Intake of food additive preservatives and incidence of cancer: results from the NutriNet-Santé prospective cohort

Anaïs Hasenböhler,[1,2] Guillaume Javaux,[1] Marie Payen de la Garanderie,[1,2] Fabien Szabo de Edelenyi,[1] Paola Yvroud-Hoyos,[1] Cédric Agaësse,[1] Alexandre De Sa,[1] Inge Huybrechts,[2,3] Fabrice Pierre,[2,4] Marc Audebert,[2,4] Xavier Coumoul,[2,5] Chantal Julia,[1,6] Emmanuelle Kesse-Guyot,[1,2] Benjamin Allès,[1] Valérie Deschamps,[7] Serge Hercberg,[1,2,6] Benoit Chassaing,[2,8] Bernard Srour,[1,2] Mélanie Deschasaux-Tanguy,[1,2] Mathilde Touvier[1,2]

For numbered affiliations see end of the article

Correspondence to: M Touvier m.touvier@eren.smbh.univ-paris13.fr; (ORCID 0000-0002-8322-8857)

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ABSTRACT

OBJECTIVE

To investigate the association between intake of food additive preservatives and cancer incidence in a large prospective cohort.

DESIGN

Prospective cohort.

SETTING

French NutriNet-Santé cohort, 2009-23.

PARTICIPANTS

105 260 participants (≥15 years) without prevalent cancer who completed at least two 24 hour dietary records at baseline.

MAIN OUTCOME MEASURES

Cumulative time dependent intake of preservatives, including those in industrial food brands, assessed using repeated 24 hour dietary records and evaluated through multiple composition databases and ad hoc laboratory assays in food products for the most frequently consumed additive-food pairs. Associations between intake of three categories of preservatives (defined as sex specific thirds if preservative was consumed by at least a third of participants, otherwise defined as non-consumers and lower or higher consumers separated by the sex specific median) and cancer incidence were characterised using multivariable proportional hazards Cox models adjusted for potential confounders.

RESULTS

Mean age of participants was 42.0 years (standard deviation (SD 14.5) years), and 78.7% were women. 4226 participants received a diagnosis of incident cancer (mean follow-up 7.57 (SD 4.56) years), comprising 1208 breast, 508 prostate, 352 colorectal, and 2158 other cancers). Higher intakes of several preservatives were associated with higher cancer incidence: total non-antioxidants with overall cancer (hazard ratio for higher *v* non-consumers or lower consumers 1.16 (95% confidence interval (CI) 1.07 to 1.26); absolute risk of cancer at age 60 years, respectively, 13.3%, 12.1%) and breast cancer (1.22 (1.05 to 1.41); 5.7%, 4.8%); total sorbates, specifically potassium sorbate, with overall cancer (1.14 (1.04 to 1.24); 13.4%, 11.8%) and breast cancer (1.26 (1.07 to 1.49); 5.7%, 4.6%); total sulfites with overall cancer (1.12 (1.02 to 1.24); 13.4%, 11.9%); potassium metabisulfite with overall cancer (1.11 (1.03 to 1.20); 13.5%, 12.0%) and breast cancer (1.20 (1.04 to 1.38); 5.7%, 4.9%); sodium nitrite with prostate cancer (1.32 (1.02 to 1.70); 4.2%, 3.4%); potassium nitrate with overall cancer (1.13 (1.05 to 1.23); 14.0%, 12.0%) and breast cancer (1.22 (1.05 to 1.41); 5.9%, 4.8%); total acetates with overall cancer (1.15 (1.06 to 1.25); 14.3%, 12.2%) and breast cancer (1.25 (1.07 to 1.45); 6.1%, 4.9%); acetic acid with overall cancer (1.12 (1.01 to 1.25); 14.4%, 12.4%); and sodium erythorbate with overall cancer (1.12 (1.04 to 1.22); 13.5%, 11.9%) and breast cancer (1.21 (1.04 to 1.41); 5.7%, 4.8%). 11 of the 17 individually studied preservatives were not associated with cancer incidence.

CONCLUSION

Multiple positive associations between intake of preservatives widely used in industrial foods and higher cancer incidence (overall, breast, and prostate) were observed in this large prospective cohort. Epidemiology based on health effect biomarkers and experimental research are needed to gain insight into outcome pathways. If confirmed, these new data call for the re-evaluation of regulations governing the food industry's use of these additives, to improve consumer protection. In the meantime, the findings support recommendations for consumers to favour freshly made, minimally processed foods.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03335644.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Preservatives are substances added to packaged foods to prolong shelf life, protecting against deterioration caused by micro-organisms and oxidation

Experimental in vivo and in vitro studies suggested negative impacts of preservatives through mechanisms involving advanced glycation end products, as well as mutagenic and potentially carcinogenic activities

WHAT THIS STUDY ADDS

Multiple positive associations between intake of preservatives widely used in industrial foods and higher cancer incidence (overall, breast, prostate) were observed in this large prospective cohort

If confirmed, these new data call for the re-evaluation of regulations governing the use of these additives by the food industry, to improve consumer protection and support recommendations for consumers to favour freshly made, minimally processed foods

Introduction

Adding preservative additives to foods has become a standard practice in today's food industry. In 2024, more than 20% of food items on the Open Food Facts World database contained at least one of these

additives.[1] The European parliament defines food additives as substances added to packaged products to prolong shelf life: protecting the foods against deterioration due to microorganisms, growth of pathogenic microorganisms, and deterioration as a result of oxidation, such as rancidity and colour changes.[2]

Between 2004 and 2025, the European Food Safety Authority (EFSA) re-evaluated 25 food preservative groups. This resulted in the establishment of reference values for acceptable daily intake of 16 preservatives or their respective groups.[3] Acceptable daily intakes concerned a range of toxicological endpoints, including behavioural, carcinogenic, developmental, haematological, reproductive, and thyroid toxicity, as well as growth retardation, increased blood methaemoglobin levels, and increased mortality, all based on experimental data. A recent in vitro evaluation of the toxic effects of food additives in four human cell models suggested that some preservatives may have cytotoxic properties or enhance cell proliferation.[4] It was suggested that several preservatives induce the production of advanced glycation end products[5] and exert mutagenic[5] and potentially carcinogenic activities.[6-8] Some preservatives (such as ascorbic acid and alpha tocopherol) also occur in their natural forms in foods and beverages (eg, antioxidant vitamins C and E). Some epidemiological studies associated the consumption of these substances through natural dietary sources (eg, fruit, vegetables) with lower cancer risk.[9] Such a beneficial property could be hypothesised to apply to the corresponding food additives. Other studies, however, raised the possibility that supplementation with these naturally occurring compounds may have harmful effects.[10] Potentially, the same substance may involve different biochemical activities and have different health effects depending on the dose and the food matrix in which it is incorporated, with, for instance, the cell environment modulating a switch from antioxidant to pro-oxidant activity.[11] Yet, these studies did not investigate food additives specifically. Except for rare preservatives such as nitrites and nitrates[12-16] used in a limited number of products (ie, mostly processed meat), no data on intake of food preservatives were available in previous cohort studies owing to the lack of brand specific information and important variability in composition of the additives between commercial products. We therefore quantified the cumulative time dependent intake of preservatives and examined the associations with cancer incidence in a large prospective cohort with detailed dietary data.

Methods

This study followed the STROBE-NUT statement for observational studies in nutritional epidemiology.[17] We used data from the French NutriNet-Santé prospective e-cohort, launched in 2009, to investigate the association between nutrition and health.[18] The NutriNet-Santé protocol is available on the study website (https://info.etude-nutrinet-sante.fr/siteinfo/article/3). Participants aged 15 years and older were invited to participate in the study through a dedicated web based platform (https://etude-nutrinet-sante.fr/) and regularly answered questionnaires on dietary intakes, health, anthropometric measures,[19 20] physical activity,[21] lifestyle, and sociodemographic factors.[22] Each participant provided an electronic informed consent form from the NutriNet-Santé cohort before enrolment.

Dietary data collection

At registration and every six months, participants completed series of three validated[23-25] web based 24 hour dietary records. At each period, the dietary records were randomly assigned to three non-consecutive days over two weeks (two weekdays and one weekend day). Supplementary eMethod1 provides details on collection of dietary data and identification of individuals who reported unrealistically lower or higher energy intakes. Dietary intakes of energy, fibre, macronutrients, and micronutrients (including vitamins C and E) were assessed by merging with the NutriNet-Santé food composition table.[26] Using multiple sources, we quantified participants' intakes of naturally occurring acetic and citric acids, nitrites, nitrates, and sulfites (see supplementary eMethod2 for details).

Intakes of food additive preservatives

Assessment of food additive intake in the NutriNet-santé cohort through brand specific data from the 24 hour dietary records has been described previously (also see supplementary eMethod2).[27] Briefly, we merged three composition databases with the NutriNet-Santé database to determine the presence of any specific food additives in industrial products. Dynamic matching was used to account for potential reformulations: products were matched on dates, and each participant's date of consumption of each food or beverage was used to match the product to the closest composition data available, thus accounting for potential reformulations. Doses were determined by ad hoc laboratory analyses for the most frequently consumed additive-food pairs and doses retrieved from other sources such as the European Food Safety Authority after an official request for public access to the document. The 80 preservatives listed in the Codex General Standard for Food Additives database[28] or UK Food Standards Agency[29] were eligible for the present study. We decided to include preservatives in themselves as defined by regulation (EC) No 1333/2008[2] and antioxidants as both prevent the spoilage of food, with the latter preserving food through an antioxidant mode of action specifically. In this paper, we included preservatives with either non-antioxidant or antioxidant mode of action and all food additives with preservative properties. Some preservatives possessed additional key properties (eg, emulsification). We summed individual food preservatives with similar chemical structures into several groups: sorbates (European codes E200,

E202, E203), benzoates (E210, E211, E212), sulfites (E220, E221, E222, E223, E224, E225, E228), nitrites (E249, E250), nitrates (E251, E252), acetates (E260, E261, E262, E263), propionates (E280, E281, E282), ascorbates (E300, E301, E302, E304), tocopherols (E306, E307, E307b, E307c), erythorbates (E315, E316), butylates (E319, E320, E321), citrates (E330, E332, E333), and EDTA (ethylenediaminetetra-acetate) (E385, E386).

Cancer ascertainment

We used a multi-source approach to ascertain participants with incident cancer. Throughout follow-up, participants could report health events, medical treatment, and examinations through the biannual health questionnaires or at any time directly through the health interface of their account. A physician expert committee validated every cancer event against official medical records. Moreover, the NutriNet-Santé cohort was linked to the national health insurance system database to collect additional information on medical treatments and consultations, and to the French national mortality registry to identify deaths and causes of death. Cases were then classified using ICD-10 (international classification of diseases, 10th revision) codes.[30] In this study, we considered incident cancer to include all primary cancers diagnosed between enrolment and 31 December 2023, except for basal cell carcinoma of the skin.

