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Associations of base excision repair genotypes with incident, sporadic colorectal adenoma according to antioxidant enzyme genotypes and oxidative balance-related environmental exposures

By

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Master of Science in Public Health

Epidemiology

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B.M.S., Hebei Medical University, 2013

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Abstract

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By Tengteng Wang

Associations of individual base excision repair (BER) genotypes with colorectal adenoma risk are unclear, but likely modest. However, genetic risk scores (GRS) that aggregate information from multiple genetic variants might be useful for assessing genetic predisposition to colorectal adenoma. We conducted an analysis of 1,073 Caucasians aged from 30–74 years using data pooled from the three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma that collected blood for genotyping and extensive dietary and other data. Associations of individual single nucleotide polymorphisms (SNPs) were assessed and used to combine information from multiple risk variants into a BER GRS based on 74 SNPs in 14 BER genes and an antioxidant enzymes GRS based on 22 SNPs in 3 antioxidant enzyme genes using two methods: a simple variant allele count method (count GRS) and a weighted method (weighted GRS). We also considered 15 extrinsic factors with known pro- or anti-oxidant properties to construct an oxidative balance score (OBS). Multivariable unconditional logistic regression was used to assess associations of BER genotypes with incident, sporadic colorectal adenoma, overall and according to the antioxidant enzyme GRS and the OBS. The odds ratio (OR) for those in the highest relative to the lowest tertile of the weighted BER GRS was 2.65 (95% confidence interval [CI], 1.58-4.43; P_{trend} <0.001). However, there were no clear patterns to suggest possible BER GRS-antioxidant enzymes GRS or -OBS interactions. Our findings suggest that BER genotypes collectively may be associated with risk for incident sporadic colorectal adenomas.

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CHAPTER I: BACKGROUND

Colorectal cancer is the third most common cancer diagnosed in men and women, and is the second leading cause of cancer death in men and women combined in the United States (1). In 2014, there were approximately 136,830 individuals diagnosed with colorectal cancer and 50,310 deaths from this disease in the United States (1). Colorectal cancer incidence and mortality rates have been decreasing rapidly in the US during the past decade, and has largely been attributed to the detection and removal of precancerous polyps as a result of increased colorectal cancer screening, reinforcing the patho-genetic relationship between colorectal adenomas and cancer (2). It had been widely accepted that most colorectal cancers develop from colorectal adenomas in a morphological and genetic progression termed the adenoma– carcinoma sequence (3). Therefore, the identification of risk factors for adenoma has significant public health implications.

There are many known factors that increase or decrease risk of colorectal adenoma; some of these factors are modifiable while others are not. Non-modifiable risk factors include a personal or family history of colorectal cancer or adenomatous polyps and a personal history of chronic inflammatory bowel disease (4). Modifiable risk factors include physical inactivity, obesity, high consumption of red and/or processed meats, smoking, moderate-to-heavy alcohol consumption and folate deficiency (5, 6), whereas folate supplementation may promote progression of established adenomas (7). The National Cancer Institute estimates that at least two-thirds of colorectal cancers are potentially preventable (8). The substantial international variation in colorectal cancer incidence (9) and several migration studies (10-12) all suggest that this type of cancer is a disease largely related to Western diet and lifestyle (13). However, with few exceptions, most of the associations have been either modest or not entirely consistent. Since colorectal cancer is a multifactorial disease determined jointly by genetic susceptibility and

exposures to environmental factors, one possible explanation for the modest or inconsistent results in relation to various dietary and other lifestyle factors could be that the associations differ by genotype, distributions of which may differ across study populations (14). Therefore, it is important to identify genetic factors that serve as effect modifiers of the associations of colorectal neoplasms with its major modifiable risk factors.

A deficient response to DNA damage resulting from both exogenous and endogenous agents may lead to genetic alterations favoring malignancy and an increased risk of colorectal neoplasms. DNA repair systems play an important role in protecting the genome from oxidative damage. The four major pathways for repairing DNA damage are nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR), and mismatch repair (MMR). The NER pathway is the most versatile mechanism of DNA repair, removing a large number of structurally unrelated DNA lesions: bulky lesions such as pyrimidine dimers, other photoproducts, larger chemical adducts, and cross-links (15). The BER pathway operates on small lesions such as oxidized or reduced bases, fragmented or non-bulky adducts, or those produced by methylating agents (16). DSBR removes the damages produced by replication errors and by exogenous agents, such as ionizing radiation (17). MMR removes nucleotides mispaired by DNA polymerases and insertion/deletion loops that result from slippage during replication of repetitive sequences or during recombination (18).

Among the four pathways, BER may be particularly important for the prevention of colorectal neoplasms because it removes small lesions and non-bulky adducts caused by oxidative damage and alkylating agents (19, 20). BER consists of two major sub-pathways: short-patch BER and long-patch BER (21). In both pathways, a DNA glycosylase cleaves the damaged base from the DNA backbone, creating an abasic site. Depending on the type of DNA glycosylase that removed the damaged base, AP endo-nuclease 1 (*APEX1*) either nicks the DNA backbone 5' of this site or

removes the 3' residue (22). In short-patch BER, DNA polymerase β (*POLβ*) replaces the missing nucleotide, and the gap is sealed by the DNA ligase III (*LIG3*) or the x-ray repair cross complementing group (*XRCC1*) complex with the help of Poly (ADP-Ribose) Polymerase 1 (*PARP1*) (23). In long-patch BER, an oligonucleotide of two to seven bases is synthesized by *POLβ*. A flap-endonuclease then removes the damaged strand, allowing the newly synthesized nucleotides to fill the gap, and DNA ligase I (*LIG1*) seals the gap (22).

Other genes also play a key role in the base excision repair of DNA damage. 8-oxoguanine DNA glycosylase (*OGG1*) is a DNA glycosylase that removes 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxo-G), which is the most stable form of a highly mutagenic oxidative DNA adduct that pairs with cytosine (24). Nth Endonuclease III-Like 1 (*NTHL*) helps remove the damaged base from 8-oxo G: G base-pairs (25). MutY homolog (*MUTYH*) is another DNA glycosylase that removes adenine paired with 8-oxo-G or 1, 2-dihy-dro-2-oxoadenine (2-OH-A) paired with guanine (25). Both thymine-DNA glycosylase (*TDG*) and methyl-binding domain protein 4 (*MBD4*) prevent mutagenic impact of cytosine at the 5-position (5mC) deamination by excising thymine from T:G mispairs that is replaced by cytosine (26). N-methyl-purine DNA glycosylase (*MPG*) removes a diverse group of damaged bases, including cytotoxic and mutagenic alkylation adducts of purine. Uracil-DNA glycosylase (*UNG*) removes uracil in DNA resulting from deamination of cytosine or replicative incorporation of dUMP, and single-strand-selective monofunctional uracil-DNA glycosy-lase 1 (*SMUG1*) removes uracil from single- and double-stranded DNA in nuclear chromatin (22). In addition, polynucleotide kinase 3'-phosphatase (*PNKp*) ensures that DNA termini are compatible with extension and ligation by either removing 3'-phosphates from, or by phosphorylating 5'-hydroxyl groups on, the ribose sugar of the DNA backbone (27).

An increasing number of studies have investigated the role of polymorphisms in the base excision repair genes above on individual susceptibility to colorectal cancer with inconclusive outcomes.

With several exceptions, they have been limited to a handful of candidate SNPs within the *APEX1, MUTYH, OGG1,* and *XRCC1* genes. A total of 18 SNPs have been reported in *APEX1*, but the most extensively studied polymorphism is a T to G transversion, Asp148Glu (rs3136820) (28-33). A meta-analysis that included eight case-control studies with 2,597 cases and 3,063 controls did not find a statistically significant association of the *APEX1* Asp148Glu polymorphism with colorectal cancer (OR 1.17; 95% CI 0.88-1.55) (34). For the gene *MUTYH*, the only SNP that was marginally statistically significantly associated with colorectal cancer in the meta-analysis was rs3219489 (*MUTYH* Q338H), under a recessive model (OR 1.08; 95% CI 1.00-1.17) based on 14 studies comprising a total of more than 8,000 cases and 6,000 controls (35). For the gene *OGG1*, in a meta-analysis that included 5,235 cases and 8,438 controls, there was a statistically significant higher risk for colon cancer among those with the *OGG1* Ser326Cys polymorphism (OR 1.14; 95% CI 1.02–1.27) (36). For *XRCC1*, the findings for associations of XRCC1 Arg194Trp, Arg399Arg, and Arg399Gln gene polymorphisms with colorectal cancer risk have been inconsistent. A meta-analysis that included 26 studies with 6,979 cases and 11,470 controls found the *XRCC1* Arg399Gln polymorphism to be statistically significantly associated with higher risk of colorectal cancer in all genetic contrast models (OR 1.13, 95 % CI 1.03–1.23) (37). However, no statistically significant associations were observed for *XRCC1* Arg399Gln or Arg194Trp in another meta-analysis that included 4,501 cases and 8,038 controls (42). Data on associations of polymorphisms of other BER genes (*LIG1, LIG3, MBD4, MPG, NTHL1, PNKP, POLβ, SMUG, TDG, UNG*) with risk of colorectal cancer and adenoma are sparse (27, 38-42).

As noted above, BER is important in repairing oxidative DNA damage that can result from exogenous exposures. How much oxidative DNA damage someone sustains may be determined by that person's oxidative balance (i.e., balance between pro- and antioxidant exposures). Oxidative stress, defined as a disturbance in the ratio of pro-oxidants to antioxidants in favor of the former, is the primary cause of reactive oxygen and nitrogen species (RONS)–induced

cellular injury and is considered to be involved in the pathogenesis of colorectal cancer (43, 44). It is thought that the role of RONS in carcinogenesis is mediated via three main mechanisms. RONS can directly alter nucleic acids, leading to mutations, exchanges, and aberrations that can lead to cell proliferation, either directly or through compensatory proliferation (45, 46). RONS can also damage cells by reacting with membrane lipids and denaturing proteins, which can lead to cell death and compensatory hyper-proliferation. Last, RONS can modulate gene expression of initiated cells through affecting genes that regulate cell growth and differentiation (46, 47).

Diet and other modifiable lifestyle factors, such as alcohol intake, affect RONS production and oxidative balance and are valid targets for reducing oxidative stress *in vivo* (48). There is convincing evidence from the literature that smoking, alcohol intake, and obesity are associated with higher levels of blood and tissue markers of oxidative stress (49). Also, higher levels of physical activity, which have been consistently inversely associated with risk for colorectal cancer, have also been found to decrease levels of biomarkers of oxidative stress (50). However, epidemiological studies of associations of individual dietary factors thought to be related to oxidative stress with colorectal neoplasms are conflicting (49).

For example, several antioxidants, such as β-carotene, vitamin A, vitamin C, vitamin E, and selenium are thought to have a cancer preventive role since they fight free-radicals that may cause oxidative DNA damage and ultimately cancer development (50). To date, there have been several large (at least 7,000 participants) trials that tested the efficacy of antioxidant supplements in preventing cancer (51). Despite the encouraging results from earlier observational studies, the intervention trials did find a reduction in colorectal neoplasms incidence. A randomized placebo-controlled trial designed to examine antioxidant supplements such as oral selenium (200 μg/d) and vitamin E (400 IU/d), did not find any pre-specified cancer risk reduction, including colorectal cancer (52). In another trial of vitamin C, vitamin E, and β-carotene supplements in

individuals with prior adenoma, no reduction in adenoma recurrence was found (53). A meta-analysis of eight placebo-controlled trials with a total of 17,620 participants found no convincing evidence that antioxidant supplements including β-carotene and vitamins A, C, and E, had a significant beneficial effect on primary or secondary prevention of colorectal adenomas (54).

