and ELIR = 2·79, 95 % CI (1·96, 3·97), $P < 0·001$). However, no association was found between the EDIH score and the risk of CRC.

Association between the empirical indices for assessing insulinemic potential and colorectal cancer risk by anatomic subsite

Table 4 presents the associations between the empirical indices for assessing insulinemic potential and the risk of CRC based on the anatomic subsite of either colon or rectal cancer. Compared with the lowest quartiles of the empirical indices for assessing insulinemic potential in colon cancer, the participants in the highest quartiles of the ELIH, EDIR and ELIR had a significantly increased risk except for EDIH (OR Q4 *v.* Q1, $P_{\text{for trend}}$: ELIH = 3·49, 95 % CI (2·16, 5·63), $P_{\text{for trend}} < 0·001$; EDIR = 4·10, 95 % CI (2·57, 6·56), $P < 0·001$; and ELIR = 3·29, 95 % CI (2·08, 5·19), $P < 0·001$). Similarly, higher scores on the ELIH, EDIR and ELIR were associated with a lower risk of rectal cancer (OR Q4 *v.* Q1, 95 % CI, $P_{\text{for trend}}$: ELIH = 2·68, 95 % CI (1·67, 4·28), $P_{\text{for trend}} < 0·001$; EDIR = 3·03, 95 % CI (1·91, 4·80), $P < 0·001$; and ELIR = 2·57, 95 % CI (1·61, 4·09), $P < 0·001$).

Association of the rs2423279 polymorphism with colorectal cancer risk

Table 5 shows that after adjustment for covariates, the rs2423279 polymorphism was significantly associated with an increased risk of CRC (OR 1·60, C/C *v.* T/T, 95 % CI (1·07, 2·40), $P = 0·023$). According to the anatomic subsite, an increased magnitude of the C allele for rs2423279 was found in colon cancer (OR 1·88, C/C *v.* T/T, 95 % CI (1·17, 3·02), $P = 0·01$).

Interaction between the empirical lifestyle index of insulin resistance and the rs2423279 polymorphism on the risk of colorectal cancer

Table 6 describes whether the empirical lifestyle index of insulin resistance derived from dietary and lifestyle factors can modulate the effect of the rs2423279 variant regarding the risk of CRC. The significant association between the risk of CRC and only the ELIR among the four empirical indices was stronger among C allele carriers of rs2423279 than among T/T carriers in the dominant genetic model (OR 2·50, 95 % CI (1·78, 3·51), $P_{\text{or interaction}} = 0·034$, T/C + C/C carriers with a high score on the ELIR *v.* T/T carriers with a low score on the ELIR). However, there was no association with the anatomic subsite (online Supplementary Table S5).

Discussion

This study was conducted to explore whether the insulinemic potential comprising dietary and lifestyle patterns is associated with the risk of CRC on the basis of the metabolic impact of the insulin response to colorectal carcinogenesis. We assessed the four types of empirical indices and observed that the risk of CRC was increased in those with scores in the highest quartiles

British Journal of Nutrition

Table 1. General characteristics of the study participants (Mean values and standard deviations; numbers and percentages)

