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Gene-diet interactions and their impact on colorectal cancer risk

Elizabeth D. Kantor[1] and **Edward L. Giovannucci**[1,2]

[1] Department of Epidemiology, Harvard School of Public Health, Boston, MA, 02115

[2] Department of Nutrition, Harvard School of Public Health, Boston, MA, 02115

Abstract

A number of studies have evaluated the role of gene-diet interaction in the etiology of colorectal cancer (CRC). Historically, these studies focused on established dietary risk factors and genes involved in their metabolism. However, results from these candidate gene studies were inconsistent, possibly due to multiple testing and publication bias. In recent years, genome-wide association studies have identified a number of CRC susceptibility loci, and subsequent meta-analyses have observed limited evidence that diet may modify the risk associated with these susceptibility loci. Statistical techniques have been recently developed to evaluate the presence of interaction across the entire genome; results from these genome-wide studies have demonstrated limited evidence of interaction and have failed to replicate results from candidate gene studies and those using established susceptibility loci. However, larger sample sizes are likely needed to elucidate modest or weak interaction in genome-wide studies of gene-diet interaction.

Keywords

Diet; genes; gene-environment interaction; colorectal cancer; review

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer among men and women in the United States.[1] A number of dietary factors have been associated with CRC risk, including: folate,[2] alcohol,[3] vitamin D,[4] calcium,[5] fiber,[6] fruit,[7] vegetables,[7] and red/processed meat.[8] Identifying subsets of the population for whom these dietary risk factors may confer more or less risk may help inform intervention efforts. Furthermore, elucidating gene-diet interaction may help us better understand the mechanisms by which dietary factors affect risk of CRC, consequently improving our understanding of CRC etiology and supporting a causal role of diet in the development of CRC.

* *corresponding author* Edward L. Giovannucci, MD ScD MPH, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Building II, Room 371 Boston, MA, 02115. Elizabeth D. Kantor, PhD MPH, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA, 02115, Phone: 617.432.1194, Fax: 617.566.7805, ekantor@hsph.harvard.edu.

Conflict of Interest

Elizabeth D. Kantor and Edward L. Giovannucci declare that they have no conflict of interest

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Historically, the study of gene-diet interaction was often approached by focusing on a given dietary risk factor and candidate gene(s) involved in the metabolism of that dietary factor. However, with the widespread availability of genetic data in epidemiologic research, genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) associated with CRC risk, and subsequent research has evaluated whether known dietary CRC risk factors might modify the risk associated with these susceptibility loci. Most recently, research has assessed the presence of gene-diet interaction across the genome, irrespective of marginal associations between the genetic variants and CRC risk.

In this review, we will provide an overview of the literature within these three main domains of gene-diet interaction studies: those involving candidate genes, those involving GWAS-identified susceptibility loci, and those involving evaluation of interaction across the entire genome. We will conclude with a brief discussion of the literature.

GENE-DIET INTERACTION: DIETARY RISK FACTORS AND CANDIDATE GENES

Folate

High folate intake has been linked to decreased risk of both adenoma and CRC in observational studies, and it is posited that folate may reduce risk of CRC through effects on DNA synthesis, repair, and methylation.[9] Corroborating evidence suggests that genetic polymorphisms in the methylenetetrahydrofolate reductase (*MTHFR*) gene, which encodes an enzyme involved in folate metabolism, may decrease risk of CRC.[10, 11] However, a trial found that folate increased the risk of recurrent polyps,[12] suggesting that folate may decrease risk up until a certain point, after which it may act to promote carcinogenesis.[13] However, a recent pooled study of randomized trials did not show an enhancing effect of folate late in carcinogenesis,[14] and further research suggests that the putative protective effect of folate may manifest only after decades of exposure.[2]