Statistical analyses

Participants from the NutriNet-Santé cohort were included in the analysis if they completed at least two 24 hour dietary records during their first two years of follow-up, did not under-report or over-report energy intake, and did not have any prevalent cancer. Baseline participants' characteristics are described as mean (standard deviation (SD)) for quantitative variables and as number (percentage) for qualitative variables for the overall population and according to each baseline sex specific third of total preservative intake. Baseline daily intakes of preservatives are reported as mean (SD) and median (interquartile range (IQR)), including per kilogram of body weight. We also computed the variations of preservative intake in participants with at least two intake periods, between the first and second half of follow-up (see supplementary eTable1). A correlation matrix was generated to visualise the Spearman correlations between intakes of individual additives (see supplementary eFigure1). For each studied preservative or group of preservatives, we categorised participants into lower, medium, and higher consumers defined as sex specific thirds if the preservative was consumed by at least a third of participants, and as non-consumers and lower or higher consumers separated by the sex specific median otherwise (cut-offs provided in supplementary eTable2). The relations between intake of preservatives coded as cumulative time dependent variables and cancer incidence were investigated using multivariable proportional hazard Cox models, with age as the time scale. Hazard ratios and 95% confidence intervals (CIs) were calculated. Participants contributed person time to the models from their age at enrolment in the cohort until age at the date of cancer diagnosis, death, last contact, or 31 December 2023, whichever occurred first. A counting process structure was used, with cumulative time dependent dietary variables updated every two years (preservative intake and dietary covariates). Intake during a specific period was computed using a weighted average of the most recent two year period and previous periods (see supplementary eMethod3), thereby using all available dietary record data. Based on the directed acyclic graph (see supplementary eFigure2), we adjusted the main model for sociodemographic (age (time scale), sex, educational level), anthropometric (body mass index, height), lifestyle and behavioural (physical activity, smoking status, number of smoked cigarettes in pack years), genetic predisposition (family history of cancer), and dietary factors (number of dietary records, time dependent daily intakes of energy without alcohol, alcohol, saturated fats, sodium, fibre, sugars, fruit and vegetables, dairy products, and red and processed meats—or haem iron for nitrites and nitrates models only). Breast cancer models were additionally adjusted for reproductive and hormonal factors: ever use of oral contraception (overall breast and premenopausal models only), age at menarche, number of biological children, menopausal status (overall breast model only), and hormonal treatment for menopause (overall breast and postmenopausal models only). In addition, when applicable we adjusted each model for intake of the corresponding substance from natural sources. We computed restricted cubic splines to investigate non-linear dose-response associations and tested the proportional hazard assumption using the Schoenfeld residual method. P values with and without correction for multiple testing by the false discovery rate were computed.[31] Supplementary eMethods3 provides additional information and sensitivity analyses (mutual adjustment for preservatives other than the one studied; adjustment for percentage of total intake weight from ultra-processed foods; for intakes of colours, emulsifiers, and artificial sweeteners; for industrial trans fatty acid intake; for intakes of polyunsaturated fatty acids and haem iron; for standard deviation of individual participant intakes between periods, restricted to participants with at least two or three follow-up periods; and main model without update of intake cut-offs (defined at period 1)). Interactions between each preservative intake and percentage of ultra-processed foods in the diet (in weight), the number of dietary records per period, and antioxidants and smoking status were tested by entering the product of the two variables into Cox models.

Patient and public involvement

The research question in this article resulted from a strong concern of the participants involved in the NutriNet-Santé cohort, and of the public in

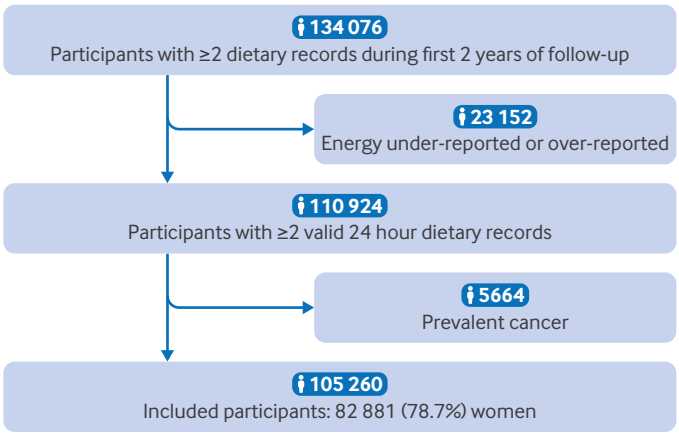

Fig 1 | Flow chart of participants from NutriNet-Santé cohort, 2009-23 (n=105 260)

general. Participants were not asked to advise on data interpretation or manuscript writing. This was primarily due to the lack of infrastructure, resources, funding, and time necessary to support public involvement in these aspects of the research process. However, participants provided feedback on our questionnaires and study design during follow-up, which we incorporated when feasible.

Results

Descriptive characteristics

The population study comprised 105 260 adults (fig 1), 78.7% of whom were women. On average, participants completed a total of 21 (SD 18) 24 hour dietary records. Mean age at baseline was 42.0 (SD 14.5) years. Compared with lower consumers (lowest third), higher consumers of total food preservatives (upper third) tended to be younger, less physically active, and less likely to have a family history of cancer, and they were likely to consume less alcohol and more ultra-processed foods and drinks (table 1). Table 2 and table 3 show the intakes of non-antioxidant and antioxidant preservatives, respectively. Overall, 99.7% of participants consumed food additive preservatives in the first two years of follow-up. Out of the 58 preservatives investigated in this study, 17 were consumed by at least 10% of the participants and thus were individually evaluated in association with cancer incidence (table 2 and table 3). In terms of proportion of consumers, the main preservatives were citric acid (91.7% of consumers), lecithins (87.1%), total sulfites (83.5%), ascorbic acid (83.5%), sodium nitrite (73.8%), potassium sorbate (65.5%), sodium erythorbate (52.7%), sodium ascorbate (50.3%), potassium metabisulfite (44.5%), and potassium nitrate (32.6%). No strong correlation between intakes of preservatives was identified (see supplementary eFigure1). Supplementary eTable1 displays the variations in preservative intake in participants with at least two intake periods, between the first and second half of follow-up. For all preservatives studied, most of the participants had stable intakes during the follow-up period, and when variations were observed, similar proportions of participants showed decreased and increased intakes.

Manufacturers used preservatives ubiquitously across various food groups (fig 2 and supplementary eTable3). Some were, however, more specific to given food groups—for example, 85.4% of sulfite intake was from alcoholic drinks; 53.8% of nitrites, 80.3% of nitrates, and 42.3% of erythorbates from processed meat (apart from processed red meat, offal, and poultry); 43.7% of propionates from refined grains and cereals and 30.4% from whole grains and cereals; 50.4% of ascorbates and 25.4% of citrates from processed fruit and vegetables; and 30.4% of tocopherols from breakfast cereals. In all, 34.6% of preservatives were consumed through ultra-processed foods in this population study (data not tabulated). For food additives that also occurred naturally in the diet, the relative contribution of the source of the food additive preservative varied depending on the compound: from on average 1% for tocopherols or 5% for acetates to 17% for citric acid, 29% for ascorbates, and 63% for sulfites.

No participants exceeded EFSA's acceptable daily intake for sorbates, erythorbates, or nitrates.[3] However, 90 participants exceeded the acceptable daily intake for sulfites, with a mean daily intake of 0.86 (SD 0.17) mg sulfur dioxide/kg body weight mg (median 0.81 (interquartile range 0.75-0.93) mg) and 54 exceeded the acceptable daily intake for nitrites, with a mean daily intake of 0.10 (0.03) mg nitrite ion/kg body weight (0.09 (0.08-0.10) mg).

Associations between preservative intake and cancer incidence

Participants' mean follow-up was 7.57 (SD 4.56) years (796 944 person years). Between 2009 and 2023, 4226 participants received a diagnosis of incident overall cancer, comprising 1208 breast (387 premenopausal and 821 post-menopausal), 508 prostate, 352 colorectal, and 2158 other cancers. Schoenfeld residuals did not refute the proportional hazard assumption (see supplementary eFigure3).

Restricted cubic spline plots (see supplementary eFigure4) generally did not indicate a departure from linearity (P≥0.05 for non-linearity); P values for trend are provided below and in figure 3. For some associations, restricted cubic splines suggested a dose-response relation with plateau effect (P<0.05 for non-linearity)—in this case, the likelihood ratio overall P values (requiring no underlying hypothesis of linearity) are displayed thereafter and in forest plots. Both P trends and overall P values are provided for all tested preservatives in the main model (see supplementary eTable4) and in sensitivity analyses (see supplementary eTable5).

The results of Cox models are presented in figure 3 (non-antioxidants) and figure 4 (antioxidants) for overall (all sites), breast, and prostate cancers (see supplementary eTable4 for premenopausal and post-menopausal breast cancer and colorectal cancer models). No association was observed between total

Table 1 | Baseline characteristics of participants from NutriNet-Santé cohort, 2009-23 (n=105 260). Values are number (percentage) unless stated otherwise

