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Assessing the role of ultra-processed foods in colorectal cancer incidence: insights from the EPIC cohort

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Abstract

Background Studies have reported associations between ultra-processed food (UPF) consumption and colorectal cancer (CRC) incidence, yet the magnitude of these associations remains unclear. This study estimated the cohort-associated fraction (CAF), adapted from the population-attributable fraction metric, between UPF consumption and CRC incidence and explored the potential benefits of substituting UPFs with unprocessed or minimally processed foods.

Methods Using data from 416,081 middle-aged adults in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, including 5,845 incident CRC cases, Cox proportional hazards models were applied to estimate associations between UPF consumption (grams/day) and CRC, colon and rectal cancer risks. Substitution analyses were also carried out to estimate associations of replacing UPFs with unprocessed or minimally processed foods, to reflect potentially more interpretable estimates. CAFs quantified the magnitude of these associations.

Results UPF consumption was positively associated with colon cancer ($HR_{1-SD \text{ increment}}: 1.04$ [95%CI: 1.01; 1.08]) and CRC ($HR_{1-SD \text{ increment}}: 1.04$ [95%CI: 1.01; 1.07]) but not with rectal cancer incidence. The CAF for UPF consumption was 5.58% (95%CI: 0.55; 10.50) for colon, and 5.10% (1.10; 9.02) for CRC incidence. Substituting 1-SD of UPFs with unprocessed or minimally processed foods was inversely associated with colon cancer ($HR: 0.93$, [95%CI: 0.89; 0.97]) and CRC incidence ($HR: 0.94$, [95%CI: 0.92; 0.98]), in energy- and nutrient-adjusted models. In substitution models, the CAF increased to 9.67% (4.36; 14.85) for colon cancer and 7.30% (3.05; 11.48) for CRC incidence.

Conclusion We estimated the magnitude of associations between UPF consumption and CRC incidence, highlighting the potential public health relevance of reducing UPF intake. Given the rising consumption of UPFs and

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burden of CRC incidence, public health interventions and continued research are needed to address this growing issue.

Keywords Ultra-processed foods (UPF), Colorectal cancer (CRC), Cohort-attributable fraction (CAF), Cancer epidemiology, EPIC cohort, Food processing

Background

Cancer stands as the second leading cause of death worldwide [1], with colorectal cancer (CRC) being a major contributor to this burden. In 2022, CRC accounted for an estimated 247,842 deaths in Europe, representing approximately 12% of all cancer cases [2]. Despite rising CRC incidence in younger generations, advancements in screening, early diagnosis, and treatment have led to improved survival rates [3].

Lifestyle factors such as physical inactivity and smoking are well-established contributors to CRC development [4, 5]. Recently, growing evidence has highlighted the critical role of dietary behaviours in CRC prevention [6]. It is estimated that 30–50% of cancer cases could potentially be prevented through lifestyle and dietary modifications. In high-income countries, modern diets, characterized by the high consumption of ultra-processed foods (UPFs), make it crucial to understand the extent to which UPFs contribute to CRC [7].

UPFs are industrially processed products that contain additives and are typically derived from a limited variety of crops and animals. They are often energy-dense, high in salt, sugar, and fat, and low in fibre and essential nutrients [8]. Emerging evidence suggests that ingredients in UPFs, such as sweeteners and emulsifiers, may disrupt host-microbiota interactions, promoting metabolic abnormalities and a pro-inflammatory environment conducive to colonic carcinogenesis. Additionally, some food additives used in UPFs, such as artificial sweeteners, might have carcinogenic properties [9–11]. Over recent decades, UPF consumption has risen sharply, while the consumption of unprocessed or minimally processed foods—rich in fibre, vitamins, and minerals—has declined [12, 13]. These unprocessed or minimally processed foods support gut health and play a significant role in CRC prevention, offering anti-inflammatory properties and beneficial effects on the gut microbiota [14, 15].

Growing evidence links higher UPF consumption to an increased risk of adverse health outcomes, including colorectal cancer (CRC), extending beyond their poor nutritional profile [13, 16–18]. A study from three large U.S. prospective cohorts also reported positive associations between higher UPF intake and increased risk of CRC precursors [19]. These associations appear robust even after adjusting for established risk factors, including body mass index (BMI) and overall diet quality. Previous findings from the European Prospective Investigation

into Cancer and Nutrition (EPIC) cohort have shown positive associations between UPF consumption, measured in proportional intakes of grams per day, and colon cancer incidence. In addition, substitution models within the EPIC analysis also revealed inverse associations between replacing UPFs with unprocessed or minimally processed foods and a reduced risk of colon cancer [16].

However, methodological challenges limit the translation of these associations into actionable public health guidance. Previous studies have employed varying analytical approaches, including different exposure measurement units (weight-based vs. caloric intake), proportional rather than absolute intake assessments, and diverse statistical modelling frameworks. This methodological heterogeneity complicates the interpretation of UPF-CRC associations and makes it difficult to estimate the potential magnitude of disease burden attributable to UPF consumption. Moreover, the practical implications of substituting UPFs with healthier alternatives have not been systematically quantified using population-level impact assessment methodologies. These limitations underscore the need for standardized approaches that can provide interpretable estimates of disease burden and evaluate realistic dietary intervention strategies.

This study aims to explore the public health relevance of the associations between UPF consumption and CRC risk by employing the population-attributable fraction (PAF) methodology. The aims are to: (1) quantify the magnitude of UPF-CRC associations using the cohort-associated fraction (CAF) methodology, adapted from PAF; (2) employing systematic substitution analyses using absolute intake measures to provide realistic dietary guidance; (3) examining practical intervention scenarios by assessing CAF at various UPF intake thresholds; and (4) providing methodologically robust estimates that can inform evidence-based public health interventions and dietary recommendations. The CAF translates hazard ratios into more interpretable estimates of association, reflecting the potential link between UPF consumption and CRC incidence within the cohort, without implying causation. Additionally, this study examines the potential benefits of substituting UPFs with unprocessed or minimally processed alternatives, providing estimates of the CAF associated with such substitution strategies.

