Selenium intake, *IL-10* and colorectal cancer

The interaction effect of dietary selenium intake and the *IL10* rs1800871 polymorphism on the risk of colorectal cancer: a case–control study in Korea

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Abstract

The importance of selenium in human health has received much attention due to its antioxidant properties when it is consumed at an appropriate level. However, the existing evidence is limited to obtain an effective conclusion for colorectal cancer (CRC). Notably, an adequate intake of selenium was reported for Koreans. Furthermore, cytokine secretion and immune function may be affected by dietary selenium. Our study aimed to explore whether selenium potentially reduces CRC risk and whether the *IL10* rs1800871 polymorphism has an effect on this association. We designed a case–control study with 1,420 cases and 2,840 controls. A semiquantitative food frequency questionnaire was used to obtain information on selenium intake. We determined *IL10* rs1800871 through genetic analysis. Different models were developed to explore selenium intake related to CRC risk by calculating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. A reduced risk of CRC was found as selenium intake increased, with an OR (95% CI) of 0.44 (0.35–0.55) (p for trend <0.001). However, this association seems to be allele specific and only present among risk variant allele carriers (GA/GG) with a significant interaction between dietary selenium and *IL10* rs1800871 (P interaction=0.043). We emphasized that a reduction in CRC risk is associated with appropriate selenium intake. However, the *IL10* rs1800871 polymorphism has an impact on this reduction, with a greater effect on variant allele carriers. These findings suggest the importance of considering an individual's genetic characteristics when developing nutritional strategies for CRC prevention.

Keywords: selenium, colorectal cancer, *IL10* rs1800871, case–control, Korea.

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; IL10, interleukin 10; NF-κB, nuclear factor kappa-B; OR, odds ratio; SNP, single nucleotide polymorphism.

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Introduction

As the incidence of colorectal cancer (CRC) has recently increased, it has become one of the most common cancers globally. Specifically, the number of reported cases doubled between 1990 and 2019 [1]. According to GLOBOCAN, an estimated 1.9 million cases of CRC were diagnosed in 2020, and CRC was recognized as the third most common cancer [2]. The incidence of CRC has been documented to be greater in developed countries than in middle- and low-income countries [3]. In the Asia-Pacific region, there is a growing public health challenge due to an increasing burden, particularly in Eastern Asia, where high incidence rates have been observed [4]. South Korea is not an exception because it is one of the most commonly diagnosed cancers [4, 5].

The increasing trend in CRC incidence is strongly affected by several risk factors including sex, race, genetics and environmental factors related to Western lifestyles and diet [3]. The Western diet typically involves low fruit and vegetable consumption and overuse of refined sugar and salt, which has been indicated to have a detrimental effect on the immune system [6]. Notably, dietary selenium, primarily through its incorporation into selenoproteins, plays a certain role in immunity and inflammation by inhibiting activation of nuclear factor kappa-B (NF-κB) and C-reactive protein production [7, 8]. Additionally, selenium is recognized as a micronutrient with cancer-prevention properties [9].

To date, the importance of selenium in human health has received much attention due to its antioxidant properties when it is consumed at an appropriate level [10, 11]. However, due to contradictory results, the existing evidence on CRC prevention efficacy is limited. Previous studies have provided insights into the role of a high selenium concentration in relation to a substantially reduced CRC risk [10, 12]. Similarly, the beneficial effect on colorectal carcinogenesis was reinforced by the findings of another study [13]. In contrast, a meta-analysis of 69 studies revealed that cancer-prevention agents were effective for breast, gastric, lung, oesophageal, and prostate cancers but not for CRC [14]. Additionally, there is no evidence to support a role for high selenium concentrations in cancer prevention from the other meta-analysis. However, further studies should take into consideration individuals' genetic backgrounds to explore selenium in relation to cancer risk [15].

Furthermore, epidemiologic evidence is sufficient to support the causal link between inflammation and cancer progression [16]. Interleukin 10 (IL10) is known to be an anti-inflammatory cytokine that is produced by type 1 regulatory T cells and other cells [17]. It may suppress the Th1-mediated immune response and cell-mediated immune response and reciprocally enhances antibody-mediated responses [18]. IL10 plays a critical role in various physiological processes that maintain homeostasis in the gastrointestinal tract. It helps to regulate intestinal inflammation and various pathophysiological processes, including inflammatory bowel diseases, which are related to an elevated susceptibility to CRC [19]. The association between IL10 and CRC susceptibility was well recognized in a previous study. In detail, IL-10 levels were significantly greater in CRC patients than in healthy individuals. Importantly, the highest IL10 levels were identified in patients with stage IV disease, which was significantly greater than that in patients with stage I, II, or III disease. Thus, an increased IL-10 level was strongly associated with the progression of CRC. In contrast, no associations between IL-17 or IFNα levels and CRC was found [20]. Additionally, the expression of IL-10 was highlighted as an indicator of the prognosis of CRC patients in another study [21]. Notably, the *IL10* gene is located on at chromosomal region 1q31-1q32, and polymorphisms in this gene, especially polymorphisms in the promoter region, have been implicated in cancer because they can affect *IL10* gene transcription and translation [19, 22, 23]. Rs1800871 is a single-nucleotide polymorphism (SNP) in the promoter of the *IL10* gene in the Korean population. Notably, the interaction effect of genetics and diet provides a unique environment for cancer development and suppression. Individuals with high-risk genetic variants and particular dietary habits may exhibit a greater cancer risk than individuals without high-risk genetic variants [24]. Dietary selenium was indicated to have an effect on cytokine secretion and immune function [25]. A strong association between selenium and IL-10 has been documented. Selenium supplementation of immune cells led to increased IL10 expression in B cells and reduced induction of proinflammatory cytokines in B and CD4+ T cells. IL-10 production in response to selenium was confirmed to be linked to the activation of the ERK and Akt pathways [26]. Additionally, the oxidative stress-induced release of cytokines, including IL10, can be prevented by selenium [27]. Importantly, genetic background should be considered when assessing selenium intake or supplementation in relation to cancer [15]. Thus, we formulated a hypothesis regarding the interactive effect of selenium and the common variant *IL10* rs1800871, found in the *IL10* gene within the Korean population, on colorectal carcinogenesis.