Characteristics	Overall n=105 260	Sex specific thirds of food preservative intake			P value*
		First n=35 087	Second n=35 086	Third n=35 087	
Mean (SD) age (years)	42.0 (14.5)	45.2 (14.6)	42.4 (14.3)	38.4 (13.7)	<0.001
Women	82 881.0 (78.7)	27 627.0 (78.7)	27 627.0 (78.7)	27 627.0 (78.7)	NA
Mean (SD) height (cm)†	166.8 (8.1)	166.2 (8.1)	166.7 (8.1)	167.4 (8.3)	<0.001
Mean (SD) BMI†	23.7 (4.5)	23.5 (4.3)	23.6 (4.3)	23.9 (4.8)	<0.001
Family history of cancer†‡	35 359.0 (33.7)	13 050.0 (37.3)	11 967.0 (34.2)	10 342.0 (29.5)	<0.001
Educational level†:					
Less than a high school degree	18 291.0 (17.5)	6823.0 (19.7)	6005.0 (17.3)	5463.0 (15.7)	<0.001
≤3 years after high school	51 095.0 (49.0)	16 462.0 (47.4)	16 794.0 (48.3)	17 839.0 (51.3)	
>3 years after high school	34 876.0 (33.5)	11 421.0 (32.9)	11 970.0 (34.4)	11 485.0 (33.0)	
Smoking status†:					
Never	52 973.0 (50.5)	16 685.0 (47.7)	17 858.0 (51.0)	18 430.0 (52.6)	<0.001
Former	33 848.0 (32.3)	12 250.0 (35.0)	11 378.0 (32.5)	10 220.0 (29.2)	
Current	18 129.0 (17.3)	6020.0 (17.2)	5750.0 (16.4)	6359.0 (18.2)	
IPAQ physical activity level†:					
Low	22 047.0 (24.2)	6909.0 (22.7)	7327.0 (24.1)	7811.0 (26.0)	<0.001
Moderate	39 181.0 (43.1)	12 743.0 (41.9)	13 436.0 (44.1)	13 002.0 (43.3)	
High	29 698.0 (32.7)	10 778.0 (35.4)	9699.0 (31.8)	9221.0 (30.7)	
Age at menarche†§:					
Never menstruated	88.0 (0.1)	31.0 (0.1)	24.0 (0.1)	33.0 (0.1)	0.71
<12 years	15 352.0 (18.6)	5134.0 (18.7)	5077.0 (18.4)	5141.0 (18.7)	
≥12 years	67 167.0 (81.3)	22 351.0 (81.2)	22 437.0 (81.5)	22 379.0 (81.2)	
No of biological children at baseline§	1.2 (1.2)	1.4 (1.2)	1.3 (1.2)	1.1 (1.2)	<0.001
Menopausal status at baseline†§:					<0.001
Premenopausal	60 419.0 (72.9)	18 009.0 (65.2)	20 122.0 (72.9)	22 288.0 (80.7)	
Post-menopausal	22 415.0 (27.1)	9599.0 (34.8)	7493.0 (27.1)	5323.0 (19.3)	
Use of oral contraception§	28 756.0 (34.7)	7292.0 (26.4)	9746.0 (35.3)	11 718.0 (42.4)	<0.001
Use of hormonal menopausal treatment§	6876.0 (8.3)	2700.0 (9.8)	2457.0 (8.9)	1719.0 (6.2)	<0.001
Mean (SD) intakes:					
Energy without alcohol (kcal/d)	1856.8 (458.1)	1731.4 (418.8)	1856.4 (426.0)	1982.6 (491.0)	<0.001
Alcohol (g/d)	7.7 (11.8)	8.2 (12.4)	7.9 (11.6)	7.1 (11.4)	<0.001
Saturated fat (g/d)	33.3 (12.2)	29.9 (11.1)	33.6 (11.4)	36.5 (13.2)	<0.001
Sodium (mg/d)	2729.8 (896.4)	2590.4 (878.4)	2740.6 (856.8)	2858.6 (932.1)	<0.001
Fibre (g/d)	20.1 (10.1)	20.4 (11.2)	20.1 (9.6)	19.8 (9.4)	<0.001
Sugar (g/d)	93.1 (33.9)	82.9 (31.4)	92.4 (30.1)	104.0 (36.4)	<0.001
Fruit and vegetables (g/d)	464.0 (232.7)	476.0 (246.6)	465.7 (217.0)	450.4 (233.0)	<0.001
Dairy products (g/d)	159.1 (148.0)	152.3 (150.1)	160.3 (144.0)	164.6 (149.7)	<0.001
Red and processed meat (g/d)	76.3 (53.2)	70.9 (54.1)	76.2 (50.2)	81.7 (54.5)	<0.001
Haem iron (mg/d)	1.2 (1.2)	1.2 (1.3)	1.2 (1.1)	1.2 (1.2)	<0.001
Ultra-processed food (% of weight intake)	17.4 (9.9)	14.3 (8.2)	16.4 (8.4)	21.6 (11.5)	<0.001
Total preservative food additive exposure (mg/d)	546.4 (615.9)	163.8 (81.9)	415.8 (76.9)	1059.7 (835.7)	<0.001

IPAQ=International Physical Activity Questionnaire; NA=not applicable; SD=Standard deviation.
All dietary intake data in this table were calculated as the mean daily intake across all records during the first two years of participation in the study (mean number of 24 hour records for each person 6 (SD 3)).
*Kruskal-Wallis rank sum test for continuous variables; Pearson's χ^2 test for categorical variables.
†Missing values: height n=2963 (low consumers: 867; medium consumers: 939; high consumers: 1157); BMI n=2963 (867; 939; 1157); family history of cancer n=316 (136; 117; 63); education level n=998 (381; 317; 300); smoking status n=310 (132; 100; 78); IPAQ physical activity level n=14 334 (4657; 4624; 5053); age at menarche n=274 (in women: 111; 89; 74); and menopausal status at baseline n=47 (in women: 19; 12; 16).
‡Family history of cancer in first degree relatives.
§In women only.

preservatives and cancer incidence (P=0.89 for overall cancer, P=0.95 for breast cancer, P=0.98 for prostate cancer, P=0.80 for colorectal cancer). Higher intakes of several preservatives were associated with higher cancer incidence: total non-antioxidants with overall cancer (P=0.001; absolute risks of cancer at age 60 years in higher consumers versus non-consumers or lower consumers 13.3%, 12.1%) and breast cancer (P=0.02; 5.7%, 4.8%); total sorbates with overall cancer (P=0.01; 13.1%, 12.3%) and breast cancer (P=0.02; 5.6%, 4.9%); potassium sorbate with overall cancer (P=0.01; 13.4%, 11.8%) and breast cancer (P=0.02; 5.7%, 4.6%); total sulfites with overall cancer (P=0.03; 13.4%, 11.9%); potassium metabisulfite with overall cancer (P=0.01; 13.5%, 12.0%) and breast cancer (P=0.01; 5.7%, 4.9%); total nitrites with overall cancer (P=0.004; 12.8%, 12.2%), prostate cancer (P=0.02; 4.3%, 3.4%), and breast cancer (P=0.003; 5.4%, 5.1%); sodium nitrite with overall cancer (P=0.003; 12.8%, 12.2%), prostate cancer (P=0.03; 4.2%, 3.4%), and breast cancer (P=0.002; 5.4%, 5.1%); total nitrates with overall cancer (P=0.001; 14.0%, 12.0%) and breast cancer (P=0.003; 5.9%, 4.8%); potassium nitrate with overall cancer (P=0.001; 14.0%, 12.0%) and breast cancer (P=0.003; 5.9%, 4.8%); total acetates with overall

Table 2 | Daily intake of non-antioxidant food preservatives among study participants from NutriNet-Santé cohort, 2009-23 (n=105 260)

		Total participants				Consumers only		
Preservative type	European code	Mean (SD) mg/d/kg of body weight	Median (IQR) mg/d/kg of body weight	Mean (SD) mg/d	Median (IQR) mg/d	Mean (SD) mg/d	Median (IQR) mg/d	Proportion (%)
Total preservatives		8.5 (9.5)	6.3 (3.6-10.4)	546.4 (615.9)	410.2 (234.3-665.2)	547.9 (616.1)	411.3 (235.8-666.1)	99.7
Total non-antioxidants:		0.9 (1.5)	0.4 (0.1-1.0)	55.4 (96.8)	23.3 (6.1-63.7)	57.1 (97.8)	24.9 (7.2-65.7)	97.0
Total sorbates		0.3 (0.5)	0.1 (0.0-0.4)	19.7 (32.0)	7.2 (0.0-26.3)	28.8 (35.1)	17.3 (6.8-37.8)	68.2
Sorbic acid	E200	0.0 (0.1)	0.0 (0.0-0.0)	0.7 (4.9)	0.0 (0.0-0.0)	11.9 (16.4)	6.8 (2.2-15.0)	5.9
Potassium sorbate	E202	0.3 (0.5)	0.1 (0.0-0.3)	17.1 (30.1)	5.4 (0.0-21.3)	26.1 (33.9)	14.4 (5.7-33.7)	65.5
Calcium sorbate	E203	0.0 (0.2)	0.0 (0.0-0.0)	1.9 (9.7)	0.0 (0.0-0.0)	27.7 (25.6)	20.4 (11.4-35.7)	6.8
Total benzoates		0.0 (0.0)	0.0 (0.0-0.0)	0.2 (2.3)	0.0 (0.0-0.0)	6.0 (9.7)	3.0 (1.0-7.0)	4.0
Benzoic acid	E210	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.1)	0.0 (0.0-0.0)	8.9 (6.6)	9.1 (3.1-9.9)	0.0
Sodium benzoate	E211	0.0 (0.0)	0.0 (0.0-0.0)	0.2 (1.9)	0.0 (0.0-0.0)	5.2 (8.8)	2.5 (0.8-5.9)	3.5
Potassium benzoate	E212	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (1.2)	0.0 (0.0-0.0)	10.1 (12.8)	5.9 (2.9-11.9)	0.5
Total sulfites		0.1 (0.1)	0.0 (0.0-0.1)	3.9 (5.7)	1.8 (0.2-5.2)	4.6 (5.9)	2.6 (0.8-6.2)	83.5
Sulfur dioxide	E220	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (0.6)	0.0 (0.0-0.0)	0.7 (1.4)	0.4 (0.2-0.8)	13.3
Sodium sulfite	E221	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	0.2 (0.2)	0.1 (0.1-0.3)	1.2
Sodium hydrogen sulfite	E222	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.2)	0.0 (0.0-0.0)	0.3 (0.8)	0.1 (0.0-0.2)	3.8
Sodium metabisulfite	E223	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (1.0)	0.0 (0.0-0.0)	1.3 (2.9)	0.7 (0.4-1.3)	9.6
Potassium metabisulfite	E224	0.0 (0.0)	0.0 (0.0-0.0)	0.3 (0.7)	0.0 (0.0-0.2)	0.6 (1.0)	0.2 (0.1-0.6)	44.5
Potassium sulfite	E225	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	2.3 (NA)	2.3 (2.3-2.3)	0.0
Potassium hydrogen sulfite	E228	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (0.5)	0.0 (0.0-0.0)	1.0 (1.5)	0.5 (0.2-1.1)	7.0
Nisin	E234	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (0.1)	0.0 (0.0-0.1)	2.3
Natamycin	E235	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	0.7
Hexamethylene tetramine	E239	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.1)	0.0 (0.0-0.0)	0.3
Dimethyl dicarbonate	E242	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.7)	0.0 (0.0-0.0)	20.2 (28.5)	10.7 (6.7-22.3)	0.0
Total nitrites		0.0 (0.0)	0.0 (0.0-0.0)	0.2 (0.3)	0.1 (0.0-0.3)	0.3 (0.3)	0.2 (0.1-0.4)	73.8
Potassium nitrite	E249	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (0.1)	0.1 (0.0-0.1)	0.8
Sodium nitrite	E250	0.0 (0.0)	0.0 (0.0-0.0)	0.2 (0.3)	0.1 (0.0-0.3)	0.3 (0.3)	0.2 (0.1-0.4)	73.8
Total nitrates		0.0 (0.0)	0.0 (0.0-0.0)	0.2 (0.5)	0.0 (0.0-0.2)	0.6 (0.8)	0.4 (0.2-0.8)	32.6
Sodium nitrate	E251	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.1)	0.0 (0.0-0.0)	0.3 (0.6)	0.0 (0.0-0.3)	0.9
Potassium nitrate	E252	0.0 (0.0)	0.0 (0.0-0.0)	0.2 (0.5)	0.0 (0.0-0.2)	0.6 (0.8)	0.4 (0.2-0.8)	32.6
Total acetates		0.3 (1.2)	0.0 (0.0-0.0)	18.4 (73.2)	0.0 (0.0-0.0)	100.0 (144.8)	47.6 (14.7-129.3)	18.4
Acetic acid	E260	0.2 (1.1)	0.0 (0.0-0.0)	16.0 (71.4)	0.0 (0.0-0.0)	157.0 (166.7)	107.1 (57.5-197.1)	10.2
Sodium acetates	E262	0.0 (0.2)	0.0 (0.0-0.0)	2.4 (11.8)	0.0 (0.0-0.0)	23.2 (29.7)	14.2 (7.1-28.3)	10.2
Total propionates		0.2 (0.5)	0.0 (0.0-0.1)	12.6 (32.6)	0.0 (0.0-5.6)	48.6 (48.6)	33.6 (17.9-61.9)	25.9
Propionic acid	E280	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.3)	0.0 (0.0-0.0)	4.1 (4.1)	2.8 (1.4-5.3)	0.2
Sodium propionate	E281	0.0 (0.1)	0.0 (0.0-0.0)	0.2 (5.4)	0.0 (0.0-0.0)	33.5 (54.4)	17.1 (9.6-34.3)	0.7
Calcium propionate	E282	0.2 (0.5)	0.0 (0.0-0.1)	12.3 (32.1)	0.0 (0.0-3.8)	48.5 (48)	33.7 (18.1-61.9)	25.4
Sodium tetraborate (borax)	E285	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	4.5 (NA)	4.5 (4.5-4.5)	0.0
Lysozyme	E1105	0.0 (0.0)	0.0 (0.0-0.0)	0.2 (2.1)	0.0 (0.0-0.0)	7.1 (10.2)	2.9 (1.0-9.1)	2.8

