

## Association between CA repeat polymorphism in IGF1 gene promoter and colorectal cancer risk in a native Chinese population

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Received January 17, 2019 / Accepted April 16, 2019

Insulin-like growth factor 1 (IGF1) is implicated in normal cell growth. It has been reported that IGF1 has a mitogenic and anti-apoptotic effect on colorectal cancer cells. However, results of studies on the association between cytosine-adenine (CA) repeat polymorphism in IGF1 gene promoter and colorectal cancer (CRC) risk are inconsistent. We aimed to evaluate the association between CA repeat polymorphism and CRC risk, as well as the relationship with the clinicopathological characteristics of CRC and circulating IGF1 level in a native Chinese population. There were 734 participants who were native Chinese in this case-control study, including 367 CRC cases and 367 age- and sex-matched controls. CA repeat polymorphism was genotyped by PCR and fragment analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were evaluated by unconditional logistic regression analysis. Circulating level of IGF1 in cases was significantly higher than that in controls ( $p=0.002$ ), particularly in males. Less than 38 CA repeats were associated with decreased CRC risk after adjusting for age and sex (37 versus 38 CA repeats: OR=0.45; 95% CI=0.26–0.78), especially in males. (CA)18/19 genotype showed approximately half reduced CRC risk comparing to (CA)19/19 genotype (OR=0.46; 95% CI=0.25–0.85). There was a significant association between the sum of CA repeats and degree of differentiation of CRC ( $p=0.044$ ). We observed a trend that circulating level of IGF1 in individuals with CA  $\leq 38$  repeats was lower than that in individuals with CA  $>38$  repeats with a borderline statistical significance in overall and males. In conclusion, our findings support the possible role of CA repeat polymorphism in CRC risk.

*Key words: insulin-like growth factor 1, polymorphism, CA repeat, colorectal cancer*

Colorectal cancer (CRC) has become a global burden due to its high incidence and mortality worldwide. It has been recently reported an estimation of over 1.8 million new CRC cases and 881 000 deaths in 2018 worldwide. CRC ranks third for overall incidence and second for mortality [1]. However, the age-standardized incidence rate of CRC has been reported to rise from 16.1 to 17.5 per 100 000 from 2010 to 2014 in China, while the age-standardized mortality rate fluctuates between 7.6 and 7.9 per 100 000 [2]. It has been known that CRC is a complicated disease as tumors can occur in various subsites of colorectum and risk factors are different between males and females, which is totally distinct from breast cancer and prostate cancer. Both environmental and genetic factors may contribute to carcinogenesis of colorectum. Insulin-like growth factor 1 (IGF1) may be one of the factors.

IGF1, a polypeptide with 70 amino acids, is a component of IGF1 pathway important for the regulation of cell growth,

differentiation and survival [3]. *In vitro* studies have demonstrated that IGF1 is a potent mitogenic factor for colorectal carcinoma cell lines, as well as an important anti-apoptotic factor in colon cancer cells [4, 5]. As it is considered as a regulator of cell proliferation and apoptosis, IGF1 may be implicated in carcinogenesis. A meta-analysis has shown that higher IGF1 circulating level is significantly associated with increased overall cancer risk, the association is particularly obvious in CRC, premenopausal breast cancer and prostate cancer [6]. However, circulating level of IGF1 is influenced by many factors. Both lifestyle and genetic factors are related to circulating level of IGF1 [7–9]. Twin study has indicated that 38% variation in circulating level of IGF1 derives from genetic effects [9]. A known genetic polymorphism, cytosine-adenine (CA) repeat polymorphism in IGF1 gene promoter has become the focus of a number of studies.

CA repeat polymorphism with variable length composed of multiple cytosine-adenine dinucleotides is located in the

promoter region 969 bp upstream from transcription start site of the IGF1 gene, which has been proved to be related to serum IGF1 level in an early study [10]. The range of CA repeat numbers varies in different populations, generally the most common CA repeat number is 19 [11–13]. Although the results are controversial, IGF1 CA repeat polymorphism has been extensively evaluated in relation to the risk of various cancers in many studies, including breast cancer [12–15], prostate cancer [16–19], and CRC [11, 20–24]. Some studies have demonstrated that CA repeat polymorphism in the promoter of IGF1 gene is associated with the CRC risk [11, 21, 23, 24], however, some studies have indicated that there is no such association [20, 22]. The role of CA repeat polymorphism in the carcinogenesis of CRC remains ambiguous. Due to inconsistent results in different populations and races, we suppose that the association between CA repeat polymorphism and CRC risk may be related to the characteristics of specific population and ethnicity or race. To our knowledge, there has been no report on the association between CA repeat polymorphism and CRC risk in a native Chinese population up to now, only a Singapore Chinese population has been analyzed [11]. Furthermore, the classification methods of CA repeat polymorphism are not uniform when analyzed in different studies, which may affect the results.

