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RESEARCH PAPER

Polymorphisms in the selenoprotein S and 15-kDa selenoprotein genes are associated with altered susceptibility to colorectal cancer

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Abstract Selenium (Se), a dietary trace metal essential for human health, is incorporated into ~25 selenoproteins including selenoprotein S (SelS) and the 15-kDa selenoprotein (Sep15) both of which have functions in the endoplasmic reticulum protein unfolding response. The aim of this study was to investigate whether genetic variants in such selenoprotein genes are associated with altered risk of colorectal cancer (CRC). A Korean population of 827 patients with CRC and 733 healthy controls was genotyped for 7 SNPs in selenoprotein genes and one SNP in the gene encoding manganese superoxide dismutase using Sequenom technology. Multivariate logistic regression analysis showed that after adjustment for lifestyle factors three SNP variants were associated with altered disease risk. There was a mean odds ratio of 2.25 [95% CI 1.13,4.48] in females homozygous TT for rs34713741 in ***SELS*** with the T variant being associated with higher risk of rectal cancer, and odds ratios of 2.47 and 2.51, respectively, for rs5845 and rs5859 in ***SEP15*** with the minor A and T alleles being associated with increased risk of male rectal cancer. The data indicate that the minor alleles for rs5845, rs5859 and rs34713741 are associated with increased rectal cancer risk and that the effects of the three SNPs are dependent on gender. The results highlight potential links between Se, the function of two selenoproteins involved in the protein unfolding response and CRC risk. Further studies are required to investigate whether the effects of the variants on CRC risk are also modulated by dietary Se intake.

Keywords Selenium · Rectal cancer · 15-kDa selenoprotein · Selenoprotein S · SNP

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Introduction

Selenium (Se) is a dietary micronutrient that is essential for human health [23, 29]. Cancer mortality is inversely correlated with estimated Se intake [8, 29]. Low Se intake or low plasma Se concentrations are associated with increased risk of colorectal cancer (CRC) [7, 25] whereas in contrast, higher Se status is associated with lower risk of a recurrence of colonic tumours [15]. In the United States, daily supplementation with 200 μg

Se has been found to lead to reduced mortality from CRC [6].

The biological functions of Se are thought to be brought about through its presence as the amino acid selenocysteine in ~25 selenoproteins [2, 19]. Selenocysteine is incorporated into selenoproteins during their synthesis with a specific stem-loop structure in the 3′untranslated region (3′UTR) of the mRNAs required to recode a UGA codon from "stop" to selenocysteine [2]. These selenoproteins include the family of glutathione peroxidises [4], selenoprotein P (SePP) which has a Se transport role [5], selenoprotein S which is an endoplasmic reticulum protein involved in removing unfolded proteins and the 15-kDa selenoprotein which is also an endoplasmic reticulum protein involved in the unfolded protein response [11, 18]. Because the selenoproteins have important roles in cell stress responses and redox control [2, 4], it is possible that genetic variation due to single nucleotide polymorphisms (SNP) in the genes encoding the selenoproteins may influence susceptibility to cancer and Se requirements for optimal health.

Several SNPs in selenoprotein genes have been reported to have functional consequences. For example, rs1050450 causes a Pro-Leu amino acid change in glutathione peroxidise 1 and affects protein function [12], rs713041 causes a T-C substitution in a region of the glutathione peroxidise 4 (***GPX4***) gene corresponding to the 3′UTR of the mRNA and alters the protein binding to the 3′UTR and reporter gene activity [3, 21], rs5859 and rs5845 in the 3′UTR of the 15-kDa selenoprotein affect reporter gene activity [13] and rs7579 and rs3877899 in the ***SEPP1*** gene affect biomarkers of selenoprotein status in vivo [20]. Variants in the promoter of ***SELS*** are functional in that they modulate SelS expression and plasma levels of inflammatory cytokines [10].

