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Nature, Nurture and cancer risks: Genetic and nutritional contributions to cancer

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Abstract

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

Keywords

Diet; genes; cancer; interaction; nutrigenetics; colorectal cancer; breast cancer; prostate cancer; lung cancer; stomach cancer

Introduction

Diet and cancer

Diet can be defined as the sum of food consumed by a person. Dietary habits are the habitual decisions an individual makes when choosing what foods to eat. Although humans are omnivores, each person may hold food preferences or even taboos due to personal tastes, local custom or ethical reasons. Individual dietary choices may or may not play a significant role in the quality of life, health and longevity. Nutritional epidemiology, the study of the

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relationship between nutrition and health is a challenging and quickly expanding field with a number of limitations resulting in inconsistencies in the published literature.

There were an estimated 14.1 million cancer cases diagnosed globally in 2012 (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 (1.7 million new cases) and colorectal cancer being the third most common cancer (1.4 million new cases). The age-standardised 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, USA, Ireland, S. 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 that have 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 in the 1940s suggested that caloric restriction reduced the occurrence of cancer in rodents. Several decades of epidemiological research has followed with numerous reports linking diet and cancer (20). For instance, a search in MEDLINE on “diet” and “cancer” resulted in 40,666 hits including 2,137 classified for Type of Article as “clinical trials” and 7,489 “reviews” (455 of which have included a “meta-analysis”; date of search 04/10/2016). It is widely believed that diet and nutrients can act as cancer risk modifiers across the entire process of carcinogenesis including initiation, promotion, progression, and/or conversion. Numerous nutrients or foods have been suggested to be linked to cancer but the majority of claimed associations have not been consistently replicated in future studies.

The World Cancer Research Fund (WCRF) has produced Expert Reports summarizing published research on cancer prevention and survivorship through diet/nutrition and physical activity. Their second Expert Report was published in 2007 (118) and WCRF has also been collating findings from new cancer prevention research published around the world for the Continuous Update Project. WCRF 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 31% of cases in the USA are preventable through healthy diet, being physically active and maintaining a healthy weight. Estimates for other countries are 32% for the UK, 25% for Brazil and 24% for China (http://www.wcrf.org/). However, these impressive estimates make the assumptions that (1) the published literature is valid and (2) 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

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single base pair and are known as single nucleotide polymorphisms (SNPs) (24). 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) (24).

Nutritional genomics is the science that studies the relationship between human genome, nutrition and health. Nutrigenomics assesses how dietary substances may cause changes, e.g. mutations on the genome or may cause changes in gene expression but without changing the DNA sequence (nutritional epigenetics). Nutrigenetics aims to understand how the genetic makeup of an individual coordinates their response to diet. In other words, nutrigenetics studies try to identify and characterize gene variants associated with differential responses to nutrients, and to relate this variation to disease states (gene-diet interactions) (87).

Aim of the review

We collected and evaluated the evidence across existing meta-analyses of observational studies in dietary risk factors and gene x diet interactions for the five most common cancers (breast, ling, prostate, colorectal and stomach cancer). First, we overviewed the range and validity of the reported dietary associations with cancer by evaluating and categorising the existing evidence using a number of set 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 of gene-diet interactions in cancer.

Methods

We reviewed the current literature and established knowledge about the association between 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 (MT, ET). When more than one meta-analysis on the same research question was eligible, the meta-analysis with the largest number of component studies was retained for the main analyses. Data extraction was performed by two investigators (MT, ET), and in discrepancies the final decision was made after discussion. Details of the literature searches, data extraction, statistical analysis and strength of evidence evaluation are presented below.

Diet and cancer

Search strategy and eligibility criteria—We included meta-analyses of the associations between dietary risk factors and cancer as presented in WCRF Second Expert Report (2007) and subsequent continuous update projects when available (CUP). An additional search in MEDLINE was conducted to identify more recent meta-analyses of prospective observational studies and randomised clinical trials (RCTs) published since the corresponding continuous update projects. The search strategy and MESH terms used for each cancer are presented in Supplementary Box 1.

Data extraction—From each eligible article, we recorded the first author, journal, year of publication, the examined dietary risk factor, the number of studies considered, the study-

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specific relative risk estimates (standardized mean difference (SMD), risk ratio (RR), odds ratio (OR), hazard ratio (HR)) along with the corresponding 95% confidence intervals (CI), the number of cases and of total participants and p value for Cochran's Q test and/or the I^2 that measures the heterogeneity of the included studies 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 (9) and I^2 with 95% CI (64). To categorise the dietary risk factors in terms of strength of evidence we applied a set of criteria (19). In particular, convincing evidence (Class I) required >1000 cases, highly significant summary associations ($p < 10^{-6}$ by random-effects), 95% prediction interval (PI) not including one, no evidence of small-study effects (p>0.10), no evidence of excess significance bias (p>0.10) and not large heterogeneity ($I^2 < 50\%$). Highly suggestive evidence (Class II) required >1000 cases, highly significant summary associations ($p < 10^{-6}$ by random-effects) and largest study with 95% CI excluding the one value. Suggestive evidence (Class III) required >1000 cases and $p < 0.001$ by random-effects. All other risk factors with nominally significant summary associations ($p < 0.05$) were coined as having weak evidence (Class IV). Non-significant (NS) associations were those with $p > 0.05$. To distinguish between class I and class II evidence as described above we calculated: a) the 95% prediction intervals 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 to larger studies according to the regression asymmetry test (42); and c) the excess significance bias, which measures whether the observed (O) number of studies with nominally significant results ($p < 0.05$) is larger than their expected (E) number (65).

Gene-diet interactions in cancer

Search strategy and eligibility criteria—We performed systematic literature review in MEDLINE 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 in foods and nutrients that were classified as class I, II or III in the evaluation of the dietary studies. The search strategy and MESH terms used for each cancer is presented in Supplementary Box 2.

Additionally we performed a search to explore the main effects of the genetic variants of the identified gene-environment interactions. We searched the NHGRI-EBI catalogue of genome-wide association studies (GWAS) (115) and the GWAS central database (18) to identify published associations between genetic variants and the risk of breast, colon, prostate, lung and stomach cancers. Both of the datasets have specific internal curating procedures and strict eligibility criteria for data extraction, which are summarised in Supplementary Box 3. Additionally to cover candidate-based studies looking for the main effect of genetic variants on cancer risk (that are not included in the NHGRI-EBI GWAS catalogue and GWAS central) we carried out a literature search in MEDLINE to identify meta-analyses and field synopses. The search strategy and MESH terms used for each cancer is presented in Supplementary Box 4.

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Data extraction—From each eligible article of gene-diet interaction, we recorded the first author, year of publication, the examined dietary and genetic risk factors, the number of studies considered, the study-specific relative risk estimates (standardized mean difference, risk ratio, odds ratio, hazard ratio) along with the corresponding 95% CI, the number of cases and total participants, the p-value of interaction and the p-value (or I^2) of the heterogeneity. For the eligible articles of the genetic association studies, we recorded the first author, year of publication, ethnicity of the study participants, numbers of cases and controls in discovery and replication sets, p value for the main effect of variants, as well as study specific estimates (odds ratios and risk ratios) and 95% CI when available.

Statistical analysis and strength of evidence evaluation—We followed a set of guidelines to assess the strength of the evidence in gene-diet association meta-analyses (22).

Firstly, we scored the strength of the evidence for main effects. The score for the dietary exposure was based on the classification of evidence in the previous chapter of this review. Genetic associations were classified using HuGENet Venice criteria (63, 110). Only genetic effects with p value $<10^{-5}$ were considered for evaluation. On the basis of a combination of three criteria (amount of evidence, degree of replication and protection from bias), each of which can be scored A, B and C, the epidemiological evidence for an effect of the genotype is classified as strong, moderate or weak.

Secondly, we established a prior score category (*expected*) for the gene-diet interactions using the framework presented in Boffetta P et al (22) (also reproduced in Supplementary Box 5). This score is based on the scores for the evidence of the main dietary and genetic effects.

Thirdly, we scored the strength of the *observed* evidence for interaction between the dietary exposure and the genetic variants based on an extension of the HuGENet Venice criteria (22, 63). Each gene-diet association was graded based on the amount of evidence, the extent of replication and protection of bias. For amount of evidence, a grade A, B and C was assigned when the sample size for the smallest comparison group in the meta-analyses was greater than 1000, 100-1000, or less than 100, respectively. When sample size for the smallest comparison group was not available, it was calculated using the rare genotype frequency and prevalence of environmental exposure when appropriate. For replication consistency, we used I^2 <25% to assign grade A, 25%-50% to assign grade B and I^2>50% or p value for heterogeneity <0.10 to assign grade C. For protection from bias three aspects of gene-environment association were taken into account as suggested by Boffetta and co-authors (22): protection from bias for environmental exposure, for the genetic analysis and 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.

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

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Overview of the role of nutrition in most common types on cancer

A summary of the published evidence of the role of nutrition in cancer risk is presented in Table 1 and Supplementary Tables 1-6. Below we present the findings of the literature review of all evidence of the role of nutrition in breast, lung, prostate, colorectal and stomach cancer based on the WCFR/AICR second expert report (118), the Continuous Update Project (CUP) reports (1–4) and a summary of all identified meta-analyses of prospective cohorts and/or randomised clinical trials published since the last CUP. We have classified the evidence in 4 groups (Class I-IV) based on the criteria presented in the methods.