Material and methods

EPIC cohort

The EPIC study is a large-scale multicentre cohort study designed to investigate the interactions between metabolic, lifestyle, and environmental factors and their impact on cancer and chronic diseases. From 1992 to 2000, EPIC recruited over 500,000 individuals aged 25–70 years across 23 centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Participants were primarily from the general population within specific geographic regions, towns, or provinces. Exceptions include France, where participants were exclusively female members of a health insurance scheme for school employees; Oxford, where the cohort primarily comprised individuals adhering to a vegetarian and health-conscious dietary regimen; Ragusa, consisting of blood donors and their spouses; and Utrecht, where participants were attendees of breast cancer screening programs. Study participants provided informed consent and completed detailed questionnaires covering their dietary intake, lifestyle behaviours, and medical history. The study received ethical approval from relevant local ethics committees as well as from the International Agency for Research on Cancer (IARC) in Lyon, France [20].

Exclusions were made for missing data, extreme energy to intake ratios, lack of follow-up, and prevalent cancers at baseline. The analysis included 416,081 participants, after the additional exclusion of EPIC-Greece and EPIC-Norway cohorts due to administrative constraints (Supplemental Fig. 1).

Dietary assessment and Nova classification

In the EPIC study, participants' usual food intake over the previous 12 months was assessed only at baseline using country-specific dietary questionnaires. Three dietary assessment methods were applied to assess food consumption from the previous 12 months: 1) diet history questionnaire in France and Spain, 2) semi-quantitative food frequency questionnaires (FFQ) in Italy, the Netherlands and Denmark, 3) a FFQ in the UK, Germany, Umeå and Norway, and combined with 7-day food records in Malmö [21]. The reported food items from each dietary questionnaire were categorized into harmonized food groups common across all questionnaires.

In this study the Nova classification system was selected, one of the most widely used and validated frameworks for food processing research, which has also been specifically validated within the EPIC cohort using dietary biomarkers [21]. Using the standardized list of EPIC food items, generic or multi-ingredient foods were broken down into their components and then classified according to the Nova system. The Nova classification

categorizes food items into four groups. Nova 1 includes unprocessed or minimally processed foods such as fresh, dried, or frozen fruits and vegetables, grains, flour, and pasta. Nova 2 consists of processed culinary ingredients like table sugar, oils, and salt. Nova 3 encompasses PFs, including cheese, beer, wine, and fruits in syrup. Finally, Nova 4 refers to UPFs, which include items such as soft drinks, savoury packaged snacks, sweets snacks, and processed meat.

To address uncertainty in classifying food items due to the dietary assessment methods, and potential changes in food processing over time, three scenarios were created: lower-bound, middle-bound, and upper-bound. The "middle-bound" scenario, which was validated using biomarkers and deemed the most applicable, was used in this study [21].

Outcome measures

CRC cases (ICD-10 codes: C18 for colon cancer, C19 for rectosigmoid junction, and C20 for rectal cancer) were identified from recruitment until December 31, 2013. Case identification was conducted using cancer registries, as well as through a combination of sources including cancer and pathology centres, health insurance records, and active participant follow-up. The end of follow-up was determined by the earliest of the following dates: date of cancer diagnosis, the date of death, or the end of the follow-up period. Censoring dates from cancer registries ranged between December 2009 and December 2013.

Study covariates

Covariates were selected based on a priori knowledge and existing literature, and the relationships illustrated by the directed acyclic graph (DAG), which represented the hypothesized pathways through which socio-demographic, lifestyle, and dietary factors may influence the association between UPF consumption and colorectal cancer (CRC) risk (Fig. 1). At baseline, socio-demographic, lifestyle, and other relevant factors were collected through validated questionnaires [20]. The variables included were age at recruitment (in years), sex (male, female), marital status (single, married or living together, missing), educational level (none, primary school, secondary school/technical school, higher education, missing), smoking status at baseline (never, former, current, missing), levels of physical activity (inactive, moderately inactive, moderately active, active, missing) [22], body mass index (BMI, kg/m²), and height (cm). Dietary covariates were derived using nutrient values from the USDA database [23]. These included intakes of carbohydrates, fats, protein, and fibre, expressed in grams per day; vitamin D, expressed in micrograms per day; and vitamin C and calcium, expressed in milligrams per day.

