Introduction

Selenoproteins are a class of proteins with the amino acid selenocysteine that contains the active form of selenium [1]. Studies reporting associations between selenium and cancer, and particularly colon cancer [2,3], have directed attention to role of selenoproteins in the carcinogenic process. Twenty-five human selenoprotein genes have been identified [4], with most research focusing on the glutathione peroxidases (GPXs) and selenoprotein P (SePP1) which is involved in selenium transport [5]. However, given the biological properties of selenoproteins and their roles in control of intracellular redox environment, cellular growth, and defense against oxidative stress, it is feasible that other selenoproteins, such as thioredoxin reductase (TXNRD), selenoprotein W (SelW), selenoprotein N (SelN), selenoprotein S (SelS), selenoprotein H (SelH), selenoprotein X (SelX), and 15-kDa selenoprotein (SeP15) also may be involved in the carcinogenic process [4,6].

Thioredoxin reductases catalyze the NADPH-dependent reduction of oxidized thioredoxin [7]. Thioredoxins are catalyzing agents that prevent cumulative oxidative stress, a factor that has been linked to cell death and carcinogenesis and is an important factor for controlling cellular redox regulation [8]. Humans have three thioredoxin reductases which reduce different substrates in different cellular compartments [9,10,11]: thioredoxin reductase 1 (TXNRD1), thioredoxin reductase 2 (TXNRD2), and thioredoxin reductase 3 (TXNRD3). SeP15 is structurally similar to the thioredoxin family. It is located primarily in the endoplasmic reticulum and is involved in the induction of apoptosis and exhibits redox activity [1,12]. SepW has been shown to be expressed in the intestinal tract and studies have shown that it also exhibits oxidation-reduction activity and possible antioxidant properties [13,14]. SelS attenuates inflammation by decreasing pro-inflammatory cytokines [15]. SelN, SelH and SelX, although thought to have biological functions that involve redox functions and antioxidant properties, have been less well studied [4,14].
In this paper we evaluate associations between genetic polymorphism in \textit{TXNRD1}, \textit{TXNRD2}, \textit{TXNRD3}, \textit{C11orf31} (i.e. \textit{SelH}), \textit{SelW}, \textit{SelN1}, \textit{SelS}, \textit{SepX}, and \textit{SelP} and colon and rectal cancer. Results on \textit{GPX} and \textit{SelF} from study data have been previously assessed [16]. Given the hypothesized association between these genes and oxidative stress, we evaluate diet and lifestyle exposures that may influence observed colorectal cancer risk associated with these genes. Dietary antioxidants have been associated with other genes that mediate oxidative stress [17] and could likewise interact with these genes. Cigarette smoking can increase levels of oxidative stress; use of aspirin and non-steroidal anti-inflammatory drugs can reduce inflammation and thus reduce oxidative stress; BMI has been associated with increased inflammatory which can lead to oxidative stress. We evaluate estrogen status since studies have shown an association between estrogen status and selenium [18,19]; HRT use has been shown to reduce risk of colorectal cancer. We also evaluate if genetic variation in these selenoprotein genes influences survival after diagnosis with colon or rectal cancer since previous studies shown that \textit{SeP15} is associated with metastasis of colon cancer cells [20]. This expands on the work of others that have proposed that a combination of low selenium and SNPs in selenoprotein genes can enhance the risk of colorectal cancer [14].

Methods

Two study populations are included. The first, a population-based case-control study of colon cancer, included cases (\(n = 1,555\)) and controls (\(n = 1,956\)) identified between October 1, 1991 and September 30, 1994 living in the Twin Cities Metropolitan Area, Kaiser Permanente Medical Care Program of Northern California (KPMCP) and a seven-county area of Utah [21]. The second study used identical data collection methods as the first study but included population-based cases with cancer of the rectosigmoid junction or rectum (\(n = 754\)) and controls (\(n = 959\)) who were identified between May 1997 and May 2001 in Utah and KPMCP [22]. Eligible cases were between 30 and 79 years old at time of diagnosis, English speaking, mentally competent to complete the interview, no previous history of CRC, and no known (as indicated on the pathology report) familial adenomatous polyposis, ulcerative colitis, or Crohn’s disease. Controls were matched to cases by sex and by 5-year age groups. At KPMCP, controls were randomly selected from membership lists. In Utah, controls 65 years and older were randomly selected from the Health Care Financing Administration lists and controls younger than 65 years were randomly selected from driver’s license lists. In Minnesota, controls were selected from driver’s license and state-identification lists. Study details have been reported [21,22]. The Study was approved by the Institutional Review Board at the University of Utah. All participants signed informed consent.

Data were collected by trained and certified interviewers using laptop computers. All interviews were audio-taped and reviewed for quality control purposes [23]. The referent period for recall of diet and physical activity was two years prior to diagnosis for cases and prior to selection for controls. Detailed information was collected on diet [24], physical activity, medical history, cigarette smoking history, regular use of aspirin and non-steroidal anti-inflammatory drugs, and body size. Dietary data were collected on all participants using an extensive diet history questionnaire [25]. For those foods reported, we obtained information on quantity, frequency, and method of preparation. Foods were converted to nutrients using the Minnesota Nutrition Coding Center nutrient database. The body mass index (BMI) of kg/m\(^2\) was calculated from height measured at the time of the interview and weight recalled for the referent period of two years prior to diagnosis or selection. In instances where weight two years prior to diagnosis was unavailable, we used weight reported for five years prior to diagnosis or interview. Recalled weight was used to avoid possible misclassification of weight from weight loss attributed to cancer.

Tumor registry data were obtained to determine disease stage at diagnosis, months of survival after diagnosis, cause of death and contributing cause of death. Disease stage was categorized by Surveillance, Epidemiology, and End Results (SEER) staging of local, regional, and distant disease as well as by the American Joint Committee on Cancer (AJCC) staging criteria.

TagSNPs were selected using the following parameters: LD blocks were defined using a Caucasian LD map and an \(r^2 = 0.8\); minor allele frequency (MAF) \(>0.1\); range \(= -1500\) bps from the initiation codon to +1500 bps from the termination codon; and 1 SNP/LD bin. This procedure generated two markers for \textit{SelS}, three for \textit{SelP}, five for \textit{SelN1}, three for \textit{SelW1}, two for \textit{SepX1}, one for \textit{C11orf31}, eight for \textit{TXNRD1}, twenty for \textit{TXNRD2}, and five for \textit{TXNRD3}. All markers were genotyped using a multiplexed bead-array assay format based on GoldenGate chemistry (Illumina, San Diego, California). A genotyping call rate of 99.85% was attained. Blinded internal replicates represented 4.4% of the sample set; the duplicate concordance rate was 100%. Individuals with missing genotype data were not included in the analysis for that specific marker.

