Lead Article

Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk

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Context: *Evidence of an association between dietary patterns derived* a posteriori *and risk of cancer has not been reviewed comprehensively.* ***Objective:*** *The aim of this review was to investigate the relation between* a posteriori*–derived dietary patterns, grouped as healthy or unhealthy, and cancer risk. The relation between cancer risk and background characteristics associated with adherence to dietary patterns was also examined.* ***Data Sources:*** *PubMed and Embase electronic databases were searched.* ***Study Selection:*** *A total of 93 studies including over 85 000 cases, 100 000 controls, and 2 000 000 exposed individuals were selected.* ***Data Extraction:*** *Data were extracted from each identified study using a standardized form by two independent authors.* ***Results:*** *The most convincing evidence (significant results from prospective cohort studies) supported an association between healthy dietary patterns and decreased risk of colon and breast cancer, especially in postmenopausal, hormone receptor–negative women, and an association between unhealthy dietary patterns and increased risk of colon cancer. Limited evidence of a relation between an unhealthy dietary pattern and risk of upper aerodigestive tract, pancreatic, ovarian, endometrial, and prostatic cancers relied only on case–control studies. Unhealthy dietary patterns were associated with higher body mass index and energy intake, while healthy patterns were associated with higher education, physical activity, and less smoking. Potential differences across geographical regions require further evaluation.* ***Conclusions:*** *The results suggest a potential role of diet in certain cancers, but the evidence is not conclusive and may be driven or mediated by lifestyle factors.*

INTRODUCTION

Cancer is among the leading causes of mortality worldwide, representing a major public health issue. The Global Burden of Disease evaluation estimated the incidence of cancer at 14.9 million cases, accounting for 8.2 million deaths and 196.3 million disability-adjusted life-years, with prostate cancer and breast cancer causing the

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greatest impact in men and women, respectively.[1] Ongoing research on modifiable risk factors, including dietary habits, estimated that a large percentage of cancer is preventable by behavior modification. Numerous studies have explored and produced evidence of an association between individual nutrients or foods and risk of cancer. While the study of single foods or nutrients provides evidence of the effects of individual components of the diet, it fails to encompass the complexity of the whole diet, including the interactions between all dietary components. The examination of existing dietary patterns and their association with cancer risk could provide a wider and more realistic estimation of the relation between food habits and health in a particular population.

A number of studies have been conducted on the potential association between *a posteriori*–derived dietary patterns and certain types of cancer, such as esophageal,[2] gastric,[3] colorectal,[4] and breast.[5] However, using principal component analysis and exploratory factor analysis, no comprehensive evaluation of all cancer sites has been conducted. Moreover, an association between cancer and unhealthy behaviors has been previously discussed but not quantitatively investigated. Thus, the aim of the present study was threefold. The first aim was to update and summarize current knowledge on the relation between adherence to *a posteriori*–derived healthy or unhealthy dietary patterns (characterized by, but not limited to, red and processed meat, sugary drinks and salty snacks, starchy foods, and refined carbohydrates) and cancer risk in epidemiological studies. The second aim was to provide risk estimation of different cancer types associated with similar dietary patterns to test consistency of findings. The final aim was to explore the association between the dietary patterns investigated and factors potentially clustering together to mediate or confound the resulting association.

METHODS

Study selection

The design, analysis, and reporting of this study is compliant with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.[6] A systematic search of the PubMed and Embase databases for all English-language studies published up to December 2015 was performed. The search terms used for the study selection were "dietary patterns" associated with the target cancer sites, including "esophagus, esophageal", "stomach, gastric," "colon, rectal, rectum, colorectal, colorectum," "liver/hepatic," "pancreas/pancreatic," "ovarian," "breast," "endometrial, endometrium," "prostate, prostatic," "lung," and "thyroid." Studies were included if they met the following inclusion criteria (Table 1): (1) case–control or prospective study design; (2) dietary patterns derived empirically with *a posteriori* methods using principal component analysis and exploratory factor analysis; and (3) estimated odds ratios (ORs) or hazard ratios for a well-defined outcome, namely a specific cancer site. Exclusion criteria were the lack of statistics or results and the lack of an assessed composite outcome (eg, overall cancer mortality). Reference lists of included manuscripts were also checked for studies not identified previously. If more than 1 study was conducted on the same population, only the most recent was included. However, all patterns identified in each study conducted on the same population were considered, and those that were more consistent and comparable with others were included. If more than 1 article was published that used the same sample or cohort, only the study that included the entire cohort or the study with the longest follow-up or the most comparable dietary patterns identified was included.

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Parameter	Description
Participants	General population
Intervention/exposure	Adherence to *a posteriori*–derived dietary pattern
Comparison	Highest vs lowest category of exposure
Outcome	Cancer risk/incidence
Study design	Cohort and case–control studies

Data extraction

Data were abstracted from each identified study using a standardized form. The following information was collected: tumor site; name of first author, year of publication; study location; study design; name of study cohort (when available); number of participants/controls; number of cases; age range and body mass index (BMI) at baseline; sex of participants; dietary assessment method; dietary patterns identified; food items included; energy intake (in kilocalories per day) and amount of main food group consumed (in grams per day) in the highest and the lowest categories of exposure; covariates used in adjustments; and ORs or hazard ratios and 95%CIs for the highest vs the lowest category of exposure. This process was performed independently by two authors (G.G. and J.G.), and discrepancies were discussed and resolved by consensus.

Level of evidence

In accordance with the modified Joint World Health Organization–Food and Agriculture Expert

Consultation criteria for evidence in nutrition,[7] a "possible" association was considered when results were supported by meta-analysis of prospective studies with no evidence of significant heterogeneity or publication bias, a "limited" association was considered when results were supported by meta-analysis of prospective studies with high heterogeneity or meta-analysis of case–control studies, and "insufficient evidence" was considered when meta-analysis included 2 or fewer studies.