Only a very limited number of studies have explored whether allelic variants of SNPs in selenoprotein genes are associated with altered disease susceptibility, and only three studies have investigated association with CRC or adenoma risk. Variants of a SNP in the promoter of the selenoprotein P gene (***SEPP1***) were not associated with altered risk of CRC [1], but a more recent study indicated that three variants in ***SEPP1*** and one in the thioredoxin reductase 1 gene *TXNRD1* showed an association with risk of adenoma [22]. In addition, a relatively small case–control study in the United Kingdom showed an association of the C variant of rs713041 in ***GPX4*** with increased risk of CRC [3]. The aim of the present work was to extend these studies by investigating the association between a series of SNPs and CRC risk, focusing on SNPs present in selenoprotein genes and known to be functional. To do this, we analysed DNA from a case–control study of a Korean population.

Subjects and methods

Subjects

The cases comprised of a consecutive series of patients with histologically confirmed incident colorectal adenocarcinomas, who were admitted to two university hospitals in Seoul, Korea between 1998 and 2004. At diagnosis, distinction was made between colon and rectal cancers. Tumours in the sigmoid colon were classified as colonic and those at rectosigmoid junction as rectal. A total of 827 patients were recruited. Seven hundred and thirty-three controls were selected from patients admitted to orthopaedics, general surgery, or otorhinolaryngology wards, for a wide spectrum of non-neoplastic conditions, including acute appendicitis, acute otitis media, inguinal hernia, and non-traumatic orthopaedic disorder, during the same period as the case admissions; those with a prior history of malignant neoplasms were excluded. The gender distribution of the two groups was similar with ~57% being men in both case and control groups. The demographic and lifestyle characteristics of the cases and controls are shown in Table 1. Venous blood was taken at the time of interview with written informed consent.

SNP Genotyping

After centrifugation of blood, DNA was extracted from the buffy coat using a commercial kit *(QIAGEN)* as described previously [16]. All participants were genotyped for 7 SNPs in selenoprotein genes: rs1050450 in ***GPX1***, rs713041 in ***GPX4***, rs5859 and rs5845 in the 15-kDa selenoprotein gene (***SEP15***), rs34713741 in ***SELS*** and rs7579 and rs3877899 in ***SEPP1***. In addition, since an association between rs1050450 in ***GPX1*** and breast cancer has been found to depend on genotype for the SNP in manganese superoxide dismutase gene that causes a Val/Ala change [9], the participants were also genotyped for SNP rs4880 in this gene. All SNPs with the exception of rs1050450 in ***GPX1*** were genotyped using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry of primer extension products (Sequenom iPlex system, Hamburg, Germany), especially suited to high throughput genotyping. The primer sequences were determined with Sequenom SpectroDESIGNER software, and amplification primers and extension primers are shown in Table 2. All reactions were carried out in a final volume of 5 μl according to manufacturer's conditions. Genotyping of 10% of the samples was repeated blind to confirm assay fidelity. The genotyping success rate was >93%.

Table 1 Demographic and lifestyle characteristics of subjects

	Case $N = 837$	Control $N = 739$	P value
Demographic characteristics			
Sex women (%)	41.3	45.5	0.099
Age (%)			
<55	29.4	37.4	<0.001
55–64	37.0	36.4	
65≤	33.6	26.2	
Education years (%)			
<9	28.5	25.8	0.133
9–12	42.7	40.4	
13≤	28.8	33.8	
Family history of CRC (%)	5.9	1.7	<0.001
BMI (kg/m^2), Mean(SD)	23.3 (3.0)	24.0 (3.1)	<0.001
BMI at 2 years ago(kg/m^2), Mean(SD)	24.2 (3.1)	24.2 (3.0)	0.728
Life style			
Regular intake of multi-vitamin[a] (%)	16.3	17.1	0.675
Smoking (%)			
None	54.4	63.7	0.001
Ex	14.3	11.7	
Current	31.3	24.6	
Alcohol intake (%)			
None	48.5	57.4	<0.001
Ex	8.7	4.9	
Current	42.8	37.7	
Participate in vigorous activity[b] (%)	27.5	31.4	0.103
Intakes of food items			
Red meat intake (times/week) (%)			
<2	32.2	33.5	0.724
2–3	43.4	41.4	
4≤	24.4	25.1	
Vegetable intake (times/week) (%)			
<9	40.9	34.0	0.026
9–19	32.6	36.0	
20 ≤	26.5	30.0	
Fruit intake (times/week) (%)			
<5	33.8	29.1	0.005
5–7	44.1	41.6	
8≤	22.1	29.3	