Based on the premise that populations with a high intake of fish have low colorectal cancer incidence and mortality, some studies evaluated the role of omega-3 as a possible protective factor (55). While some observational studies suggested that there was an inverse association between diet with higher rates of fish consumption and colorectal cancer (56), others did not (57). A meta-analysis of 33 observational studies found a 12% lower risk for colorectal cancer among those with higher fish consumption. The statistically significant inverse association was more pronounced for rectal cancer (OR 0.79; 95% CI: 0.65-0.97) (58). There are no reports of interventional trials that have addressed fish consumption in relation to colorectal cancer.

Dietary iron is a measure of total heme and non-heme iron from all food sources. The primary sources of dietary iron are red meat, poultry, beans, leafy vegetables, fruit juice, and fortified breads and cereals (59). It is biologically plausible that dietary iron may increase colorectal cancer risk due to its catalytic activity on the formation of reactive oxygen species (49). However, this role has not been confirmed in animal studies and the results from studies that assessed dietary iron intake and colorectal cancer risk were also mixed. Two cohort studies that assessed dietary iron intake deserve special mention. In one study of non-institutionalized men and women between 24-74 years of age in the U.S., dietary iron was found to be positively associated with incident colorectal cancer (60). In contrast, the largest study of diet and health ever conducted – the NIH-AARP cohort (also known as the Diet & Health Study) by Cross et al. found an inverse association between dietary iron and colorectal cancer (61).

In addition to the exogenous exposures, oxidative balance is also maintained to a large extent by endogenous enzymatic mechanisms. In order to prevent DNA damage, the body also uses enzymatic cellular defense mechanisms to regulate oxidative stress and RONS levels (45). Such mechanisms include several antioxidant enzymes, including superoxide dismutases (*SOD*), catalase (*CAT*), and Se-glutathione peroxidase (*GSTP1*) (62-64). The gene *SOD* is responsible for converting superoxide anions ($O2^{\cdot -}$) to hydrogen peroxide, which is then removed by catalase or glutathione peroxidase. In humans, there are three forms of *SOD*: cytosolic, mitochondrial, and extracellular (65). The decreased activity of mitochondrial *MnSOD*, a tumor suppressor gene, has been proposed as a factor in the etiology of colon cancer (66). A case-control study (n=976) of colorectal adenoma found that a *MnSOD* polymorphism in the mitochondrial targeting sequence was modestly inversely associated with distal colorectal adenomas, but the finding was not statistically significant (67). The role of GST enzymes is to catalyze the conjugation of glutathione to various carcinogenic compounds, including RONS (68). There are four main families of GST enzymes: GST-alpha (*GSTA*), GST-mu (*GSTM*), GST-pi (*GSTP*), and GST-theta (*GSTT*) (69). *GSTP1* has a distinct role in glutathione peroxidase's activity towards lipid peroxides and sensitivity to active oxygen species. A comprehensive meta-analysis of the association between *GSTP1* and colorectal cancer risk yielded no statistically significant findings (70). Last, the gene *CAT* helps eliminate ROS by breaking down hydrogen peroxide to water (71). A small case-control study (n=82) on the suitability of catalase as a biomarker of colorectal risk found that catalase activity was statistically significantly lower in colorectal cancer patients than in controls and participants with colorectal polyps (72).

As noted above, it is unlikely that any single oxidative balance-related exogenous exposure, antioxidant enzyme genotype, or BER genotype substantially affects risk of incident, sporadic colorectal cancer or adenoma. Therefore, it was suggested that combining multiple exogenous pro- and antioxidant exposures into an oxidative balance score (OBS) (73) and multiple BER or

antioxidant enzyme polymorphisms into genetic risk scores (GRS) (74) (75) (76) may facilitate investigating and understanding the possible inter-relationships among oxidative balance and BER.

In previous studies, OBS have been reported to be statistically significantly associated with lower risk of incident colorectal adenoma, prostate cancer, and oxidative stress biomarkers in several colonoscopy-based colorectal adenoma studies, and a population-based prostate cancer study (45, 73, 77-79). By contrast, the individual components of the score were weakly associated or not associated with the outcomes (73, 77, 78). The same group of investigators also developed and validated three novel weighting methods (literature review–derived, study data–based, and a Bayesian method that combines prior knowledge with study data) to incorporate components into a pathway score for oxidative balance, in addition to a commonly used method that assumes all components contribute equally to the score (79). The results were generally consistent across the weighting methods and support the use of comprehensive measures of oxidative balance in studies of colorectal adenoma risk. Recently, the OBS was also investigated in relation to colorectal cancer incidence in the Cancer Prevention Study II Nutrition Cohort using the same different weighting methods (48). For the OBS, 16 dietary and non-dietary lifestyle factors were included. Higher values of all four versions of the OBS were associated with 41%–53% lower risk of colorectal cancer (48). Other investigators, using slightly different methods to create an OBS, have mostly reported similar results for other cancers and cancer mortality (79-81).

Combining individual loci into a genetic risk score (GRS) has been also applied in relation to colorectal neoplasms and prostate cancer. A pooled study investigated whether five polymorphisms in *GC*, *CYP2R1*, *CYP24A1*, and *DHCR7/NADSYN1*, genes previously found to be associated with circulating 25(OH)D levels, were associated with colorectal cancer risk in a case-control study in which 10,061 cases and 12,768 controls were drawn from 13 studies included in

the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) (75). However, they did not observe a statistically significant association between the 25(OH)D-associated SNPs and colorectal cancer as a vitamin D additive genetic risk score (GRS) (75). In another consortium for prostate cancer, the investigators genotyped 25 prostate cancer susceptibility loci in 40,414 individuals and derived a polygenic risk score (PRS) (76). They found that prostate cancer risk among men in the top 1% of the PRS distribution was statistically significantly 30.6-fold higher than men in the bottom 1%, and 4.2-fold higher than the median risk (76).

To our knowledge, there are no previous reports of investigations of a BER GRS, alone or in interaction with an antioxidant enzyme GRS or an OBS in relation to risk for colorectal adenoma. Accordingly, herein we report the results of such an investigation using data pooled from three previously conducted colonoscopy-based case-control studies of incident, sporadic colorectal adenoma.

CHAPTER II: MANUSCRIPT

Associations of base excision repair genotypes with incident, sporadic colorectal adenoma according to antioxidant enzyme genotypes and oxidative balance-related environmental exposures

By Tengteng Wang

ABSTRACT

Associations of individual base excision repair (BER) genotypes with colorectal adenoma risk are unclear, but likely modest. However, genetic risk scores (GRS) that aggregate information from multiple genetic variants might be useful for assessing genetic predisposition to colorectal adenoma. We conducted an analysis of 1,073 Caucasians aged from 30–74 years using data pooled from the three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma that collected blood for genotyping and extensive dietary and other data. Associations of individual single nucleotide polymorphisms (SNPs) were assessed and used to combine information from multiple risk variants into a BER GRS based on 74 SNPs in 14 BER genes and an antioxidant enzymes GRS based on 22 SNPs in 3 antioxidant enzyme genes using two methods: a simple variant allele count method (count GRS) and a weighted method (weighted GRS). We also considered 15 extrinsic factors with known pro- or anti-oxidant properties to construct an oxidative balance score (OBS). Multivariable unconditional logistic regression was used to assess associations of BER genotypes with incident, sporadic colorectal adenoma, overall

and according to the antioxidant enzyme GRS and the OBS. The odds ratio (OR) for those in the highest relative to the lowest tertile of the weighted BER GRS was 2.65 (95% confidence interval [CI], 1.58-4.43; P_{trend} <0.001). However, there were no clear patterns to suggest possible BER GRS-antioxidant enzymes GRS or -OBS interactions. Our findings suggest that BER genotypes collectively may be associated with risk for incident sporadic colorectal adenomas.

INTRODUCTION

Colorectal cancer is the second leading cause of cancer death in men and women combined in the United States (1). It is widely accepted that most colorectal cancers develop from colorectal adenomatous polyps (3). Therefore, identification of risk factors for adenoma to inform preventive interventions and risk stratification for screening may have important public health implications.

A deficient response to DNA damage from exogenous and endogenous agents may lead to genetic alterations favoring the development of a colorectal adenoma and subsequent malignancy (82). There are four major pathways for repairing DNA damage, including nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR), and mismatch repair (MMR). BER may be particularly important for the prevention of colorectal adenoma and cancer because it removes small lesions and non-bulky adducts caused by oxidative damage and alkylating agents (22, 83). An increasing number of studies have investigated associations of polymorphisms in base excision repair genes with risk for colorectal cancer, but the results have been inconclusive. With several exceptions (27, 38, 40, 41), these studies were limited to a handful of candidate SNPs within the *XRCC1*, *OGG1*, *APEX1*, and *MUTYH* genes.

As noted above, BER is important in repairing oxidative DNA damage that can result from exogenous exposures. How much oxidative DNA damage someone sustains may be determined by that person's oxidative balance (i.e., balance between pro- and antioxidant exposures). Furthermore, antioxidant exposures may include both exogenous exposures and the activity of endogenous antioxidant enzymes. Therefore, it would be of interest to consider interactions among exogenous pro-oxidant and antioxidant exposures, antioxidant enzyme genotypes, and BER genotypes in relation to risk for colorectal adenoma or other health conditions.

Because it is unlikely that any single oxidative balance-related exogenous exposure, antioxidant enzyme genotype, or BER genotype substantially affects risk, combining multiple exogenous pro- and antioxidant exposures into an oxidative balance score (OBS) and multiple BER or antioxidant enzyme polymorphisms into genetic risk scores may facilitate investigating and understanding the possible inter-relationships among oxidative balance and BER. In previous studies, OBS have been reported to be statistically significantly associated with lower risk of incident colorectal cancer and adenoma, but the individual components of the score were weakly associated or not associated with either (48, 79). Other investigators, using slightly different methods to create an OBS, have mostly reported similar results for other cancers and cancer mortality (79-81). Combining individual loci into a genetic risk score (GRS) has also been applied in relation to colorectal neoplasms and possibly prostate cancer (75, 76, 84).

To our knowledge, there are no previous reports of investigations of a BER GRS, alone or in interaction with an antioxidant enzyme GRS or an OBS in relation to risk for colorectal adenoma. Accordingly, herein we report the results of such an investigation using data pooled from three previously conducted colonoscopy-based case-control studies of incident, sporadic colorectal adenoma.

METHODS

Study design and population

The data used for this analysis were pooled from three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma conducted between 1991 and 2002 by the same principal investigator using essentially the same recruitment and data collection protocols. The three pooled studies (85), which have been described in detail elsewhere, include the Minnesota Cancer

Prevention Research Study (CPRU) (86), the Markers of Adenomatous Polyps I study (MAP I) (87), and the Markers of Adenomatous Polyps II study (MAP II) (88). Eligible participants were 30–74 years of age and scheduled for elective, outpatient colonoscopy in major gastroenterology clinics in the study locations. Subjects with a history of familial adenomatous polyposis, inflammatory bowel disease, bowel resection, previous adenomatous polyps, incident colon cancer, or past or prevalent cancer other than non-melanoma skin cancer were excluded. The CPRU study was conducted from 1991-1994 in a large, multi-site gastroenterology practice in the Minneapolis, Minnesota metropolitan area. A total of 3,126 patients were identified, of whom 1,886 met final eligibility criteria and consented. MAP I was conducted from 1994-1997 in Winston-Salem and Charlotte, North Carolina. A total of 400 consenting participants met final eligibility criteria from 2,246 identified. The final study, MAP II, was conducted in 2002 in Columbia, South Carolina. During a five-month period, 351 patients were identified, with 232 eligible participants enrolling. This yielded a starting pooled sample size of 2,489. Of these, we excluded from genotyping 686 subjects without adenoma who had hyperplastic polyps, thus leaving 1,803 subjects eligible for genetic analysis.