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To our knowledge, there are a limited number of epidemiologic studies on the association of dietary selenium intake with CRC development. Furthermore, the ambiguous findings of previous studies raise questions about the potential protective role of selenium in CRC. Additionally, the effect of the *IL10* rs1800871 polymorphism on the association between the selenium concentration and CRC has not been studied. Thus, our study aimed to explore whether selenium has a potential preventative effect on CRC and whether the *IL10* rs1800871polymorphism has an impact on this association.

Materials and Methods

Study design and participants

We designed a case–control study by enrolling participants from the National Cancer Center (NCC) in Korea. We defined cases as individuals newly diagnosed with CRC at the Center for CRC of the NCC from August 2010 to September 2020. The participants who visited the Center for Cancer Prevention and Detection for Health Screening Program from October 2007 to December 2022 were considered controls. We used sex and age (±5 years) to match one case with two controls after excluding 290 cases and 5,409 controls with incomplete questionnaires or semiquantitative food frequency questionnaire (SQFFQ) results and 13 cases and 196 controls with implausible energy intake (<400 and ≥5000 kcal/day). Additionally, we excluded 57 cases with non-CRC and 1,305 controls with previous diagnosis with any cancer. Finally, we investigated dietary selenium intake in relation to CRC risk in 1,420 CRC cases and 2,840 controls. Furthermore, a total of 437 cases and 1,063 controls with missing information on *IL10* rs1800871 were excluded from the genetic analyses (**Figure 1**). This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Institutional Review Board of the National Cancer Center Korea (IRB numbers: NCCNCS-10-350 and NCC 2015-0202). Written informed consent was obtained from all subjects/patients.

Dietary assessment

The food consumption frequency of each participant and their portion size during the previous year were collected to assess dietary intake based on the 106-item SQFFQ. A previous report provided information on the reproducibility and validity of the SQFFQ [28]. The calculation of total energy and selenium intake was performed with CAN-Pro 5.0 (Computer Aided Nutritional Analysis Program, The Korean Nutrition Society, Seoul, Korea). Daily selenium intake was calculated as the sum of the selenium obtained from all foods consumed throughout the day (μg/day). Furthermore, information on demographics and lifestyle was provided using a self-administered questionnaire completed by participants.

Genotype measurement

We extracted genomic DNA from the blood samples of participants with MagAttract DNA Blood M48 Kit (Qiagen, Hilden, Germany) and BioRobot M48 automatic extraction equipment (Qiagen). The Illumina MEGA-Expanded Array (Illumina, Inc., CA, USA), which included 123K variants, was used for genotyping. A detailed description of this method has been provided in a previous publication [(29)]. The performance of genotype imputation was conducted using the Asian population (n=504) in the 1,000 Genomes haplotypes phase III integrated variant set release GRch37/hg19 (https://www.1000genomes.org/) as a reference panel. Genetic markers with deviation from Hardy–Weinberg equilibrium p values<$1x10^{-6}$, a minor allele frequency (MAF)<0.05, and a low call rate (<98%) were discarded. We used SHAPEIT (v2.r837) and IMPUTE2 (2.3.2) for phasing and single nucleotide polymorphism (SNP) imputation, respectively. The quality control criteria were applied after filtering for an INFO score over 0.6. Finally, *IL10* rs1800871 was selected as a candidate SNP for our analysis.

Statistical analyses

We analysed the differences in demographic and lifestyle factors between the cases and controls with t tests and chi-square tests. We adjusted the selenium concentration for total energy intake using a residual method [(30)]. The selenium intake quartiles were determined based on the distribution in the control group. We examined dose–response relationships based on the median value of each selenium category. We developed different models to explore selenium intake in relation to CRC risk by calculating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. We kept missing values for each variable as a category in the analysis. Additionally, multinomial logistic regression models were utilized to examine whether dietary selenium intake is associated with each anatomical subsite (proximal colon, distal colon or rectal cancer) of CRC patients. We used the Wald test to assess heterogeneity between sex groups. A dominant model was used for genetic analysis. The interaction effect between selenium and SNP was analyzed using the likelihood ratio test between the models with and without the interaction term (selenium*SNPs). SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used for all the statistical analyses, and a two-sided *P* value less than 0.05 was considered significant.