Statistical analysis

The mean amount of alcohol, fruit, vegetable, and meat consumption per day in the highest category of exposure to healthy and unhealthy dietary patterns was calculated. Random-effects models were used to calculate pooled relative risks (RRs) and 95%CIs for the highest vs the lowest category of exposure. Prospective and case–control studies were considered separately. The risk estimate from the most fully adjusted models in the analysis of the pooled RR was used. Heterogeneity was assessed by using the Q test and the I^2 statistic. The level of significance for the Q test was defined as $P < 0.10$. The I^2 statistic represented the amount of total variation that could be attributed to heterogeneity. I^2 values $\geq 50\%$ indicated significant heterogeneity. To test for the potential source of heterogeneity, several subgroup analyses were performed. First, since the definition of an unhealthy dietary pattern was substantially arbitrary and included different key characteristics, further subgroup analyses were conducted in which foods were grouped into the following dietary patterns: "alcohol" pattern, including foods associated with alcohol drinking; "carbohydrate/refined" pattern, including refined sugars, sugary drinks, and sweets; "fat/salty" pattern, including fatty or salty snacks and fast foods; "animal/meat" pattern, including mainly red and processed meat; and "Western" pattern, when defined as such in the reference. Second, the possible influence of geographical area on the relation between dietary patterns and cancer risk was tested. The possible presence of publication bias was tested through visual examination of funnel plots. Publication bias was further evaluated by performing a sensitivity analysis using a single dataset that referred to 1 dietary pattern per study, in order to avoid to prevent individual publications from being weighted too heavily.

To identify a potential relation between dietary patterns and lifestyle factors, data on baseline BMI values and relative standard deviations (SDs) by category of exposure (quantiles of dietary patterns) were extracted. Missing SDs were imputed by considering the average of existing values according to guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*[8]; the difference between the highest and the lowest quantiles of each dietary pattern investigated was calculated, and values were subsequently meta-analyzed to estimate the mean difference using random-effects models. To identify other factors potentially related to dietary patterns, data on smoking status, education, and physical activity were collected, the ORs between the highest and the lowest (reference) quantiles of each dietary pattern investigated were calculated, and the results were meta-analyzed using random-effects models. The same strategies to control for heterogeneity and publication bias were adopted. All analyses were conducted by using Review Manager (RevMan) software, version 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Study characteristics

The literature search process is shown in Figure 1. The search strategy led to full-text examination of articles reporting 141 studies, 51 of which were excluded for the following reasons: 15 used a priori dietary pattern scores; 12 explored the association with cancer risk between dietary patterns (not adherence within individual patterns); 7 were conducted on the same population; 6 were conducted on the same cohort but had shorter follow-up; 5 used other methods to assess dietary patterns; and 4 explored the association with cancer survival. One study was added through manual search of references; thus, 93 studies were included in the quantitative analysis, divided by site of cancer as follows: mouth/pharynx (n = 3),[9–11] larynx (n = 2),[9,10] esophagus (n = 8),[9,12–18] stomach (n = 9),[9,12,14,19–24] colorectum (n = 21),[25–45] pancreas (n = 5),[46–50] liver (n = 1),[51] breast (n = 31),[9,31,52–80] endometrium (n = 5),[81–85] ovarian (n = 3),[55,86,87] lung (n = 4),[9,88–90] thyroid (n = 1),[91] urinary tract (n = 2),[9,92] prostate (n = 10).[9,93–101]

The main characteristics of the studies included, grouped by cancer site, are reported in Table S1 in the Supporting Information online. Studies included have been conducted in various geographic areas, including the United States, South America, Europe, Asia, and Australia. The average age range of the population included was 40–80 years. Most of the studies included covariates that may significantly influence cancer risk, such as age, sex (when not analyzed separately), and education, as well as factors that may be strongly associated with healthy/unhealthy dietary patterns (ie, BMI) and more general lifestyle behaviors (ie, physical activity and smoking status) (see Table S1 in the Supporting

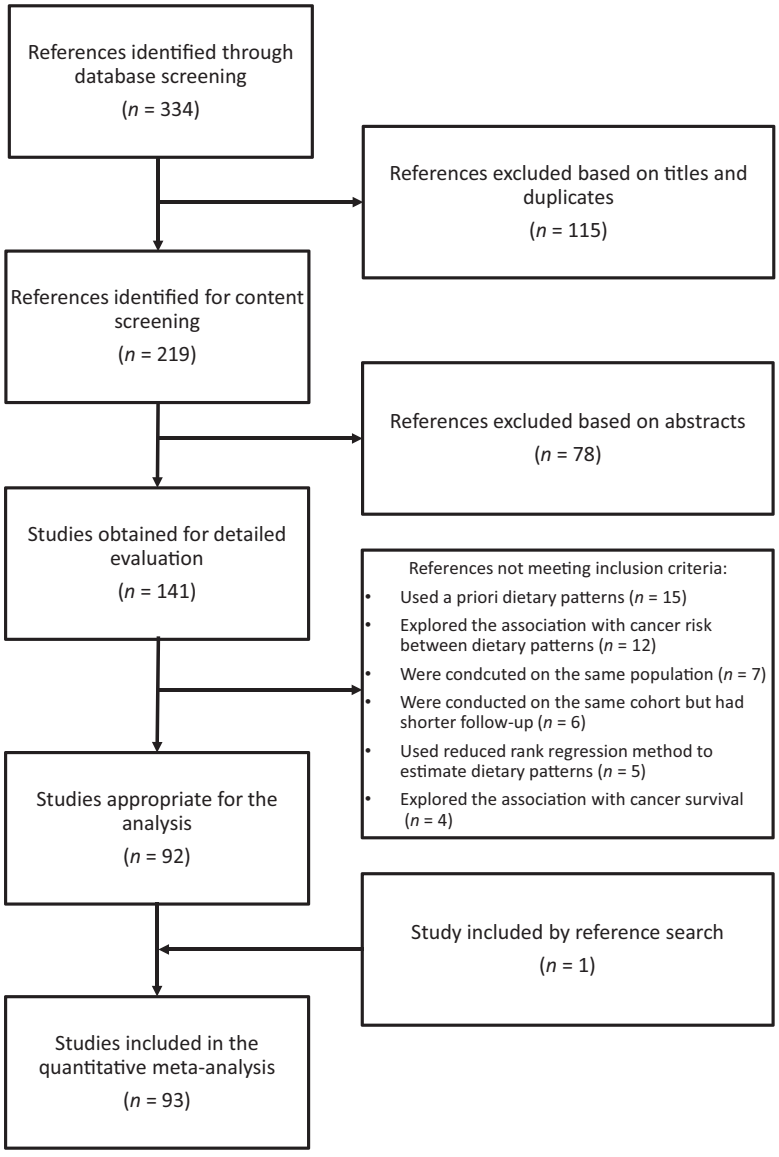

Figure 1 **Flow diagram of the literature search process.**

Information online). A total of over 85 000 cases, 100 000 controls, and 2 000 000 exposed individuals were considered in the analyses (see Table S2 in the Supporting Information online). The number of cases varied greatly, according to the primary site of cancer; cancers of the breast, colorectum, and prostate were the most commonly studied (see Table S2 in the Supporting Information online).