IQR=interquartile range; NA=not applicable; SD=standard deviation.
All baseline food additive intake data are calculated as the mean intake during the first two years of participation in the study.
The proportion of consumers was nil for the several authorised food preservatives: calcium benzoate (E213), ethyl p-hydroxybenzoate (E214), sodium ethyl p-hydroxybenzoate (E215), methyl p-hydroxybenzoate (E218), sodium methyl p-hydroxybenzoate (E219), potassium acetate (E261), calcium acetate (E263), and carbon dioxide (E290).
The type of the food additive is defined by the Codex General Standard for Food Additives (https://www.fao.org/gsfaonline/additives/index.html).

cancer (P=0.003; 14.3%, 12.2%) and breast cancer (P=0.02; 6.1%, 4.9%); acetic acid with overall cancer (P=0.01; 14.4%, 12.4%); total erythorbates with overall cancer (P<0.001; 13.5%, 11.9%) and breast cancer (P=0.01; 5.7%, 4.8%); and sodium erythorbate with overall cancer (P<0.001; 13.5%, 11.9%) and breast cancer (P=0.01; 5.7%, 4.8%). For colorectal cancer, the statistical power was limited owing to a lower number of participants with a diagnosis; no association was detected except for a suggested inverse relation with rosemary extracts (P=0.04; 1.0%, 1.2%).

Overall, associations were similar across all sensitivity analyses (see supplementary eTable4). Only a few exceptions were borderline with a restriction to participants with at least two two-year follow-up periods and lost statistical significance with ≥3 periods (eg, for total and sodium nitrites and overall and prostate cancers), probably owing to a reduced number of participants with incident cancer per person years (exclusion of more recently enrolled participants). No interaction was detected with percentage of ultra-processed foods in the diet (in weight), with number of dietary records in each period, or between antioxidants and smoking status (all P>0.05, data not tabulated).

Discussion

This study found multiple associations between preservatives that are widely used in industrial foods and beverages on the European market (potassium sorbate, potassium metabisulfite, sodium nitrite, potassium nitrate, acetic acid, and sodium erythorbate) and higher incidences of overall, breast, and prostate cancers. Most associations were observed for non-antioxidant preservatives. Among antioxidant preservatives, only total erythorbates and specific

Table 3 | Daily intake of antioxidant food preservatives among study participants from NutriNet-Santé cohort, 2009-23 (n=105 260)

		Total participants				Consumers only		
Preservative type	European code	Mean (SD) mg/d/kg of body weight	Median (IQR) mg/d/kg of body weight	Mean (SD) mg/d	Median (IQR) mg/d	Mean (SD) mg/d	Median (IQR) mg/d	Proportion (%)
Total preservatives		8.5 (9.5)	6.3 (3.6-10.4)	546.4 (615.9)	410.2 (234.3-665.2)	547.9 (616.1)	411.3 (235.8-666.1)	99.7
Total antioxidants		7.6 (9.2)	5.6 (3.0-9.2)	491.1 (598.7)	359.8 (198.2-593)	494.8 (599.5)	362.2 (202.0-596.0)	99.2
Total ascorbates		1.1 (1.5)	0.5 (0.1-1.5)	68.3 (90.7)	35.4 (7.7-96.1)	76.4 (92.6)	45.1 (14.0-105.5)	89.4
Ascorbic acid	E300	1.0 (1.4)	0.4 (0.0-1.4)	61.2 (89.7)	24.9 (2.2-87.8)	73.3 (93.5)	41.9 (7.7-104.8)	83.5
Sodium ascorbate	E301	0.1 (0.2)	0.0 (0.0-0.2)	6.9 (11.6)	0.3 (0.0-10.1)	13.6 (13.3)	10.0 (5.1-17.7)	50.3
Calcium ascorbate	E302	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.1)	0.0 (0.0-0.0)	1.3 (1.4)	0.9 (0.4-1.5)	0.1
Fatty acid esters of ascorbic acid	E304	0.0 (0.0)	0.0 (0.0-0.0)	0.2 (3.1)	0.0 (0.0-0.0)	7.0 (15.4)	1.1 (0.4-5.7)	3.4
Total tocopherols		0.0 (0.0)	0.0 (0.0-0.0)	0.8 (3.0)	0.0 (0.0-0.0)	3.4 (5.5)	1.6 (0.6-3.8)	23.4
Tocopherol-rich extract	E306	0.0 (0.0)	0.0 (0.0-0.0)	0.5 (2.5)	0.0 (0.0-0.0)	3.6 (5.9)	1.8 (0.7-4.1)	13.4
Alpha tocopherol	E307	0.0 (0.0)	0.0 (0.0-0.0)	0.3 (1.5)	0.0 (0.0-0.0)	2.3 (3.7)	1.0 (0.4-2.5)	12.8
Concentrated tocopherol	E307b	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	1.8 (1.1)	1.7 (1.1-2.4)	0.0
DL alpha tocopherol	E307c	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.4)	0.0 (0.0-0.0)	3.4 (4.3)	2.1 (1.2-4.2)	0.5
Propyl gallate	E310	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (1.4)	0.0 (0.0-0.0)	11.9 (11.7)	7.6 (5.0-14.3)	0.7
Total erythorbates		0.1 (0.3)	0.0 (0.0-0.2)	8.4 (16.6)	1.4 (0.0-10.0)	15.9 (20.1)	9.4 (4.4-19.6)	52.7
Erythorbic acid	E315	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.1)	0.0 (0.0-0.0)	2.8 (2.2)	2.2 (1.3-3.3)	0.1
Sodium erythorbate	E316	0.1 (0.3)	0.0 (0.0-0.2)	8.4 (16.6)	1.4 (0.0-10.0)	15.9 (20.1)	9.4 (4.4-19.6)	52.7
Total butylates		0.0 (0.0)	0.0 (0.0-0.0)	0.1 (1.5)	0.0 (0.0-0.0)	4.7 (8.0)	0.8 (0.2-6.3)	2.6
Tertiary butylhydroquinone (TBHQ)	E319	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.1)	0.0 (0.0-0.0)	2.6 (4.2)	0.7 (0.5-2.5)	0.0
Butylated hydroxyanisole (BHA)	E320	0.0 (0.0)	0.0 (0.0-0.0)	0.1 (1.5)	0.0 (0.0-0.0)	8.1 (9.3)	5.7 (1.5-10.6)	1.4
Butylated hydroxytoluene (BHT)	E321	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.1)	0.0 (0.0-0.0)	0.4 (0.6)	0.2 (0.1-0.3)	1.2
Lecithins	E322	0.9 (2.2)	0.6 (0.2-1.2)	57.8 (146.8)	35.9 (10.1-75.0)	66.4 (155.5)	44.0 (19.5-82.8)	87.1
Total citrates		5.1 (8.4)	3.1 (1.1-6.1)	327.6 (543.0)	203.8 (73.9-390.6)	357.2 (557.6)	227.0 (106.8-416.1)	91.7
Citric acid	E330	5.1 (8.4)	3.1 (1.1-6.1)	327.6 (543.0)	203.8 (73.9-390.6)	357.2 (557.6)	227.0 (106.8-416.1)	91.7
Tartaric acid	E334	0.1 (0.5)	0.0 (0.0-0.0)	5.0 (32.1)	0.0 (0.0-0.0)	78.3 (102.6)	45.0 (8.6-104.3)	6.3
Phosphoric acid	E338	0.2 (0.7)	0.0 (0.0-0.0)	14.0 (45.8)	0.0 (0.0-0.0)	66.2 (80.6)	41.2 (19.8-80.3)	21.1
Total EDTA		0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.2)	0.0 (0.0-0.0)	0.3 (0.6)	0.2 (0.1-0.3)	6.1
Calcium disodium EDTA	E385	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.2)	0.0 (0.0-0.0)	0.3 (0.6)	0.2 (0.1-0.3)	4.9
Disodium EDTA	E386	0.0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0)	0.0 (0.0-0.0)	0.2 (0.2)	0.2 (0.1-0.3)	1.3
Extracts of rosemary	E392	0.0 (0.0)	0.0 (0.0-0.0)	0.4 (1.5)	0.0 (0.0-0.0)	1.9 (2.7)	1.0 (0.4-2.3)	22.2
Citric acid esters of monoglycerides and diglycerides of fatty acids	E472c	0.1 (0.9)	0.0 (0.0-0.0)	8.5 (59.9)	0.0 (0.0-0.0)	119.4 (192.1)	53.9 (21.6-142.6)	7.2

EDTA=ethylenediaminetetra-acetate; IQR=interquartile range; SD=standard deviation.
All baseline data are calculated as the mean intake during the first two years of study participation.
The proportion of consumers was nil for several authorised preservatives: gamma tocopherol (E308), delta tocopherol (E309), sodium lactate (E325), potassium lactate (E326), potassium citrate (E332), calcium citrate (E333), 4-hexylresorcinol (E586), and nitrous oxide (E942).
For definitions of preservatives see Codex General Standard for Food Additives (https://www.fao.org/gsfaonline/additives/index.html).

sodium erythorbate were found to be associated with higher incidence of cancer.

Comparison with other population studies

For some preservatives, EFSA data were available to compare intake levels with those observed in our population study (see supplementary eTable6). The order of magnitude was consistent overall. Relatively similar intakes were observed for sorbates, nitrates, propionates, ascorbates, lecithins, and extracts of rosemary. Compared with EFSA data, intakes tended to be lower in the NutriNet-Santé cohort for sulfites, nitrites, and alpha tocopherol, and higher for erythorbates. These differences may result from variations between methods for intake assessment (with data in the NutriNet-Santé cohort based on brand specific repeated 24 hour dietary records versus generic food items, and a generally lower number of records or recalls in studies on which EFSA estimates are based) and from differences in dates of assessment and study populations—for instance, the NutriNet-Santé cohort comprised more women and older participants with lower alcohol and processed meat intakes compared with the French general population.