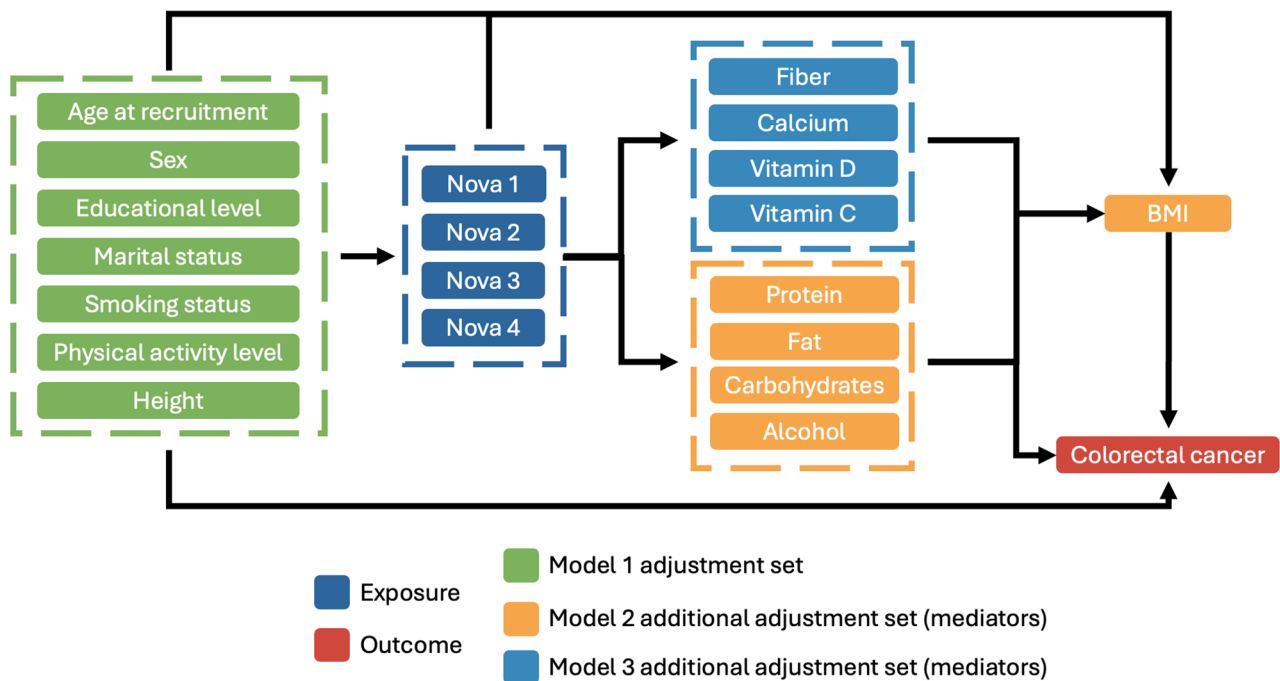


Fig. 1 Directed Acyclic Graph (DAG) illustrating the relationships between the Nova food classification (measured in grams per day) and colorectal cancer incidence, with potential confounders and mediators. Green nodes represent the covariates included in Model 1 (marital status, educational level, smoking status, physical activity, and height), constituting the minimally sufficient adjustment set for estimating the total association between ultra-processed food intake and colorectal cancer. Orange nodes represent additional variables included in Model 2 (BMI and macronutrients: protein, carbohydrates, fat, and alcohol intake). Blue nodes represent further dietary variables included in Model 3 (fibre, vitamin D, vitamin C, and calcium intake). The latter variables may lie on the causal pathway and were included to estimate composition-adjusted associations. Arrows depict the hypothesised causal relationships between exposure, mediators, and outcome

Statistical analysis

Individuals' daily intake, expressed in absolute intakes in grams per day was used, to account for foods that may not contribute significantly to overall energy intake. Daily consumption of UPFs was modelled both continuously (per 1 standard deviation increment) and categorically, with each exposure variable divided into sex-specific quartiles. The first quartile served as the reference category.

To examine the associations between the intake of the Nova groups (in grams per day) and the risk of colon and rectal cancers, multivariable-adjusted Cox proportional hazards models were applied. The DAG was used to find covariates to adjust for. The models were stratified by age at recruitment (in 1-year categories), sex, and centre, and adjusted for smoking status, marital status, educational level, physical activity, and height (Model 1). To estimate associations independent of energy content, Model 2 included additional adjustments for body size and energy-containing nutrients, specifically BMI, carbohydrate, protein, fat, and alcohol intake (in grams per day) at recruitment. Model 3 was further adjusted for protective dietary factors, including fibre, calcium, vitamin D, and vitamin C intake. In all models, age at recruitment was used as the time of entry, while the time of exit was

defined as the earliest of age at cancer diagnosis, end of follow-up, loss to follow-up, or death.

Additionally, specified substitution analyses were performed using the 'leave-one-out' method to estimate the relative risk associated with replacing a 1-standard deviation (SD) increment of UPF intake, estimated using the overall cohort, with an equivalent amount of unprocessed or minimally processed foods, while holding total intake constant. For example, the model for substituting Nova 4 with Nova 1 was parameterized as follows:

$$\log(h(t)) = \log(h_0(t)) + \gamma_1 \text{Nova } 1 + \gamma_2 \text{Nova } 2 + \gamma_3 \text{Nova } 3 + \gamma_T \text{Total Intake} + \text{covariates}$$

where:

$$\text{Total Intake} = \text{Nova } 1 + \text{Nova } 2 + \text{Nova } 3 + \text{Nova } 4$$

Nova 4 is not entered separately. It is implied $\text{Total Nova} - (\text{Nova } 1 + \text{Nova } 2 + \text{Nova } 3)$, therefore $\text{HR}_{\text{substitution}}$ is equal to γ_1 , representing the estimate of substituting a given amount of Nova 4 with an equivalent amount of Nova 1.

Cox proportional hazards model assumptions were evaluated using log–log survival plots, Schoenfeld residual tests, and assessments of log-linearity for continuous variables with martingale residuals and restricted cubic splines. We also examined beta statistics to identify influential outliers, checked multicollinearity (all VIFs < 3), and assessed model fit using concordance and likelihood ratio tests. No violations of proportional hazards, log-linearity, or model fit were detected for UPF consumption, the main exposure of interest, supporting the validity of the Cox models (global test $p > 0.05$).

Cohort-associated fraction

To estimate the magnitude of the association between UPF consumption and CRC incidence within the EPIC cohort, in this study the Levin-based PAF methodology was applied, adapted from Shield [24]; in this study termed CAF. The CAF estimates the proportion of CRC cases associated with UPF consumption, based on a theoretical minimum-risk exposure scenario that assumes no intake of UPF at baseline. CAF estimates range from 0% (no cases associated with UPF consumption) to 100% (all CRC cases associated with UPF consumption).

The CAF was calculated using hazard ratios (HRs) for UPF consumption derived from Cox regression models and the following formula:

$$CAF = \frac{\int_0^{max} [P(x) [HR(x)]] - 1}{\int_0^{max} [P(x) [HR(x)]]}$$

where x represents the amount of UPF consumed, with the upper limit of integration set at the maximum observed intake in the cohort, and $P(x)$ represents the proportion of individuals consuming x amount of UPF at baseline.