The protocols of each study were approved by the institutional review boards of the corresponding institutions: the University of Minnesota and each Digestive Healthcare colonoscopy site for the CPRU study, Wake Forest University School of Medicine for the MAPI study, and the University of South Carolina for the MAP II study. All participants provided informed consent.

Data collection

Prior to undergoing colonoscopy, all participants completed mailed questionnaires. The questionnaires were used to collect information on demographics, family and medical history, body size, lifestyle, hormonal and reproductive history (in women), and diet (evaluated using

semi-quantitative Willett food frequency questionnaires).

For all studies, preparation for colonoscopy included a 12-hour fast and bowel cleansing with polyethylene glycol. Polyps detected and removed during colonoscopy were reviewed by an index study pathologist using diagnostic criteria established by the National Polyp Study. On the basis of colonoscopy and pathology findings, participants were assigned to one of the following 3 groups: 1) an adenomatous polyp group, 2) a hyperplastic polyp-only group, or 3) a colonoscopy-negative control group. Cases were defined as participants with pathologist-confirmed colorectal adenoma at colonoscopy, and controls were identified as participants without hyperplastic or adenomatous polyps.

For all three studies, blood was collected, handled, and stored for micronutrient analyses and genotyping. Fasting venous blood samples were drawn into pre-chilled Vacutainer tubes shielded from light. The blood draw and handling protocols were similar for all studies, with the exception of the interval between drawing and processing samples and the use of antioxidant preservatives. For the CPRU study, blood samples were frozen at -70 C within 12 hours of blood draw and no antioxidant preservatives were used. In contrast, for the MAP studies, samples were processed, lipid and aqueous soluble antioxidant preservatives (BHT and salicylic acid, respectively) added to the aliquot vials, and frozen at -70°C immediately after they were drawn (45).

Single nucleotide polymorphisms (SNPs) for genotyping were selected based on being common polymorphisms in a pathway and/or having a minor allele frequency greater than 5%, using tagSNPs when available. Using these criteria and also excluding SNPs not in Hardy–Weinberg equilibrium (HWE) among the controls, for the base excision repair pathway, 3 SNPs were selected for *APEX1*, 14 for *LIG1*, 5 for *LIG3*, 6 for *MBD4*, 3 for *MPG*, 5 for *MUTYH*, 1 for *FEN1*, 5 for *OGG1*, 2 for *PNKP*, 3 for *POLβ*, 3 for *SMUG1*, 12 for *TDG*, 3 for *UNG*, and 9 for

XRCC1 (See Appendix Table 1). For the antioxidant enzymes genotypes, 6 SNPs were selected for *MnSOD*, 11 for *CAT*, and 5 for *GSTP1* (See Appendix Table 3). Genotyping was conducted using the iPLEX Sequenom genotyping platform at the Biomedical Genomics Center, the core genotyping laboratory at the University of Minnesota. Genotyping of 64 pairs of blinded duplicate samples showed a concordance ≥ 95% for these SNPs.

Exclusions

After pooling the data from the three studies, some additional exclusions were made. Because there were so few non-white participants (113; 6.3%), they were excluded. We also excluded 583 (32.3%) individuals for whom we did not have genetic data on the SNPs of our interest, who were missing data on more than 20% of the SNPs of interest (n=25; 1.4%), and participants who reported an implausible total energy intake (<600 kcal or >6,000 kcal) or left ≥ 10% of the food frequency questionnaire blank (n=9; 0.5%). This left a final sample size of 1,073 participants, including 474 cases and 599 controls.

OBS components

We calculated an OBS with 15 components (Table 1) determined a priori based on their expected physiological effects on oxidative processes. The dietary components were derived from the food frequency questionnaires; nutrient values included dietary and supplemental sources. Supplemental selenium was not included in the OBS because fewer than 5% of the participants reported regular use of selenium supplements. All nutrient values were energy-adjusted according to the residual regression method, and all nutrients except lutein were analyzed as continuous variables. In the CPRU study, lutein intake was available only as servings of lutein-rich fruits and vegetables, whereas in both of the MAP studies, serum lutein measurement was available. Consequently, a summary exposure variable was created to reflect study-specific tertiles of lutein exposures. Non-dietary lifestyle variables included in the OBS were smoking (current, former, or

never smoker), alcohol intake (<1, 1–6, or ≥7 drinks/week), obesity (body mass index [weight in kg)/height in meters squared] <30 and waist:hip ratio <1.0 in men or <0.8 in women; either body mass index ≥30 or waist:hip ratio ≥1.0 in men or ≥0.8 in women; or body mass index ≥30 and waist:hip ratio ≥1.0 in men or ≥0.8 in women), and physical activity (in metabolic equivalents of task [METs]).

The OBS was constructed using the equal weight method, which we previously found to yield similar results to more complex weighted and Bayesian methods. For the equal weight method, it is assumed that all components are equally important and should contribute similar weights. Expected pro-oxidants (alcohol consumption, smoking, obesity, iron, ω-6 fatty acids, saturated fat,) were categorized on a 0, 1, 2 scale such that high intakes of pro-oxidants received the lowest values. In contrast, expected antioxidants (physical activity, carotenoids, lutein, lycopene, vitamin C, vitamin E, ω-3 fatty acids, flavonoids, glucosinolates) were categorized on a 2, 1, 0 scale such that high antioxidant intakes received the highest values. The OBS was then created by summing its 15 components. The score was then categorized into two or three approximately equal groups.

Statistical analysis

Chi-square tests and pooled two-sample t-tests were used for comparisons of means and proportions of selected characteristics of the cases and controls. Continuous variables were log transformed to improve normality when necessary. All analyses were conducted using SAS version 9.4 (SAS institute, Cary, NC).

Using unconditional logistic regression, we calculated the odds ratio (OR) and corresponding 95% confidence interval (CI) for the association of each genotype for each individual SNP with incident, sporadic colorectal adenoma, adjusted for age and sex. Co-dominant and additive genetic models were evaluated with reference to the “non-risk” allele as defined elsewhere (34,

36, 89, 90). If there was no reference for us to define the 'non-risk' allele among several SNPs, we chose the most common homozygote among controls as the referent group. When too few participants were homozygous for a variant allele to ensure a stable model, those with at least one variant allele were combined.

After individual assessment of each BER and antioxidant enzyme gene SNP, the genetic risk scores were created using two methods: a simple count method (count GRS) and a weighted method (weighted GRS). In the first method, each genotype was assigned a value of 0, 1, or 2 based on whether the genotype was homozygous for the common allele, heterozygous, or homozygous for the variant allele, respectively. The values for each of the SNPs were then summed. For the weighted GRS, each SNP was weighted by the β-coefficient obtained from the individual assessment of each SNP from the adjusted logistic model above. Then, the weighted GRS was calculated by multiplying each β-coefficient by the number of corresponding risk alleles (0, 1, or 2) and then summing the products. The scores were analyzed as both continuous and categorical variables. For the categorical analyses, the continuous scores were categorized based on the median and tertile cutpoints of the distributions of the scores in the controls. In addition to creating separate BER and antioxidant enzyme GRS, we calculated a combined overall GRS by summing standardized continuous BER GRS and standardized continuous antioxidant enzyme GRS together (standardized GRS= [(individual GRS – mean of the population GRS) / standard deviation of the population GRS]).

Multiple established and hypothesized risk factors for colorectal neoplasms identified based on previous literature were considered as potential confounding variables. The covariates included in final models were chosen based on the presence at least one of the following criteria: biological plausibility, whether or not the p-value for the covariate when included in the model was ≤ 0.1, and whether its inclusion in the model affected the odds ratios (OR) for the primary exposure

variable by ≥ 10%. A correlation analysis was conducted to ensure that highly correlated variables were not simultaneously included in the model. The covariates selected for the final model included age, sex, family history of colorectal cancer in a first degree relative, nonsteroidal anti-inflammatory drug (NSAID) use, hormone replacement therapy use in women, total energy intake, total intakes of calcium and dietary fiber, circulating 25-OH-vitamin D3 levels, and the oxidative balance score (OBS).

Multivariable unconditional logistic regression was then used to estimate the odds ratios and 95% confidence intervals for the associations of the BER and antioxidant enzyme GRS with incident, sporadic colorectal adenoma. Each GRS was evaluated as a continuous and as a categorical variable. When a GRS was analyzed as a categorical variable, the lowest GRS category was assigned as the referent group. A multivariable joint effect analysis was conducted to assess whether there was an interaction between the BER and antioxidant enzyme gene GRSs, with the persons who were in the lowest category of both the BER GRS and the antioxidant enzyme GRS as the reference group. Finally, to assess whether the OBS-adenoma association differed according to the BER GRS, the multivariable model was stratified on BER GRS categories as well as included as a GRS-OBS interaction term in the model. The overall GRS was assessed in a similar manner.

RESULTS

Selected characteristics of the cases and controls are summarized in Table 1. Cases were statistically significantly more likely to be male, current smokers, not take a NSAID regularly, and have a lower education level compared with controls. On average, cases were also older, taller, weighed more, had a larger waist-to-hip ratio, and consumed more alcohol, energy, and saturated fat. However, the controls were more likely to have a history of colorectal cancer in a

first-degree relative, and, on average had higher OBS scores and lower weighted BER and antioxidant enzyme genes GRS.

Crude and adjusted analyses of associations of the BER GRS, the antioxidant enzyme GRS, and the overall GRS with incident, sporadic colorectal adenoma are shown in Table 2. There was no substantial or statistically significant association of the count BER GRS and colorectal adenoma. However, the weighted BER GRS was associated with increasing risk with increasing scores. When the weighted BER GRS was treated as a continuous variable, with adjustment for age and sex, there was a statistically significant 30% increase in risk for each unit increase in the score. When the score was categorized into tertiles, with adjustment for age and sex, there was a statistically significant trend across the tertiles and a 2.19-fold higher risk for those in the highest relative to the lowest tertile of the score. After multivariable adjustment, these findings became stronger. Across the different analyses, there were no consistent patterns of associations of the antioxidant enzymes GRS with risk for adenoma. The estimated associations of the overall GRS with adenoma were very similar to those for the BER GRS.

The joint/combined associations of the BER and antioxidant enzyme GRS with risk of incident, sporadic colorectal adenomas are shown in Tables 3. In the analysis involving the weighted scores, the estimated risk for those who were high on both scores (OR 2.80; 95% CI 1.54 – 5.09) was only marginally higher than for those who were high on only the BER GRS (OR 2.52; 95% CI 1.37 – 4.61) relative to those who were low on both scores. In the analysis involving the count scores, none of the estimated risk estimates was statistically significant. The multiplicative interaction terms for the BER and antioxidant enzyme scores, whether analyzed as count or weighted GRS, were not statistically significant.

The associations between the oxidative balance score (OBS) with incident, sporadic colorectal adenomas, overall and stratified by the BER GRS and the overall GRS are shown in Tables 4 and 5, respectively. Overall, a higher oxidative balance score was inversely associated with colorectal adenoma (OR 0.56; 95% CI 0.34–0.93). However, across the count and weighted GRS analyses, there were no clear, consistent patterns for differences in the OBS-adenoma association according to the BER or overall GRS, and none of the OBS-gene-related multiplicative interaction terms was statistically significant in the multivariate models.

