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Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; DWAS, diet-wide association study; EPIC, European Prospective Investigation into Cancer and Nutrition; FDR, false discovery rate; HR, hazard ratio; MR, Mendelian randomization; NLCS, Netherlands Cohort Study; WCRF, World Cancer Research Fund.

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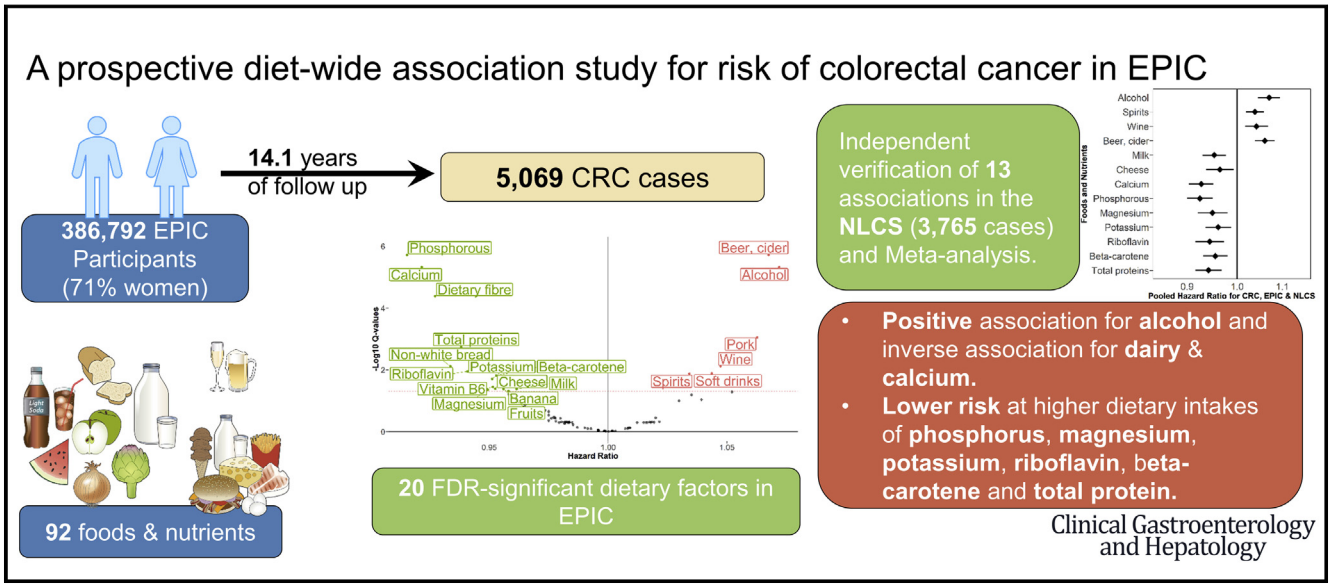

BACKGROUND & AIMS: **Evidence regarding the association of dietary exposures with colorectal cancer (CRC) risk is not consistent with a few exceptions. Therefore, we conducted a diet-wide association study (DWAS) in the European Prospective Investigation into Cancer and Nutrition (EPIC) to evaluate the associations between several dietary exposures with CRC risk.**

METHODS: **The association of 92 food and nutrient intakes with CRC risk was assessed in 386,792 participants, 5069 of whom developed incident CRC. Correction for multiple comparisons was performed using the false discovery rate, and emerging associations were examined in the Netherlands Cohort Study (NLCS). Multiplicative gene-nutrient interactions were also tested in EPIC based on known CRC-associated loci.**

RESULTS: **In EPIC, alcohol, liquor/spirits, wine, beer/cider, soft drinks, and pork were positively associated with CRC, whereas milk, cheese, calcium, phosphorus, magnesium, potassium, riboflavin, vitamin B6, beta carotene, fruit, fiber, nonwhite bread, banana, and total protein intakes were inversely associated. Of these 20 associations, 13 were replicated in the NLCS, for which a meta-analysis was performed, namely alcohol (summary hazard ratio [HR] per 1-SD increment in intake: 1.07; 95% confidence interval [CI], 1.04–1.09), liquor/spirits (HR per 1-SD increment in intake, 1.04; 95% CI, 1.02–1.06), wine (HR per 1-SD increment in intake, 1.04; 95% CI, 1.02–1.07), beer/cider (HR per 1-SD increment in intake, 1.06; 95% CI, 1.04–1.08), milk (HR per 1-SD increment in intake, 0.95; 95% CI, 0.93–0.98), cheese (HR per 1-SD increment in intake, 0.96; 95% CI, 0.94–0.99), calcium (HR per 1-SD increment in intake, 0.93; 95% CI, 0.90–0.95), phosphorus (HR per 1-SD increment in intake, 0.92; 95% CI, 0.90–0.95), magnesium (HR per 1-SD increment in intake, 0.95; 95% CI, 0.92–0.98), potassium (HR per 1-SD increment in intake, 0.96; 95% CI, 0.94–0.99), riboflavin (HR per 1-SD increment in intake, 0.94; 95% CI, 0.92–0.97), beta carotene (HR per 1-SD increment in intake, 0.96; 95% CI, 0.93–0.98), and total protein (HR per 1-SD increment in intake, 0.94; 95% CI, 0.92–0.97). None of the gene-nutrient interactions were significant after adjustment for multiple comparisons.**

CONCLUSIONS: **Our findings confirm a positive association for alcohol and an inverse association for dairy products and calcium with CRC risk, and also suggest a lower risk at higher dietary intakes of phosphorus, magnesium, potassium, riboflavin, beta carotene, and total protein.**

Keywords: nutrition; cohort study; colorectal cancer; epidemiology.

Colorectal cancer (CRC) is the third most common type of cancer worldwide with over 1.8 million new cases and over 800,000 deaths in 2018.[1] The incidence rates are higher in high income countries, but there has been a recent large increase in the rates in low- and middle-income countries potentially due to the "Westernization" of these societies.[1] Several aspects of the Western lifestyle such as obesity and lack of physical activity are well-established risk factors of CRC,[2,3] but evidence regarding diet, and in particular the association of specific foods and nutrients with CRC, is not consistent, with a few exceptions.[4] The World Cancer Research Fund (WCRF) Third Expert Report identified strong evidence that consuming processed meat, red meat, and alcohol increases risk of CRC, whereas consumption of whole grains, foods containing dietary fiber, and dairy products lowers CRC risk.[4] Associations for other foods and nutrients and CRC risk exist but are inconsistent and currently provide limited evidence according to WCRF.[4]

The aim of this study was to systematically examine the associations between a wide set of dietary factors and risk of CRC in the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Netherlands Cohort Study (NLCS), by conducting a diet-wide association study (DWAS).[5] The DWAS takes an analogous strategy to that of a genome-wide association study by separately estimating associations for each food and nutrient, using adjustments for multiple comparisons, and replicating promising associations in an independent study.

What You Need to Know

Background

Obesity and lack of physical activity are well-established risk factors of colorectal cancer (CRC) risk but evidence regarding the association of specific foods and nutrients with CRC is not consistent, with a few exceptions.

Findings

In an analysis of 92 foods and nutrients from over 350,000 participants in the European Prospective Investigation into Cancer and Nutrition cohort and replication analyses in the Netherlands Cohort Study, we demonstrate positive associations for alcohol and inverse associations for dairy and calcium intake. Additionally, lower CRC risk is observed at higher dietary intakes of phosphorus, magnesium, potassium, riboflavin, beta carotene, and total protein.

Implications for patient care

Consumption of alcohol increases the risk of CRC and should be discouraged, while dairy and calcium intake seems to reduce the risk of CRC and should be encouraged along with other nutritious dietary choices.

Materials and Methods

Study Populations

EPIC is a large European multicenter prospective cohort that consists of 521,324 participants, mostly between 35 and 70 years of age, recruited between 1992 and 2000 from 23 centers across 10 European countries.[6] A total of 386,792 participants (71% women) were included in the present analysis after pertinent exclusions (Supplementary Methods).

NLCS is a prospective cohort study of 120,852 participants, between 55 and 69 years of age and recruited in 1986 from 204 computerized population registries across the Netherlands that uses a case-cohort approach.[7] Of the 5000 subcohort participants, 3893 were included in the current analysis after pertinent exclusions (Supplementary Methods).

Assessment of Dietary Factors

In EPIC, consumption of foods over the last 12 months was assessed at baseline using validated country-specific food questionnaires.[6] In total, 92 dietary factors (63 foods and 29 nutrients) were included in the current analysis.

In the NLCS, information on dietary intake over the preceding 12 months was assessed at baseline using a semi-quantitative 150-item food frequency questionnaire, which has been validated and tested for reproducibility (Supplementary Methods).[8]

Identification of CRC Cases

In EPIC and NLCS, incident CRC cases were identified by record linkage with population-based cancer registries or a combination of registries, insurance records, and active follow up of the study participants or their relatives. More details are provided in the Supplementary Methods.

Statistical Analyses

In EPIC, separate Cox proportional hazards regression models were used to investigate the associations between each of the dietary factors with CRC risk. In the NLCS, given the case-cohort design, Prentice-weighted Cox proportional hazards regression models with robust SE estimation were implemented.[9] All of the models were adjusted for total energy intake, smoking, body mass index, physical activity, diabetes history, level of education, and family history of CRC (in the NLCS only) and further stratified by sex, age, and in EPIC also by center.

To account for multiple comparisons, the false discovery rate (FDR)–adjusted *P* values (or *q* values) were estimated for each association analysed.[10] The dietary factors with an FDR <0.05 were subsequently selected for replication in the NLCS, and fixed-effects meta-analysis was performed to combine the results from the 2 cohorts when heterogeneity was low or moderate (*P* value for heterogeneity > .1 and/or $I^2 \leq 50\%$). To further investigate the robustness of the associations that were replicated in the NLCS, a mutual adjustment model was used. Presence of nonlinear associations was investigated using restricted cubic spline models. More details on the statistical analyses methods are provided in the Supplementary Methods.

Results

Study Characteristics

After a mean follow-up of 14.1 ± 3.9 years, a total of 5069 (56.8% in women) incident malignant CRC cases were identified among the 386,792 included EPIC participants, of which 3143 were identified as colon (1495 proximal, 1435 distal, 213 unspecified) and 1715 as rectal cancers. In the NLCS, 3765 cases (42.8% female) with incident and microscopically confirmed CRC were included in the present analysis, of which 2612 were colon (1348 proximal, 1187 distal) and 801 were rectal cancers.