Additionally, the proportion of CRC cases potentially associated with reducing UPF consumption to a specific threshold was estimated using the following formula:

$$CAF = \frac{\int_0^{max} [P(x) [HR(x)]] - \int_0^Q [P(x) [HR(x)]]}{\int_0^{max} [P(x) [HR(x)]]}$$

where Q denotes the specific threshold of maximum UPF consumption. $P(x)$ represents the proportion of individuals consuming x amount of UPF consumed. $P'(x)$ represents the proportion of individuals consuming x amount of UPF where all above this threshold are moved to Q .

CAF estimates were only performed for model 1, as models 2 and 3 adjust for dietary factors, including potential mediators, which makes associations more challenging to interpret from a causal lens. By focusing on model 1, we

aimed to evaluate the total effect of UPF consumption, encompassing both direct and indirect effects.

Missing lifestyle data was categorized as ‘unknown’. Sensitivity analyses were conducted by excluding alcoholic beverages from the Nova classification to isolate the impact of UPF consumption, separate from the effects of alcohol. In these models separate adjustments for alcohol intake (g/day) were made. Also, analyses excluding the first two years of follow-up and subgroup analyses by sex were performed. All statistical analyses were conducted in R (version 4.0.4.1), using the survival package for Cox proportional hazards modelling. CAFs were calculated using HRs derived from the Cox models and implemented using custom functions in base R. Two-sided testing was applied, with statistical significance set at $P < 0.05$.

Results

A total of 521,324 participants were recruited into the EPIC study, of which 416,081 were included in this analysis (Supplemental Fig. 1). Among these, 284,683 (68.4%) were female and 131,398 (31.6%) were male. There were 5,845 cases of CRC diagnosed, with 3,199 men and 2,646 women affected, during a mean (SD) follow-up of 14.2 years (4.1). At recruitment, participants had a mean age of 51.4 years (10.0) and a mean BMI of 25.3 kg/m² (4.2). On average, participants consumed 362 g (271) of UPFs per day.

Those in the highest quartile of UPF consumption were typically younger, taller, and more likely to be single, divorced, separated, or widowed. They also exhibited higher levels of physical activity and had greater intakes of carbohydrates, fat, and protein compared to those in the lowest quartile (Table 1).

Associations between ultra-processed food consumption and colorectal cancer incidence

Consumption of UPFs was positively associated with CRC incidence. In the base model (Model 1), the HR for a 1-SD increment in UPF intake was 1.04 (95%CI:1.01;1.07). This association remained statistically significant after adjusting for BMI, carbohydrate, fat, protein, and alcohol intake at recruitment (Model 2) [1.07 (1.03;1.11)], and further adjustments for fibre, vitamin D, vitamin C, and calcium intake (Model 3) [1.05 (1.01;1.10)]. UPF consumption was positively associated with colon cancer incidence in model 1 [1.04 (1.01–1.08)] and model 2 [1.06 (1.01;1.11)], while this association was attenuated in model 3 [1.03 (0.98;1.09)]. In contrast, for rectal cancer, the association was statistically significant in model 2 [1.09 (1.03; 1.17)] and model 3 [1.09 (1.09;1.17)], while there was no evidence of statistical significance in model 1 [1.03 (0.98;1.09)] (Table 2). Unprocessed or minimally processed foods was inversely associated with CRC

Table 1 Baseline characteristics across sex-specific quartiles of the daily consumption of ultra-processed foods in grams/day of 416,081 middle-aged adults enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