Results

Sociodemographic characteristics of the study population

A greater proportion of CRC patients than controls had a first-degree family history of CRC (10.1% vs. 5.4%, P<0.001). Similarly, the cases had a higher likelihood of being former alcohol consumers and less educated compared to controls (14.4% vs. 9.6%, P<0.001 and 17.8% vs. 6.1%, P<0.001, respectively). Furthermore, in comparison with healthy individuals, CRC patients tended to have lower levels of regular exercise, lower-status occupations, and lower incomes (35.5% vs. 56.0%, P<0.001; 23.4% vs. 27.9%, P<0.001; and 23.1% vs. 36.1%, P<0.001) **(Table 1)**.

Dietary selenium intake and CRC risk

The cases and controls exhibited significant differences in total energy and selenium intake. Specifically, total energy intake was greater in the cases than in the healthy individuals (P<0.001). Conversely, we observed a lower selenium consumption in these patients (44.1±16.9 µg/day vs. 50.9±19.1 µg/day) (P<0.001).

A higher dietary selenium intake seems to lead to a lower risk of colorectal carcinogenesis. Notably, significant associations were detected with both the unadjusted unconditional logistic regression model and the adjusted model; the ORs (95% CIs) were 0.35 (0.29–0.42) and 0.44 (0.35–0.55), respectively, P for trend <0.001. Notably, our findings consistently demonstrated a significant reduction in CRC risk for both males and females with a high selenium intake (OR=0.45 (0.33-0.60) and OR=0.46 (0.32-0.68), respectively) **(Table 2)**. Furthermore, the difference in the risk of CRC associated with selenium intake was different in proximal colon cancer risks across each gender (*p* heterogeneity <0.001). In detail, selenium tended to reduce distal colon cancer and rectal cancer risk but not proximal colon cancer risk in male individuals, whereas it contributed to decreased proximal colon cancer and rectal cancer risk among females **(Supplementary Table 1)**.

IL10 rs1800871 genetic polymorphisms and CRC risk

We investigated the *IL10* rs1800871 genetic polymorphism in relation to CRC risk using the dominant model with two groups of genotypes (AA and GA/GG) after excluding participants with missing information on the *IL10* rs1800871 gene. A total of 983 CRC cases and 1,774 controls were involved in the genetic analyses. According to the unadjusted model, variant allele carriers were more susceptible to developing CRC (OR=1.17 [1.00-1.37]). However, this greater risk disappeared after potential confounders were added to the model (OR=1.17 (0.97-1.40)). Furthermore, a marginal significance was observed for female participants carrying a minor allele compared to those with a homozygous wild-type (OR=1.34 (0.99-1.80)) **(Table 3).**

Interaction between the *IL10* rs1800871 genetic polymorphism and selenium and CRC risk

IL10 rs1800871 modified the association between selenium and colorectal carcinogenesis, suggesting that individual's CRC risk may differ based on genetic background. An association with a reduced CRC risk tended to be limited to *IL10* rs1800871 G-allele carriers with a high intake of selenium; the ORs (95% CIs) in the unadjusted unconditional logistic regression and adjusted models were 0.44 (0.32-0.61) and 0.61 (0.42-0.87), respectively. In contrast, participants with a homozygous wild-type allele exhibited a nonsignificant association between dietary selenium intake and CRC development. Notably, selenium and *IL10* rs1800871 were suggested to have a significant interaction on CRC susceptibility (P interaction=0.043).

Discussion

In this study, involving 4,260 participants, we emphasized the significant association between an appropriate selenium intake and CRC risk. Specifically, a high intake of selenium was associated with a reduced risk of CRC. Furthermore, we observed that the *IL10* rs1800871 polymorphism had an impact on this inverse association, with the effect being allele specific and present only among variant allele carriers.

Selenium has received significant attention for its potential anticarcinogenic properties, particularly in populations with low intake [(15)]. However, the role of selenium in CRC prevention is still debated, and a clear conclusion has not been reached due to previous contradictory results. For example, the selenium content in the diet is suggested to be a trace element for CRC prevention because a high dietary selenium concentration has been linked to a decrease in CRC risk [(13)]. Similarly, the risk of colorectal carcinoma decreased significantly with higher levels of selenium. The beneficial effect was more pronounced for females than for males. Thus, increasing selenium intake may be considered a strategy for reducing the risk of colorectal carcinoma, especially in patients who have suboptimal selenium intake [(31)]. Additionally, the anticancer effect of selenium intake was revealed in another study [12]. However, the aforementioned association was not supported by the conclusions of a previous study [14].