To better understand the role of folate in colorectal carcinogenesis, many studies have evaluated whether folate, or other dietary factors converging on the folate pathway, including methionine, alcohol, and B vitamins, may interact with genes involved in folate metabolism to affect risk of colorectal adenoma or cancer. Most of these studies have focused on a polymorphism (rs1801133) in the *MTHFR* gene, *MTHFR*-677. Although inconsistent, some data suggest that the *MTHFR*-677T→7C mutation is protective when there is folate sufficiency and is neutral or even deleterious in the context of folate deficiency.[10, 15-20] In support of this hypothesis, a recent study observed that a pathway of one-carbon metabolism genes was significantly associated with advanced colorectal adenoma only among those with low folate intake.[21] Further work has evaluated whether the association between folate (or dietary exposures associated with folate metabolism) and adenoma/CRC may be modified by genes involved in one-carbon metabolism or folate uptake/distribution, including: *MTHFR*, C-1-tetrahydrofolate synthase (*MTHFD1*), thymidylate synthetase (*TYMS*), methionine synthase (*MTR*), thymidylate synthase enhancer region (*TSER*), reduced folate carrier (*RFC*), DNA methyltransferase 3b (*DNMT3b*), and

alcohol dehydrogenase 3 (*ADH3*); taken together, these studies do not indicate a clear pattern of association.[16-20, 22-30] Given that folate may take decades to affect CRC risk, inconsistencies between studies may reflect differences in the timing/duration of folate measurement relative to assessment of CRC.

Alcohol

Alcohol intake has been consistently associated with increased CRC risk. In a meta-analysis of 27 cohort and 34 case-control studies, those drinking 2-3 drinks/day experienced 21% higher risk of colorectal cancer than non-drinkers/occasional drinkers (RR:1.21;95%CI: 1.13-1.28), while those drinking 4+ drinks/day experienced 52% higher risk (RR:1.52;95% CI:1.27-1.81).[3] Categorically, light drinking (≤1 drink/day) was not associated with CRC, although dose-response analyses using fractional polynomials suggest a weak association between light drinking and CRC risk (RR corresponding to 10g alcohol/day: 1.07;95% CI: 1.04-1.10). Alcohol may increase CRC risk through a number of mechanisms, including anti-folate effects, as well as through the production of reactive oxygen species, inflammation, and the carcinogenic intermediate, acetaldehyde.[31, 32]

Corroborating the putative anti-folate effect of alcohol, some research suggests that the protective effect of the *MTHFR* 677 T→7C genotype may be diminished by high alcohol consumption.[11, 15, 17] Strikingly, one study observed that those with the homozygous mutation who drank little/no alcohol experienced an eightfold lower risk of CRC than those with the homozygous wild-type; those who drank a modest amount experienced a two-fold lower risk, and heavy drinkers with this mutation did not experience any difference in risk. [15] There is some suggestion that interaction between alcohol and *MTHFR* may hold for adenomas, [20, 33, 34] and a similar pattern of association has been observed for the *MTR* gene, which is also involved in folate metabolism.[28, 35]

Additional work has evaluated whether the association between alcohol and CRC varies by polymorphisms in the alcohol dehydrogenase gene, *ADH3* (also known as *ADH1C*). Those with the wild-type *ADH3* oxidize alcohol to acetaldehyde faster than those with the variant allele,[31] and it has been hypothesized that those with the wild-type *ADH3* may experience increased risk of CRC due to prolonged exposure to this carcinogenic intermediate. Supporting this hypothesis, one study showed a stronger association between alcohol intake and adenoma among persons with the wild-type (fast metabolizers) than among those with the variant genotype.[36] However, other studies have shown the opposite, with some suggestion that alcohol intake is associated with increased risk of colorectal adenoma[20, 25] and CRC[37] only among slow metabolizers. Although the reasons underlying this inconsistency remain unclear, it is possible that production of acetaldehyde in the large bowel is influenced largely by bacteria rather than the human enzyme; [38] if this is the case, then slow metabolism of ethanol could actually enhance acetaldehyde production by bacteria, thereby increasing CRC risk among slow metabolizers.

Given that inflammation may be one of the mechanisms by which alcohol affects risk of CRC, another study evaluated whether the association between alcohol intake and CRC was modified by 13 polymorphisms in genes involved in the inflammatory response.[39] A significant interaction was observed between alcohol and *PPARγ* Pro12Ala (rs1801282), in

which alcohol use was associated with CRC among carriers of the variant allele, but not among those with the homozygous wild-type (p-interaction:0.02). Further work suggests that the association between alcohol and CRC is not modified by mutation in the DNA repair gene O^6-methylguanine-DNA methyltransferase (*MGMT*)[40] or by polymorphisms in the adenomatous polyposis coli (*APC*) tumor suppressor gene.[41]