Breast cancer

No association was classified as convincing (class I). The association between alcohol intake and ER+ breast cancer was classified as highly suggestive (Class II) based on a meta-analysis of 20 prospective studies (≥30g/d of alcohol consumption versus non-drinkers RR (95% CI): 1.35 (1.23, 1.48, p-value=$5.2x10^{-10}$, I^2=26%, $P_{small\ effect\ bias}$ = 0.184, $P_{excess\ significance\ bias}$ = $4x10^{-8}$)(70). There was some evidence of heterogeneity of effects by ER status with the association between alcohol and ER- status breast cancers being classified as weak (Class IV) (RR 1.28; 95% CI 1.10, 1.49, I^2=0%) (70) (Table 1, Supplementary table 1). A recent bigger meta-analysis of 37 prospective studies also suggested strong effect of moderate alcohol intake on the risk of overall breast cancer (moderate alcohol consumption of 12.5-50 g/per day versus non-drinkers RR (95% CI): 1.22 (1.17, 1.27), p-value = $<10^{-6}$, I^2=33%), but it was not possible to test for small study effect or excess significance in that meta-analysis (16). Associations with dietary intakes of α-carotene (57) and of vegetables in ER- breast cancer (69) were classified as suggestive (class III, Table 1). In particular dietary Intake of α-carotene was associated with a 9% reduction of risk of total breast cancer (RR for highest vs lowest category 0.91, 95% CI 0.87, 0.96, p-value=0.0002, I^2=1%) and dietary intake of vegetables with a 18% reduction (RR for highest vs lowest quintiles of total vegetables consumption 0.82, 95% CI 0.74, 0.90, p-value $8.1x10^{-5}$, I^2<50%).

Based on the available evidence the associations between breast cancer risk and eggs, dairy products, polyunsaturated fat, processed meat, alcohol intake and 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 (serum/plasma), n-3/n-6 PUFAs ratio in serum (plasma), dietary fibre and lycopene concentration in serum/plasma were classified as weak (class IV; Supplementary Table 1). Among other nutrients that were investigated in prospective cohorts 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 (106, 122), animal fat (7), dietary acrilamid (91), dietary (32, 81) and circulated folate level (32) and folic acid supplementation (92, 111), calcium (31), vitamins C and E (49), vitamin D (75), vitamin B6 (121), vitamin B12 (121), methionine (121), multivitamins (27), β-Cryptoxanthin (43), lutein/zeaxanthine (57), iron (48), cadmium (35), linolenic acid (131), saturated fatty acids (122), mono-unsaturated fat (106), poly-unsaturated fatty acids (106) and glycemic load

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(39). Among other food items that were investigated in prospective cohorts studies, but did not show evidence of association with breast cancer risk in categorical and dose-response meta-analyses were milk (40), fish (131), red meat (6), coffee (68) and green tea (119).

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 recent 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-value = 10^{-6}, I^2=32%; Class II – highly suggestive) as well as a significant inverse association in dose-response meta-analyses (107) (Table 1, Supplementary Table 2). This meta-analysis though showed evidence of small-study effects (p for Egger's test <0.01) and the effects seemed to be restricted to current smokers only, thus suggesting possible residual confounding (107). Similar effects were noted in an analysis restricted to **citrus fruits** (RR for highest vs lowest intake 0.85, 95% CI 0.78, 0.93, p-value=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 (107). Finally the associations with β-cryptoxanthin (RR for highest vs lowest 0.80, 95% CI 0.72, 0.89, p-value = $4.4x10^{-5}$, I^2=0%) and carotenoids (RR for highest vs lowest 0.79, 95% CI 0.71, 0.87, p-value = $7.1x10^{-6}$, I^2=0%) were classified as suggestive (class III) (50). Interestingly in a meta-analysis of four randomised clinical trials, association between beta-carotene supplementation and lung cancer risk was classified as suggestive for increased, rather than decreased risk (class III, RR 1.21, 95%CI 1.09, 1.32, p=0.0001, I^2=32.5%), with effects being stronger among current smokers (RR 1.24, 95%CI 1.10, 1.39, p=0.0002, I^2=42.1%) (Supplementary Table 6) (100). Finally the WCFR/AICR second expert report (118) classified the association between beta-carotene supplementation and cancer risk in smokers as convincing, though only 1 RCT was included (118).

Based on the available 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; Supplementary Table 2). Among other nutrients that were evaluated in recent meta-analyses of prospective studies, but had p>0.05 were dietary lutein intake (50), vitamin C (33), vitamin E (33) and folate (33). Among other food items that were investigated in prospective cohorts 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 (16) and black and green tea drinking (112).

Prostate cancer

No association was classified as convincing (class I) or highly suggestive (class II). Calcium supplementation was associated with almost 50% risk reduction in a meta-analysis of four RCTs (RR 0.54, 95% CI 0.30, 0.96; p=0.04, I^2=0%) (23) (Table 1, Supplementary Table 3). However the evidence is not consistent and a recent meta-analysis of dietary calcium intake showed increase in risk for those who were in the highest category of dietary intake compare

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to the lowest category (RR 1.18, 95% CI 1.08, 1.30, p-value = 0.0005, I^2=53.4%; class III) (14), though the association was limited to dairy calcium only (RR for highest vs lowest 1.13, 95% CI 1.02, 1.24, I^2 = 46%) and not observed for non-dairy calcium (RR for highest vs lowest category of dietary intake 0.91, 95% CI 0.79, 1.05)(14). Another association classified as suggestive (class III) was with selenium intake investigated in a big Cochrane meta-analysis of observational studies and RCTs. While association with prostate cancer reduction was noted in a meta-analysis of observational studies (RR for highest vs lowest category of intake 0.79, 95% CI 0.69, 0.90, p-value = 0.0005, I^2=23%), no effect was observed when meta-analysis was limited to RCTs (109).

Based on the available evidence the associations between prostate cancer risk and alpha - 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; Supplementary Table 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, pentadecanoic, heptadecanoic acid, palmitic acid, palmitoleic acid, docosahexaenoic acid, dihomo-γ- linoleic acid, arachidonic acid and oleic acid (37). No statistically significant association with total prostate cancer risk was detected for allium vegetables (133), fruits (85), tomato/lycopene (30), carrots (124), eggs (73) and yogurt (14) 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) based on a meta-analysis of 4 prospective studies (high vs. low intake RR (95% CI): 0.79 (0.72, 0.86), p-value=$3.1x10^{-7}$, I^2 = 0%, $P_{small\ effect\ bias}$ = 0.947, $P_{excess\ significance\ bias}$ = 0.11) (10). Heavy alcohol intake (≥50g/day) was also classified as convincing (Class I) based on a meta-analysis of 7 prospective studies (RR (95% CI): 1.57 (1.38, 1.80), p-value=$4.2x10^{-11}$, I^2=0%, $P_{small\ effect\ bias}$ = 0.802, $P_{excess\ significance\ bias}$ = 0.254) (Fedirko et al., 2011). Moderate alcohol intake (12.5-50 g per day) compared to non-drinking or occasional drinking was also associated with increased risk (RR (95% CI): 1.23 (1.14, 1.28), p-value < $1x10^{-6}$, I^2=54%, $P_{small\ effect\ bias}$ < 0.001, $P_{excess\ significance\ bias}$ = 0.047) (45) though the evidence was classified as highly suggestive (class II) due to the of 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-value=$4.8x10^{-9}$, I^2=47%, n=15 studies) (72) and was classified as class II (highly suggestive). This is consistent with findings of previous meta-analyses (34, 59). Calcium supplements were also associated with reduced colorectal cancer risk in a meta-analysis of 8 cohort studies (RR 0.86, 95% CI 0.79, 0.95 for use vs. no use; class IV) (53), but not in meta-analyses of RCTs(23, 26) including a meta-analysis of 8 RCTs (n=9,540, supplementation of > 500 mg/d of elemental Ca or calcium supplementation plus vitamin D vs. placebo, HR (95% CI) 1.38 (0.89, 2.15), I^2=0%) (23). Despite the lack of statistically significant association in this meta-analysis of RCTs, no conclusion can be drawn since it only included 83 events.

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Associations between colorectal cancer and fibre (RR 0.88, 95% CI 0.82, 0.94, p-value=0.0003, I^2=0%, n=19 studies) (10), vegetables (RR 0.91, 95% CI 0.86, 0.96, p-value = 0.0008, I^2=0%, n=16 studies) (12), dairy products (RR 0.81, 95% CI 0.74, 0.90, p-value = $2.9x10^{-5}$, I^2=0%, n=12 studies) (13), non-fermented milk (RR 0.85, 95% CI 0.77, 0.93, p-value = 0.0008, I^2=0%, n=14 studies) (93), milk (RR 0.91, 95% CI 0.85, 0.94, p-value = 0.0003, I^2=0%, n=9 studies) (13), processed meat (RR 1.18, 95% CI 1.10, 1.28, p-value = $2.3x10^{-5}$, I^2=12%, n=9 studies) (28) and circulating levels of vitamin D (25(OH)D) (OR 0.66, 95% CI 0.54, 0.81, p-value = $6.8x10^{-5}$, I^2= not available, n=8 studies) (76) were classified as suggestive (class III) (Table 1, Supplementary Table 4).