	Cases (*n* 923)		Controls (*n* 1846)		
	n	%	*n*	%	*P**†
Age (years)					
Mean		56·58		56·09	0·20
SD		9·71		9·12	
Sex					
Male	625	67·71	1250	67·71	> 0·99
Female	298	32·29	596	32·29	
BMI (kg/m^2)					
Mean		24·03		24·26	0·07
SD		3·35		2·86	
<25	598	64·8	1168	63·25	0·44
≥25	325	35·3	678	36·8	
Prior BMI (kg/m^2)					
Mean		24·53		24·24	**0·024**
SD		3·12		2·79	
<25	496	53·80	1095	59·84	**0·003**
≥25	426	46·20	735	40·16	
Diabetes mellitus status					
Yes	132	14·30	147	7·69	<**0·001**
No	791	85·70	1699	92·04	
Education level					
Middle school or less	321	34·78	282	15·64	<**0·001**
High school	369	39·98	587	32·56	
College or more	233	25·24	934	51·80	
Occupation					
Professionals, administrative, management and office jobs	189	20·48	481	26·39	<**0·001**
Sales and service positions	38	4·12	403	22·11	
Agriculture, manufacturing, mining and army service	141	15·28	241	13·22	
Housekeeping, unemployment and others	555	60·13	698	38·29	
Income (10 000 won/month)					
<200	321	34·78	388	23·0	<**0·001**
200–400	387	41·93	754	44·69	
> 400	215	23·29	545	32·31	
Smoking status					
None	409	44·31	818	44·31	0·16
Ex-smoker	318	34·45	687	37·22	
Current smoker	196	21·24	341	18·47	
Pack-years of smoking (years)					
Mean		27·71		20·86	<**0·001**
SD		18·06		15·15	
Alcohol drinking status					
None	279	30·23	560	30·34	<**0·001**
Ex-drinker	129	13·98	169	9·15	
Current drinker	515	55·80	1117	60·51	
Alcohol consumption (g/d)					
Mean		18·51		17·81	<**0·001**
SD		70·43		49·93	
Physical activity status					
Yes	311	33·69	1047	58·17	<**0·001**
No	612	66·31	753	41·83	
MET-min/week					
Mean		2236·69		2731·01	0·10
SD		2025·33		2945·47	
First-degree family history of CRC					
Yes	86	9·32	99	5·37	<**0·001**
No	837	90·68	1743	94·63	

CRC, colorectal cancer.
* *P*-values were calculated using χ^2 test for categorical variables and *t* test for continuous variables.
† The Wilcoxon signed-rank test was used for significant *P*-values that met the 5% level are marked in bold.

of the ELIH, EDIR and ELIR. In terms of the gene–diet interaction, the effect of the ELIR, which assesses the insulin resistance potential based on diet and lifestyle factors, in those who were carriers of the C allele of rs2423279, a common risk variant for CRC, was stronger than in those who were homozygous for the T allele and had a low score on the ELIR.

Epidemiological evidence of the association between insulin and the risk of CRC has been reported along with either type 2

Table 2. Comparison of the empirical indices of insulinemic potential (Mean values and standard deviations)

	Cases (*n* 923)		Controls (*n* 1846)		
	Mean	SD	Mean	SD	*P**
Total energetic intake (kcal/d)	2026·34	533·96	1689·60	560·43	**<0·001**
EDIH†	14·37	24·98	17·49	194·91	**0·001**
ELIH†	-4·49	56·78	-25·47	262·57	**<0·001**
EDIR†	79·08	46·95	63·73	307·74	**<0·001**
ELIR†	58·23	70·19	45·22	303·91	**0·002**

EDIH, empirical dietary index for hyperinsulinemia; ELIH, empirical lifestyle index for hyperinsulinemia; EDIR, empirical dietary index for insulin resistance; ELIR, empirical lifestyle index for insulin resistance.
* The Wilcoxon signed-rank test was used for significant *P*-values that met the 5 % level are marked in bold.
† Empirical indices were adjusted for total energy intake using the residual method.