The main baseline characteristics of the study participants are shown in Supplementary Table 1. In EPIC, approximately 30% of the participants were men, and 47% were overweight or obese. About 50% of the participants were never smokers, and 47% were physically active. More than half of the NLCS subcohort participants were male (54%), 47% were overweight or obese, one-third (33%) were never smokers, and 48% spent more than 60 min/d on nonoccupational physical activities.

DWAS in EPIC

Of the 92 dietary factors that were examined in EPIC, 20 were associated with CRC risk (FDR <0.05) (Figure 1; Supplementary Table 2). Higher intakes of alcohol, liquor/spirits, wine, beer/cider, soft drinks, and pork were positively associated with CRC, whereas higher milk, cheese, calcium, phosphorus, magnesium, potassium, riboflavin, vitamin B6, beta carotene, fruit, fiber, nonwhite bread, banana, and total protein intakes were associated with a lower CRC risk.

After conducting the analysis by tumor subsite, evidence of heterogeneity between colon and rectal cancer was observed for intakes of magnesium, potassium, vitamin B6, and banana, with associations being inverse for colon cancer and null for rectal cancer (Supplementary Table 3). Regarding proximal vs distal colon subsites, only total alcohol and wine had heterogeneous results, whereby the associations were positive only for distal colon cancer (Supplementary Table 4). Additionally, heterogeneous associations were observed by sex, for total alcohol and spirits, magnesium, fiber, and

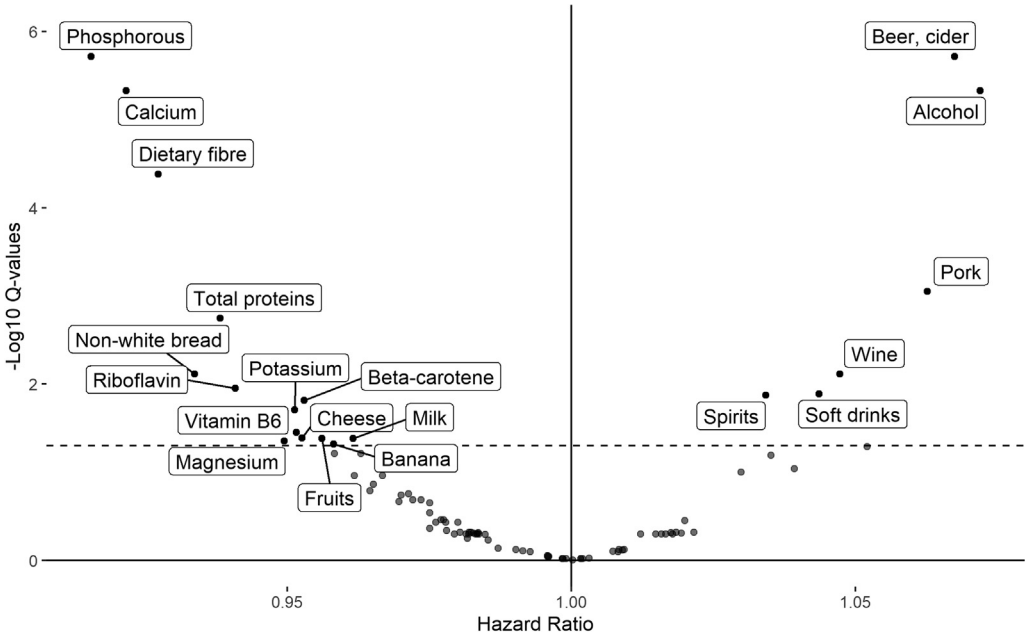

Figure 1. Volcano plot showing results from the DWAS regarding the association between 92 dietary factors and CRC risk in EPIC. The y-axis shows the FDR adjusted *P* values in –log10 scale from the Cox proportional hazards models for each dietary factor. The x-axis shows the estimated HR for each dietary factor per 1-SD increase in daily consumption. The dashed horizontal line represents the level of significance corresponding to FDR of 5%.

nonwhite bread, in which the associations were only observed in men (Supplementary Table 5). When we investigated the association of red and processed meat with CRC risk by follow-up duration, a trend toward smaller HRs was observed as follow-up increased (Supplementary Figure 1). There was some evidence for nonlinearity ($P = .028$) in the association of alcohol intake and CRC risk (Supplementary Figure 2).

Replication Analysis in the NLCS

Of the 20 associations with an FDR <0.05 in EPIC, 4 associations reached nominal statistical significance ($P < .05$) in the NLCS cohort in the analysis for CRC (Figure 2; Supplementary Table 6), namely alcohol and liquor/spirits (positively) and milk and calcium intake (inversely). An additional 4 associations, namely phosphorus, magnesium, riboflavin, and total protein, had a borderline inverse association in the NLCS, and the point estimates were almost identical to the ones calculated in EPIC.

In a separate analysis by tumor subsite in the NLCS, we found that most associations were consistent across the different subsites with heterogeneous associations only evident for phosphorus, potassium, vitamin B6, beta carotene, and total protein in the analysis for colon vs rectal cancer (Supplementary Tables 7 and 8). Little heterogeneity was observed by sex for CRC risk (Supplementary Table 9).

Meta-analysis of EPIC and NLCS

The associations for most of the 20 dietary variables with CRC risk were homogeneous between EPIC and NLCS, except for soft drinks, vitamin B6, fruit, fiber, nonwhite bread, banana, and pork (P value for heterogeneity $< .1$ and/or $I^2 > 50\%$), in which the associations were null in the NLCS and therefore a meta-analysis was not performed. The remaining 13 associations yielded a nominally significant summary finding: alcohol (HR per 1-SD increment in intake per day, 1.07; 95% CI, 1.04–1.09), liquor/spirits (HR per 1-SD increment in intake per day, 1.04; 95% CI, 1.02–1.06), wine (HR per 1-SD increment in intake per day, 1.04; 95% CI, 1.02–1.07), beer/cider (HR per 1-SD increment in intake per day, 1.06; 95% CI, 1.04–1.08), milk (HR per 1-SD increment in intake per day, 0.95; 95% CI, 0.93–0.98), cheese (HR per 1-SD increment in intake per day, 0.96; 95% CI, 0.94–0.99), calcium (HR per 1-SD increment in intake per day, 0.93; 95% CI, 0.90–0.95), phosphorus (HR per 1-SD increment in intake per day, 0.92; 95% CI, 0.90–0.95), magnesium (HR per 1-SD increment in intake per day, 0.95; 95% CI, 0.92–0.98), potassium (HR per 1-SD increment in intake per day, 0.96; 95% CI, 0.94–0.99), riboflavin (HR per 1-SD increment in intake per day, 0.94; 95% CI, 0.92–0.97), beta carotene (HR per 1-SD increment in intake per day, 0.96; 95% CI, 0.93–0.98), and total protein (HR per 1-SD increment in intake per day, 0.94; 95% CI, 0.92–0.97) (Figure 2; Supplementary Table 6).

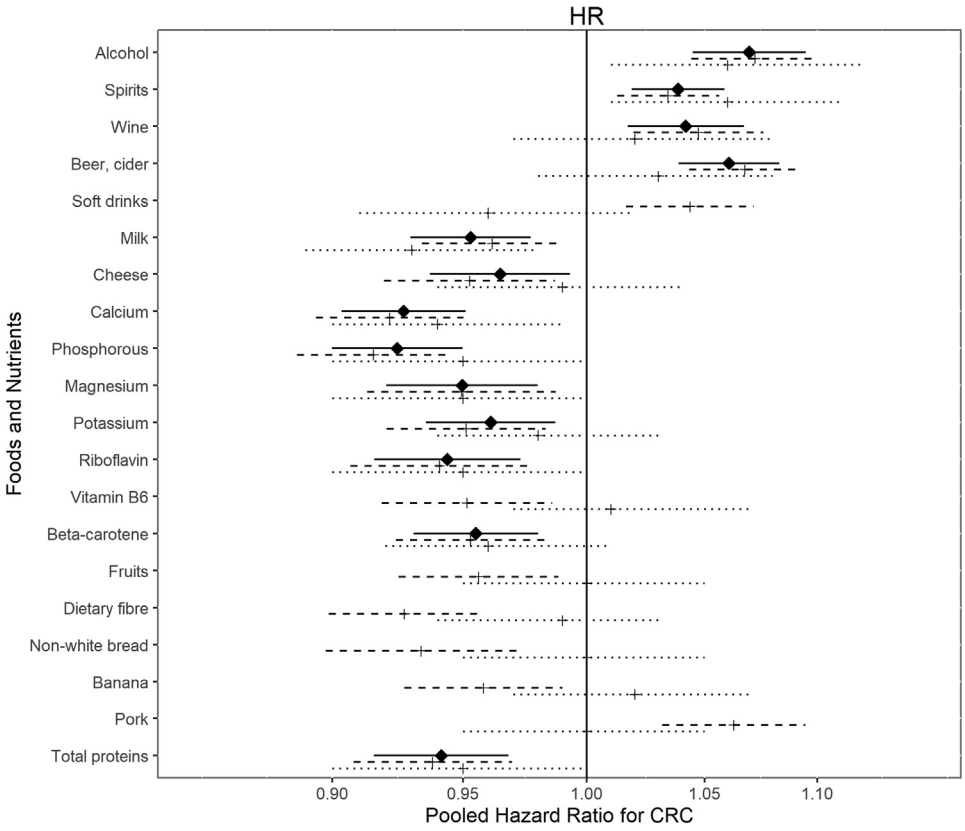

Figure 2. Forest plot showing the hazard ratios and 95% confidence intervals for the 20 FDR significant associations (FDR <5%), in EPIC (—) and NLCS (• • •), as well as the results from a meta-analysis (MA) (—). The x-axis shows the estimated HR for each dietary factor for 1-SD increase in daily consumption. The diamond and the solid line represent the pooled HR and 95% CI of the MA. MA was not performed when heterogeneity was high.

Pairwise Correlations and Mutual-Adjustment Analysis

Most of the pair-wise correlation coefficients for the 20 FDR-significant foods/nutrients in EPIC were weak and ranged from −0.25 to 0.79 (Figure 3).