On the basis of food or nutrient constituents of the dietary patterns described in the studies, 315 datasets on healthy patterns and 358 datasets on unhealthy patterns were identified. The former included mainly fruit- and vegetable-based dietary patterns, named "healthy" or "prudent," and some "traditional" patterns (see Table S3 in the Supporting Information online). Traditional patterns were a more heterogeneous group of dietary patterns and were described as "Western," "animal," "fat and salty," or "refined" and included not only animal products but also salty/sweet snacks, fatty foods, and refined foods (see Table S3 in the Supporting Information online). Only 6 studies provided individual amounts of main food groups by category of exposure.[9,34,46,70,73,75] On average, the highest quantile of healthy and unhealthy dietary patterns contained, respectively, 11.5 (SD = 17.1) and 26.4 (SD = 41.6) grams of alcohol per day, 390.6 (SD = 494.9) and 230.5 (SD = 194.8) grams of fruit per day, 287 (SD = 263) and 175.9 (SD = 113) grams of vegetables per day, and 67.8 (SD = 42.5) and 95.8 (SD = 67.6) grams of meat per day.

Table 2 **Summary of results on the association between high adherence to healthy dietary patterns and risk of cancer, by type of cancer and study design**

Type of cancer	Study design						
	Case–control			Prospective			
	No. of datasets	RR (95%CI)	I^2 (%)	No. of datasets	RR (95%CI)	95%CI	I^2 (%)
Oral/pharyngeal	3	0.63 (0.42–0.94)	69	NA	NA	NA	NA
Laryngeal	2	0.50 (0.36–0.71)	10	NA	NA	NA	NA
Esophageal squamous cell carcinoma	18	0.65 (0.51–0.82)	76	NA	NA	NA	NA
Esophageal squamous cell carcinoma, M	5	0.67 (0.41–1.09)	86	NA	NA	NA	NA
Esophageal squamous cell carcinoma, F	4	0.76 (0.45–1.30)	79	NA	NA	NA	NA
Esophageal adenocarcinoma	7	0.98 (0.63–1.54)	83	NA	NA	NA	NA
Stomach	13	0.72 (0.58–0.90)	70	4	0.98 (0.74–1.29)		43
Stomach, gastric cardia	5	0.86 (0.68–1.09)	28	NA	NA	NA	NA
Stomach, M	2	0.64 (0.23–1.75)	93	2	1.14 (0.89–1.46)		0
Stomach, F	2	0.81 (0.40–1.67)	73	2	0.76 (0.44–1.33)		59
Colorectal	13	0.48 (0.27–0.84)	97	15	0.89 (0.83–0.95)		12
Colorectal, M	3	0.53 (0.40–0.69)	0	5	0.89 (0.78–1.01)		43
Colorectal, F	2	0.45 (0.30–0.67)	5	8	0.92 (0.83–1.02)		0
Colon	9	0.79 (0.68–0.92)	27	14	0.87 (0.81–0.94)		0
Colon, M	2	0.62 (0.41–0.93)	0	6	0.87 (0.79–0.97)		0
Colon, F	1	0.45 (0.24–0.84)	NA	7	0.86 (0.76–0.98)		0
Colon, proximal	3	0.97 (0.67–1.39)	19	10	0.89 (0.79–1.00)		0
Colon, distal	3	0.75 (0.43–1.31)	70	9	0.85 (0.75–0.96)		0
Rectal	10	0.76 (0.59–0.98)	72	13	0.95 (0.78–1.16)		59
Rectal, M	2	0.55 (0.38–0.80)	0	5	0.90 (0.64–1.26)		74
Rectal, F	1	0.66 (0.33–1.32)	NA	6	1.11 (0.92–1.34)		0
Pancreatic	6	0.67 (0.50–0.91)	52	7	1.09 (0.92–1.31)		12
Pancreatic, M	2	0.53 (0.37–0.76)	0	1	1.88 (1.06–3.33)		NA
Pancreatic, F	2	0.73 (0.36–1.49)	67	6	1.04 (0.87–1.24)		0
Endometrial	6	0.83 (0.67–1.04)	32	2	0.96 (0.82–1.12)		0
Ovarian	3	0.86 (0.73–1.00)	0	2	1.33 (0.89–1.97)		46
Lung	3	0.86 (0.52–1.40)	73	4	0.78 (0.65–0.93)		0
Liver	NA	NA	NA	4	0.80 (0.50–1.29)		68
Thyroid	1	0.68 (0.36–1.28)	NA	NA	NA	NA	NA
Urinary tract	5	0.88 (0.61–1.25)	24	NA	NA	NA	NA
Breast	20	0.66 (0.55–0.80)	87	13	0.90 (0.84–0.96)		26
Breast, premenopausal	7	0.64 (0.43–0.94)	80	10	0.95 (0.83–1.10)		27
Breast, postmenopausal	10	0.73 (0.55–0.96)	89	13	0.93 (0.87–1.00)		19
Breast, receptor positive	2	0.40 (0.05–2.88)	97	8	0.93 (0.85–1.02)		35
Breast, receptor negative	2	0.42 (0.08–2.31)	92	8	0.79 (0.65–0.95)		41
Prostate	9	0.99 (0.85–1.15)	18	5	0.99 (0.90–1.08)		0
Prostate, low grade	3	1.07 (0.76–1.51)	0	4	0.97 (0.87–1.09)		13
Prostate, high grade	3	1.13 (0.82–1.55)	0	4	1.00 (0.82–1.21)		0

Abbreviations: F, female; M, male; NA, not applicable; RR, relative risk.