[a] Regular intake of multi-vitamin ≥ 4 times/week

[b] Participate in vigorous activity ≥ MET 6.0

Statistical analysis

The case–control association studies were analysed using χ^2 tests on 2 × 2 and 2 × 3 contingency tables for allele and genotype frequencies, respectively. No significant deviation from Hardy–Weinberg equilibrium was observed for any of the SNPs in this study, at the 5% level. Regression analysis was performed using the software program STATA (version 10.0). Initially, univariate logistic regression was used to assess the relationship between each variant and CRC risk. Subsequently, data were stratified according to disease subsite, and multivariate logistic analysis was carried out to calculate odds ratios, 95% confidence intervals (CI) and P for trend values after adjustment for age and gender only or for age, sex, intake of aspirin, intake of multivitamins, family history of colorectal cancer, smoking, alcohol, intake of red meat, vegetables and fruit, and physical activity.

Results

All the SNPs tested were in Hardy–Weinberg equilibrium. As indicated in Table 1, the control group was significantly younger than the CRC group, smoked less, had less family history of CRC and reported significant differences in alcohol, fruit and vegetable intake. Therefore, the genotype data were adjusted for age, intake of aspirin, intake of multivitamin, family history of colorectal cancer, smoking, alcohol, intakes of red meat, vegetables and fruits, and physical activity.

As shown in Table 3, after adjustment for age, sex and lifestyle factors, logistic regression analysis showed a mean odds ratio of 1.25 (95% CI 0.99,1.57, P for trend = 0.26) for carriage of one variant T allele of rs34713741 in ***SELS***. Stratification of the data according to disease subsite (rectal or colon cancer) showed a statistically significant increase in risk of rectal cancer for carriage of one T allele of this SNP (OR 1.4 [95% CI 1.04,1.89], P for trend = 0.018) and a borderline increase (OR 1.57 [95% CI 0.98,2.51]) for the homozygous TT individuals (Table 4). This variant did not appear to alter risk of colon cancer. When the data were analysed according to gender, the association of the T variant allele for rs34713741 with increased risk of CRC was not observed in men but was associated with increased risk of rectal cancer in women (Table 5) with an odds ratios of 2.25 (95% CI 1.13,4.48, P for trend = 0.017) for TT individuals.

As shown in Table 6, analysis of the data according to gender also showed that in men there was an increased risk of rectal cancer was associated with carriage of one variant allele of either rs5845 or rs5859 in the ***SEP15*** gene and this was of borderline statistical significance (OR 2.47; [95% CI 0.99,6.19], and OR 2.51; [95% CI 1.00,6.28], $P = 0.052$ and $P = 0.049$, respectively). There was, however, no increased risk in women or in patients with