DISCUSSION

The findings from this pooled case-control study provide support for the hypothesis that base excision repair (BER) genotypes collectively may be associated with risk for incident, sporadic colorectal adenoma. We also found no strong evidence for interactions of our BER GRS with our antioxidant enzyme GRS or with oxidative balance (as represented by our OBS).

In the analyses of the genotypes for each investigated individual SNP in the 14 BER genes, we found statistically significant associations between polymorphisms in the *APEX1* gene (rs3136814), *MUTYH* (rs3219476), and *OGG1* (rs125701, rs3219008 and rs293795) with adenomas (See Appendix Table 2, 3). The direction and magnitude of the associations of *APEX1* rs3136814 with adenoma was consistent with previously reported findings (34, 35). There were no previous studies that investigated associations of the other four polymorphisms with adenoma. Although some of the individual SNPs were statistically significantly associated with adenoma, the associations were modest, thus limiting their clinical utility when considered individually. A GRS that aggregates information from 74 multiple genetic variants in BER might be useful for assessing genetic predisposition to colorectal adenoma. It is noted that the participants in our study who had a higher BER GRS were at a statistically significant two to three-fold higher risk for incident, sporadic colorectal adenoma.

The two methods we used to create the GRS were also applied in other studies (74, 91), but our study is the first comprehensive examination of the role of BER genotypes in relation to colorectal adenoma risk using both count and weighted genetic risk scores. The simple count method is easy to use and performs well, even when the true genetic model is unknown or wrongly specified (92). However, the count method is less likely to represent the true biological contributions of individual contributors to base excision repair capacity, and inclusion of SNPs that have no effect into the score may attenuate associations of the gene score with an outcome; therefore, we computed a weighted GRS by using the β-coefficients from the models for the associations of the individual SNPs with adenoma in our study population (91). Because little information is available on the strengths of associations of the individual genotypes with adenomas, our coefficients represent the best risk estimates available at this time (74). The BER GRS-adenoma associations were much stronger with the weighted than with the count GRS. Because the directions of the associations and the weights were derived from the study population, this would be expected. It is arguable whether the results represent merely methodological artifact, truth, or both. That multiple genotypes collectively contribute to risk more than any individual genotype, that some variants increase and some decrease risk, and that the individual genotypes contribute unequally seems plausible.

The body has antioxidant enzymatic cellular defense mechanisms to regulate oxidative stress and reactive oxygen species (RONS) levels (93, 94). Despite these defense mechanisms, oxidative DNA damage occurs and if not repaired needs either to be repaired or for the cell to be deleted. BER genes remove small lesions and non-bulky adducts caused by oxidative damage and alkylating agents. Thus, both the antioxidant enzyme cellular defense mechanisms and the BER system may be important for preventing oxidative damage-related colorectal carcinogenesis (95). So, it is biologically plausible that there may be a synergistic interaction between the BER GRS and antioxidant enzyme GRS in relation to risk of incident, sporadic colorectal adenomas. To our

knowledge, our study is the first to investigate a possible interaction between BER genes and antioxidant enzyme genes. However, our findings provide limited support for this hypothesized interaction. This may have been the result of our use of a GRS that aggregates information from multiple genetic variants for assessing gene-gene interaction. Both of the methods we used for creating a GRS assumed each SNP to be independently associated with risk. However, a gene-gene interaction is often described as "epistasis," which is defined as a non-independence of effect (96). In other words, when the effect of one locus is not predictable unless the value of another locus is known, these effects are referred to as "epistatic." Many of the important biological consequences of gene interactions depend on specific locus-to-locus interactions, rather than on some average level of interaction (97).

Based on previous basic science research, it is also biologically plausible that base excision repair capacity and antioxidant enzymes may individually or collectively influence the effects of diet and lifestyle on oxidative balance. Dietary and lifestyle pro- and anti-oxidants are known to affect levels of RONS in the body, thereby influencing oxidative balance (45, 79, 98, 99). A low capacity for DNA repair may lead to increased levels of oxidative damage. This, combined with the role of antioxidant enzymes in regulating oxidative balance and RONS levels, leads to the reasonable hypothesis that base excision repair capacity and antioxidant enzymes can act to modify the impact of dietary and lifestyle pro- and anti-oxidants on oxidative balance and risk for diseases, such as colorectal neoplasms (45).

Our findings regarding the overall association of the OBS with adenomas are consistent with those reported in previous epidemiologic studies, which found inverse associations of oxidative balance scores with colorectal adenoma, prostate cancer, esophageal cancer, lung cancer, and total cancer mortality (77, 79, 100). The results for our joint/combined analyses of associations of an OBS with both BER GRS versions were not fully consistent with one another; however, if the

weighted GRS is a truer representation of the combined effects of BER genotypes, then our results would suggest that an OBS-adenoma association may be somewhat more strongly inverse among those with a higher BER GRS. If true, this finding would suggest that diet and lifestyle that promote a stronger, more positive oxidative balance (i.e., a greater balance of antioxidant to pro-oxidant exposures) may be of particular importance to persons who have a less favorable BER genetic profile. On the other hand, our sample size was small for stratified analyses and our findings may have been due to chance such that the estimated associations in the strata could have been either under or over estimates of the true associations.

Strengths and limitations

This study has several limitations. First, as noted above, the β-coefficients we obtained to create the weighted GRS were from the individual SNPs analysis in our study population, not from previous genome-wide meta-analyses as has been done in other studies. However, none of our loci of interest has been identified in genome-wide studies, although some were investigated in candidate gene association studies. That none of our SNPs of interest were identified in GWAS may have been because of limitations in which SNPs were included in the GWAS SNP arrays and/or because none of the SNPs individually were sufficiently strongly associated with risk to be identified using the agnostic GWAS approach. In lieu of having genome-wide meta-analysis data on which to derive weights for a BER GRS, another approach would be to derive the weights from previous candidate gene association studies. However, the results from such studies have been inconsistent and difficult to interpret. One of the issues likely contributing to this inconsistency has likely been the small sample sizes (89), especially considering the likely weak strengths of associations of the individual SNPs with risk. For these and the other considerations of the limitations of using a within-study weighted GRS discussed further above, using the β-coefficients obtained from the individual SNPs analysis of our own study was our only feasible method.

A second limitation of our study is that, because of population differences in allele frequencies, linkage disequilibrium patterns, and risk factor prevalence, our findings cannot be generalized to other ethnic groups, but merits further investigation. Third, FFQs have known limitations, ranging from seasonal variability in participants' responses to recall error and recall bias; however, we used a previously validated FFQ and the questionnaires were completed prior to colonoscopies and diagnoses to minimize bias (79). Fourth, the data used in this study were collected before colorectal cancer screening by colonoscopy was common, resulting in an apparent family history bias such that individuals with a family history of colorectal cancer were more likely to be screened prior to the development of an adenoma and were thus overrepresented in the control group (85). However, the results of our analyses were similar within family history strata, inclusion of family history in the models had minimal impact, and it seems likely that such a bias would have tended to attenuate our results (45). Fifth, our sample size was limited and we made multiple comparisons. Finally, it was not feasible to consider every possible SNP for each of the genes of interest. Thus, there may be some influential SNPs that were not evaluated in our analyses.

Strengths of our study include colonoscopy evaluation of both cases and controls and histologically verified adenoma cases, both of which reduce outcome misclassification. In addition, selection bias is a common concern in case-control studies when participation depends jointly on exposure and disease status. However, the assessment of gene-environment interactions will not be subject to selection bias under the assumption that genotype does not influence participation conditional on exposure and disease status (101). Third, detailed information was collected on covariates, which decreases unmeasured confounding, and questionnaires were administered prior to diagnosis, which reduces recall bias. Finally, we conducted in-depth analyses of SNPs encoding BER and antioxidant enzyme genes with adenoma with alternative

methods of creating a BER GRS and assessing an association of the BER GRS with colorectal adenoma, including investigating individual SNPs, joint effect analyses, and stratified analyses.

In conclusion, our findings suggest that base excision repair (BER) genotypes collectively may be associated with risk for incident, sporadic colorectal adenoma and warrant further investigation. Of particular importance for future studies would be to address the limitations of our study in relation to creating a weighted BER GRS. A larger sample size for investigating a possible BER GRS-antioxidant enzymes GRS interaction and a prospective design for investigating a possible exogenous exposure oxidative balance score-BER GRS interaction would be desirable.

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Table 1. Selected Characteristics of Participants (n=1,073) in a Pooled Case–Control Analysis of Incident, Sporadic Colorectal Adenomas, United States, 1991–2002 (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

Selected Characteristics	Cases (n = 474)		Controls (n = 599)		P-value[a]
	Mean (SD)	%	Mean (SD)	%	
Age (years)	57.8 (9.3)		53.9 (10.4)		<0.0001
Male		60.1		38.1	<0.0001
College graduate or higher education		30.6		32.4	0.04
Family history of colorectal cancer in 1st degree relative		16.3		29.6	<0.0001
Height (m)	1.7 (0.1)		1.7 (0.1)		<0.0001
Weight (kg)	81.7 (18.1)		77.2 (17.0)		<0.0001
HRT use in women		47.5		56.0	0.06
Regular (≥ once/week) NSAID use		14.6		26.7	<0.0001
Total energy intake (kcal/day)	2,051 (770)		1,942 (706)		0.02
Fruits and vegetable (servings/day)	34.0 (23.5)		34.4 (25.1)		0.57
Red meat (servings/day)	4.8 (3.5)		4.6 (4.0)		0.44
Dietary fiber intake (g/day)	21.4 (9.8)		20.9 (9.6)		0.44
Total calcium intake (mg/day)[b]	935.2 (524.4)		943.1 (497.2)		0.47
Total folate intake (mcg/day)[b]	420.2 (248.2)		426.4 (245.6)		0.66
Circulating 25-OH-vitamin D_3 levels	24.5 (10.2)		25.5 (10.6)		0.16
Oxidative Balance Score (OBS) components					
Physical activity (METs/week)	230.7 (243.0)		225.2 (204.3)		0.79
Smoking					<0.0001
Former		44.8		38.5	
Current		24.0		12.9	
Alcohol					0.02
1-6 drinks/week		22.8		19.8	
7+ drinks/week		67.9		65.4	
BMI (kg/m^2)	27.5 (5.4)		27.3 (5.5)		0.35
WHR	0.9 (0.1)		0.9 (0.1)		<0.0001
Carotene intake (IU/day)	9,593 (9,211)		9,397 (9,280)		0.45
High level of lutein intake[c]		31.2		35.6	
Lycopene intake (μg/day)	27.0 (12.6)		27.4 (13.2)		0.63
Total vitamin C intake (mg/day)[b]	260.2 (316.7)		272.9 (312.6)		0.46
Total vitamin E intake (mg/day)[b]	69.6 (157.5)		68.6 (150.6)		0.97
Omega-3 fatty acid intake (marine, g/day)	1.3 (1.1)		1.4 (1.2)		0.32
Flavonoids intake (mg/day)	302.3 (270.3)		289.7 (269.2)		0.43
Glucosinolates intake (mg/day)	18.6 (21.1)		15.8 (15.9)		0.12
Total dietary iron intake (mg/day)[b]	20.6 (18.1)		19.7 (16.4)		0.54
Omega-6 fatty acid intake (g/day)	11.3 (3.2)		11.1 (3.6)		
Saturated fat intake (gm/day)	24.8 (12.5)		23.0 (11.0)		0.03
OBS	-1.1 (5.2)		0.1(5.4)		0.0004
Count genetic risk score (GRS) for base excision repair genes[d,e]	23.7 (4.5)		23.9 (4.3)		0.62
Count genetic risk score for antioxidant genes[d,e]	12.2 (2.8)		12.0 (2.8)		0.50
Weighted genetic risk score for base excision repair genes[d,f]	-0.1 (1.5)		-0.6 (1.5)		<0.0001
Weighted genetic risk score for antioxidant genes[d,f]	0.04 (0.5)		-0.02 (0.5)		0.04

Abbreviations: CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; SD, standard deviation; HRT, hormone replacement therapy; NSAID, nonsteroidal anti-inflammatory drug; OBS, oxidative balance score (see text for details); MET, metabolic equivalents of task; BMI, Body mass index; WHR, waist-hip ratio; GRS, genetic risk score

[a] From t-test for continuous variables and chi square test for categorical variables

[b] Total intake = dietary + supplemental

[c] In the CPRU study, lutein intake was available only as servings of lutein-rich fruits and vegetables, whereas in both of the MAP studies, serum lutein measurement was available. Consequently, a summary exposure variable was created to reflect study-specific tertiles of lutein exposures.

