Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort

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ABSTRACT

OBJECTIVE
To assess the prospective associations between consumption of ultra-processed food and risk of cancer.

DESIGN
Population based cohort study.

SETTING AND PARTICIPANTS
104 980 participants aged at least 18 years (median age 42.8 years) from the French NutriNet-Santé cohort (2009-17). Dietary intakes were collected using repeated 24 hour dietary records, designed to register participants’ usual consumption for 3300 different food items. These were categorised according to their degree of processing by the NOVA classification.

MAIN OUTCOME MEASURES
Associations between ultra-processed food intake and risk of overall, breast, prostate, and colorectal cancer assessed by multivariable Cox proportional hazard models adjusted for known risk factors.

RESULTS
Ultra-processed food intake was associated with higher overall cancer risk (n=2228 cases; hazard ratio for a 10% increment in the proportion of ultra-processed food in the diet 1.12 (95% confidence interval 1.06 to 1.18); P for trend<0.001) and breast cancer risk (n=739 cases; hazard ratio 1.11 (1.02 to 1.22); P for trend=0.02). These results remained statistically significant after adjustment for several markers of the nutritional quality of the diet (lipid, sodium, and carbohydrate intakes and/or a Western pattern derived by principal component analysis).

CONCLUSIONS
In this large prospective study, a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer. Further studies are needed to better understand the relative effect of the various dimensions of processing (nutritional composition, food additives, contact materials, and neoformed contaminants) in these associations.

STUDY REGISTRATION
Clinicaltrials.gov NCT03335644.

Introduction
Cancer represents a major worldwide burden, with 14.1 million new cases diagnosed in 2012. According to the World Cancer Research Fund/American Institute for Cancer Research, about a third of the most common neoplasms could be avoided by changing lifestyle and dietary habits in developed countries. Therefore, reaching a balanced and diversified diet (along with avoidance of tobacco use and reduction in alcohol intake) should be considered one of the most important modifiable risk factors in the primary prevention of cancer.

At the same time, during the past decades, diets in many countries have shifted towards a dramatic increase in consumption of ultra-processed foods. After undergoing multiple physical, biological, and/or chemical processes, these food products are conceived to be microbiologically safe, convenient, highly palatable, and affordable. Several surveys (in Europe, the US, Canada, New Zealand, and Brazil) assessing individual food intake, household food expenses, or supermarket sales have suggested that ultra-processed food products contribute to between 25% and 50% of total daily energy intake. This dietary trend may be concerning and deserves investigation. Several characteristics of ultra-processed foods may be involved in causing disease, particularly cancer. Firstly, ultra-processed foods often have a higher content of total fat, saturated fat, and added sugar and salt, along with a lower fibre and vitamin density. Beyond nutritional composition, neoformed contaminants, some of which have carcinogenic properties (such as acrylamide, heterocyclic amines, and polycyclic aromatic

WHAT IS ALREADY KNOWN ON THIS TOPIC
Ultra-processed foods are often characterised by lower nutritional quality and the presence of additives, substances from packaging in contact with food, and compounds formed during production, processing, and storage.

A few studies have observed ultra-processed food intake to be associated with a higher incidence of dyslipidaemia in Brazilian children and higher risks of overweight, obesity, and hypertension in Spanish university students.

Although epidemiological data relating to cancer risk are lacking, mechanistic studies suggest potential carcinogenic effects of several components commonly found in ultra-processed foods.

WHAT THIS STUDY ADDS
This study assessed the associations between ultra-processed food consumption and risk of cancer in a large prospective cohort.

A 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of more than 10% in the risks of overall and breast cancer.