Statistical analyses were performed for each study independently using SAS \textregistered version 9.2 (SAS Institute, Cary, NC). The minor allele frequency (MAF) and test for Hardy-Weinberg Equilibrium (HWE) were calculated among white controls using the SAS ALLELE procedure. We report odds ratios (ORs) and 95% confidence intervals (CIs) assessed from adjusted multiple logistic regression models adjusting for age, center, race/ethnicity, and sex, which were matching variables for the original studies. Analysis for interaction was based on tagSNPs within each gene. All other SNPs were evaluated first by comparing the heterozygote and homozygote variant to the homozygote wildtype and subsequently assessing the dominant and recessive models; the best fitting model is presented.

Diet and lifestyle variables for assessment with candidate genes were selected because of their biological plausibility for involvement in this candidate pathway. Interactions between genes and hypothesized exposures associated with inflammation and oxidative stress included daily consumption of vitamin C, vitamin E, selenium, and beta carotene, recent aspirin or NSAID use, cigarette smoking status, BMI, and estrogen status. Nutrients reported were categorized based on sex-specific quartiles among the controls, collapsing the second and third quartiles to form an intermediate group. In addition to the minimal adjustments, logistic regression models involving dietary variables also control for total energy intake. P values for interaction were determined using a 1df likelihood-ratio test comparing a full model that included an interaction term with a reduced model without an interaction term. For genetic and environmental factors that have a 20% prevalence among controls with have 30% power to detect an OR of 1.87 for colon cancer and 2.30 for rectal cancer; for those with a 30% prevalence we have power to detect a 1.77 for colon and 2.15 for rectal when using a 5% significance levels The p values based on 1 degree of freedom (1-df) Wald test statistics for the main effect models were adjusted for multiple comparisons taking into account tagSNPs within the gene, using the methods of Connelly and Boehnke [26] via R version 2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). The interaction p values, based on 1-df likelihood-ratio tests, were adjusted using the
Table 1. tagSNPs analyzed.

| Symbol | Alias | Chromosome Location | SNP | Major/Minor Allele | FDR HWE | MAF1 |
|--------|-------|---------------------|-----|---------------------|---------|------|
| C11orf31 | C17orf10, SELH | 11q12.1 | rs9420 | G/A | 0.32 | 0.95 |
| Sel5 | AD-015, ADO15 | 15q26.3 | rs9874 | A/G | 0.14 | 1.00 |
| MGC104346, MGC2553 | | | rs4965814 | T/C | 0.18 | 1.00 |
| SBB18, SEPS1, VIMP | | | | | | |
| Sep15 | | 1p31 | rs2783974 | G/A | 0.12 | 0.75 |
| | | | rs486133 | T/C | 0.20 | 1.00 |
| | | | rs9433110 | G/A | 0.07 | 0.95 |
| SelN1 | FLJ24021 | 1p36.13 | rs718391 | C/G | 0.47 | 1.00 |
| | MDR51 | | rs2072749 | A/G | 0.27 | 1.00 |
| | RSMD1 | | rs11247735 | G/A | 0.47 | 1.00 |
| | RSS | | rs4659382 | C/G | 0.28 | 0.96 |
| | SEPN | | rs2294228 | T/G | 0.21 | 1.00 |
| SelW1 | SepW | 19q13.3 | rs10412896 | T/C | 0.35 | 0.98 |
| | | | rs3786777 | G/T | 0.49 | 1.00 |
| | | | rs2042286 | C/T | 0.39 | 0.98 |
| SepX1 | HSPC270, MGC3344 | 16p13.3 | rs13331553 | T/C | 0.29 | 1.00 |
| | M5R81, SELR, SELX | | rs732510 | A/G | 0.43 | 1.00 |
| TXNRD1 | GRIM-12 | 12q23-q24.1 | rs4964778 | C/G | 0.18 | 0.97 |
| | MGC9145 | | rs4964779 | T/C | 0.11 | 1.00 |
| | TR | | rs4523760 | T/C | 0.23 | 0.74 |
| | TR1 | | rs5018287 | G/A | 0.45 | 1.00 |
| | TRXR1 | | rs4964287 | C/T | 0.32 | 0.91 |
| | TXNR | | rs17202060 | C/T | 0.34 | 0.58 |
| | | | rs7962759 | C/G | 0.22 | 1.00 |
| | | | rs11610799 | G/C | 0.08 | 1.00 |
| TXNRD2 | SELZ | 22q11.21 | rs1044732 | A/G | 0.15 | 0.95 |
| | TR | | rs3788305 | A/G | 0.47 | 1.00 |
| | TR-BETA | | rs3788306 | T/C | 0.30 | 1.00 |
| | TR3 | | rs2073750 | G/A | 0.23 | 1.00 |
| | TRXR2 | | rs9606173 | A/T | 0.15 | 0.96 |
| | | | rs5992493 | A/G | 0.17 | 1.00 |
| | | | rs3788314 | G/A | 0.46 | 1.00 |
| | | | rs3788317 | G/T | 0.23 | 0.98 |
| | | | rs7410379 | G/A | 0.29 | 1.00 |
| | | | rs756661 | T/C | 0.45 | 0.97 |
| | | | rs5748469 | C/A | 0.35 | 0.98 |
| | | | rs17745445 | G/A | 0.15 | 1.00 |
| | | | rs1978058 | C/T | 0.38 | 0.81 |
| | | | rs8141691 | G/A | 0.37 | 0.68 |
| | | | rs9306229 | C/T | 0.24 | 0.48 |
| | | | rs4333017 | C/T | 0.14 | 0.98 |
| | | | rs5746847 | C/T | 0.44 | 1.00 |
| | | | rs9605030 | C/T | 0.14 | 1.00 |
| | | | rs6518591 | A/G | 0.19 | 0.58 |
| | | | rs2020917 | C/T | 0.27 | 0.97 |
| TXNRD3 | TGR | 3q21.3 | rs4679274 | C/T | 0.34 | 1.00 |
| | TR2 | | rs7777226 | G/A | 0.22 | 0.95 |
| | TRXR3 | | rs7777238 | C/T | 0.13 | 0.68 |
Table 1. Cont.

| Symbol | Alias | SNP | Major/Minor Allele | Chromosome Location | FDR HWE |
|--------|-------|-----|---------------------|---------------------|---------|
|        |       |     |                     |                     |         |
| rs9637365 |       | C/T | 0.42               |                     | 0.85    |
| rs11718498 |       | G/A | 0.42               |                     | 0.05    |

1Minor Allele Frequency (MAF) and FDR-adjusted Hardy-Weinberg Equilibrium (FDR HWE) based on white control population.