Table 2 PCR primer sequences used for amplification of DNA for Sequenom analysis

Gene/SNP	PCR primers (Fwr, Rev)	Extension primer
MnSOD (SOD2)	ACGTTGGATGTTCTGCCTGGAGCCCAGATA	AGCCCAGATACCCCAAA
rs4880	and	
	ACGTTGGATGCTGTGCTTTCTCGTCTTCAG	
SELS	ACGTTGGATGGGAACGTTCTGTGCTATCTC	CTATCTCTTGGCTTGAGT
rs34713741	and	
	ACGTTGGATGTCGGTAAGAAATCCGTGAAC	
SEPP1	ACGTTGGATGGCTTATGGTGGTGATGAAGG	AGCAGGATGAGTAGGAG
rs3877899	and	
	ACGTTGGATGGCTTTCAGAGAATCAGCAAC	
SEPP1	ACGTTGGATGGTGTCTAGACTAAATTGGGG	ACTAAATTGGGGAGTATGT
rs7579	and	
	ACGTTGGATGCAGGCAAAAAAGTGAGAATG	
SEP15	ACGTTGGATGTGGTCCAGTTTTACGAACAA	AGTTTTACGAACAACAGATTT
rs5845	and	
	ACGTTGGATGACACAGCACATGAGGCATAG	
SEP15	ACGTTGGATGTGCGTTAATGAAGACTACAC	AGACTACACAGAAAACCTTTCTA
rs5859	and	
	ACGTTGGATGGCCAAGTATGTATCTGATCC	
GPX4	ACGTTGGATGCACAAGTGTGTGGCCCCGC	CCCTGCCCACGCCCT
rs713041	and	
	ACGTTGGATGTTTGCAGGCAGGCCGTCAT	

Individuals were genotyped for seven SNPs using Sequenom analysis. Amplification and extension primers used for the multiplex analysis are shown

colon cancer. There was no difference in allele frequencies between patients with either rectal cancer or colon cancer and controls for rs1050450, rs713041, rs4880 and rs3877899.

Discussion

The results presented here show that for three SNPs in selenoprotein genes, rs5845 and rs5859 in the ***SEP15*** gene and rs34713741 in the ***SELS*** gene, there were differences in allele frequency between patients with rectal cancer and healthy controls in a Korean population; the results suggest that the minor allele for all three SNPs is associated with increased disease risk. These SNPs are found in regulatory gene regions, one in the ***SELS*** promoter and two in the region of the ***SEP15*** gene corresponding to the 3′UTR of the mRNA. Regulatory elements within the 3′UTR are essential for selenium incorporation into selenoproteins [2] and therefore, SNPs in gene regions corresponding to the 3′UTR of selenoprotein mRNAs have the potential to influence selenoprotein expression. Indeed, minor allelic variants of rs5845 and rs5859 in ***SEP15*** have been shown to have functional consequences [13]. There are no available data on the functional effects of rs34713741, but it is situated very close (~100 bp) to rs28665122, a SNP that has been shown to modulate SelS expression and plasma levels of inflammatory cytokines [10]. This is the first report of an association of these SNPs with risk of CRC, but replication in a second and larger cohort is necessary to rule out the possibility that the findings could be explained by chance.

In the case of all three SNPs, the association of the minor allele with increased disease risk was modulated by gender. The effect of rs5845 and rs5859 in ***SEP15*** on rectal cancer risk was only significant in men, and the effect of rs34713741 in the ***SELS*** gene was only found in women (Tables 5, 6). The precise reason for this is not clear but it most likely reflects gender-specific differences in selenoprotein metabolism since such differences have been observed previously [24, 26]. In addition, all three SNPs affected risk of rectal but not colon cancer. The reason for this is not clear, and nothing is known of

Table 3 Genotype frequencies in Korean patients with colorectal cancer and controls