If confirmed in other populations and settings, these results suggest that the rapidly increasing consumption of ultra-processed foods may drive an increasing burden of cancer in the next decades.
overweight, obesity, and hypertension in a prospective dyslipidaemia in Brazilian children and higher risks of food intake was associated with a higher incidence of few studies performed observed that ultra-processed up to date assessment of dietary intake. cancer, based on a large cohort study with detailed and of ultra-processed food products and the incidence of to evaluate the association between the consumption suggested in animal or cellular models.23 24

Studying potential effects on health of ultra-processed foods is a very recent field of research, facilitated by the development of the NOVA classification of products according to their degree of food processing.3 Nevertheless, epidemiological evidence linking intake of ultra-processed food to risk of disease is still very scarce and mostly based on cross sectional and ecological studies.25-27 The few studies performed observed that ultra-processed food intake was associated with a higher incidence of dyslipidaemia in Brazilian children and higher risks of overweight, obesity, and hypertension in a prospective cohort of Spanish university students.28-30

To our knowledge, this prospective study was the first to evaluate the association between the consumption of ultra-processed food products and the incidence of cancer, based on a large cohort study with detailed and up to date assessment of dietary intake.

Methods
Study population
The NutriNet-Santé study is an ongoing web based cohort launched in 2009 in France with the objective of studying the associations between nutrition and health, as well as the determinants of dietary behaviours and nutritional status. This cohort has been previously described in detail.31 Briefly, participants aged over 18 years with access to the internet have been continuously recruited from among the general population since May 2009 by means of vast multimedia campaigns. All questionnaires are completed online using a dedicated website (www.etude-nutrinet-sante.fr). Participants are followed using an online platform connected to their email address. They can change their email address, phone number, or postal address at any time on the NutriNet-Santé website. Newsletters and alerts about new questionnaires are sent by email. In case of non-delivery, participants are contacted by telephone and then by regular mail. The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines, and electronic informed consent is obtained from each participant.

Data collection
At inclusion, participants completed a set of five questionnaires related to sociodemographic and lifestyle characteristics (for example, date of birth, sex, occupation, educational level, smoking status, number of children),32 anthropometry (height, weight), dietary intakes (see below),33 35 physical activity (validated seven day International Physical Activity Questionnaire (IPAQ)),35 and health status (personal and family history of diseases, drug use including use of hormonal treatment for menopause and oral contraceptives, and menopausal status).

Participants were invited to complete a series of three non-consecutive, validated, web based 24 hour dietary records every six months (to vary the season of completion), randomly assigned over a two week period (two weekdays and one weekend day).36-38 To be included in the nutrition component of the NutriNet-Santé cohort, only two dietary records were mandatory. We did not exclude participants if they did not complete all optional questionnaires. We averaged mean dietary intakes from all the 24 hour dietary records available during the first two years of each participant’s follow-up and considered these as baseline usual dietary intakes in this prospective analysis. The NutriNet-Santé web based, self administered 24 hour dietary records have been tested and validated against an interview by a trained dietitian and against blood and urinary biomarkers.36 37 Participants used the dedicated web interface to declare all food and drinks consumed during a 24 hour period for each of the three main meals (breakfast, lunch, dinner) and any other eating occasion. Portion sizes were estimated using previously validated photographs or usual containers.39 We identified dietary under-reporting on the basis of the method proposed by Black, using the basal metabolic rate and Goldberg cutoff, and excluded under-reporters of energy intake.40 We calculated mean daily alcohol, micronutrient and macronutrient, and energy intake by using the NutriNet-Santé food composition database, which contains more than 3300 different items.41 We estimated amounts consumed from composite dishes by using French recipes validated by nutrition professionals. Sodium intake was assessed via a specific module included in the 24 hour records, taking into account native sodium in foods, salt added during the cooking, and salt added on the plate. It has been validated against sodium urinary excretion biomarkers.37

Degree of food processing
We categorised all food and drink items of the NutriNet-Santé composition table into one of the four food groups in NOVA, a food classification system based on the extent and purpose of industrial food processing.9 42 43 This study primarily focused on the “ultra-processed foods” NOVA group. This group includes mass produced packaged breads and buns; sweet or savoury packaged snacks; industrialised confectionery and desserts; sodas and sweetened drinks; meat balls, poultry and fish nuggets, and other reconstituted meat products transformed with addition of preservatives other than salt (for example, nitrates); instant noodles and soups; frozen or shelf stable ready meals; and other food products made mostly or entirely from sugar, oils and fats, and other substances not commonly used in culinary preparations such as hydrogenated oils, modified starches, and protein isolates. Industrial processes
notably include hydrogenation, hydrolysis, extruding, moulding, reshaping, and pre-processing by frying. Flavouring agents, colours, emulsifiers, humectants, non-sugar sweeteners, and other cosmetic additives are often added to these products to imitate sensorial properties of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product.