When alcohol, milk, cheese, calcium, phosphorus, magnesium, potassium, riboflavin, beta carotene, and total protein were included in a single multivariable-adjusted model in EPIC, only alcohol remained significantly associated with CRC risk (HR, 1.05; 95% CI, 1.03–1.11) (Supplementary Table 10).

Gene-Nutrient Interaction Analysis

Of the 73 × 20 gene-nutrient multiplicative interactions that were tested, using the Bonferroni-adjusted P value threshold of 3.4×10^{-5}, no interaction remained significant (Supplementary Table 11).

Discussion

We used the DWAS approach to systematically evaluate the association between dietary intakes of 92 foods

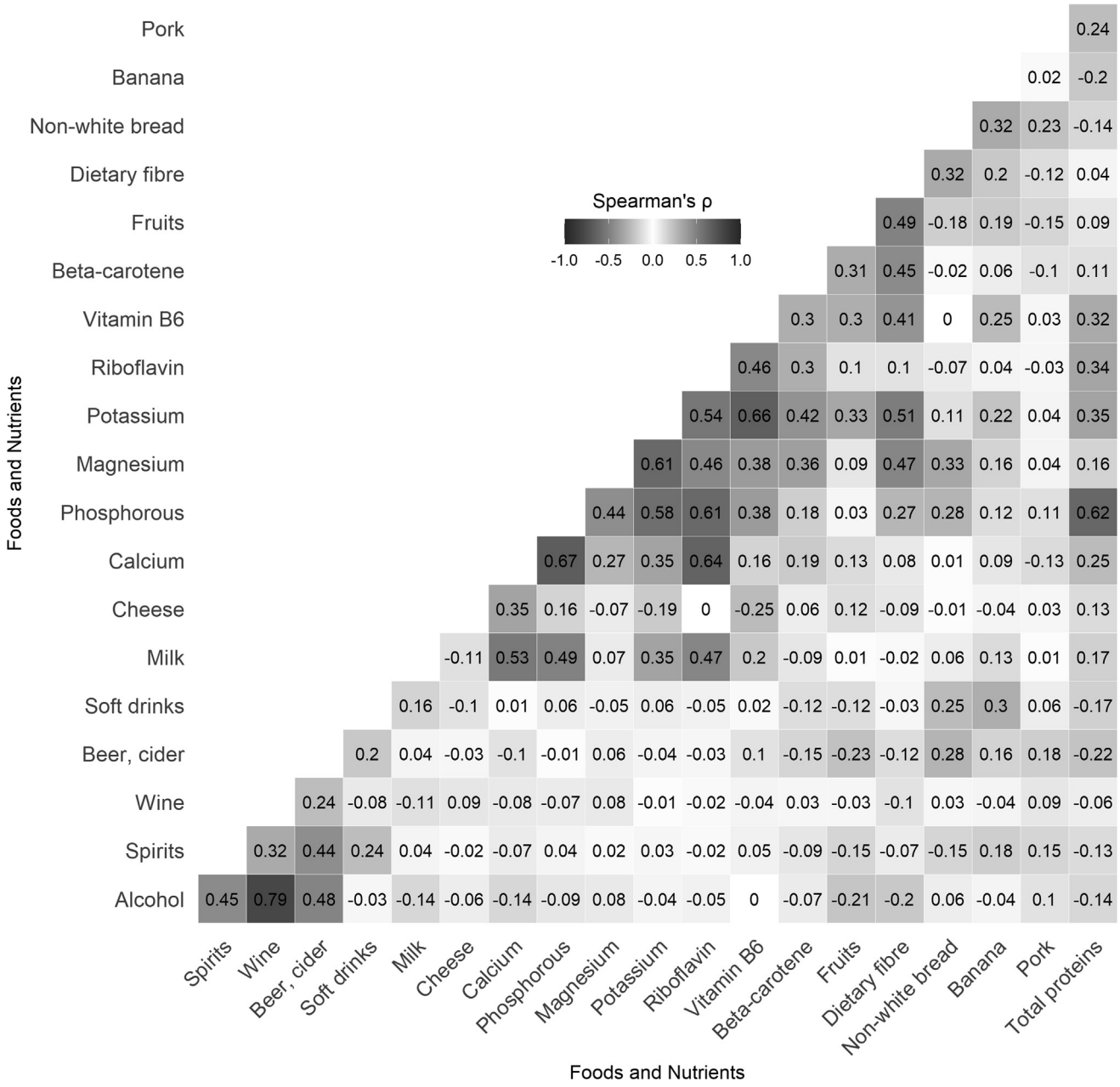

Figure 3. Pairwise partial correlation coefficients (Spearman's ρ) of the 20 FDR-significant foods/nutrients in EPIC, adjusting for age, sex, and center.

and nutrients and risk of CRC in EPIC and NLCS. We confirmed well-described associations in the literature for alcoholic beverages (positive) and milk and calcium (inverse) with risk of CRC. In addition, our analysis showed that higher intakes of phosphorus, magnesium, potassium, riboflavin, beta carotene, and total protein were associated with a lower risk of CRC.

Alcohol consumption was positively associated with risk of CRC in EPIC and the NLCS, and this association was not different between colon and rectal cancer subsites or by type of alcoholic beverage. In agreement, the WCRF Third Expert Report has graded the quality of this evidence as strong.[4] Persons with higher total alcohol consumption had a higher risk of CRC (summary HR per SD increment in intake/day, 1.07; 95% CI, 1.04–1.09), colon, and rectal cancer in the meta-analysis of EPIC and the NLCS. When we evaluated this association by proximal vs. distal colon cancer and by sex, we found heterogeneous associations in EPIC, with associations only present for distal colon cancer and in men, but these findings were not confirmed in the NLCS. The majority of the literature agrees that the positive association of alcohol consumption with CRC risk is consistent by anatomical subsite and sex.[11,12] Acetaldehyde, as a metabolite of ethanol oxidation, can be carcinogenic in colonocytes.[13] Mendelian randomization (MR) studies have failed to demonstrate an association between genetically proxied alcohol consumption and CRC risk, but this analysis was underpowered to detect relatively small effects.[14]

Our study also confirmed the inverse association between intake of dairy products and calcium with risk of CRC, where individuals with higher calcium consumption had a 7% lower risk of CRC per 334.5 mg increment in intake/day. One of the most prominent mechanisms by which calcium is thought to act to reduce CRC risk is by its ability to bind unconjugated bile acids and free fatty acids, diminishing their potential toxic effects on the colorectum.[15] Heterogeneity by anatomical subsite or sex was not observed, in agreement with the WCRF meta-analysis and a more recent publication in the Nurses' Health Study.[4,11] Dairy products are also a rich source of phosphorus, which was also inversely associated with CRC risk in our study but has been infrequently studied in other publications. A previous analysis of nutrient patterns in EPIC identified a pattern characterized by total protein, riboflavin, phosphorus and calcium that was associated with a 4% decreased CRC risk.[16] All these nutrients were analyzed independently in our analysis and yielded inverse associations in EPIC that were robust after correcting for multiple testing and were replicated in the NLCS. Since several of these nutrients share common sources of intake, a correlation of approximately 0.50–0.70 was observed in EPIC, which makes it challenging to distinguish their independent effects.[17] Evidence from MR studies suggests that genetically proxied milk consumption is associated with a reduced CRC risk but failed to demonstrate an association for genetically proxied calcium or phosphorus concentrations.[18,19] Additionally, although previous randomized controlled trials have showed null associations for calcium supplementation in relation to CRC risk, a 13% decreased risk of colorectal adenoma recurrence has been reported in a meta-analysis of 4 randomized controlled trials, with daily doses of calcium ranging from 1200 to 2000 mg.[20]

Many studies have investigated the association between red meat or processed meat consumption and risk of CRC. A dose-response meta-analysis by the WCRF third Expert Report concluded that there is strong evidence that consuming red meat (including beef, pork, lamb, and goat from domesticated animals) or processed meat (meat preserved by smoking, curing, salting, or addition of chemical preservatives) increases the risk of CRC by 12% per 100-g/d increment for red meat and 16% per 50-g/d for processed meat.[4] A combination of mechanisms may contribute to the higher risk of colorectal tumorigenesis among individuals consuming larger amounts of red or processed meat. Cooking meat at high temperatures may lead to the formation of heterocyclic amines and polycyclic aromatic hydrocarbons, which have been associated with colorectal carcinogenesis in experimental studies.[21] Red meat also contains haem iron at high levels that may stimulate the endogenous formation of carcinogenic N-nitroso compounds, which promote colorectal tumorigenesis.[22] Additionally, processed meat can be an exogenous source of N-nitroso compounds. Although accumulated evidence supports that higher intakes of red or processed meat are associated with higher risk of CRC, these findings were not replicated in our analysis in EPIC (HR per 36.2 g of red meat intake daily, 1.02; 95% CI, 0.98–1.05; HR per 31.5 g of processed meat intake daily, 1.04; 95% CI, 1.00–1.08). An earlier report from EPIC in 2005, with a mean follow-up of 4.8 years and 1329 incident CRC cases, observed a positive association between red and processed meat consumption with CRC risk.[23] A potential reason for this discrepancy is that EPIC, as most other cohorts, has assessed meat consumption only during recruitment in the 1990s; thus, the current analysis assumes that consumption has stayed stable over 2 decades. However, a notable decrease in bovine meat consumption between 2000 and 2013 has been noticed in Europe, which was accompanied by an analogous increase in cheese, fish, dairy, and poultry consumption. In the current paper, we observed a trend toward smaller HRs in the association of red and processed meat with CRC risk as follow-up increased. A recent time-varying exposure analysis in the Nurses' Health Study and the Health Professionals Follow-up Study showed that a decrease in red meat consumption and simultaneous increases in healthy alternative food choices over time were associated with a lower risk of all-cause mortality.[24]

The current DWAS study observed an inverse association of magnesium intake with risk of CRC, which agreed with the results of a recent meta-analysis of 7

observational studies.[25] One purported mechanism by which magnesium may be implicated in lower CRC risk is by its potential to inhibit *c-Myc* oncogene expression in colon cancer cells.[26] Furthermore, magnesium has been shown to improve insulin sensitivity and lower plasma insulin concentrations, which may have an impact on CRC development.[27] No association of genetically proxied circulating concentrations of magnesium was found in a recent MR study.[19]

We also observed an inverse association between intake of beta carotene and risk of CRC, but few other studies have investigated this association.[28] Our findings agree with a previous report from EPIC in 2014.[28] However, a cohort analysis in the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) trial, comprising 26,951 middle-aged male smokers, showed no association between dietary beta carotene and risk of CRC.[29] No evidence of association between genetically proxied circulating concentrations of beta carotene and CRC have been reported in MR studies.[19]

Vitamins B2 and B6 are among the micronutrients that play a pivotal role in one-carbon metabolism, which has been related to carcinogenesis because of its involvement in the synthesis of purines and pyrimidines for subsequent DNA synthesis and in the synthesis of methionine for DNA methylation.[30] Inverse associations between riboflavin (vitamin B2) and vitamin B6 intake and CRC risk were observed in EPIC, but only the association with riboflavin was replicated in the NLCS. Previous studies on the association between riboflavin intake and CRC risk are scarce.[31] Results from the Women's Health Initiative Observational Study indicated a 25% decreased CRC risk for the highest compared with the lowest quartile of total riboflavin intake but was not statistically significant when only dietary intake of riboflavin was considered.[31] A meta-analysis of 8 studies did not show an association between vitamin B6 intake and CRC risk, but blood levels of its active form, pyridoxal 5-phosphate, were associated with lower CRC risk.[32]

Little is known on the role that potassium may play in relation to CRC risk, and epidemiological evidence thus far is limited.[33] We cannot rule out the possibility that the inverse association observed in our study may mirror the effect of other nutrients, such as vitamin B6 or dietary fiber, which share common dietary sources with potassium.