According to the NOVA definition,[32] food preservatives are not necessarily markers of ultra-processing (unlike other food additives, such as artificial sweeteners and colours). The proportion of additive preservatives from ultra-processed foods in this population study was 34.6%. This probably contributed to the results still being statistically significant after adjustment for the proportion of ultra-processed food in the diet.

That no other cohort study has investigated the associations between intakes of preservatives and cancer incidence probably relates to a lack of data on the consumption of specific industrial foods and thus great variations in additive content from one brand to

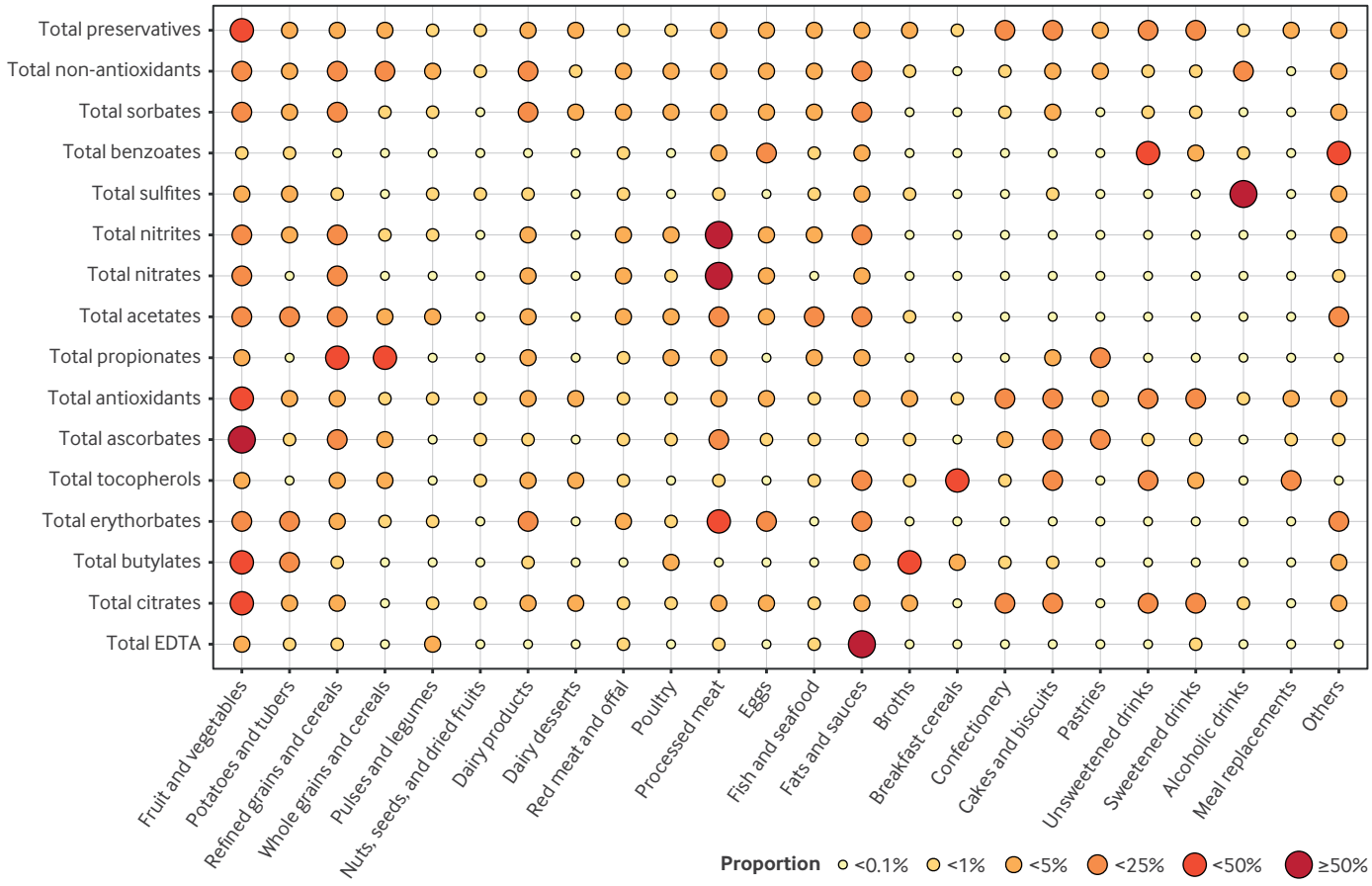

Fig 2 | Dietary sources of food additive preservative intakes among study participants from NutriNet-Santé cohort, 2009-23 (n=105 260). Groups of preservatives were defined as (European codes): total sorbates (E200, E202, E203), total benzoates (E210, E211, E212), total sulfites (E220, E221, E222, E223, E224, E225, E228), total nitrites (E249, E250), total nitrates (E251, E252), total acetates (E260, E261, E262, E263), total propionates (E280, E281, E282), total ascorbates (E300, E301, E302, E304), total tocopherols (E306, E307, E307b, E307c), total erythorbates (E315, E316), total butylates (E319, E320, E321), and total EDTA (E385, E386). See supplementary eTable 3 for detailed percentages. EDTA=ethylenediaminetetra-acetate

another. Comparison with epidemiological literature is therefore not straightforward. Our group published a study on nitrites and nitrates and cancer incidence in NutriNet-Santé.[12] Despite updated methodology (using time dependent cumulative intake) and longer follow-up (two additional years), the results remained globally stable, suggesting that higher intake of additive-originated nitrites was associated with higher incidence of prostate cancer, whereas intake of additive-originated nitrates was associated with higher incidence of breast cancer. A prospective investigation in the Netherlands Cohort Study found a positive association between higher intakes of nitrites from processed meat and pancreatic cancer.[16] Another prospective study in the Iowa Women's Health Study found a positive association between nitrites from processed meat and renal cancer among older women.[15] Two other prospective studies reported positive associations between meat related nitrite and nitrate intakes and colorectal cancer.[13 14] Consistently, the International Agency for Research on Cancer[6] and French Food Safety Agency[33] now recognise food additive nitrites and nitrates as probably carcinogenic if ingested under conditions that result in endogenous nitrosation, mainly for colorectal cancer. In the present study, the trend towards a positive association between colorectal cancer and nitrites (1.26 (0.95 to 1.68), P=0.1) and nitrates (1.23 (0.93 to 1.64), P=0.1) did not reach statistical significance, probably due to the limited number of incident colorectal cancers.

Some studies investigated workplace exposure to sulfites in factory workers, with mixed results.[34 35] None, however, investigated dietary intake of food additives and cancer incidence.

A 2018 systematic review and dose-response meta-analysis of prospective studies found that although higher dietary intakes of vitamins C and E from natural sources and/or blood concentrations of vitamin C and alpha tocopherol were associated with reduced risk of total cancer, no evidence was available to support beneficial preventive effects of these antioxidants from other sources, and none of the included studies provided data specifically on food additives.[9] In our study, we found no association between intakes of the corresponding food additives of those vitamins (E300, E301, E306, and E307) and cancer incidence. We were