The ultra-processed food group is defined by opposition to the other NOVA groups: “unprocessed or minimally processed foods” (fresh, dried, ground, chilled, frozen, pasteurised, or fermented staple foods such as fruits, vegetables, pulses, rice, pasta, eggs, meat, fish, or milk), “processed culinary ingredients” (salt, vegetable oils, butter, sugar, and other substances extracted from foods and used in kitchens to transform unprocessed or minimally processed foods into culinary preparations), and “processed foods” (canned vegetables with added salt, sugar coated dried fruits, meat products preserved only by salting, cheeses, freshly made unpackaged breads, and other products manufactured with the addition of salt, sugar, or other substances of the “processed culinary ingredients” group). As previously described, we identified homemade and artisanal food preparations, decomposed them using standardised recipes, and applied the NOVA classification to their ingredients. Precision and examples are shown in appendix 1.

Case ascertainment
Participants self declared health events through the yearly health status questionnaire, through a specific check-up questionnaire for health events (every three months), or at any time through a specific interface on the study website. For each incident cancer declared, a physician from the study team contacted participants and asked them to provide any relevant medical records. If necessary, the study physicians contacted the patient’s physician and/or hospitals to collect additional information. Afterwards, an expert committee of physicians reviewed all medical data. Our research team was the first in France to obtain the authorisation by decree in the Council of State (No 2013-175) to link data from our cohorts to medico-administrative databases of the national health insurance system (SNIIRAM databases). We therefore completed declared health events with the information from these databases, thereby limiting any potential bias due to participants with cancer who may not report their disease to the study investigators. Lastly, we used an additional linkage to the French national cause specific mortality registry (CépiDc) to detect deaths and potentially missed cases of cancer for deceased participants. We classified cancer cases by using the international classification of diseases, 10th revision (ICD-10). In this study, we considered all first primary cancers diagnosed between the inclusion date and 1 January 2017 to be cases, except for basal cell skin carcinoma, which we did not consider as cancer.

We obtained medical records for more than 90% of cancer cases. Because of the high validity of self reports (95% of self reported cancers for which a medical record was obtained were confirmed by our physicians), we included as cases all participants who self reported incident cancers, unless they were identified as non-case participants by a pathology report, in which case we classified them as non-cases.

Statistical analysis
Up to 1 January 2017, we included 104 980 participants without cancer at baseline who provided at least two valid 24 hour dietary records during their two first years of follow-up. The flowchart is in appendix 2. For each participant, we calculated the proportion (percentage g/day) of ultra-processed foods in the total diet. We determined the proportion of ultra-processed foods in the diet by calculating a weight ratio rather than an energy ratio to take into account processed foods that do not provide any energy (in particular artificially sweetened drinks) and non-nutritional factors related to food processing (for example, neoformed contaminants, food additives, and alterations to the structure of raw foods). For all covariates except physical activity, less than 5% of values were missing and were imputed to the modal value (for categorical variables) or to the median (for continuous variables). Corresponding values are provided in the footnote to table 1. The proportion of missing values was higher for physical activity (14%), as the answers to all IPAQ questions were needed to calculate the score. To avoid massive imputation for a non-negligible number of participants or exclusion of those with missing data and risk of selection bias, we included a missing class into the models for this variable. We examined differences in participants’ baseline characteristics between sex specific quarters of the proportion of ultra-processed food in the diet by using analysis of variance or χ² tests wherever appropriate. We used Cox proportional hazards models with age as the primary timescale to evaluate the association between the proportion of ultra-processed foods in the diet (coded as a continuous variable or as sex specific quarters) and incidence of overall, breast, prostate, and colorectal cancer. In these models, cancers at other locations than the one studied were censored at the date of diagnosis (that is, we considered them to be non-cases for the cancer of interest and they contributed person years until the date of diagnosis of their cancer). We estimated hazard ratios and 95% confidence intervals with the lowest quarter as the reference category. We generated log-log (survival) versus log-time plots to confirm risk proportionality assumptions. We tested for linear trend by using the ordinal score on sex specific quarters of ultra-processed food. Participants contributed person time until the date of diagnosis of cancer, the date of last completed questionnaire, the date of death, or 1 January 2017, whichever occurred first. Breast cancer analyses were additionally stratified by menopausal status. For these, women contributed person time to the “premenopause model” until their age at menopause and to the “postmenopause model” from their age at menopause.
age at menopause by using the yearly health status questionnaires completed during follow-up.