Healthy dietary patterns and cancer risk

The comprehensive evaluation of the association between greater adherence to a healthy dietary pattern and cancer risk by study design (case–control/prospective) is presented in Table 2. Among prospective studies, a higher adherence to healthy dietary patterns was associated with a decreased risk of colorectal cancer (RR = 0.89; 95%CI 0.83–0.95), with no evidence of heterogeneity or publication bias (see Figure S1 and Figure S2 in the Supporting Information online). When analysis was restricted to a specific digestive tract location, a significantly decreased risk was found for the colon (RR = 0.87; 95%CI 0.81–0.94; $I^2 = 27\%$). A decreased risk was also found in analyses stratified by specific colon location (proximal/distal) and sex, but not in analyses restricted to rectal cancer (Table 2). When the association between risk of other cancers and adherence to healthy dietary patterns was examined prospectively, lung and breast cancer risk was significantly decreased (RR = 0.78, 95%CI 0.65–0.93, and RR = 0.90, 95%CI 0.84–0.96, respectively), with little evidence of heterogeneity and no evidence of publication bias (see Figure S1, Figure S3, and Figure S4 in the Supporting Information online). However, the analysis of lung cancer risk was based on only 2 studies. Analyses of breast cancer risk stratified by menopausal status and hormone receptor status showed a significantly decreased

risk in postmenopausal women (RR = 0.93; 95%CI 0.87–1.00) and in receptor-negative women (RR = 0.79; 95%CI 0.65–0.95). For no other cancer was there evidence of an association when prospective studies were analyzed, but analysis was based on a low number of studies for most cancers; only pancreatic cancer (n = 7 studies) and prostate cancer (n = 5 studies) were represented by more than a few studies.

Among the case–control studies, inverse associations were confirmed for colorectal and breast cancers, with effect estimates being considerably stronger than those for prospective studies (Table 2). An association was not confirmed for lung cancer, but only 2 studies were reported. Some other cancers, such as gastric (see Figure S5 in the Supporting Information online), pancreatic (see Figure S6 in the Supporting Information online), and ovarian (see Figure S7 in the Supporting Information online), were significantly related to healthy dietary patterns in meta-analyses of case–control studies (Table 2). Adherence to healthy dietary patterns was also associated with a significantly reduced risk of oral/pharyngeal, laryngeal (see Figure S8 in the Supporting Information online), and esophageal cancers (see Figure S9 in the Supporting Information online), though evidence of heterogeneity was high (Table 2). No significant results were found for thyroid, urinary tract, endometrial (see Figure S10 in the Supporting Information online), or prostate cancer (see Figure S11 in the Supporting Information online).

Unhealthy dietary patterns and cancer risk

The results of the analysis of high adherence to unhealthy dietary patterns and cancer risk are shown in Table 3. In prospective studies, unhealthy dietary patterns were associated with a higher risk of colorectal cancer (RR = 1.13; 95%CI 1.03–1.23; $I^2 = 31\%$), with no evidence of publication bias (see Figure S12 and Figure S13 in the Supporting Information online). Subanalyses by cancer site showed significant results for colon cancer (proximal and distal) in prospective studies (Table 3). Pooled analysis of prospective studies on colon cancer showed that higher adherence to unhealthy dietary patterns was associated with an 18% increased risk of cancer (RR = 1.18; 95%CI 1.06–1.31), with evidence of moderate heterogeneity ($I^2 = 31\%$). Heterogeneity was reduced when colon sites were analyzed separately (Table 3). For both colorectal and colon cancer, analysis by sex showed a higher association of unhealthy dietary patterns with increased cancer risk only among women (with negligible heterogeneity between prospective studies), while no significant results were found for rectal cancer when men and women were analyzed separately. For colorectal cancer, all results of prospective studies were concordant with results of case–control studies, though the magnitude of the association was stronger for the latter (Table 3). Results for ovarian cancer were significant when prospective studies were analyzed, but this was based on only 2 studies (see Figure S14 in the Supporting Information online). Analyses of case–control studies on ovarian cancer, again based on only 2 studies, were compatible, but the association was not significant.

For breast cancer (see Figure S15 in the Supporting Information online), pancreatic cancer (see Figure S16 in the Supporting Information online), lung cancer (see Figure S17 in the Supporting Information online), and prostatic cancer (see Figure S18 in the Supporting Information online), adherence to unhealthy dietary patterns was associated with an increased risk in case–control studies, but results from prospective studies were null, and the point estimates were incompatible with those from case–control studies. For gastric cancer (see Figure S19 in the Supporting Information online) and endometrial cancer (see Figure S20 in the Supporting Information online), a positive association was observed in case–control studies, but the number of prospective studies was not adequate to confirm or refute these findings. Results from pooled case–control analyses on laryngeal and esophageal squamous cell carcinoma (see Figure S21 in the Supporting Information online) were also significant; no prospective data were available (Table 3). No significant results were found for liver, thyroid, urinary tract, or oral/pharyngeal cancers (see Figure S21 in the Supporting Information online), though only oral/pharyngeal cancers were represented by more than a few studies.

Subgroup analyses

When grouping unhealthy dietary patterns by the key component characterizing them, only dietary patterns related to alcohol consumption were associated with increased cancer risk in prospective studies, whereas inconclusive results were found for all other dietary patterns identified (see Table S4 in the Supporting Information online). Notably, most of analyses were conducted on a very limited number of prospective studies, with the exception of the animal/meat and Western dietary patterns. By contrast, irrespective of the number of case–control studies analyzed, all analyses showed a significantly higher cancer risk for high adherence to any of the unhealthy dietary patterns identified (see Table S4 in the Supporting Information online). However, when prospective studies that showed an association between unhealthy dietary patterns and individual cancer sites were analyzed, the animal dietary

Table 3 **Summary of results on the association between high adherence to unhealthy dietary patterns and risk of cancer, by type of cancer and study design**

