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Nature, Nurture, and Cancer Risks: Genetic and Nutritional Contributions to Cancer

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Keywords

diet, genes, cancer, interaction, nutrigenetics, colorectal cancer, breast cancer, prostate cancer, lung cancer, stomach cancer

Abstract

It is speculated that genetic variants are associated with differential responses to nutrients (known as gene–diet interactions) and that these variations may be linked to different cancer risks. In this review, we critically evaluate the evidence across 314 meta-analyses of observational studies and randomized controlled trials of dietary risk factors and the five most common cancers (breast, lung, prostate, colorectal, and stomach). We also critically evaluate the evidence across 13 meta-analyses of observational studies of gene–diet interactions for the same cancers. Convincing evidence for association was found only for the intake of alcohol and whole grains in relation to colorectal cancer risk. Three nutrient associations had highly suggestive evidence and another 15 associations had suggestive evidence. Among the examined gene–diet interactions, only one had moderately strong evidence.

Contents

INTRODUCTION

Diet can be defined as the sum of food consumed by a person. Dietary habits are the habitual decisions an individual makes when choosing which foods to eat. Although humans are omnivores, each person may hold food preferences or even taboos due to personal tastes, local customs, or ethical reasons. Individual dietary choices may or may not play a significant part in the quality of life, health, and longevity. Nutritional epidemiology—the study of the relationship between nutrition and health—is a challenging and quickly expanding field with a number of limitations resulting in inconsistencies in the published literature.

Diet and Cancer

In 2012, an estimated 14.1 million cancer cases were diagnosed globally (7.4 million cases in men and 6.7 million in women). This number may increase to 24 million by 2035. Lung cancer was the most common cancer worldwide, contributing 13% of the total number of new cases diagnosed in 2012 (1.8 million new cases), with breast cancer being the second most common (1.7 million new cases), and colorectal cancer being the third most common cancer (1.4 million new cases). The age-standardized rate for all cancers (excluding non-melanoma skin cancer) for men and women combined was 182 per 100,000 in 2012 (205 per 100,000 for men; 165 per 100,000 for women). The

cancer rate was at least 300 per 100,000 for nine countries (Denmark, France, Australia, Belgium, Norway, United States, Ireland, South Korea, and Netherlands). These countries may have higher rates than other countries because they have more intensive ascertainment of cancer cases or because they genuinely have populations with higher genetic, lifestyle, or other risks that contribute to malignancies. Although cancer is often considered to be more of a developed world issue, in fact 57% of all cancers (excluding non-melanoma skin cancer) occur in less developed countries.

Laboratory mouse studies of the 1940s suggested that caloric restriction reduced the occurrence of cancer in rodents. Several decades of epidemiological research have followed, with numerous reports linking diet and cancer (16). For instance, searching MEDLINE for "diet" and "cancer" resulted in 40,666 hits, including 2,137 classified by type of article as "clinical trials" and 7,489 as "reviews" (455 of which included a "meta-analysis"; date of search: April 10, 2016). It is widely believed that diet and nutrients can act as cancer risk modifiers across the entire process of carcinogenesis including initiation, promotion, progression, conversion, or a combination thereof. Numerous nutrients or foods have been suggested to be linked to cancer, but the majority of claimed associations have not been consistently replicated in subsequent studies.

The World Cancer Research Fund International (WCRF)/American Institute for Cancer Research (AICR) has summarized published research on the relationships among cancer prevention and survivorship and diet, nutrition, and physical activity. Its Second Expert Report was published in 2007 (114) and WCRF/AICR has also been collating findings from new cancer prevention research published around the world for the Continuous Update Project (115–118). WCRF/AICR also produces estimates on how many cases of cancer could be prevented by changes in nutrition and physical activity. They have estimated that for the 13 most common cancers, 29% of cases in the United States could be prevented by eating a healthy diet, being physically active, and maintaining a healthy weight. Estimates for other countries are 29% of cases could be prevented in the United Kingdom, 22% in Brazil, and 19% in China (**http://www.wcrf.org/cancer-preventability-estimates**; accessed on May 18, 2017). However, these impressive estimates assume that (*a*) the published literature is valid and (*b*) associations can be translated to preventive interventions. Both assumptions are highly questionable.

Nutritional Genomics and Cancer

Genes are responsible for protein formation and metabolic function. Natural genetic variations that occur with fairly high frequency (1–50%) in the general population are known as polymorphisms. The most common type of polymorphism involves variation at a single base pair known as a single nucleotide polymorphism (SNP) (20). Genes can be turned on and off in response to metabolic signals that the nucleus receives from internal factors (e.g., hormones) or external factors (e.g., diet) (20).

Nutritional genomics is the science that studies the relationship among the human genome, nutrition, and health. Nutrigenomics assesses how dietary substances may cause changes such as mutations of the genome, or changes in gene expression without changing the DNA sequence (nutritional epigenetics). Nutrigenetics aims to understand how the genetic makeup of individuals coordinates their responses to diet. In other words, nutrigenetics studies try to identify and characterize genetic variants associated with differential responses to nutrients and to relate these variations to disease states (gene–diet interactions) (84).

Aim of the Review

We collected and evaluated the evidence across existing meta-analyses of observational studies of dietary risk factors and gene–diet interactions for the five most common cancers (breast, lung,

prostate, colorectal, and stomach). First, we evaluated the range and validity of the reported dietary associations with cancer by categorizing the evidence using a number of preselected criteria. Then, for the dietary associations with the strongest evidence, we reviewed the joint effects of genes and dietary factors, and we used a proposed set of guidelines to evaluate the cumulative evidence for gene–diet interactions in cancer.

METHODS

We reviewed the literature and established knowledge about the associations among nutrition, genes, and gene–diet interactions, and the most common types of cancer, including breast, lung, prostate, colon, and stomach. The full text of potentially eligible articles was scrutinized independently by two investigators (E. Theodoratou, M. Timofeeva). When more than one meta-analysis of the same research question was eligible for inclusion, the meta-analysis with the largest number of component studies was retained for the main analyses. Data extraction was performed by the same two investigators, and in the case of discrepancies, the final decision was made after discussion.

Diet and Cancer

Details of the literature searches, data extraction, statistical analyses, and evaluations of the strength of the evidence for the role of diet in cancer are presented below.

Search strategy and eligibility criteria. We included meta-analyses of the associations between dietary risk factors and cancer as presented in the WCRF/AICR Second Expert Report (114) and information from subsequent Continuous Update Projects when available. An additional MEDLINE search was conducted to identify more recent meta-analyses of prospective observational studies and randomized controlled trials (RCTs) published since the corresponding Continuous Update Projects. The search strategy and MeSH (Medical Subject Headings) terms used for each type of cancer are presented in **Supplemental Box 1** (see **Supplemental Table 1**).

Supplemental Material

Data extraction. For each eligible article, we recorded the first author, journal, year of publication, the examined dietary risk factor, the number of studies considered, the study-specific relative risk estimates [standardized mean difference, risk ratio (RR), odds ratio (OR), hazard ratio (HR)] and their corresponding 95% confidence intervals (CIs), the number of cases and total participants, and the P value for Cochran's Q test or the I^2, which measures the heterogeneity of the studies included in each meta-analysis.

Statistical analysis and strength of evidence evaluation. For each meta-analysis, we estimated the P value of the reported summary effect (5) and I^2 with 95% CI (60). To categorize dietary risk factors in terms of the strength of the evidence, we applied a set of criteria (15). In particular, convincing evidence (class I) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), a 95% prediction interval that did not include 1, no evidence of small-study effects ($P > 0.10$), no evidence of excess significance bias ($P > 0.10$), and $I^2 < 50\%$. Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), and the 95% CI in the largest study had to exclude 1. Suggestive evidence (class III) required >1,000 cases and $P < 0.001$ by random effects. All other risk factors with nominally significant summary associations ($P < 0.05$) were classed as having weak evidence (class IV). Nonsignificant (NS) associations were those in which $P > 0.05$. To distinguish between

class I and class II evidence, we calculated (*a*) the 95% prediction interval, which accounts for between-study heterogeneity and evaluates the uncertainty for the effect that would be expected in a new study addressing that same association; (*b*) the small-study effect, i.e., whether smaller studies give substantially larger estimates of effect size compared with larger studies, according to the regression asymmetry test (38); and (*c*) the excess significance bias, which measures whether the observed number of studies with nominally significant results ($P < 0.05$) is larger than the expected number (61).

