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

Journal:	*BMJ*
Manuscript ID	BMJ.2017.040538
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	31-Jul-2017
Complete List of Authors:	Fiolet, Thibault; Nutritional Epidemiology Research Team (EREN), Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University Srour, Bernard; Inserm - French National Institute of Health and Medical Research, Nutritional Epidemiology Research Team (EREN), Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University Sellem, Laury; Nutritional Epidemiology Research Team (EREN), Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University Kesse-Guyot, Emmanuelle; Université Paris 13, COMUE Sorbonne-Paris-Cité, Equipe de Recherche en Epidémiologie Nutritionnelle (EREN), Centre d'Epidémiologie et Biostatistiques Paris Nord, Inserm (U1153), Inra (U1125), Cnam, COMUE Sorbonne-Paris-Cité, Equipe de Recherche en Epidémiologie Nutritionnelle Alles, Benjamin; Université Paris 13, Equipe de Recherche en Epidémiologie Nutritionnelle, Centre de Recherche en Epidémiologie et Statistiques, Inserm (U1153), Inra (U1125), Cnam, COMUE Sorbonne Paris Cité Méjean, Caroline; INRA, UMR 1110 MISA, 34000 Montpellier, France Deschasaux, Mélanie; Sorbonne Paris Cité Epidemiology and Statistics Research Center, Inserm U1153, Inra U1125, Cnam, Paris 13 University, Nutritional Epidemiology Research Team (EREN) Fassier, Philippine; Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Nutritional Epidemiology Research Team (EREN):, ; Latino-Martel, Paule; Nutritional Epidemiology Research Team (EREN), Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University Beslay, Marie; Nutritional Epidemiology Research Team (EREN), Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University Hercberg, Serge; Université Paris 13, Equipe de Recherche en Epidémiologie Nutritionnelle (EREN), Centre d'Epidémiologie et Statistiques Sorbonne Paris Cité, Inserm (U1153), Inra (U1125), Cnam, COMUE Sorbonne Paris Cité; Département de Santé Publique, Hôpital Avicenne, F-93017, Bobigny Cedex, France.

	Lavalette, Céline; Nutritional Epidemiology Research Team (EREN), Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University Monteiro, Carlos; University of Sao Paulo, Julia, Chantal; Nutritional Epidemiology Research Team (EREN), Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University; Département de Santé Publique, Hôpital Avicenne, F-93017, Bobigny Cedex, France. Touvier, Mathilde; Université Paris 13, Equipe de Recherche en Epidémiologie Nutritionnelle, Centre de Recherche en Epidémiologie et Statistiques, Inserm (U1153), Inra (U1125), Cnam, COMUE Sorbonne Paris Cité,
Keywords:	ultra-processed food, food processing, cancer, prospective cohort, NOVA classification

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

Thibault Fiolet[1], Bernard Srour[1], Laury Sellem[1], Emmanuelle Kesse-Guyot[1], Benjamin Allès[1], Caroline Méjean[2], Mélanie Deschasaux[1], Philippine Fassier[1], Paule Latino-Martel[1], Marie Beslay[1], Serge Hercberg[1, 4], Céline Lavalette[1], Carlos A. Monteiro[3], Chantal Julia[1, 4], Mathilde Touvier[1]

Running Head: Ultra-processed foods and cancer risk

Affiliations:

[1] Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University, Nutritional Epidemiology Research Team (EREN), Bobigny, France

[2] INRA, UMR 1110 MOISA, 34000 Montpellier, France

[3] Department of Nutrition, School of Public Health, University of São Paulo, Av. Dr Arnaldo 715,São Paulo 01246-904, Brazil

[4]Public Health Department, Avicenne Hospital, AP-HP, Bobigny, France

Corresponding author:

Bernard Srour

Equipe de Recherche en Epidémiologie Nutritionnelle (EREN)

Centre de Recherche en Epidémiologie et Statistiques Sorbonne Paris Cité, Inserm (U1153), Inra(U1125), Cnam, Université Paris 13

SMBH Paris 13, 74 rue Marcel Cachin F-93017 Bobigny Cedex. France

Tel : +33 1 48 38 89 68

E-mail : b.srour@eren.smbh.univ-paris13.fr

Sources of support: The NutriNet-Santé study was supported by the following public institutions: Ministère de la Santé, Institut de Veille Sanitaire (InVS), Institut National de la Prévention et de l'Education pour la Santé (INPES), Région Ile-de-France (CORDDIM), Institut National de la Santé et de la Recherche Médicale (INSERM), Institut National de la Recherche Agronomique (INRA), Conservatoire National des Arts et Métiers (CNAM) and Université Paris 13. Mélanie Deschasaux and Philippine Fassier were funded by a PhD grant from the Cancéropôle Ile de France / Région Ile de France (public funding). Bernard Srour was funded by the French National Cancer Institute (grant number INCa_8085).

Patient involvement

The research question developped in this article corresponds to a strong concern of the participants involved in the NutriNet-Santé cohort, and of the public in general.

Participants to the study are thanked in the Acknowledgements section.

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

Conflict of interest: The authors have no conflict of interest to disclose.