Type of cancer	Study design					
	Case–control			Prospective		
	No. of datasets	RR (95%CI)	I^2 (%)	No. of datasets	RR (95%CI)	I^2 (%)
Oral/pharyngeal	8	1.17 (0.88–1.57)	83	NA	NA	NA
Laryngeal	5	1.64 (1.40–1.92)	0	NA	NA	NA
Esophageal squamous cell carcinoma	19	1.78 (1.10–2.87)	96	NA	NA	NA
Esophageal squamous cell carcinoma, M	6	1.66 (1.09–2.52)	84	NA	NA	NA
Esophageal squamous cell carcinoma, F	3	1.36 (0.55–3.35)	89	NA	NA	NA
Esophageal adenocarcinoma	8	1.42 (0.95–2.13)	80	NA	NA	NA
Stomach	21	1.41 (1.15–1.72)	73	8	1.18 (0.85–1.64)	78
Stomach, gastric cardia	4	1.16 (0.74–1.83)	73	NA		NA
Stomach, M	4	1.36 (1.05–1.76)	37	4	1.13 (0.68–1.86)	87
Stomach, F	4	1.22 (0.73–2.02)	65	4	1.26 (0.80–1.97)	66
Colorectal	15	1.54 (1.31–1.82)	51	18	1.13 (1.03–1.23)	31
Colorectal, M	4	1.34 (1.04–1.72)	0	5	1.08 (0.91–1.27)	26
Colorectal, F	3	1.40 (0.93–2.12)	37	10	1.26 (1.10–1.43)	19
Colon	15	1.24 (1.00–1.54)	82	18	1.18 (1.06–1.31)	31
Colon, M	2	2.03 (1.33–3.10)	0	7	1.11 (0.97–1.26)	0
Colon, F	2	1.58 (1.04–2.42)	0	9	1.36 (1.15–1.62)	36
Colon, proximal	3	1.58 (0.89–2.82)	66	10	1.18 (1.00–1.41)	15
Colon, distal	3	1.64 (0.82–3.28)	75	10	1.28 (1.09–1.50)	0
Rectal	11	1.23 (1.02–1.48)	51	15	1.06 (0.90–1.25)	27
Rectal, M	2	1.03 (0.66–1.60)	24	5	1.04 (0.72–1.50)	56
Rectal, F	2	0.77 (0.45–1.30)	0	8	1.01 (0.78–1.31)	25
Pancreatic	8	1.47 (1.17–1.85)	28	3	0.81 (0.59–1.12)	0
Pancreatic, M	3	1.63 (1.16–2.28)	12	1	0.89 (0.47–1.69)	NA
Pancreatic, F	3	1.05 (0.75–1.48)	0	2	0.79 (0.54–1.14)	0
Endometrial	8	1.19 (0.99–1.43)	44	3	1.10 (0.94–1.29)	0
Ovarian	4	1.27 (0.70–2.32)	93	2	1.46 (1.02–2.08)	0
Lung	7	1.24 (0.99–1.56)	54	12	1.11 (0.91–1.35)	66
Liver	NA	NA	NA	1	0.96 (0.50–1.84)	NA
Thyroid	1	0.96 (0.50–1.84)	NA	NA	NA	NA
Urinary tract	8	1.01 (0.71–1.44)	77	NA	NA	NA
Breast	29	1.33 (1.15–1.53)	88	13	1.00 (0.93–1.08)	40
Breast, premenopausal	8	1.17 (1.00–1.38)	45	6	0.98 (0.85–1.13)	2
Breast, postmenopausal	9	1.15 (0.96–1.39)	75	8	1.07 (0.98–1.17)	24
Breast, receptor positive	3	1.14 (0.80–1.62)	67	6	1.11 (0.97–1.27)	64
Breast, receptor negative	3	0.78 (0.56–1.10)	29	6	0.94 (0.80–1.10)	0
Prostate	16	1.44 (1.21–1.71)	62	4	0.87 (0.71–1.07)	59
Prostate, low grade	4	1.29 (0.73–2.28)	58	2	0.98 (0.82–1.17)	43
Prostate, high grade	4	1.28 (0.78–2.07)	52	2	1.06 (0.83–1.35)	0

Abbreviations: F, female; M, male; NA, not applicable; RR, relative risk.

pattern was significantly associated with an increased risk of colorectal cancer (RR = 1.15; 95%CI 1.00–1.32).

In another subgroup analysis, the relation between adherence to healthy or unhealthy dietary patterns and cancer risk was evaluated by country (see Table S5 in the Supporting Information online). Regardless of the cancer site, adherence to healthy dietary patterns was associated with decreased cancer risk of roughly 5% to 10% in case–control and prospective studies conducted in both North America and Europe (for prospective studies, RR = 0.94, 95%CI 0.89–0.99, and RR = 0.89, 95%CI 0.83–0.96, respectively), with no evidence of heterogeneity or publication bias. The meta-analysis of studies involving adherence to unhealthy dietary patterns showed significantly increased risk of cancer in Europe and North America in case–control studies, but findings among prospective studies were significant only for those conducted in North America (RR = 1.07; 95%CI 1.00–1.14).

Association between dietary patterns and lifestyle factors

A total of 34 studies[9,12,13,16,20,23,30–35,38,43,46,49–51,53,54,59,62,63,70,73,75,80,82,87,91,93,95,97,99] provided data for the analysis of the associations between dietary patterns and lifestyle risk factors. Although all analyses were affected by high heterogeneity, the difference in BMI between the highest and the lowest categories of exposure was not significant across healthy dietary patterns, while

Table 4 **Mean difference in body mass index (BMI) between the highest and the lowest categories of exposure to healthy and unhealthy dietary patterns, in total and by study design, sex, and geographical area**

	Healthy patterns		Unhealthy patterns	
	No. of datasets	Mean difference in BMI[a] (95%CI)	No. of datasets	Mean difference in BMI[a] (95%CI)
Total, all studies	38	0.21 (−0.14, 0.57)	56	0.29 (0.10–0.48)
Study design				
Case–control	23	0.31 (−0.08, 0.71)	38	0.24 (0.00–0.48)
Prospective	15	0.07 (−0.54, 0.68)	18	0.38 (0.03–0.73)
Sex				
Male	11	0.03 (−0.40, 0.46)	16	0.16 (−0.32, 0.65)
Female	17	0.17 (−0.50, 0.85)	26	0.51 (0.21–0.80)
Geographical area				
North America	10	−0.13 (−1.05, 0.79)	5	1.2 (0.75–1.65)
Europe	7	0.28 (−0.41, 0.98)	3	0.6 (−0.32, 1.52)
Asia	15	0.31 (−0.14, 0.76)	10	−0.1 (−0.41, 0.21)

[a]All analyses showed significant heterogeneity.

it was greater with higher adherence to unhealthy dietary patterns (RR = 0.29; 95%CI 0.10–0.48; Table 4). The results were consistent both in case–control and in prospective studies, and in women (Table 4). Interestingly, analyses by geographical region, despite being limited to a relatively low number of datasets, revealed that the mean difference in BMI between high and low adherence to unhealthy dietary patterns was significant (and particularly higher) only when considering studies conducted in North America (mean difference = 1.2; 95%CI 0.75–1.65; Table 4).