Gene/SNP	Case/cont	OR[a] (95% CI)	OR[b] (95% CI)
SOD2			
RS4880			
AA	665/583	1.0	1.0
GA	145/128	1.01(0.77–1.31)	0.98 (0.74–1.29)
GG	9/9	0.85 (0.33–2.17)	0.96 (0.36–2.56)
P for trend		*0.918*	*0.854*
SELS			
RS34713741			
CC	284/283	1.0	1.0
CT	441/351	1.24 (0.99–1.54)	1.25 (0.99–1.57)
TT	73/70	1.04 (0.72–1.50)	1.05 (0.71–1.56)
P for trend		*0.277*	*0.261*
SEPP1			
RS3877899			
CC	797/710	1.0	1.0
CT	5/1	5.02 (0.58–43.56)	5.99 (0.67–53.83)
SEPP1			
RS7579			
CC	409/363	1.0	1.0
CT	270/239	0.98 (0.71–1.06)	0.98 (0.77–1.25)
TT	66/67	0.86 (0.60–1.25)	0.93 (0.62–1.39)
P for trend		*0.516*	*0.856*
SEP15			
RS5845			
GG	793/707	1.0	1.0
GA	34/25	1.20 (0.71–2.04)	1.31(0.75–2.29)
P		*0.498*	*0.338*
SEP15			
RS5859			
CC	790/705	1.0	1.0
CT	34/25	1.20 (0.71–3.04)	1.31(0.75–2.30)
P		*0.496*	*0.337*
GPX4			
RS713041			
CC	339/275	1.0	1.0
CT	356/325	0.89 (0.72–1.11)	0.94 (0.74–1.18)
TT	101/97	0.85 (0.62–1.18)	0.95 (0.67–1.34)
P for trend		*0.240*	*0.659*
GPX1			
RS1050450			
CC	637/547	1.0	1.0
CT + TT	115/121	0.81(0.61–1.07)	0.89 (0.66–1.20)

Cases and controls were genotyped for the nine SNPS indicated and multivariate logistic regression was used to assess the relationship between each variant and CRC risk. Adjusted mean odds ratios (OR) with 95% confidence limits are shown. *P* for trend values (and *P* values for rs 5845 and 5859 where there are only two values) are indicated in italics

[a] Adjusted for age and sex

[b] Adjusted for age, sex, intake of aspirin, intake of multivitamins, family history of colorectal cancer, smoking, alcohol, intake of red meat, vegetables and fruit, and physical activity

selenoprotein expression in the rectum when compared to the colon.

Selenoprotein S is an endoplasmic reticulum protein involved in removing misfolded proteins, and SNP rs28665122 in the ***SELS*** promoter has been reported to be associated with altered levels of pro-inflammatory cytokines [10]. The observed difference in allele frequency of rs34713741 between patients with rectal cancer and controls (Tables 3, 4, 5) may reflect the close proximity (~100 bp) and likely linkage of rs28665122 and rs3471374 and changes in inflammatory events in the rectum, especially since altered inflammatory processes have been associated with increased CRC risk [17]. The previous failure to find any association between genotype for rs28665122 and susceptibility to inflammatory bowel disease [27] may reflect the small size of the population examined in that study. The present results suggest investigation of ***SELS*** association with gut inflammation using either mechanistic approaches or larger population groups would be worthwhile.

Sep15, a member of a novel family of selenoproteins, is also involved in protein folding mechanisms within the endoplasmic reticulum [11, 18]. Rs5845 and rs5859 are SNPs in a region of the ***SEP15*** gene corresponding to the 3′UTR; they are closely linked, and their modulation of the ability of the 3′UTR to promote reporter gene activity [13] indicates that they have functional consequences. Furthermore, the SNPs have been reported to affect breast cancer risk [13] and risk of lung cancer in smokers [14]. The present results indicate that the SNPs influence rectal cancer risk in men.

Glutathione peroxidise 4 has functions in detoxification of reactive oxygen species, especially lipid hydroperoxides [4] and has been implicated in regulation of inflammatory and apoptotic pathways [28]. A previous study of rs713041, a T-C substitution in ***GPX4***, indicated that in a cohort of Caucasians carriage of the T allele was associated with lower risk of with CRC [3]. The present data fail to confirm this observation, and this may reflect the larger size of the present cohort, ethnic or gender distribution differences in the populations studied (Caucasians in United Kingdom versus Koreans), or dietary and/or other environmental factors that differed in the two study groups.