	Mean (SD) / N (%)				
	All	Q1	Q2	Q3	Q4
	(n=416,081)	(n=104,029)	(n=104,021)	(n=104,021)	(n=104,010)
Nova 4 (g/day)	362 (271)	115 (50.9)	245 (56.0)	377 (73.1)	710 (293)
Nova 3 (g/day)	375 (313)	398 (299)	384 (311)	367 (316)	351 (323)
Nova 2 (g/day)	30.1 (23.8)	39.5 (22.6)	30.8 (23.7)	26.2 (22.9)	23.8 (22.8)
Nova 1 (g/day)	2030 (828)	1690 (799)	2040 (817)	2180 (792)	2190 (803)
Age at recruitment (years)	51.4 (10.0)	52.1 (8.13)	52.2 (9.15)	51.8 (10.2)	49.4 (12.0)
Sex					
Male	131398 (31.6%)	32854 (31.6%)	32849 (31.6%)	32850 (31.6%)	32845 (31.6%)
Female	284683 (68.4%)	71175 (68.4%)	71172 (68.4%)	71171 (68.4%)	71165 (68.4%)
Country					
France	67397 (16.2%)	27161 (26.1%)	22729 (21.9%)	12430 (11.9%)	5077 (4.9%)
Italy	44545 (10.7%)	26290 (25.3%)	11301 (10.9%)	4736 (4.6%)	2218 (2.1%)
Spain	39989 (9.6%)	28670 (27.6%)	7040 (6.8%)	2895 (2.8%)	1384 (1.3%)
United Kingdom	75368 (18.1%)	2437 (2.3%)	12154 (11.7%)	24307 (23.4%)	36470 (35.1%)
The Netherlands	36538 (8.8%)	1779 (1.7%)	7885 (7.6%)	12995 (12.5%)	13879 (13.3%)
Germany	48556 (11.7%)	4674 (4.5%)	11972 (11.5%)	14284 (13.7%)	17626 (16.9%)
Sweden	48674 (11.7%)	10341 (9.9%)	17157 (16.5%)	12895 (12.4%)	8281 (8.0%)
Denmark	55014 (13.2%)	2677 (2.6%)	13783 (13.3%)	19479 (18.7%)	19075 (18.3%)
Marital status					
Single, divorced, separated, or widowed	72409 (17.4%)	12966 (12.5%)	17400 (16.7%)	19167 (18.4%)	22876 (22.0%)
Married or living together	242221 (58.2%)	57315 (55.1%)	64100 (61.6%)	61229 (58.9%)	59577 (57.3%)
Unknown	101451 (24.4%)	33748 (32.4%)	22521 (21.7%)	23625 (22.7%)	21557 (20.7%)
Education					
None or primary school completed	118809 (28.6%)	43478 (41.8%)	28131 (27.0%)	24076 (23.1%)	23124 (22.2%)
Technical/professional school	91607 (22.0%)	11439 (11.0%)	20664 (19.9%)	27330 (26.3%)	32174 (30.9%)
Secondary school	84118 (20.2%)	24474 (23.5%)	23765 (22.8%)	19527 (18.8%)	16352 (15.7%)
Longer education (including university degree)	104681 (25.2%)	22700 (21.8%)	28317 (27.2%)	28215 (27.1%)	25449 (24.5%)
Unknown	16866 (4.1%)	1938 (1.9%)	3144 (3.0%)	4873 (4.7%)	6911 (6.6%)
Smoking status					
Never	207625 (49.9%)	54422 (52.3%)	52137 (50.1%)	50736 (48.8%)	50330 (48.4%)
Current	112741 (27.1%)	24815 (23.9%)	28509 (27.4%)	30293 (29.1%)	29124 (28.0%)
Former	89209 (21.4%)	22949 (22.1%)	21507 (20.7%)	21499 (20.7%)	23254 (22.4%)
Unknown	6506 (1.6%)	1843 (1.8%)	1868 (1.8%)	1493 (1.4%)	1302 (1.3%)
Physical activity level					
Inactive	86761 (20.9%)	29800 (28.6%)	20817 (20.0%)	18196 (17.5%)	17948 (17.3%)
Moderately inactive	142657 (34.3%)	37487 (36.0%)	37517 (36.1%)	34954 (33.6%)	32699 (31.4%)
Moderately active	100750 (24.2%)	23108 (22.2%)	26320 (25.3%)	26283 (25.3%)	25039 (24.1%)
Active	79058 (19.0%)	13291 (12.8%)	18072 (17.4%)	22303 (21.4%)	25392 (24.4%)
Missing	6855 (1.6%)	343 (0.3%)	1295 (1.2%)	2285 (2.2%)	2932 (2.8%)
Height (cm)	166 (9.07)	163 (8.79)	166 (9.05)	167 (8.93)	168 (8.91)
BMI (kg/m2)	25.3 (4.21)	25.7 (4.31)	25.0 (4.03)	25.1 (4.05)	25.5 (4.41)
Carbohydrate (g/day)	258 (81.2)	225 (73.8)	234 (67.8)	258 (65.5)	315 (85.0)
Fat intake (g/day)	83.3 (29.7)	75.6 (26.8)	79.3 (27.4)	84.8 (28.3)	93.3 (32.9)
Protein intake (g/day)	83.4 (25.9)	81.5 (27.2)	80.2 (25.4)	83.1 (24.2)	88.8 (26.0)
Alcohol intake (g/day)	13.8 (18.7)	13.9 (20.2)	14.2 (18.6)	14.2 (18.1)	13.0 (17.8)
Fibre intake (g/day)	24.1 (8.73)	23.0 (8.57)	22.4 (7.73)	24.1 (7.98)	27.0 (9.77)
Vitamin C intake (mg/day)	118 (67.6)	121 (73.4)	110 (63.4)	114 (61.5)	129 (70.0)
Vitamin D intake (µg/day)	3.08 (2.14)	2.81 (1.85)	3.11 (2.12)	3.20 (2.22)	3.19 (2.33)
Calcium intake (mg/day)	1090 (453)	1040 (457)	1060 (455)	1100 (433)	1170 (454)

Table 2 Hazard ratios (HRs) for a 1 standard deviation (SD) increment in ultra-processed (Nova 4) foods in the total diet by mass (g) per day, and cohort-associated fractions (CAF) for colorectal cancer incidence among 416,081 adults enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

	HR (95% CI) per 1 SD increment		CAF (95% CI)	
	Including alcohol	Excluding alcohol	Including alcohol	Excluding alcohol
Colon (n = 3790)				
Model 1	1.04 (1.01; 1.08)*	1.04 (1.00; 1.08)*	5.58 (0.55; 10.50)	5.13 (0.17; 9.99)
Model 2	1.06 (1.01; 1.11)*	1.05 (1.00; 1.11)*	/	/
Model 3	1.03 (0.98; 1.09)	1.03 (0.97; 1.09)	/	/
Rectal (n = 2055)				
Model 1	1.03 (0.98; 1.09)	1.03 (0.98; 1.08)	4.12 (-2.54; 10.58)	3.78 (-2.79; 10.19)
Model 2	1.09 (1.03; 1.17)**	1.09 (1.02; 1.16)**	/	/
Model 3	1.09 (1.01; 1.17)*	1.08 (1.00; 1.16)*	/	/
Colorectal (n = 5845)				
Model 1	1.04 (1.01; 1.07)*	1.04 (1.01; 1.07)*	5.10 (1.10; 9.02)	4.68 (0.73; 8.56)
Model 2	1.07 (1.03; 1.11)**	1.07 (1.02; 1.11)**	/	/
Model 3	1.05 (1.01; 1.10)*	1.05 (1.01; 1.10)*	/	/

All models were stratified by age at recruitment (in years), sex (male, female), and center. Model 1 was adjusted for marital status (single, married or living together, missing), educational level (none, primary school, secondary school/technical school, higher education, missing), smoking status at baseline (never, former, current, missing), levels of physical activity (inactive, moderately inactive, moderately active, active, missing), and height (cm). Model 2 was further adjusted for body mass index (BMI, kg/m²), protein, carbohydrates, fat, and alcohol intake, measured in grams per day. Model 3 was further adjusted for fibre, vitamin D, vitamin C, and calcium intake

HR (95% CI) Hazard ratio (95% Confidence Interval), CAF (95% CI) Cohort-associated fractions (95% Confidence Interval)