Gene–Diet Interactions in Cancer

Details of the literature searches, data extraction, statistical analyses, and evaluations of the strength of the evidence for gene–diet interaction in cancer are presented below.

Search strategy and eligibility criteria. We performed a systematic MEDLINE literature review to identify meta-analyses of observational studies that explored the interaction effects between genes and diet in the most common types of cancer. We restricted our search to foods and nutrients for which the evidence was classified as I, II, or III in the evaluation of the dietary studies. The search strategy and MeSH terms used for each cancer are presented in **Supplemental Box 2**.

Supplemental Material

Additionally, we performed a search to explore the main effects of the genetic variants of the identified gene–environment interactions. We searched the National Human Genome Research Institute–European Bioinformatics Institute catalog of genome-wide association studies (GWAS) (111) and the GWAS central database (14) to identify published associations between genetic variants and the risk of breast, colon, prostate, lung, and stomach cancers. Both of the data sets have specific internal curatorial procedures and strict eligibility criteria for data extraction, which are summarized in **Supplemental Box 3**. To cover candidate-based studies looking for the main effect of genetic variants on cancer risk (which are not included in the GWAS catalog and in the GWAS central database), we carried out a MEDLINE literature search to identify meta-analyses and field synopses. The search strategy and MeSH terms used for each cancer are presented in **Supplemental Box 4**.

Data extraction. From each eligible article about gene–diet interactions, we recorded the first author, the year of publication, the examined dietary and genetic risk factors, the number of studies considered, the study-specific relative risk estimates (standardized mean difference, RR, OR, HR) and their corresponding 95% CIs, the number of cases and total participants, the *P* value of the interaction, and the *P* value (or I^2) for heterogeneity. From the eligible articles of the genetic association studies, we recorded the first author, the year of publication, the ethnicity of the study participants, the numbers of cases and controls in discovery and replication sets, and the *P* value for the main effect of variants, as well as study-specific estimates (ORs and RRs) and 95% CIs when available.

Statistical analysis and strength of evidence evaluation. We followed predetermined guidelines to assess the strength of the evidence in the meta-analyses of the associations between genes and diet (18). First, we scored the strength of the evidence for main effects. The score for dietary exposure was based on the classification of evidence in the section of this review on Diet and Cancer. Genetic associations were classified using the Human Genome Epidemiology Network's Venice criteria (59, 106). Only genetic effects with $P < 10^{-5}$ were considered for evaluation. The epidemiological evidence for an effect of the genotype was classified as strong, moderate, or weak on the basis of a combination of three criteria (amount of evidence, degree of replication, and

protection from bias), each of which is scored A, B, or C. Grade A is assigned for large-scale evidence (amount of evidence), little between-study inconsistency (degree of replication), and absence of or little bias that will not change the presence of an association (protection of bias). Grade B is assigned for moderate amount of evidence, moderate between-study inconsistency, and no obvious bias. Grade C is assigned for little evidence, large inconsistency between studies, and a strong possibility of bias that would render the finding of an association invalid (59).

Supplemental Material

Second, we established a prior score category (expected) for gene–diet interactions using the framework presented by Boffetta et al. (18) (also reproduced in **Supplemental Box 5**). This score is based on the scores for the evidence of the main dietary and genetic effects.

Third, we scored the strength of the observed evidence for interaction between the dietary exposure and the genetic variants on the basis of an extension of the Venice criteria (18, 59). As for the main effects, the grade for each gene–diet association was based on the amount of evidence, the extent of replication, and the protection of bias. For the amount of evidence, a grade of A, B, or C was assigned when the sample size for the smallest comparison group in the meta-analyses was greater than 1,000, 100–1,000, or less than 100, respectively. When the sample size for the smallest comparison group was not available, it was calculated, when appropriate, using the rare genotype frequency and prevalence of environmental exposure. For replication consistency, we used $I^2 < 25\%$ to assign grade A, $I^2 = 25$–50% to assign grade B, and $I^2 > 50\%$ or a P value for heterogeneity <0.10 to assign grade C. For protection from bias, three aspects of the gene–environment association were taken into account, as suggested by Boffetta et al. (18): protection from bias for environmental exposure, for the genetic analysis, and for overall interaction. Grade A means that bias, if present, may change the magnitude but not the presence of an association; grade B means that there is no evidence of bias that would invalidate an association, but important information is missing; and grade C means that there is a strong possibility of bias that would render the finding of an association invalid.

Fourth, we examined the overall plausibility of each interaction by comparing the prior score and the score based on the strength of the observed evidence.

OVERVIEW OF THE ROLE OF NUTRITION IN MOST COMMON TYPES OF CANCER

A summary of the published evidence for the role nutrition has in cancer risk is presented in **Table 1** and **Supplemental Tables 1–6**. In the subsequent sections, we present the findings of the literature review of all evidence for the role nutrition has in breast, lung, prostate, colorectal, and stomach cancers based on the WCRF/AICR Second Expert Report (114), the Continuous Update Project reports (115–118), and a summary of all identified meta-analyses of prospective cohorts and RCTs published since the last update project. Evidence has been classified into four groups on the basis of the criteria presented in the methods.

Breast Cancer

No association was classified as convincing (class I). The association between alcohol intake and estrogen receptor–positive (ER+) breast cancer was classified as highly suggestive (class II) on the basis of a meta-analysis of 20 prospective studies [≥30 g/day of alcohol consumption versus nondrinkers RR (95% CI), 1.35 (1.23–1.48); $P = 5.2 \times 10^{-10}$; $I^2 = 26\%$; P for small-effect bias = 0.184; P for excess significance bias $= 4 \times 10^{-8}$] (66). There was evidence of heterogeneity in effects by ER status, with the association between alcohol and ER− breast cancers classified as weak (class IV) [RR, 1.28 (95% CI, 1.10–1.49); $I^2 = 0\%$] (66) (**Table 1**, **Supplemental Table 1**).

Table 1 Summary characteristics for class I–III dietary evidence for breast, lung, prostate, colon, and stomach cancers[a]

Type of cancer and risk factor	Reference	Unit of comparison	Events	Number of studies	Relative risk (95% CI)	*P* value	Prediction interval	I^2(%)	Evidence class
Breast cancer									
Nutrient or dietary factor									
Alcoholic drinks	66[b]	≥30 g/day of alcohol consumption versus nondrinkers	ER+: 21,232 ER−: 4,343	ER+: 20 ER−: 17	ER+: 1.35 (1.23–1.48) ER−: 1.28 (1.10–1.49)	ER+:5.2 × 10^{-10} ER−: 0.001	ER+: 1.07, 1.70	ER+: 26 ER−: 0	ER+: II[c]; ER−: IV
Vegetables	65	Highest versus lowest quintiles of total vegetable consumption	4,821	20	0.82 (0.74–0.90)	8.1 × 10^{-5}	NA	<50	III
α-Carotene	53	Per 1,500 μg/day of dietary intake	7,298	4	0.91 (0.87–0.96)	0.0002	NA	1	III
Lung cancer									
Nutrient or dietary factor									
β-Cryptoxanthin	46	Highest versus lowest category of intake	4,894	8	0.80 (0.72–0.89)	4.4 × 10^{-5}	NA	0	III
Carotenoids	46	Highest versus lowest category of intake	4,310	8	0.79 (0.71–0.87)	7.1 × 10^{-6}	NA	0	III
Fruits	103	Highest versus lowest intake	15,599	29	0.82 (0.76–0.89)	1 × 10^{-6}	0.62, 1.07	32	II
Citrus fruits	103	Highest versus lowest intake	12,021	15	0.85 (0.78–0.93)	0.0003	NA	30	III
Prostate cancer									
Nutrient or dietary factor									
Dietary calcium	10	High versus low intake	35,493	15	1.18 (1.08–1.30)	0.0005	NA	53	III
Selenium	105	Highest versus lowest category of intake and biochemical selenium level	6,532	17	0.79 (0.69–0.90)	0.0005	NA	23	III