Considering the high incidence of CRC worldwide, growing incidence of CRC in China and inconsistent view on the role of CA repeat polymorphism in CRC risk, we investigate the association between CA repeat polymorphism and CRC risk, as well as the relation to the clinicopathological characteristics of CRC in a native Chinese population. In addition, we evaluate the relationship between CA repeat polymorphism and circulating level of IGF1 in this study.

## Patients and methods

**Study population.** Subjects were recruited from Tianjin Union Medical Center between May 2011 and November 2015, with a case-control design. All subjects were native Chinese from the same ethnicity, Han Chinese. Cases were ascertained by professional pathologists and were at first diagnosis of colorectal cancer confirmed historically. All cases were excluded of diabetes and other malignant disease. There were 367 cases diagnosed with colon cancer or rectal cancer included. The pathological characteristics (Dukes stage, degree of differentiation, tumor location) of colorectal cancer were directly extracted from the Pathological Report of patients. Controls matched to cases by age and sex were selected from physical examination population. We selected 367 controls at the exclusion of diabetes, cardiovascular and malignant disease by laboratory and imaging tests. Total subjects included in this study provided the informed consent. Our study was approved by the Academic Committees of Tianjin Union Medical Center.

**Blood specimens and laboratory assays.** Venous blood samples were drawn into coagulant tubes from all subjects in

the early morning after fasting for 8 hours. Chemiluminescence assay with the reagent kit from Siemens was used to determine serum levels of IGF1 by Immulite 2000 (Siemens, Germany). In addition, 3 ml of whole blood was drawn into EDTA anticoagulant tube from every subject, then the blood samples were stored at  $-80^{\circ}\text{C}$  until experimental use.

**DNA extraction.** Genomic DNA was extracted from blood leukocytes using TIANamp Blood DNA Midi Kit (Tiangen Biotech, Beijing, China), referring to instructions of the manufacturer. The extracted DNA samples were stored at  $-80^{\circ}\text{C}$  for further analysis.

**Genotyping.** IGF1 CA repeat polymorphism was measured by PCR and fragment analysis using ABI-3730XL DNA Sequencer (Applied Biosystems, Foster City, CA). PCR amplification was performed using the primers, 5'-AGAAAA-CACACTCTGGCACAC-3' and 5'-GCAAAGACTCTGCC-GAGCTG-3' (Invitrogen, Shanghai, China). The 5' end of the forward primer was labeled with FAM for fluorescence detection. A total volume of 50  $\mu\text{l}$  of the PCR reaction mixture consisted of 10 ng DNA, 2  $\mu\text{l}$  each of the 5  $\mu\text{M}$  primers, 4  $\mu\text{l}$  2 mM dNTPs, 5  $\mu\text{l}$  10x PCR buffer, 1.6  $\mu\text{l}$  50 mM  $\text{MgCl}_2$  and 1.5U Platinum<sup>®</sup> Taq DNA polymerase (Invitrogen, Shanghai, China). The amplification conditions were: 1 cycle of 5 min at  $95^{\circ}\text{C}$  followed by 35 thermal cycles constituting of 30 s at  $95^{\circ}\text{C}$  (denaturation), 30 s at  $60^{\circ}\text{C}$  (annealing) and 30 s at  $72^{\circ}\text{C}$  (extension), and a final extension step at  $72^{\circ}\text{C}$  for 5 min. GeneScan 3.0 and GeneMapper software (Applied Biosystems) were used to determine the length of amplified fragments.