Results for other lifestyle factors are presented in Table 5. High exposure to healthy dietary patterns was significantly associated with high physical activity (OR = 1.53; 95%CI 1.22–1.91) and high education level (OR = 1.39; 95%CI 1.06–1.82), while no significant associations between unhealthy dietary patterns and lifestyle factors were found. Results for healthy dietary patterns and high physical activity were relatively stable over each subgroup analysis (no differences between types of study design or between males and females), despite the lack of significant results for the limited number of European studies (Table 5). In contrast, results for high education level were significant only among prospective studies involving males outside of North America (Table 5). Finally, both healthy and unhealthy dietary patterns were associated with smoking status (for current smoker: OR = 0.48, 95%CI 0.36–0.65; and OR = 1.35, 95%CI 1.07–1.69, respectively) (Table 5).

DISCUSSION

Despite the subjective nomenclature applied in each study included in this meta-analysis, dietary patterns based on healthy and unhealthy food choices were identified, and cancer risk was examined by cancer site, pattern type, and geographical area of the study. The average consumption of selected food groups in healthy dietary patterns was roughly in line with general dietary guidelines, ie, 2–2.5 cups of fruit and vegetables per day and 12.5 oz of meat per week.[102] Alcohol consumption was equivalent to 1 serving of wine or beer per day. When considering data from prospective studies, most of the significant results were limited to the association between high adherence to a healthy dietary pattern and decreased risk of colon, breast, and lung cancer and the association between high adherence to an unhealthy dietary pattern and increased risk of colon cancer. The risk of cancer at several other sites was also associated with dietary pattern, but evidence was mainly driven by case–control studies. However, an overall trend toward increased and decreased cancer risk associated with unhealthy and healthy dietary patterns, respectively, was found, suggesting that diet-related choices could significantly affect the risk of cancer. The present analysis examined the relation between dietary patterns and lifestyle behaviors, using, for the first time, a quantitative synthesis of the literature. The results show that unhealthy dietary patterns (including red and processed meat, sugary drinks and salty snacks, starchy foods, and refined carbohydrates) are associated with a higher BMI, while healthy dietary patterns are related to healthier lifestyle factors and background (including education, physical activity, and smoking habit).

Mechanisms linking dietary patterns and risk of cancer may rely on 2 main aspects: (1) the specific content of the diet, and (2) the association between dietary pattern and altered energy imbalance, body weight, and consequent homeostasis alterations. Diets rich in fruit, vegetables, legumes, and whole grains may have beneficial effects stemming from the balanced ratio of fatty acids, the high fiber content, and the substantial amounts of antioxidant compounds, which inhibit multiple cancer-related

Table 5 **Association of lifestyle factors at baseline/controls between the highest vs the lowest category (reference) of exposure to healthy and unhealthy dietary patterns, in total and by study design, sex, and geographical area**

Lifestyle factor	Healthy patterns		Unhealthy patterns	
	No. of datasets	OR (95%CI)[a]	No. of datasets	OR (95%CI)[a]
High physical activity				
Total	25	1.53 (1.22–1.91)	34	0.9 (0.78–1.04)
Study design				
Case–control	13	1.53 (1.18–1.98)	20	0.85 (0.72–1.01)
Prospective	12	1.53 (1.12–2.10)	14	0.97 (0.79–1.20)
Sex				
Male	9	1.6 (1.36–1.88)	12	0.92 (0.66–1.28)
Female	10	1.69 (1.10–2.58)	16	0.86 (0.71–1.04)
Geographical area				
North America	7	1.76 (1.05–2.94)	6	0.69 (0.43–1,11)
Europe	4	1.15 (0.68–1.96)	9	1.06 (0.85–1.32)
Asia	10	1.56 (1.12–2.17)	12	0.92 (0.74–1.15)
High education level				
Total	21	1.39 (1.06–1.82)	28	1.05 (0.85–1.31)
Study design				
Case–control	7	1.3 (0.97–1.75)	13	1.35 (0.74–2.47)
Prospective	14	1.45 (1.05–2.01)	15	0.86 (0.66–1.14)
Sex				
Male	6	1.48 (1.02–2.17)	8	0.61 (0.44–0.84)
Female	10	1.26 (0.80–1.97)	11	1.1 (0.85–1.43)
Geographical area				
North America	9	1.36 (0.83–2.22)	9	0.85 (0.53–1.37)
Europe	1	1.28 (1.24–1.32)	3	1.03 (0.68–1.56)
Asia	8	1.64 (1.27–2.12)	9	1.18 (0.74–1.88)
Smoking (current)				
Total	19	0.48 (0.36–0.65)	53	1.35 (1.07–1.69)
Study design				
Case–control	19	0.49 (0.34–0.70)	31	1.29 (1.00–1.67)
Prospective	11	0.42 (0.27–0.65)	22	1.4 (0.99–1.98)
Sex				
Male	15	0.59 (0.39–0.89)	15	1.46 (1.12–1.90)
Female	13	0.4 (0.24–0.68)	22	1.2 (0.82–1.77)
Geographical area				
North America	5	0.73 (0.56–0.95)	12	1.4 (0.79–2.49)
Europe	14	0.54 (0.36–0.79)	8	1.39 (0.77–2.51)
Asia	10	0.47 (0.28–0.77)	17	1.21 (0.82–1.77)