In conclusion, the present study of a Korean population group shows that allele frequencies for three SNPs in selenoprotein genes, rs5845 and 5859 in the ***SEP15*** gene and rs34713741 in the ***SELS*** gene differ between patients with rectal cancer and healthy controls. The results suggest that the minor alleles for all three SNPs are associated with increased rectal cancer risk and that the effects of the SNPs are dependent on gender. It is notable that these SNPs are in genes that code for two selenoproteins involved in

Table 4 Genotype frequencies in Korean patients with colorectal cancer and controls stratified according to disease subsite

Gene/SNP	Colon cancer			Rectal cancer		
	Case/cont	OR[a] (95% CI)	OR[b] (95% CI)	Case/cont	OR[a] (95% CI)	OR[b] (95% CI)
SOD2						
RS4880						
AA	305/583	1.0	1.0	278/583	1.0	1.0
GA	66/128	0.99 (0.72–1.38)	0.96 (0.68–1.36)	65/128	1.08 (0.78–1.51)	1.04 (0.74–1.48)
GG	6/9	1.26 (0.44–3.58)	1.45 (0.49–4.30)	3/9	0.69 (0.19–2.59)	0.79 (0.20–3.05)
P for trend		*0.851*	*0.905*		*0.867*	*0.961*
SELS						
RS34713741						
CC	143/283	1.0	1.0	111/283	1.0	1.0
CT	203/351	1.12 (0.86–1.47)	1.09 (0.82–1.44)	187/351	**1.35 (1.01–1.79)**	**1.40 (1.04–1.89)**
TT	23/70	0.65 (0.39–1.09)	0.63 (0.37–1.07)	40/70	1.46 (0.93–2.29)	1.57 (0.98–2.51)
P for trend		*0.525*	*0.397*		***0.032***	***0.018***
SEPP1						
RS3877899						
CC	369/710	1.0	1.0	337/710	1.0	1.0
CT	1/1	0.266 (0.16–43.2)	3.21 (0.20–52.7)	2/1	4.74 (0.42–53.1)	5.35 (0.47–61.5)
SEPP1						
RS7579						
CC	190/363	1.0	1.0	176/363	1.0	1.0
CT	121/239	0.95 (0.72–1.26)	0.95 (0.70–1.27)	111/239	0.94 (0.70–1.25)	0.99 (0.73–1.36)
TT	32/67	0.90 (0.57–1.42)	0.96 (0.59–1.57)	26/67	0.78 (0.48–1.27)	0.86 (0.51–1.45)
P for trend		*0.634*	*0.863*		*0.331*	*0.728*
SEP15						
RS5845						
GG	368/707	1.0	1.0	333/707	1.0	1.0
GA	14/25	1.08 (0.55–2.10)	1.17 (0.58–2.35)	15/25	1.24 (0.64–2.38)	1.33 (0.67–2.64)
P		0.827	0.658		*0.524*	*0.411*
SEP15						
RS5859						
CC	369/705	1.0	1.0	329/705	1.0	1.0
CT	14/25	1.07 (0.55–2.09)	1.16 (0.58–2.34)	15/25	1.25 (0.65–2.41)	1.34 (0.68–2.66)
P	*P* for trend	0.84	0.671		*0.507*	*0.399*
GPX4						
RS713041						
CC	160/275	1.0	1.0	131/275	1.0	1.0
CT	161/325	0.85 (0.65–1.12)	0.93 (0.70–1.71)	159/325	1.03 (0.78–1.37)	1.07 (0.79–1.44)
TT	50/97	0.89 (0.60–1.32)	1.01 (0.67–1.55)	42/97	0.90 (0.59–1.37)	0.99 (0.64–1.56)
P for trend		*0.367*	*0.906*		*0.74*	*0.874*
GPX1						
RS1050450						
CC	385/547	1.0	1.0	271/547	1.0	1.0
CT + TT	53/121	0.80 (0.56–1.14)	0.89 (0.61–1.29)	48/121	0.80 (0.55–1.15)	0.89 (0.60–1.30)

Multivariate logistic regression was used to assess the relationship between each genetic variant and CRC risk. Adjusted mean odds ratios (OR) with 95% confidence limits are shown and those in bold indicate they are statistically significant. *P* for trend values (and *P* values for rs 5845 and 5859 where there are only two values) are indicated in italics