diabetes or obesity[15–17]. Previously conducted prospective studies indicated that type 2 diabetes showed a positive association with CRC depending on the duration of type 2 diabetes or sex[18,19]. To examine the hyperinsulinemia or insulin resistance as it relates to CRC patients who suffer from either type 2 diabetes or obesity, several serologic markers were used, including insulin, insulin-like growth factor 1 (IGF-1), fasting plasma C-peptide or plasma resistin levels, not only as biomarkers but also as key mediators[20–23]. However, findings relevant to the association of insulin resistance with the risk of CRC are limited due to the increasing resistance to insulin of the cells over time. The four empirical indices to assess the insulinemic potential that we used for this study were validated in two large independent cohort studies, suggesting the usefulness of the assessment for the long-term effects of diet on insulin response[8]. Moreover, the indices of the insulin resistance pathway, that is, the EDIR and ELIR, derived from the TAG/HDL-cholesterol ratio, could reasonably measure the predictive ability of insulin resistance for the assessment of the long-term insulinemic potential of the whole diet as well as lifestyle. To date, the dietary insulinemic potential for hyperinsulinemia has shown a significant association with type 2 diabetes, prostate cancer and CRC survival[24–26]. The effect of insulinemic potential not only on hyperinsulinemia but also on insulin resistance was significant in diabetes, multiple myeloma and hepatocellular carcinoma[27–29]. Yue *et al.* reported that the insulinemic potential of a hyperinsulinemic diet and lifestyle, as assessed by both the EDIH and ELIH, showed an association with CRC among younger women[30]. The present study indicated that those with scores in the highest quartiles for the ELIH, EDIR and ELIR had a significantly increased risk of CRC compared with those with scores in the lowest quartiles.

Among the research on dietary factors for cancer prevention, dietary patterns based on biological markers or processes for carcinogenesis have received attention due to the synergistic and interactive effects between individual foods and nutrients[31]. Previous studies have investigated whether dietary patterns linked to the mechanisms of inflammatory stimulation, such as the glycaemic index or the dietary inflammatory index, show significant associations with the risk of CRC and have suggested that the glycaemic index is limited due to short-term metabolic effects of the diet on insulin responses[32,33]. The results of the present study suggest that insulinemic dietary patterns are more effective in reducing the risk of CRC along with obesity and diabetes mellitus.

The SNP rs2423279, newly identified as a CRC susceptibility locus through genome-wide association studies analyses in East Asians, is located near the *HAO1* and *PLCB1* genes, suggesting a potential relationship between glyoxylate metabolism and colorectal carcinogenesis[10]. Expression of the *HAO1* gene occurs mainly in the liver and pancreas and is linked to the generation of hepatic glucose and the release of insulin from β cells[34]. In addition, overexpression of the *PLCB1* gene, located adjacent to the rs2423279 SNP, is known to have a significant association with CRC, and activation of this gene is involved in the intracellular transduction of extracellular signals that might be relevant to the multiple cellular signalling pathways of insulin resistance[10,35]. Regarding the linkage between glyoxylate metabolism and insulin resistance, a recent study demonstrated the activation of glyoxylate metabolism in fat-induced hepatic insulin resistance, suggesting that the glyoxylate pathway is linked to gluconeogenesis from fatty acids, resulting in the increased production of hepatic glucose and type 2 diabetes[11]. Nikiforova *et al.* showed that elevated glyoxylate levels were associated with hyperglycaemia and advanced glycation end products leading to diabetes-associated complications[12]. Although the molecular biology of insulin action and insulin resistance has yet to be fully understood, it seems plausible that insulin plays a role in the process of CRC development[7]. Elevated levels of insulin may have oncogenic potential in colorectal carcinogenesis[36]. Hyperinsulinemia and increased insulin resistance give rise to the decreased production of hepatic IGF-binding proteins leading to increased IGF-1 levels derived from hepatic IGF-1 synthesis[20]. In tumorigenesis, increasing levels of IGF-1 and other growth factors stimulate the growth of cells by promoting cellular proliferation and inhibiting apoptosis, resulting in tumour progression with mitogenic and antiapoptotic activity[37]. The inflammatory mechanism underlying obesity and insulin resistance is promoted by: inducing the generation of free fatty acids, TNF-α, IL-6 and leptin; decreasing the secretion of adiponectin; and altering NF-κB activity in adipose tissue along with cytokine abnormalities, thus contributing to an increased risk of CRC[38]. Moreover, given the critical role of insulin and insulin resistance, several previous studies have identified that the risk of CRC was increased in insulin-resistant patients[23,39–41].