Based on the available evidence the associations between colorectal cancer risk and multi-vitamin supplements, vitamin A supplements, vitamin C, vitamin E, calcium supplements, folic acid supplements, folate, haem iron, zink, magnesium, glycemic index, tea, fruit and vegetables combined, fruits, fish, red meat, beef, lamb, poultry and circulating levels of total n-3 PUFAs were classified as weak (class IV; Supplementary Table 4). Among other nutrients evaluated through meta-analyses of prospective observational studies and RCTs but did not show statistically significant associations with colorectal cancer risk were acrylamide (91), methionine (135), total flavonoids (117), carbohydrate (11), total fat (80), animal fat (5), vitamin E supplements (53), glycemic load (36). Among other food items that were evaluated through recent meta-analyses but did not show statistically significant associations with colorectal cancer risk were coffee (67, 129), green tea (114), sugar-sweetened carbonated soft drinks (129), allium vegetables (136), onions (105), garlic (58), soy intake (125), cruciferous vegetables (103), fermented milk (93), cheese (13) and eggs (104).

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-value = $4.7x10^{-5}$, I^2= 26%, n=8 studies) (44) and the association was classified as suggestive (class III). However, the recent CUP report published in 2016 (CUP Report: Diet, Nutrition, Physical Activity and Stomach Cancer, 2016) classified evidence for total and added salt as “limited – no conclusion”, mainly due to difficulties of accurate measurement of salt consumption (Table 1, Supplementary Table 5).

Based on the available evidence the associations between stomach cancer risk and 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 and sausage intakes were classified as weak (class IV; Supplementary Table 5). Among other nutrients 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 (77), α- and γ-tocopherol (77), dietary fiber (130), isoflavones (117), nitrate, nitrite and nitrosodimethylamine (44), saturated fat, monounsaturated and polyunsaturated fat (52). Among other food items that were recently evaluated through meta-analyses but did not show statistically significant associations with stomach cancer risk were coffee (44, 123), black and green tea (44, 88), juice (44), citrus fruits (15), apples and pears (44); vegetables, including raw and cooked and green-yellow vegetables separately (44, 113), cruciferous

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vegetables and cabbage (44, 120), tomatoes and tomato products (44, 126), carrots, lettuce, spinach, seaweed, mushrooms, legumes and beans, potatoes (44), allium vegetables (44, 134), fermented and non-fermented soy products (74) and Tofu (44), total grains/cereals, bread and rice (44), dairy products, milk, butter, margarine and cheese (44, 99, 102), eggs (44), miso soup (44), fish (44, 128), red meat (44, 137), beef, pork, poultry and liver (44).

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 that were classified as class I, II or III. The search strategies, number of hits and retained studies are presented in Supplementary Box 2. The summary of evidence for all identified gene-environment interactions is presented in Supplementary Table 7. We further extracted all genetic variants identified through studies on gene-environment interactions and searched the literature to identify meta-analyses, GWAS or large pooled analysis that evaluated effects of genetic variants on cancer risk. The search strategy and number of hits are presented in Supplementary Box 4. The evidence for all identified gene-environment interactions was categorized by (i) taking into account prior scores based on genetic and environmental main effects and (ii) 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, Supplementary Tables 7 and 8.

Breast cancer

Gene – Alcohol interactions—A large number of nested case-control studies and prospective studies have explored the interaction relationships between alcohol consumption and genes involved in the alcohol metabolism pathway (including *ADH* and *ALDH*) with inconsistent findings. A meta-analysis on 1,969 breast cancer patients and 2,244 controls from 4 related case-control studies estimated the association between *ADH1C* (rs698) and breast cancer risk. They also performed a stratified analyses according to participants' alcohol consumption based on 3 articles (6 populations, 3 non-drinker populations, and 3 drinker populations). Compared with the reference (ADH1C $^{2\text{-}2}$), genotypes of ADH1C $^{1\text{-}1}$ + ADH1C $^{1\text{-}2}$ were associated with an increased risk of breast cancer in drinkers (OR (95% CI): 1.35 (1.03, 1.76)), whereas no such relationship was found between ADH1C $^{1\text{-}1}$ + ADH1C $^{1\text{-}2}$ and the risk of breast cancer in non-drinkers (OR (95% CI): 1.16 (0.86, 1.57)) (Supplementary Table 7). Despite of significant effects in drinkers only, no formal test for interaction was performed and Cochran's Q test did not show any heterogeneity between subgroup of drinkers and non-drinkers ($p_{\text{heterogeneity}}$ =0.46). Main effect of rs698 variant on breast cancer risk was not significant in a meta-analysis of 5 studies totalling 13,511 breast cancer cases (Supplementary Table 8), thus giving only weak (3) prior score for the possible gene-alcohol interactions (Table 2), while a combined score could not be properly evaluated due to the lack of formal testing for interaction.

Genome Wide Scans of interactions between genetic variants and alcohol intake is gradually being explored in a few meta-analyses and large cohort consortia (17, 25, 89)

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(Supplementary Table 7). Analysis of the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium (BPC3) data (25), which includes data from 6 large prospective studies did not identify any statistical 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) (89) provided some weak evidence that the breast cancer risk associated with a *CASP8* variant (rs17468277) is altered by high alcohol consumption (P for interaction = 3.1×10^{-4}; Supplementary Table 7). However a later meta-analysis that included both the BCAC and BPC3 data (17) (>79,000 women) did not replicate this finding. Finally, current evidence suggest absence of statistically significant interaction between alcohol and rs4880 (*MnSOD*) (79) or A10398G (*ND3*) (21).

Gene – other food/nutrient interactions (vegetables, alpha carotene)—No meta-analyses on gene - vegetables/ a-carotene interactions in relation to breast cancer risk were identified. One meta-analysis explored gene - total carotenoids interactions but with no evidence for an interaction (90).

Lung cancer

Gene – other food/nutrient interactions (β-cryptoxanthin, carotenoids, fruits, citrus fruits)—No meta-analyses on gene – and β-cryptoxanthin/ carotenoids/ fruits/ citrus fruits in relation to lung cancer risk were identified.

Prostate cancer

Gene – calcium interactions—No meta-analyses on gene – and calcium in relation to prostate cancer risk were identified.

Gene – selenium interactions—No meta-analyses on gene – and selenium in relation to prostate cancer risk were identified. A recent Cochrane systematic literature review on the role of selenium on cancer risk and survival has also explored the interaction between selenium intake and genetic variants in genes coding for selenoproteins (108). They reported that the null results of the most recent low-bias RCTs on prostate cancer risk (8, 78, 83) did not suggest that at least the most frequent genotypes might strongly influence the selenium and cancer relation. An earlier review though (29) reported that gene-diet interactions have been observed for selenium in relation to prostate cancer risk and progression. In particular they 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 have looked at the interaction effects of certain genetic variants and selenium administration or selenium serum/plasma levels with inconsistent findings. The genes in which genetic variants were examined include *NKX3.1* (codes for androgen-regulated prostate tumour suppressor protein), *Selenoprotein P genes* (*SEP15, SEPP1, GPX1, and GPX4*), *OGG1*, *MnSOD*, *SELK, TXNRD2, TXNRD1.*

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Colorectal cancer

Gene – diet interactions in GWAS consortia (calcium, fibre, alcohol, vegetables, processed meat)—The possible interactions between genetic variants identified through GWAS on colorectal cancer and intakes of alcohol, dietary calcium, dietary fibre, 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 Colon Cancer Family Registry (CCFR) (60, 71). In particular, potential effect-modification between the first ten 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 (60). Following this, interaction analysis was performed for the next 16 SNPs identified through GWAS in a meta-analysis of 9,160 cases and 9,280 controls (71). Results from both meta-analyses suggested no evidence of strong gene-diet interactions involving the recently identified 26 susceptibility loci for colorectal cancer when taken one at a time, since 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 (60) and in Supplementary table S2 in (71)). 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; Supplementary table 7). Based on 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) with the overall plausibility score being weak (Table 2).

Furthermore, within the GECCO/ CCFR consortium a genome-wide diet-gene interaction analysis for risk of colorectal cancer was performed to investigate multiplicative interactions between 2.7 million genetic variants and meat, fruits, vegetables, fibre and calcium (41, 46). No statistically significant interaction was observed between the examined SNPs and fruits, vegetables, fibre and calcium (total, dietary or supplemental) intake. A significant interaction was detected between rs4143094 (10p14/near GATA3) and processed meat consumption (OR = 1.17; p value = 8.7E-09), which was consistently observed across studies (p heterogeneity = 0.78; Supplementary table 7) (46). Based on the amount of evidence and despite of no main genetic effects (Supplementary Table 8) the GATA3 – processed meat interaction was given a moderate plausibility score (Table 2). An additional study was set out to investigate if 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 that can be imputed from publicly available sequence data. In this study a two-tiered approach was adopted comprising a case-only screening stage I (314 cases) and a case–control validation stage II (259 cases, 1,002 controls). Interactions with the smallest p value in stage I were verified in stage II using multiple logistic regression analysis adjusted for sex and age. No gene-alcohol interaction passed the multiple-test correction threshold (96). Finally, in a systematic search for gene-environment interactions using genome-wide data from the Colon Cancer Family Registry that included 1,191 cases of microsatellite stable or microsatellite instability–low colorectal cancer and 999 controls genotyped (using either the

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Illumina Human1M or Human1M-Duo BeadChip) interactions between genotypes and 14 environmental factors (including alcohol, folate, fibre, fruit, vegetables and red meat intakes) were explored. In this study no gene-environment interactions that reached genome-wide significance were identified (47).