[a] Adjusted for age and sex

[b] Adjusted for age, sex, intake of aspirin, intake of multivitamin, family history of colorectal cancer, smoking, alcohol, intake of red meat, vegetables and fruits, and physical activities

Table 5 Genotype frequencies in female Korean patients with colorectal cancer and controls stratified according to disease subsite

Gene/SNP	Colon cancer			Rectal cancer		
	Case/cont	OR[a] (95% CI)	OR[b] (95% CI)	Case/cont	OR[a] (95% CI)	OR[b] (95% CI)
SOD2						
RS4880						
AA	126/265	1.0	1.0	114/265	1.0	1.0
GA + GG	29/56	1.14 (0.42–3.12)	1.16 (0.41–3.28)	32/56	8.56 (1.08–67.8)	8.52 (1.04–69.5)
SELS						
RS34713741						
CC	57/132	1.0	1.0	46/132	1.0	1.0
CT	87/151	1.32 (0.87–1.98)	1.35 (0.87–2.07)	75/151	1.42 (0.92–2.20)	1.43 (0.91–2.27)
TT	10/31	0.77 (0.35–1.68)	0.73 (0.32–1.68)	20/31	1.87 (0.97–3.61)	**2.25 (1.13–4.48)**
P for trend		*0.772*	*0.79*		***0.037***	***0.017***
SEPP1						
RS7579						
CC	96/171	1.0	1.0	75/171	1.0	1.0
CT	39/105	0.68 (0.43–1.06)	0.65 (0.40–1.05)	43/105	0.94 (0.60–1.47)	0.99 (0.62–1.59)
TT	13/26	0.90 (0.44–1.83)	1.01 (0.47–2.19)	13/26	1.15 (0.56–2.36)	1.35 (0.62–2.91)
P for trend		*0.242*	*0.343*		*0.895*	*0.609*
SEP15						
RS5845						
GG	152/317	1.0	1.0	144/317	1.0	1.0
GA	6/13	0.95 (0.35–2.56)	0.94 (0.34–2.59)	3/13	0.50 (0.14–1.79)	0.49 (0.13–1.78)
P		0.921	0.913		*0.286*	*0.278*
SEP15						
RS5859						
CC	152/315	1.0	1.0	142/315	1.0	1.0
CT	6/13	0.94 (0.35–2.54)	0.93 (0.34–2.57)	3/13	0.50 (0.14–1.80)	0.49 (0.14–1.79)
P		0.909	0.908		*0.291*	*0.281*
GPX4						
RS713041						
CC	57/125	1.0	1.0	50/125	1.0	1.0
CT	75/141	1.17 (0.76–1.78)	1.22 (0.79–1.89)	74/141	1.31 (0.85–2.02)	1.28 (0.82–2.01)
TT	22/49	0.98 (0.54–1.78)	1.02 (0.54–1.90)	16/49	0.81 (0.42–2.56)	0.79 (0.40–1.58)
P for trend		*0.846*	*0.69*		*0.960*	*0.914*
GPX1						
RS1050450						
CC	130/254	1.0	1.0	111/254	1.0	1.0
CT + TT	18/54	0.64 (0.36–1.15)	0.65 (0.35–1.19)	23/54	0.96 (0.56–1.65)	1.09 (0.62–1.91)

Multivariate logistic regression was used to assess the relationship between each genetic variant and CRC risk. Adjusted mean odds ratios (OR) with 95% confidence limits are shown and those in bold indicate statistical significance. *P* for trend values (and *P* values for rs 5845 and 5859 where there are only two values) are indicated in italics

[a] Adjusted for age and sex

[b] Adjusted for age, sex, intake of aspirin, intake of multivitamin, family history of colorectal cancer, smoking, alcohol, intake of red meat, vegetables and fruits, and physical activities

the metabolism of unfolded or misfolded proteins. Thus, the present results suggest that Se and these two selenoproteins have an important role in the unfolded protein response in cells of the large bowel and that genetic variation in these mechanisms may underlie rectal cancer susceptibility. Further studies are required to define the