**Statistical analysis.** For descriptive characteristics of cases and controls, categorical variables were expressed as numbers (percentage), and were evaluated using chi-square test. Continuous normal distribution variables were given as mean  $\pm$  standard deviation and were analyzed by independent sample t-test. Allele frequencies of CA repeat polymorphism between cases and controls were compared by chi-square test. To estimate the relation to CRC risk, CA repeat polymorphism was classified as three groups: i) group 1: classical group as analyzed in most studies, (CA)19 repeat status in both alleles, homozygous (CA)19/19 repeat, heterozygous CA19/non-19, homozygous (CA)non-19/non-19; ii) group 2: the sum of CA repeats in both alleles according to Simons et al. [24], CA  $\leq 36, 37, 38, 39$  and  $\geq 40$  repeats; iii) group 3: four of the most common genotypes, (CA) 19/19, 19/21, 18/19 and 18/21 in both of cases and controls. Odds ratio (OR) with 95% confidence intervals (95% CI) was determined by unconditional logistic regression models adjusted for age and sex to evaluate the association between CA repeat polymorphism and CRC risk. The relationship between CA repeat polymorphism and clinicopathologic characteristics of CRC was assessed by chi-square test according to group 1 as above mentioned, the sum of CA repeats  $\leq 38$  and  $> 38$  in both alleles respectively. The relationship between CA repeat polymorphism and circulating level of IGF1 was evaluated via independent sample t-test, which

classified as the presence of (CA)19 allele and the absence of (CA)19 allele(non-19), the sum of CA repeats  $\leq 38$  and  $>38$  in both alleles. SPSS 20.0 software was used for all statistical analyses. A two-side  $p < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Descriptive characteristics of cases and controls are shown in Table 1.** A total of 367 cases and 367 controls were included in this study. Cases did not differ obviously from controls for age and sex as they were matched. However, circulating levels of IGF1 in cases were significantly higher compared with controls for overall individuals, nevertheless, the difference was evident only in males but not females after stratification by sex. There were 120 patients with colon cancers and 247 patients with rectal cancers. 211 cases were in stage A and B for Dukes stage, while 156 cases were in stage C and D. The dominant degree of differentiation was moderate differentiation in cases, the following was well (high/high-moderate) differentiation, while the proportion of poor (moderate-low/low) differentiation was the smallest within the cases.

**The frequency distribution of CA repeat allele in cases and controls is listed in Table 2.** The range of CA repeat in cases was different from controls. The (CA)19 repeat allele was the most frequent allele in both cases and controls for total subjects, males and females. 36.2% of cases and 33.9% of controls carried the (CA)19 allele in total subjects. There was no significant difference in frequency distribution of CA repeat allele between cases and controls for total subjects ( $p = 0.199$ ), males ( $p = 0.175$ ) and females ( $p = 0.706$ ).

**The association between CA repeat polymorphism and CRC risk is shown in Table 3.** The (CA)19 repeat genotype was not associated with CRC risk in group 1. Individuals with 37 CA repeats for the sum of CA repeats in both alleles had approximately half CRC risk comparing to individuals with 38 CA repeats after adjusting for age and sex in group 2 ( $OR = 0.45$ ;  $95\% CI = 0.26-0.78$ ). There was a borderline statistically significant association of decreased CRC risk with  $\leq 36$  CA repeats. However, there was no significant association between  $>38$  CA repeats and CRC risk. Comparing to (CA)19/19 genotype, (CA)18/19 but not (CA)19/21

or (CA)18/21 genotype was significantly associated with approximately half reduced CRC risk in group 3 ( $OR = 0.46$ ;  $95\% CI = 0.25-0.85$ ). Then the relation of CA repeat polymorphism with CRC risk evaluated after stratification by sex is shown in Table 4 (considering the sample size was small after classification, we classified the sum of CA repeats as  $<38$  repeats, 38 repeats and  $>38$  repeats). The uncorrelation between (CA)19 repeat polymorphism and CRC risk did not change after stratification by sex. Nevertheless, carrying  $<38$  CA repeats but not  $>38$  CA repeats was significantly associated with reduced risk of CRC, comparing to carrying 38 CA repeats in males ( $OR = 0.48$ ;  $95\% CI = 0.28-0.81$ ), while there was no correlation of  $<38$  CA repeats with decreased risk of CRC in females.

**The association between CA repeat polymorphism and clinicopathologic characteristics of CRC in 367 cases (Table 5 and Table 6).** (CA)19 repeat polymorphism was not related to clinicopathologic characteristics of CRC. Nevertheless, the sum of CA repeats was associated with degree

Table 1. Descriptive characteristics of study participants.