Vitamin D

Increasing vitamin D has been consistently associated with reduced risk of CRC, measured by vitamin D intake from diet and supplements, and also by blood levels of 25-hydroxyvitamin D [25(OH)D]. Notably, a recent meta-analysis reported that a 10ng/mL increase in blood levels of 25(OH)D was associated with a 26% reduced risk of CRC (RR: 0.74;95% CI:0.63-0.89).[4]

Several studies have evaluated whether the association between vitamin D and CRC is modified by variation in the vitamin D receptor (*VDR*), with most research focusing on SNPs in *Fok1* (rs2228570) and *Bsml* (rs1544410). These studies do not support the presence of statistically significant interaction for either CRC[42-44] or adenoma.[45-48] Similarly, the association between vitamin D and colon cancer/CRC does not appear to be modified by variation in the vitamin D binding protein[43] and the association between plasma levels of 25(OH)D and CRC does not appear to be modified by a genetic risk score of variants proximal to increased VDR binding.[49] Furthermore, research does not support the presence of interaction between total vitamin D and 12 SNPs in *CYP24A1* and 1 SNP in *CYP27B1*, which act to inactivate vitamin D metabolites and convert vitamin D into its active VDR-binding form, respectively.[50] Lastly, the association between vitamin D and CRC does not appear to be modified by variation in the calcium-sensing receptor (*CaSR*) gene.[42, 51] These results consistently suggest no evidence of interaction between vitamin D and candidate genes, regardless of whether vitamin D was measured by dietary intake, total intake, or by blood measures of 25(OH)D.

Calcium

Epidemiologic studies suggest that calcium intake is inversely associated with CRC risk: a recent meta-analysis demonstrated that a 300 mg/day increase in calcium was associated with an 8% reduction in CRC risk (RR:0.92;95% CI:0.89-0.95).[5] Calcium may reduce CRC risk through binding of bile acids in the lumen and by mitigating the pro-inflammatory response to flora in the colon. Calcium may also reduce CRC risk through its effects on cellular proliferation and differentiation, which are induced by binding to *CaSR*.[5, 51] Given the putative role of *CaSR* in colorectal carcinogenesis and its expression in the colon, candidate gene studies have evaluated whether calcium interacts with polymorphisms in the *CaSR* gene, observing no compelling evidence of interaction on colon cancer[51] or adenoma.[52]

In total, the association between calcium and CRC/adenoma does not appear to vary by polymorphisms in *VDR*, [42-46, 48] although there is some suggestion of interaction for rectal cancer.[44] Further, the association between calcium and CRC/adenoma does not appear to vary by variation in the vitamin D binding protein[43] or by SNPs in *CYP24A1* or

CYP27B1.[50] However, in a study of 80 tagging SNPs in 9 ion transporter regions, an interaction was observed between calcium intake and rs2855798, a SNP in the potassium inwardly-rectifying channel subfamily (*KCNJ1*) gene.[53] Specifically, among those consuming <1000 mg/day of calcium, having 1 or more variant alleles was associated with a 35% increased risk of adenoma and a 72% increased risk of multiple or advanced adenoma, while a modest inverse association was observed among those consuming 1000+ mg/day of calcium.

Fiber

In a meta-analysis of 16 studies, a 10 gram/day increase in total dietary fiber was associated with a 10% lower risk of CRC (RR:0.90;95% CI:0.86-0.94).[6] Fiber may reduce risk of CRC through a number of mechanisms, including: reduced transit time, increased stool bulk and dilution of carcinogens, the fermentation of fiber to short-chain fatty acids, and decreased insulin resistance.[54, 55] In addition, fiber may reduce inflammation,[56] and consequently, it has been evaluated whether the fiber-CRC association is modified by SNPs rs1800872 and rs3024505 in the gene encoding anti-inflammatory cytokine interleukin (IL)-10.[57] A significant interaction (p-interaction:0.01) was observed between dietary fiber and rs3024505 in which increasing fiber was associated with reduced risk of CRC among those with the homozygous wild-type, but not among those with variant alleles. Further, the association between fiber and CRC does not appear to vary by candidate pathway of genes involved in insulin sensitivity and metabolic signaling,[58] or by polymorphisms in *MGMT*[40] or *ABCC2*.[59]