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step-down Bonferroni correction or the Holm’s test [27]. Wald p values from the main effect models and interaction p values based on likelihood-ratio tests were used to calculate multiple comparisons. We consider a p value of 0.10 to be potentially important for adjusted main effects and survival analysis given the candidate pathway approach we have used in this study. Since we are using the highly conservative Bonferroni method for adjustment of multiple comparisons for interactions, we consider a p value of 0.15 or less as potentially important so that we are able to consider both type 1 and type 2 errors. Additionally, we used a maxT permutations procedure [28] to further evaluate interactions and correspondingly adjust for multiple comparisons. Using the highly efficient methods of Welbourn [29], 100,000 max T permutations were performed for GXE pairing. Hypothesis tests involving genotype and lifestyle exposure combinations between an individual SNP and a single lifestyle variable were mutually adjusted by comparing each observed test statistic to the permutation null distribution of the maximum test statistic over all tests conducted upon that SNP. This adjustment was then expanded to similarly adjust for all pairings between a single lifestyle variable and all SNPs within a gene. This method also allowed for partitioning of the data to better identify and categorize the most meaningful groups where the interactions occurred. The maxT statistic complements other methods of multiple comparison adjustment by further defining the interaction as well as by using a more robust permutations adjustment for multiple comparisons. For survival analysis, multiple comparison adjustments were done using the false discovery rate (FDR) adjusted p values using the SAS MULTTEST procedure.

Survival-months were calculated based on month and year of diagnosis and month and year of death or date of last contact. Associations between SNPs and risk of death due to colorectal cancer were evaluated using Cox proportional hazards models to obtain adjusted hazard rate ratios (HRRs) and corresponding 95% confidence intervals. We adjusted for age at diagnosis, study center, race, sex, tumor molecular phenotype, and AJCC stage to estimate HRRs and censored individuals at date of last contact or death. Tumor molecular phenotype was determined from DNA sequenced hot spots for KRAS, and assessed CpG Island Methylator Phenotype (CIMP), and microsatellite instability (MSI).

Results

The tagSNPs analyzed are shown in Table 1; all SNPs are in HWE. SNPs that were independently associated with colon and rectal cancer are shown in Table 2. Although three SNPs in TXNRD1, TXNRD2 and SelN1 were associated with colon cancer, none remained statistically significant after adjustment for multiple comparisons as indicated by the pACT. TXNRD2 (3 SNPs), TXNRD3 (3 SNPs), SelN1 (3 SNPs), and SepX1 (1 SNP) were associated with rectal cancer. While SNPs in TXNRD2 and SepX1 did not remain statistically significant after adjustment for multiple comparisons, those in TXNRD3 and SelN1 were statistically significant after multiple comparison adjustments with pACT.

We observed statistically significant interaction with aspirin/NSAIDs and smoking with several candidate genes (Table 3). The most common interaction with aspirin followed the pattern of lower risk for the variant allele among NSAID users. Interactions between aspirin/NSAIDs with TXNRD1 rs4964778 remained statistically significant for colon cancer after adjustment for multiple comparisons; rs17745445 of TXNRD2 was borderline significant after adjustment for multiple comparison with the step-down Bonferroni correction. Two SNPs in TXNRD2 interacted significant with cigarette smoking for colon cancer where those who smoked were at greater risk with the variant allele; associations were not statistically significant after adjustment for multiple comparisons. For rectal cancer four SNPs in TXNRD1, TXNRD2, and TXNRD3 interacted with aspirin/NSAID use and two SNPs in TXNRD1 interacted with cigarette smoking; the step-down Bonferroni correction was greater than 0.15 for all of these associations. For rectal cancer and aspirin, the greatest effect of the genes appeared to be among non-NSAID users while among those who smoked cigarettes the variant allele appeared to reduce the risk of rectal cancer associated with smoking. The maxT, which is more robust for adjustment of multiple comparisons than the step-down Bonferroni correction, showed statistically significant interaction with all SNPs identified as interacting with aspirin/NSAID use for both colon and rectal cancer.

Only TXNRD3 rs11718498 and rs777226 were associated with vitamin E and beta carotene respectively after adjustment for multiple comparisons (Table S1) showing dietary variables associated with SNPs prior to adjustment and the corresponding p value after multiple comparison adjustment). In both instances those with low intake had reduced colon cancer risk in the presence of the variant genotype, while those with high intake were at reduced intake in the presence of wildtype and heterozygote variant.

We observed numerous statistically significant interactions between candidate genes, TXNRD2, SelS, SepP15, and SelN1 and estrogen status for both colon and rectal cancer (Table 4). While the variant alleles often increased risk among those not exposed to estrogen, they appeared to reduce risk among those exposed to estrogen. Roughly 50% of the SNPs initially associated showed a significant interaction after adjustment for multiple comparisons. Utilization of the maxT highlighted the focus of the interactive effects with most interactions remained statistically significant with this approach. In general, the estrogen status had a more pronounced effect depending on genotype of these candidate selenoprotein genes.

TXNRD1, TXNRD2, TXNRD3, and SelN1 interacted with BMI to alter risk of colon cancer and TXNRD1 interacted with BMI to statistically alter risk associated with rectal cancer (Table 5). The adjusted risk for SelN1 and colon cancer and both TXNRD1 SNPs and rectal cancer remained statistically significant after adjustment.
for multiple comparisons. The pattern of association implied that the cancer risk associated with obesity was influenced by genotype.