Characteristics	Cases (n=367)	Controls (n=367)	p-value
Age (y)	65.80±9.53	65.80±9.39	0.975 <sup>a</sup>
Sex			0.449 <sup>b</sup>
Male	219 (59.7)	229 (62.4)	
Female	148 (40.3)	138 (37.6)	
IGF1 (ng/ml)			
Overall	146.91±69.55	132.88±46.96	0.002 <sup>a</sup>
Male	159.42±69.46	138.65±45.51	<0.010 <sup>a</sup>
Female	128.41±65.65	122.72±47.93	0.413 <sup>a</sup>
Tumor location		-	-
Colon	120 (32.7)		
Rectum	247 (67.3)		
Dukes stage		-	-
A+B	211 (57.5)		
C+D	156 (42.5)		
Degree of differentiation		-	-
High/High-moderate	94 (25.6)		
Moderate	210 (57.2)		
Moderate-low/Low	63 (17.2)		

<sup>a</sup>based on independent sample t-test, <sup>b</sup>based on chi-square test.

Table 2. Distribution of IGF1 CA repeat allele frequencies in study population.

CA repeats	Total subjects		Male		Female	
	Cases (%)	Controls (%)	Cases (%)	Controls (%)	Cases (%)	Controls (%)
$\leq 17$	71 (9.7)	89 (12.1)	38 (8.7)	55 (12.0)	33 (11.1)	34 (12.3)
18	136 (18.5)	145 (19.8)	80 (18.3)	97 (21.2)	56 (18.9)	48 (17.4)
19	266 (36.2)	249 (33.9)	156 (35.6)	148 (32.3)	110 (37.2)	101 (36.6)
20	81 (11.0)	61 (8.3)	49 (11.2)	40 (8.7)	32 (10.8)	21 (7.6)
21	154 (21.0)	154 (21.0)	100 (22.8)	94 (20.5)	54 (18.2)	60 (21.7)
$\geq 22$	26 (3.5)	36 (4.9)	15 (3.4)	24 (5.2)	11 (3.7)	12 (4.3)
Range	11-24	13-26	11-24	13-26	15-24	14-24

of differentiation of CRC ( $p=0.044$ ), the percentage of poor (moderate-low/low) differentiation in patients carrying CA  $\leq 38$  repeats was higher than that in patients carrying CA  $>38$  repeats (20.5% versus 13.4%), but the percentage of well (high/high-moderate) differentiation was opposite. There was no significant association between sex, tumor location, Dukes stage of CRC and the sum of CA repeats.

**The association between IGF1 genotype and circulating level of IGF1 in 367 controls (Table 7).** There was no significant relationship between (CA)19 repeat polymorphism and circulating level of IGF1. Although there was just a borderline statistical significance, we found a trend that circulating level of IGF1 in individuals with CA  $\leq 38$  repeats was lower than that in individuals with CA  $>38$  repeats in overall and males, but not females.

**Table 3. ORs and 95% CIs for the IGF1 CA repeat polymorphism and CRC risk**

CA repeat groups	Cases/Controls (n = 367/n = 367)	OR <sup>a</sup> (95% CI)	p-value
Group 1			
(CA)19/19	65/50	1.00 (reference)	
(CA)19/non-19	136/148	0.71 (0.46–1.10)	0.126
(CA)non-19/non-19	166/169	0.76 (0.50–1.17)	0.209
Group 2			
$\leq 36$ repeats	64/73	0.66 (0.42–1.04)	0.075
37 repeats	30/50	0.45 (0.26–0.78)	0.004
38 repeats	101/76	1.00 (reference)	
39 repeats	57/48	0.92 (0.56–1.50)	0.734
$\geq 40$ repeats	115/120	0.73 (0.49–1.08)	0.110
Group 3			
(CA)19/19	65/50	1.00 (reference)	
(CA)19/21	55/47	0.90 (0.53–1.54)	0.701
(CA)18/19	25/43	0.46 (0.25–0.85)	0.013
(CA)18/21	35/31	0.89 (0.48–1.64)	0.702