Our study adds to the growing body of evidence supporting the hypothesis regarding the significant role of appropriate intake of selenium in preventing the progression and development of CRC. However, extremely high selenium intake can cause adverse effects [11]. These finding are reinforced by potential biological mechanisms that underlie the anticarcinogenic properties of selenium. First, selenium has been reported to have antioxidant effects, which are believed to account for its preventative effects. The antioxidant effects of selenium are primarily attributed to its role as a constituent of redox-active selenoproteins, specifically those containing selenocysteine. These proteins contribute to reducing oxygen species and intra- and intermolecular disulfides or mixed disulfides/selenides [32]. Second, several selenproteins have been shown to affect various biological processes [32]. For example, glutathione peroxidases, including GPx2, contribute to mucosal integrity through antiapoptotic effects in colon crypts and reduce peroxide levels in the gut; thioredoxin reductases are involved in controlling transcription factor expression, cell proliferation and apoptosis [13]. Third, several metals are known to increase cancer risk. Notably, selenium can chemically interact with metals. Cadmium is a key element in the development of breast and prostate cancers; for example, selenium has a protective role against cadmium-induced peroxidative damage [32]. Fourth, the impact of selenium on the p53 protein has been documented, including its ability to inhibit proliferation, stimulate DNA repair, and promote apoptosis [33]. Fifth, NF-κB is associated with an enhanced inflammatory response, and selenium may inhibit its activation by modulating the expression of selenoprotein genes [8].

Chronic inflammation is well accepted to be involved in the aetiology of CRC, and inflammation occurs at the early stage of CRC progression and facilitates the progression of preneoplastic lesions into metastatic tumours. Anti-inflammatory cytokines and proinflammatory agents are important mediators and regulators of the immune response and contribute significantly to tumorigenesis by regulating tumour-related inflammation [19]. IL10, an anti-inflammatory cytokine, has been discussed as a regulator of carcinogenesis and tumour growth [34]. The SNPs located in the promoter region of the *IL10* gene are in relation to changes in transcription and expression. Thus, these promoter polymorphisms are thought to be related to cancer risk [23, 34]; however, the conclusion remains controversial. One of the *IL10* promoter

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polymorphisms is rs1800871, which has attracted increased amounts of attention from epidemiological studies because of its unclear association with cancer susceptibility. A previous study conducted in Croatia representing a European population concluded that this polymorphism may be associated with CRC risk. [35]. In contrast, another study based on Americans in Bethesda, Maryland, indicated a nonsignificant association where those results were consistent with the current study [36]. However, additional studies with larger sample sizes are necessary to provide reliable conclusions overall and by ethnicity [34].

A previous study suggested that focusing on genetic background is needed when assessing selenium intake or supplementation in relation to cancer [15]. Notably, the association between selenium and CRC appears to be allele specific in our study, further emphasizing the importance of considering genetic factors in such assessments. Specifically, an inverse association between selenium and colorectal carcinogenesis seemed to be limited to individuals who carry the minor G allele of *IL10* rs180087, for which the interaction effect of dietary selenium-*IL10* was significant. Although the exact mechanisms underlying the modification effect of *IL10* rs1800871 on this relationship are not fully understood, we propose probable explanations. A previous study highlighted the relationship between selenium and immune function and suggested that low and high selenium levels can have an impact on cytokine secretion and impair immune function in mice [25]. Furthermore, selenium deficiency can lead to an increase in the expression of NF-κB and HIF-1α. Additionally, the regulation of inflammatory cytokines is affected, and there is a decrease in the expression of *IL10* [37]. Another possible explanation may be that selenium inhibits the release of cytokines such as IL10, which may suppress cell-mediated immunity [27]. Taken together, the interaction between selenium and *IL10* may account for the different effects of selenium intake on CRC development, which depend on the genetic background of the participants.

Additionally, SNPs are known to play certain roles in regulating protein expression, which contributes to differences in disease susceptibility and severity among individuals. Rs1800896, rs1800871, and rs1800872 are three common SNPs located in the *IL10* gene that are associated with increased production of *IL10* and impact the expression and functions of proteins [38]. Notably, complete linkage disequilibrium was found between rs1800871 and rs1800872 [38]. A previous study indicated that participants with the AC or AC/CC genotype of rs1800872 exhibited a reduction in CRC risk compared to those with the AA genotype [39]. Thus, further

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studies are needed to confirm our findings, with a focus on the linkage disequilibrium between rs1800871 and rs1800872.

Furthermore, CRC risk has been shown to vary among males and females. Compared with males, females have a more aggressive form of neoplasia because the risk of right-sided (proximal) colon cancer seems to be greater. Importantly, dietary factors have been shown to be associated with tumour location. Thus, greater emphasis should be placed on sex-specific estimates of dietary risk factors to establish guidelines on dietary intake for cancer prevention [(40)]. Notably, there were discrepancies in selenium levels between females and males. Sex-specific nutritional and health behaviours, variations in selenium metabolism and selenium distribution across body compartments may explain these discrepancies [(15)]. Thus, we investigated the differences in the association between selenium intake and CRC between males and females. We found significant associations within the total population as well as for both males and females. Importantly, there is variation in dietary patterns between sex groups, highlighting the significance of adjusting for sex as a crucial confounder [(41)]. Thus, our results are more accurate and reliable because we adjusted for sex. Additionally, a significant interaction effect of the *IL10* rs1800871 genetic polymorphism and selenium intake on CRC risk was detected in the total population but not in males or females. The limited sample size may be a possible explanation for this observation.