Regarding the role of glyoxylate metabolism linked to the SNP rs2423279, accumulating evidence has reported that the glyoxylate metabolic pathway observed in various cancers, including CRC, was associated with tumour cell differentiation with an antiproliferative effect[42,43]. Recent studies have suggested that glyoxylate metabolism could regulate insulin resistance and glucose generation[11,12]. Given the association between insulin resistance and the development of CRC, the glyoxylate metabolic pathway of rs2423279 is linked to the regulation of insulin resistance, which can lead to colorectal carcinogenesis. The results of this study could support these plausible mechanisms based on the effect of components of the ELIR. Among the sixteen components of the ELIR, CRC patients had

Table 3. Association between the empirical indices of insulinemic potential and CRC risk (Odd ratio and 95 % confidence intervals)

	Q1		Q2		Q3		Q4		
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
EDIH	<5·81		5·81– <14·27		14·27– <26·20		≥26·20		
No. of cases/controls	168/462		390/461		252/462		113/461		
Crude OR (95 % CI)	1·0	Ref	2·33	1·86, 2·91	1·50	1·19, 1·90	0·67	0·51, 0·88	**<0·001**
Multivariable OR (95 % CI)*	1·0	Ref	1·86	1·41, 2·46	1·49	1·12, 2·00	1·14	0·81, 1·60	0·87
ELIH	<−11·78		−11·78– <−3·69		−3·69– <1·30		≥1·30		
No. of cases/controls	70/461		179/462		366/462		308/461		
Crude OR (95 % CI)	1·0	Ref	2·55	1·88, 3·46	5·22	3·92, 6·95	4·40	3·29, 5·88	**<0·001**
Multivariable OR (95 % CI)*	1·0	Ref	1·74	1·21, 2·51	3·15	2·21, 4·51	2·90	2·01, 4·19	**<0·001**
EDIR	<60·88		60·88– <76·84		76·84– <96·33		≥96·33		
No. of cases/controls	139/462		215/461		370/461		199/462		
Crude OR (95 % CI)	1·0	Ref	1·55	1·21, 1·99	2·67	2·11, 3·37	1·43	1·11, 1·84	**<0·001**
Multivariable OR (95 % CI)*	1·0	Ref	1·77	1·27, 2·39	3·55	2·59, 4·85	3·32	2·32, 4·74	**<0·001**
ELIR	<46·01		46·01– <59·44		59·44– <72·81		≥72·81		
No. of cases/controls	141/461		248/462		344/461		190/462		
Crude OR (95 % CI)	1·0	Ref	1·76	1·38, 2·24	2·44	1·93, 3·09	1·35	1·04, 1·73	**0·004**
Multivariable OR (95 % CI)*	1·0	Ref	2·02	1·48, 2·75	3·46	2·53, 4·73	2·79	1·96, 3·97	**<0·001**

CRC, colorectal cancer; Q, quartile; EDIH, empirical dietary index for hyperinsulinemia; ELIH, empirical lifestyle index for hyperinsulinemia; EDIR, empirical dietary index for insulin resistance; ELIR, empirical lifestyle index for insulin resistance.

* Multivariable model was adjusted for age (<50 years or ≥50 years), sex (male or female), BMI (<25 kg/m^2 or ≥25 kg/m^2), prior BMI (<25 kg/m^2 or ≥25 kg/m^2), education level, occupation, income, smoking status (never or ever), alcohol drinking status (never or ever), regular physical activity status (yes or no), first-degree family history of CRC (yes or no), diabetes mellitus status (yes or no) and total energy intake.

Significant *P*-values that met the 5 % level are in bold.