We evaluated these candidate selenoprotein genes with hazard of dying of colorectal cancer after diagnosis with colon or rectal cancer (Table 6). TXNRD1, TXNRD3, SeP15, and SepX1 were associated with survival after colon cancer diagnosis; SeP15 and SepX1 remained significant after FDR multiple comparison adjustment (HRR 1.47, 95% CI 1.13,1.90 and HRR 1.47 95% CI 1.13, 1.90).

| Table 2. Associations between TXNRD1, TXDRD2, TXNRD3, SelN1, and SepX1 and colon and rectal cancer. |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Colon Cancer                             | Controls                                          | Cases                                          | OR (95% CI)    | Raw P  | PR_{ACT} |
| TXNRD1 (rs17202060)                      |                                                |                                               |                |        |          |
| CC/CT                                     | 1722                                             | 1324                                          | 1.00            | 0.0209 | 0.1251   |
| TT                                        | 232                                              | 222                                           | 1.26 (1.04, 1.54) |        |          |
| TXNRD2 (rs3788317)                       |                                                |                                               |                |        |          |
| GG/GT                                     | 1859                                             | 1448                                          | 1.00            | 0.0266 | 0.3341   |
| TT                                        | 96                                               | 107                                           | 1.38 (1.04, 1.84) |        |          |
| SelN1 (rs4659382)                        |                                                |                                               |                |        |          |
| CC/CG                                     | 1797                                             | 1458                                          | 1.00            |        | 0.0383   | 0.1428   |
| GG                                        | 156                                              | 95                                            | 0.76 (0.58, 0.98) |        |          |
| Rectal Cancer                            |                                                   |                                               |                |        |          |
| TXNRD2 (rs1044732)                       |                                                |                                               |                | 0.0361 | 0.4002   |
| AA                                        | 685                                              | 575                                           | 1.00            |        |          |
| AG/GG                                     | 270                                              | 176                                           | 0.79 (0.63, 0.98) |        |          |
| TXNRD2 (rs5748469)                       |                                                |                                               |                | 0.0139 | 0.2017   |
| CC/CA                                     | 833                                              | 620                                           | 1.00            |        |          |
| AA                                        | 125                                              | 134                                           | 1.40 (1.07, 1.83) |        |          |
| TXNRD2 (rs5992493)                       |                                                |                                               |                |        |          |
| AA                                        | 619                                              | 521                                           | 1.00            |        |          |
| AG/GG                                     | 340                                              | 233                                           | 0.79 (0.65, 0.98) |        |          |
| TXNRD3 (rs11718498)                      |                                                |                                               |                | 0.0008 | 0.0036   |
| GG                                        | 361                                              | 227                                           | 1.00            |        |          |
| GA/AH                                     | 598                                              | 527                                           | 1.42 (1.16, 1.74) |        |          |
| TXNRD3 (rs4679274)                       |                                                |                                               |                | 0.0339 | 0.0919   |
| CC/CT                                     | 824                                              | 670                                           | 1.00            |        |          |
| TT                                        | 135                                              | 83                                            | 0.73 (0.54, 0.98) |        |          |
| TXNRD3 (rs9637365)                       |                                                |                                               |                | 0.0059 | 0.0208   |
| CC/CT                                     | 757                                              | 631                                           | 1.00            |        |          |
| TT                                        | 202                                              | 123                                           | 0.70 (0.55, 0.90) |        |          |
| SelN1 (rs11247735)                       |                                                |                                               |                | 0.0213 | 0.0410   |
| GG/GA                                     | 753                                              | 554                                           | 1.00            |        |          |
| AA                                        | 206                                              | 200                                           | 1.30 (1.04, 1.63) |        |          |
| SelN1 (rs2072749)                        |                                                |                                               |                | 0.0035 | 0.0159   |
| AA                                        | 484                                              | 422                                           | 1.00            |        |          |
| AG/P                                       | 394                                              | 294                                           | 0.86 (0.70, 1.05) |        |          |
| GG                                        | 81                                               | 38                                            | 0.53 (0.36, 0.80) |        |          |
| SelN1 (rs4659382)                        |                                                |                                               |                |        |          |
| CC/CG                                     | 876                                              | 716                                           | 1.00            |        | 0.0067   | 0.0247   |
| GG                                        | 81                                               | 38                                            | 0.58 (0.39, 0.86) |        |          |
| SelN1 (rs718391)                         |                                                |                                               |                | 0.0113 | 0.0300   |
| CC                                        | 250                                              | 239                                           | 1.00            |        |          |
| CG/GG                                     | 709                                              | 515                                           | 0.76 (0.62, 0.94) |        |          |
| SepX1 (rs732510)                         |                                                |                                               |                | 0.0310 | 0.0565   |
| AA/AG                                     | 763                                              | 563                                           | 1.00            |        |          |
| GG                                        | 192                                              | 187                                           | 1.29 (1.02, 1.63) |        |          |

{1} Associations adjusted for age, sex, race, and study center.
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Table 3. Associations between TXNRD and selenoprotein SNPs, recent regular use of aspirin/NSAID, cigarette smoking and risk of colon and rectal cancer.