(*Continued*)

Table 1 (*Continued*)

Type of cancer and risk factor	Reference	Unit of comparison	Events	Number of studies	Relative risk (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
Colorectal cancer									
Nutrient or dietary factor									
Alcoholic drinks	41[d]	Heavy drinkers (≥50 g/day) versus nondrinkers/occasional drinkers	1,208	7	1.57 (1.38–1.80)	4.2×10^{-11}	1.32, 1.87	0	I[e]
Calcium	68	300 mg daily increment of calcium intake	12,305	15	0.92 (0.89–0.94)	4.8×10^{-9}	0.85, 1.01	47	II
Total fiber	6	High versus low intake	14,794	19	0.88 (0.82–0.94)	0.0003	NA	0	III
Vegetables	8	Highest versus lowest intake	16,057	16	0.91 (0.86–0.96)	0.0008	0.86, 0.96	0	III
Whole grains	6	High versus low intake	>4,523	4	0.79 (0.72–0.86)	3.1×10^{-7}	0.65, 0.96	0	I[f]
Dairy products	9	Highest versus lowest dietary intake	11,579	12	0.81 (0.74–0.90)	2.9×10^{-5}	NA	42	III
Nonfermented milk	90	Highest versus lowest category	7,735	14	0.85 (0.77–0.93)	0.0008	NA	0	III
Milk	9	Per 200 g/day intake	4,510	9	0.91 (0.85–0.94)	0.0003	NA	0	III
Processed meat	24	Per 50 g/day	10,863	9	1.18 (1.10–1.28)	2.3×10^{-5}	NA	12	III
Biomarkers									
Circulating vitamin D [25(OH)D]	72	Top versus bottom quantiles of circulating 25(OH)D levels	1,822 colon cancer and 868 rectal cancer cases	8	0.66 (0.54–0.81)	6.8×10^{-5}	NA	NA	III

(*Continued*)

Table 1 (*Continued*)

Type of cancer and risk factor	Reference	Unit of comparison	Events	Number of studies	Relative risk (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
Stomach cancer									
Nutrient or dietary factor									
Salt	40	Highest versus lowest intake	14,850	8	1.11 (1.05–1.16)	4.7×10^{-5}	NA	26	III

Abbreviations: CI, confidence interval; ER, estrogen receptor; NA, not applicable.

[a]Evidence class was decided using the following criteria: Convincing evidence (class I) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), a 95% prediction interval not including the null, no evidence of small-study effects, no evidence of excess significance bias, and low heterogeneity values ($I^2 < 50\%$). Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), and the largest study to have a 95% confidence interval that excluded 1. Suggestive evidence (class III) required only >1,000 cases and $P < 0.001$ by random effects. Evidence was considered weak (class IV) when all other risk factors had only nominally significant summary associations ($P < 0.05$). Nonsignificant associations (NS) were those with $P > 0.05$.

[b]The current study was used instead of the bigger meta-analysis of 7 cohort studies on alcohol consumption and breast cancer risk by Bagnardi et al. (12) (risk ratio for heavy drinkers versus nondrinkers: 1.50; 95% CI: 1.19,1.89) due to the limited information on summary statistics and included studies.

[c]The evidence was classified as highly suggestive (class II) due to the presence of excess significance bias (*P* for excess significance bias $= 4 \times 10^{-8}$; *P* for small effect bias $= 0.184$).

[d]The current study was used instead of the bigger meta-analysis of 14 cohort studies on alcohol consumption and colorectal cancer risk by Bagnardi et al. (12) (risk ratio for heavy drinkers versus nondrinkers: 1.41; 95% CI: 1.23–1.63) due to the limited information on summary statistics and included studies.

[e]There was no evidences of small effect bias (*P* for small effect bias $= 0.802$) or excess significance bias (*P* for excess significance bias $= 0.254$).

[f]There was no evidences of small effect bias (*P* for small effect bias $= 0.947$) or excess significance bias (*P* for excess significance bias $= 0.11$).

A bigger meta-analysis that included 37 prospective studies also suggested a strong effect for moderate alcohol intake on the overall risk of breast cancer [moderate alcohol consumption of 12.5–50 g/day versus nondrinkers RR, 1.22 (1.17–1.27); $P = <10^{-6}$; $I^2 = 33\%$], but it was not possible to test for small-study effect or excess significance in that meta-analysis (12). Associations with dietary intakes of α-carotene (53) and of vegetables in ER− breast cancer (65) were classified as suggestive (class III; **Table 1**). In particular, dietary intake of α-carotene was associated with a 9% reduction in total risk for breast cancer [RR for highest versus lowest category, 0.91 (0.87–0.96); $P = 0.0002$; $I^2 = 1\%$], and dietary intake of vegetables was associated with an 18% reduction [RR for highest versus lowest quintiles of total vegetable consumption, 0.82 (0.74–0.90); $P = 8.1 \times 10^{-5}$; $I^2 < 50\%$].

On the basis of the evidence, the associations between breast cancer risk and the following were classified as weak (class IV): eggs, dairy products, polyunsaturated fat, processed meat, alcohol intake (only in ER− breast cancer), soy, isoflavones, cruciferous vegetables, fruits and vegetables combined, fruits, retinol, vitamin A, glycemic index, marine *n*-3 polyunsaturated fatty acids, β-carotene, total carotenoids (in serum and plasma), the ratio of *n*-3 to *n*-6 polyunsaturated fatty acids in serum (plasma), dietary fiber, and lycopene concentration in serum and plasma (**Supplemental Table 1**). Among other nutrients that were investigated in prospective cohort studies but did not show evidence of association with cancer risk in categorical and dose-response meta-analyses ($P > 0.05$) were intakes of total and saturated fat (103, 122), animal fat (3), dietary acrylamide (88), dietary (28, 77) and circulated (28) folate levels and folic acid supplementation (89, 107), calcium (27), vitamins C and E (45), vitamin D (71), vitamins B_6 and B_{12} (121), methionine (121), multivitamins (23), β-cryptoxanthin (39), lutein/zeaxanthin (53), iron (44), cadmium (31), linolenic acid (131), saturated fatty acids (122), monounsaturated fat (103), polyunsaturated fatty acids (103), and glycemic load (35). Among other food items that were investigated in prospective cohort studies but did not show evidence of association with breast cancer risk in categorical and dose-response meta-analyses were milk (36), fish (131), red meat (2), coffee (64), and green tea (119).