Table 4. Association between the empirical indices of insulinemic potential and CRC risk by anatomic subsite (Odd ratio and 95 % confidence intervals)

	Q1		Q2		Q3		Q4		$P_{for\ trend}$
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	
Colon cancer									
EDIH	<5·81		5·81– <14·27		14·27– <26·20		≥26·20		
No. of cases/controls	82/462		193/461		126/462		58/461		
Crude OR (95 % CI)	1·0	Ref	2·36	1·77, 3·15	1·54	1·13, 2·09	0·71	0·49, 1·02	**<0·001**
MultivariableOR (95 % CI)*	1·0	Ref	2·13	1·50, 3·02	1·64	1·13, 2·37	1·20	0·78, 1·85	0·81
ELIH	<−11·78		−11·78– <−3·69		−3·69– <1·30		≥1·30		
No. of cases/controls	31/461		97/462		184/462		147/461		
Crude OR (95 % CI)	1·0	Ref	3·12	2·04, 4·77	5·92	3·96, 8·85	4·74	3·15, 7·13	**<0·001**
MultivariableOR (95 % CI)*	1·0	Ref	2·19	1·36, 3·54	3·81	2·39, 6·08	3·49	2·16, 5·63	**<0·001**
EDIR	<60·88		60·88– <76·84		76·84– <96·33		≥96·33		
No. of cases/controls	67/462		110/461		183/461		99/462		
Crude OR (95 % CI)	1·0	Ref	1·65	1·18, 2·29	2·74	2·01, 3·73	1·48	1·06, 2·07	**0·006**
Multivariable OR (95 % CI)*	1·0	Ref	2·16	1·44, 3·25	4·45	2·96, 6·69	4·10	2·57, 6·56	**<0·001**
ELIR	<46·01		46·01– <59·44		59·44– <72·81		≥72·81		
No. of cases/controls	69/461		123/462		166/461		101/462		
Crude OR (95 % CI)	1·0	Ref	1·78	1·29, 2·45	2·41	1·77, 3·28	1·46	1·05, 2·04	**0·012**
Multivariable OR (95 % CI)*	1·0	Ref	2·29	1·54, 3·40	3·91	2·62, 5·84	3·29	2·08, 5·19	**<0·001**
Rectal cancer									
EDIH	<5·81		5·81– <14·27		14·27– <26·20		≥26·20		
No. of cases/controls	84/462		185/461		123/462		52/461		
Crude OR (95 % CI)	1·0		2·21	1·65, 2·95	1·46	1·08, 1·99	0·62	0·43, 0·90	**<0·001**
MultivariableOR (95 % CI)*	1·0	Ref	1·56	1·10, 2·22	1·37	0·95, 1·97	0·96	0·62, 1·50	0·68
ELIH	<−11·78		-11·78– <−3·69		−3·69– <1·30		≥1·30		
No. of cases/controls	37/461		81/462		171/462		155/461		
Crude OR (95 % CI)	1·0	Ref	2·18	1·45, 3·29	4·61	3·16, 6·73	4·19	2·86, 6·13	**<0·001**
Multivariable OR (95 % CI)*	1·0	Ref	1·53	0·95, 2·46	2·93	1·85, 4·64	2·68	1·67, 4·28	**<0·001**
EDIR	<60·88		60·88– <76·84		76·84– <96·33		≥96·33		
No. of cases/controls	68/462		99/461		181/461		96/462		
Crude OR (95 % CI)	1·0	Ref	1·46	1·04, 2·04	2·67	1·96, 3·63	1·41	1·01, 1·98	**0·007**
Multivariable OR (95 % CI)*	1·0	Ref	1·60	1·06, 2·40	3·48	2·33, 5·19	3·03	1·91, 4·80	**<0·001**
ELIR	<46·01		46·01– <59·44		59·44– <72·81		≥72·81		
No. of cases/controls	67/461		121/462		171/461		85/462		
Crude OR (95 % CI)	1·0	Ref	1·80	1·30, 2·50	2·55	1·87, 3·48	1·27	0·90, 1·79	0·06
Multivariable OR (95 % CI)*	1·0	Ref	2·09	1·41, 3·11	3·60	2·42, 5·36	2·57	1·61, 4·09	**<0·001**

CRC, colorectal cancer; Q, quartile; EDIH, empirical dietary index for hyperinsulinemia; ELIH, empirical lifestyle index for hyperinsulinemia; EDIR, empirical dietary index for insulin resistance; ELIR, empirical lifestyle index for insulin resistance.