Strengths of this study include its large size and long follow-up duration and the DWAS approach that involved a comprehensive assessment of foods and nutrients while accounting for multiplicity of tests and replication of findings in an independent cohort. Another strength was the ability to explore associations according to different anatomical subsites as well as by sex. The primary limitation was that the analysis relied on a single dietary assessment at recruitment, not allowing to capture potential changes in dietary habits over time. In addition, intercorrelations between dietary exposures and overall dietary patterns were not accounted for. Intercorrelations between dietary exposures may have led to low precision of the estimates, even though variance inflation factors were relatively small, which might explain that none of the dietary factors remained in the multivariable adjusted model. Furthermore, it is possible that there might be an association for foods or nutrients that were not included in this analysis. Additionally, the data derived from the Dutch food composition table were not checked against the use of ENDB for nutrient calculation, so discrepancies may have occurred, hence it is possible that some of the discrepancies observed between the 2 cohorts for some dietary exposures are in part due to poor reproducibility in measurements. Among the exposures for which heterogeneity was observed between EPIC and NLCS, correlation between the baseline food-frequency questionnaires and 24-hour diet recalls has been reported to be good for fruit, fiber, vitamin B6 and beverage consumption in the NLCS and fairly good for fiber and fruit across most EPIC centers, but for exposures like nonwhite bread or vitamin B6 no information was available.[8,34] Finally, we cannot exclude the possibility of residual confounding, although we adjusted for several potential confounders.

In conclusion, our study confirmed the well-established positive association for alcohol consumption and inverse association for dairy products and calcium intake with CRC risk. The study further suggested that higher intakes of magnesium, phosphorus, potassium, riboflavin, beta carotene, and total protein are associated with lower CRC risk.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.04.028.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Methods

Study populations

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large European multicenter prospective cohort that consists of 521,324 participants, mostly between 35 and 70 years of age, recruited between 1992 and 2000 from 23 centers across 10 European countries, namely Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom.[1] Of the 491,992 participants with complete data on length of follow-up and without a cancer diagnosis before the baseline assessment, 6259 were excluded because they did not complete the lifestyle or dietary questionnaires at baseline, 9573 participants were excluded due to extreme values (top or bottom 1%) of the energy intake-to-energy requirement ratio, and 64,671 were further excluded due to missing values in any of the covariates of interest (diabetes history: 38,972; level of education: 16,931; smoking status: 9678; physical activity: 8824). Data from Greece were also excluded from the current analysis, leaving 386,792 participants (71% women) in the final analytical sample. All participants gave written informed consent while approval for the study was obtained from the ethical review boards of the International Agency for Research on Cancer and all local institutions in the participating countries.

The Netherlands Cohort Study (NLCS) is a prospective cohort study of 120,852 participants, between 55 and 69 years of age and recruited in 1986 from 204 computerized population registries across the Netherlands.[2] The NLCS used a case-cohort approach for efficiency reasons, whereby a subcohort of 5000 participants was selected at random immediately after baseline.[2] Of the 5000 participants, 3893 were included in the current analysis after excluding 226 with prevalent cancer at recruitment, 690 with incomplete or inconsistent dietary data, and 191 participants with missing data on confounders. NLCS was approved by the institutional review boards of the Nederlandse Organisatie voor Toegepast Natuurwetenschappehlijk Onderzoek Quality of Life research institute (Zeist, the Netherlands) and Maastricht University (Maastricht, the Netherlands).

Assessment of dietary factors

In EPIC, consumption of foods over the last 12 months was assessed at baseline using validated country-specific food questionnaires.[1] In most countries and centers the questionnaires were self-administered apart from Ragusa (Italy) and Spain, where interviewers were used. In Malmö (Sweden), a food record was used for cooked meals and a food frequency questionnaire was used for breakfast and foods consumed between the main meals. The EPIC Nutrient Database was used to calculate standardized nutrient intakes.[3] In total, 92 dietary factors (63 foods and 29 nutrients) that were available in at least 8 of the 9 countries were included in the current analysis.

In NLCS, information on dietary intake over the preceding 12 months was assessed at baseline using a semiquantitative 150-item food frequency questionnaire, which has been validated and tested for reproducibility.[4,5] The Dutch food composition table was used for the conversion of the data obtained from the food questionnaires to nutrient intakes.[6]

Identification of colorectal cancer cases

In EPIC, incident colorectal cancer (CRC) cases were identified by record linkage with population-based cancer registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom, or a combination of registries, insurance records, and active follow-up of the study participants or their relatives in France, Germany, and Naples (Italy). The International Classification of Diseases–Tenth Revision and the second revision of the International Classification of Diseases for Oncology were used to determine CRC cases (codes C18-C20).

In NLCS, incident CRC cases were identified by record linkage to the Netherlands Cancer Registry and the Dutch National Pathology Registry record.[7] CRC cases were classified according to International Classification of Diseases for Oncology–Third Edition (codes C18–C20).

In addition to overall CRC, we also examined associations for the following subsites: proximal colon (C18.0–18.5), distal colon (C18.6–18.7), and rectum (C19–C20).

Statistical analyses

In EPIC, separate Cox proportional hazards regression models with age as the time scale were used to investigate the associations between each of the dietary factors with CRC risk. Age at recruitment was set as the age at entry. Age at exit was defined either as the age at cancer diagnosis or the age at death or age at the last follow-up, whichever occurred first. In NLCS, given the case-cohort design, Prentice-weighted Cox proportional hazards regression models with robust standard error estimation were implemented.[8] In both EPIC and NLCS, the proportionality of the hazard ratios was verified by examining the slope of the Schoenfeld residuals, and no violations were found. Intakes of foods and nutrients were adjusted for energy intake using the residual method and standardized prior to modeling.[9] All of the models were adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index (body mass index, $<$20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, $\geq$35 kg/m^2); physical activity (EPIC: Cambridge index [inactive, moderately inactive,

moderately active, active], NLCS: nonoccupational physical activity [≤30, >30–60, >60–90, >90 min/d]); diabetes history (no, yes); level of education (none/primary school, technical/professional school, secondary school, longer education), and family history of CRC (no, yes; in the NLCS only), and reflect associations per 1-SD increase in daily consumption. Additionally, all models were further stratified by sex, age at recruitment (5-year intervals), and in EPIC also by center in order to control for center-specific differences like questionnaire design and follow-up procedures.[10]

To account for multiple comparisons, the false discovery rate (FDR)–adjusted *P* values (or *q* values) were estimated for each association analyzed using the sequential *P*-value approach proposed by Benjamini and Hochberg.[11] The dietary factors with an FDR <0.05 were subsequently selected for replication in the NLCS, and fixed effects meta-analysis was performed to combine the results from the 2 cohorts when heterogeneity was low or moderate (*P* value for heterogeneity > .1 and/or $I^2 \leq 50\%$). To further investigate the robustness of the associations that were replicated in the NLCS, a mutual adjustment model was used. Potential nonlinear associations were investigated using restricted cubic spline models (5 knots). Nonlinearity was tested by using a likelihood ratio test comparing the model containing the cubic spline terms with the model containing only the linear term.

Separate analyses for the FDR-significant dietary exposures were conducted in men and women and also by anatomical subsite of CRC. For the FDR-significant foods or nutrients in EPIC, the pairwise partial correlation coefficients were quantified, adjusting for age, sex and center, using Spearman's rho (ρ). Additionally, the impact of follow-up duration in the association of red and processed meat with CRC risk was investigated. All analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Gene-Nutrient interactions

Potential multiplicative gene-nutrient interactions in EPIC were systematically investigated, between the food components that met the FDR threshold and known CRC-associated genetic variants from genome-wide association study.[12] Of the approximately 100 genome-wide association study–identified single nucleotide polymorphisms associated with CRC, data for 73 single nucleotide polymorphisms or their proxies were available for 3361 participants. Nutrients were included in the interaction analyses as standardized continuous variables and the same covariates as in the diet-wide association study Cox proportional hazards regression models were used. *P* values were adjusted for multiple comparisons using the Bonferroni correction based on the number of independent tests, with a corrected *P* value threshold at 3.4×10^{-5}.