Models were adjusted for age (timescale), sex, body mass index (kg/m², continuous), height (cm, continuous), physical activity (high, moderate, low, calculated according to IPAQ recommendations), smoking status (never or former smokers, current smokers), number of 24 hour dietary records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, kcal/d, continuous), family history of cancer (yes/no), and educational level (less than high school degree, less than two years after high school degree, two or more years after high school degree). For breast cancer analyses, we made additional adjustments for the number of biological children (continuous), menopausal status at baseline (menopausal/perimenopausal/non-menopausal), hormonal treatment for menopause at baseline (for postmenopausal analyses, yes/no), and oral contraception use at baseline (for premenopausal analyses, yes/no) (model 1–main model). To test for the potential influence of the nutritional quality of the diet in the relation between intake of ultra-processed food and risk of cancer, this model was additionally adjusted for lipid, sodium, and carbohydrate intakes (model 2), for a Western dietary pattern derived from principal component analysis (model 3) (details in appendix 3), or for all these nutritional factors together (model 4). In addition, we did mediation analyses according to the method proposed by Lange et al to evaluate the direct and indirect effect of the relation between the exposure and the outcome through the following nutritional mediators: intakes of sodium, total lipids, saturated, mono-unsaturated and polyunsaturated fatty acids, carbohydrates, and a Western-type dietary pattern. The methods are described in appendix 4.

We did sensitivity analyses based on model 1 by excluding cases of cancer diagnosed during the first two years of each participant’s follow-up to avoid reverse causality bias, testing sex specific fifths of the proportion of ultra-processed foods in the diet instead of sex specific quarters, and testing further adjustments for prevalent depression at baseline (yes/no), dietary supplement use at baseline (yes/no), healthy dietary pattern (continuous, details in appendix 3), number of cigarettes smoked in pack years (continuous), overall fruit and vegetable consumption (continuous), and...
season of inclusion in the cohort (spring/summer/ autumn/winter). We also investigated the association between ultra-processed food and overall cancer risk separately in different strata of the population: men, women, younger adults (under 40 years), older adults (40 years or over), smokers, non-smokers, participants with a high level of physical activity, and those with a low to moderate level of physical activity. We also tested models after restriction of the study population to the participants with at least six 24 hour dietary records during the first two years of follow-up. Similarly, we tested models including all participants with at least one 24 hour dietary record during the first two years of follow-up. We also tested associations between the quantity (g/d) of each ultra-processed food group and risk of cancer.

Secondary analyses tested the associations between the proportion of ultra-processed food in the diet of each of the three other NOVA categories of food processing (continuous) and risk of cancer, using multivariate Cox models adjusted for model 1 covariates. All tests were two sided, with P<0.05 considered to be statistically significant. We used SAS version 9.4 for the analyses.

**Patient involvement**

The research question developed in this article corresponds to a strong concern of the participants involved in the NutriNet-Santé cohort and of the public in general. The results of this study will be disseminated to the NutriNet-Santé participants through the cohort website, public seminars, and a press release.