Word count (Title to References): 3,177 ; **Tables**: 2 ; **Figures**: 2

Keywords: ultra-processed food; food processing; cancer; prospective cohort; NOVA classification

Supplemental material: None

ABSTRACT

Background: Dietary habits are shifting in many countries through an upsurge in the consumption of ultra-processed foods, which are often characterized by a lower nutritional quality but also the presence of food additives, food contact materials, and neoformed compounds. Although epidemiological data regarding their relevance to cancer risk are lacking, mechanistic studies suggest potential carcinogenic effects of several components commonly found in ultra-processed foods.

Objective: For the first time, this prospective study aimed at assessing the prospective associations between ultra-processed food consumption and cancer risk.

Methods: In all, 104,980 participants aged ≥18y from the French NutriNet-Santé cohort (2009-2017) were included. Dietary intakes were collected using repeated 24h-dietary records, designed to register participants' usual consumption for 3300 different food items. These were categorized according to their degree of processing by the NOVA classification. Multivariable Cox models were performed.

Results: Ultra-processed food intake was associated with higher overall cancer risk (n=2,228 cases, $HR_{\text{for a 10\% increment in the proportion of ultra-processed food in the diet}}$=1.12 (1.06-1.18), P-trend<.0001) and breast cancer risk (n=739 cases, HR= 1.11 (1.02-1.22), P-trend=0.02). These results remained significant after adjustment for several markers of the nutritional quality of the diet (lipid, sodium and carbohydrate intakes and/or a Western pattern).

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

INTRODUCTION

Cancer represents a major worldwide burden with 14.1 million new cases diagnosed in 2012 [1]. According to the World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR), about one third of the most common neoplasms could be avoided by changing lifestyle and dietary habits in developed countries [2]. Therefore, reaching a balanced and diversified diet (along with tobacco avoidance and alcohol reduction) should be considered as one of the most important modifiable risk factors in the primary prevention of cancer [3].

At the same time, during the last decades, in many countries, diets have shifted towards a dramatic increase in ultra-processed foods consumption [4-9]. After undergoing multiple physical, biological and/or chemical processes, these food products are conceived to be microbiologically safe, convenient, highly palatable and affordable [10;11].National and regional surveys on individual food intake, household food expenses and supermarket sales have shown that ultra-processed food products already contribute to between one quarter to more than half of total food energy supply in countries such as Brazil, Spain, the Netherlands, Germany, the USA, the UK and Canada [11-20].

This dietary trend may be concerning and deserves investigation. Indeed, several characteristics of ultra-processed foods may be involved in disease – in particular cancer – aetiology. First, ultra-processed foods often have a higher content in total fat, saturated fat, added sugar and salt, along with a lower fibre and vitamin density [11;13-21]. Beyond nutritional composition, neoformed contaminants, some of which having carcinogenic properties (such as acrylamide, heterocyclic amines, polycyclic aromatic hydrocarbons, etc.) are present in heat-treated processed food products due to the Maillard reaction [22]. Next, the packaging of ultra-processed foods may contain some contact materials for which carcinogenic and endocrine disruptor properties have been postulated such as Bisphenol A [23]. Finally, ultra-processed foods contain authorized [24]but controversial food additives such as sodium nitrite in processed meat or titanium dioxide (TiO_2, white food pigment), for which carcinogenicity has been suggested in animal or cellular models [25;26].

Studying potential health impacts 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 [10].

Nonetheless, epidemiological evidence linking ultra-processed food intake to disease risk is still very scarce[8;27-30] and mostly based on cross-sectional and ecological studies. The few studies performed observed that ultra-processed food intake was associated with higher dyslipidaemia in Brazilian children [31] and overweight and obesity [32] and hypertension [33] in a cohort of Spanish University students.

To our knowledge, the present 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 dietary intake assessment.

MATERIAL AND METHODS

Study population

The NutriNet-Santé study is an ongoing web-based cohort launched in 2009 in France with the objective to study the associations between nutrition and health as well as the determinants of dietary behaviors and nutritional status. This cohort has been previously described in details [34]. Briefly, participants aged over 18 years with access to the Internet are continuously recruited since May 2009 among the general population by means of vast multimedia campaigns. All questionnaires are completed online using a dedicated website (www.etude-nutrinet-sante.fr). The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines and was approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB Inserm n°0000388FWA00005831) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL n°908450/n°909216). Electronic informed consent is obtained from each participant (EudraCT no. 2013-000929-31).

Data collection

At inclusion, participants completed a set of five questionnaires related to socio-demographic and lifestyle characteristics [35] (e.g. date of birth, sex, occupation, educational level, smoking status, number of children), anthropometry [36;37] (e.g. height, weight), dietary intakes (see below), physical activity (validated 7-day International Physical Activity Questionnaire [IPAQ]) [38], and health status (e.g. personal and family history

of diseases, medication use including use of hormonal treatment for menopause, oral contraceptive, and menopausal status).