Supplemental Material

Lung Cancer

Smoking, including passive exposure to tobacco, is the principal cause of lung cancer. There is, however, increasing evidence that nutritional factors and diet may also affect the risk of the disease. No association was classified as convincing (class I). A meta-analysis of prospective studies on lung cancer risk and food intake published in 2016 demonstrated statistically significant, albeit small, inverse associations between high fruit intake and lung cancer risk [RR, 0.82 (95% CI, 0.76–0.89); $P = 10^{-6}$; $I^2 = 32\%$; class II, or highly suggestive] as well as a significant inverse association in dose-response meta-analyses (104) (**Table 1**, **Supplemental Table 2**). This meta-analysis showed evidence of small-study effects (P for Egger's test <0.01), and the effects seemed to be restricted only to current smokers, thus suggesting possible residual confounding (104). Similar effects were noted in an analysis restricted to citrus fruits [RR for highest versus lowest intake, 0.85 (0.78–0.93); $P = 0.0003$; $I^2 = 32\%$], although this association was classified as suggestive (class III). Again, the evidence was restricted to current and former smokers and evidence of small-study effects was noted (104). Finally, the associations with β-cryptoxanthin [RR for highest versus lowest intake, 0.80 (0.72–0.89); $P = 4.4 \times 10^{-5}$; $I^2 = 0\%$] and carotenoids [RR for highest versus lowest intake, 0.79 (0.71–0.87); $P = 7.1 \times 10^{-6}$; $I^2 = 0\%$] were classified as suggestive (class III) (46). Interestingly, in a meta-analysis of four randomized clinical trials, association between β-carotene supplementation and lung cancer risk was classified as suggestive (class III) for increased rather than decreased risk [RR, 1.21 (95% CI, 1.09–1.32); $P = 0.0001$; $I^2 = 32.5\%$], with effects stronger

among current smokers [RR, 1.24 (95% CI, 1.10–1.39); $P = 0.0002$; $I^2 = 42.1\%$] (**Supplemental Table 6**) (97). Finally, the WCRF/AICR Second Expert Report (114) classified the association between β-carotene supplementation and cancer risk in smokers as convincing, although only one RCT was included (114).

Supplemental Material

On the basis of the evidence, the associations between lung cancer risk and α-carotene, β-carotene, lycopene, lutein/zeaxanthin, vitamin A, soy, soy isoflavones, vegetables, cruciferous vegetables, total fruits and vegetables, and flavonoids were classified as weak (class IV; **Supplemental Table 2**). Among other nutrients that were evaluated in recent meta-analyses of prospective studies but had $P > 0.05$ were dietary lutein intake (46), vitamins C and E (29), and folate (29). Among other food items that were investigated in prospective cohort studies but did not show evidence of association with lung cancer risk in categorical and dose-response meta-analyses were fish (127), poultry (127), alcohol (12), and black and green teas (108).

Prostate Cancer

No association was classified as convincing (class I) or highly suggestive (class II). Calcium supplementation was associated with an almost 50% reduction in risk for prostate cancer in a meta-analysis of four RCTs [RR, 0.54 (95% CI, 0.30–0.96); $P = 0.04$; $I^2 = 0\%$] (19) (**Table 1**, **Supplemental Table 3**). However, the evidence is not consistent and a recent meta-analysis of dietary calcium intake showed an increase in risk for those who were in the highest category of dietary intake compared with those in the lowest category [RR, 1.18 (95% CI, 1.08–1.30); $P = 0.0005$; $I^2 = 53.4\%$; class III) (10), although the association was limited to dairy calcium only [RR for highest versus lowest intake, 1.13 (1.02–1.24); $I^2 = 46\%$] and not observed for nondairy calcium [RR for highest versus lowest dietary intake, 0.91 (0.79–1.05)] (10). Another association classified as suggestive (class III) was selenium intake investigated in a large Cochrane meta-analysis of observational studies and RCTs. Although an association with prostate cancer reduction was noted in a meta-analysis of observational studies [RR for highest versus lowest intake, 0.79 (0.69–0.90); $P = 0.0005$; $I^2 = 23\%$], no effect was observed when meta-analysis was limited to RCTs (105).

On the basis of the evidence, the associations between prostate cancer risk and α-linolenic acid, soy and soy isoflavones, dairy, milk, whole milk, low-fat milk, cheese, eggs, and plasma levels of stearic acid, eicosapentaenoic acid, docosapentaenoic acid, linoleic acid, and folate were classified as weak (class IV; **Supplemental Tables 3** and **6**). Among other nutrients that were recently evaluated in meta-analyses of prospective studies and RCTs but did not show any statistically significant association with prostate cancer risk were plasma concentrations of myristic acid, pentadecanoic acid, heptadecanoic acid, palmitic acid, palmitoleic acid, docosahexaenoic acid, dihomo-γ-linoleic acid, arachidonic acid, and oleic acid (33). No statistically significant association between total prostate cancer risk and allium vegetables (133), fruits (82), tomato/lycopene (26), carrots (124), eggs (69), and yogurt (10) was detected in meta-analyses of prospective studies and RCTs.

Colorectal Cancer

The association between whole grains intake and colorectal cancer was classified as convincing (class I) on the basis of a meta-analysis of four prospective studies [high versus low intake RR, 0.79 (95% CI, 0.72–0.86); $P = 3.1 \times 10^{-7}$; $I^2 = 0\%$; $P_{\text{small effect bias}} = 0.947$; $P_{\text{excess significance bias}} = 0.11$] (6). Heavy alcohol intake (≥50 g/day) was also classified as convincing (class I) on the basis of a meta-analysis of seven prospective studies [RR, 1.57 (95% CI, 1.38–1.80); $P = 4.2 \times 10^{-11}$; $I^2 = 0\%$; $P_{\text{small effect bias}} = 0.802$; $P_{\text{excess significance bias}} = 0.254$] (41). Moderate alcohol intake

(12.5–50 g/day), compared with nondrinking or occasional drinking, was also associated with increased risk [RR, 1.23 (95% CI, 1.14–1.28); $P < 1 \times 10^{-6}$; $I^2 = 54\%$; $P_{\text{small effect bias}} < 0.001$; $P_{\text{excess significance bias}} = 0.047$] (41), though the evidence was classified as highly suggestive (class II) owing to the high heterogeneity between the studies and the presence of small effects and excess significance bias. In addition, the latest meta-analysis of the association between dietary calcium and colorectal cancer showed a small 8% reduction in cancer risk with a 300 mg/day increase in total calcium intake [RR, 0.92 (95% CI, 0.89–0.94); $P = 4.8 \times 10^{-9}$; $I^2 = 47\%$; $n = 15$ studies] (68) and was classified as class II (highly suggestive). This finding is consistent with findings of previous meta-analyses (30, 55).

Calcium supplements were also associated with reduced colorectal cancer risk in a meta-analysis of eight cohort studies [RR, 0.86 (95% CI, 0.79–0.95 for use versus no use); class IV] (49) but not in meta-analyses of RCTs (19, 22), including a meta-analysis of eight RCTs [$n = 9{,}540$; supplementation of >500 mg/day of elemental Ca or calcium supplementation plus vitamin D versus placebo HR, 1.38 (0.89–2.15); $I^2 = 0\%$] (19). Despite the lack of statistically significant association in this meta-analysis of RCTs, no conclusion can be drawn because it included only 83 events. Associations between colorectal cancer and fiber [RR, 0.88 (95% CI, 0.82–0.94); $P = 0.0003$; $I^2 = 0\%$; $n = 19$ studies] (6), vegetables [RR, 0.91 (95% CI, 0.86–0.96); $P = 0.0008$; $I^2 = 0\%$; $n = 16$ studies] (8), dairy products [RR, 0.81 (95% CI, 0.74–0.90); $P = 2.9 \times 10^{-5}$; $I^2 = 0\%$; $n = 12$ studies] (9), nonfermented milk [RR, 0.85 (95% CI, 0.77–0.93); $P = 0.0008$; $I^2 = 0\%$; $n = 14$ studies] (90), milk [RR, 0.91 (95% CI, 0.85–0.94); $P = 0.0003$; $I^2 = 0\%$; $n = 9$ studies] (9), processed meat [RR, 1.18 (95% CI, 1.10–1.28); $P = 2.3 \times 10^{-5}$; $I^2 = 12\%$; $n = 9$ studies] (24), and circulating levels of vitamin D [OR, 0.66 (95% CI, 0.54–0.81); $P = 6.8 \times 10^{-5}$; $I^2 =$ not available; $n = 8$ studies] (72) were classified as suggestive (class III) (**Table 1**, **Supplemental Table 4**).