Fruit and Vegetables

Fruit contain many nutrients which may help prevent cancer, including fiber and a number of putative anti-oxidants. A recent meta-analysis observed that high versus low fruit intake was associated with a 10% lower risk of CRC (RR:0.90;95% CI:0.83-0,98).[7] Research suggests that the association between fruit intake and CRC is not modified by polymorphisms in the genes posited to play a role in the metabolism of carcinogens or anti-carcinogens, including: Cytochrome P450 (*CYP1A1*), Glutathione S-transferases (*GSTT1, GSTM1, GSTP1*), Epoxide hydrolase (*EPHX1*), and NAD(P)H dehydrogenase quinone (*NQO1*).[60]

Vegetables are rich in bioactive compounds and nutrients which may reduce risk of colorectal cancer, including folate, fiber, and carotenoids.[61] Increasing vegetable consumption is modestly associated with reduced risk of CRC, with a meta-analysis reporting that those consuming high vegetable intake experienced a 9% lower risk of CRC than those consuming low vegetable intake (RR:0.91;95% CI:0.86-0.96).[7] Much interest has developed around cruciferous vegetable consumption, as these vegetables are particularly rich in glucosinolates. These sulfur-containing chemicals break down into isothyocyanates (ITCs), which are posited to have a range of protective anti-cancer effects, including: detoxification of carcinogens, inhibition of carcinogen-activating enzymes, inhibition of angiogenesis, apoptosis, and arrest of the cell cycle.[62] To this end, a meta-analysis reported that high intake of cruciferous vegetables is associated with an 18% reduced risk of CRC (OR:0.82;95% CI:0.75-0.90).[63]

Glutathione S-transferases (GST)-T, -M, and -P, comprise a family of detoxification enzymes which act to metabolize ITCs, and studies have evaluated whether variation in the genes encoding these detoxification enzymes modifies the association between vegetable intake and CRC risk. To this end, it has been observed that the inverse association between vegetable intake and CRC risk is only present among those with deficient/intermediate *GSTT1* phenotype.[60] A few studies have further evaluated whether polymorphisms in GST genes modify the association between cruciferous vegetable intake (or urinary ITC levels) and CRC. While some studies observed no evidence of significant interaction between cruciferous vegetable/ITC levels and the *GSTM1*,[64-66] *GSTT1*,[64, 65] or *GSTP1*[64] in relation to CRC (or colon cancer) risk, an inverse association has been observed between broccoli and colorectal adenoma only among those with the *GSTM1* null genotype (p-interaction:0.01).[67] Another study found that increasing dietary ITC intake was inversely associated with CRC risk among individuals who are jointly *GSTM1* null and GSST1 null (OR:0.43;95% CI:0.20-0.96); however, in contrast to the above-mentioned study, this association was not apparent when examining associations stratified by the *GSTM1* genotype alone.[68]

Meat

A recent meta-analysis demonstrated a 100 g/day increase in unprocessed red meat consumption to be associated with a 17% increased risk of CRC (RR:1.17;95% CI: 1.05-1.31), while a 50 g/day increase in processed meat was associated with an 18% increased risk (RR:1.18; 95% CI:1.10-1.28).[8] This association does not appear to be mediated by the fat content in meat, but possibly by the presence of carcinogenic heterocyclic amines (HCAs), which are often present in grilled meat due to extended cooking at high temperatures.[69] N-acetyltransferase 2 (NAT2) activates HCAs, and consequently rapid NAT2 acetylators may have longer exposure to carcinogens and increased risk for DNA adduct formation. Corroborating evidence suggests that the association between meat intake and colorectal cancer[70-73] and adenoma[70] is stronger among rapid acetylators than slow acetylators, although not all studies support the presence of interaction.[74-76] It is also conceivable that the association between red meat and CRC may be, in part, attributable to the presence of polyaromatic hydrocarbons (PAHs), which form when barbequing meat. Given that GSTs are involved in the metabolism of these carcinogens,[77] some have sought to evaluate whether the association between red meat and CRC varies by variants in GST genes.[60, 76] There does not appear to be evidence of significant interaction involving *GSTM1*[60, 76] or *GSTT1*,[60] although one study showed weak interaction between red meat and the *GSTP1* $Ile_{105}Val$ polymorphism, but not the *GSTP1* $Ala_{114}Val$ polymorphism.[60] Further, as carcinogens, such as HCAs and PAHs, are transported into the intestinal lumen by ATP-binding cassette (ABC) transporters P-glycoprotein and the Breast Cancer Resistance Protein, one study evaluated whether the association between red meat intake and CRC varied by the SNPs in genes encoding these proteins, *ABCB1*/*MDR1* C3435T/G-rs3789243-A (rs1045642, rs3789243) and *ABCG2*/*BCRP* C421A (rs2231142), respectively.[78] The investigators observed that a 25 gram/day increase in red/processed meat was associated with an 8% increased risk of CRC among persons with the homozygous *MDR1* C3435T C-allele, with no association observed among those with the variant allele. The other two SNPs evaluated in this study did not modify the

association, and a later study further found no evidence of interaction between red/processed meat intake and *ABCC2*, a gene encoding another intestinal transporter.[59]