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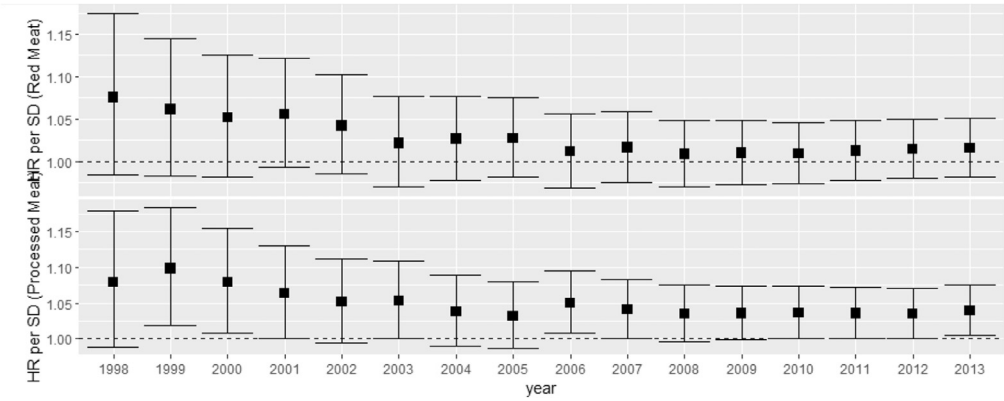
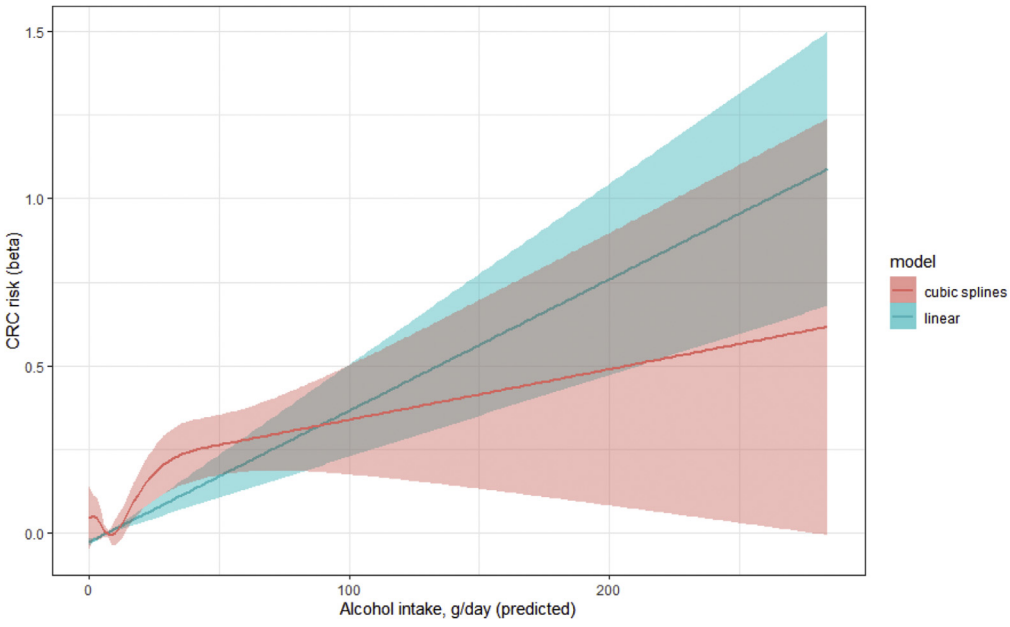


	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
events	668	919	1179	1481	1806	2129	2460	2830	3182	3574	3927	4283	4603	4847	5031	5069
mean_py	3.26	4.23	5.18	6.13	7.05	7.97	8.87	9.74	10.59	11.4	12.13	12.78	13.34	13.72	14.05	14.09

Supplementary Figure 1. Estimated hazard ratio of red meat (top panel) and processed meat (bottom panel) in relation to CRC risk in EPIC, per cumulative year of follow-up. The y-axis shows the estimated HR for each dietary factor for 1-SD increase in daily consumption. The models were adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index (<20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, active); diabetes history (no, yes); education status (none/primary, technical/professional, secondary, longer); and stratified by sex, age at recruitment (5-year intervals), and center.



Supplementary Figure 2. Comparison of 2 separate modeling approaches. Solid lines represent the fitted regression lines and the shaded area represent the 95% confidence intervals. The Cox regression using a linear prediction of alcohol intake is represented by the red color and shade and the Cox regression that further includes cubic splines (at 5 nots) is represented by the light blue color and shade, conditioned at average values of covariates and confounders.

Supplementary Table 1. Baseline Demographic Characteristics in EPIC and the NLCS Subcohort

	EPIC			NLCS		
	Total	Noncases	Cases	Total	Noncases	Cases
Total	386,792	381,723	5069	7496	3731	3765
Sex						
Male	112,788 (29.2)	110,597 (29.0)	2191 (43.2)	4023 (53.7)	1871 (50.1)	2152 (57.2)
Female	274,004 (70.8)	271,126 (71.0)	2878 (56.8)	3473 (46.3)	1860 (49.9)	1613 (42.8)
Age at recruitment						
<40 y	47,425 (12.3)	47,331 (12.4)	94 (1.9)	—	—	—
40–44.9 y	52,795 (13.6)	52,548 (13.8)	247 (4.9)	—	—	—
45–49.9 y	68,307 (17.7)	67,778 (17.8)	529 (10.4)	—	—	—
50–54.9 y	88,025 (22.8)	86,807 (22.7)	1218 (24.0)	—	—	—
55–59.9 y	64,757 (16.7)	63,557 (16.7)	1200 (23.7)	2718 (36.3)	1446 (38.8)	1272 (33.8)
60–64.9 y	49,840 (12.9)	48,519 (12.7)	1321 (26.1)	2658 (35.5)	1273 (34.1)	1385 (36.8)
65–69.9 y	12,218 (3.2)	11,884 (3.1)	334 (6.6)	2120 (28.3)	1012 (27.1)	1108 (29.4)
70–74.9 y	3011 (0.8)	2900 (0.8)	111 (2.2)			
>75 y	414 (0.1)	399 (0.1)	15 (0.3)			
Smoking status						
Never	194,087 (50.2)	191,990 (50.3)	2097 (41.4)	2474 (33.0)	1303 (34.9)	1171 (31.1)
Former	103,942 (26.9)	102,268 (26.8)	1674 (33)	2991 (39.9)	1364 (36.6)	1627 (43.2)
Current	88,763 (22.9)	87,465 (22.9)	1298 (25.6)	2031 (27.1)	1064 (28.5)	967 (25.7)
Education[a]						
None/primary School	112,507 (29.1)	110,607 (29.0)	1900 (37.5)	2040 (27.2)	1038 (27.8)	1002 (26.6)
Technical/professional school	87,563 (22.6)	86,290 (22.6)	1273 (25.1)	1599 (21.3)	798 (21.4)	801 (21.3)
Secondary school	86,072 (22.3)	85,224 (22.3)	848 (16.7)	2697 (36.0)	1349 (36.2)	1348 (35.8)
Longer education (incl. university degree)	100,650 (26.0)	99,602 (26.1)	1048 (20.7)	1160 (15.5)	546 (14.6)	614 (16.3)
BMI						
<20 kg/m^2	26,550 (6.9)	26,385 (6.9)	165 (3.3)	243 (3.2)	139 (3.7)	104 (2.8)
20–22.9 kg/m^2	99,036 (25.6)	98,100 (25.7)	936 (18.5)	1528 (20.4)	783 (21.0)	745 (19.8)
23–24.9 kg/m^2	81,112 (21.0)	80,111 (21.0)	1001 (19.7)	2231 (29.8)	1129 (30.3)	1102 (29.3)
25–29.9 kg/m^2	131,871 (34.1)	129,747 (34.0)	2124 (41.9)	3037 (40.5)	1445 (38.7)	1592 (42.3)
30–34.9 kg/m^2	38,125 (9.9)	37,464 (9.8)	661 (13.0)	403 (5.4)	208 (5.6)	195 (5.2)
≥35 kg/m^2	10,098 (2.6)	9916 (2.6)	182 (3.6)	54 (0.7)	27 (0.7)	27 (0.7)
Physical activity[b]						
Inactive	72,301 (18.7)	71,167 (18.6)	1134 (22.4)	1546 (20.6)	765 (20.5)	781 (20.7)
Moderately inactive	132,369 (34.2)	130,641 (34.2)	1728 (34.1)	2350 (31.4)	1172 (31.4)	1178 (31.3)
Moderately active	106,613 (27.6)	105,417 (27.6)	1196 (23.6)	1623 (21.7)	798 (21.4)	825 (21.9)
Active	75,509 (19.5)	74,498 (19.5)	1011 (19.9)	1977 (26.4)	996 (26.7)	981 (26.1)
Diabetes						
No	376,678 (97.4)	371,832 (97.4)	4846 (95.6)	7271 (97.0)	3608 (96.7)	3663 (97.3)
Yes	10,114 (2.6)	9891 (2.6)	223 (4.4)	225 (3.0)	123 (3.3)	102 (2.7)
Family history of CRC						
No	—	—	—	6935 (92.5)	3527 (94.5)	3408 (90.5)
Yes	—	—	—	561 (7.5)	204 (5.5)	357 (9.5)

Values are n or n (%).

BMI, body mass index; CRC, colorectal cancer; EPIC, European Prospective Investigation into Cancer and Nutrition; NLCS, Netherlands Cohort Study.

[a]The 4 educational level categories in the NLCS were formed as follows: primary school; lower vocational school; secondary, medium vocational; higher vocational, university.

[b]The 4 physical activity categories in the NLCS were based on nonoccupational physical activity and formed as follows: ≤30 min/d; >30 to ≤60 min/d; >60 to ≤90 min/d; >90 min/d.