* Multivariable model was adjusted for age (<50 years or ≥50 years), sex (male or female), BMI (<25 kg/m^2 or ≥25 kg/m^2), prior BMI (<25 kg/m^2 or ≥25 kg/m^2), education level, occupation, income, smoking status (never or ever), alcohol drinking status (never or ever), regular physical activity status (yes or no), first-degree family history of CRC (yes or no), diabetes mellitus status (yes or no) and total energy intake.

Significant *P*-values that met the 5 % level are in bold.

Table 5. Association of rs2423279 polymorphism with CRC risk (Odd ratio and 95 % confidence intervals)

rs2423279	No. of cases	%	No. of controls	%	Crude OR		95 % CI	*P*	Multivariable OR*		95 % CI	*P*
CRC												
T/T	341	49·1	751	53·6	1·0	Ref			1·0	Ref		
T/C	288	41·4	550	39·3	1·15		0·95, 1·40	0·14	1·09		0·86, 1·37	0·49
C/C	66	9·5	99	7·1	1·47		1·05, 2·06	0·025	1·60		1·07, 2·40	**0·023**
Colon cancer												
T/T	175	49·7	–		1·0	Ref			1·0	Ref		
T/C	138	39·2	–		1·08		0·84, 1·38	0·56	1·05		0·78, 1·41	0·76
C/C	39	11·1	–		1·69		1·13, 2·54	0·011	1·88		1·17, 3·02	**0·01**
Rectal cancer												
T/T	159	48·0	–		1·0	Ref			1·0	Ref		
T/C	146	44·1	–		1·25		0·98, 1·61	0·08	1·16		0·86, 1·56	0·33
C/C	26	7·9	–		1·24		0·78, 1·97	0·36	1·27		0·74, 2·18	0·39

CRC, colorectal cancer.
* Multivariable model was adjusted for age (<50 years or ≥50 years), sex (male or female), BMI (<25 kg/m^2 or ≥25 kg/m^2), prior BMI (<25 kg/m^2 or ≥25 kg/m^2), education level, occupation, income, smoking status (never or ever), alcohol drinking status (never or ever), regular physical activity status (yes or no), first-degree family history of CRC (yes or no), diabetes mellitus status (yes or no) and total energy intake.
† Successful rs2423279 genotyping was performed with T > C, 1400 controls and 695 cases.
‡ *P*-values were calculated using the χ^2 test and significant *P*-values that met the 5 % level are in bold.

Table 6. Interaction between the empirical lifestyle index of insulin resistance and rs2423279 polymorphism on CRC risk (Odd ratio and 95 % confidence intervals)

	T/T		T/T		T/C + C/C		T/C + C/C		
	Low		High		Low		High		
rs2423279 (dominant model)	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	$P_{\text{for interaction}}$
EDIH									
No. of cases/controls	195/365		146/386		226/335		128/314		
Crude OR (95 % CI)	1·0	Ref	0·71	0·55, 0·92	1·26	0·99, 1·61	0·76	0·58, 1·00	0·40
Multivariable OR (95 % CI)*	1·0	Ref	1·17	0·84, 1·61	1·31	0·97, 1·77	1·17	0·83, 1·63	0·24
ELIH									
No. of cases/controls	88/381		253/370		94/319		260/330		
Crude OR (95 % CI)	1·0	Ref	2·96	2·23, 3·92	1·28	0·92, 1·77	3·41	2·57, 4·53	0·62
Multivariable OR (95 % CI)*	1·0	Ref	2·67	1·89, 3·78	1·48	1·01, 2·16	2·75	1·94, 3·90	0·14
EDIR									
No. of cases/controls	140/368		201/383		134/332		220/317		
Crude OR (95 % CI)	1·0	Ref	1·38	1·07, 1·79	1·06	0·80, 1·40	1·82	1·41, 2·37	0·24
MultivariableOR (95 % CI)*	1·0	Ref	1·97	1·41, 2·76	0·93	0·66, 1·31	2·78	1·97, 3·91	0·07
ELIR									
No. of cases/controls	144/361		197/390		138/339		216/310		
Crude OR (95 % CI)	1·0	Ref	1·27	0·98, 1·64	1·02	0·77, 1·35	1·75	1·35, 2·27	0·11
Multivariable OR (95 % CI)*	1·0	Ref	1·71	1·22, 2·40	0·89	0·63, 1·25	2·50	1·78, 3·51	**0·034**