<sup>a</sup>adjusted for age and sex

## Discussion

Our results have shown an association between the sum of CA repeats polymorphism in the promoter region of IGF1 gene and CRC risk in a native Chinese population. We found the protective effect of  $<38$  CA repeats for CRC risk, particularly in males. While a Netherlands Cohort Study indicated carrying  $<38$  CA repeats but not  $>38$  CA repeats was related to half decreased CRC risk ( $\leq 36$  versus 38 repeats: HR=0.44; 95% CI=0.33–0.58; p-trend  $<0.001$ ) in females but not males [24]. It is possible that the association between CRC risk and the sum of CA repeats may be influenced by sex for different populations. Further studies are needed to verify the role of  $<38$  CA repeats in CRC risk in other populations, and whether their association is affected by sex. In contrast, it has been reported that  $<38$  CA repeats was not significantly associated with breast cancer risk in either pre- or postmenopausal women using  $\geq 38$  CA repeats as reference in a case-control study among Arab Omani women [25], which indicated there was no protective effect of  $<38$  CA repeats for breast cancer. It implies that the role of the sum of CA repeats in cancer risk may vary with the type of cancer. But considering there has been a few studies on the association between  $<38$  CA repeats and cancer risk, it needs to be further confirmed in more studies.

There was a trend for  $\leq 38$  CA repeats presenting lower circulating level of IGF1 than  $>38$  CA repeats in controls in our study. A meta-analysis demonstrated that higher circulating level of IGF1 significantly increased overall cancer risk, including CRC risk [6]. Similarly, circulating level of IGF1 in patients was significantly higher than that in controls in our study, especially in males. It seems that the association between the sum of CA repeats and CRC risk depends on the effect of the sum of CA repeats in IGF1 gene on circulating level of IGF1. Nevertheless, due to the lack of convincing evidence, it remains uncertain whether the sum of CA repeats

**Table 4. ORs and 95% CIs for the IGF1 CA repeat polymorphism and CRC risk stratified by sex.**

CA repeat groups	Male			Female		
	Cases/Controls (n=229/n=219)	OR <sup>a</sup> (95% CI)	p-value	Cases/Controls (n=138/n=148)	OR <sup>a</sup> (95% CI)	p-value
Group 1						
(CA)19/19	28/36	1.00 (reference)		22/29	1.00 (reference)	
(CA)19/non-19	91/84	0.72 (0.40–1.28)	0.259	57/52	0.69 (0.35–1.35)	0.279
(CA)non-19/non-19	110/99	0.70 (0.40–1.23)	0.216	59/67	0.86 (0.45–1.66)	0.655
Group 2						
$<38$ repeats	78/52	0.48 (0.28–0.81)	0.007	45/42	0.74 (0.40–1.37)	0.339
38 repeats	40/56	1.00 (reference)		36/45	1.00 (reference)	
$>38$ repeats	111/111	0.71 (0.44–1.16)	0.173	57/61	0.85 (0.48–1.51)	0.585

<sup>a</sup>adjusted for age.

**Table 5. Association between (CA)19 repeat polymorphism and clinicopathologic characteristics of CRC.**

Clinical characteristics n (%)	(CA)19 repeat genotype (n=367)			p-value <sup>a</sup>
	(CA) 19/19	(CA) 19/non-19	(CA) non-19/non-19	
Sex				0.689
Female	29 (44.6)	52 (38.2)	67 (40.4)	
Male	36 (55.4)	84 (61.8)	99 (59.6)	
Tumor location				0.992
Colon	21 (32.3)	45 (33.1)	54 (32.5)	
Rectum	44 (67.7)	91 (66.9)	112 (67.5)	
Dukes stage				0.768
A+B	40 (61.5)	77 (56.6)	94 (56.6)	
C+D	25 (38.5)	59 (43.4)	72 (43.4)	
Degree of differentiation				0.244
High/High-moderate	12 (18.5)	38 (27.9)	44 (26.5)	
Moderate	36 (55.4)	77 (56.6)	97 (58.4)	
Moderate-low/Low	17 (26.1)	21 (15.5)	25 (15.1)	

<sup>a</sup>based on chi-square test.**Table 6. Association between the sum of CA repeats in both alleles and clinicopathologic characteristics of CRC.**