Supplementary Table 2. HRs and 95% CIs for the Association of 92 Food and Nutrient Intakes in Relation to Colorectal Cancer Risk in the EPIC Study

Dietary Variable	HR (95% CI)[a]	*P* Value	FDR	SD
FDR-significant associations				
Alcohol	1.07 (1.04–1.10)	<.001	<0.001	17.8
Spirits[b]	1.03 (1.01–1.06)	.002	0.013	12.2
Wine	1.05 (1.02–1.08)	.001	0.008	133
Beer, cider	1.07 (1.04–1.09)	<.001	<0.001	244
Soft drinks	1.04 (1.02–1.07)	.002	0.013	165.8
Milk	0.96 (0.93–0.99)	.008	0.041	208.3
Cheese	0.95 (0.92–0.99)	.007	0.041	34.2
Calcium	0.92 (0.89–0.95)	<.001	<0.001	334.5
Phosphorous	0.92 (0.89–0.94)	<.001	<0.001	273.6
Magnesium	0.95 (0.91–0.99)	.009	0.044	82.3
Potassium	0.95 (0.92–0.98)	.003	0.02	717.2
Riboflavin	0.94 (0.91–0.98)	.001	0.011	0.6
Vitamin B6	0.95 (0.92–0.99)	.006	0.035	0.4
Beta carotene	0.95 (0.92–0.98)	.002	0.015	2780.8
Fruits	0.96 (0.92–0.99)	.008	0.041	178.1
Dietary fiber	0.93 (0.90–0.96)	<.001	<0.001	6.2
Nonwhite bread	0.93 (0.90–0.97)	.001	0.008	72.9
Banana	0.96 (0.93–0.99)	.01	0.048	36.9
Pork	1.06 (1.03–1.09)	<.001	0.001	17.5
Total proteins	0.94 (0.91–0.97)	<.001	0.002	15.5
Non–FDR-significant associations				
Foods and food groups				
Breads and cereals				
White bread	1.05 (1.01–1.09)	.012	0.052	73.6
Breakfast cereals[c]	0.97 (0.94–1.00)	.065	0.181	42.8
Bread	0.98 (0.94–1.01)	.23	0.46	79.7
Crispbread, rusks	0.99 (0.96–1.03)	.688	0.801	17.1
Pasta, rice, other grains	1.01 (0.97–1.05)	.679	0.801	65.5
Salty biscuits, crackers	1.00 (0.97–1.03)	.919	0.955	6.4
Fruits and vegetables				
Root vegetables	0.96 (0.93–0.99)	.016	0.062	30.2
Apple, pear	0.97 (0.95–1.00)	.076	0.205	85.4
Berries[d]	0.97 (0.94–1.00)	.085	0.216	12.5
Stone fruits[e]	0.98 (0.94–1.01)	.214	0.437	45.6
Mushrooms[e]	1.02 (0.98–1.06)	.267	0.482	9
Citrus fruits	0.98 (0.95–1.02)	.302	0.497	62.5
Leafy vegetables[e]	0.98 (0.94–1.02)	.347	0.507	41.1
Cabbage[f]	0.98 (0.94–1.02)	.367	0.507	30.9
Stalk vegetables, sprouts[e]	1.02 (0.98–1.05)	.355	0.507	12.8
Grain and pod vegetables[e]	0.99 (0.94–1.03)	.563	0.73	12.7
Grapes[g]	1.01 (0.98–1.04)	.59	0.753	15.3
Potatoes	1.01 (0.98–1.04)	.607	0.755	74.8
Onion, garlic[h]	0.99 (0.95–1.03)	.605	0.755	14.7
Fruiting vegetables[i]	1.00 (0.97–1.04)	.923	0.955	52.8
Fruit and vegetables juice	1.00 (0.96–1.03)	.935	0.956	115.3
Dairy products				
Yoghurt	0.98 (0.95–1.01)	.176	0.371	89
Meat and meat products				
Processed meat	1.04 (1.00–1.08)	.026	0.092	31.5
Liver[j]	1.02 (0.99–1.05)	.259	0.482	4.7
Red meat	1.02 (0.98–1.05)	.369	0.507	36.2
Beef[k]	0.98 (0.95–1.02)	.34	0.507	19.2
Offal[i]	1.01 (0.97–1.04)	.664	0.793	6.2
Poultry	1.00 (0.97–1.03)	.952	0.962	19.8
Lamb[l]	1.00 (0.97–1.04)	.991	0.991	7.9
Fish and seafood				
Fish	0.96 (0.93–1.00)	.033	0.109	31
Fatty fish[m]	0.97 (0.94–1.00)	.034	0.109	14.5
Fish products[n]	0.97 (0.93–1.00)	.045	0.137	8.7
Crustaceans[o]	1.01 (0.98–1.05)	.347	0.507	6.1
Lean fish[p]	0.99 (0.95–1.02)	.451	0.592	23.4
Eggs				
Eggs[q]	1.04 (1.01–1.07)	.018	0.064	17.5
Dietary fats				
Mayonnaise[r]	1.02 (0.98–1.06)	.34	0.507	5.7
Margarine	1.01 (0.97–1.05)	.621	0.762	16.2
Butter	1.00 (0.97–1.03)	.92	0.955	8.6
Margarine (vegetables)	1.00 (0.97–1.03)	.899	0.955	13.1
Nuts, seeds, and legumes				
Legumes[s]	0.94 (0.90–0.99)	.015	0.061	26.1
Nuts	0.98 (0.95–1.02)	.265	0.482	8.4
Confectionery				
Ice cream	1.03 (1.00–1.06)	.029	0.1	11.3

Supplementary Table 2. Continued

Dietary Variable	HR (95% CI)[a]	*P* Value	FDR	SD
Confectionery (nonchocolate)[t]	1.02 (0.99–1.05)	.158	0.354	12.4
Sugars (Sugar, honey, jam, and syrup)	0.98 (0.95–1.01)	.25	0.482	20.3
Cream puddings/ desserts[u]	0.98 (0.95–1.01)	.29	0.494	23.3
Dry cakes, biscuits[f]	0.98 (0.95–1.02)	.313	0.506	12.3
Cakes, sweets (non–milk based)	0.98 (0.95–1.02)	.344	0.507	38.5
Chocolate	1.00 (0.96–1.03)	.818	0.907	13.6
Beverages (nonalcoholic)				
Tea[i]	1.00 (0.96–1.03)	.809	0.907	304.1
Coffee	1.00 (0.96–1.03)	.8	0.907	375.7
Alcohol and alcoholic beverages				
Fortified wines[v]	1.00 (0.97–1.02)	.768	0.884	15.8
Combination foods				
Soup[w]	1.02 (0.98–1.06)	.296	0.495	79.3
Condiments and sauces				
Sauces[x]	1.00 (0.97–1.04)	.865	0.948	18.9
Nutrients				
Carbohydrates				
Carbohydrates	0.97 (0.94–1.00)	.061	0.176	36.9
Total sugars	0.98 (0.95–1.01)	.151	0.348	32.3
Starch	0.98 (0.95–1.01)	.173	0.371	32.6
Dietary fats				
Saturated fats	0.97 (0.94–1.00)	.078	0.206	7.7
Total fats	0.98 (0.95–1.00)	.09	0.223	13.5
Monounsaturated fats	0.98 (0.94–1.01)	.177	0.371	7.3
Fats (animal)	0.98 (0.95–1.01)	.261	0.482	13
Cholesterol	1.02 (0.99–1.05)	.28	0.486	115.8
Fats (plant)	0.98 (0.94–1.02)	.359	0.507	13.1
Polyunsaturated fats	1.00 (0.97–1.03)	.924	0.955	4.5
Proteins				
Protein (animal)	0.96 (0.93–0.99)	.016	0.062	18.4
Protein (plant)	0.96 (0.93–1.00)	.055	0.163	7.8
Vitamins				
Vitamin C	0.98 (0.95–1.01)	.151	0.348	60.7
Vitamin B12	0.98 (0.95–1.01)	.28	0.486	3.6
Retinol, units	1.01 (0.99–1.04)	.365	0.507	694.9
Vitamin E	0.98 (0.95–1.02)	.375	0.508	4.4
Thiamine	0.98 (0.94–1.03)	.421	0.561	0.4
Vitamin D	0.99 (0.96–1.03)	.645	0.78	3.5
Minerals				
Iron	0.98 (0.94–1.01)	.12	0.291	2.6

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FDR, false discovery rate; HR, hazard ratio.

[a]All dietary factors entered the models as standardized continuous variables and reflect associations per 1-SD increase in daily consumption. Nutrient intakes were adjusted for total energy intake using the regression residual method. The models were adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index <20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, active); diabetes history (no, yes); education status (none/primary, technical/professional, secondary, longer [including university]). They were further stratified by age at recruitment (<40, 40–44.9, 45–49.9, 50–54.9, 55–59.9, 60–64.9, 65–69.9, 70–74.9, ≥75 years), sex, and recruitment center.

[b]Intake of spirits was missing for participants from Italy and Norway (9.2% missing across EPIC).

[c]Intake of breakfast cereals was missing for participants from Italy (10.2% missing across EPIC).

[d]Intake of berries was missing for participants from Norway and the United Kingdom (16.6% missing across EPIC).

[e]Intake for mushrooms, leafy vegetables, stone fruits, stalk vegetables, pod vegetables was missing for participants from Norway and Sweden (12.6% missing across EPIC).

[f]Intake of cabbage and biscuits was missing for participants from Sweden (6.1% missing across EPIC).

[g]Intake of grapes was missing for participants from Norway and Sweden (26.1% missing across EPIC).

[h]Intake for onion and garlic was missing for participants from France, Norway, and Sweden (28.4% missing across EPIC).

[i]Intake of offal, tea, and fruiting vegetables was missing for participants from Norway (6.4% missing across EPIC).

[j]Intake of liver was missing for participants from the Netherlands, Norway, and Sweden (20.7% missing across EPIC).

[k]Intake of beef was missing for participants from Sweden (6.1% missing across EPIC).

[l]Intake of lamb was missing for participants from the Netherlands, Italy and Sweden (22.9% missing across EPIC).

[m]Intake of fatty fish was missing for participants from Germany (6.6% missing across EPIC).

[n]Intake of fish products was missing for participants from France and Italy (24.4% missing across EPIC).

[o]Intake of crustaceans was missing for participants from Germany (12.5% missing across EPIC).

[p]Intake of lean fish was missing for participants from Germany, Italy and Sweden (19.9% missing across EPIC).

[q]Intake of egg was missing for participants from Sweden (6.1% missing across EPIC).

[r]Intake of mayonnaise was missing for participants from Italy, Norway, and Sweden (13.9% missing across EPIC).

[s]Intake of legumes was missing for participants from Denmark and Norway (20.0% missing across EPIC).

[t]Intake of confectionary was missing for participants from Germany and Norway (19.0% missing across EPIC).

[u]Intake of cream puddings/desserts was missing for participants from Italy and Sweden (17.6% missing across EPIC).

[v]Intake of fortified wines was missing for participants from Italy, Norway, and Sweden (15.4% missing across EPIC).

[w]Intake of soup was missing for participants from Denmark, Italy, and Norway (21.2% missing across EPIC).

[x]Intake of sauces was missing for participants from Italy (1.3% missing across EPIC).