CRC, colorectal cancer; EDIH, empirical dietary index for hyperinsulinemia; ELIH, empirical lifestyle index for hyperinsulinemia; EDIR, empirical dietary index for insulin resistance; ELIR, empirical lifestyle index for insulin resistance.
* Multivariable model was adjusted for age (<50 years or ≥50 years), sex (male or female), BMI (<25 kg/m^2 or ≥25 kg/m^2), prior BMI (<25 kg/m^2 or ≥25 kg/m^2), education level, occupation, income, smoking status (never or ever), alcohol drinking status (never or ever), regular physical activity status (yes or no), first-degree family history of CRC (yes or no), diabetes mellitus status (yes or no) and total energy intake.
† The empirical indices were categorised into low and high groups based on the median level of their control group's score (EDIH = 14·22, ELIH = −3·67, EDIR = 77·59 and ELIR = 59·16).
‡ Significant *P*-values that met the 5 % level are in bold.

lower intakes of refined grains and green leafy vegetables as potential indicators of insulin resistance but not for hyperinsulinemia (online Supplementary Table S4). Epidemiological studies have determined that the intakes of refined grains and green leafy vegetables were associated with the risk of CRC-regulating insulin resistance[44–47]. Furthermore, the ELIR included modifiable lifestyle factors such as BMI and physical activity, which are known risk factors for CRC according to the WCRF/AICR[4]. The individual components of the ELIR may have a synergistic effect on the risk of CRC with risk allele C of rs2423279 linked to glyoxylate metabolism and insulin resistance. Further investigation is required to explore the actual mechanism and bioavailability of nutrients from these foods for stabilising insulin and glucose levels to regulate insulin

resistance and reduce the risk of CRC. Our findings showed that dietary and lifestyle patterns contributing to insulin resistance had a suggestive association with the risk of CRC, providing insight into possible determinants of insulin resistance for CRC prevention.

The strength of the present study is that the determinants for insulin resistance based on dietary and lifestyle factors were assessed as they related to the risk of CRC and the underlying common genetic variant of rs2423279 for CRC susceptibility. Through a validated and reliable questionnaire, this study collected the intended information on dietary and lifestyle factors relevant to insulinemic potential. Despite these strengths, several limitations should be considered. This research was designed as a hospital-based sex and age frequency-matched case–control study; thus, it may suffer from recall and selection bias in the collection of information or enrolment of subjects. In addition, it was limited to exploring and suggesting the causality between insulinemic potential and the risk of CRC. The assessment of biomarkers derived from participants' blood or biopsy would enable the ability to assess determinants of hyperinsulinemia and insulin resistance. Moreover, the number of participants with diabetes in this study was relatively small for conducting stratified analyses, and thus, further prospective studies need to recruit a greater number of subjects who have diabetes to examine the association between insulinemic potential and the risk of CRC in subgroups of diabetes mellitus.

In conclusion, the empirical insulinemic potential indices composed of diet and lifestyle factors for hyperinsulinemia and insulin resistance were significantly associated with the risk of CRC. An interactive effect of empirical dietary and lifestyle factors for assessing insulin resistance on the risk of CRC was found to be associated with a common genetic variant of CRC. This study may provide insight into the possible benefits of the insulinemic resistance potential based on dietary and lifestyle factors to introduce new strategies to prevent CRC.

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The authors declare no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452200085X

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