**Results**

A total of 104 980 participants (22 821 (21.7%) men and 82 159 (78.3%) women) were included in the study. The mean age of participants was 42.8 (SD 14.8, range 18.0-72.8) years. The mean number of dietary records per participant over their first two years of follow-up was 5.4 (SD 2.9); the minimum was 2, but it represented only 7.2% (7558/104 980) of the participants. After the launching of the study by the end of May 2009, half of the records were filled between June and November and the other half between December and May. Table 1 shows the main baseline characteristics of participants according to quarters of the proportion of ultra-processed foods in the diet. Compared with the lowest quarter, participants in the highest quarter of ultra-processed food intake tended to be younger, current smokers, and less educated, with less family history of cancer and a lower physical activity level. Furthermore, they had higher intakes of energy, lipids, carbohydrates, and sodium, along with lower alcohol intake. Although there was a higher proportion of women than men in this cohort, the contribution of ultra-processed foods to the overall diet was very similar between men and women (18.74% for men and 18.71% for women; P=0.7). The distribution of the proportion of ultra-processed food in the diet in the study population is shown in appendix 5. Main food groups contributing to ultra-processed food intake were sugary products (26%) and drinks (20%), followed by starchy foods and breakfast cereals (16%) and ultra-processed fruits and vegetables (15%) (fig 1).

During follow-up (426 362 person years, median follow-up time five years), 2228 first incident cases of cancer were diagnosed and validated, among which were 739 breast cancers (264 premenopausal, 475 postmenopausal), 281 prostate cancers, and 153 colorectal cancers. Among these 2228 cases, 108 (4.8%) were identified during mortality follow-up with the national CépiDC database. The dropout rate in the NutriNet-Santé cohort was 6.7%. Table 2 shows associations between the proportion of ultra-processed foods in the diet and risks of overall, breast, prostate, and colorectal cancer. Figure 2 shows the corresponding cumulative incidence curves. In model 1, ultra-processed food intake was associated with increased risks of overall cancer (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.12 (95% confidence interval 1.06 to 1.18), P<0.001) and breast cancer (1.11 (1.02 to 1.22), P=0.02). The latter association was more specifically observed for postmenopausal breast cancer (P=0.04) but not for premenopausal breast cancer (P=0.2). The association with overall cancer risk was statistically significant in all strata of the population investigated, after adjustment for model 1 covariates: in men (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.12 (1.02 to 1.24), P=0.02, 663 cases and 22 158 non-cases), in women (1.13 (1.06 to 1.20), P<0.001, 1565 cases and 80 594 non-cases), in younger adults (<40 years old 1.21 (1.09 to 1.35), P<0.001, 287 cases and 48 627 cases), in older adults (>40 years old 1.09 (1.03 to 1.16), P=0.03, 19 414 cases and 54 485 non-cases), in smokers (including adjustment for pack years of cigarettes smoked 1.18 (1.04 to 1.33), P=0.01, 255 cases and 15 355 non-cases), in non-smokers (1.11 (1.05 to 1.17), P<0.001, 19 434 cases and 85 219 non-cases), in participants with low to moderate levels of physical activity (1.07 (1.00 to 1.15), P=0.04, 1216 cases and 59 546 non-cases), and in those with a high level of physical activity (1.19 (1.09 to 1.30), P<0.001, 744 cases and 28 859 non-cases).

More specifically, ultra-processed fats and sauces (P=0.002) and sugary products (P=0.03) and drinks...
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by these nutritional factors showed no statistically significant mediation effect of any of the factors tested.\textsuperscript{45} The mediated effects ranged between 0% and 2%, with all $P>0.05$ (appendix 4).

No association was statistically significant for prostate and colorectal cancers. However, we observed a borderline non-significant trend of increased risk of colorectal cancer associated with ultra-processed food intake (hazard ratio for quarter 4 versus quarter 1: 1.23 (1.08 to 1.40), $P$ for trend=0.07) in model 4.

Sensitivity analyses (adjusted for model 1 covariates, data not tabulated) excluding cancer cases diagnosed during the first two years of follow-up provided similar results (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.10 (1.03 to 1.17), $P=0.005$ for overall cancer risk, 1367 cases and 102 502 non-cases included; 1.15 (1.03 to 1.29), $P=0.02$ for breast cancer risk, 441 cases and 80 940 non-cases included). Similarly, results were unchanged when we excluded non-validated cancer cases (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.11 (1.05 to 1.17), $P<0.001$ for overall cancer risk, 1967 cases and 102 752 non-cases included; 1.12 (1.02 to 1.23), $P=0.02$ for breast cancer risk, 677 cases and 81 274 non-cases included).