[d] BER GRS created based on 74 SNPs in 14 BER genes, and antioxidant enzymes GRS created based on 22 SNPs in 3 antioxidant enzyme genes; see complete list of genes and SNPs in the text and appendix table 1.

[e] The count GRS was calculated by applying a linear weighting of 0, 1, and 2 to genotypes containing 0, 1, or 2 risk alleles, respectively, and then summing the values for each of the SNPs.

[f] The weighted GRS was calculated by multiplying the unconditional logistic regression β-coefficient for the association of each individual genotype with adenoma by the number of corresponding risk alleles (0, 1, or 2) and then summing the products.

Table 2. Associations of Base Excision Repair and Antioxidant Genes Genetic Risk Scores (GRS) with Colorectal Adenoma in a Pooled Case–Control Analysis of Incident, Sporadic Colorectal Adenomas, United States, 1991–2002 (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

	Continuous GRS [a]	GRS [a], dichotomized		GRS [a], in tertiles			
		Low	High	Low	Medium	High	*P-trend*
Count GRS for base excision repair genes [b]							
Cases/controls, n	474/599	277/331	197/268	193/222	153/222	128/155	
OR (95% CI)							
Crude [d]	0.99 (0.97 - 1.02)	1.00 (Ref)	0.89 (0.69 - 1.12)	1.00 (Ref)	0.79 (0.60 - 1.05)	0.95 (0.70 - 1.29)	0.25
Age- and sex- adjusted	0.99 (0.96 - 1.02)	1.00 (Ref)	0.87 (0.67 - 1.12)	1.00 (Ref)	0.79 (0.59 - 1.06)	0.94 (0.69 - 1.29)	0.26
Multivariable-adjusted [e]	1.01 (0.97 - 1.06)	1.00 (Ref)	1.10 (0.73 - 1.68)	1.00 (Ref)	0.88 (0.54 - 1.42)	1.18 (0.70 - 1.99)	0.57
Weighted GRS for base excision repair genes [c]							
Cases/controls, n	474/599	195/341	279/258	128/229	156/203	190/167	
OR (95% CI)							
Crude [d]	1.26 (0.16 - 1.38)	1.00 (Ref)	1.89 (1.48 - 2.41)	1.00 (Ref)	1.38 (1.02 - 1.86)	2.04 (1.51 - 2.75)	<0.0001
Age- and sex- adjusted	1.30 (1.19 - 1.43)	1.00 (Ref)	2.00 (1.55 - 2.59)	1.00 (Ref)	1.49 (1.09 - 2.04)	2.19 (1.60 - 3.00)	<0.0001
Multivariable-adjusted [e]	1.37 (1.18 - 1.58)	1.00 (Ref)	1.22 (0.81 - 1.84)	1.00 (Ref)	1.43 (0.84 - 2.45)	2.65 (1.58 - 4.43)	0.001
Count GRS for antioxidant enzymes genes [c]							
Cases/controls, n	474/599	255/351	219/248	183/236	138/194	153/169	
OR (95% CI)							
Crude [d]	1.02 (0.97 - 1.06)	1.00 (Ref)	1.22 (0.95 - 1.55)	1.00 (Ref)	0.92 (0.69 - 1.23)	1.17 (0.87 - 1.56)	0.30
Age- and sex- adjusted	1.03 (0.98 - 1.07)	1.00 (Ref)	1.35 (1.05 - 1.75)	1.00 (Ref)	0.94 (0.69 - 1.28)	1.24 (0.92 - 1.68)	0.21
Multivariate-adjusted [e]	1.01 (0.93 - 1.09)	1.00 (Ref)	1.21 (0.80 - 1.82)	1.00 (Ref)	0.71 (0.43 - 1.17)	1.12 (0.69 - 1.83)	0.21
Weighted GRS for antioxidant enzymes genes [c]							
Cases/controls, n	474/599	221/313	253/286	159/198	144/213	171/188	
OR (95% CI)							
Crude [d]	1.32 (1.02 - 1.71)	1.00 (Ref)	1.25 (0.98 - 1.60)	1.00 (Ref)	0.84 (0.63 - 1.13)	1.13 (0.84 - 1.52)	0.14
Age- and sex- adjusted	1.36 (1.03 - 1.79)	1.00 (Ref)	1.27 (0.98 - 1.63)	1.00 (Ref)	0.78 (0.57 - 1.06)	1.15 (0.85 - 1.56)	0.05
Multivariable-adjusted [e]	1.28 (0.82 - 2.01)	1.00 (Ref)	1.22 (0.81 - 1.84)	1.00 (Ref)	0.78 (0.47 - 1.30)	0.97 (0.59 - 1.59)	0.59
Count overall GRS [c,f]							
Cases/controls, n	474/599	234/313	240/286	153/206	160/188	161/205	
OR (95% CI)							
Crude [d]	1.01 (0.92 - 1.10)	1.00 (Ref)	1.12 (0.88 - 1.43)	1.00 (Ref)	1.14 (0.85 - 1.54)	1.06 (0.79 - 1.42)	0.67
Age- and sex- adjusted	1.13 (0.93 - 1.11)	1.00 (Ref)	1.12 (0.88 - 1.45)	1.00 (Ref)	1.22 (0.90 - 1.67	1.08 (0.80 - 1.47)	0.45
Multivariate-adjusted [e]	1.04 (0.89 - 1.22)	1.00 (Ref)	1.31 (0.87 -1.98)	1.00 (Ref)	0.98 (0.59 - 1.61)	1.21 (0.73 – 2.03)	0.67
Weighted overall GRS [c,f]							
Cases/controls, n	474/599	207/330	267/269	135/222	147/211	192/166	
OR (95% CI)							
Crude [d]	1.26 (1.15 - 1.37)	1.00 (Ref)	1.58 (1.24 - 2.02)	1.00 (Ref)	1.14 (0.85 - 1.55)	1.90 (1.41 - 2.56)	<0.0001
Age- and sex- adjusted	1.29 (1.18 - 1.42)	1.00 (Ref)	1.66 (1.28 - 2.14)	1.00 (Ref)	1.15 (0.84 - 1.57)	2.00 (1.46 - 2.73)	<0.0001
Multivariable-adjusted [e]	1.32 (1.13 – 1.52)	1.00 (Ref)	2.07 (1.36 - 3.15)	1.00 (Ref)	1.04 (0.61 - 1.78)	2.21 (1.33 – 3.67)	0.002

Abbreviations: CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; GRS, genetic risk score; OR, odds ratio; CI, confidence interval; Ref, Reference

[a] BER GRS created based on 74 SNPs in 14 BER genes, and antioxidant enzymes GRS created based on 22 SNPs in 3 antioxidant enzyme genes; see complete list of genes and SNPs in the text and appendix table 1.

[b] Count GRS calculated by applying a linear weighting of 0, 1, and 2 to genotypes containing 0, 1, or 2 risk alleles, respectively, and then summing the values for each of the SNPs

[c] Weighted GRS calculated by multiplying the unconditional logistic regression β-coefficient for the association of each individual genotype with adenoma by the number of corresponding risk alleles (0, 1, or 2) and then summing the products

[d] No covariates in the model

[e] Adjusted for age, sex, family history of colorectal cancer in a first degree relative, nonsteroidal anti-inflammatory drug (NSAID) use, hormone replacement therapy use in women, total energy intake, total intakes of calcium, dietary fiber, circulating 25-OH-vitamin D_3 levels, and oxidative balance scores (OBS). OBS was included in the model as a continuous predictor when the GRS assessed as a continuous variable, or as a categorical predictor when the GRS assessed as a categorical variable. High values of OBS expected to reflect higher levels of antioxidants relative to pro-oxidants.

[f] The overall GRS was calculated by summing the standardized base excision repair GRS and the standardized antioxidant GRS.

Table 3. Multivariable-Adjusted[a] Joint/Combined Associations of Base Excision Repair GRS[b] and Antioxidant Enzymes GRS[c] with Risk for Colorectal Adenoma in a Pooled Case–Control Analysis of Incident, Sporadic Colorectal Adenomas, United States, 1991–2002 (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

Characteristic		GRS for antioxidant enzymes genes [d]			
		Low		High	
		Cases/controls, n	OR (95% CI)	Cases/controls, n	OR (95% CI)
Count GRS[e] for base excision repair genes					
	Low	140/202	1.00 (Ref)	137/129	1.31 (0.76 - 2.24)
	High	115/149	1.20 (0.69 - 2.11)	82/119	1.30 (0.71 - 2.37)
Weighted GRS[f] for base excision repair genes					
	Low	92/186	1.00 (Ref)	103/155	1.31 (0.70 - 2.48)
	High	129/127	2.52 (1.37 - 4.61)	150/131	2.80 (1.54 - 5.09)

Abbreviations: GRS, genetic risk scores; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OR, odds ratio; CI, confidence interval; Ref, reference

[a] Adjusted for age, sex, family history of colorectal cancer in a first degree relative, nonsteroidal anti-inflammatory drug (NSAID) use, hormone replacement therapy use in women, total energy intake, total intake of calcium, dietary fiber, circulating 25-OH-vitamin D_3 levels, and oxidative balance score (OBS). OBS was included in the model as a categorical predictor, with high values to reflect higher levels of antioxidants relative to pro-oxidants.

[b] BER GRS created based on 74 SNPs in 14 BER genes; see complete list of genes and SNPs in the text and appendix table 1.

[c] Antioxidant enzymes GRS created based on 22 SNPs in 3 antioxidant enzyme genes; see complete list of genes and SNPs in the text and appendix table 1.

[d] Joint effect analyses was conducted between count BER GRS[e] and count antioxidant enzyme GRS[e] (first two rows of data), and then between weighted BER GRS[f] and weighted antioxidant GRS[f] (third and fourth rows of data).

[e] Count GRS calculated by applying a linear weighting of 0, 1, and 2 to genotypes containing 0, 1, or 2 risk alleles, respectively, and then summing the values for each of the SNPs.

[f] Weighted GRS calculated by multiplying the unconditional logistic regression β-coefficient for the association of each individual genotype with adenoma by the number of corresponding risk alleles (0, 1, or 2) and then summing the products.