The colon and rectum exhibit different receptor patterns because the colon arises from the midgut, and the rectum arises from the hindgut. Additionally, colon and rectal cancers have different functions and are exposed to faeces for different durations [(42)]. Furthermore, different genes are involved in oncogenesis in the colon and rectum. Notably, the proximal and distal colon were emphasized to have differences in clinical and molecular aspects. Familial polyposis syndrome arises first in the rectum and distal colon, whereas hereditary nonpolyposis coli arises in the proximal colon [(42)]. Thus, susceptibility to risk factors may vary between the distal and proximal colon. Furthermore, the aetiology of the anatomical site has been documented to have sex-specific disparities [(40)]. These findings are in line with our findings, which highlight the different effects of selenium on CRC risk between the distal and proximal colon in males and females.

Our study is the first to focus on the negative association between selenium and CRC involving an interaction with an inflammatory gene. Additionally, a validated SQFFQ, which was designed for the Korean population, was used in our study. Thus, we collected precise and representative dietary intake data from our study participants. Information on potential confounders was collected and adjusted for in our study. However, our study has several limitations. First, we had some degree of recall bias and selection bias due to the case–control design. Second, several important variables related to the selenium content in foods were not considered. Third, although the other probable genes may affect on the association between selenium and CRC, these genes were not considered in our study. Additionally, *IL10* rs1800871 has been demonstrated to have complete linkage disequilibrium with rs1800872 [38]. Thus, further studies are needed to focus on other genes beyond *IL10* and linkage disequilibrium between *IL10* rs1800871 and rs1800872 to reach an effective conclusion. Fourth, the small number of genotypes may have affected the statistical power of the genetic associations. Fifth, information on important variables, such as the serum selenium concentration and supplemental use, was not available for consideration as possible confounders in our analysis.

In conclusion, we provided evidence to support the notion that appropriate intake of selenium may reduce cancer risk. However, the potential benefit of selenium against colorectal carcinogenesis depends on the individual's genetic background; in detail, high selenium intake was emphasized to have a greater effect on variant allele carriers of *IL10* rs1800871. Our findings suggest that individual genetic characteristics should be considered in nutritional strategies for CRC prevention. However, further studies with crossover analyses are needed to confirm the established interaction between dietary selenium and the *IL10* rs1800871.

Statements and Declarations

Conflict of Interest: The authors declare that they have no conflicts of interests.

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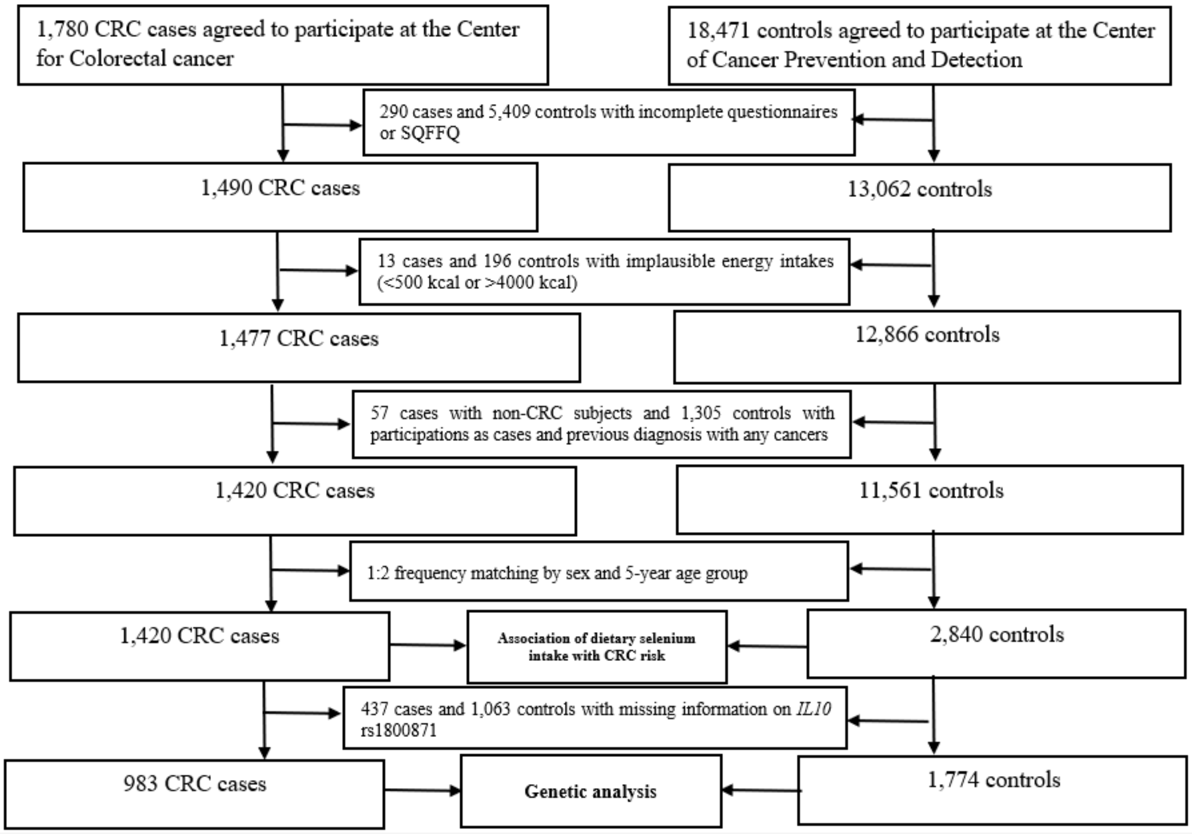