We obtained similar results when we included only participants with at least six 24 hour records (overall cancer risk: hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.13 (1.06 to 1.21), $P<0.001$, 1694 cases and 47 920 non-cases included) and when we re-included participants with only one 24 hour record (overall cancer risk: 1.11 (1.06 to 1.16), $P<0.001$, 2383 cases and 122 196 non-cases included).

Findings were also similar when we coded the proportion of ultra-processed food in the diet as sex specific fifths instead of quarters (overall cancer risk: hazard ratio for highest versus lowest fifth 1.25 (1.08 to 1.47), $P$ for trend<0.001; breast cancer risk: 1.25 (0.96 to 1.63), $P$ for trend<0.03).

Further adjustment for the following variables, in addition to model 1 covariates, did not modify the results: dietary supplement use in the baseline (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.12 (1.06 to 1.17), $P<0.001$ for overall cancer; 1.11 (1.02 to 1.22), $P=0.02$ for breast cancer), prevalent depression at baseline (1.11 (1.06 to 1.17), $P<0.001$ for overall cancer; 1.11 (1.01 to 1.22), $P=0.02$ for breast cancer), healthy dietary pattern (1.11 (1.05 to 1.17), $P<0.001$ for overall cancer; 1.11 (1.06 to 1.17), $P=0.04$ for breast cancer), overall fruit and vegetable consumption in g/d (1.10 (1.04 to 1.16), $P<0.001$ for overall cancer; 1.11 (1.01 to 1.22), $P=0.03$ for breast cancer), number of smoked cigarettes in pack years (1.13 (1.07 to 1.19), $P<0.001$ for overall cancer; 1.13 (1.03 to 1.26), $P=0.009$ for breast cancer), and season of inclusion in the cohort (1.12 (1.06 to 1.18), $P<0.001$ for overall cancer; 1.12 (1.02 to 1.22), $P=0.02$ for breast cancer).

We also tested other methods for handling missing data, such as multiple imputation and complete case analysis (that is, exclusion of participants with missing data for at least one covariate).\textsuperscript{46} The results were very similar for the multiple imputation analysis (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.11 (1.06 to 1.17), $P<0.001$, 2228 cases and 10 2752 non-cases for overall cancer; 1.11 (1.01 to 1.21), $P=0.02$, 739 cases and 81 420 non-cases for breast cancer) and for the complete case analysis (1.11 (1.05 to 1.18), $P<0.001$, 1813 cases and 82 824 non-cases for overall cancer; 1.14 (1.03 to 1.26), $P=0.01$, 579 cases and 64 642 non-cases for breast cancer).

As a secondary analysis, we also tested associations between the proportions of the three other NOVA degrees of food processing and risk of cancer. We found no significant associations between the proportions of “processed culinary ingredients” or “processed foods” with risk of cancer at any location (all $P>0.05$). However, and consistent with our findings, the consumption of “minimally/unprocessed foods” was associated with lower risks of overall and breast cancers (hazard ratio for a 10 point increment in the proportion of unprocessed foods in the diet 0.91 (0.87 to 0.95), $P<0.001$, 2228 cases and 10 2752 non-cases for overall cancer; 0.42 (0.19 to 0.91), $P=0.03$, 739 cases and 81 420 non-cases for breast cancer), in multivariable analyses adjusted for model 1 covariates.

Discussion

In this large prospective cohort, a 10% increase in the proportion of ultra-processed foods in the diet was associated with significant increases of 12% in the risk of overall cancer and 11% in the risk of breast cancer. A few studies have previously suggested that ultra-processed foods contribute to increasing the risk of cardiometabolic disorders—such as obesity,\textsuperscript{29} hypertension,\textsuperscript{30} and dyslipidaemia\textsuperscript{28}—but no previous prospective epidemiological study has evaluated the association between food processing and risk cancer.