Abbreviation: OR, odds ratio.
[a]All analyses showed significant heterogeneity.

biological pathways, including carcinogen bioactivation, cell signaling, cell cycle regulation, angiogenesis, and inflammation.[103] With regard to colon cancer in particular, a dietary pattern rich in fiber may improve fecal bulking, increase satiety, viscosity, and short-chain fatty acid production, enhance fermentation of metabolites, increase stool bulk (thus reducing transit time and contact of carcinogens with the colonic mucosa), and act as a probiotic.[104]

In contrast, unhealthy dietary patterns are characterized by, but not limited to, red and processed meat, sugary drinks and salty snacks, starchy foods, and refined carbohydrates. Red and, especially, processed meats are rich in salt, *N*-nitroso compounds, heterocyclic amines, heme iron, and, following cooking at high temperature, polycyclic aromatic hydrocarbons, which have been considered responsible for the carcinogenic effects of meat consumption.[105] Alcohol-related dietary patterns are characterized by a high intake of spirits and fortified wines, demonstrated to increase the risk of cancer.[106] High alcohol consumption may lead to higher estrogen concentrations resulting from decreased metabolic clearance, thereby potentially increasing the risk of breast cancer.[107] It can also increase the permeability of membranes to carcinogens and inhibit the detoxification of carcinogens.[107] By contrast, diets containing antioxidant vitamins could have protective effects via anti-inflammatory action on estrogen metabolism and reduction of cell proliferation.[108] Finally, a diet rich in antioxidants may counter chronic inflammation caused by unhealthy lifestyle factors (ie, smoking), which may explain the association between healthy dietary patterns and decreased risk of lung cancer, especially in smokers.[109]

In this study, there was also an indication of a possible relation between adherence to healthy or unhealthy dietary patterns and risk of esophageal, laryngeal, gastric, ovarian, and pancreatic cancers, although evidence was limited to case–control studies. Moreover, despite no evidence of a benefit of healthy dietary patterns against prostate cancer risk, a significantly increased risk associated with unhealthy dietary patterns was found when examining case–control studies. Overall, the mechanisms responsible for an association between dietary patterns and the types of cancer mentioned above in this paragraph may be similar to those previously reported, including the potential direct effects of certain foods on specific types of cancer (eg, the effect of salted foods on upper aerodigestive tract cancers)[110] and the effects of hormonal alterations related to age (ie, menopause) or weight status.[111] For prostate cancer risk specifically, it is noteworthy that the effects of diet on cancer risk are more likely to be observed with advanced rather than total prostate cancers.[111] However, additional prospective studies are needed to verify whether the associations in case–control studies found in this meta-analysis can be confirmed.

Besides the qualitative aspects of dietary patterns, it is hypothesized that unhealthy dietary patterns may lead to increased body weight, leading to increased risk of obesity-related cancer. In support of such hypothesis, the results showed that unhealthy dietary patterns were associated with higher BMI in a summary meta-analysis of study populations, in line with the hypothesis that individuals who adhere to an unhealthy dietary pattern may have a higher cancer risk through the mediating effect of increased body weight and obesity. A diet rich in saturated fats and refined sugars may lead to increased body fat accumulation and impaired glucose and insulin regulation, which in turn alters physiological hormonal homeostasis and ultimately increases cancer risk.[112] Indeed, refined sugars may affect both the glycemic index (which indicates the absorption of carbohydrates and, hence, measures insulin demand) and the glycemic load (which measures both the quality and the quantity of carbohydrate consumed), which have been related to cancer risk because of the potential role of insulin and insulin-like growth factor in cancer promotion.[113] Adipocytes and visceral adipose tissue produce leptin and adiponectin, 2 hormones with the capacity to regulate immune function, inflammatory cytokines, angiogenesis, insulin resistance, and other biological processes that have been associated with some cancers.[7,114] Adipose tissue is also responsible for a low-grade, subclinical state of chronic inflammation, characterized by increased circulating inflammatory cytokines (interleukin 1β, interleukin 6, tumor necrosis factor-α, monocyte chemoattractant protein 1, and C-reactive protein, all of which, in turn, are associated with intracellular transcription factors involved in cell proliferation, apoptosis, inflammation, metastasis, and angiogenesis.[115] Other mechanisms potentially linking increased BMI to cancer risk are related to vascular perturbations (ie, mediated by circulating levels of vascular endothelial growth factor) and epithelial-to-mesenchymal transition.[115]

In contrast to unhealthy dietary patterns, healthy diets were not associated with weight status, suggesting that other factors may play a role in their potential contribution to the development of cancer. Healthy dietary patterns have been associated with higher odds of being more physically active and more highly educated and lower odds of being a smoker. Leisure-time physical activity is associated with an overall lower risk for many types of cancer.[116] Smoking status is a known risk factor for several cancers, including lung and colorectal, which were associated with healthy dietary patterns.[117] It can be hypothesized that more-educated individuals are more conscious about their health, may be more aware of nutrition-related health issues, and, ultimately, may adopt an overall healthier lifestyle, including not only healthy food choices but also involvement in physical activities and abstinence from smoking.

The main advantage of analyzing *a posteriori*–derived dietary patterns is that dietary habits are evaluated globally.[118] Nevertheless, the methods used involve important limitations. Factor analysis typically explains only a small proportion of the variation in diets, and the dietary pattern identified may not fully capture an ideal healthful or unhealthful diet. This is probably less of an issue with healthy dietary patterns because the main characteristics of a healthy diet are more universally recognized and more easily reproduced and compared across a population. In contrast, unhealthy dietary patterns may differ widely from one other, and individual components may have a more harmful effect on specific cancer sites (eg, an unhealthy dietary pattern characterized by processed meat may strongly affect colon cancer risk, or a diet rich in salted foods may be associated with a higher risk of gastric cancer but not other cancers). An attempt was made to test whether each dietary pattern characterized by a main component was associated with increased cancer risk. Subgroup analyses of these patterns resulted in significant findings, despite being affected by substantial heterogeneity. However, none of the patterns, with the exception of the alcohol-related dietary pattern, showed significant results when analysis was limited to prospective studies only. The limited number of studies included in each subgroup analysis besides the animal/meat and Western dietary patterns precluded more

definitive results. When individual cancer sites were analyzed, animal dietary patterns were significantly associated with increased colorectal cancer risk. The current scientific literature shows that heavy alcohol drinking is among the main causes of increased cancer risk, accounting for up to a 5% increased risk of digestive tract and breast cancers.[119] Increasing evidence suggests that red and processed meat may directly increase the risk of colorectal cancer.[120]