Table 4. Associations of Colorectal Adenoma with an Oxidative Balance Score (OBS), Overall and Stratified by Base Excision Repair GRS, in a Pooled Case–Control Study of Incident, Sporadic Colorectal Adenomas; United States, 1991–2002 (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

Characteristic		Overall [b]		GRS for Base Excision Repair Genes [a]			
				Low [b]		High [b]	
		Cases/controls, n	OR (95% CI)	Cases/controls, n	OR (95% CI)	Cases/controls, n	OR (95% CI)
Oxidative Balance Score (OBS) [c]							
	Low	237/226	1.00 (Ref)	148/124	1.00 (Ref)	89/102	1.00 (Ref)
	High	236/367	0.56 (0.34 - 0.93)	128/204	0.46 (0.24 - 0.87)	108/163	0.83 (0.36 - 1.93)
Oxidative Balance Score (OBS) [d]							
	Low	237/226	1.00 (Ref)	92/130	1.00 (Ref)	145/96	1.00 (Ref)
	High	236/367	0.56 (0.34 - 0.93)	103/208	0.70 (0.33 - 1.48)	133/159	0.43 (0.20 - 0.92)

Abbreviations: OBS, oxidative balance score; GRS, genetic risk score; GRS, genetic risk score; CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; OR, odds ratio; CI, confidence interval; Ref, Reference

[a] BER GRS was created based on 74 SNPs in 14 BER genes; see complete list of genes and SNPs in the text and appendix table 1.

[b] The "overall" models included the GRS as a covariate and used all observations; the "low" models included only participants in the low category of the GRS, and the "high" models included only participants in the low category of the GRS. All models were adjusted for age, sex, family history of colorectal cancer in a first degree relative, nonsteroidal anti-inflammatory drug (NSAID) use, hormone replacement therapy use in women, total energy intake, total intakes of calcium, dietary fiber, circulating 25-OH-vitamin D_3 levels.

[c] Count Genetic Risk Scores for Base Excision Repair Genes was used for stratification. Count GRS was calculated by applying a linear weighting of 0, 1, and 2 to genotypes containing 0, 1, or 2 risk alleles, respectively, and then summing the values for each of the SNPs.

[d] Weighted Genetic Risk Scores for Base Excision Repair Genes was used for stratification. Weighted GRS was calculated by multiplying the unconditional logistic regression β-coefficient for the association of each individual genotype with adenoma by the number of corresponding risk alleles (0, 1, or 2) and then summing the products.

Table 5. Associations of Colorectal Adenoma with an Oxidative Balance Score (OBS), Overall and Stratified by Overall GRS, in a Pooled Case–Control Study of Incident, Sporadic Colorectal Adenomas; United States, 1991–2002 (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

Characteristic		Overall [b]		Overall GRS [a]			
				Low [b]		High [b]	
		Cases/controls, n	OR (95% CI)	Cases/controls, n	OR (95% CI)	Cases/controls, n	OR (95% CI)
Oxidative Balance Scores (OBS) [c]							
	Low	237/226	1.00 (Ref)	144/146	1.00 (Ref)	124/119	1.00 (Ref)
	High	236/367	0.56 (0.34 - 0.93)	90/162	0.47 (0.24 – 0.92)	115/166	0.67 (0.32 - 1.39)
Oxidative Balance Scores (OBS) [d]							
	Low	237/226	1.00 (Ref)	124/251	1.00 (Ref)	144/114	1.00 (Ref)
	High	236/367	0.56 (0.34 - 0.93)	83/176	0.61 (0.30 - 1.23)	122/152	0.47 (0.22 - 0.99)

Abbreviations: CPRU, Cancer Prevention Research Unit; MAP, Markers of Adenomatous Polyps; GRS, genetic risk scores; OR, odds ratio; CI, confidence interval. Ref, Reference.

[a] The overall GRS was calculated by summing the standardized base excision repair GRS and the standardized antioxidant GRS together. BER GRS was created based on 74 SNPs in 14 BER genes and the antioxidant enzymes GRS was created based on 22 SNPs in 3 antioxidant enzyme genes; see complete list of genes and SNPs in the text and appendix table 1.

[b] The "overall" model included the GRS as a covariate and used all observations, the "low" model included only participants in the low category of the corresponding GRS, and the "high" models included only participants in the low category of the corresponding GRS. All models also adjusted for age, sex, family history of colorectal cancer in a first degree relative, nonsteroidal anti-inflammatory drug (NSAID) use, hormone replacement therapy use in women, total energy intake, total intakes of calcium, dietary fiber, circulating 25-OH-vitamin D_3 levels.

[c] Count Genetic Risk Scores for Base Excision Repair Genes was used for stratification. Count GRS was calculated by applying a linear weighting of 0, 1, and 2 to genotypes containing 0, 1, or 2 risk alleles, respectively, and then summing the values for each of the SNPs.

[d] Weighted Genetic Risk Scores for Base Excision Repair Genes was used for stratification. Weighted GRS was calculated by multiplying the unconditional logistic regression β-coefficient for the association of each individual genotype with adenoma by the number of corresponding risk alleles (0, 1, or 2) and then summing the products.

CHAPTER III: SUMMARY

Public health implications

Personalized medicine, an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease, is being advanced through data from the Human Genome Project. There are several published studies that found that when individual genotypes only modestly associated with risk were combined into genetic risk scores (GRS), the risk scores were substantially associated with risk. The logical next step is to combine the information provided by a genetic risk score (GRS) with information on environmental risk factors in order to identify subsets of the population who may be at high risk for colorectal adenoma and are most likely to benefit from more aggressive preventive interventions and screening programs. Therefore, our study can be seen as a preliminary analysis that may help lead to providing personalized medicine one day for preventing colorectal adenoma and cancer. In addition, since the advent of genome-wide association studies, the rate of colorectal cancer loci discovery has also increased considerably. As additional novel loci can be added to the GRS, our ability to characterize genetically susceptible individuals will continue to improve.

Possible future directions

Of particular importance for future studies would be to address the limitations of our study in relation to creating a weighted BER GRS. Possible next steps could include 1) determining the effects (or lack of effects) of each SNP on DNA repair capacity so that the most biologically relevant gene scores can be devised; 2) applying our weights for the BER GRS in another adenoma case-control study population; 3) re-deriving the weights for a BER GRS in a large prospective study and then testing the performance of the BER GRS in another large

prospectively studied, similar population; and 4) re-deriving the weights based on findings across many populations and then applying them in individual studies. Ideally, a subsequent study would be large enough to investigate possible BER GRS-antioxidant enzymes GRS and exogenous exposure oxidative balance score-BER GRS interactions.

Appendix

Appendix Table 1. Base Excision Repair Pathway genes investigated

SNP base (NCBI Build 37)	SNP rs ID	Alleles	Minor Allele	Genes
20923297	rs3136814	C/ A	C	APEX1
20925154	rs1130409	G/ T	G	APEX1
20923149	rs1760944	T/ G	T	APEX1
61560261	rs412334	T/ C	T	FEN1
33313729	rs3135967	G/ A	G	LIG3
33315445	rs3135974	A/ G	A	LIG3
33320143	rs3135989	G/ T	G	LIG3
33322322	rs3135998	A/ G	A	LIG3
33326017	rs2074516	G/ C	G	LIG3
48623224	rs3731037	A/ G	A	LIG1
48631408	rs156641	T/ C	T	LIG1
48639912	rs2288881	T/ C	T	LIG1
48640625	rs419664	A/ C	A	LIG1
48641574	rs411073	A/ G	A	LIG1
48643270	rs3730947	T/ C	T	LIG1
48652626	rs3730914	A/ G	A	LIG1
48652835	rs3730912	T/ G	T	LIG1
48653800	rs3730908	A/ G	A	LIG1
48654553	rs20580	T/ G	T	LIG1
48658682	rs3730881	A/ G	A	LIG1
48660445	rs274862	C/ T	C	LIG1
48668830	rs20579	A/ G	A	LIG1
48674356	rs3730837	C/ T	C	LIG1
129150385	rs2307293	G/ C	G	MBD4
129151170	rs3138360	T/ C	T	MBD4
129151667	rs2005618	G/ A	G	MBD4
129155670	rs10342	A/ C	A	MBD4
129159839	rs2311394	G/ A	G	MBD4
129160029	rs3138326	A/ T	A	MBD4
136258	rs2541622	A/ G	A	MPG
132510	rs3176415	A/ G	A	MPG
133878	rs3176424	G/ A	G	MPG
45796269	rs3219493	G/ C	G	MUTYH
45797505	rs3219489	G/ C	G	MUTYH
45800156	rs3219484	T/ C	T	MUTYH
45802670	rs3219476	C/ A	C	MUTYH
45806432	rs3219463	T/ C	T	MUTYH
9798140	rs2072668	G/ C	G	OGG1
9799113	rs293795	G/ A	G	OGG1
9790478	rs125701	A/ G	A	OGG1
9795543	rs3219008	G/ A	G	OGG1
9789875	rs159153	C/ T	C	OGG1
50364721	rs3739206	C/ A	C	PNKP
50370066	rs2257103	T/ C	T	PNKP
42209504	rs2979896	C/ A	C	POLB
42226805	rs3136797	G/ C	G	POLB
42228618	rs3136811	G/ C	G	POLB
54577147	rs3136386	C/ G	C	SMUG1
54575458	rs971	T/ C	T	SMUG1
54581064	rs2279402	A/ G	A	SMUG1

104361176	rs2629768	T/ C	T	TDG
104365511	rs4135061	G/ A	G	TDG
104365690	rs4135064	T/ C	T	TDG
104369046	rs4135081	G/ A	G	TDG
104369126	rs2723877	T/ C	T	TDG
104370393	rs322109	C/ T	C	TDG
104358331	rs322107	A/ G	A	TDG
104371367	rs167715	G/ A	G	TDG
104373370	rs4135093	C/ T	C	TDG
104373462	rs4135094	C/ T	C	TDG
104373955	rs3829301	C/ A	C	TDG
104376693	rs4135113	A/ G	A	TDG
109536559	rs3219211	C/ A	C	UNG
109542531	rs3219245	T/ G	T	UNG
109547060	rs246079	A/ G	A	UNG
44055726	rs25487	T/ C	T	XRCC1
44056412	rs25489	T/ C	T	XRCC1
44057227	rs915927	C/ T	C	XRCC1
44065388	rs1001581	T/ C	T	XRCC1
44068401	rs939460	A/ G	A	XRCC1
44068575	rs939461	C/ A	C	XRCC1
44077507	rs3213255	G/ A	G	XRCC1
44078736	rs3213247	A/ C	A	XRCC1
44046728	rs3213403	C/ T	C	XRCC1

Appendix Table 2. Associations of Base Excision Repair Genotypes with Colorectal Adenoma in a Pooled Case–Control Analysis of Incident, Sporadic Colorectal Adenomas, United States, 1991–2002