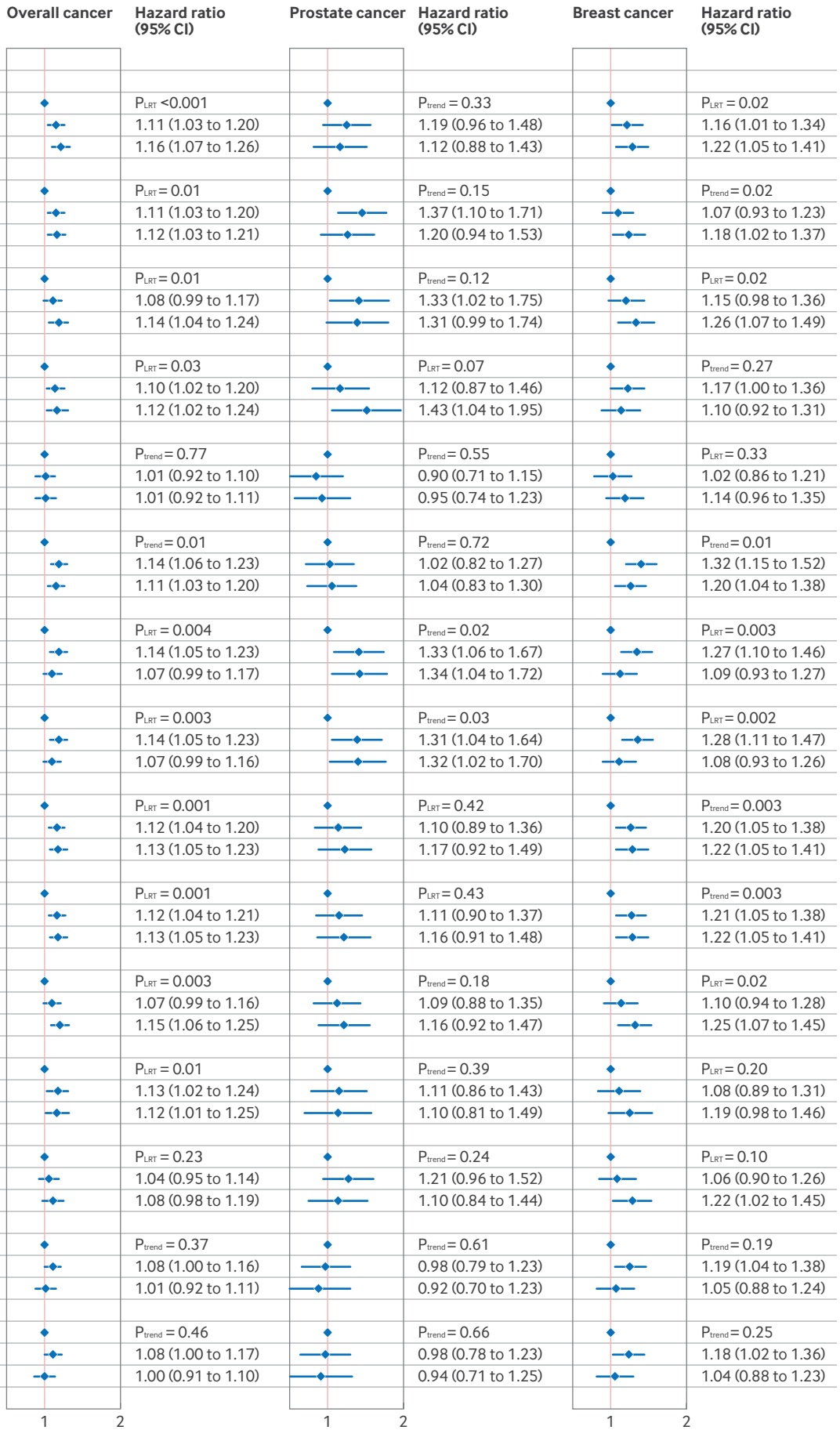

Fig 3 | Associations between intake of non-antioxidant food additive preservatives and incidence of overall, breast, and prostate cancer among study participants from NutriNet-Santé cohort, 2009-23 (n=105 260 participants; 4226 overall, 508 prostate, and 1208 breast incident cancers). The three categories were defined as sex specific thirds of intake: for total preservatives (non-antioxidants), total sorbates, total sulfites, total nitrites, and sodium nitrite (E250); otherwise, 1 represents non-consumers, 2 lower consumers, and 3 higher consumers, the last two separated by the sex specific median: for potassium sorbate (E202), sulfur dioxide (E220), potassium metabisulfite (E224), total nitrates, potassium nitrate (E252), total acetates, acetic acid (E260), sodium acetates (E262), total propionates, and calcium propionate (E282). Cut-offs were recalculated for each period (see supplementary eTable2). Details of all investigated associations between preservatives and cancer incidence are provided in supplementary eTable3. Based on the linearity test from restricted cubic splines presented in supplementary eFigure4, the P value in the forest plot is either P for trend (when P≥0.05 for non-linearity) or the likelihood ratio test overall P value (when P<0.05 for non-linearity). Supplementary eTable3 provides both P values for all additives. Multivariable Cox proportional hazard models adjusted for age (time scale), sex, baseline height (continuous, m), body mass index (continuous), physical activity (categorical IPAQ variable: high, moderate, low), smoking status (never, former, current), number of smoked cigarettes in pack years (continuous), educational level (less than high school degree, ≤3 years after high school degree, >3 years after high school degree), family history of cancer (yes/no), number of dietary records (continuous), time dependent daily intakes of energy (continuous) without alcohol (kcal/d), alcohol (g/d), saturated fats (g/d), sodium (mg/d), dietary fibre (g/d), sugars (g/d), fruit and vegetables (g/d), dairy products (g/d), red and processed meats (g/d), and haem iron (mg/d, for nitrites and nitrates models only). In addition, when applicable, each model was adjusted for the intake of the corresponding substance coming from natural sources (continuous, mg/d): sulfites for total sulfites, sulfur dioxide (E220), and potassium metabisulfite (E224); nitrites and the sum of natural nitrates and added nitrates for total nitrites, and sodium nitrite (E250); nitrates and the sum of natural and added nitrites for total nitrates, and potassium nitrate (E252); and acetic acid for total acetates, acetic acid (E260), and sodium acetates (E262). For the breast cancer outcome, each model was adjusted for age at menarche (never, <12 years, ≥12 years), number of biological children at baseline (continuous), menopausal status at baseline (premenopausal, post-menopausal), use of oral contraception (yes/no), and use of hormonal menopausal treatment (yes/no). CI=confidence interval; IPAQ=International Physical Activity Questionnaire; P_{LRT}=P value for likelihood ratio test; P_{trend}=P value for linear trend

unable to find an epidemiological study that focused on food additive sources with which we could compare our results on other food preservatives.

Mechanistic plausibility

An in vitro study (24 hour treatment on four human cell models) on food additives suggested no cytotoxicity or genotoxicity for lecithins but cytotoxicity for potassium sorbate, sodium nitrite, sodium ascorbate, and sodium erythorbate, and enhanced cell proliferation for potassium metabisulfite, ascorbic acid, and citric acid.[4] Potassium sorbate and sodium acetate could bind with serum albumin.[5] Potassium sorbate might promote glycation of serum albumin, which is also associated with the production of advanced glycation end products.[36] The compounds can alter immune and inflammatory pathways,[2] potentially triggering immunosuppression and therefore the development of cancer. Additionally, sodium acetate (≤12.5 mM) has been reported to stimulate proliferation in human gastric adenocarcinoma cells and increase levels of interleukin 1β, interleukin 8, and tumour necrosis factor (TNF alpha) protein and mRNAs; therefore, potentially inflammatory conditions associated with cancer development.[37] In another experimental study, high doses of potassium sorbate led to chromosomal aberrations in human blood lymphocytes.[38] Potassium metabisulfite showed no carcinogenicity in mice models[39] but enhanced gastric carcinogenicity in one rat study.[40] We previously discussed the mechanistic plausibility of nitrites and nitrates.[12] Briefly, hypotheses rely on the stepwise conversion of nitrate into nitrite in the body, followed by the formation of *N*-nitroso compounds, which according to the International Agency for Research on Cancer are probably carcinogenic to humans.[6] Mechanistic studies suggest that the presence of nitrosatable compounds found in meat accelerate the formation of these *N*-nitroso compounds, whereas vitamin C and other antioxidants often found in fruit and vegetables inhibit it.[6 41] In our models, associations between nitrites and nitrates and cancer incidences persisted after adjustment for intakes of haem iron, polyunsaturated fatty acids, and vitamins C and E. Vitamin C activity can switch from an antioxidant to pro-oxidant mode of action depending on the cell environment.[11] We did not observe associations for ascorbic acid itself, but we did observe higher incidences of overall and breast cancers associated with erythorbates, which are isomers of ascorbates (but which do not impact vitamin C blood status[3]). Moreover, dosages in beverages in the USA have shown that benzene, a carcinogen to humans, may form at a nanogram per gram level when both benzoate salts and ascorbic or erythorbic acids are present.[7] The result for an inverse association between rosemary extract and incidence of colorectal cancer in the present study should be considered with caution, given the limited number of participants with incident colorectal cancer. Rosemary contains phenolic compounds, including the two main molecules from which the food additive E392 is made (ie, carnosic acid and carnosol); polyphenols may modulate oxidative stress, cell growth, and cell differentiation thus potentially interfering with tumour development and progression.[42] A rat model study suggested a chemopreventive action of rosemary extract for experimental mammary tumorigenesis.[43] More generally, data are currently lacking, but it could be hypothesised that certain preservatives (some of which have antimicrobial properties) have an impact on gut microbiome and intestinal permeability (which in turn impacts on immune mechanisms, notably T regulatory cells[44]), as it has been shown for other type of additives (eg, some sweeteners and emulsifiers[45-47]). Additional studies are needed to better understand mechanisms linking food preservatives to the development of cancer, the differences in susceptibility to cancer location, and why erythorbates were the only

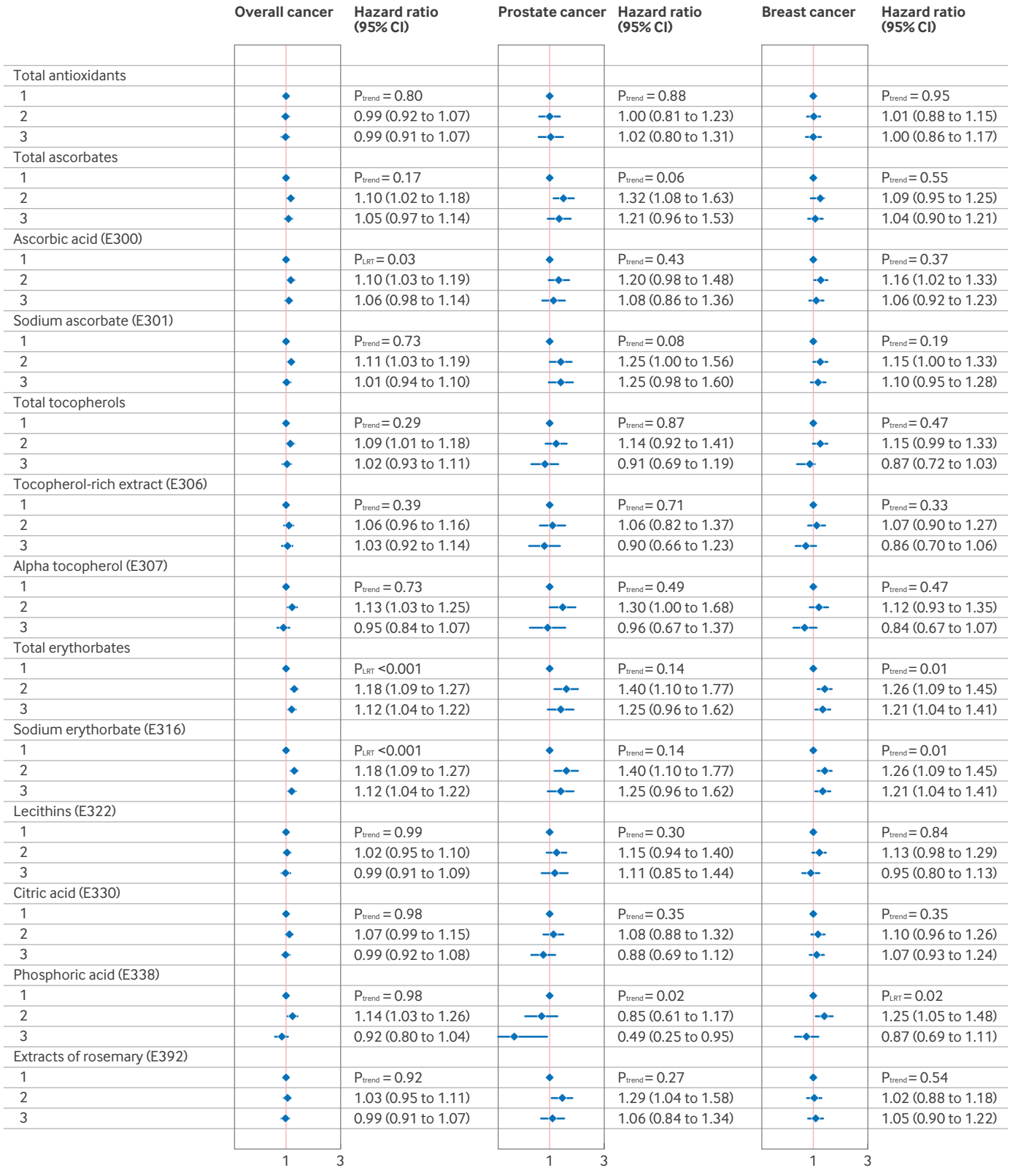

Fig 4 | Associations between intake of antioxidant food additive preservatives and incidence of overall, breast, and prostate cancer among study participants from NutriNet-Santé cohort, 2009-23 (n=105 260 participants; 4226 overall, 508 prostate, and 1208 breast incident cancers). The three categories of preservative intake were defined: sex specific thirds if proportion of participants with intakes >2/3: for total preservatives (antioxidant), total ascorbates, ascorbic acid (E300), lecithins (E322), and citric acid (E330); otherwise, 1 represents non-consumers, 2 lower consumers, and 3 higher consumers, the last two being separated by the sex specific median: for sodium ascorbate (E301), total tocopherols, tocopherol-rich extract (E306), alpha tocopherol (E307), total erythorbates, sodium erythorbate (E316), phosphoric acid (E338), and extracts of rosemary (E392). Cut-offs were re-calculated for each period (see supplementary eTable2). Supplementary eTable3 provides full details for all investigated associations between preservatives and cancer incidence for each category. Based on the linearity test from restricted cubic splines