Interpretation and comparison with other studies

No estimate is available of the proportion of ultra-processed food in the diet at the national level in France. However, in the nationally representative INCA3 study conducted by the French Food safety Agency in 2016,\textsuperscript{4} “transformed” foods included sweet pastries, biscuits, dairy desserts, ice cream, fruit purée and fruit in syrup, fruit and vegetable juices, soups and broths, sandwiches, pizzas, and salted pastries, as well as mixed dishes composed of egg, meat, fish, vegetable, and/or starchy foods (cereals, legumes, or potatoes). More than half of the “transformed” foods consumed outside catering establishments by adults aged 18-79 were manufactured industrially, about a third were homemade, and the rest was handcrafted (for example, by caterers). These figures illustrate the important share of processed, and especially industrially processed, foods in the diet of French adults.
Several hypotheses could be put forward to explain our findings. The first one relates to the generally poorer nutritional quality of diets rich in ultra-processed foods. Diets that include a higher proportion of processed food products tended to be richer in energy, sodium, fat, and sugar and poorer in fibres and various micronutrients in several studies conducted in various countries.\textsuperscript{10-17} Ultra-processed foods have also been associated with a higher glycaemic response and a lower satiety effect.\textsuperscript{29} Although not the unique determinant, excessive energy, fat, and sugar intakes contribute to weight gain and risk of obesity, with obesity recognised as a major risk factor for post-menopausal breast, stomach, liver, colorectal, oesophagus, pancreas, kidney, gallbladder, endometrium, ovary, liver, and (advanced) prostate cancers and haematological malignancies.\textsuperscript{29} For instance, body fatness in post-menopausal women is estimated to contribute 17\% of the breast cancer burden.\textsuperscript{2} Furthermore, most ultra-processed foods, such as dehydrated soups, processed meats, biscuits, and sauces, have a high salt content. Foods preserved with salt are associated with an increased risk of gastric cancer.\textsuperscript{29} Conversely, dietary fibre intake decreases the risk of colorectal cancer, with a convincing level of evidence,\textsuperscript{3,29} and may also reduce the risk of breast cancer.\textsuperscript{3} However, the associations between ultra-processed food intake and risk of cancer observed in this study were statistically significant despite adjustment for body mass index and remained significant after further adjustment for a Western-type dietary pattern and/or the energy, fat, sugar, and salt content of the diet. Mediation analyses did not support a strong effect of the “nutritional quality” component in this association, suggesting that other bioactive compounds contained in ultra-processed food may contribute to explain the observed associations.

A second hypothesis concerns the wide range of additives contained in ultra-processed foods. Although maximum authorised levels normally protect the consumers against adverse effects of each individual substance in a given food product,\textsuperscript{48} the effect on health of the cumulative intake across all ingested foods and potential cocktail/interaction effects remain largely unknown. More than 250 different additives are authorised for addition to food products in Europe and the US.\textsuperscript{22,49} For some of them, experimental studies in animal or cellular models have suggested carcinogenic properties that deserve further investigation in humans.\textsuperscript{23,24,50-53} One example is titanium dioxide (TiO\textsubscript{2}), a common food additive that contains nanoscale particles and that is used as a whitening agent or in packaging in contact with food or drinks to provide a better texture and antimicrobial properties. Experimental studies, mainly conducted in rodent models, suggest that this additive could initiate or promote the development of pre-neoplastic lesions in the colon, as well as chronic intestinal inflammation. The World Health Organization and the International Agency for Research on Cancer evaluated TiO\textsubscript{2} as “possibly carcinogenic to humans” (group 2B).\textsuperscript{24} The effects of intense artificial sweeteners such as aspartame on human metabolism and on the composition and functioning of gut microbiota are also controversial.\textsuperscript{53} Although previous experimental studies in animals confirmed the safety of aspartame, their relevance to human health outcomes has been questioned, particularly regarding potential long term carcinogenicity.\textsuperscript{24} Another concern is the formation of carcinogenic nitrosamines in meats containing sodium nitrite when meat is charred or overcooked. These N-nitroso compounds may be involved in causing colorectal cancer.\textsuperscript{23,52}