|                      | Controls | Cases     | OR¹ (95% CI) | Controls | Cases     | OR (95% CI) | Wald P | Holm P | Interaction Level (L) Test² maxT P |
|----------------------|----------|-----------|--------------|----------|-----------|--------------|--------|--------|-----------------------------------|
| **Colon Cancer**     |          |           |              |          |           |              |        |        |                                   |
| TXNRD1 (rs4523760)   |          |           |              |          |           |              |        |        |                                   |
| TT                   | 686      | 612       | 1            | 459      | 304       | 0.75 (0.62, 0.90) | 0.0234 | 0.1638 | G = [1,2] & E = 1 <0.0001          |
| TC/CC                | 449      | 439       | 1.09 (0.92, 1.30) | 345 | 180       | 0.59 (0.47, 0.72) |        |        |                                   |
| TXNRD1 (rs49644778)  |          |           |              |          |           |              |        |        |                                   |
| CC                   | 779      | 691       | 1.00         | 524      | 350       | 0.76 (0.64, 0.90) | 0.0026 | 0.0208 | G = [1,2] & E = 1 <0.0001          |
| CG/GG                | 356      | 361       | 1.14 (0.95, 1.37) | 280 | 135       | 0.54 (0.43, 0.68) |        |        |                                   |
| TXNRD2 (rs17745445)  |          |           |              |          |           |              |        |        |                                   |
| GG                   | 855      | 756       | 1.00         | 580      | 375       | 0.74 (0.63, 0.87) | 0.0039 | 0.0780 | G = [1,2] & E = 1 0.0020          |
| GA/AA                | 281      | 297       | 1.20 (1.00, 1.46) | 223 | 110       | 0.55 (0.43, 0.71) |        |        |                                   |
| TXNRD2 (rs3788314)   |          |           |              |          |           |              |        |        |                                   |
| GG                   | 350      | 271       | 1.00         | 237      | 145       | 0.80 (0.62, 1.05) | 0.0198 | 0.3762 | G = [1,2] & E = 0 <0.0001          |
| GA                   | 561      | 527       | 1.22 (1.00, 1.48) | 381 | 239       | 0.81 (0.65, 1.02) |        |        |                                   |
| AA                   | 225      | 251       | 1.41 (1.11, 1.80) | 181 | 101       | 0.70 (0.52, 0.94) |        |        |                                   |
| TXNRD2 (rs5992493)   |          |           |              |          |           |              |        |        |                                   |
| AA                   | 794      | 691       | 1.00         | 553      | 349       | 0.73 (0.62, 0.87) | 0.0207 | 0.3762 | G = [1,2] & E = 0 0.0023          |
| AG/GG                | 342      | 362       | 1.20 (1.00, 1.43) | 250 | 136       | 0.61 (0.48, 0.77) |        |        |                                   |
| TXNRD2 (rs756661)    |          |           |              |          |           |              |        |        |                                   |
| TT                   | 353      | 364       | 1.00         | 257      | 141       | 0.53 (0.41, 0.68) | 0.0401 | 0.6817 | G in [0, 1] & E = 0 <0.0001       |
| TC                   | 548      | 503       | 0.90 (0.75, 1.10) | 373 | 239       | 0.63 (0.51, 0.79) |        |        |                                   |
| CC                   | 235      | 184       | 0.78 (0.61, 0.99) | 172 | 105       | 0.62 (0.46, 0.82) |        |        |                                   |
| TXNRD2 (rs17745445)  |          |           |              |          |           |              |        |        |                                   |
| GG                   | 1180     | 920       | 1.00         | 265      | 223       | 1.04 (0.85, 1.28) | 0.0388 | 0.7372 | G = [1,2] & E = 1 0.4918          |
| GA/AA                | 428      | 314       | 0.94 (0.79, 1.11) | 81    | 95        | 1.47 (1.08, 2.00) |        |        |                                   |
| TXNRD2 (rs5992493)   |          |           |              |          |           |              |        |        |                                   |
| AA                   | 1102     | 846       | 1.00         | 254      | 206       | 1.02 (0.83, 1.26) | 0.0241 | 0.4820 | G = [1,2] & E = 1 0.1540          |
| AG/GG                | 506      | 388       | 0.97 (0.83, 1.14) | 92    | 112       | 1.52 (1.13, 2.03) |        |        |                                   |
| Rectal Cancer        |          |           |              |          |           |              |        |        |                                   |
| TXNRD1 (rs49644778)  |          |           |              |          |           |              |        |        |                                   |
| CC                   | 364      | 321       | 1.00         | 283      | 198       | 0.80 (0.63, 1.02) | 0.0380 | 0.3040 | G = [1,2] & E = 1 0.0004          |
| CG/GG                | 157      | 156       | 1.15 (0.88, 1.50) | 144 | 73        | 0.59 (0.43, 0.81) |        |        |                                   |
| TXNRD2 (rs1978058)   |          |           |              |          |           |              |        |        |                                   |
| CC                   | 203      | 214       | 1.00         | 190      | 110       | 0.56 (0.41, 0.75) | 0.0446 | 0.8474 | G = [0,1] & E = 1 0.0141          |
| CT                   | 248      | 202       | 0.78 (0.60, 1.02) | 186 | 119       | 0.62 (0.46, 0.84) |        |        |                                   |
| TT                   | 70       | 61        | 0.84 (0.57, 1.25) | 51    | 42        | 0.80 (0.51, 1.26) |        |        |                                   |
| TXNRD2 (rs9606173)   |          |           |              |          |           |              |        |        |                                   |
| AA                   | 344      | 334       | 1.00         | 316      | 185       | 0.61 (0.48, 0.77) | 0.0353 | 0.7060 | G = 0 & E = 1 0.0145              |
| AT/TT                | 177      | 143       | 0.83 (0.63, 1.08) | 111 | 86        | 0.80 (0.58, 1.10) |        |        |                                   |
We observed associations between selenoprotein genes and colon and rectal cancer risk overall as well as from interacting with variables that may influence oxidative stress, including NSAIDs, cigarette smoking, BMI, and estrogen status. However, we observed only minimal interaction with dietary antioxidants, including selenium. In these data TXNRD1, TXNRD2, TXNRD3, SepX1, and SelN1 were associated with survival after diagnosis with rectal cancer, SelN1 rs718391 (HRR 1.67, 95% CI 1.11, 2.51) and SepX1 rs13331553 (HRR 1.46 95% CI 1.07, 2.00) and SelS were associated with colorectal cancer through either main or interaction association. CTNRD2 rs17202060 and TXNRD3 rs35009941 and colorectal adenomas [37]. Given the extremely rare minor allele frequency of that SNP (only one case of 747 were homozygote variant and four were heterozygote for the variant allele in their study), we did not genotype that SNP. A study by Meplan and colleagues also evaluated several of these genes combining colon and rectal cancers [38]. They observed a significant association with SelS, attributing to an inflammation-related pathway; SelS has been shown to attenuate inflammation by decreasing pro-inflammatory cytokines [15]. We did not observe an independent association with SelS. Hesketh and Meplan have hypothesized that genetic factors could modulate effects at multiple points along a network of pathways [39]. Pathways they cite as potentially important links between selenium, selenoproteins, and colon cancer involve oxidative stress, inflammation, and apoptosis.

Given the hypothesized influence of selenoproteins on oxidative stress and inflammation-related pathways, it is reasonable to determine if factors that alter inflammation such as aspirin/NSAID use and cigarette smoking could modify the risk associated with the genes. We observed that TXNRD1 and TXNRD2 interacted with both aspirin and cigarette smoking to alter colon and rectal cancer risk. TXNRD3 also interacted with aspirin/NSAID use to modify risk of rectal cancer, in that those with the variant genotype who did not use aspirin/NSAID had a similar reduced risk of rectal cancer as those who used aspirin/NSAID. These findings suggest that the risk associated with either not using aspirin/NSAID or smoking cigarettes may be influenced by genotype of several selenoprotein genes.