Fig 4 | (Continued)

presented in supplementary eFigure4, the P value in the forest plot is either P for trend (when P≥0.05 for non-linearity) or the likelihood ratio test overall P value (when P<0.05 for non-linearity). Supplementary eTable3 provides both P values for all additives. Caution is needed when interpreting the finding for phosphoric acid (E338) and prostate cancer, as there were <10 incident cancers in at least one intake category. Multivariable Cox proportional hazard models adjusted for age (time scale), sex, baseline height (continuous, m), body mass index (continuous),physical activity (categorical IPAQ variable: high, moderate, low), smoking status (never, former, current), number of smoked cigarettes in pack years (continuous), educational level (less than high school degree, ≤3 years after high school degree, >3 years after high school degree), family history of cancer (yes/no), number of dietary records (continuous), time dependent daily intakes of energy (continuous) without alcohol (kcal/d), alcohol (g/d), saturated fats (g/d), sodium (mg/d), dietary fibre (g/d), sugars (g/d), fruit and vegetables (g/d), dairy products (g/d), red and processed meats (g/d), and haem iron (mg/d, for nitrites and nitrates models only). In addition, when applicable, each model was adjusted for the intake of the corresponding substance coming from natural sources (continuous, mg/d): sulfites for total sulfites, sulfur dioxide (E220), and potassium metabisulfite (E224); nitrites and the sum of natural nitrates and added nitrates for total nitrites, and sodium nitrite (E250); nitrates and the sum of natural and added nitrites for total nitrates, and potassium nitrate (E252); and acetic acid for total acetates, acetic acid (E260), and sodium acetates (E262). For the breast cancer outcome, each model was adjusted for age at menarche (never, <12 years, ≥12 years), number of biological children at baseline (continuous), menopausal status at baseline (premenopausal, post-menopausal), use of oral contraception (yes/no), and use of hormonal menopausal treatment (yes/no). CI=confidence interval; P_{LRT}=P value for likelihood ratio test; P_{trend}=P value for linear trend

preservative antioxidant associated with higher cancer incidence in this study. In the meantime, caution is needed in claiming innocuity of other antioxidant preservatives than erythorbates based on this study only, especially since this study focused on cancer and does not exclude potential effects on other health outcomes (eg, cardiometabolic health).

Strengths and limitations of this study

This prospective epidemiological study was based on a large cohort with highly detailed brand specific 24 hour dietary records for 14 years of follow-up (enabling assessment of time dependent cumulative intake). The cohort was linked to multiple food composition databases, ad hoc laboratory assays in the most frequently consumed additive-food pairs in food products, and dynamic matching accounting for reformulations, thereby providing access to unique information on food preservative intakes.

However, several limitations should be acknowledged. Firstly, the observational design does not allow for causality of the studied associations to be assumed based on this study alone. Residual confounding cannot be fully ruled out. The multivariable models were, however, adjusted for a broad spectrum of possible sociodemographic, anthropometric, lifestyle, and dietary confounding factors, limiting this potential bias. In particular, the food vectors of preservatives were diverse, encompassing variations in nutritional composition, which limited the risk of systematic bias by a same type of (poor) nutritional profile. For instance, for potassium sorbate, 26.3% of the intake was from fruit based and vegetable based products, whereas 21.6% was from fats and sauces. To limit confounding bias linked to nutritional profiles of vector foods as much as possible, we adjusted all models for energy, saturated fats, sodium, dietary fibre, and sugar intakes. Besides, mechanistic data from in vivo and in vitro studies support a potential causal involvement of these additives in carcinogenesis. Secondly, the generalisability of these results, collected though a web based study, should be considered. Validation studies comparing the NutriNet-Santé online dietary record versus interview with a trained dietitian[25] and versus blood and urinary biomarkers of nutrient intakes,[23 24] found that web based dietary studies appear as efficient and strategic tools for the collection of extensive and detailed information on dietary intakes for nutrition research.[48 49] Integrated automated controls and pop-up warning messages contribute to limit errors (eg, aberrant food quantities, food omissions). It has also been suggested that the use of the internet reduces social desirability bias,[50] which may enhance the quality of the data collected but also provide access to populations more difficult to reach otherwise. Nearly 95% of the French population has access to the internet,[51] and we have shown that the study population was not limited to digitally fluent individuals.[52] As in other studies investigating health and diet in which people enrol voluntarily, this study included more women, with a higher educational level and healthier lifestyles than the general French population.[53 54] However, daily energy intake as well as proportion of energy from ultra-processed foods were similar in our population study compared with estimates from French nationally representative surveys, supporting the generalisability of our findings.[55 56] Overall, the geographical distribution of the cohort also matched that of the general population in mainland France.[57] Thirdly, although the assessment of intake was highly detailed, classification bias can never be totally excluded. For instance, using the Australian Food Composition Database to estimate naturally occurring acetic and citric acids was not optimal since variations between countries may occur, but French or European composition tables were not available or were less complete for these natural sources. Similarly, quantifying the intakes of the natural form of substances that also exist as food additive preservatives was impossible for some of them owing to limited data (eg, natural lecithins). Fourthly, it was not possible to investigate the association of several infrequently consumed preservatives with cancer (eg, benzoates). However, these limited proportions of consumers reflected a low occurrence on the French market, thus less potential for an impact of these substances on public health. Similarly, statistical power was limited for cancer locations other

than the two most frequent in France (ie, breast and prostate), which may have limited our ability to detect associations for colorectal cancer in this study. Fifthly, the latency period between exposure to a carcinogen and the development of cancer varied from a short time to many years. Bioactive compounds may participate in the initiation of cancer but also trigger the development of pre-existing latent tumours due to other risk factors. Several large randomised controlled trials testing the impact of vitamin or mineral supplementation on cancer risk found that dietary factors can affect cancer risk with durations of use comparable to those in our study (eg, eight years for the SU.Vi.MAX trial[58]). Besides, associations were similar when restricting our population study to participants with longer follow-up. It will be interesting to re-run these analyses in the future to investigate longer term effects. Additional epidemiological and experimental studies are needed to better comprehend how food preservatives interact between themselves and with other food additives and food chemicals. Lastly, results were presented with and without adjustment for multiple testing by the false discovery rate method, with mostly stable results. Adjusting for multiple testing decreases type I error but also increases type II error (risk of false negative) and may lead to missing existing associations, which is why this adjustment is debated.[59] Our results were, however, supported by mechanistic plausibility, and hazard ratios for most detected associations in our study were >1 (except for rosemary extract and colorectal cancer), strongly suggesting the associations were not going in random directions (which would have been the case if they were due to chance).

Conclusions

This large prospective cohort showed multiple positive associations between intake of widely consumed preservatives and increased incidence of overall, breast, and prostate cancers. These findings may have important public health implications given the ubiquitous use of these additives in a wide range of foods and beverages. Although replication in other epidemiological cohorts as well as additional in vivo and in vitro studies and short term trials are needed to better understand underlying mechanisms, these results are consistent with existing experimental data suggesting adverse cancer related effects of several of these compounds. This study brings new insights for the future re-evaluation of the safety of these food additives by health agencies, considering the balance between benefit and risk for food preservation and cancer. In the meantime, these results should encourage manufacturers to limit the use of unnecessary preservatives. Public health policies should be strengthened to promote and make accessible and affordable fresh, seasonal, homemade products to consumers, or even canned and other industrial foods, although minimally processed, that limit the use of preservatives and superfluous additives. Health professionals (general practitioners, dietitians) could play a key role in conveying these prevention recommendations to their patients.

AUTHOR AFFILIATIONS

[1]Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, Centre for Research in Epidemiology and StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), F-93017 Bobigny, France

[2]Nutrition And Cancer Research Network (NACRe network), Jouy-en-Josas, France

[3]International Agency for Research on Cancer, World Health Organization, Lyon, France

[4]Toxalim (Research Centre in Food Toxicology), Université de Toulouse, INRAE, ENVT, INP-Purpan, UPS, Toulouse, France

[5]INSERM T3S, UMR-S 1124, Université Paris Cité, Paris, France

[6]Public Health Department, Groupe Hospitalier Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, France

[7]Nutritional Epidemiology Surveillance Team (ESEN), Santé publique France, The French Public Health Agency, Bobigny, France

[8]Microbiome-Host Interactions, Institut Pasteur, INSERM U1306, CNRS UMR6047, Université Paris Cité, Paris, France

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Data sharing: Researchers from public institutions can submit a request to have access to the data for strict reproducibility analysis (systematically accepted) or for a new collaboration, including information on the institution and a brief description of the project to collaboration@etude-nutrinet-sante.fr. The steering committee of the NutriNet-Santé study will review all requests. If the collaboration is accepted, a data access agreement will be necessary and appropriate authorisations from the competent administrative authorities may be needed. In accordance with existing regulations, no identifiable personal data will be accessible. R and SAS codes for this study are provided in the supplementary information.

Transparency: The guarantor (MT) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of the present study will be disseminated to the NutriNet-Santé participants through the cohort website, public seminars, and a press release.