* $p < 0.05$, ** $p < 0.01$

Table 3 Hazard ratios (HRs) for substituting 1 standard deviation (SD) of ultra-processed (Nova 4) foods by mass (g) per day with minimally processed foods (Nova 1), and cohort-associated fractions (CAF) for colorectal cancer incidence among 416,081 adults enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

	HR (95% CI) per 1 SD		CAF (95% CI)	
	Including alcohol	Excluding alcohol	Including alcohol	Excluding alcohol
Colon (n = 3790)				
Model 1	0.93 (0.89; 0.97)**	0.93 (0.89; 0.97)**	9.67 (4.36; 14.85)	9.29 (4.06; 14.40)
Model 2	0.93 (0.88; 0.97)**	0.93 (0.88; 0.97)**	/	/
Model 3	0.94 (0.90; 1.00)	0.95 (0.90; 1.00)	/	/
Rectal (n = 2055)				
Model 1	0.98 (0.93; 1.03)	0.98 (0.93; 1.03)	3.10 (-4.09; 10.08)	3.04 (-4.02; 9.90)
Model 2	0.94 (0.88; 1.00)	0.94 (0.88; 1.01)	/	/
Model 3	0.95 (0.88; 1.02)	0.96 (0.89; 1.03)	/	/
Colorectal (n = 5845)				
Model 1	0.94 (0.92; 0.98)**	0.94 (0.92; 0.98)**	7.30 (3.05; 11.48)	7.03 (2.84; 11.14)
Model 2	0.93 (0.89; 0.96)**	0.93 (0.89; 0.97)**	/	/
Model 3	0.95 (0.91; 0.99)*	0.95 (0.92; 0.99)*	/	/

All models were stratified by age at recruitment (in years), sex (male, female), and center. Model 1 was adjusted for marital status (single, married or living together, missing), educational level (none, primary school, secondary school/technical school, higher education, missing), smoking status at baseline (never, former, current, missing), levels of physical activity (inactive, moderately inactive, moderately active, active, missing), and height (cm). Model 2 was further adjusted for body mass index (BMI, kg/m²), protein, carbohydrates, fat, and alcohol intake, measured in grams per day. Model 3 was further adjusted for fibre, vitamin D, vitamin C, and calcium intake

HR (95% CI) Hazard ratio (95% Confidence Interval), CAF (95% CI) Cohort-associated fractions (95% Confidence Interval)

* $p < 0.05$, ** $p < 0.01$

incidence, only in model 1, with HR for a 1-SD increment 0.95 (0.92;0.98). Inverse associations were observed between unprocessed or minimally processed foods and colon cancer in all three models, while for rectal cancer, positive associations were observed in models 2 and 3, for UPF consumption expressed as continuous variable, but not for quartile analyses (Supplemental Table 2–3).

In the substitution analysis, replacing 1-SD of UPFs with an equivalent amount of unprocessed or minimally processed food resulted in inverse associations with CRC incidence across all three models (Table 3). For colon cancer, models 1 and 2 also showed inverse associations. However, for rectal cancer, the associations between UPF consumption and incidence were insignificant across all models.

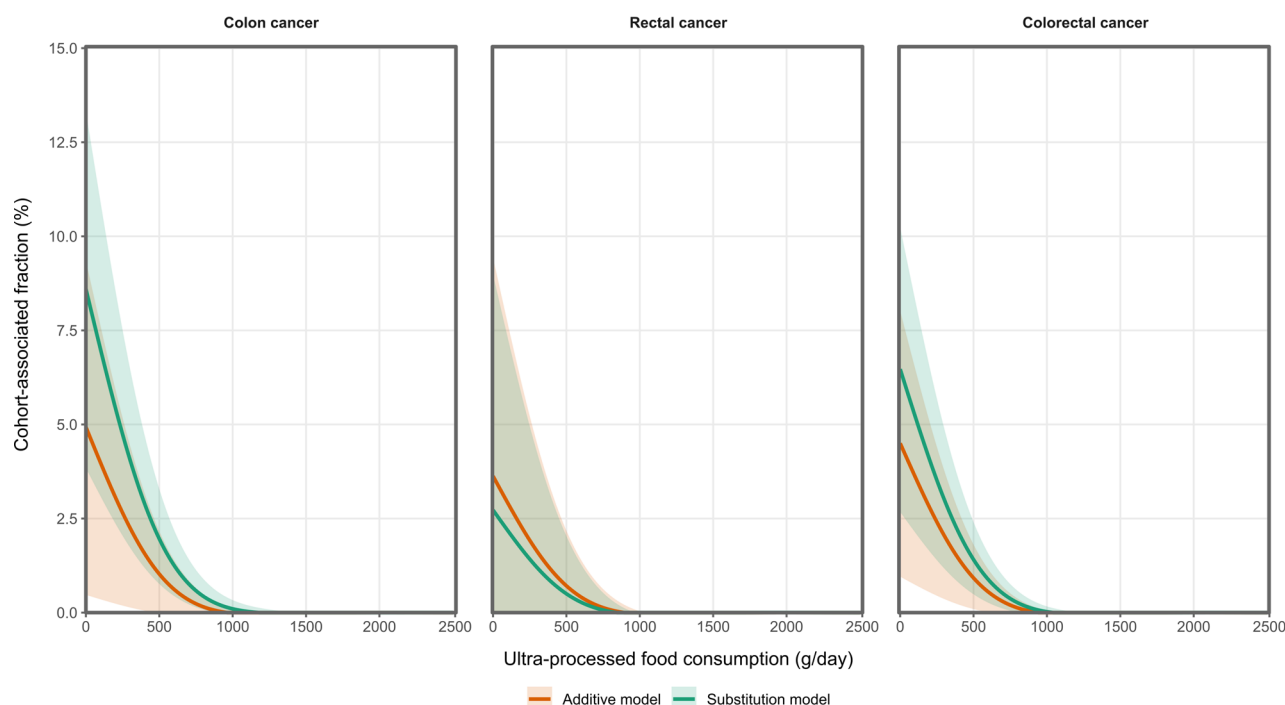


Fig. 2 Cohort-associated fractions (CAF) for colon, rectal, and colorectal cancer incidence, estimated for various maximum intake thresholds of ultra-processed (Nova 4) food intake by mass (g) in total diets, based on model 1. Model 1 was stratified by age at recruitment (in years), sex (male, female), and center and adjusted for marital status (single, married or living together, missing), educational level (none, primary school, secondary school/technical school, higher education, missing), smoking status at baseline (never, former, current, missing), levels of physical activity (inactive, moderately inactive, moderately active, active, missing), and height (cm)