Figure 1. Flow chart of the study participants

After excluding participants with incomplete semi-quantitative food frequency questionnaire or a self-administered questionnaire, a total of 1,420 CRC cases and 2,840 controls were included in our analysis to investigate dietary selenium intake in relation to CRC risk. We additional excluded 437 cases and 1,063 controls with missing information on *IL10* rs1800871 for genetic analysis.

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Table 1. General characteristics of the subjects

	Total (n=4260)			Males (n=2748)			Females (n=1512)		
	Controls (n=2840)	**Cases (n=1420)**	***P*-value[a]**	**Controls (n=1832)**	**Cases (n=916)**	***P*-value[a]**	**Controls (n=1008)**	**Cases (n=504)**	***P*-value[a]**
Age (years)[b]	57.6±9.5	58.1±10.3	0.109	57.9±9.1	58.5±9.9	0.118	57.1±10.2	57.4±10.8	0.525
BMI (kg/m^2), n (%)									
<25	1752 (61.7)	907 (63.9)	0.354	1041 (56.8)	580 (63.3)	**0.004**	711 (70.5)	327 (64.9)	**0.014**
≥25	1047 (36.9)	509 (35.9)		760 (41.5)	333 (36.4)		287 (28.5)	176 (34.9)	
Missing	41 (1.4)	4 (0.2)		31 (1.7)	3 (0.3)		10 (1.0)	1 (0.2)	
First-degree family history of CRC, n (%)									
No	2683 (94.5)	1276 (89.9)	**<0.001**	1741 (95.0)	819 (89.4)	**<0.001**	942 (93.6)	457 (90.7)	**0.045**
Yes	153 (5.4)	144 (10.1)		88 (4.8)	97 (10.6)		65 (6.3)	47 (9.3)	
Missing	4 (0.1)	0 (0)		3 (0.2)	0 (0)		1 (0.1)	0 (0)	
Smoking status, n (%)									
Non-smoker	1311 (46.2)	689 (48.5)	0.319	372 (20.3)	234 (25.6)	0.008	939 (93.2)	455 (90.3)	0.149
Ex-smoker	1058 (37.3)	500 (35.2)		1014 (55.4)	472 (51.5)		44 (4.4)	28 (5.6)	
Current smoker	471 (16.5)	230 (16.2)		446 (24.3)	210 (22.9)		25 (2.4)	20 (4.0)	
Missing	0 (0)	1 (0.1)		0 (0)	0 (0)		0 (0)	1 (0.1)	
Alcohol consumption, n (%)									
Non-drinker	858 (30.2)	530 (37.3)	**<0.001**	306 (16.7)	204 (22.3)	**<0.001**	552 (54.7)	326 (64.7)	**<0.001**
Ex-drinker	272 (9.6)	204 (14.4)		227 (12.4)	161 (17.6)		45 (4.5)	43 (8.5)	
Current drinker	1710 (60.2)	685 (48.2)		1299 (70.9)	551 (60.1)		411 (40.8)	134 (26.6)	
Missing	0 (0)	1 (0.1)		0 (0)	0 (0)		0 (0)	1 (0.2)	
Regular exercise, n (%)									
Yes	1589 (56.0)	504 (35.5)	**<0.001**	1070 (58.4)	344 (37.6)	**<0.001**	519 (51.5)	160 (31.8)	**<0.001**
No	1101 (38.7)	916 (64.5)		732 (40.0)	572 (62.4)		369 (36.5)	344 (68.2)	
Missing	150 (5.3)	0 (0)		30 (1.6)	0 (0)		120 (12.0)	0 (0)	
Education n (%)									
Elementary school and lower	174 (6.1)	253 (17.8)	**<0.001**	77 (4.2)	114 (12.5)	**<0.001**	97 (9.6)	139 (27.6)	**<0.001**
Middle school	205 (7.2)	204 (14.3)		127 (6.9)	135 (14.7)		78 (7.8)	69 (13.7)	
High school	878 (30.9)	592 (41.7)		491 (26.8)	395 (43.1)		387 (38.3)	197 (39.1)	
College and higher	1542 (54.4)	369 (26.0)		1105 (60.4)	272 (29.7)		437 (43.4)	97 (19.3)	