Supplemental Material

On the basis of the evidence, the associations between colorectal cancer risk and multivitamin supplements, vitamin A supplements, vitamin C, vitamin E, calcium supplements, folic acid supplements, folate, heme iron, zinc, magnesium, glycemic index, tea, fruit and vegetables combined, fruits, fish, red meat, beef, lamb, poultry, and circulating levels of total *n*-3 polyunsaturated fatty acids were classified as weak (class IV; **Supplemental Table 4**). Among other nutrients that were evaluated through meta-analyses of prospective observational studies and RCTs but did not show statistically significant associations with colorectal cancer risk were acrylamide (88), methionine (135), total flavonoids (113), carbohydrate (7), total fat (76), animal fat (1), vitamin E supplements (49), and glycemic load (32). Among other food items that were evaluated through recent meta-analyses but did not show statistically significant associations with colorectal cancer risk were coffee (63, 129), green tea (110), sugar-sweetened carbonated soft drinks (129), allium vegetables (136), onions (102), garlic (54), soy intake (125), cruciferous vegetables (100), fermented milk (90), cheese (9), and eggs (101).

Stomach Cancer

No association was classified as convincing (class I) or highly suggestive (class II). High salt intake was associated with an increased risk of stomach cancer [RR, 1.11 (95% CI, 1.05–1.16); $P = 4.7 \times 10^{-5}$; $I^2 = 26\%$; $n = 8$ studies] (40), and the association was classified as suggestive (class III). However, the latest Continuous Update Project report (118) classified evidence for total and added salt as "limited – no conclusion," owing mainly to difficulties of accurately measuring salt consumption (**Table 1**, **Supplemental Table 5**).

On the basis of the evidence, the associations between stomach cancer risk and intakes of vitamin E, vitamin C, high salt food, alcohol, beer, liquor, fruits, citrus fruits, white vegetables, pickled vegetables, tomatoes, spinach, pickled food, salted fish, processed meat, ham, bacon, or

sausage were classified as weak (class IV; **Supplemental Table 5**). Among other nutrients that were recently evaluated in comprehensive meta-analyses of prospective studies but did not show statistically significant associations with stomach cancer risk were α- and β-carotene (73), α- and γ-tocopherol (73), dietary fiber (130), isoflavones (113), nitrate, nitrite, and *N*-nitrosodimethylamine (40), and saturated fat and monounsaturated and polyunsaturated fats (48). Among other food items that were recently evaluated through meta-analyses but did not show statistically significant associations with stomach cancer risk were coffee (40, 123); black and green teas (40, 85), juice (40); citrus fruits (11); apples and pears (40), vegetables, including raw and cooked green and yellow vegetables (40, 109); cruciferous vegetables and cabbage (40, 120); tomatoes and tomato products (40, 126); carrots, lettuce, spinach, seaweed, mushrooms, legumes and beans, and potatoes (40); allium vegetables (40, 134); fermented and nonfermented soy products (70) and tofu (40); total grains/cereals, bread, and rice (40); dairy products, milk, butter, margarine, and cheese (40, 96, 99); eggs (40); miso soup (40); fish (40, 128); red meat (40, 137); and beef, pork, poultry, and liver (40).

NUTRITIONAL GENETICS AND CANCER

We searched the literature to identify meta-analyses, GWAS, or large consortia that explored gene–diet interactions in relation to breast, lung, prostate, colorectal, and stomach cancer risk for all dietary factors classified as I, II, or III. The search strategies, number of hits, and retained studies are presented in **Supplemental Box 2**. The summary of evidence for all identified gene–diet interactions is presented in **Supplemental Table 7**. We further extracted all genetic variants identified through studies on gene–diet interactions and searched the literature to identify meta-analyses, GWAS, or large pooled analyses that evaluated the effects of genetic variants on cancer risk. The search strategy and number of hits are presented in **Supplemental Box 4**. The evidence for all identified gene–diet interactions was categorized by (*a*) taking into account prior scores based on genetic and dietary main effects and (*b*) evaluating the overall plausibility of interaction by combining the prior score and the strength of the evidence. The summary of evidence including prior scores and combined scores are presented in **Table 2** and **Supplemental Tables 7** and **8**.

Breast Cancer

Here, we present the evidence for all identified gene–diet interactions in relation to breast cancer risk.

Gene–alcohol interactions. Numerous nested case-control studies and prospective studies have explored the interactions between alcohol consumption and genes involved in the alcohol metabolism pathway (including *ADH* and *ALDH*); their findings have been inconsistent. A meta-analysis (79) of 1,969 breast cancer patients and 2,244 controls from four case-control studies estimated the association between *ADH1C* (rs698) and breast cancer risk. It also performed a stratified analysis according to participants' alcohol consumption based on three articles (6 populations, 3 nondrinker populations, and 3 drinker populations). Compared with the reference ($ADH1C^{2-2}$), genotypes of $ADH1C^{1-1}$ + $ADH1C^{1-2}$ were associated with an increased risk of breast cancer in drinkers [OR, 1.35 (95% CI, 1.03,–1.76)], whereas no such relationship was found in nondrinkers [OR, 1.16 (95% CI, 0.86–1.57)] (**Supplemental Table 7**). Despite significant effects in drinkers only, no formal test for interaction was performed and the Cochran's *Q* test did not show any heterogeneity between a subgroup of drinkers and nondrinkers ($P_{heterogeneity} = 0.46$). The main effect of the rs698 variant on breast cancer risk was not significant in a meta-analysis of five studies totaling 13,511 breast cancer cases (**Supplemental Table 8**), thus giving only a weak prior score

Table 2 Evaluation of evidence of gene–environment interactions for the five major cancers

Type of cancer and nutrient or food	Genetic variant	Gene (or near gene)	Score for nutrient evidence (evidence class)	Score for genetic evidence/ Venice criteria[a]	Prior score[b]	Score based on observed evidence[c]	Combined score[d]
Breast cancer							
Alcohol	rs4880	*MnSOD*	II	NS	Weak: 3	CCC	No evidence
	rs17468277/ rs1045485[e]	*CASP8*	II	NS	Weak: 3	CBC/CCC	No evidence
	rs2853826 (A10398G)	*ND3*	II	NS	Weak: 3	C-C	No evidence
	rs698	*ADH1C*	II	NS	Weak: 3	--C	Not possible to evaluate
Carotenoids	rs2333227 (G463A)	*MPO*	III	NS	Weak: 3	BBC	No evidence
Colorectal cancer							
Alcohol	rs1805087 (A2756G)	*MTR*	I	NS	Weak: 3	-BB	Weak
	rs1042522 (Pro72Arg)	*p53*	I	NS	Weak: 3	--C	No evidence
Vegetables	rs16892766	8q23.3	III	Strong/AAA	Moderate: 2	CBB	Weak
Cruciferous vegetables	Present/null	*GSTM1* and *GSTT1*	NA; III for vegetables	NS[f]	Weak: 3	-CB	No evidence
	Present/ null	*GSTM1*	–	NS[f]	Weak: 3	-CB	No evidence
	Present/null	*GSTT1*	–	NS[f]	Weak: 3	-CB	Weak
Processed meat	rs4143094	10p14	III	NS	Weak: 3	BBB	Moderate

Abbreviation: NA, not applicable.

[a]NS indicates nonsignificant ($P < 10^{-5}$) evidence for the main genetic effects.

[b]This score is based on scores for nutrient evidence and genetic evidence.

[c]The strength of the observed evidence for the interaction between the dietary exposure and the genetic variants was based on an extension of the Human Genome Epidemiology Network's Venice criteria used for assessing cumulative evidence for genetic associations. The grade for each gene–diet association was based on the amount of evidence, the extent of replication, and protection against bias. Dashes indicate that one, two, or three elements of the Venice criteria cannot be decided. A complete score should have three letters, corresponding to amount of evidence, degree of replication, and protection from bias components of the Venice criteria. If one element is missing, the score is represented by a single dash and two letters. If two elements are missing, the score is represented by two dashes and a letter.