Furthermore, one study observed that the association between red meat and/or processed meat and CRC may be weakly modified by genetic variation in transcription factor nuclear factor kappa-B (NFkB)-94 insertion/deletion ATTG (rs28362491);[79] however, no evidence of significant effect modification has been observed involving genetic variation in other inflammation-related genes, including: *IL-10*,[57] cyclooxgenase-2 (*COX-2*),[78] or *PPAR*.[80] Lastly, a significant interaction has been observed between red/processed meat intake and the DNA repair *MGMT* gene, with increased risk observed among those with the variant genotype only.[40]

GENE-DIET INTERACTION: GWAS-IDENTIFIED SNPS

Instead of relying on a candidate gene approach, some studies have sought to identify gene-diet interaction involving established CRC susceptibility loci. In the Genetics of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR), interactions involving 10 GWAS-identified susceptibility loci and a set of 'environmental factors' were evaluated, including alcohol use, and dietary intakes of calcium, folate, red meat, processed meat, vegetables, fruit, and fiber.[81] In this large study, only one interaction, between rs16892766, located on chromosome 8q23.3, near the *EIF3H* and *UTP23* genes, remained significant after accounting for multiple comparisons. Specifically, the magnitude of association between the SNP and CRC strengthened with each increasing quartile of vegetable consumption; however, it is difficult to understand why this SNP may modify the association between vegetable intake and CRC risk, as the functional relationship between these genes and CRC remains unclear. Recently, this analysis was expanded to evaluate the presence of interactions between 16 newly identified susceptibility loci and the same set of dietary factors, with no significant interaction observed after adjustment for multiple comparisons.[82]

Some have taken a more targeted approach, instead focusing on a single GWAS-identified SNP.[83, 84] Specifically, an analysis of 4 studies sought to evaluate how the association between 9p24 risk locus rs719725 and colorectal tumor varied by several environmental factors, including: alcohol intake, folate intake, calcium intake, and red meat consumption, observing no evidence of interaction.[83] Similarly, in a small case-control study of adenoma, no evidence of interaction was observed for the association between the GWAS-identified SNP rs6983267, in the chromosome 8q24 region, and colorectal adenoma for any of the following dietary factors: alcohol, blood 25-OH-vitamin D3 levels, or intakes of total energy, calcium, red meat, vegetable and fruit, and folate.[84]

Others have used GWAS-identified SNPs to create a summary genetic risk score, and have evaluated whether this measure of genetic risk modifies the association between a given dietary factor and CRC.[49, 85] In a small nested case-control study, it was observed that the association between fatty fish intake and CRC risk varied by a risk score comprised of 16 CRC susceptibility loci.[85] Specifically, increasing fatty fish intake was associated with reduced risk of CRC among those with low genetic risk, and was associated with increased

risk among those with high genetic risk, although it is unclear why the association between fish intake and CRC would vary by a composite measure of overall genetic risk. A similar approach using a risk score of 18 GWAS-identified susceptibility loci observed no interaction between an overall genetic risk score and circulating 25(OH)D.[49]

GENE-DIET INTERACTION: GENOME-WIDE ANALYSIS

The presence of gene-environment interaction may obscure marginal effects of genetic variants, and therefore focusing only on interactions involving established CRC susceptibility loci might miss gene-diet interactions. To address this issue and seek confirmation of results from candidate gene studies, research has turned to a genome-wide approach, in which a given dietary factor is tested for interaction across the entire genome.