Of interest was the observed interaction between a number of SNPs in selenoprotein genes and estrogen status. Estrogen has anti-inflammatory properties, which could explain some of these associations. However, it also has been shown that estrogen influences tissue distribution and metabolism of selenium [19]. In vitro interaction studies have shown interaction between a splicing variant of TXNRD1b and both ERα and ERβ and concluded that it was an important modulator of estrogen signaling [18]. Other selenoproteins could have similar associations with estrogen status. In this study, we observed significant interactions with TXNRD2, SelS, SepX1, and SelW with estrogen status, although significance was reduced after multiple comparison adjustment. Although the same SNPs were not associated with colon and rectal cancer, both TXNRD2 and SelW were associated with both tumor sites. Recent estrogen exposure has been associated with reduced risk of colon and rectal cancer; selenoprotein genotypes appear to influence that association. Of interest was the observation that BMI reacted in a similar manner with TXNRD1, TXNRD2, and TXNRD3 as did aspirin/NSAIDs, and smoking cigarettes, and estrogen status. The mechanism underlying these interactions could involve both an inflammation-related pathway and an estrogen-related pathway. The colon and rectal cancer risk associated with BMI was influenced by genotype of these genes. The interaction with BMI

### Discussion

The thioredoxin system is a major antioxidant system central to intracellular oxidation processes [34,35,36]. The major independent associations were observed with survival after diagnosis with rectal cancer, SelN1 rs718391 (HRR 1.67, 95% CI 1.11, 2.51) and SepX1 rs13331553 (HRR 1.46 95% CI 1.07, 2.00) and SepX1 rs732510 (HRR 1.68 95% CI 1.09, 2.60) had FDR of <0.10.

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### Table 3.

|                | Controls | Cases | OR  (95% CI) | Controls | Cases | OR  (95% CI) | Wald P | Holm P | Test2 | maxT P |
|----------------|----------|-------|--------------|----------|-------|--------------|--------|--------|-------|--------|
| TXNRD3 (rs9637365) |          |       |              |          |       |              | 0.0265 | 0.1325 |       | 0.0002 |
| CC             | 164      | 179   | 1.00         | 147      | 83    | 0.52 (0.37, 0.74) |        |        |       |        |
| CT             | 241      | 226   | 0.86 (0.65, 1.14) | 197      | 138   | 0.65 (0.48, 0.88) |        |        |       |        |
| TT             | 116      | 72    | 0.55 (0.38, 0.79) | 84       | 50    | 0.53 (0.35, 0.81) |        |        |       |        |
| TXNRD1 (rs17202060) |         |       |              |          |       |              | 0.0274 | 0.2192 |       | 0.1078 |
| CC             | 369      | 237   | 1.00         | 64       | 76    | 1.82 (1.25, 2.64) | 0.0274 | 0.2192 |       | 0.1078 |
| CT             | 329      | 290   | 1.38 (1.10, 1.73) | 65       | 58    | 1.35 (0.91, 2.00) |        |        |       |        |
| TT             | 110      | 75    | 1.06 (0.76, 1.48) | 21       | 14    | 0.97 (0.48, 1.96) |        |        |       |        |

1 Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study center, race, and sex.
2 G = numerical coding (i.e., 0, 1, 2) for the SNP; E = numerical coding (i.e., 0, 1) for the environmental factor.
was greater for colon cancer than for rectal cancer, however associations with BMI overall appear to influence colon but not rectal cancer [21,40]. We are unaware of others evaluating the interaction between lifestyle factors and genetic variation in selenoprotein genes. Our results suggest that genetic risk is modified by lifestyle, but confirmation of these findings by others is needed.

Studies have shown that the thioredoxin system can predict prognosis of other types of cancer [34]. SeP15 has been shown to inhibit tumorigenicity and metastasis of colon cancer cells [20]. In the study by Irons, they observed that SeP15 influenced expression patterns of over 1000 genes in mice. Those genes that were most commonly influenced were those whose biological function included cellular growth and proliferation. We observed differences in likelihood of dying for several selenoprotein genes, Table 4.