Clinical characteristics n (%)	the sum of CA repeats (n = 367)		p-value <sup>a</sup>
	CA ≤38 repeats	CA >38 repeats	
Sex			0.075
Female	87 (44.6)	61 (35.5)	
Male	108 (55.4)	111 (64.5)	
Tumor location			0.782
Colon	65 (33.3)	55 (32.0)	
Rectum	130 (66.7)	117 (68.0)	
Dukes stage			0.814
A+B	111 (56.9)	100 (58.1)	
C+D	84 (43.1)	72 (41.9)	
Degree of differentiation			0.044
High/High-moderate	41 (21.0)	53 (30.8)	
Moderate	114 (58.5)	96 (55.8)	
Moderate-low/Low	40 (20.5)	23 (13.4)	

<sup>a</sup>based on chi-square test.**Table 7. Association between IGF1 CA genotype and circulating level of IGF1 in controls.**

IGF1 CA genotype	Circulating level of IGF1		
	Overall	Male	Female
CA ≤38 repeats	129.02±47.21	133.30±44.82	122.25±50.33
CA >38 repeats	137.56±46.39	144.58±45.76	123.38±44.80
p-value <sup>a</sup>	0.098	0.071	0.899
Presence of (CA)19	130.84±43.19	136.98±40.88	120.75±45.26
Absence of (CA)19	135.18±50.92	140.44±50.13	125.17±51.38
p-value <sup>a</sup>	0.399	0.581	0.616

<sup>a</sup>based on independent sample t-test.

influences CRC risk by itself or by its regulation on circulating level of IGF1, which needs to be explored further. In addition, our results revealed that patients carrying ≤38 CA repeats tended to have poor differentiation of CRC. This may be one of evidences for clinicians to estimate the prognosis of CRC patients. Nevertheless, this result should be explained cautiously due to the limited number of patients in our study. Greater numbers of patients are needed to deeply investigate the relationship between CA repeat polymorphism and clinicopathologic features of CRC.

Moreover, it has been shown that the (CA)18/19 genotype was significantly related to the decreased risk of CRC in the native Chinese population in our study, nevertheless, it suggested that (CA)21 repeat allele was associated with reduced CRC risk in a Singapore Chinese population (CA21/21 genotype versus other genotype, OR=0.48; 95% CI=0.28–0.84) [11].

The most common allele was (CA)19 repeat allele in this native Chinese population, which was consistent with a Singapore Chinese [11], German [22], African American and White population [23], but the range of CA repeats was variable in different populations. Most studies focused on the role of (CA)19 repeat allele in CRC risk. Some studies obtained the same conclusion as we gained that there was no association between (CA)19 repeat polymorphism and CRC risk [11, 20, 22], so were another two meta-analyses [26, 27]. Nevertheless, some studies indicated a significant association between CRC risk and (CA)19 repeat polymorphism [21, 23, 24], which was inconsistent with our finding. Morimoto et al. [21] demonstrated that other genotype was moderately related to CRC risk compared with (CA)19/19 genotype (OR=1.3; 95% CI=1.0–1.6), while this association was limited to females after stratification by sex. Similarly, Keku et al. [23] and Simons et al. [24] also confirmed the significant association between (CA)19 repeat polymorphism and CRC risk. Therefore, there is no consensus on the association between (CA)19 repeat allele and CRC risk. The inconsistency of these results may attribute to some possible factors: 1) the frequency distribution of CA alleles and the range of CA repeat vary in different populations; 2) the sample size is diverse in different studies; and 3) the confounding factors adjusted in various studies are not exactly the same. In addition, our results have shown no association between (CA)19 repeat polymorphism and circulating level of IGF1 in controls, which was similar to the conclusion of a meta-analysis [6].

Some limitations should be pointed out in our study. First of all, circulating level of IGF1 was determined only at single time point, which may not actually reflect long term level of IGF1 as it could be influenced by many factors as widely known. Then, the recruited participants were all Han Chinese, and the power to explain results was finite due to the limited sample size, greater number of populations and comparison with other ethnicities in China are needed in further studies. Moreover, CRC is a complicated disease as carcinogen-

esis may be a result of a combination of environmental and genetic factors, we cannot adjust for all confounding factors when the association between CA repeat polymorphism and CRC risk is evaluated.

In conclusion, the present study shows that individuals carrying <38 CA repeats but not >38 CA repeats is associated with decreased risk of CRC in comparison with individuals carrying 38 CA repeats, especially in males after stratification by sex. Our findings support the possible role of CA repeat polymorphism in CRC risk.

Acknowledgements: We sincerely thank all participants for providing blood specimen. The study was financially supported by A Key Project of Tianjin Bureau of Public Health (No. 12KG104).

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