[d]The overall plausibility of an interaction was examined by comparing the prior score and the score for the strength of the observed evidence.

[e]Genetic variants rs17468277 and rs1045485 are in linkage disequilibrium and have $r^2 = 1$ and $D' = 1$ in HapMap European populations. Both variants are often used interchangeably in genetic association studies and meta-analyses. For rs17468277, evidence of interaction with alcohol was classified as weak in the combined score; however, a subsequent and bigger meta-analysis (13) did not observe any interaction with the correlated rs1045485 variant. Therefore, the combined score for *CASP8* and alcohol interaction was set to no evidence.

[f]The effect of *GSTM1* and *GSTT1* deletion polymorphisms reached nominal significance ($P < 0.05$), but did not reach $P < 10^{-5}$, which was used as the cutoff for significant association in this review.

for the possible gene–alcohol interactions (**Table 2**); a combined score could not be properly evaluated owing to the lack of formal testing for interaction.

Genome-wide scans of interactions between genetic variants and alcohol intake are gradually being explored in a few meta-analyses and large cohort consortia (13, 21, 86) (**Supplemental Table 7**). An analysis of the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium (BPC3) data (21), which include data from six large prospective studies, did not identify any statistically significant interactions between alcohol and SNPs that were previously identified in breast cancer GWAS (data not shown). A pooled analysis of 24 studies of the Breast Cancer Association Consortium (BCAC) (86) provided weak evidence that the breast cancer risk associated with a *CASP8* variant (rs17468277) is altered by high alcohol consumption (P for interaction $= 3.1 \times 10^{-4}$; **Supplemental Table 7**). However, a subsequent meta-analysis that included both the BCAC and BPC3 data (13) (>79,000 women) did not replicate this finding. Finally, current evidence suggests the absence of statistically significant interaction between alcohol and rs4880 (*MnSOD*) (75) or A10398G (*ND3*) (17).

Supplemental Material

Interactions between genes and other foods and nutrients. No meta-analyses identified interactions between genes and vegetables or α-carotene in relation to breast cancer risk. One meta-analysis found no evidence of an interaction between genes and total carotenoids (87).

Lung Cancer

Here, we present the evidence for all identified gene–diet interactions in relation to lung cancer risk.

Interactions between genes and other foods and nutrients. No meta-analyses identified interactions between genes and β-cryptoxanthin, carotenoids, fruits, or citrus fruits in relation to lung cancer risk.

Prostate Cancer

Here, we present the evidence for all identified gene–diet interactions in relation to prostate cancer risk.

Gene–calcium interactions. No meta-analyses identified interactions between genes and calcium in relation to prostate cancer risk.

Gene–selenium interactions. No meta-analyses identified interactions between genes and selenium in relation to prostate cancer risk. A Cochrane systematic literature review of the role selenium has on cancer risk and survival has also explored the interaction between selenium intake and genetic variants in genes coding for selenoproteins (105). It reported that the null results of the most recent low-bias RCTs on prostate cancer risk (4, 74, 80) did not suggest in the least that the most frequent genotypes might strongly influence the selenium and cancer relation. However, an earlier review (25) reported gene–diet interactions for selenium in relation to prostate cancer risk and progression. In particular, it had suggested that the manganese-superoxide dismutase (MnSOD), which is a mitochondrial antioxidant enzyme, Ala/Ala genotype may confer protection when antioxidant (including selenium) levels are adequate but may be deleterious when antioxidant levels are low. Furthermore, a series of nested case-control studies of interaction effects of certain genetic variants and selenium administration or selenium serum/plasma levels resulted in

inconsistent findings. The genes in which genetic variants were examined include *NKX3.1* (codes for androgen-regulated prostate tumor suppressor protein), selenoprotein P genes (*SEP15*, *SEPP1*, *GPX1*, and *GPX4*), *OGG1*, *MnSOD*, *SELK*, *TXNRD2*, and *TXNRD1*.

Colorectal Cancer

Here, we present the evidence for all identified gene–diet interactions in relation to colorectal cancer risk.

Gene–diet interactions identified through GWAS consortia. The possible interactions between genetic variants identified through GWAS on colorectal cancer and intakes of alcohol, dietary calcium, dietary fiber, dietary folate, red meat, processed meat, fruit, and vegetables were explored in two meta-analyses from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and the Colon Cancer Family Registry (CCFR) (56, 67). In particular, potential effect-modification between the first 10 SNPs identified through GWAS and probable or established environmental risk factors were examined in the first meta-analysis of 7,016 colorectal cancer cases and 9,723 controls from nine cohort and case-control studies (56). Following this, interaction analysis was performed for the next 16 SNPs identified through GWAS in a meta-analysis of 9,160 colorectal cancer cases and 9,280 controls (67). Results from both meta-analyses suggested no evidence for strong gene–diet interactions involving the recently identified 26 susceptibility loci for colorectal cancer when examined one at a time, because almost all of the *P* values adjusted for multiple testing did not reach statistical significance (all interaction results are presented in supplementary table S4 in Reference 56 and in supplementary table S2 in Reference 67). The strongest statistical evidence for a gene–environment interaction was for vegetable consumption and rs16892766, located on chromosome 8q23.3, near the *EIF3H* and *UTP23* genes (adjusted *P* for interaction = 0.02; **Supplemental Table 7**). On the basis of the strong main genetic and weak (class III) environmental effects of vegetable intake on cancer risk, the possible 8q23.3 locus–diet interaction in relation to colorectal cancer risk was given a moderate prior score (Moderate – 2) and a weak overall plausibility score (**Table 2**).

Supplemental Material

Furthermore, within the GECCO/CCFR consortium a genome-wide gene–diet interaction analysis for risk of colorectal cancer was performed to investigate multiplicative interactions between 2.7 million genetic variants and meat, fruits, vegetables, fiber, and calcium (37, 42). No statistically significant interaction between the examined SNPs and intakes of fruits, vegetables, fiber, and calcium (total, dietary, or supplemental) was observed. A significant interaction between rs4143094 (10p14/near *GATA3*) and processed meat consumption (OR = 1.17; *P* = 8.7E-09) was detected, which was consistently observed across studies ($P_{\text{heterogeneity}} = 0.78$; **Supplemental Table 7**) (42). On the basis of the amount of evidence and despite no main genetic effects (**Supplemental Table 8**), the interaction between *GATA3* and processed meat was given a moderate plausibility score (**Table 2**).

An additional study investigated whether and how the three major environmental colorectal cancer risk factors—overweight, smoking, and alcohol consumption—modify the association between colorectal cancer and genetic variants that are either included in whole-genome SNP arrays or imputed from publicly available sequence data. This study adopted a two-tiered approach comprising case-only screening (stage I) (314 cases) and case-control validation (stage II) (259 cases, 1,002 controls). Interactions with the smallest *P* value in stage I were verified in stage II by multiple logistic regression analysis adjusted for sex and age. No gene–alcohol interaction passed the multiple-test correction threshold (93).

Finally, in a systematic search for gene–environment interactions using genome-wide data from the CCFR that included 1,191 cases of microsatellite stable or microsatellite instability-low colorectal cancer and 999 controls genotyped using either the Illumina Human1M or the Human1M-Duo BeadChip explored interactions between genotypes and 14 environmental factors (including intake of alcohol, folate, fiber, fruit, vegetables, and red meat). No gene–diet interactions of genome-wide significance were identified (43).