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1 Open Food Facts. [cited 19 Jan 2024]. https://world.openfoodfacts.org/discover
2 European Parliament. Council. Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. Regulation (EC) No 1333/2008. 16 Dec 2008. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX%3A32008R1333
3 Food additives. EFSA. 2024 [cited 22 Mar 2024]. https://www.efsa.europa.eu/en/topics/topic/food-additives
4 Recoules C, Touvier M, Pierre F, Audebert M. Evaluation of the toxic effects of food additives, alone or in mixture, in four human cell models. *Food Chem Toxicol* 2025;196:115198. doi:10.1016/j.fct.2024.115198
5 Mohammadzadeh-Aghdash H, Akbari N, Esazadeh K, Ezzati Nazhad Dolatabadi J. Molecular and technical aspects on the interaction of serum albumin with multifunctional food preservatives. *Food Chem* 2019;293:491-8. doi:10.1016/j.foodchem.2019.04.119
6 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. International Agency for Research on Cancer; 2010. 1. (IARC monographs on the evaluation of carcinogenic risks to humans).
7 Nyman PJ, Diachenko GW, Perfetti GA, McNeal TP, Hiatt MH, Morehouse KM. Survey results of benzene in soft drinks and other beverages by headspace gas chromatography/mass spectrometry. *J Agric Food Chem* 2008;56:571-6. doi:10.1021/jf072479l
8 International Agency for Research on Cancer/WHO. Sulfur Dioxide and Some Sulfites, Bisulfites and Metabisulfites. In: Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals. International Agency for Research on Cancer; 1992 [cited 18 Dec 2024]. https://www.ncbi.nlm.nih.gov/books/NBK424660/
9 Aune D, Keum N, Giovannucci E, et al. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. *Am J Clin Nutr* 2018;108:1069-91. doi:10.1093/ajcn/nqy097
10 Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;330:1029-35. doi:10.1056/NEJM199404143301501
11 Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A, Karwowski BT. Two Faces of Vitamin C-Antioxidative and Pro-Oxidative Agent. *Nutrients* 2020;12:1501. doi:10.3390/nu12051501
12 Chazelas E, Pierre F, Druesne-Pecollo N, et al. Nitrites and nitrates from food additives and natural sources and cancer risk: results from the NutriNet-Santé cohort. *Int J Epidemiol* 2022;51:1106-19. doi:10.1093/ije/dyac046
13 Etemadi A, Sinha R, Ward MH, et al. Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP Diet and Health Study: population based cohort study. *BMJ* 2017;357:j1957. doi:10.1136/bmj.j1957
14 Cross AJ, Ferrucci LM, Risch A, et al. A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res* 2010;70:2406-14. doi:10.1158/0008-5472.CAN-09-3929
15 Jones RR, Weyer PJ, DellaValle CT, et al. Ingested Nitrate, Disinfection By-products, and Kidney Cancer Risk in Older Women. *Epidemiology* 2017;28:703-11. doi:10.1097/EDE.0000000000000647
16 Quist AJL, Inoue-Choi M, Weyer PJ, et al. Ingested nitrate and nitrite, disinfection by-products, and pancreatic cancer risk in postmenopausal women. *Int J Cancer* 2018;142:251-61. doi:10.1002/ijc.31055
17 Lachat C, Hawwash D, Ocké MC, et al. Strengthening the Reporting of Observational Studies in Epidemiology-Nutritional Epidemiology (STROBE-nut): An Extension of the STROBE Statement. *PLoS Med* 2016;13:e1002036. doi:10.1371/journal.pmed.1002036
18 Hercberg S, Castetbon K, Czernichow S, et al. The Nutrinet-Santé Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. *BMC Public Health* 2010;10:242. doi:10.1186/1471-2458-10-242
19 Lassale C, Péneau S, Touvier M, et al. Validity of web-based self-reported weight and height: results of the Nutrinet-Santé study. *J Med Internet Res* 2013;15:e152. doi:10.2196/jmir.2575
20 Touvier M, Méjean C, Kesse-Guyot E, et al. Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. *Eur J Epidemiol* 2010;25:287-96. doi:10.1007/s10654-010-9433-9
21 IPAQ Research Committee. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)-Short and Long Forms. http://www.ipaq.ki.se/scoring.pdf. 2005 [cited 26 Feb 2023]; https://cir.nii.ac.jp/crid/1573950400545533440
22 Vergnaud AC, Touvier M, Méjean C, et al. Agreement between web-based and paper versions of a socio-demographic questionnaire in the NutriNet-Santé study. *Int J Public Health* 2011;56:407-17. doi:10.1007/s00038-011-0257-5
23 Lassale C, Castetbon K, Laporte F, et al. Correlations between Fruit, Vegetables, Fish, Vitamins, and Fatty Acids Estimated by Web-Based Nonconsecutive Dietary Records and Respective Biomarkers of Nutritional Status. *J Acad Nutr Diet* 2016;116:427-438.e5. doi:10.1016/j.jand.2015.09.017
24 Lassale C, Castetbon K, Laporte F, et al. Validation of a Web-based, self-administered, non-consecutive-day dietary record tool against urinary biomarkers. *Br J Nutr* 2015;113:953-62. doi:10.1017/S0007114515000057
25 Touvier M, Kesse-Guyot E, Méjean C, et al. Comparison between an interactive web-based self-administered 24 h dietary record and an interview by a dietitian for large-scale epidemiological studies. *Br J Nutr* 2011;105:1055-64. doi:10.1017/S0007114510004617
26 Arnault N, Caillot L, Castetbon K, et al. Table de composition des aliments, étude NutriNet-Santé. [Food composition table, NutriNet-Santé study] (in French). 2013.
27 Chazelas E, Druesne-Pecollo N, Esseddik Y, et al. Exposure to food additive mixtures in 106,000 French adults from the NutriNet-Santé cohort. *Sci Rep* 2021;11:19680. doi:10.1038/s41598-021-98496-6
28 Online Food Additive Index GSFA. [cited 7 Feb 2024]. https://www.fao.org/gsfaonline/additives/index.html?lang=en
29 Food Standards Agency. Approved additives and E numbers. [cited 19 Jan 2024]. https://www.food.gov.uk/business-guidance/approved-additives-and-e-numbers
30 World Health Organization. *ICD-10: international statistical classification of diseases and related health problems*. WHO, 2011.
31 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc B* 1995;57:289-300. doi:10.1111/j.2517-6161.1995.tb02031.x
32 Martinez-Steele E, Khandpur N, Batis C, et al. Best practices for applying the Nova food classification system. *Nat Food* 2023;4:445-8. doi:10.1038/s43016-023-00779-w

33 French Agency for Food. Environmental and Occupational Health & Safety (ANSES). Évaluation des risques liés à la consommation de nitrates et nitrites. France: ANSES; 2022 [cited 14 Jan 2025]. https://www.anses.fr/fr/system/files/ERCA2020SA0106Ra.pdf
34 Andersson E, Nilsson T, Persson B, Wingren G, Torén K. Mortality from asthma and cancer among sulfite mill workers. *Scand J Work Environ Health* 1998;24:12-7. doi:10.5271/sjweh.273
35 Englander V, Sjöberg A, Hagmar L, et al. Mortality and cancer morbidity in workers exposed to sulphur dioxide in a sulphuric acid plant. *Int Arch Occup Environ Health* 1988;61:157-62. doi:10.1007/BF00381012
36 Taghavi F, Moosavi-Movahedi AA, Bohlooli M, et al. Potassium sorbate as an AGE activator for human serum albumin in the presence and absence of glucose. *Int J Biol Macromol* 2013;62:146-54. doi:10.1016/j.ijbiomac.2013.08.045
37 Sun J, Bi L, Chi Y, Aoki K, Misumi J. Effect of sodium acetate on cell proliferation and induction of proinflammatory cytokines: a preliminary evaluation. *Food Chem Toxicol* 2005;43:1773-80. doi:10.1016/j.fct.2005.05.020
38 Mamur S, Yüzbaşioğlu D, Ünal F, Yilmaz S. Does potassium sorbate induce genotoxic or mutagenic effects in lymphocytes?*Toxicol In Vitro* 2010;24:790-4. doi:10.1016/j.tiv.2009.12.021
39 Tanaka T, Fujii M, Mori H, Hirono I. Carcinogenicity test of potassium metabisulfite in mice. *Ecotoxicol Environ Saf* 1979;3:451-3. doi:10.1016/0147-6513(79)90034-4
40 Takahashi M, Hasegawa R, Furukawa F, Toyoda K, Sato H, Hayashi Y. Effects of ethanol, potassium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initiation with N-methyl-N'-nitro-N-nitrosoguanidine. *Jpn J Cancer Res* 1986;77:118-24.
41 Pierre FH, Martin OC, Santarelli RL, et al. Calcium and α-tocopherol suppress cured-meat promotion of chemically induced colon carcinogenesis in rats and reduce associated biomarkers in human volunteers. *Am J Clin Nutr* 2013;98:1255-62. doi:10.3945/ajcn.113.061069
42 Andrade JM, Faustino C, Garcia C, Ladeiras D, Reis CP, Rijo P. *Rosmarinus officinalis* L.: an update review of its phytochemistry and biological activity. *Future Sci OA* 2018;4:FSO283. doi:10.4155/fsoa-2017-0124
43 Singletary K, MacDonald C, Wallig M. Inhibition by rosemary and carnosol of 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced rat mammary tumorigenesis and in vivo DMBA-DNA adduct formation. *Cancer Lett* 1996;104:43-8. doi:10.1016/0304-3835(96)04227-9
44 Harrison OJ, Powrie FM. Regulatory T cells and immune tolerance in the intestine. *Cold Spring Harb Perspect Biol* 2013;5:a018341. doi:10.1101/cshperspect.a018341
45 Viennois E, Merlin D, Gewirtz AT, Chassaing B. Dietary emulsifier-induced low-grade inflammation promotes colon carcinogenesis. *Cancer Res* 2017;77:27-40. doi:10.1158/0008-5472.CAN-16-1359
46 Viennois E, Chassaing B. Consumption of Select Dietary Emulsifiers Exacerbates the Development of Spontaneous Intestinal Adenoma. *Int J Mol Sci* 2021;22:2602. doi:10.3390/ijms22052602
47 Whelan K, Bancil AS, Lindsay JO, Chassaing B. Ultra-processed foods and food additives in gut health and disease. *Nat Rev Gastroenterol Hepatol* 2024;21:406-27. doi:10.1038/s41575-024-00893-5
48 Cade JE, Warthon-Medina M, Albar S, et al, DIET@NET consortium. DIET@NET: Best Practice Guidelines for dietary assessment in health research. *BMC Med* 2017;15:202. doi:10.1186/s12916-017-0962-x
49 Illner AK, Freisling H, Boeing H, Huybrechts I, Crispim SP, Slimani N. Review and evaluation of innovative technologies for measuring diet in nutritional epidemiology. *Int J Epidemiol* 2012;41:1187-203. doi:10.1093/ije/dys105
50 Joinson A. Social desirability, anonymity, and Internet-based questionnaires. *Behav Res Methods Instrum Comput* 1999;31:433-8. doi:10.3758/BF03200723
51 INSEE. Internet Access and Use in the European Union. [cited 7 Jun 2025]. https://www.insee.fr/fr/statistiques/2385835
52 Pouchieu C, Méjean C, Andreeva VA, et al. How computer literacy and socioeconomic status affect attitudes toward a Web-based cohort: results from the NutriNet-Santé study. *J Med Internet Res* 2015;17:e34. doi:10.2196/jmir.3813
53 Smith LH. Selection Mechanisms and Their Consequences: Understanding and Addressing Selection Bias. *Curr Epidemiol Rep* 2020;7:179-89doi:10.1007/s40471-020-00241-6.
54 Andreeva VA, Deschamps V, Salanave B, et al. Comparison of Dietary Intakes Between a Large Online Cohort Study (Etude NutriNet-Santé) and a Nationally Representative Cross-Sectional Study (Etude Nationale Nutrition Santé) in France: Addressing the Issue of Generalizability in E-Epidemiology. *Am J Epidemiol* 2016;184:660-9. doi:10.1093/aje/kww016
55 ANSES. Etude Individuelle Nationale des Consommations Alimentaires 3 (INCA 3). 2017.
56 Calixto Andrade G, Julia C, Deschamps V, et al. Consumption of Ultra-Processed Food and Its Association with Sociodemographic Characteristics and Diet Quality in a Representative Sample of French Adults. *Nutrients* 2021;13:682. doi:10.3390/nu13020682
57 Kesse-Guyot E, Assmann K, Andreeva V, et al. Lessons Learned From Methodological Validation Research in E-Epidemiology. *JMIR Public Health Surveill* 2016;2:e5880doi:10.2196/publichealth.5880.
58 Hercberg S, Galan P, Preziosi P, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 2004;164:2335-42. doi:10.1001/archinte.164.21.2335
59 Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;1:43-6. doi:10.1097/00001648-199001000-00010

Supplementary information: eMethod1-eMethod3, eFigure1-eFigure4, eTable 1-eTable 6, references, and R and SAS codes