Supplementary Table 3. HRs and 95% CIs for the Association of the 20 Food and Nutrient Intakes With Colorectal Cancer Risk by Tumor Location (Colon vs Rectal) in the EPIC Study

Dietary Variables	Colon, HR (95% CI)[a]	Rectum, HR (95% CI)[a]	*P* Value for Heterogeneity
Alcohol	1.06 (1.02–1.10)	1.09 (1.04–1.14)	.309
Spirits[b]	1.02 (0.99–1.05)	1.06 (1.02–1.09)	.113
Wine	1.04 (1.00–1.07)	1.07 (1.02–1.12)	.278
Beer, cider	1.06 (1.02–1.09)	1.07 (1.04–1.11)	.509
Soft drinks	1.04 (1.01–1.08)	1.04 (1.00–1.09)	.988
Milk	0.96 (0.92–0.99)	0.96 (0.91–1.01)	.946
Cheese	0.96 (0.92–1.01)	0.94 (0.88–1.00)	.491
Calcium	0.93 (0.89–0.96)	0.91 (0.86–0.96)	.552
Phosphorous	0.91 (0.87–0.95)	0.92 (0.87–0.97)	.790
Magnesium	0.91 (0.87–0.96)	1.01 (0.95–1.08)	.011
Potassium	0.92 (0.88–0.96)	1.01 (0.95–1.07)	.008
Riboflavin	0.92 (0.88–0.97)	0.96 (0.90–1.02)	.344
Vitamin B6	0.91 (0.87–0.95)	1.02 (0.96–1.08)	.002
Beta carotene	0.95 (0.91–0.98)	0.96 (0.91–1.01)	.602
Fruits	0.95 (0.91–0.99)	0.97 (0.92–1.03)	.569
Dietary fiber	0.92 (0.88–0.95)	0.95 (0.90–1.00)	.306
Nonwhite bread	0.93 (0.88–0.98)	0.95 (0.89–1.01)	.669
Banana	0.94 (0.90–0.98)	1.00 (0.95–1.06)	.041
Pork	1.06 (1.01–1.10)	1.07 (1.02–1.12)	.686
Total proteins	0.93 (0.89–0.97)	0.95 (0.90–1.01)	.409

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

[a]All dietary factors entered the models as standardized continuous variables and reflect associations per 1-SD increase in daily consumption. Nutrient intakes were adjusted for total energy intake using the regression residual method. The models were adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index $<$20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, $\geq$35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, active); diabetes history (no, yes); education status (none/primary, technical/professional, secondary, longer [including university]). They were further stratified by age at recruitment ($<$40, 40–44.9, 45–49.9, 50–54.9, 55–59.9, 60–64.9, 65–69.9, 70–74.9, $\geq$75 years), sex, and recruitment center.

[b]Intake of spirits was missing for participants from Italy and Norway (9.2% missing across EPIC).

Supplementary Table 4. HRs[a] and 95% CIs for the Association of the 20 Food and Nutrient Intakes With Colon Cancer Risk by Tumor Location (Proximal vs Distal) in the EPIC Study

Dietary Variables	Proximal, HR (95% CI)[a]	Distal, HR (95% CI)[a]	*P* Value for Heterogeneity
Alcohol	1.01 (0.96–1.07)	1.11 (1.05–1.16)	.015
Spirits[b]	1.02 (0.98–1.07)	1.00 (0.96–1.05)	.564
Wine	1.00 (0.95–1.06)	1.07 (1.02–1.12)	.087
Beer, cider	1.04 (0.99–1.09)	1.08 (1.03–1.12)	.298
Soft drinks	1.02 (0.97–1.08)	1.06 (1.01–1.11)	.311
Milk	0.97 (0.92–1.02)	0.96 (0.91–1.02)	.931
Cheese	0.98 (0.92–1.05)	0.93 (0.87–0.99)	.245
Calcium	0.94 (0.89–0.99)	0.91 (0.86–0.97)	.432
Phosphorous	0.93 (0.87–0.98)	0.90 (0.85–0.96)	.546
Magnesium	0.96 (0.89–1.03)	0.88 (0.82–0.95)	.138
Potassium	0.94 (0.88–1.00)	0.92 (0.86–0.98)	.599
Riboflavin	0.95 (0.89–1.02)	0.90 (0.84–0.97)	.309
Vitamin B6	0.90 (0.85–0.96)	0.94 (0.88–1.01)	.366
Beta carotene	0.94 (0.88–0.99)	0.97 (0.91–1.02)	.431
Fruits	0.95 (0.89–1.01)	0.97 (0.91–1.03)	.659
Dietary fiber	0.94 (0.88–0.99)	0.91 (0.86–0.96)	.457
Nonwhite bread	0.95 (0.88–1.02)	0.93 (0.86–1.00)	.643
Banana	0.91 (0.86–0.97)	0.98 (0.92–1.04)	.128
Pork	1.03 (0.97–1.09)	1.08 (1.02–1.14)	.263
Total proteins	0.92 (0.86–0.98)	0.93 (0.88–0.99)	.702

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

[a]All dietary factors entered the models as standardized continuous variables and reflect associations per 1-SD increase in daily consumption. Nutrient intakes were adjusted for total energy intake using the regression residual method. The models were adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index $<$20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, $\geq$35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, active); diabetes history (no, yes); education status (none/primary, technical/professional, secondary, longer [including university]). They were further stratified by age at recruitment ($<$40, 40–44.9, 45–49.9, 50–54.9, 55–59.9, 60–64.9, 65–69.9, 70–74.9, $\geq$75 years), sex, and recruitment center.

[b]Intake of spirits was missing for participants from Italy and Norway (9.2% missing across EPIC).

Supplementary Table 5. HRs and 95% CIs for the Association of the 20 Food and Nutrient Intakes With Colorectal Cancer Risk by Sex (Men vs Women) in the EPIC Study

Dietary Variables	Men, HR (95% CI)[a]	Women, HR (95% CI)[a]	*P* Value for Heterogeneity
Alcohol	1.12 (1.08–1.16)	1.03 (0.99–1.07)	.002
Spirits[b]	1.05 (1.03–1.07)	0.98 (0.93–1.03)	.010
Wine	1.04 (1.00–1.07)	1.06 (1.02–1.12)	.386
Beer, cider	1.07 (1.05–1.10)	1.01 (0.93–1.10)	.220
Soft drinks	1.03 (0.99–1.07)	1.06 (1.02–1.10)	.376
Milk	0.96 (0.92–1.00)	0.97 (0.93–1.01)	.777
Cheese	0.95 (0.90–1.00)	0.95 (0.91–1.00)	.866
Calcium	0.91 (0.86–0.95)	0.93 (0.90–0.97)	.407
Phosphorous	0.91 (0.86–0.95)	0.92 (0.89–0.96)	.621
Magnesium	0.89 (0.84–0.96)	0.98 (0.93–1.03)	.033
Potassium	0.92 (0.88–0.98)	0.97 (0.93–1.01)	.170
Riboflavin	0.95 (0.89–1.01)	0.94 (0.90–0.98)	.789
Vitamin B6	0.97 (0.92–1.02)	0.94 (0.90–0.98)	.404
Beta carotene	0.94 (0.88–0.99)	0.96 (0.93–1.00)	.434
Fruits	0.95 (0.90–1.00)	0.96 (0.92–1.00)	.688
Dietary fiber	0.88 (0.84–0.93)	0.96 (0.93–1.01)	.006
Nonwhite bread	0.89 (0.84–0.94)	0.99 (0.94–1.05)	.008
Banana	0.97 (0.92–1.01)	0.95 (0.91–0.99)	.653
Pork	1.05 (1.01–1.09)	1.08 (1.03–1.14)	.303
Total proteins	0.94 (0.89–0.99)	0.94 (0.90–0.98)	.909

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

[a]All dietary factors entered the models as standardized continuous variables and reflect associations per 1-SD increase in daily consumption. Nutrient intakes were adjusted for total energy intake using the regression residual method. The models were adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index $<$20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, $\geq$35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, active); diabetes history (no, yes); education status (none/primary, technical/professional, secondary, longer [including university]). They were further stratified by age at recruitment ($<$40, 40–44.9, 45–49.9, 50–54.9, 55–59.9, 60–64.9, 65–69.9, 70–74.9, $\geq$75 years), sex, and recruitment center.

[b]Intake of spirits was missing for participants from Italy and Norway (9.2% missing across EPIC).

Supplementary Table 6. HRs and 95% CIs for the Association of the 20 Food and Nutrient Intakes With Colorectal Cancer Risk in the EPIC and the NLCS Study

Dietary Variables	EPIC Study, HR (95% CI)[a]	NLCS Study, HR[b] (95% CI)[a]	*P* Value for Heterogeneity
Alcohol	1.07 (1.04–1.10)	1.06 (1.01–1.12)	.704
Spirits[c]	1.03 (1.01–1.06)	1.06 (1.01–1.11)	.350
Wine	1.05 (1.02–1.08)	1.02 (0.97–1.08)	.389
Beer, cider	1.07 (1.04–1.09)	1.03 (0.98–1.08)	.192
Soft drinks	1.04 (1.02–1.07)	0.96 (0.91–1.02)	.009
Milk	0.96 (0.93–0.99)	0.93 (0.89–0.98)	.245
Cheese	0.95 (0.92–0.99)	0.99 (0.94–1.04)	.221
Calcium	0.92 (0.89–0.95)	0.94 (0.90–0.99)	.494
Phosphorus	0.92 (0.89–0.94)	0.95 (0.90–1.00)	.237
Magnesium	0.95 (0.91–0.99)	0.95 (0.90–1.00)	.986
Potassium	0.95 (0.92–0.98)	0.98 (0.94–1.03)	.300
Riboflavin	0.94 (0.91–0.98)	0.95 (0.90–1.00)	.768
Vitamin B6	0.95 (0.92–0.99)	1.01 (0.97–1.07)	.053
Beta carotene	0.95 (0.92–0.98)	0.96 (0.92–1.01)	.795
Fruit	0.96 (0.92–0.99)	1.00 (0.95–1.05)	.142
Fiber	0.93 (0.90–0.96)	0.99 (0.94–1.03)	.021
Nonwhite bread	0.93 (0.90–0.97)	1.00 (0.95–1.05)	.035
Bananas	0.96 (0.93–0.99)	1.02 (0.97–1.07)	.038
Pork	1.06 (1.03–1.09)	1.00 (0.95–1.05)	.040
Total protein	0.94 (0.91–0.97)	0.95 (0.90–1.00)	.692

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

[a]All dietary factors entered the models as standardized continuous variables and reflect associations per 1-SD increase in daily consumption. Nutrient intakes were adjusted for total energy intake using the regression residual method. The models were adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index <20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, active); diabetes history (no, yes); education status (none/primary, technical/professional, secondary, longer [including university]). They were further stratified by age at recruitment (<40, 40–44.9, 45–49.9, 50–54.9, 55–59.9, 60–64.9, 65–69.9, 70–74.9, ≥75 years), sex, and recruitment center.