Regardless of the type of unhealthy dietary pattern adopted within a population, dietary pattern is strongly related to cultural habits and country-specific factors (eg, food availability). Thus, geographical area as a potential source of heterogeneity within the same group of dietary patterns was also assessed. Neither healthy nor unhealthy dietary patterns were unequivocally associated with cancer risk. In fact, the former showed a stronger association with cancer risk in studies conducted in North America and Europe, while the latter showed increased cancer risk only in North American studies, as most of the other evidence was supported only by case–control studies. Possible explanations for the geographical differences may be variation in the amount and proportion of individual unhealthy foods consumed, different food quality between geographical areas, and background characteristics that may interact with dietary habits. Of note, unhealthy dietary patterns were associated with higher BMI and higher cancer risk mainly in studies conducted in North America, which reinforces the hypothesis that BMI may mediate the effect of unhealthy dietary choices. The effect of confounding factors on individual food patterns should be further investigated in future studies, ideally to better characterize the differences between North American and European unhealthy dietary behaviors and to test whether 1 or more discriminant factors exist.

The methodology used to assess *a posteriori*–derived dietary patterns is also affected by other limitations, mainly those related to the arbitrariness of the approach. First, the estimation of dietary patterns depends on the number of items included in the food frequency questionnaires used for data collection.[121] Second, methods to estimate dietary patterns may lack robustness and be poorly reproducible when evaluated in different populations or when based on different numbers of dietary components.[118] Third, methodological homogeneity across studies with potential differences in dietary patterns was assumed. Similar subjective names for dietary patterns (eg, Western, animal-based, fat-rich, etc) may have included different components (ie, red meat vs processed meat vs fatty foods), and each component could have been weighted differently in a pattern or, by contrast, could have been represented in more than 1 pattern identified, thus limiting the comparability of the results. However, besides the effort to group dietary patterns into qualitative groups on the basis of both arbitrary judgment and the nomenclature used by original authors of studies included, a significant level of heterogeneity across studies was found (especially among case–control studies) and impossible to deal with, making generalizability of results rather weak. Other limitations are related to the general study design of some of the studies included in the meta-analyses and comprise recall bias, selection bias, sample size, length of follow-up, and region studied (developed vs nondeveloped countries). Finally, the number of studies and datasets included for extraction, calculation, or imputation of data on food group consumption, energy intake, and lifestyle factors was often too limited to provide representative estimates.

CONCLUSION

The findings obtained from this study may have important public health implications. The evidence presented here suggests that a healthy diet has potential to modulate cancer risk, especially the risk of colon, breast, and lung cancers. In contrast, unhealthy dietary patterns showed a trend of association with increased cancer risk. Healthy dietary patterns have been found to be part of overall healthier lifestyle choices, which may explain in part their association with decreased cancer risk. Unhealthy dietary patterns were associated with a higher BMI, suggesting the potential mediating effect of obesity on cancer risk. Further investigation is needed to confirm the results of this meta-analysis, especially as related to those cancer sites for which evidence was based mainly on case–control studies. Moreover, further study is required to understand the geographical and interindividual variations in diet and lifestyle exposures and their relative contributions to cancer risk.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **Main characteristics of studies included in the meta-analysis**

Table S2 **Number of studies, cases, and controls/exposed individuals included in the meta-analyses**

Table S3 **Dietary patterns identified in the included studies**

Table S4 **Subgroup analyses by specific type of unhealthy dietary pattern identified and risk of cancer**

Table S5 **Subgroup analyses by geographical area for healthy and unhealthy dietary patterns identified and risk of cancer**

Figure S1 **Funnel plots of studies evaluating the association between healthy dietary patterns and cancer risk**

Figure S2 **Forest plot of studies evaluating pooled risk ratios (RRs) of colorectal cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S3 **Forest plot of studies evaluating pooled risk ratios (RRs) of lung cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S4 **Forest plot of studies evaluating pooled risk ratios (RRs) of breast cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S5 **Forest plot of studies evaluating pooled risk ratios (RRs) of gastric cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S6 **Forest plot of studies evaluating pooled risk ratios (RRs) of ovarian cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S7 **Forest plot of studies evaluating pooled risk ratios (RRs) of ovarian cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S8 **Forest plot of studies evaluating pooled risk ratios (RRs) of oral/pharyngeal and laryngeal cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S9 **Forest plot of studies evaluating pooled risk ratios (RRs) of esophageal cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S10 **Forest plot of studies evaluating pooled risk ratios (RRs) of endometrial cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S11 **Forest plot of studies evaluating pooled risk ratios (RRs) of prostate cancer by adoption of healthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S12 **Funnel plots of studies evaluating the association between unhealthy dietary patterns and cancer risk**

Figure S13 **Forest plot of studies evaluating pooled risk ratios (RRs) of colorectal cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figures S14 **Forest plot of studies evaluating pooled risk ratios (RRs) of ovarian cancer by adoption of unhealthy dietary patterns**. Squares represent

risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figures S15 **Forest plot of studies evaluating pooled risk ratios (RRs) of gastric cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S16 **Forest plot of studies evaluating pooled risk ratios (RRs) of pancreatic cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S17 **Forest plot of studies evaluating pooled risk ratios (RRs) of lung cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S18 **Forest plot of studies evaluating pooled risk ratios (RRs) of prostate cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S19 **Forest plot of studies evaluating pooled risk ratios (RRs) of gastric cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S20 **Forest plot of studies evaluating pooled risk ratios (RRs) of endometrial cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

Figure S21 **Forest plot of studies evaluating pooled risk ratios (RRs) of esophageal cancer by adoption of unhealthy dietary patterns**. Squares represent risk estimates of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95%CIs of risk assessed for the highest vs the lowest category of adherence to the dietary pattern

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