Gene–alcohol interactions. One meta-analysis of 27 studies, including 13,465 colorectal cancer cases and 20,430 controls, summarized the evidence for the association between *MTR* A2756G polymorphism and colorectal cancer. Only 4 studies reported data on alcohol stratification. Using a dominant genetic model, a meta-analysis of these 4 studies showed that heavy alcohol drinkers (≥50 g ethanol/day at ≥5 day/week) with the G allele of *MTR* A2756G variant rather than the wild AA genotype had a significantly increased risk of colorectal cancer with an OR of 2.00 (95% CI, 1.28–3.09; $P = 0.002$; $P_{\text{heterogeneity}} = 0.38$) (34) (**Supplemental Table 7**). On the basis of the prior score and the amount of evidence in the current study, the overall plausibility of *MTR*–alcohol interaction was classified as weak (**Table 2**). Finally, a meta-analysis of two Asian studies found no interaction between alcohol and the *p53* Arg72Pro genetic polymorphism (78) (**Table 2**, **Supplemental Table 7**).

Supplemental Material

Gene–vegetable interactions. A recent meta-analysis of cruciferous vegetables and risk of colorectal neoplasms reported a statistically significant protective effect of cruciferous vegetable consumption against colorectal neoplasms (including cancers and adenomas, $P < 0.05$) among individuals with a single null *GSTT1* genotype, but not for the single null *GSTM1* or the double null *GSST1/GSTM1* genotypes (100) (**Supplemental Table 7**). The overall plausibility score for the interaction between the *GSTT1* deletion genotype and vegetable intake was classified as weak, with no evidence for combined interaction effects of *GSTM1* or *GSTT1/GSTM1* on colorectal cancer risk (**Table 2**).

Interactions between genes and other foods and nutrients. No meta-analyses identified interactions between genes and dairy products, nonfermented milk, milk, or whole grains in relation to colorectal cancer risk.

Stomach Cancer

Here, we present the evidence for all identified gene–diet interactions in relation to stomach cancer risk.

Gene–salt interactions. No meta-analyses identified interactions between genes and salt in relation to stomach cancer risk.

DISCUSSION

Finding gene–diet interactions may help us understand, prevent, and better manage cancer. It could also lead to more specific risk assessments, which could be useful for early-detection or prevention strategies and to further our understanding of biological pathways and mechanisms of disease etiology (98). In this review, we first summarized the evidence for the main effects of foods and nutrients for the five most common cancers (breast, prostate, lung, colorectal, and

stomach) and then evaluated the literature on gene–diet interactions. Only meta-analyses and pooled analyses were used to comprehensively evaluate the amount of evidence. We observed very little evidence for nutrient associations and hardly any evidence for gene–diet interactions. We cannot, however, exclude the possibility of having missed interactions with small effect sizes.

Main Findings

Despite the amount of identified studies, only a limited number of diet and nutrient associations were classified as convincing (class I; alcohol and colorectal cancer risk, whole grains and colorectal cancer risk) or highly suggestive (class II; heavy alcohol intake and breast cancer risk, fruit intake and lung cancer risk, calcium and colorectal cancer risk). Furthermore, meta-analyses of RCTs have not validated some of these associations, e.g., calcium and colorectal cancer. Even convincing class I epidemiological evidence does not solidly prove causation.

These food items and nutrients may act as potential cancer risk modifiers at tumor initiation, promotion, progression, or conversion. The mechanism of alcohol carcinogenesis is probably closely attributed to metabolism of ethanol and its most toxic metabolite acetaldehyde, which is able to bind to DNA and cause DNA damage. Additionally, at the tumor initiation stage ethanol may act through various procarcinogens present in food, smoke, and the environment activated by ethanol-induced cytochrome P450 2E1 (*CYP2E1*). At the cancer promotion stage alcohol may affect DNA methylation, which can change the expression of oncogenes and tumor suppressor genes. Furthermore, alcohol metabolism leads to the generation of toxic metabolites that may cause changes in cell cycle behavior. Ethanol also increases estrogen levels, which may be important in breast cancer development. Finally, at the progression stage alcohol may facilitate tumor cell spread by suppressing the immune system (92).

Another food item that has a class I epidemiological association with colorectal cancer risk reduction is whole grains. It is believed that the protective mechanism of whole grains is explained mainly by dietary fiber, resistant starch, and oligosaccharides. However, the evidence for the protective effects of total fiber was classified only as suggestive in our review and therefore could not completely explain the protective effects of whole grains. Whole grains are also rich in antioxidants that could prevent DNA from oxidative damage and mutation during tumor initiation, but this is also largely speculative. Another speculated mechanism is through insulin and glucose responses. Although lower glycemic load and lower glycemic index have been linked to diabetes and obesity, our review classified the evidence for colorectal cancer and glycemic index as weak. Finally, whole grains contain many other compounds such as phytate, phytoestrogens, vitamins, and minerals that have been proposed as candidates for protecting against cancer (94).

We explored the literature on gene–diet interactions for all food and nutrient associations that were classified as convincing (class I), highly suggestive (class II), or suggestive (class III) and classified them as strong, moderate, weak, or no evidence. We examined the overall plausibility of interaction by combining a prior possibility score (18) with a score based on the observed strength of the evidence (evaluated by applying a modified version of the Venice criteria). Of all the evaluated gene–diet interactions with prior weak, moderate, or high scores, only the interaction between the 10p14 locus and processed meat in relation to colorectal cancer risk (42) was categorized as moderate (grade BBB). Interactions between alcohol and rs17468277 (*CASP8*) in relation to breast cancer risk, and interactions between alcohol and rs1805087 (*MTR*) (34), vegetables and rs16892766 (8q23.3) (56), and cruciferous vegetables and *GSTT1* deletion polymorphism (100) in relation to colorectal cancer risk were classified as weak according to the Venice criteria. The remaining studied associations did not show any evidence of interaction. On the basis of prior and observed scores, the combined plausibility score was moderate for the interaction between

processed meat and rs4143094 (10p14/*GATA3*) in relation to colorectal cancer risk and weak for the interactions between *GSTT1* and cruciferous vegetable intake, *MTR* and alcohol consumption, and rs16892766 (8q23.3) and overall vegetable intake, all in relation to colorectal cancer.

We expected some of the detected interactions to have weak and moderate combined scores because of our prior knowledge of gene function and suggested mechanisms of action of nutrients and food. Glutathione *S*-transferase theta-1 (GSTT1) protein conjugates binding of glutathione to various hydrophobic and electrophilic compounds and thus is involved in the metabolism of isothiocyanate (IST). IST is a biologically active compound of glucosinolate metabolism (51). Glucosinolates are abundant in cruciferous vegetables, especially broccoli, and this abundance is speculated to explain some of the chemoprotective properties of cruciferous vegetables (50).

The interaction between the polymorphism in the methionine synthase (*MTR*) gene and alcohol consumption is biologically plausible, although observational evidence is weak. *MTR* plays a central role in maintaining adequate intracellular folate, methionine, and normal homocysteine concentrations, whereas alcohol consumption affects folate absorption and folate serum concentrations and can directly interfere with methionine synthase activity (47). However, the evidence for the association between folate and colorectal cancer risk was weak and there was no evidence for the folate–*MTR* interaction. The precise mechanism of interaction between the rs4143094 variant in the 10p14/*GATA3* region and high consumption of red meat is even less clear. GATA binding protein 3 (*GATA3*) has been associated with T cell development and Th2 cell differentiation (52). It was speculated that processed meat and red meat could trigger an inflammatory or immunological response that requires normal GATA function and that the lack of which could lead to cancer initiation and development (42). Similarly, little is known about the functional impact of rs16892766 at 8q23.3. It is located close to the eukaryotic translation initiation factor 3 subunit H (*EIF3H*) gene; however, it seems to affect the expression of *UTP23* (small subunit processome component). It is unclear what the biological mechanism of action for this interaction would be, and together with only a weak combined plausibility score the observed interaction is highly questionable.

Most gene–diet interactions included in our study were investigated using candidate-gene studies. In this type of research, the first step is to establish an association with a dietary factor and the next step is to explore interactions with variants of a gene or genes that are involved in pathways that metabolize the specific dietary factor. Only a few studies based on agnostic searches with no prior hypotheses in large GWAS consortia investigated interactions between a very large number of common polymorphisms (>1 M SNPs) with selected dietary factors and risk of cancer, and this approach may need to be applied to more data sets and consortia that collect information on the genome and dietary factors.