[b]Multivariable analyses were stratified for age at baseline (55–59, 60–64, 65–69 years), sex, and adjusted for smoking status (never, ex, current), body mass index (<20, 20–<23, 23–<25, 25–<30, 30–<35, ≥35 kg/m^2), nonoccupational physical activity (≤30, >30–60, >60–90, >90 min/d), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), family history of colorectal cancer (no, yes), history of diabetes, energy intake (kcal, continuous).

[c]Intake of spirits was missing for participants from Italy and Norway (9.2% missing across EPIC).

Supplementary Table 7. HRs and 95% CIs for the Association of the 20 Food and Nutrients With Colorectal Cancer Risk by Tumor Location (Colon vs Rectal) in the NLCS Study

Dietary Variables	Colon, HR (95% CI)[a]	Rectum, HR (95% CI)[a]	*P* Value for Heterogeneity
Alcohol	1.03 (0.98–1.09)	1.11 (1.04–1.20)	.100
Spirits	1.05 (0.99–1.10)	1.08 (1.00–1.16)	.544
Wine	1.01 (0.95–1.06)	1.05 (0.97–1.14)	.435
Beer, cider	0.99 (0.94–1.05)	1.06 (1.00–1.14)	.118
Soft drinks	0.97 (0.92–1.03)	0.96 (0.87–1.06)	.858
Milk	0.94 (0.89–0.99)	0.95 (0.88–1.03)	.827
Cheese	0.98 (0.93–1.04)	1.04 (0.96–1.13)	.239
Calcium	0.95 (0.90–1.00)	0.99 (0.91–1.07)	.403
Phosphorus	0.93 (0.89–0.99)	1.04 (0.96–1.12)	.019
Magnesium	0.94 (0.89–0.99)	1.00 (0.93–1.08)	.186
Potassium	0.96 (0.91–1.01)	1.08 (1.00–1.17)	.014
Riboflavin	0.94 (0.89–1.00)	1.00 (0.92–1.08)	.221
Vitamin B6	0.98 (0.93–1.03)	1.12 (1.04–1.21)	.004
Beta carotene	0.93 (0.88–0.98)	1.02 (0.94–1.10)	.057
Fruits	0.99 (0.94–1.05)	1.02 (0.94–1.10)	.543
Fiber	0.97 (0.92–1.03)	1.02 (0.95–1.10)	.287
Nonwhite bread	0.98 (0.93–1.04)	1.06 (0.98–1.14)	.102
Bananas	1.02 (0.96–1.08)	1.04 (0.96–1.12)	.695
Pork	0.98 (0.93–1.03)	1.03 (0.95–1.12)	.314
Total protein	0.93 (0.88–0.99)	1.02 (0.94–1.11)	.076

[a]Multivariable analyses were stratified for age at baseline (55–59, 60–64, 65–69 years), sex, and adjusted for smoking status (never, ex, current), body mass index (<20, 20–<23, 23–<25, 25–<30, 30–<35, ≥35 kg/m^2), nonoccupational physical activity (≤30, >30–60, >60–90, >90 min/d), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), family history of colorectal cancer (no, yes), history of diabetes, energy intake (kcal, continuous).

Supplementary Table 8. HRs and 95% CIs for the Association of the 20 Food and Nutrient Intakes With Colon Cancer Risk by Tumor Location (Proximal vs Distal) in the NLCS Study

Dietary Variables	Proximal, HR (95% CI)[a]	Distal, HR (95% CI)[a]	*P* Value for Heterogeneity
Alcohol	1.04 (0.97–1.11)	1.03 (0.96–1.10)	.843
Spirits	1.05 (0.99–1.12)	1.04 (0.97–1.11)	.837
Wine	1.01 (0.94–1.08)	1.00 (0.93–1.07)	.843
Beer, cider	0.99 (0.92–1.06)	1.00 (0.93–1.07)	.843
Soft drinks	0.97 (0.90–1.05)	0.98 (0.90–1.06)	.858
Milk	0.94 (0.87–1.00)	0.95 (0.89–1.02)	.831
Cheese	1.00 (0.93–1.07)	0.98 (0.91–1.06)	.702
Calcium	0.96 (0.90–1.03)	0.95 (0.89–1.02)	.831
Phosphorus	0.95 (0.89–1.01)	0.94 (0.87–1.00)	.825
Magnesium	0.95 (0.89–1.02)	0.93 (0.87–1.00)	.669
Potassium	0.97 (0.90–1.04)	0.96 (0.90–1.03)	.837
Riboflavin	0.94 (0.88–1.01)	0.96 (0.90–1.03)	.669
Vitamin B6	0.99 (0.92–1.06)	0.97 (0.91–1.05)	.691
Beta carotene	0.96 (0.89–1.02)	0.89 (0.82–0.96)	.154
Fruits	1.01 (0.94–1.08)	0.98 (0.91–1.05)	.553
Fiber	0.98 (0.92–1.05)	0.97 (0.91–1.04)	.831
Nonwhite bread	0.97 (0.91–1.05)	1.00 (0.93–1.07)	.551
Bananas	1.01 (0.94–1.08)	1.03 (0.95–1.11)	.712
Pork	0.97 (0.91–1.04)	0.99 (0.92–1.06)	.681
Total protein	0.93 (0.86–1.00)	0.94 (0.87–1.01)	.843

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

[a]Multivariable analyses were stratified for age at baseline (55–59, 60–64, 65–69 years), sex, and adjusted for smoking status (never, ex, current), body mass index (<20, 20–<23, 23–<25, 25–<30, 30–<35, ≥35 kg/m^2), nonoccupational physical activity (≤30, >30–60, >60–90, >90 min/d), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), family history of colorectal cancer (no, yes), history of diabetes, energy intake (kcal, continuous).

Supplementary Table 9. HRs[a] and 95% CIs for the Association of the 20 Food and Nutrient Intakes With Colorectal Cancer Risk by Sex (Men vs Women) in the NLCS Study

Dietary Variables	Men, HR (95% CI)	Women, HR (95% CI)	*P* Value for Heterogeneity
Alcohol	1.07 (1.01–1.13)	1.06 (0.94–1.18)	.848
Spirits	1.06 (1.01–1.12)	1.05 (0.90–1.23)	.839
Wine	1.02 (0.95–1.09)	1.04 (0.96–1.12)	.700
Beer, cider	1.02 (0.97–1.08)	0.99 (0.76–1.29)	.557
Soft drinks	0.99 (0.91–1.07)	0.91 (0.83–1.01)	.142
Milk	0.92 (0.86–0.98)	0.95 (0.88–1.03)	.519
Cheese	1.01 (0.95–1.08)	0.95 (0.88–1.03)	.247
Calcium	0.94 (0.88–1.01)	0.96 (0.89–1.03)	.667
Phosphorus	0.96 (0.90–1.02)	0.94 (0.87–1.02)	.661
Magnesium	0.95 (0.90–1.02)	0.95 (0.87–1.03)	1.000
Potassium	0.99 (0.92–1.05)	0.99 (0.92–1.07)	1.000
Riboflavin	0.94 (0.88–1.00)	0.97 (0.90–1.05)	.523
Vitamin B6	1.02 (0.96–1.08)	1.02 (0.94–1.10)	1.000
Beta carotene	0.96 (0.90–1.02)	0.97 (0.90–1.04)	.845
Fruits	1.01 (0.94–1.08)	0.99 (0.92–1.06)	.694
Fiber	0.99 (0.94–1.05)	0.98 (0.91–1.06)	.832
Nonwhite bread	1.00 (0.95–1.07)	1.00 (0.91–1.11)	1.000
Bananas	1.01 (0.94–1.08)	1.03 (0.96–1.11)	.712
Pork	1.00 (0.94–1.07)	0.99 (0.92–1.07)	.840
Total protein	0.96 (0.89–1.03)	0.94 (0.86–1.02)	.697

[a]Multivariable analyses were stratified for age at baseline (55–59, 60–64, 65–69 years), sex, and adjusted for smoking status (never, ex, current), body mass index (<20, 20–<23, 23–<25, 25–<30, 30–<35, ≥35 kg/m^2), nonoccupational physical activity (≤30, >30–60, >60–90, >90 min/d), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), family history of colorectal cancer (no, yes), history of diabetes, energy intake (kcal, continuous).

Supplementary Table 10. Multivariable Analysis of Mutually Adjusted Foods and Nutrients

Variable	Beta[a]	SE	HR	Z Value	*P* Value	VIF
Alcohol	0.0530	0.0140	1.0544	3.7784	.0002	1.2
Milk	0.0052	0.0244	1.0052	0.2133	.8311	2.9
Cheese	–0.0013	0.0260	0.9987	–0.0493	.9607	2.4
Calcium	–0.0498	0.0380	0.9514	–1.3091	.1905	6.1
Phosphorous	–0.0574	0.0450	0.9442	–1.2768	.2017	8.0
Magnesium	–0.0084	0.0283	0.9916	–0.2982	.7655	2.1
Potassium	0.0047	0.0267	1.0047	0.1764	.8600	2.6
Riboflavin	0.0432	0.0328	1.0441	1.3155	.1884	3.1
Beta carotene	–0.0328	0.0170	0.9677	–1.9263	.0541	1.2
Total proteins	–0.0013	0.0288	0.9987	–0.0463	.9630	3.1

A value >10 is indicative of multicollinearity.

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; VIF, variance inflation factor.

[a]Also adjusted for total energy intake (kcal, continuous); smoking status (never, former, current); body mass index <20, 20–22.9, 23–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, active); diabetes history (no, yes); education status (none/primary, technical/professional, secondary, longer [including university]) and stratified by age at recruitment (<40, 40–44.9, 45–49.9, 50–54.9, 55–59.9, 60–64.9, 65–69.9, 70–74.9, ≥75 years), sex, and recruitment center.