To isolate the effects of food processing from alcoholic beverage consumption, both the overall and substitution analyses were repeated after excluding alcoholic drinks (Tables 2 and 3). This resulted in very similar magnitudes of associations between UPFs and CRC, suggesting that the observed associations were not significantly influenced by alcohol consumption. Subgroup analyses by sex revealed that the associations between UPF consumption and CRC were apparent in women but not in men (Supplemental tables 4–5).

Cohort-associated fraction

In model 1, the CAFs for UPF consumption were estimated to be 5.58% (95%CI: 0.55;10.50) for colon cancer, 4.12% (−2.54;10.58) for rectal cancer, and 5.10% (1.10;9.02) for CRC incidence (Table 2). This corresponds to 211 (20; 398) colon, 85 (−52; 217) rectal, and 298 (64; 527) colorectal cancer cases in the EPIC cohort over the whole follow-up period that could have potentially been prevented, if the participants had no exposure to UPFs.

The substitution analysis provided more realistic estimates of how dietary changes could reduce CRC incidence (Table 3). In model 1, substituting UPFs with unprocessed or minimally processed foods resulted in a CAF of 9.67% (4.36;14.85) for colon cancer, 3.10% (−4.09;10.08) for rectal cancer, and 7.30% (3.05;11.48)

for CRC incidence. This corresponds to 366 (165; 562) colon, 63 (−84; 207) rectal, and 427 (178; 671) colorectal cancer cases in the EPIC cohort. Results were similar when excluding alcoholic beverages from the Nova classification.

When examining the potential effects of limiting UPF intake, setting a maximum of 500 g per day in the substitution model was associated with a CAF for CRC of 1.13% (0.3; 1.98). Similarly, limiting UPF intake to 200 g per day was associated with a CAF for CRC of 3.81% (1.15; 6.16), though no significant reduction was observed for colon cancer (Fig. 2).

Excluding the first two years of follow-up did not alter the findings (results not shown).

Discussion

In this large-scale European cohort study comprising 5,845 CRC cases, we assessed the association between UPF consumption and CRC incidence. Additionally, the CAF, adapted from the PAF methodology, was estimated to quantify the fractions of CRC incidence potentially associated with UPF consumption. UPF consumption was positively associated with CRC incidence while substituting UPFs with unprocessed or minimally processed foods was inversely associated. The CAF for CRC was 7.30%, corresponding to 427 cases that could have been

potentially prevented if individuals had no intake of UPFs at baseline. These findings emphasize the importance of investigating the health impacts of UPF consumption given their growing prevalence in diets, and the increasing incidence rates of colorectal cancer.

Unlike previous studies, which often used proportional intake measures, this study used absolute quantities in grams per day, providing a more straightforward interpretation of UPF associations with CRC incidence [25]. This allowed for the use of substitution models that can provide more nuanced, and realistic estimates. Our findings diverge from cohort studies like Nutrinet-Santé, and the UK Biobank, which reported no clear associations between UPF intake and colon or rectal cancer incidence [16, 17, 26]. These discrepancies may stem from differences in functional units used to express UPF intake (grams vs kilocalories and/or absolute vs relative intakes), dietary assessment methods, statistical power, socio-demographic profiles, or follow-up durations that are shorter than in EPIC. Additionally, the heterogeneity of diets across several countries in the EPIC cohort could be an important advantage. Conversely, consistent with our results, several meta-analyses and reviews have supported a positive association between UPF consumption and CRC incidence [13, 18, 27].

This study found positive associations between UPF consumption and CRC incidence among women, while similar but statistically non-significant associations were observed among men. The lack of statistical significance in men may reflect lower statistical power or differences in dietary behaviours. To our knowledge, this is the first study to assess the potential burden of UPF consumption associated with CRC in the EPIC cohort. One previous study was identified, that examined the PAF of premature deaths attributable to UPF consumption in the Brazilian population and reported that a 10% reduction in UPF intake could potentially prevent 10.5% of such deaths [28].

To interpret CAF results, it is crucial to acknowledge that causality cannot be assumed, as evidence linking UPFs to CRC remains suggestive [24]. The CAF, therefore, emphasizes associations rather than causation, making interpretation still hard, although reflecting the specific dietary habits of the EPIC cohort baseline. Nevertheless, it is well-acknowledged that dietary factors play an important role in the development of CRC [29]. For example, robust evidence indicates that CRC incidence can be reduced by the consumption of whole grains, dairy products, and fibre-rich foods, whereas red, and processed meats, as well as alcohol, are associated with increased risk [30]. Given the broad spectrum of foods classified as UPFs, it is plausible that divergent associations between specific UPFs and health outcomes exist, which could explain the wide confidence intervals

observed in our estimates. This suggests that future studies may benefit from investigating specific food subgroups or the common industrially derived ingredients and additives used in many UPFs.

In our study, CAFs were only estimated for the first model, as it had to reflect the total 'effect' on CRC incidence. Our findings suggest that the association between UPF consumption and CRC may be mediated by protective nutrients found in unprocessed or minimally processed foods, such as fibre, calcium, and vitamin D, and vitamin C. Adjusting for these nutrients slightly reduced the strength of inverse associations in substitution models, highlighting the importance of accounting for nutrient differences. This underscores the need for clearly defined research questions, as analytical choices can influence observed associations.