Missing	41 (1.4)	2 (0.2)		32 (1.7)	0 (0)		9 (0.9)	2 (0.3)	
Occupation, n (%)									
Group 1: Professional, administrative or office workers	792 (27.9)	332 (23.4)	**<0.001**	604 (33.0)	268 (29.3)	**<0.001**	188 (18.7)	64 (12.7)	**<0.001**
Group 2: Sales or service industry workers	574 (20.2)	90 (6.3)		437 (23.9)	60 (6.6)		137 (13.6)	30 (6.0)	
Group 3: agriculturist, soldier or manufacturing workers	376 (13.2)	168 (11.8)		328 (17.9)	144 (15.7)		48 (4.8)	24 (4.8)	
Group 4: housekeeper, the jobless or others	1068 (37.6)	829 (58.4)		441 (24.0)	444 (48.4)		627 (62.2)	385 (76.4)	
Missing	30 (1.1)	1 (0.1)		22 (1.2)	0 (0)		8 (0.7)	1 (0.1)	
Marital status, n (%)									
Married	2404 (84.7)	1243 (87.5)	**0.038**	1637 (89.4)	830 (90.6)	0.500	767 (76.1)	413 (81.9)	0.022
Others	407 (14.3)	172 (12.1)		182 (9.9)	84 (9.2)		225 (22.3)	88 (17.5)	
Missing	29 (1.0)	5 (0.4)		13 (0.7)	2 (0.2)		16 (1.6)	3 (0.6)	
Monthly income, n (%) (10,000 Korean won/mo)									
<200	652 (22.9)	561 (39.5)	**<0.001**	365 (19.8)	359 (39.2)	**<0.001**	287 (28.5)	202 (40.1)	**<0.001**
200-400	1075 (37.9)	518 (36.5)		718 (39.2)	330 (36.0)		357 (35.5)	188 (37.3)	
≥400	1025 (36.1)	328 (23.1)		693 (37.9)	220 (24.0)		332 (32.9)	108 (21.4)	
Missing	88 (3.1)	13 (0.9)		56 (3.1)	7 (0.8)		32 (3.1)	6 (1.2)	
Total energy intake (kcal/day)[b]	1741.1±567.0	2043.6±575.2	**<0.001**	1785.1±547.8	2162.6±542.5	**<0.001**	1661.1±592.4	1827.3±570.4	**<0.001**
Selenium (μg/day)[b]	50.9±19.1	44.1±16.9	**<0.001**	49.7±18.7	43.1±16.2	**<0.001**	53.3±19.8	46.0±17.9	**<0.001**

Selenium was adjusted for total energy intake using the residuals method.

[a] *t-test and χ^2 test were used for continuous and categorical variables, respectively.*

[b] *mean ± SD.*

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Table 2. Odds ratios and 95% confidence intervals of CRC according to the *quartiles* of dietary selenium intake

Selenium (µg/day)	No.of controls (%)	No.of cases (%)	Model 1	Model 2
Total (n=4260)				
Q1 (<37.06)	710 (25.0)	549 (38.7)	1	1
Q2 (37.06–49.18)	710 (25.0)	422 (29.7)	0.77 (0.65–0.91)	0.88 (0.73–1.07)
Q3 (49.18–61.88)	710 (25.0)	258 (18.2)	0.47 (0.39–0.56)	**0.59 (0.48–0.74)**
Q4 (≥61.88)	710 (25.0)	191 (13.4)	0.35 (0.29–0.42)	**0.44 (0.35–0.55)**
P for trend			<0.001	**<0.001**
Males (n=2748)				
Q1 (<36.12)	458 (25.0)	342 (37.3)	1	1
Q2 (36.12–48.12)	458 (25.0)	287 (31.3)	0.84 (0.69–1.03)	1.00 (0.78–1.27)
Q3 (48.12–60.73)	458 (25.0)	171 (18.7)	0.50 (0.40–0.63)	**0.69 (0.53–0.90)**
Q4 (≥60.73)	458 (25.0)	116 (12.7)	0.34 (0.27–0.43)	**0.45 (0.33–0.60)**
P for trend			<0.001	**<0.001**
Females (n=1512)				
Q1 (<39.81)	252 (25.0)	207 (41.1)	1	1
Q2 (39.81–51.39)	252 (25.0)	139 (27.6)	0.67 (0.51–0.89)	0.78 (0.57–1.08)
Q3 (51.39–65.92)	252 (25.0)	92 (18.3)	0.44 (0.33–0.60)	**0.55 (0.38–0.78)**
Q4 (≥65.92)	252 (25.0)	66 (13.0)	0.32 (0.23–0.44)	**0.46 (0.32–0.68)**
P for trend			<0.001	**<0.001**

***Model 1**: unadjusted unconditional logistic regression model;* ***Model 2**: adjusted for age, BMI, first-degree family history of CRC, regular exercise, smoking status, alcohol consumption, occupation, education, and income. In the total subjects, model 2 was additionally adjusted for sex.*

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Table 3. Associations of *IL10* rs1800871 genetic polymorphisms with CRC risk in the dominant model