Challenges for Gene–Diet Interaction Studies

All analytical methods are associated with measurement error, and nondifferential misclassification attenuates estimates of disease risk and reduces statistical power, so that a correlation between the measured factor and disease might be obscured. In dietary studies, this is traditionally corrected with factors that are derived after comparing results from one method (for example, a food frequency questionnaire) with those from another method that is assumed to be more accurate (for example, food records). However, errors between both methods used for measuring diet can be correlated, so that results from the reference method are not independent of those derived from the test method. Therefore, the extent of measurement error might still be underestimated (112).

Dietary biomarkers have been developed so that more accurate factors for correction can be obtained. This validation method ensures that questionnaire or records errors are not correlated

with biomarker errors; therefore, spurious validation results can be avoided. However, it is still technically challenging to implement owing to the costs, as well as measurements errors and normal variations in individuals' levels between measurements. In particular, biomarker levels of a particular nutrient depend only on dietary intakes but also on other lifestyle choices, physiological characteristics, and genetic variants. Biomarker measurements are also subject to laboratory and technical errors and to variations in daily dietary intake. In addition, appropriate biomarkers are available for only a few specific nutrients. Therefore, the intake of several nutrients cannot be validated by this method (112). Finally, few studies have linked diet, biological risk markers (such as plasma hormone levels), and cancer risk.

In most dietary association studies, the food and nutrient estimations derive from self-reporting questionnaires. With self-reporting questionnaires, the study participants may intentionally or unintentionally over- or underreport a particular food item. In addition, participants are asked to complete the food questionnaires for a particular reference period (in case-control studies, most commonly a year prior to their diagnosis). However, their dietary habits for even up to 10 years prior to their diagnosis might have affected the initiation and progression of the disease. In case-control studies there is also often a difference in participation rates between cases and controls, which might be due to the fact that cases are more eager than population controls to take part in a study that investigates their disease. Therefore, controls that agree to participate might have had a healthier diet and lifestyle and thus are more eager to participate in a case-control study asking about their lifestyle choices and dietary habits (also known as participation bias). Some of these problems are addressed more appropriately in prospective cohort studies, but even then, nutritional measurement can be inaccurate. Additionally, the exposure to environmental risk and protection factors through diet is not the same as individual effect dose, which may be different for some individuals even with the same dietary consumption of nutrients because of such subjective factors as cooking methods, dietary habits (e.g., frequency of meals, portion sizes, eating out), and individual metabolic background.

One important challenge in gene–diet interaction studies is that sample size requirements can be very big. The key determinants of power/sample size requirements in gene–diet interaction studies are study design, the prevalence of the dietary exposure, the allele frequency of the genetic variant, the mode of inheritance (dominant, recessive, or additive), the interaction OR, the ORs for the main effects, and the significance level. As a rule of thumb, the detection of a gene–diet interaction requires thousands of cases in candidate-gene studies, and tens of thousands in genome-wide scans (98). It is therefore likely that the lack of positive findings or the poor track record of replicating claims of gene–diet interactions is partly due to underpowered studies (62, 81). The number of cases or events in the meta-analyses of gene–diet interactions classified as moderate or weak in relation to colorectal cancer risk was 9,287 for *GATA3* and processed meat intake (moderate), 3,556 for *GSTT1* and cruciferous vegetable intake, 1,398 for *MTR* and alcohol consumption, and 7,016 for rs16892766 (8q23.3) and overall vegetable intake. In contrast, the mean number of events for interactions for which there was no evidence was 2,691. It is possible that with larger sample sizes some of these interactions may acquire stronger support. Still, they would most likely reflect small effect sizes; thus, their practical importance is still unlikely.

A statistically significant interaction between rs4143094 (10p14/near *GATA3*) and processed meat consumption was detected and consistently observed across studies (42). On the basis of the amount of evidence and despite no main genetic effects, the *GATA3*–processed meat interaction was given a moderate plausibility score. Despite claims that the interaction in the absence of main effects is spurious, there are counterarguments (83). Furthermore, simulation studies have shown that a range of interaction effect sizes can be detected in a GWAS even when the marginal effects are not detectable (98).

Heterogeneity between the combined studies of meta-analyses is an important challenge to consider. When comparing studies that use different diet assessment tools, have different distributions of the dietary exposure, or adjust for different confounders (or do not include any confounders in the analysis), the potential for true heterogeneity is magnified. Finally, additional factors specific to each cancer may further increase the heterogeneity. One example is the metabolome, the role of gut microflora, and its interaction with diet in colorectal cancer. There is evidence (albeit preliminary) that the diversity and the content of the metabolome are influenced by diet as well as other external factors such as antibiotics (132). It is biologically possible that interaction between the metabolome and diet may influence the risk of cancer development.

Limitations of the Current Review

Although we performed a systematic and thorough search of the published literature, our approach would miss associations that have not yet been assessed through meta-analysis. The caveats in the umbrella review methodology include interpretation of tests for statistical bias and the potential of effect inflation even in the largest studies. As in all literature reviews, the quality is directly related to the quality of the included studies. Furthermore, because this is a review of meta-analyses, we also depend on the assessment of study quality of the original meta-analyses. Although we have formed our criteria for scoring the evidence with a focus on biases and other issues that may have led to false-positive associations, false-negatives are also possible, especially for associations for which limited evidence is available or sample size is limited. Finally, the current review does not cover interactions among epigenetic factors, diet, and cancer risk, because we did not find any meta-analyses on epigenome effects in relation to diet and the five cancers examined in this review.

CONCLUSIONS

Acknowledging the limitations of our overview, our assessment maps the status of the evidence for gene–diet interactions for the five most common cancers. Despite the large number of published studies, only a limited number of diet–cancer associations were classified as convincing (class I: alcohol and colorectal cancer risk, whole grains and colorectal cancer risk) or highly suggestive (class II; heavy alcohol intake and breast cancer risk, fruit intake and lung cancer risk, calcium and colorectal cancer risk). Similarly, there was no evidence for a strong gene–diet interaction in relation to any of the examined studies, and a moderate combined (prior and observed) plausibility score was observed for processed meat intake and rs4143094 (10p14) in relation to colorectal cancer risk. The overall evidence to date suggests that single nutrient–gene effects on cancer are less spectacular than originally postulated, extremely difficult to decipher, or both. Single studies may provide nominally statistically significant results for a large number of associations (91), but most seem to be spurious when large-scale systematic evidence is assessed. Continuing the pursuit of study designs that have not yielded reproducible inferences to date may not be the best possible investment in this field.

To overcome the limitations of observational epidemiology in relation to dietary studies, promising statistical (for example, instrumental variable methods) and machine-learning (variational Bayesian methods) methods have been proposed but they also need very large sample sizes and their performance needs to be validated. One may still consider conducting single-nutrient-based RCTs for those nutrients for which the observational evidence is promising and that may have potentially large public health importance should the associations prove to be causal. However, most evidence from single-nutrient dietary interventional trials to date has not indicated cancer prevention benefits. Large-scale, transparent, preregistered, long-term, follow-up

trials with clinical outcomes may still need to be performed for nutritional interventions, but they should probably focus on more complex diets than on single nutrients (58). Performing fewer such studies may be preferable to continuing the conduct of hundreds of thousands of observational nutrition analyses that seem to have very little yield of reproducible, let alone useful, results (57). Finally, instrumental variable methods such as Mendelian randomization studies may also be of some value (95), in particular for exploring associations with a postulated increased risk of cancer in which both genes and dietary factors may be implicated. However, at the moment the feasibility of performing such studies is limited owing to lack of knowledge about the genetic architecture of many biomarkers that are affected by dietary factors.

DISCLOSURE STATEMENT

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