Gene – alcohol intake interactions—One meta-analysis of 27 studies, including 13,465 colorectal cancer cases and 20,430 controls summarised the evidence on the association between MTR A2756G polymorphism and colorectal cancer. Only 4 studies reported data on alcohol stratification. A meta-analysis of these four studies using a dominant genetic model, showed that heavy alcohol drinkers (≥50 g ethanol/d on ≥5 day/ week) with the G allele of MTR A2756G variant compared to the wild AA genotype had a significantly increased colorectal cancer risk with an OR of 2.00 (95% CI: 1.28, 3.09; p value = 0.002, P heterogeneity = 0.38) (38) (Supplementary Table 7). Based on the prior score and the amount of evidence in the current study the overall plausibility of MTR – alcohol interaction was classified as weak only (Table 2). Finally in a meta-analysis of two Asian studies no interaction between alcohol and the *p53* Arg72Pro genetic polymorphism was found (82) (Supplementary Table 7, Table 2)

Gene – vegetables intake interactions—A recent meta-analysis on 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 (103)(Supplementary Table 7). The overall plausibility score for interaction between *GSTT1* deletion genotype and vegetable intake was classified as weak, with no evidence for *GSTM1* or *GSTT1/ GSTM1* combined interaction effects on colorectal cancer risk (Table 2).

Gene –other food/nutrient interactions (dairy products, non-fermented milk, milk, plasma levels of vitamin D, whole grains)—No meta-analyses on gene – and dairy products/ non-fermented milk/ milk/ whole grains in relation to colorectal cancer risk were identified.

Stomach cancer

Gene – salt interactions—No meta-analyses on gene – and salt in relation to stomach cancer risk were identified.

Discussion

Main findings

Finding gene–diet interactions may be useful in the understanding, prevention and better management of cancer. It can allow for a more specific risk assessment that could be useful for early detection or prevention strategies and moreover to further our understanding of biological pathways and mechanisms of disease aetiology (101). In this review we firstly summarized the available evidence on the main effects of foods and nutrients for the top 5 cancers (breast, prostate, lung, colorectal and stomach) and then evaluated the literature on

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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 exclude however the possibility of having missed interactions with small effect sizes.

In relation to the diet and nutrient associations, despite the amount of identified studies only a limited number of observations were classified as convincing (class I: alcohol – colorectal cancer risk; whole grains – colorectal cancer risk) or highly suggestive (class II; heavy alcohol intake – breast cancer risk, fruit intake - lung cancer risk, calcium - 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 evidence in epidemiological evidence does not solidly prove causation.

These food items and nutrients can may act as potential cancer risk modifiers at tumour initiation, promotion, progression, and/or conversion. 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 stage of initiation ethanol may act through activation of various pro-carcinogens present in food, smoke and environment by induction of cytochome P450 2E1 (CYP2E1). At the cancer promotion stage alcohol may affect DNA methylation and that can change the expression of oncogenes and tumour-suppressor genes. Furthermore alcohol metabolism leads to the generation of toxic metabolites that may cause changes in cell-cycle behaviour. Ethanol also increases oestrogen levels and this increase may be important in breast cancer development. Finally, at the stage of progression alcohol may facilitate tumour cell spread by causing immune suppression (95).

Another food item that was found in this review to have a class I epidemiological association with colorectal cancer risk reduction was intake of whole grains. It is believed that the protective mechanism of whole grains is mainly explained by dietary fibre, resistant starch and oligosaccharides. However, the evidence for protective effects of total fibre was classified only as suggestive in our review and therefore could not explain the protective effects of whole grains completely. Whole grains are also rich in antioxidants that could prevent DNA from oxidative damage and mutation at the stage of tumour initiation, but this is also largely speculative. Another speculated mechanism is through insulin and glucose responses. Although lower glycaemic load and glycaemic index have been linked to diabetes and obesity, our review classified evidence for colorectal cancer and glycaemic index as weak only. Finally, whole grains contain many other compounds such as phytate, phyto-oestrogens, vitamins and minerals that have been proposed as candidates for protecting against cancer (97).

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 (22) with a score based on the observed strength of evidence (evaluated by applying a modified version of Venice criteria). From all the evaluated gene-diet interactions with prior weak, moderate or high

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scores, only the interaction between 10p14 locus and processed meat in relation to colorectal cancer risk (46) was categorised as moderate (grade BBB). Interactions between alcohol and rs17468277 (*CASP8*) in breast cancer risk, alcohol and rs1805087 (*MTR*) (38), vegetables and rs16892766 (8q23.3) (60), and cruciferous vegetables and *GSTT1* deletion polymorphism (103) in relation to colorectal cancer risk were classified as weak according to Venice criteria. The remaining studied associations did not show any evidence of interaction. Based on prior and observed scores, combined plausibility score was moderate for processed meat and rs4143094 (10p14/GATA3) interaction in relation to colorectal cancer risk and weak for *GSTT1* and cruciferous vegetable intake, *MTR* and alcohol consumption and rs16892766 (8q23.3) and overall vegetable intake, all in relation to colorectal cancer.

Some of the detected interactions with weak and moderate combined scores were expected based on our prior knowledge of gene function and suggested mechanisms of actions 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 glucosinolates metabolism (55). Glucosinolates are known to be in abundance in cruciferous vegetables, especially broccoli and it is speculated to explain some of the chemoprotective properties of cruciferous vegetables (54). Another interaction that is biologically plausible, though observational evidence is weak, is an interaction between the polymorphism in methionine synthase (*MTR*) gene and alcohol consumption. MTR plays a central role in maintaining adequate intracellular folate, methionine and normal homocysteine concentrations, while alcohol consumption affects folate absorption and folate serum concentration and it can directly interfere with methionine synthase activity (51). However, only weak evidence was observed for the association between folate and colorectal cancer risk and no evidence was observed for the folate-*MTR* interaction. The precise mechanism of interaction between the rs4143094 variant in 10p14/GATA3 region and high dose red meat consumption is even less clear. GATA binding protein 3 (*GATA3*) has been associated with T cell development and Th2 cell differentiation (56). It was speculated that processed and red meat could trigger an inflammatory or immunological response that require normal GATA function and lack of that can potentially lead to cancer initiation and development (46). Similarly little is known about the functional impact of rs16892766 at 8q23.3. It is located close to eukaryotic translation initiation factor 3 subunit H (*EIF3H*) gene, however it seems to be affecting the gene expression of UTP23 (small subunit processsome component) gene. It is unclear what would be the biological mechanism of action for this interaction and together with only weak combined plausibility score the observed interaction is highly questionable.

The majority of gene-diet interactions included in our study were investigated using candidate-gene studies. In this type of research the starting point is an established 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 known to metabolise the specific dietary factor. Only few studies were based on agnostic searches with no prior hypotheses in large genome wide association consortia to investigate interactions between a very large number of common polymorphisms (>1M SNPs) with selected dietary factors and risk of cancer and

this approach may need to be applied to more datasets and consortia that collect information on both the genome and dietary factors.

Challenges for gene-diet interaction studies

All analytical methods are associated with measurement error and non-differential 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, it has been shown that errors between both methods used for measuring diet can be correlated, so that results from the reference method are not independent of those that are derived from the test method. Therefore the extent of measurement error might still be underestimated (116). Biomarkers of diet have been developed in order that more accurate factors for correction can be obtained. The advantage of this validation method is that questionnaire or records errors are not correlated with biomarker errors and therefore spurious validation results can be avoided. However it is still technically challenging to implement due to the costs, as well as measurements errors and normal variations in individuals levels between measurements. In particular, usually biomarker levels of a particular nutrient do not depend only on dietary intakes, but also on other lifestyle choices, physiological characteristics and genetic variants. In addition, biomarker measurements are subject to laboratory and technical errors as well as to daily dietary intake variations. In addition, appropriate biomarkers are only available for a few specific nutrients and therefore, by applying this validation method intakes of several nutrients cannot be validated (116). 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 under-report 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 initiation and progression of the disease. In case-control studies there is also often 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 therefore 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/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 due to such subjective factors as cooking methods, dietary habits (frequency of meals, portion sizes, eating out) and individual metabolic background.