In addition to being high in energy and low in nutritional quality, other mechanisms may contribute to the harmful effects of UPFs [12, 13]. For example, ultra-processing can alter food matrices, affecting nutrient bioavailability and bioaccessibility [31]. High-temperature processing generates neo-formed contaminants, such as acrylamide, classified as carcinogenic and genotoxic by the International Agency for Research on Cancer and the European Food Safety Authority [32, 33]. Furthermore, the processing of meat can produce potential carcinogens like sodium nitrite, which may increase CRC risk [30, 34]. Moreover, UPFs often include additives like emulsifiers and artificial sweeteners, which alter the gut microbiome, promoting inflammation and carcinogenesis [9]. Furthermore, UPF packaging may contain carcinogenic substances such as bisphenols, which are endocrine-disrupting chemicals found in food packaging materials. Higher urinary concentrations of these substances have been observed in individuals with higher UPF consumption [9]. Bisphenol A, in particular, has been identified by the European Food Safety Authority as a substance of concern [9, 35]. Experimental studies using cellular models have demonstrated that bisphenol A contributes to the development and progression of colon cancer [36].

Key strengths of this study include its prospective study design, large sample size, and diet heterogeneity. Additionally, this study utilized a comprehensive approach to adjust for various factors, applying a causal inference perspective. For example, rather than relying on a compound variable like total energy intake, the study instead adjusted for total energy intake using an all-component approach. This method avoids potential bias that might arise from mixing different units, such as grams and calories per day, which could obscure interpretations in substitution analyses. For instance, substituting 10 g of UPFs with 10 g of unprocessed or minimally processed foods may involve differences in energy intake that are not fully accounted for if only total energy intake is adjusted for

[25]. Also, we assessed UPF consumption in grams per day rather than as a percentage of total intake, allowing for a clearer understanding of the potential impact of increasing intake of these foods in association with CRC incidence. Additionally, by employing both additive and substitution models we provide a more comprehensive view of their associations with CRC incidence. Furthermore, this study assessed the CAF at multiple maximum intake thresholds, offering a more practical understanding of achievable risk reductions [24]. Our choice of the Nova classification system warrants discussion given the availability of multiple food processing frameworks. However, the Nova classification offers several advantages: (1) as it is the most extensively validated system in epidemiological research, enabling direct comparison with existing literature; (2) the system has demonstrated associations with health outcomes across diverse populations and dietary patterns; and (3) has been adopted by international health organizations, including the WHO and FAO, for dietary guidelines and public health recommendations. Nevertheless, we acknowledge that different classification systems might yield varying results, and future research comparing multiple processing frameworks would strengthen the evidence base.

Nevertheless, this study has several notable limitations. The cohort is not nationally representative and may over-represent individuals of white ethnicity, those of middle-age and of higher socio-economic status. The Nova classification system has been criticized for its heterogeneity of foods in each class, encompassing a wide range of products with varying nutritional properties. Dietary questionnaires, not initially designed for assessing food processing, may introduce misclassification bias. However, various methods were employed to address potential issues related to the time lag between data collection and current analysis. For instance, the use of three-bound scenarios—lower bound (reflecting the lowest degree of processing), middle bound (the most probable scenario), and upper bound (a conservative, more processed scenario), helped investigate potential effects of misclassifications or the validation of the association of food processing [21]. Additionally, by adjusting for both all energy-contributing nutrients and those known to reduce CRC risk, this study aimed to account for differences among various foods classified under UPFs. Despite these adjustments, residual confounding cannot be entirely ruled out. For instance, individuals with lower income or socio-economic status often consume higher amounts of UPFs, a factor that cannot be sufficiently accounted for in the EPIC cohort [37]. Moreover, the compound variables used for energy and nutrient adjustments may make the interpretations of associations more obscure. Also, while UPFs contributed 32% of total energy in the EPIC cohort, this might underestimate contemporary consumption

levels [38]. Misclassification of some food items might also occur due to limited information on food processing. Lastly, our study relies on baseline dietary assessments without follow-up dietary data. This approach assumes that diets remain stable throughout the follow-up period, which may not capture individual changes over time. Evidence indicates that dietary patterns can shift considerably over decades, particularly with respect to UPF consumption, which has risen sharply in European populations since the 1990s.

Conclusion

In summary, this is the first study to estimate the magnitude of associations between UPF consumption and CRC incidence, suggesting that some of the burden of CRC could potentially be mitigated through interventions promoting the consumption of unprocessed or minimally processed foods. While findings should be interpreted cautiously, they provide evidence for public health efforts to reduce UPF intake. Future research should continue to explore substitution approaches to assess potential causality. Given the rising consumption of UPFs, public health interventions and continued research are urgently needed to address the growing burden of CRC.

Abbreviations

BMI	Body mass index
CAF	Cohort-associated fraction
CRC	Colorectal cancer
DAG	Directed acyclic graph
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food frequency questionnaire
IARC	International Agency for Research on Cancer
PAF	Population-attributable fraction
UPFs	Ultra-processed foods

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12889-026-27225-3>.

Supplementary Material 1.

Inclusion

The present study is relevant to guiding local agrifood systems transformation and nutrition research. Local research teams were invited to contribute to the manuscript and were included as co-authors in accordance with ICJME criteria.

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Authors' contributions

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Data availability

EPIC data and biospecimens are available to investigators in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centres. The use of a random sample of anonymized data from the EPIC study can be requested by contacting epic@iarc.fr. For information on the EPIC data access policy and on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at iarc.who.int.

Declarations

Ethics approval and consent to participate

The EPIC study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study

participants were approved by the Internal Review Board of the International Agency for Research on Cancer (IRB-IARC). Written informed consent was obtained from all subjects. For participants who were illiterate or otherwise unable to provide written consent, informed consent was obtained from a legal guardian or an appropriate representative on their behalf.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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