Thirdly, food processing and particularly heat treatments produce neoformed contaminants (for example, acrylamide) in ultra-processed products such as fried potatoes, biscuits, bread, or coffee. A recent meta-analysis found a modest association between dietary acrylamide and risk of both kidney and endometrial cancer in non-smokers.\textsuperscript{54} In addition, the European Food Safety Agency judged that evidence from animal studies was sufficient to classify acrylamide as genotoxic.\textsuperscript{50}

Lastly, bisphenol A is another contaminant suspected of migrating from plastic packaging of ultra-processed foods. Its endocrine disruptor properties led the European Chemicals Agency to judge it as “a substance of very high concern.”\textsuperscript{55} Increasing evidence suggests involvement in the development of several non-communicable diseases, including cancer linked to endocrine disruptors.\textsuperscript{51}

**Strengths and limitations of study**

Strengths of this study pertain to its prospective design and large sample size, along with a detailed and up to date assessment of dietary intake. Repeated 24 hour dietary records (including 3300 different food items) are more accurate than either food frequency questionnaires with aggregated food groups or household purchasing data. However, some limitations should be acknowledged. Firstly, as is generally the case in volunteer based cohorts, participants in the NutriNet-Santé cohort were more often women, with health conscious behaviours and higher socio-professional and educational levels than the general French population.\textsuperscript{56} This might limit the generalisability of the findings and may have resulted in a lower incidence of cancer compared with national estimates (age and sex standardised incidence rate per 100 000 people per year: 786 cases in our cohort versus 972 cases in France\textsuperscript{57}) and an overall lower exposure to ultra-processed foods, with less contrast between extreme categories. These points would tend to lead to underestimation of the strength of the associations. However, the possibility that selection bias may have led to an overestimation of some associations cannot be totally excluded. Secondly, some misclassification in the NOVA “ultra-processed food” category cannot be ruled out. Thirdly, despite a multi-source strategy for case ascertainment (combining validation of health events declared by participants, medico-administrative databases from the health insurance,
and national death registry), exhaustive detection of cancer cases cannot be guaranteed. Furthermore, statistical power was limited for some cancer locations (such as colorectal cancer), which may have impaired our ability to detect hypothesised associations. Next, the length of follow-up was relatively limited, as the cohort was launched in 2009. It allowed us to study mostly mid-term associations between consumption of ultra-processed food and risk of cancer. As is usually the case in nutritional epidemiology, we made the assumption that the measured exposure at baseline (especially as we averaged a two year period of exposure) actually reflects more generally the usual eating habits of the individual during adulthood, including several years before his or her entry into the cohort. However, as some carcinogenic processes may take several decades, it will be important in the future to reassess the associations between ultra-processed food and cancer risk in the cohort, to investigate longer term effects. This will be one of the perspectives of our work for the upcoming five to 10 years. Lastly, although we included a large range of confounding factors in the analyses, the hypothesis of residual confounding resulting from unmeasured behavioural factors and/or imprecision in the measure of included covariates cannot be entirely excluded owing to the observational design of this study. For instance, oral contraception was a binary variable in breast cancer models, as the precise doses, type, and duration of contraceptive use across reproductive life were not available. Randomised controlled trials have long been considered the only gold standard for elimination of confounding bias, but they do not capture consumption as it is in daily life. Moreover, a trial to investigate exposure for which a deleterious effect is suspected would not be ethically feasible. Our large observational cohort was therefore particularly adapted to provide insights in this field.

Conclusions and policy implications
To our knowledge, this study was the first to investigate and highlight an increase in the risk of overall—and more specifically breast—cancer associated with ultra-processed food intake. These results should be confirmed by other large scale, population based observational studies in different populations and settings. Further studies are also needed to better understand the relative effect of nutritional composition, food additives, contact materials, and neofomed contaminants in this relation. Rapidly increasing consumption of ultra-processed foods may drive an increasing burden of cancer and other non-communicable diseases. Thus, policy actions targeting product reformulation, taxation, and marketing restrictions on ultra-processed products and promotion of fresh or minimally processed foods may contribute to primary cancer prevention.6 9 Several countries have already introduced this aspect in their official nutritional recommendations in the name of the precautionary principle.58 59

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Transparency statement: MT (the guarantor) 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.

Data sharing: No additional data available.

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Appendix 1-6