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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 odds ratio, the odds ratios 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 (101). 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 (66, 84). The number of cases/ events in the meta-analyses of gene-diet interactions classified as moderate or weak in relation to colorectal cancer was 9287 for GATA3 – processed meat (moderate), 3556 for GSTT1 and cruciferous vegetable intake, 1398 for MTR and alcohol consumption and 7016 for rs16892766 (8q23.3) and overall vegetable intake. In contrast the mean number of events for the no evidence interactions was 2691. 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 and thus their practical importance is still unlikely.

A statistically significant interaction was detected between rs4143094 (10p14/near GATA3) and processed meat consumption, which was consistently observed across studies (46). Based on the amount of evidence and despite of no main genetic effects the GATA3 – processed meat interaction was given a moderate plausibility score. Despite claims that interaction in the absence of main effects is spurious, there are counterarguments (86). Furthermore, it has been shown in simulation studies that a range of interaction effect sizes can be detected in a genome wide association study even when the marginal effects are not detectable (101).

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

Limitations of 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. Furthermore some of the caveats in the umbrella review methodology include interpretation of tests for statistical bias and the potential effect inflation even in the largest studies. As in all literature reviews, the quality is directly related to the quality of the included studies and beyond that since this is a review of meta-analyses we also depend on the assessment of study quality of the original meta-analyses. Fourth, while we have formed our criteria for

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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 where limited evidence is available or where sample sizes is limited. Finally, the current review does not cover interaction between epigenetic factors, diet and cancer risk, since 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 evidence on dietary and gene-diet interactions for 5 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 – colorectal cancer risk; whole grains – colorectal cancer) or highly suggestive. 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 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 and/or extremely difficult to decipher. Single studies may provide nominally statistically significant results for a large number of associations (94), 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 methods (Variational Bayesian 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 randomized controlled trials for those nutrients for which the observational evidence is promising and may have potentially large public health importance should associations prove to be causal. However, evidence from single nutrient dietary interventional trials to-date has been practically thoroughly negative in terms of identifying cancer prevention benefits. Large-scale, transparent, pre-registered 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 rather than single nutrients (62). Performing fewer such studies may be preferable over continuing the conduct of hundreds of thousands of observational nutrition analyses that seem to have very little yield of reproducible, let alone useful, results (61). Finally, instrumental variable methods like Mendelian randomization studies may also be of same value (98), in particular for exploring associations with postulated increased risk of cancer, where both genes and dietary factors may be implicated. However at the moment the feasibility in performing such studies is limited due to lack of knowledge of genetic architecture of many biomarkers that are affected by dietary factors.

Supplemental Material

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References

1. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report.Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer. 2010.
2. World Cancer Research Funds/American Institute for Canceer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011.
3. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report:Diet, Nutrition, Physical Activity, and Prostate Cancer. 2014.
4. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Stomach Cancer. 2016.
5. Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. Am J Clin Nutr. 2009; 89:1402–9. [PubMed: 19261724]
6. Alexander DD, Morimoto LM, Mink PJ, Cushing CA. A review and meta-analysis of red and processed meat consumption and breast cancer. Nutr Res Rev. 2010; 23:349–65. [PubMed: 21110906]
7. Alexander DD, Morimoto LM, Mink PJ, Lowe KA. Summary and meta-analysis of prospective studies of animal fat intake and breast cancer. Nutr Res Rev. 2010; 23:169–79. [PubMed: 20181297]
8. Algotar AM, Stratton MS, Ahmann FR, Ranger-Moore J, Nagle RB, et al. Phase 3 clinical trial investigating the effect of selenium supplementation in men at high-risk for prostate cancer. Prostate. 2013; 73:328–35. [PubMed: 22887343]
9. Altman DG, Bland JM. How to obtain the confidence interval from a P value. Bmj. 2011; 343:d2090. [PubMed: 21824904]
10. Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ. 2011; 343:d6617. [PubMed: 22074852]
11. Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, et al. Carbohydrates, glycemic index, glycemic load, and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2012; 23:521–35. [PubMed: 22418776]
12. Aune D, Lau R, Chan DS, Vieira R, Greenwood DC, et al. Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. Gastroenterology. 2011; 141:106–18. [PubMed: 21600207]
13. Aune D, Lau R, Chan DS, Vieira R, Greenwood DC, et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol. 2012; 23:37–45. [PubMed: 21617020]
14. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr. 2015; 101:87–117. [PubMed: 25527754]
15. Bae JM, Lee EJ, Guyatt G. Citrus fruit intake and stomach cancer risk: a quantitative systematic review. Gastric Cancer. 2008; 11:23–32. [PubMed: 18373174]
16. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015; 112:580–93. [PubMed: 25422909]
17. Barrdahl M, Canzian F, Joshi AD, Travis RC, Chang-Claude J, et al. Post-GWAS gene-environment interplay in breast cancer: results from the Breast and Prostate Cancer Cohort Consortium and a meta-analysis on 79,000 women. Hum Mol Genet. 2014; 23:5260–70. [PubMed: 24895409]
18. Beck T, Hastings RK, Gollapudi S, Free RC, Brookes AJ. GWAS Central: a comprehensive resource for the comparison and interrogation of genome-wide association studies. Eur J Hum Genet. 2014; 22:949–52. [PubMed: 24301061]

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19. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. Parkinsonism Relat Disord. 2016; 23:1–9. [PubMed: 26739246]
20. Bingham S, Riboli E. Diet and cancer--the European Prospective Investigation into Cancer and Nutrition. Nat Rev Cancer. 2004; 4:206–15. [PubMed: 14993902]
21. Blein S, Berndt S, Joshi AD, Campa D, Ziegler RG, et al. Factors associated with oxidative stress and cancer risk in the Breast and Prostate Cancer Cohort Consortium. Free Radic Res. 2014; 48:380–6. [PubMed: 24437375]
22. Boffetta P, Winn DM, Ioannidis JP, Thomas DC, Little J, et al. Recommendations and proposed guidelines for assessing the cumulative evidence on joint effects of genes and environments on cancer occurrence in humans. Int J Epidemiol. 2012; 41:686–704. [PubMed: 22596931]
23. Bristow SM, Bolland MJ, MacLennan GS, Avenell A, Grey A, et al. Calcium supplements and cancer risk: a meta-analysis of randomised controlled trials. Br J Nutr. 2013; 110:1384–93. [PubMed: 23601861]
24. Camp KM, Trujillo E. Position of the Academy of Nutrition and Dietetics: nutritional genomics. J Acad Nutr Diet. 2014; 114:299–312. [PubMed: 24439821]
25. Campa D, Kaaks R, Le Marchand L, Haiman CA, Travis RC, et al. Interactions between genetic variants and breast cancer risk factors in the breast and prostate cancer cohort consortium. J Natl Cancer Inst. 2011; 103:1252–63. [PubMed: 21791674]
26. Carroll C, Cooper K, Papaioannou D, Hind D, Pilgrim H, Tappenden P. Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. Clin Ther. 2010; 32:789–803. [PubMed: 20685491]
27. Chan AL, Leung HW, Wang SF. Multivitamin supplement use and risk of breast cancer: a meta-analysis. Ann Pharmacother. 2011; 45:476–84. [PubMed: 21487086]
28. Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One. 2011; 6:e20456. [PubMed: 21674008]
29. Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. J Clin Oncol. 2005; 23:8152–60. [PubMed: 16278466]
30. Chen J, Song Y, Zhang L. Lycopene/tomato consumption and the risk of prostate cancer: a systematic review and meta-analysis of prospective studies. J Nutr Sci Vitaminol (Tokyo). 2013; 59:213–23. [PubMed: 23883692]
31. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat. 2010; 121:469–77. [PubMed: 19851861]
32. Chen P, Li C, Li X, Li J, Chu R, Wang H. Higher dietary folate intake reduces the breast cancer risk: a systematic review and meta-analysis. Br J Cancer. 2014; 110:2327–38. [PubMed: 24667649]
33. Cho E, Hunter DJ, Spiegelman D, Albanes D, Beeson WL, et al. Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: a pooled analysis of 8 prospective studies. Int J Cancer. 2006; 118:970–8. [PubMed: 16152626]
34. Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst. 2004; 96:1015–22. [PubMed: 15240785]
35. Cho YA, Kim J, Woo HD, Kang M. Dietary cadmium intake and the risk of cancer: a meta-analysis. PLoS One. 2013; 8:e75087. [PubMed: 24069382]
36. Choi Y, Giovannucci E, Lee JE. Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis. Br J Nutr. 2012; 108:1934–47. [PubMed: 23167978]
37. Crowe FL, Appleby PN, Travis RC, Barnett M, Brasky TM, et al. Circulating fatty acids and prostate cancer risk: individual participant meta-analysis of prospective studies. J Natl Cancer Inst. 2014; 106
38. Ding W, Zhou DL, Jiang X, Lu LS. Methionine synthase A2756G polymorphism and risk of colorectal adenoma and cancer: evidence based on 27 studies. PLoS One. 2013; 8:e60508. [PubMed: 23593229]