In a study of 9,287 cases and 9,117 controls in GECCO and CCFR, investigators examined whether the associations between established dietary risk factors (red meat, processed meat, fiber, fruit, and vegetables) and CRC were modified by approximately 2.7 million SNPs across the entire genome.[86] A significant interaction was observed between processed meat intake and rs4143094 (p-interaction:8.7×10^{-9}). This SNP lies in the promoter region of *GATA3*, a gene which is involved in ulcerative colitis and which has been previously linked to colorectal cancer. Specifically, the association between processed meat and CRC was strongest among those with the rs4143094-TT genotype (OR:1.39), with a weaker association observed among those with one variant allele (TG OR:1.20) and no association among those with the GG genotype (OR:1.03). This framework was expanded within GECCO and CCFR to include calcium, with no evidence of interaction observed between calcium intake (dietary, supplemental, or total) and SNPs across the genome.[87] Similarly, a smaller study indicated no evidence of significant genome-wide interaction involving dietary factors (alcohol, folic acid, multivitamins, calcium, fruit, vegetables, and red meat) in relation to microsatellite stable/microsatellite-instability low CRC.[88]

CONCLUSION

To date, epidemiologic studies have revealed inconsistent evidence of gene-diet interaction in relation to CRC. While evidence from candidate gene studies suggests that certain dietary factors may interact with genes involved in their metabolism and studies of GWAS-identified susceptibility loci have identified an interaction between vegetable intake and rs16892766, these findings have not been corroborated by recent studies of genome-wide interaction. In fact, thus far, studies of interaction across the entire genome have identified only one interaction (processed meat and rs4143094), and this interaction had not been previously identified using other approaches.

Several factors may explain why genome-wide studies of interaction have not replicated findings from candidate gene studies and studies of GWAS-identified SNPs. Firstly, most genome-wide work to date has been conducted within the meta-analysis framework, and consequently, the environmental data have been harmonized across studies (including both retrospective and prospective studies), resulting in a loss of richness of the environmental data. Nonetheless, in GECCO/CCFR, the consortium used for many of these studies of

interaction involving susceptibility loci or genome-wide approaches, the marginal main effects of the environmental factors align with the literature.[81, 82] Even so, we may be better able to elucidate gene-diet interaction by increasing the richness of the dietary data in these meta-analyses. Similarly, it should be considered that studies of interaction involving GWAS-identified susceptibility involve tagging SNPs, not the actual causal SNP, and the use of these tagging SNPs may diminish our ability to detect gene-diet interaction in studies of GWAS-identified susceptibility loci.

Secondly, although most of these genome-wide studies of interaction have been conducted within a large consortium, it is possible even large consortia are not adequately powered to detect modest/weak interactions when accounting for multiple comparisons. As consortia grow and methods for detecting gene-environment interaction continue to develop, we may be better able to detect modest interaction, possibly increasing the consistency of results across approaches.

Thirdly, results from candidate gene studies may not replicate in genome-wide approaches, as it is possible that results from these inconsistent candidate-gene studies are more likely to reflect false positives resulting from multiple testing or publication bias.[89] Although modern approaches involving GWAS-identified SNPs or genome-wide interaction may be less prone to publication bias, the biologic basis of interactions identified in these agnostic studies remains unclear. For example, although studies of GWAS-identified SNPs and genome-wide interaction have identified two significant gene-diet interactions,[81, 86] the biologic underpinnings of these interactions are not understood.

As methods in statistical genetics continue to develop, future studies may address multifactorial gene-diet interaction, and may directly evaluate interaction involving other forms of genetic variation, such as insertions/deletions and copy-number variants (CNVs).[90] We may also wish to focus studies of gene-diet interaction on genetic variants in a particular biologic pathway, using any number of pathway-based approaches.[21, 91-94] Alternatively, we may consider whether diet, or specific components of the diet, can modify a composite of overall genetic risk score, as has been done previously.[49, 85] While this approach may be useful in identifying high-risk groups who may benefit from a dietary approach, it is unlikely to improve our understanding of the biology of this disease, as the risk score is comprised of a diverse mixture of multiple independent genetic variants. Similarly, we may evaluate gene-diet interaction involving an overall measure of diet quality or dietary patterns, as opposed to specific nutrients or food groups. Lastly, as consortia grow, we may acquire enough statistical power to evaluate gene-diet interaction by anatomic subsite or by molecular features of the tumor, such as microsatellite instability, as etiology of these cancers likely vary by molecular subtype.

In conclusion, while results thus far have not yielded much evidence of gene-diet interactions in CRC etiology, continuing work and developing methods will hopefully better elucidate the role of gene-diet interaction in the etiology of CRC.

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