Gene	SNP		Cases (n=474)	Controls (n=599)	Crude OR	95% CI		Adjusted OR*	95% CI		β_coefficient
APEX1	rs3136814										
		AA	419	543	1.00			1.00			
		AC	38	34	1.45	0.90	2.34	1.67	1.01	2.76	0.5131
		CC	0	1	NA	NA	NA	NA	NA	NA	NA
APEX1	rs1130409										
		GG	122	142	1.00			1.00			
		GT	210	278	0.88	0.65	1.19	0.88	0.64	1.21	-0.1243
		TT	111	133	0.97	0.69	1.38	0.95	0.66	1.37	-0.0488
APEX1	rs1760944										
		CC	160	199	1.00			1.00			
		CA	207	247	1.04	0.79	1.38	1.06	0.79	1.41	0.0553
		AA	55	83	0.82	0.55	1.23	0.78	0.51	1.19	-0.2489
FEN1	rs412334										
		GG	246	342	1.00			1.00			
		GA	105	118	1.24	0.91	1.69	1.20	0.87	1.66	0.1824
		AA	10	13	1.07	0.46	2.48	0.92	0.38	2.20	-0.0882
LIG1	rs419664										
		GG	149	173	1.00			1.00			
		GT	211	254	0.97	0.73	1.28	0.94	0.70	1.27	-0.0622
		TT	83	126	0.77	0.54	1.09	0.71	0.49	1.03	-0.3390
LIG1	rs156641										
		GG	126	200	1.00			1.00			
		GA	178	199	1.42	1.05	1.92	1.42	1.03	1.94	0.3469
		AA	57	74	1.22	0.81	1.84	1.30	0.85	2.00	0.2640
LIG1	rs2288881										
		GG	321	419	1.00			1.00			
		GA	39	50	1.02	0.65	1.59	0.93	0.58	1.48	-0.0778
		AA	1	4	0.33	0.04	2.93	0.48	0.05	4.60	-0.7314
LIG1	rs3730947										
		GG	359	472	1.00			1.00			
		GA	2	1	2.63	0.24	29.11	2.20	0.20	24.66	0.7881
		AA	0	0	NA	NA	NA	NA	NA	NA	NA
LIG1	rs3731037										
		CC	278	367	1.00			1.00			
		CT	75	80	1.00	0.64	1.57	1.17	0.81	1.70	0.1604
		TT	1	7	1.00	0.64	1.57	0.30	0.04	2.51	-1.2047
LIG1	rs411073										
		CC	122	138	1.00			1.00			
		CT	170	206	0.93	0.68	1.28	0.95	0.68	1.32	-0.0562
		TT	62	100	0.70	0.47	1.05	0.68	0.45	1.02	-0.3934
LIG1	rs3730908										
		CC	325	406	1.00			1.00			
		CT	28	35	1.00	0.60	1.68	0.89	0.51	1.54	-0.1173
		TT	1	3	0.42	0.04	4.03	0.41	0.04	4.37	-0.8964
LIG1	rs20579										
		CC	268	340	1.00			1.00			
		CT	84	97	1.10	0.79	1.53	1.00	0.70	1.41	-0.0044
		TT	2	7	0.36	0.08	1.76	0.49	0.10	2.48	-0.7226
LIG1	rs3730881										
		CC	349	436	1.00			1.00			
		CT	5	8	0.78	0.25	2.41	0.64	0.20	2.08	-0.4479

		TT	0	0	NA	NA	NA	NA	NA	NA	NA
LIG1	rs3730914										
		CC	240	306	1.00			1.00			
		CT	106	124	1.09	0.80	1.49	1.04	0.75	1.44	0.0395
		TT	8	14	0.73	0.30	1.77	0.74	0.29	1.91	-0.2978
LIG1	rs3730837										
		AA	287	382	1.00			1.00			
		AG	64	84	1.01	0.71	1.45	1.08	0.74	1.57	0.0789
		GG	7	10	1.86	0.59	5.93	2.23	0.67	7.42	0.8036
LIG1	rs274862										
		TT	135	196	1.00			1.00			
		TC	191	214	1.30	0.97	1.74	1.23	0.91	1.68	0.2099
		CC	64	77	1.21	0.81	1.80	1.25	0.83	1.89	0.2256
LIG1	rs3730912										
		CC	328	412	1.00			1.00			
		CA	90	109	1.04	0.76	1.42	1.00	0.72	1.39	0.0030
		AA	4	8	0.63	0.19	2.10	0.87	0.25	3.04	-0.1377
LIG1	rs20580										
		CC	105	147	1.00			1.00			
		CA	205	247	1.16	0.85	1.59	1.17	0.84	1.61	0.1531
		AA	112	135	1.16	0.82	1.66	1.21	0.83	1.75	0.1872
LIG3	rs3135974										
		GG	292	388	1.00			1.00			
		GA	65	77	1.12	0.78	1.61	1.05	0.72	1.54	0.0502
		AA	4	8	0.66	0.20	2.23	0.82	0.23	2.86	-0.2006
LIG3	rs3135998										
		GG	131	173	1.00			1.00			
		GA	174	217	1.06	0.78	1.43	1.16	0.85	1.60	0.1489
		AA	56	83	0.89	0.59	1.34	0.93	0.61	1.43	-0.0703
LIG3	rs3135989										
		TT	402	505	1.00			1.00			
		TG	47	65	0.91	0.61	1.35	0.95	0.63	1.44	-0.0510
		GG	1	4	0.31	0.04	2.82	0.23	0.02	2.24	-1.4675
LIG3	rs3135967										
		AA	104	138	1.00			1.00			
		AG	170	230	0.98	0.71	1.35	0.99	0.71	1.39	-0.0066
		GG	84	103	1.08	0.74	1.59	1.02	0.68	1.53	0.0210
LIG3	rs2074516										
		GG	345	434	1.00			1.00			
		GC	79	88	1.13	0.81	1.58	1.04	0.73	1.48	0.0390
		CC	6	11	0.69	0.25	1.87	0.72	0.26	2.02	-0.3319
MBD4	rs3138360										
		GG	318	438	1.00			1.00			
		GA	43	34	1.74	1.09	2.79	1.55	0.95	2.54	0.4399
		AA	0	1	NA	NA	NA	NA	NA	NA	NA
MBD4	rs10342										
		GG	305	400	1.00			1.00			
		GA	52	72	0.95	0.64	1.39	0.85	0.56	1.27	-0.1662
		AA	4	1	5.25	0.58	47.17	6.41	0.65	63.13	1.8574
MBD4	rs2005618										
		TT	308	396	1.00			1.00			
		TC	77	88	1.13	0.80	1.58	1.08	0.75	1.53	0.0719
		CC	5	3	2.14	0.51	9.04	2.02	0.45	9.03	0.7023
MBD4	rs2311394										

		TT	317	403	1.00			1.00			
		TC	71	81	1.07	0.75	1.52	1.00	0.69	1.45	0.0036
		CC	8	3	2.12	0.50	8.93	1.99	0.45	8.91	0.6893
MBD4	rs2307293										
		GG	426	527	1.00			1.00			
		GC	3	6	0.89	0.51	1.54	0.57	0.14	2.36	-0.5609
		CC	1	0	NA	NA	NA	NA	NA	NA	NA
MBD4	rs3138326										
		AA	378	481	1.00			1.00			
		AT	72	96	0.95	0.68	1.33	0.86	0.60	1.22	-0.1541
		TT	6	3	2.55	0.63	10.24	2.28	0.53	9.77	0.8243
MPG	rs3176415										
		GG	116	152	1.00			1.00			
		GA	186	233	1.05	0.77	1.43	1.10	0.80	1.52	0.0968
		AA	59	88	1.05	0.77	1.43	0.91	0.59	1.40	-0.0965
MPG	rs2541622										
		CC	250	326	1.00			1.00			
		CT	94	113	1.09	0.79	1.49	1.07	0.77	1.50	0.0706
		TT	10	5	2.61	0.88	7.73	3.28	1.03	10.41	1.1863
MPG	rs3176424										
		AA	349	462	1.00			1.00			
		AG	9	9	1.32	0.52	3.37	1.34	0.52	3.47	0.2908
		GG	0	0	NA	NA	NA	NA	NA	NA	NA
MUTYH	rs3219476										
		GG	205	229	1.00			1.00			
		GT	186	263	0.79	0.61	1.03	0.75	0.57	0.99	-0.2902
		TT	52	61	0.95	0.63	1.44	1.05	0.68	1.63	0.0528
MUTYH	rs3219484										
		GG	309	406	1.00			1.00			
		GA	52	64	1.07	0.72	1.58	1.12	0.74	1.70	0.1150
		AA	0	3	NA	NA	NA	NA	NA	NA	NA
MUTYH	rs3219463										
		GG	208	252	1.00			1.00			
		GA	134	196	0.83	0.62	1.10	0.81	0.60	1.09	-0.2152
		AA	19	25	0.92	0.49	1.72	0.97	0.50	1.86	-0.0333
MUTYH	rs3219489										
		GG	244	277	1.00			1.00			
		GC	161	224	0.82	0.63	1.06	0.81	0.61	1.07	-0.2148
		CC	25	32	0.89	0.51	1.54	1.00	0.56	1.76	-0.0051
MUTYH	rs3219493										
		GG	373	498	1.00			1.00			
		GC	54	34	0.76	0.53	1.10	0.77	0.53	1.14	-0.2557
		CC	3	1	3.59	0.37	34.61	4.22	0.43	41.71	1.4390
OGG1	rs125701										
		GG	263	323	1.00			1.00			
		GA	84	136	0.76	0.55	1.04	0.69	0.50	0.97	-0.3667
		AA	14	14	1.23	0.58	2.62	1.23	0.56	2.71	0.2054
OGG1	rs2072668										
		CC	251	326	1.00			1.00			
		CG	157	203	1.00	0.77	1.31	1.06	0.81	1.41	0.0622
		GG	28	26	1.40	0.80	2.45	1.52	0.85	2.71	0.4152
OGG1	rs3219008										
		AA	206	299	1.00			1.00			
		AG	129	151	1.24	0.92	1.67	1.36	1.00	1.85	0.3090
		GG	23	21	1.59	0.86	2.95	1.60	0.84	3.04	0.4714

OGG1	rs159153									
		TT	191	230	1.00			1.00			
		TC	164	234	0.97	0.73	1.28	0.89	0.66	1.20	-0.1162
		CC	35	53	0.80	0.50	1.27	0.82	0.51	1.33	-0.1981
OGG1	rs293795									
		TT	274	318	1.00			1.00			
		TC	97	153	0.74	0.54	1.00	0.68	0.49	0.93	-0.3905
		CC	19	16	1.38	0.70	2.73	1.30	0.64	2.63	0.2596
PNKP	rs3739206									
		TT	449	572	1.00			1.00			
		TG	0	0	NA	NA	NA	NA	NA	NA	NA
		GG	1	2	0.64	0.06	7.05	0.37	0.03	4.07	-1.0075
PNKP	rs2257103									
		CC	127	179	1.00			1.00			
		CT	164	201	1.15	0.85	1.56	1.18	0.85	1.62	0.1629
		TT	63	64	1.39	0.92	2.10	1.55	1.00	2.39	0.4354
POLβ	rs2979896									
		TT	393	486	1.00			1.00			
		TG	53	82	0.80	0.55	1.16	0.81	0.55	1.20	-0.2060
		GG	4	6	0.82	0.23	2.94	0.66	0.18	2.47	-0.4137
POLβ	rs3136811									
		CC	381	471	1.00			1.00			
		CG	51	78	0.81	0.55	1.18	0.81	0.55	1.21	-0.2082
		GG	4	6	0.82	0.23	2.94	0.65	0.17	2.42	-0.4349
POLβ	rs3136797									
		CC	421	542	1.00			1.00			
		CG	14	13	1.39	0.65	2.98	1.39	0.62	3.10	0.3269
		GG	1	0	NA	NA	NA	NA	NA	NA	NA
SMUG1	rs3136386									
		CC	402	514	1.00			1.00			
		CG	34	40	1.09	0.68	1.75	1.04	0.63	1.71	0.0377
		GG	0	1	NA	NA	NA	NA	NA	NA	NA
SMUG1	rs971									
		CC	161	175	1.00			1.00			
		CT	145	217	0.73	0.54	0.98	0.72	0.52	0.98	-0.3358
		TT	48	52	1.00	0.64	1.57	1.03	0.64	1.64	0.0264
SMUG1	rs2279402									
		CC	112	116	1.00			1.00			
		CT	159	220	0.75	0.54	1.04	0.79	0.56	1.12	-0.2361
		TT	83	108	0.80	0.54	1.17	0.81	0.54	1.21	-0.2124
TDG	rs3829301									
		AA	420	533	1.00			1.00			
		AC	37	41	1.15	0.72	1.82	1.13	0.70	1.82	0.1187
		CC	0	4	NA	NA	NA	NA	NA	NA	NA
TDG	rs4135113									
		GG	346	451	1.00			1.00			
		GA	15	22	0.89	0.45	1.74	0.82	0.41	1.66	-0.1965
		AA	0	0	NA	NA	NA	NA	NA	NA	NA
TDG	rs2629768									
		GG	274	341	1.00			1.00			
		GA	82	121	0.84	0.61	1.16	0.85	0.61	1.19	-0.1616
		AA	5	11	0.57	0.19	1.65	0.51	0.17	1.60	-0.6648
TDG	rs4135064									
		CC	297	370	1.00			1.00			
		CT	54	69	0.98	0.66	1.44	1.03	0.69	1.54	0.0272
		TT	3	5	0.98	0.66	1.44	0.59	0.13	2.74	-0.5267