Europe PMC Funders Author Manuscripts

39. Dong JY, Qin LQ. Dietary glycemic index, glycemic load, and risk of breast cancer: meta-analysis of prospective cohort studies. Breast Cancer Res Treat. 2011; 126:287–94. [PubMed: 21221764]
40. Dong JY, Zhang L, He K, Qin LQ. Dairy consumption and risk of breast cancer: a meta-analysis of prospective cohort studies. Breast Cancer Res Treat. 2011; 127:23–31. [PubMed: 21442197]
41. Du M, Zhang X, Hoffmeister M, Schoen RE, Baron JA, et al. No evidence of gene-calcium interactions from genome-wide analysis of colorectal cancer risk. Cancer Epidemiol Biomarkers Prev. 2014; 23:2971–6. [PubMed: 25192705]
42. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997; 315:629–34. [PubMed: 9310563]
43. Eliassen AH, Hendrickson SJ, Brinton LA, Buring JE, Campos H, et al. Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst. 2012; 104:1905–16. [PubMed: 23221879]
44. Fang X, Wei J, He X, An P, Wang H, et al. Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. Eur J Cancer. 2015; 51:2820–32. [PubMed: 26589974]
45. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol. 2011; 22:1958–72. [PubMed: 21307158]
46. Figueiredo JC, Hsu L, Hutter CM, Lin Y, Campbell PT, et al. Genome-wide diet-gene interaction analyses for risk of colorectal cancer. PLoS Genet. 2014; 10:e1004228. [PubMed: 24743840]
47. Figueiredo JC, Lewinger JP, Song C, Campbell PT, Conti DV, et al. Genotype-environment interactions in microsatellite stable/microsatellite instability-low colorectal cancer: results from a genome-wide association study. Cancer Epidemiol Biomarkers Prev. 2011; 20:758–66. [PubMed: 21357381]
48. Fonseca-Nunes A, Jakszyn P, Agudo A. Iron and cancer risk--a systematic review and meta-analysis of the epidemiological evidence. Cancer Epidemiol Biomarkers Prev. 2014; 23:12–31. [PubMed: 24243555]
49. Fulan H, Changxing J, Baina WY, Wencui Z, Chunqing L, et al. Retinol, vitamins A, C, and E and breast cancer risk: a meta-analysis and meta-regression. Cancer Causes Control. 2011; 22:1383–96. [PubMed: 21761132]
50. Gallicchio L, Boyd K, Matanoski G, Tao XG, Chen L, et al. Carotenoids and the risk of developing lung cancer: a systematic review. Am J Clin Nutr. 2008; 88:372–83. [PubMed: 18689373]
51. Giovannucci E. Alcohol, one-carbon metabolism, and colorectal cancer: recent insights from molecular studies. J Nutr. 2004; 134:2475S–81S. [PubMed: 15333745]
52. Han J, Jiang Y, Liu X, Meng Q, Xi Q, et al. Dietary Fat Intake and Risk of Gastric Cancer: A Meta-Analysis of Observational Studies. PLoS One. 2015; 10:e0138580. [PubMed: 26402223]
53. Heine-Broring RC, Winkels RM, Renkema JM, Kragt L, van Orten-Luiten AC, et al. Dietary supplement use and colorectal cancer risk: a systematic review and meta-analyses of prospective cohort studies. Int J Cancer. 2015; 136:2388–401. [PubMed: 25335850]
54. Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. Pharmacol Res. 2007; 55:224–36. [PubMed: 17317210]
55. Holst B, Williamson G. A critical review of the bioavailability of glucosinolates and related compounds. Nat Prod Rep. 2004; 21:425–47. [PubMed: 15162227]
56. Hosoya T, Maillard I, Engel JD. From the cradle to the grave: activities of GATA-3 throughout T-cell development and differentiation. Immunol Rev. 2010; 238:110–25. [PubMed: 20969588]
57. Hu F, Wang Yi B, Zhang W, Liang J, Lin C, et al. Carotenoids and breast cancer risk: a meta-analysis and meta-regression. Breast Cancer Res Treat. 2012; 131:239–53. [PubMed: 21901390]
58. Hu JY, Hu YW, Zhou JJ, Zhang MW, Li D, Zheng S. Consumption of garlic and risk of colorectal cancer: an updated meta-analysis of prospective studies. World J Gastroenterol. 2014; 20:15413–22. [PubMed: 25386091]
59. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. Nutr Cancer. 2009; 61:47–69. [PubMed: 19116875]

Europe PMC Funders Author Manuscripts

60. Hutter CM, Chang-Claude J, Slattery ML, Pflugeisen BM, Lin Y, et al. Characterization of gene-environment interactions for colorectal cancer susceptibility loci. Cancer Res. 2012; 72:2036–44. [PubMed: 22367214]
61. Ioannidis JP. Implausible results in human nutrition research. Bmj. 2013; 347:f6698. [PubMed: 24231028]
62. Ioannidis JP. We need more randomized trials in nutrition-preferably large, long-term, and with negative results. Am J Clin Nutr. 2016; 103:1385–6. [PubMed: 27146649]
63. Ioannidis JP, Boffetta P, Little J, O'Brien TR, Uitterlinden AG, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. Int J Epidemiol. 2008; 37:120–32. [PubMed: 17898028]
64. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ. 2007; 335:914–6. [PubMed: 17974687]
65. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. Clin Trials. 2007; 4:245–53. [PubMed: 17715249]
66. Ioannidis JP, Trikalinos TA, Khoury MJ. Implications of small effect sizes of individual genetic variants on the design and interpretation of genetic association studies of complex diseases. Am J Epidemiol. 2006; 164:609–14. [PubMed: 16893921]
67. Je Y, Liu W, Giovannucci E. Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. Int J Cancer. 2009; 124:1662–8. [PubMed: 19115212]
68. Jiang W, Wu Y, Jiang X. Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies. Gynecol Oncol. 2013; 129:620–9. [PubMed: 23535278]
69. Jung S, Spiegelman D, Baglietto L, Bernstein L, Boggs DA, et al. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst. 2013; 105:219–36. [PubMed: 23349252]
70. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol. 2015
71. Kantor ED, Hutter CM, Minnier J, Berndt SI, Brenner H, et al. Gene-environment interaction involving recently identified colorectal cancer susceptibility Loci. Cancer Epidemiol Biomarkers Prev. 2014; 23:1824–33. [PubMed: 24994789]
72. Keum N, Aune D, Greenwood DC, Ju W, Giovannucci EL. Calcium intake and colorectal cancer risk: dose-response meta-analysis of prospective observational studies. Int J Cancer. 2014; 135:1940–8. [PubMed: 24623471]
73. Keum N, Lee DH, Marchand N, Oh H, Liu H, et al. Egg intake and cancers of the breast, ovary and prostate: a dose-response meta-analysis of prospective observational studies. Br J Nutr. 2015; 114:1099–107. [PubMed: 26293984]
74. Kim J, Kang M, Lee JS, Inoue M, Sasazuki S, Tsugane S. Fermented and non-fermented soy food consumption and gastric cancer in Japanese and Korean populations: a meta-analysis of observational studies. Cancer Sci. 2011; 102:231–44. [PubMed: 21070479]
75. Kim Y, Je Y. Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. Br J Cancer. 2014; 110:2772–84. [PubMed: 24714744]
76. Lee JE, Li H, Chan AT, Hollis BW, Lee IM, et al. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. Cancer Prev Res (Phila). 2011; 4:735–43. [PubMed: 21430073]
77. Li P, Zhang H, Chen J, Shi Y, Cai J, et al. Association between dietary antioxidant vitamins intake/blood level and risk of gastric cancer. Int J Cancer. 2014; 135:1444–53. [PubMed: 24510802]
78. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2009; 301:39–51. [PubMed: 19066370]
79. Liu G, Sun G, Wang Y, Wang D, Hu W, Zhang J. Association between manganese superoxide dismutase gene polymorphism and breast cancer risk: a meta-analysis of 17,842 subjects. Mol Med Rep. 2012; 6:797–804. [PubMed: 22825700]