Table 6 Genotype frequencies in male Korean patients with colorectal cancer and controls stratified according to disease subsite

Gene/SNP	Colon cancer			Rectal cancer		
	Case/Cont	OR[a] (95% CI)	OR[b] (95% CI)	Case/Cont	OR[a] (95% CI)	OR[b] (95% CI)
SOD2						
RS4880						
AA	179/318	1.0	1.0	164/318	1.0	1.0
GA + GG	43/81	0.44 (0.11–1.71)	0.58 (0.14–2.34)	36/81	0.91 (0.16–5.24)	0.90 (0.15–5.37)
SELS						
RS34713741						
CC	86/151	1.0	1.0	65/151	1.0	1.0
CT	116/200	1.00 (0.71–1.42)	0.90 (0.62–1.31)	112/200	1.29 (0.88–1.87)	1.32 (0.88–1.97)
TT	13/39	0.58 (0.29–1.15)	0.52 (0.25–1.06)	20/39	1.16 (0.63–2.16)	1.12 (0.58–5.18)
P for trend		*0.284*	*0.128*		*0.335*	*0.402*
SEPP1						
RS7579						
CC	94/192	1.0	1.0	101/192	1.0	1.0
CT	82/134	1.23 (0.85–1.78)	1.18 (0.80–1.76)	68/134	0.91 (0.62–1.33)	0.93 (0.62–1.40)
TT	19/41	0.94 (0.52–1.71)	0.90 (0.47–1.71)	13/41	0.56 (0.28–1.09)	0.56 (0.27–1.15)
P for trend		*0.703*	*0.772*		*0.126*	*0.212*
SEP15						
RS5845						
GG	216/390	1.0	1.0	189/390	1.0	1.0
GA	8/12	1.20 (0.48–2.99)	1.41 (0.52–3.83)	12/12	2.01 (0.88–4.58)	**2.47 (0.99–6.19)**
P		*0.695*	*0.506*		*0.098*	***0.052***
SEP15						
RS5859						
CC	217/390	1.0	1.0	187/390	1.0	1.0
CT	8/12	1.19 (0.48–2.97)	1.40 (0.51–3.81)	12/12	2.03 (0.89–4.63)	**2.51 (1.00–6.28)**
P		*0.702*	*0.513*		*0.093*	***0.049***
GPX4						
RS713041						
CC	103/150	1.0	1.0	81/150	1.0	1.0
CT	86/184	0.68 (0.48–0.97)	0.79 (0.54–1.16)	85/184	0.86 (0.59–1.24)	0.91 (0.61–1.37)
TT	28/48	0.85 (0.50–1.44)	1.04 (0.58–1.87)	26/48	0.98 (0.56–1.70)	1.19 (0.65–2.15)
P for trend		*0.17*	*0.673*		*0.692*	*0.803*
GPX1						
RS1050450						
CC	165/293	1.0	1.0	160/293	1.0	1.0
CT + TT	35/67	0.93 (0.59–1.46)	1.13 (0.70–1.83)	25/67	0.69 (0.42–1.14)	0.78 (0.45–1.32)

Multivariate logistic regression was used to assess the relationship between each genetic variant and CRC risk. Adjusted mean odds ratios (OR) with 95% confidence limits are shown and those in bold indicate statistical significance. *P* for trend values (and *P* values for rs 5845 and 5859 where there are only two values) are indicated in italics

[a] Adjusted for age and sex

[b] Adjusted for age, sex, intake of aspirin, intake of multivitamin, family history of colorectal cancer, smoking, alcohol, intake of red meat, vegetables and fruits, and physical activities

functional effects of the variants, especially rs34713741, to confirm whether the same effects on disease risk are seen in other ethnic populations and to investigate whether the effects of the variants are influenced by dietary Se intake.

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Conflict of interest statement None.

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