	Genotype	**No (%)**		**OR (95% CI)**	
		Controls	**Cases**	**Model 1**	**Model 2**
Total	AA	897 (50.6)	458 (46.6)	1	1
	GA/GG	877 (49.4)	525 (53.4)	1.17 (1.00-1.37)	1.17 (0.97-1.40)
Males	AA	532 (49.9)	298 (47.3)	1	1
	GA/GG	534 (50.1)	332 (52.7)	1.11 (0.91-1.35)	1.06 (0.84-1.34)
Females	AA	365 (51.6)	160 (45.3)	1	1
	GA/GG	343 (48.4)	193 (54.7)	1.28 (0.99-1.66)	1.34 (0.99-1.80)

Model 1*: unadjusted unconditional logistic regression model;* ***Model 2****: adjusted for age, BMI, first-degree family history of CRC, regular exercise, smoking status, alcohol consumption, occupation, education, and income. In the total subjects, model 2 was additionally adjusted for sex.*

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Table 4. Interaction between *IL10* rs1800871 genetic polymorphisms and selenium with CRC risk in the dominant model

	Genotype	**Selenium (µg/day)**	**No (%)**		**Model 1**	***P* interaction**	**Model 2**	***P* interaction**
			Controls	**Cases**	**OR (95% CI)**		**OR (95% CI)**	
Total	**AA**	Q1 (<37.63)	212 (23.6)	170 (37.1)	1	0.087	1	**0.043**
		Q2 (37.63–49.75)	232 (25.9)	123 (26.9)	0.66 (0.49-0.89)		0.96 (0.66-1.39)	
		Q3 (49.75–62.87)	229 (25.5)	112 (24.5)	0.61 (0.45-0.83)		0.94 (0.64-1.38)	
		Q4 (≥62.87)	224 (25.0)	53 (11.5)	0.30 (0.21-0.42)		0.39 (0.25-0.60)	
	GA/GG	Q1 (<37.63)	231 (26.3)	204 (38.9)	1		1	
		Q2 (37.63–49.75)	212 (24.2)	144 (27.4)	0.77 (0.58-1.02)		0.94 (0.68-1.31)	
		Q3 (49.74–62.87)	214 (24.0)	91 (17.3)	0.48 (0.35-0.66)		**0.63 (0.44-0.90)**	
		Q4 (≥62.87)	220 (24.5)	86 (16.4)	0.44 (0.32-0.61)		**0.61 (0.42-0.87)**	
Males	**AA**	Q1 (<36.44)	121 (22.7)	109 (36.6)	1	0.085	1	0.069
		Q2 (36.44–48.72)	145 (27.3)	82 (27.5)	0.63 (0.43-0.91)		0.91 (0.56-1.49)	
		Q3 (48.72–60.93)	135 (25.4)	70 (23.5)	0.58 (0.39-0.85)		1.07 (0.65-1.77)	
		Q4 (≥60.93)	131 (24.6)	37 (12.4)	0.31 (0.20-0.49)		0.40 (0.22-0.71)	

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	GA/GG	Q1 (<36.44)	146 (27.3)	118 (35.5)	1		1	
		Q2 (36.44–48.72)	121 (22.7)	103 (31.0)	1.05 (0.74-1.51)		1.24 (0.81-1.89)	
		Q3 (48.72–60.93)	132 (24.7)	57 (17.2)	0.53 (0.36-0.79)		0.75 (0.47-1.18)	
		Q4 (≥60.93)	135 (25.3)	54 (16.3)	0.50 (0.33-0.74)		0.74 (0.47-1.18)	
Females	**AA**	Q1 (<40.07)	93 (25.5)	63 (39.4)	1	0.706	1	0.568
		Q2 (40.07-51.47)	89 (24.4)	43 (26.9)	0.71 (0.44-1.16)		0.97 (0.53-1.78)	
		Q3 (51.47–66.41)	88 (24.1)	33 (20.6)	0.55 (0.33-0.92)		0.70 (0.37-1.31)	
		Q4 (≥66.41)	95 (26.0)	21 (13.1)	0.33 (0.18-0.58)		0.44 (0.23-0.88)	
	GA/GG	Q1 (<40.07)	84 (24.5)	81 (42.0)	1		1	
		Q2 (40.07-51.47)	88 (25.7)	45 (23.3)	0.53 (0.33-0.85)		0.59 (0.34-1.04)	
		Q3 (51.47–66.41)	89 (26.0)	38 (19.7)	0.44 (0.27-0.72)		0.58 (0.33-1.03)	
		Q4 (≥66.41)	82 (23.8)	29 (15.0)	0.37 (0.22-0.62)		0.51 (0.28-0.94)	

The quartiles of selenium were re-calculated after excluding participants with missing information on IL10 rs1800871

Model 1*: unadjusted unconditional logistic regression model;* ***Model 2****: adjusted for age, BMI, first-degree family history of CRC, regular exercise, smoking status, alcohol consumption, occupation, education, and income. In the total subjects, model 2 was additionally adjusted for sex.*

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