Europe PMC Funders Author Manuscripts

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80. Liu L, Zhuang W, Wang RQ, Mukherjee R, Xiao SM, et al. Is dietary fat associated with the risk of colorectal cancer? A meta-analysis of 13 prospective cohort studies. Eur J Nutr. 2011; 50:173–84. [PubMed: 20697723]
81. Liu M, Cui LH, Ma AG, Li N, Piao JM. Lack of effects of dietary folate intake on risk of breast cancer: an updated meta-analysis of prospective studies. Asian Pac J Cancer Prev. 2014; 15:2323–8. [PubMed: 24716978]
82. Liu Y, Qin H, Zhang Y, Shi T, Liu B, et al. P53 codon 72 polymorphism and colorectal cancer: a meta-analysis of epidemiological studies. Hepatogastroenterology. 2011; 58:1926–9. [PubMed: 22234063]
83. Marshall JR, Tangen CM, Sakr WA, Wood DP Jr, Berry DL, et al. Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia: SWOG S9917. Cancer Prev Res (Phila). 2011; 4:1761–9. [PubMed: 21896650]
84. Matullo G, Berwick M, Vineis P. Gene-environment interactions: how many false positives? J Natl Cancer Inst. 2005; 97:550–1. [PubMed: 15840871]
85. Meng H, Hu W, Chen Z, Shen Y. Fruit and vegetable intake and prostate cancer risk: a meta-analysis. Asia Pac J Clin Oncol. 2014; 10:133–40. [PubMed: 23551391]
86. Moore JH. The ubiquitous nature of epistasis in determining susceptibility to common human diseases. Hum Hered. 2003; 56:73–82. [PubMed: 14614241]
87. Mutch DM, Wahli W, Williamson G. Nutrigenomics and nutrigenetics: the emerging faces of nutrition. FASEB J. 2005; 19:1602–16. [PubMed: 16195369]
88. Myung SK, Bae WK, Oh SM, Kim Y, Ju W, et al. Green tea consumption and risk of stomach cancer: a meta-analysis of epidemiologic studies. Int J Cancer. 2009; 124:670–7. [PubMed: 18973231]
89. Nickels S, Truong T, Hein R, Stevens K, Buck K, et al. Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. PLoS Genet. 2013; 9:e1003284. [PubMed: 23544014]
90. Pabalan N, Jarjanazi H, Sung L, Li H, Ozcelik H. Menopausal status modifies breast cancer risk associated with the myeloperoxidase (MPO) G463A polymorphism in Caucasian women: a meta-analysis. PLoS One. 2012; 7:e32389. [PubMed: 22427832]
91. Pelucchi C, Bosetti C, Galeone C, La Vecchia C. Dietary acrylamide and cancer risk: an updated meta-analysis. Int J Cancer. 2015; 136:2912–22. [PubMed: 25403648]
92. Qin X, Cui Y, Shen L, Sun N, Zhang Y, et al. Folic acid supplementation and cancer risk: a meta-analysis of randomized controlled trials. Int J Cancer. 2013; 133:1033–41. [PubMed: 23338728]
93. Ralston RA, Truby H, Palermo CE, Walker KZ. Colorectal cancer and nonfermented milk, solid cheese, and fermented milk consumption: a systematic review and meta-analysis of prospective studies. Crit Rev Food Sci Nutr. 2014; 54:1167–79. [PubMed: 24499149]
94. Schoenfeld JD, Ioannidis JP. Is everything we eat associated with cancer? A systematic cookbook review. Am J Clin Nutr. 2013; 97:127–34. [PubMed: 23193004]
95. Seitz HK, Becker P. Alcohol metabolism and cancer risk. Alcohol Res Health. 2007; 30:38–41. 44–7. [PubMed: 17718399]
96. Siegert S, Hampe J, Schafmayer C, von Schonfels W, Egberts JH, et al. Genome-wide investigation of gene-environment interactions in colorectal cancer. Hum Genet. 2013; 132:219–31. [PubMed: 23114982]
97. Slavin J. Why whole grains are protective: biological mechanisms. Proc Nutr Soc. 2003; 62:129–34. [PubMed: 12740067]
98. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003; 32:1–22. [PubMed: 12689998]
99. Sun Y, Lin LJ, Sang LX, Dai C, Jiang M, Zheng CQ. Dairy product consumption and gastric cancer risk: a meta-analysis. World J Gastroenterol. 2014; 20:15879–98. [PubMed: 25400475]
100. Tanvetyanon T, Bepler G. Beta-carotene in multivitamins and the possible risk of lung cancer among smokers versus former smokers: a meta-analysis and evaluation of national brands. Cancer. 2008; 113:150–7. [PubMed: 18429004]

Europe PMC Funders Author Manuscripts

101. Thomas D. Gene--environment-wide association studies: emerging approaches. Nat Rev Genet. 2010; 11:259–72. [PubMed: 20212493]
102. Tian SB, Yu JC, Kang WM, Ma ZQ, Ye X, Cao ZJ. Association between dairy intake and gastric cancer: a meta-analysis of observational studies. PLoS One. 2014; 9:e101728. [PubMed: 25006674]
103. Tse G, Eslick GD. Cruciferous vegetables and risk of colorectal neoplasms: a systematic review and meta-analysis. Nutr Cancer. 2014; 66:128–39. [PubMed: 24341734]
104. Tse G, Eslick GD. Egg consumption and risk of GI neoplasms: dose-response meta-analysis and systematic review. Eur J Nutr. 2014; 53:1581–90. [PubMed: 24500371]
105. Turati F, Guercio V, Pelucchi C, La Vecchia C, Galeone C. Colorectal cancer and adenomatous polyps in relation to allium vegetables intake: a meta-analysis of observational studies. Mol Nutr Food Res. 2014; 58:1907–14. [PubMed: 24976533]
106. Turner LB. A meta-analysis of fat intake, reproduction, and breast cancer risk: an evolutionary perspective. Am J Hum Biol. 2011; 23:601–8. [PubMed: 21681848]
107. Vieira AR, Abar L, Vingeliene S, Chan DS, Aune D, et al. Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. Ann Oncol. 2016; 27:81–96. [PubMed: 26371287]
108. Vinceti M, Dennert G, Crespi CM, Zwahlen M, Brinkman M, et al. Selenium for preventing cancer. Cochrane Database Syst Rev. 2014:Cd005195. [PubMed: 24683040]
109. Vinceti M, Dennert G, Crespi CM, Zwahlen M, Brinkman M, et al. Selenium for preventing cancer. Cochrane Database Syst Rev. 2014; 3:CD005195.
110. Vineis P, Manuguerra M, Kavvoura FK, Guarrera S, Allione A, et al. A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility. J Natl Cancer Inst. 2009; 101:24–36. [PubMed: 19116388]
111. Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet. 2013; 381:1029–36. [PubMed: 23352552]
112. Wang L, Zhang X, Liu J, Shen L, Li Z. Tea consumption and lung cancer risk: a meta-analysis of case-control and cohort studies. Nutrition. 2014; 30:1122–7. [PubMed: 25194612]
113. Wang Q, Chen Y, Wang X, Gong G, Li G, Li C. Consumption of fruit, but not vegetables, may reduce risk of gastric cancer: results from a meta-analysis of cohort studies. Eur J Cancer. 2014; 50:1498–509. [PubMed: 24613128]
114. Wang ZH, Gao QY, Fang JY. Green tea and incidence of colorectal cancer: evidence from prospective cohort studies. Nutr Cancer. 2012; 64:1143–52. [PubMed: 23163842]
115. Welter D, MacArthur J, Morales J, Burdett T, Hall P, et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res. 2014; 42:D1001–6. [PubMed: 24316577]
116. Willett W, Oxford University Press. Nutritional epidemiologyMonographs in epidemiology and biostatistics. Vol. 30. New York; Oxford: Oxford University Press; 1998. xiv–514.
117. Woo HD, Kim J. Dietary flavonoid intake and risk of stomach and colorectal cancer. World J Gastroenterol. 2013; 19:1011–9. [PubMed: 23467443]
118. World Cancer Research Fund/American Institute for Cancer Research. , editorFood, Nutrition, and Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: AICR; 2007.
119. Wu AH, Butler LM. Green tea and breast cancer. Mol Nutr Food Res. 2011; 55:921–30. [PubMed: 21538855]
120. Wu QJ, Yang Y, Wang J, Han LH, Xiang YB. Cruciferous vegetable consumption and gastric cancer risk: a meta-analysis of epidemiological studies. Cancer Sci. 2013; 104:1067–73. [PubMed: 23679348]
121. Wu W, Kang S, Zhang D. Association of vitamin B6, vitamin B12 and methionine with risk of breast cancer: a dose-response meta-analysis. Br J Cancer. 2013; 109:1926–44. [PubMed: 23907430]
122. Xia H, Ma S, Wang S, Sun G. Meta-Analysis of Saturated Fatty Acid Intake and Breast Cancer Risk. Medicine (Baltimore). 2015; 94:e2391. [PubMed: 26717389]

Europe PMC Funders Author Manuscripts

123. Xie F, Wang D, Huang Z, Guo Y. Coffee consumption and risk of gastric cancer: a large updated meta-analysis of prospective studies. Nutrients. 2014; 6:3734–46. [PubMed: 25237829]

124. Xu X, Cheng Y, Li S, Zhu Y, Xu X, et al. Dietary carrot consumption and the risk of prostate cancer. Eur J Nutr. 2014; 53:1615–23. [PubMed: 24519559]

125. Yan L, Spitznagel EL, Bosland MC. Soy consumption and colorectal cancer risk in humans: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010; 19:148–58. [PubMed: 20056634]

126. Yang T, Yang X, Wang X, Wang Y, Song Z. The role of tomato products and lycopene in the prevention of gastric cancer: a meta-analysis of epidemiologic studies. Med Hypotheses. 2013; 80:383–8. [PubMed: 23352874]

127. Yang WS, Wong MY, Vogtmann E, Tang RQ, Xie L, et al. Meat consumption and risk of lung cancer: evidence from observational studies. Ann Oncol. 2012; 23:3163–70. [PubMed: 22855553]

128. Yu XF, Zou J, Dong J. Fish consumption and risk of gastrointestinal cancers: a meta-analysis of cohort studies. World J Gastroenterol. 2014; 20:15398–412. [PubMed: 25386090]

129. Zhang X, Albanes D, Beeson WL, van den Brandt PA, Buring JE, et al. Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. J Natl Cancer Inst. 2010; 102:771–83. [PubMed: 20453203]