TDG	rs2723877									
		CC	280	344	1.00			1.00			
		CT	69	92	0.92	0.65	1.31	0.90	0.63	1.30	-0.1046
		TT	5	8	0.77	0.25	2.37	0.78	0.24	2.49	-0.2478
TDG	rs322107									
		CC	265	327	1.00			1.00			
		CT	85	108	0.97	0.70	1.35	0.95	0.68	1.34	-0.0488
		TT	4	9	0.55	0.17	1.80	0.42	0.12	1.44	-0.8755
TDG	rs4135061									
		AA	214	264	1.00			1.00			
		AG	122	181	0.83	0.62	1.11	0.81	0.60	1.10	-0.2084
		GG	22	26	1.04	0.58	1.89	0.93	0.50	1.74	-0.0697
TDG	rs4135081									
		AA	142	174	1.00			1.00			
		AG	153	216	0.87	0.64	1.18	0.92	0.67	1.26	-0.0876
		GG	63	81	0.95	0.64	1.42	1.07	0.71	1.62	0.0690
TDG	rs322109									
		AA	292	386	1.00			1.00			
		AG	58	75	1.02	0.70	1.49	0.97	0.66	1.44	-0.0280
		GG	8	10	1.06	0.41	2.71	0.94	0.36	2.47	-0.0581
TDG	rs4135093									
		TT	159	192	1.00			1.00			
		TC	168	222	1.21	0.81	1.80	0.96	0.71	1.30	-0.0369
		CC	63	73	1.04	0.70	1.55	1.16	0.77	1.75	0.1473
TDG	rs4135094									
		TT	314	391	1.00			1.00			
		TC	75	90	1.04	0.70	1.55	0.99	0.70	1.42	0.0068
		CC	1	6	0.21	0.03	1.73	0.26	0.03	2.25	-1.3428
TDG	rs167715									
		TT	311	388	1.00			1.00			
		TC	71	90	0.98	0.70	1.39	0.95	0.66	1.35	-0.0561
		CC	8	9	1.11	0.42	2.91	1.01	0.38	2.71	0.0079
UNG	rs939461									
		AA	378	475	1.00			1.00			
		AC	74	99	0.94	0.68	1.31	0.98	0.69	1.38	-0.0246
		CC	5	4	1.57	0.42	5.89	1.89	0.47	7.55	0.6370
UNG	rs3219245									
		GG	367	462	1.00			1.00			
		GT	72	88	1.03	0.73	1.45	1.03	0.72	1.47	0.0288
		TT	4	3	1.68	0.37	7.55	2.15	0.46	9.97	0.7629
UNG	rs246079									
		AA	120	157	1.00			1.00			
		AG	162	221	0.96	0.70	1.31	0.98	0.70	1.35	-0.0252
		GG	76	93	1.07	0.73	1.57	1.09	0.73	1.62	0.0836
XRCC1	rs939461									
		AA	378	475	1.00			1.00			
		AC	74	99	0.94	0.68	1.31	0.98	0.69	1.38	-0.0246
		CC	5	4	1.57	0.42	5.89	1.89	0.47	7.55	0.6370
XRCC1	rs3213247									
		GG	387	503	1.00			1.00			
		GT	54	48	1.46	0.97	2.21	1.39	0.90	2.13	0.3269
		TT	2	2	1.30	0.18	9.27	1.48	0.20	10.87	0.3920
XRCC1	rs939460									
		GG	235	307	1.00			1.00			
		GA	114	148	1.01	0.75	1.36	1.06	0.78	1.45	0.0614
		AA	12	18	0.87	0.41	1.84	1.09	0.50	2.38	0.0875

XRCC1	rs25487									
		GG	145	196	1.00			1.00			
		GA	161	231	0.94	0.70	1.26	0.84	0.62	1.14	-0.1756
		AA	55	46	1.62	1.03	2.53	1.43	0.90	2.28	0.3578
XRCC1	rs25489									
		GG	323	434	1.00			1.00			
		GA	37	37	1.34	0.83	2.17	1.25	0.76	2.07	0.2230
		AA	1	2	0.67	0.06	7.44	0.84	0.07	9.50	-0.1739
XRCC1	rs1001581									
		CC	138	166	1.00			1.00			
		CT	159	224	0.85	0.63	1.16	0.82	0.60	1.13	-0.1972
		TT	57	54	1.27	0.82	1.96	1.26	0.80	1.98	0.2278
XRCC1	rs3213403									
		AA	321	419	1.00			1.00			
		AG	37	49	0.99	0.63	1.55	0.90	0.57	1.45	-0.1006
		GG	0	3	NA	NA	NA	NA	NA	NA	NA
XRCC1	rs915927									
		AA	122	151	1.00			1.00			
		AG	156	213	0.91	0.66	1.24	0.97	0.70	1.35	-0.0265
		GG	80	107	0.93	0.64	1.35	1.00	0.68	1.48	0.0007
XRCC1	rs3213255									
		TT	139	165	1.00			1.00			
		TC	176	217	0.96	0.71	1.30	1.04	0.76	1.43	0.0409
		CC	75	105	0.85	0.58	1.23	0.90	0.61	1.33	-0.1046

*Adjusted by age and sex

Appendix Table 3. Associations of Antioxidant Enzyme Genotypes with Colorectal Adenoma in a Pooled Case–Control Analysis of Incident, Sporadic Colorectal Adenomas, United States, 1991–2002

Gene	SNP		Cases (n=474)	Controls (n=599)	Crude OR	95% CI		Adjusted OR *	95% CI		β_coefficient
CAT	rs1001179										
		GG	208	279	1.00			1.00			
		GA	135	169	1.07	0.80	1.43	1.00	0.74	1.36	0.0016
		AA	18	25	0.97	0.51	1.82	1.00	0.52	1.94	0.0026
CAT	rs7947841										
		GG	299	397	1.00			1.00			
		GA	57	71	1.07	0.73	1.56	1.14	0.76	1.70	0.1299
		AA	5	5	1.33	0.38	4.63	1.73	0.46	6.50	0.5456
CAT	rs499406										
		GG	126	158	1.00			1.00			
		GA	170	222	0.96	0.71	1.31	0.91	0.66	1.25	-0.0968
		AA	65	93	0.88	0.59	1.30	0.83	0.55	1.25	-0.1921
CAT	rs566979										
		TT	193	248	1.00			1.00			
		TG	194	244	1.02	0.78	1.33	0.99	0.75	1.31	-0.0067
		GG	63	82	0.99	0.68	1.44	0.97	0.66	1.45	-0.0269
CAT	rs16925614										
		CC	275	334	1.00			1.00			
		CT	71	99	0.87	0.62	1.23	0.89	0.62	1.27	-0.1225
		TT	8	11	0.88	0.35	2.23	0.92	0.35	2.43	-0.0798
CAT	rs11032703										
		CC	263	340	1.00			1.00			
		CT	85	95	1.16	0.83	1.62	1.07	0.75	1.51	0.0648
		TT	6	9	0.86	0.30	2.45	0.90	0.30	2.67	-0.1078
CAT	rs11604331										
		AA	137	192	1.00			1.00			
		AG	168	203	1.16	0.86	1.57	1.14	0.84	1.56	0.1315
		GG	53	76	0.98	0.65	1.48	0.95	0.62	1.46	-0.0557
CAT	rs525938										
		AA	187	240	1.00			1.00			
		AG	137	189	0.93	0.70	1.25	1.03	0.76	1.39	0.0250
		GG	34	42	1.04	0.64	1.70	1.14	0.68	1.90	0.1293
CAT	rs7104301										
		AA	204	265	1.00			1.00			
		AG	128	177	0.94	0.70	1.26	0.90	0.67	1.23	-0.1012
		GG	26	29	1.17	0.67	2.04	1.02	0.57	1.82	0.0197
CAT	rs12272630										
		GG	399	498	1.00			1.00			
		GC	31	34	1.14	0.69	1.88	1.22	0.72	2.07	0.2016
		CC	0	1	NA	NA	NA	NA	NA	NA	NA
CAT	rs7943316										
		TT	209	258							
		TA	199	261	0.94	0.73	1.22	0.01	0.77	1.33	0.0103
		AA	53	69	0.95	0.63	1.42	1.02	0.67	1.55	0.0173
GSTP1	rs4147581										
		CC	107	145	1.00			1.00			
		CG	223	283	1.07	0.79	1.45	0.95	0.69	1.31	-0.0554
		GG	106	127	1.13	0.79	1.62	1.04	0.71	1.52	0.0391
GSTP1	rs1138272										
		CC	295	376	1.00			1.00			
		CT	56	64	1.12	0.76	1.65	1.27	0.84	1.91	0.2383
		TT	3	4	0.96	0.21	4.31	1.10	0.24	5.10	0.0915

GSTP1	rs749174									
		CC	151	197	1.00			1.00		
		CT	168	203	1.08	0.80	1.45	1.05	0.77	1.43	0.0472
		TT	35	44	1.04	0.63	1.70	1.12	0.67	1.87	0.1086
GSTP1	rs1695									
		AA	153	208	1.00			1.00		
		AG	168	219	1.04	0.78	1.39	1.04	0.77	1.41	0.0397
		GG	37	44	1.14	0.70	1.86	1.26	0.76	2.08	0.2275
GSTP1	rs762803									
		CC	132	173	1.00			1.00		
		CA	220	258	1.12	0.84	1.49	1.11	0.82	1.50	0.1045
		AA	70	98	0.94	0.64	1.37	1.04	0.70	1.54	0.0370
MnSOD	rs5746151									
		GG	326	408	1.00			1.00		
		GA	33	63	0.66	0.42	1.02	0.69	0.43	1.09	-0.3785
		AA	2	2	1.25	0.18	8.93	1.96	0.24	16.18	0.6726
MnSOD	rs5746136									
		GG	191	229	1.00			1.00		
		GA	132	198	0.80	0.60	1.07	0.82	0.60	1.11	-0.2003
		AA	38	46	0.99	0.62	1.59	1.01	0.62	1.66	0.0119
MnSOD	rs4880									
		CC	87	104	1.00			1.00		
		CT	181	236	0.92	0.65	1.29	0.91	0.64	1.31	-0.0931
		TT	86	104	0.99	0.66	1.48	0.97	0.64	1.48	-0.0265
MnSOD	rs6917589									
		TT	235	286	1.00			1.00		
		TC	129	177	0.89	0.67	1.18	0.91	0.68	1.23	-0.0905
		CC	26	24	1.32	0.74	2.36	1.24	0.68	2.26	0.2148
MnSOD	rs8031									
		TT	121	153							
		TA	233	305	0.97	0.72	1.30	0.99	0.73	1.35	-0.0102
		AA	107	130	1.04	0.73	1.48	1.01	0.70	1.45	0.0079
MnSOD	rs2842980									
		AA	288	362	1.00			1.00		
		AT	147	198	0.93	0.72	1.22	0.96	0.73	1.26	-0.0439
		TT	21	20	1.32	0.70	2.48	1.28	0.66	2.48	0.2453

*Adjusted by age and sex