### Table 4. Associations between TXNRD and selenoprotein SNPs and estrogen and risk of colon and rectal cancer.

|                      | Controls | Cases | OR (95% CI) | Controls | Cases | OR (95% CI) | Wald P | Holm P | Interaction Test \( \mathbf{maxT} \) P |
|----------------------|----------|-------|-------------|----------|-------|-------------|--------|--------|-------------------------------------|
| **Colon Cancer**     |          |       |             |          |       |             |        |        |                                     |
|                      | No Recent Estrogen Exposure | Recent Estrogen Exposure |        |        |                                      |
| TXNRD2 (rs17745445) |          |       |             |          |       |             |        |        |                                     |
| GG                   | 410      | 336   | 1.00        | 251      | 180   | 0.72 (0.54, 0.95) | 0.0011 | 0.0220 | G = (1,2) & E = 1 0.0077            |
| GA/AA                | 113      | 113   | 1.24 (0.92, 1.68) | 109      | 42    | 0.39 (0.26, 0.59) |        |        |                                     |
| TXNRD2 (rs3788314)  |          |       |             |          |       |             |        |        |                                     |
| GG                   | 177      | 121   | 1.00        | 88       | 73    | 1.01 (0.67, 1.52) | 0.0015 | 0.0270 | G = (1,2) & E = 1 0.0121            |
| GA                   | 244      | 219   | 1.32 (0.98, 1.77) | 186      | 102   | 0.65 (0.46, 0.94) |        |        |                                     |
| AA                   | 98       | 107   | 1.57 (1.09, 2.25) | 86       | 46    | 0.62 (0.40, 0.98) |        |        |                                     |
| TXNRD2 (rs3788317)  |          |       |             |          |       |             |        |        |                                     |
| GG                   | 332      | 261   | 1.00        | 193      | 145   | 0.78 (0.58, 1.06) | 0.0012 | 0.0228 | G = (1,2) & E = 1 0.0083            |
| GT/TT                | 191      | 188   | 1.24 (0.96, 1.61) | 167      | 77    | 0.47 (0.34, 0.67) |        |        |                                     |
| TXNRD2 (rs5992493)  |          |       |             |          |       |             |        |        |                                     |
| AA                   | 374      | 305   | 1.00        | 241      | 167   | 0.69 (0.52, 0.92) | 0.0197 | 0.2955 | G = (1,2) & E = 1 0.1093            |
| AG/GG                | 149      | 144   | 1.15 (0.87, 1.53) | 119      | 55    | 0.46 (0.31, 0.67) |        |        |                                     |
| TXNRD2 (rs756661)   |          |       |             |          |       |             |        |        |                                     |
| TT                   | 152      | 159   | 1.00        | 132      | 63    | 0.38 (0.25, 0.56) | 0.0101 | 0.1717 | G = 0 & E = 1 0.1076               |
| TC                   | 252      | 201   | 0.79 (0.59, 1.06) | 163      | 112   | 0.55 (0.38, 0.79) |        |        |                                     |
| CC                   | 118      | 89    | 0.75 (0.52, 1.07) | 65       | 46    | 0.58 (0.36, 0.92) |        |        |                                     |
| SelS (rs9874)       |          |       |             |          |       |             |        |        |                                     |
| AA                   | 392      | 306   | 1.00        | 251      | 160   | 0.67 (0.50, 0.89) | 0.0359 | 0.0718 | G = (1,2) & E = 0 0.0109            |
| AG/GG                | 131      | 143   | 1.39 (1.05, 1.84) | 110      | 62    | 0.56 (0.39, 0.82) |        |        |                                     |
| SeP15 (rs2783974)   |          |       |             |          |       |             |        |        |                                     |
| GG                   | 412      | 379   | 1.00        | 292      | 171   | 0.52 (0.40, 0.68) | 0.0236 | 0.0708 | G = 0 & E = 0 0.0018               |
| GA/AA                | 111      | 70    | 0.69 (0.50, 0.96) | 69       | 51    | 0.66 (0.43, 1.01) |        |        |                                     |
| SepW1 (rs3786777)   |          |       |             |          |       |             |        |        |                                     |
| GG/GT                | 399      | 320   | 1.00        | 259      | 178   | 0.7 (0.53, 0.93) | 0.0037 | 0.0111 | G = 2 & E = 1 0.0168               |
| TT                   | 123      | 129   | 1.27 (0.95, 1.70) | 102      | 44    | 0.43 (0.29, 0.64) |        |        |                                     |
| **Rectal Cancer**   |          |       |             |          |       |             |        |        |                                     |
| TXNRD2 (rs2073750)  |          |       |             |          |       |             |        |        |                                     |
| GG                   | 84       | 86    | 1.00        | 151      | 84    | 0.45 (0.29, 0.69) | 0.0065 | 0.1300 | G = 0 & E = 0 0.5276               |
| GA/AA                | 85       | 55    | 0.62 (0.39, 0.97) | 98       | 77    | 0.64 (0.41, 1.01) |        |        |                                     |
| SeP15 (rs2042286)   |          |       |             |          |       |             |        |        |                                     |
| GG/GT                | 89       | 91    | 1.00        | 52       | 55    | 0.98 (0.68, 1.43) | 0.0016 | 0.0048 | G = 2 & E = 1 0.0423               |
| CC/CT                | 18       | 17    | 1.00        | 24       | 15    | 0.54 (0.34, 0.84) |        |        |                                     |
| TT                   | 17       | 22    | 1.71 (0.87, 3.38) | 38       | 10    | 0.28 (0.13, 0.59) |        |        |                                     |

1 Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study center, race, and sex.
2 G = numerical coding (i.e., 0, 1, 2) for the SNP; E = numerical coding (i.e., 0, 1) for the environmental factor.

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Table 5. Interaction between TXNRD and selenoprotein SNPs and obesity and risk of colon cancer.

|                | Normal (<25) | Overweight (25–29) | Obese (> = 30) | Colon Cancer Controls Cases OR (95% CI) | Controls Cases OR (95% CI) | Controls Cases OR (95% CI) | Wald P | Holm P | Interaction Level Test | max T | P Holm |
|----------------|--------------|---------------------|----------------|----------------------------------------|---------------------------|---------------------------|--------|--------|------------------------|-------|--------|
| TXNRD1 (rs4964779) |              |                     |                |                                        |                           |                           |        |        |                        |       |        |
| TT             | 614          | 394                 | 1.00           | 307                                    | 341                       | 1.70                      | (1.39, 2.08) |     | <0.0001 |        |       |        |
| TC/CC          | 144          | 110                 | 1.19           | 162                                    | 123                       | 1.17                      | (0.90, 1.53) |     |          | 0.0001 |       |        |
| TXNRD2 (rs1044732) |            |                     |                |                                        |                           |                           |        |        |                        |       |        |
| AA             | 530          | 378                 | 1.00           | 584                                    | 452                       | 1.08                      | (0.90, 1.30) |     | 0.0928  |        |       |        |
| AG/GG          | 227          | 126                 | 0.78           | 210                                    | 177                       | 1.16                      | (0.91, 1.47) |     |          | 0.0015 |        |        |
| TXNRD3 (rs77238) |            |                     |                |                                        |                           |                           |        |        |                        |       |        |
| GG             | 396          | 241                 | 1.00           | 389                                    | 290                       | 1.21                      | (0.97, 1.52) |     | 0.0419  |        |       |        |
| GA/AA          | 361          | 262                 | 1.18           | 406                                    | 339                       | 1.35                      | (1.09, 1.68) |     | 0.07961 |        |       |        |
| SelN1 (rs11247735) |          |                     |                |                                        |                           |                           |        |        |                        |       |        |
| CC             | 597          | 375                 | 1.00           | 575                                    | 454                       | 1.25                      | (1.04, 1.50) |     | 0.0301  |        |       |        |
| CT/TT          | 161          | 129                 | 1.27           | 221                                    | 176                       | 1.25                      | (0.98, 1.58) |     | 0.0380  |        |       |        |
| SelN1 (rs718391) |          |                     |                |                                        |                           |                           |        |        |                        |       |        |
| CC             | 200          | 148                 | 1.00           | 242                                    | 187                       | 1.02                      | (0.77, 1.37) |     | 0.0025  |        |       |        |
| CG/GG          | 558          | 356                 | 0.85           | 554                                    | 443                       | 1.06                      | (0.83, 1.36) |     | 0.0002  |        |       |        |
| Rectal Cancer  |              |                     |                |                                        |                           |                           |        |        |                        |       |        |
| TXNRD1 (rs17202060) |          |                     |                |                                        |                           |                           |        |        |                        |       |        |
| CC             | 119          | 116                 | 1.00           | 197                                    | 125                       | 0.62                      | (0.44, 0.88) |     | 0.0002  |        |       |        |
| CT             | 140          | 99                  | 0.72           | 159                                    | 144                       | 0.90                      | (0.63, 1.37) |     | 0.0001  |        |       |        |
| TT             | 52           | 28                  | 0.53           | 51                                     | 33                        | 0.63                      | (0.38, 1.00) |     | 0.0017  |        |       |        |
| TXNRD1 (rs5018287) |          |                     |                |                                        |                           |                           |        |        |                        |       |        |
| GG             | 101          | 67                  | 1.00           | 115                                    | 89                        | 1.14                      | (0.75, 1.73) |     | <0.001  |        |       |        |
| GA             | 161          | 113                 | 1.07           | 196                                    | 154                       | 1.16                      | (0.79, 1.69) |     | 0.0005  |        |       |        |
| AA             | 49           | 63                  | 1.91           | 97                                     | 59                        | 0.88                      | (0.56, 1.39) |     | 0.3025  |        |       |        |

1Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study center, race, and sex.
2G = numerical coding (i.e., 0, 1, 2) for the SNP; E = numerical coding (i.e., 0, 1, 2) for the environmental factor.
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Table 6. Association between TNXRD and Selenoprotein genes and survival after diagnosis with colon and rectal cancer.

|       | Death/Person Years | HRR (95% CI) Raw | P  | FDR P |
|-------|-------------------|------------------|----|-------|
| **Colon Cancer** |                  |                  |    |       |
| TNXRD1 (rs4964778) |                  |                  |    |       |
| CC    | 202/5585          | 1.00             |    |       |
| CG/GG | 106/2561          | 1.28 (1.01, 1.63)|    |       |
| TNXRD3 (rs11718498) |                  |                  |    |       |
| GG/GA | 265/6812          | 1.00             |    |       |
| AA    | 44/1329           | 0.70 (0.50, 0.97)|    |       |
| SepX1 (rs9433110) |                  |                  |    |       |
| GG    | 254/6961          | 1.00             |    |       |
| GA/AA | 55/1187           | 1.45 (1.07, 1.95)|    |       |
| SepX1 (rs732510) |                  |                  |    |       |
| AA/AG | 227/6370          | 1.00             |    |       |
| GG    | 81/1729           | 1.47 (1.13, 1.90)|    |       |
| **Rectal Cancer** |                  |                  |    |       |
| TNXRD2 (rs3788314) |                  |                  |    |       |
| GG    | 56/1100           | 1.00             |    |       |
| GA/AA | 115/3190          | 0.69 (0.49, 0.96)|    |       |
| TNXRD2 (rs756661) |                  |                  |    |       |
| TT/TC | 139/3607          | 1.00             |    |       |
| CC    | 32/682            | 1.50 (1.00, 2.24)|    |       |
| SepX1 (rs718391) |                  |                  |    |       |
| CC/GG | 137/3482          | 1.00             |    |       |
| GG    | 34/807            | 1.67 (1.11, 2.51)|    |       |
| SepX1 (rs13331553) |                  |                  |    |       |
| TT    | 78/2155           | 1.00             |    |       |
| TC/CC | 93/2135           | 1.46 (1.07, 2.00)|    |       |
| SepX1 (rs732510) |                  |                  |    |       |
| AA    | 41/1275           | 1.00             |    |       |
| AG    | 80/1974           | 1.22 (0.83, 1.80)|    |       |
| GG    | 49/1022           | 1.68 (1.09, 2.60)|    |       |
| P Trend | 0.0182            |                  |    |       |

1 Hazard Rate Ratios (HRR) adjusted for age, study center, race, sex, AJCC stage, and tumor markers.

Table S1: Associations between dietary variables and selenoprotein genes, adjusted for age, center, race, sex, and kcal.

including SepX5, which would support the hypothesis that genetic variation in selenoprotein genes may influence survival after diagnosis.

Major strengths of our study were the hypothesis-driven approach, the large and extensive data set that includes information on genetic, diet, and lifestyle data, and our ability to examine colon and rectal cancer separately. While we believe that the data we present are both thorough and informative, we acknowledge that limitations exist. For instance, while we have detected associations we have minimal information on the functionality of the SNPs evaluated. Additional lab-based experiments are needed to determine functionality. Through our analysis we have made many comparisons. We used several methods to adjust for multiple comparisons, the pACT which takes into account the correlated nature of the SNP data, the step-down Holm Bonferroni to adjust for interaction associations, and the maxT which relies on permutation methods. Several interactions were significant after adjusting for multiple comparisons by both methods. The maxT method partitions the data into categories that help to describe the interaction while the step-down Bonferroni statistic is based on our results from logistic regression models that rely on a common referent point and test for difference in effects across cells of environmental and genetic exposures. We believe that these two methods are complimentary, reinforcing the associations that are significant after multiple testing adjustment and helping to define the elements of the data that are interacting. However, we acknowledge the possibility of chance findings and therefore replication of these results is critical.

Several potential weakness exist. Our study relied on recalled dietary intake to evaluate nutrients such as selenium. Nutrient databases for selenium content of foods can be inaccurate given the selenium content of the soil influences selenium levels in food. Information on source of food could not be obtained in a study such as this given the lack of knowledge where foods are grown or the selenium content of soil, leaving the possibility of lack of association from misclassification of selenium intake. Unfortunately, given the study design we do not have selenium measurements that would more accurately reflect selenium levels of study participants. Additionally, we have relied on self-reported weight to calculate BMI. We were unable to evaluate change in weight that may be associated. In our study, Hispanic and African American participants had larger mean levels of BMI; however the associations with colon cancer were the same across all ethnic groups.

The study findings support an association between selenoprotein genes and colon and rectal cancer development and survival after diagnosis. Given the interactions observed, it is likely that the impact of cancer susceptibility from genotype is modified by lifestyle factors. The data presented here support the role of selenoproteins in the carcinogenic process and suggest that they may function through pathways that involve inflammation, oxidative stress, and estrogen.

Supporting Information

Table S1: Associations between dietary variables and selenoprotein genes, adjusted for age, center, race, sex, and kcal.

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Author Contributions

Conceived and designed the experiments: MS RKW. Performed the experiments: MS RKW. Analyzed the data: AL BW CC. Contributed reagents/materials/analysis tools: BW CC. Wrote the paper: MS.
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