130. Zhang Z, Xu G, Ma M, Yang J, Liu X. Dietary fiber intake reduces risk for gastric cancer: a meta-analysis. Gastroenterology. 2013; 145:113–20 e3. [PubMed: 23567349]

131. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ. 2013; 346:f3706. [PubMed: 23814120]

132. Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science. 2016; 352:565–9. [PubMed: 27126040]

133. Zhou XF, Ding ZS, Liu NB. Allium vegetables and risk of prostate cancer: evidence from 132,192 subjects. Asian Pac J Cancer Prev. 2013; 14:4131–4. [PubMed: 23991965]

134. Zhou Y, Zhuang W, Hu W, Liu GJ, Wu TX, Wu XT. Consumption of large amounts of Allium vegetables reduces risk for gastric cancer in a meta-analysis. Gastroenterology. 2011; 141:80–9. [PubMed: 21473867]

135. Zhou ZY, Wan XY, Cao JW. Dietary methionine intake and risk of incident colorectal cancer: a meta-analysis of 8 prospective studies involving 431,029 participants. PLoS One. 2013; 8:e83588. [PubMed: 24340103]

136. Zhu B, Zou L, Qi L, Zhong R, Miao X. Allium vegetables and garlic supplements do not reduce risk of colorectal cancer, based on meta-analysis of prospective studies. Clin Gastroenterol Hepatol. 2014; 12:1991–2001 e1-4. quiz e121. [PubMed: 24681077]

137. Zhu H, Yang X, Zhang C, Zhu C, Tao G, et al. Red and processed meat intake is associated with higher gastric cancer risk: a meta-analysis of epidemiological observational studies. PLoS One. 2013; 8:e70955. [PubMed: 23967140]

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Table 1

Summary characteristic for class I-III dietary evidence for breast, lung, prostate, colon and stomach cancers.

Evidence class was decided based on the following criteria: Convincing evidence (Class I) required >1000 cases, highly significant summary associations ($p < 10^{-6}$ by random-effects), 95% prediction interval not including the null, no evidence of small-study effects, no evidence of excess significance bias and not large heterogeneity ($I^2 < 50\%$). Highly suggestive evidence (Class II) required >1000 cases, highly significant summary associations ($p < 10^{-6}$ by random-effects) and largest study with 95% CI excluding one. Suggestive evidence (Class III) required only >1000 cases and $p < 0.001$ by random-effects. All other risk factors with nominally significant summary associations ($p < 0.05$) were coined as having weak evidence (Class IV). Non-significant associations (NS) were those with $p > 0.05$. (RR: relative risk, OR: odds ratio, HR: hazard ratios, CI confidence interval, SRRE summary relative risk estimates).

Risk factor	Reference	Unit of comparison	Events	N of studies	RR (95% CI)	p-value	Prediction interval	I^2	Evidence class
Breast cancer									
Nutrient/ dietary factor									
Alcoholic drinks	Jung S, 2015[1]	≥30g/d of alcohol consumption vs non-drinkers	ER+: 21232; ER-: 4343	ER+: 20; ER-: 17	ER+: 1.35 (1.23, 1.48); ER-: 1.28 (1.10, 1.49)	ER+: $5.2x10^{-10}$; ER-: 0.001	ER+: 1.07, 1.70	ER+: 26%; ER-: 0%	ER+:Class II[2]; ER-: Class IV
Vegetables	Jung S, 2012	Highest vs lowest quintiles of total vegetables consumption	4,821	20	0.82 (0.74, 0.90)	$8.1x10^{-5}$	n/a	<50%	Class III
α-carotene	Hu F, 2012	Per 1500 lg/day of dietary intake	7,298	4	0.91 (0.87, 0.96)	0.0002	n/a	1%	Class III
Lung Cancer									
Nutrient/ dietary factor									
β-crypoxanthin	Gallicchio L, 2008	Highest vs lowest category of intake	4,894	8	0.80(0.72, 0.89)	$4.4x10^{-5}$	n/a	0%	Class III
Carotenoids	Gallicchio L, 2008	Highest vs lowest category of intake	4,310	8	0.79(0.71, 0.87)	$7.1x10^{-6}$	n/a	0%	Class III
Fruits	Vieira AR, 2016	Highest vs lowest intake	15,599	29	0.82 (0.76, 0.89)	$1x10^{-6}$	0.62-1.07	32%	Class II
Citrus fruits	Vieira AR, **2016**	Highest vs lowest intake	12,021	15	0.85 (0.78, 0.93)	0.0003	n/a	30%	Class III
Prostate cancer									
Nutrient/ dietary factor									
Dietary Calcium	Aune D, 2015	High vs low intake	35,493	15	1.18(1.08, 1.30)	0.0005	n/a	53%	Class III
Selenium	Vinceti M, 2014	Highest vs lowest category of intake and biochemical selenium level	6532	17	0.79 (0.69, 0.90)	0.0005	n/a	23%	Class III
Colorectal cancer									
Nutrient/ dietary factor									
Alcoholic drinks	Fedirko V, 2011[3]	Heavy drinkers (≥50g/day) vs nondrinkers/occasional drinkers	1,208	7	1.57 (1.38, 1.80)	$4.2x10^{-11}$	1.32,1,87	0%	Class I[4]
Calcium	Keum N, 2014	300 mg daily increment of calcium intake	12,305	15	0.92 (0.89, 0.94)	$4.8x10^{-9}$	0.85-1.01	47%	Class II
Total Fibre	Aune D, 2011	High vs low intake	14,794	19	0.88 (0.82, 0.94)	0.0003	n/a	0%	Class III

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Risk factor	Reference	Unit of comparison	Events	N of studies	RR (95% CI)	p-value	Prediction interval	I^2	Evidence class
Vegetables	Aune D, 2011	Highest vs lowest intake	16,057	16	0.91 (0.86, 0.96)	0.0008	0.86, 0.96	0%	Class III
Whole grains	Aune D, 2011	High vs low intak	>4523	4	0.79 (0.72, 0.86)	$3.1x10^{-7}$	0.65-0.96	0%	Class I [5]
Dairy products	Aune D, 2012	Highest vs lowest dietary intake	11,579	12	0.81 (0.74, 0.90)	$2.9x10^{-5}$	n/a	42%	Class III
Non-fermented milk	Ralston RA, 2014	Highest vs lowest category	7,735	14	0.85 (0.77, 0.93)	0.0008	n/a	0%	Class III
Milk	Aune D, 2012	Per 200 g/day intake	4510	9	0.91 (0.85, 0.94)	0.0003	n/a	0%	Class III
Processed meat	Chan DSM, 2011	Per 50 g/day	10,863	9	1.18 (1.10, 1.28)	$2.3x10^{-5}$	n/a	12%	Class III
Biomarkers									
Circulating Vitamin D (25(OH)D)	Lee JE, 2011	Top versus bottom quantiles of circulating 25(OH)D levels.	1,822 colon and 868 rectal cancer cases	8	0.66 (0.54, 0.81)	$6.8x10^{-5}$	n/a	n/a	Class III
Stomach cancer									
Nutrient/ dietary factor									
Salt	Fang X, 2015	Highest vs lowest intake	14,850	8	1.11 (1.05, 1.16)	$4.7x10^{-5}$	n/a	26%	Class III

[1] 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., 2015 (RR for heavy drinkers vs non-drinkers = 1.50 (1.19,1.89)) due to the limited information on summary statistics and included studies in Bagnardi et al., 2015

[2] Evidence was classified as highly suggestive (class II) due to the presence of excess significance bias ($p_{\text{excess significance bias}} = 4x10^{-8}$, $P_{\text{small effect bias}} = 0.184$)

[3] 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., 2015 (RR for heavy drinkers vs non-drinkers = 1.41 (1.23,1.63)) due to the limited information on summary statistics and included studies in Bagnardi et al., 2015

[4] No evidences of small effect ($P_{\text{small effect bias}} = 0.802$) or excess significance bias ($P_{\text{excess significance bias}} = 0.254$)

[5] No evidences of small effect ($P_{\text{small effect bias}} = 0.947$) or excess significance bias ($P_{\text{excess significance bias}} = 0.11$)

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Table 2

Evaluation of evidence of gene-environment interactions for the five major cancers

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

NS – non significant (p value <10-5) evidence for the main genetic effects

[a] rs17468277 and rs1045485 variants are in linkage disequilibrium and have r2=1 and D'=1 in HapMap European populations. Both variants are often used interchangeable in genetic association studies and meta-analyses. rs17468277 – alcohol interaction was classified as week evidence in the combined score, however a later and bigger meta-analysis by Barrdahl M et al. (2014) did not observed any interaction with the correlated rs1045485 variant. Therefore, combined score for CASP8 – alcohol interaction was set to no evidence.

[b] Based on nutrient evidence and genetic evidence scores.

[c] The strength of the observed evidence for interaction between the dietary exposure and the genetic variants was based on an extension of the HuGENet Venice criteria used for assessing cumulative evidence for genetic associations. Each gene-diet association was graded based on the amount of evidence, the extent of replication and protection of bias.

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

[e] The effect of *GSTM1* and *GSTT1* deletion polymorphisms reached nominal significance ($p<0.05$), but did not reach $p<10^{-5}$ which was used to declare significant association in the present review.