Usual dietary intakes were assessed every 6-months through a series of three non-consecutive validated web-based 24h-dietary records, randomly assigned over a 2-week period (2 weekdays and 1 weekend day) [39-41]. Mean dietary intakes from all the 24h-dietary records available during the first two years of each participant's follow-up were considered as baseline usual dietary intakes in this prospective analysis. Participants used a dedicated web interface to declare all food and beverages consumed during a 24h-periodfor 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 [42]. Dietary underreporting was identified on the basis of the method proposed by Black, using the basal metabolic rate and Goldberg cut-off, and under-energy reporters were excluded [43]. Mean daily alcohol, micro- and macro-nutrient and energy intake were calculated using the NutriNet-Santé food composition database, which contains more than 3,300 different items [44]. Amounts consumed from composite dishes were estimated using French recipes validated by nutrition professionals.

Degree of food processing

All food and beverage items of the NutriNet-Santé composition table were categorized according to their degree of processing, as described in detail previously [45]. Ultra-processed products were identified based on the NOVA classification described by Moubarac et al. and Monteiro et al. [46;47]. Briefly, ultra-processed food products are ready to eat, to drink or to heat packaged formulations made mostly or entirely from substances derived from foods and several additives with little if any intact food. NOVA application was performed by a team of three dieticians trained in nutritional epidemiology, supervised by researchers. In case of uncertainty for a given food/beverage item, a consensus was reached among researchers based on the percentage of home-made and artisanal foods versus industrial brands reported by the participants.

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. Following this declaration, participants were invited to send their medical records (diagnosis, hospitalization, etc.) and, if necessary, the study physicians contacted the participants' treating physician or the medical structures to collect additional information. Then, medical data were reviewed by an independent physician expert committee for the validation of major health events. Cancer cases were classified using the International Chronic Diseases Classification, 10th Revision, Clinical Modification (ICD-10). In this study, all first primary cancers diagnosed between the inclusion and January 1st 2017 were considered as cases, except for basal cell skin carcinoma, which was not considered as cancer.

Statistical analysis

Up to January 1st 2017, 104,980 participants without cancer at baseline and who provided at least 2 valid 24h-dietary records during their 2 first years of follow-up were included (Supplementary Material). For each subject, the proportion (in weight, % g/day) of ultra-processed foods in the total diet was calculated. The proportion of ultra-processed foods in the diet was determined by making a weight ratio rather than an energy ratio in order to take into account processed food that do not provide any energy (in particular artificially sweetened beverages) and non-nutritional issues related to food processing (e.g. neo-formed contaminants, food additives and alterations to the structure of raw foods). For all covariates except physical activity, ≤ 5% of values were missing and were imputed to the modal value. For physical activity, a "missing class" (n=14,615 – 14%) was included in the statistical analyses. Differences in baseline characteristics of participants between sex-specific quartiles of the proportion of ultra-processed food in the diet were examined using ANOVA or $\chi 2$ tests wherever appropriate. Cox proportional hazards models with age as the primary time-scale were used to evaluate the association between the proportion of ultra-processed foods in the diet (coded as a continuous variable or as sex-specific quartiles) and incidence of overall, breast, prostate and colorectal cancer risk. In these models, cancers of other locations than the one studied were censored at the date of diagnosis. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated with the lowest quartile as the reference category. Log-log (survival) vs. log-time plots were

generated in order to confirm risk proportionality assumptions. Tests for linear trend were performed using the ordinal score on sex-specific quartiles of ultra-processed food. Participants contributed person-time until the date of cancer diagnosis, the date of last completed questionnaire, the date of death, or January 1st 2017, whichever occurred first. Breast cancer analyses were additionally stratified by menopausal status. For the latter, women contributed person-time to the "pre-menopause model" until their age at menopause and to the "post-menopause model" from their age at menopause. Age at menopause was determined using the yearly health status questionnaires completed during follow-up.

Models were adjusted for age (time-scale), sex, BMI (kg/m², continuous), height (cm, continuous), physical activity (high, moderate, low, computed following IPAQ recommendations (35)), smoking status (never or former smokers, current smokers), number of 24h-dietary records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, kcal/d, continuous), family history of cancer (yes/no), and educational level (<high-school degree, <2 years after high-school degree, ≥2 years after high-school degree). For breast cancer analyses, additional adjustments were performed for the number of biological children (continuous), menopausal status at baseline (menopausal/peri-menopausal/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). To test for the potential influence of the nutritional quality of the diet in the relationship between ultra-processed food intake and cancer risk, this model was additionally adjusted for lipid, sodium and carbohydrate intakes (Model 2), or for a Western dietary pattern derived from principal component analysis (Model 3), or for all these nutritional factors together (Model 4). Besides, mediation analyses were carried out according to the method proposed by Lange et al. [48] to evaluate the direct and indirect effect of the relationship between the exposure and the outcome through these following nutritional mediators: sodium intake, total lipid intake, carbohydrate intakes, and Western-type dietary pattern. Sensitivity analyses were performed by excluding cancer cases diagnosed during the first year of each participant's follow-up to avoid reverse causality bias and by testing the dietary share of ultraprocessed food weighted by energy intake instead of quantity of foods.

All tests were two-sided, and $P<0.05$ was considered statistically significant. SAS version 9.4 (SAS Institute) was used for the analyses.

RESULTS

A total of 104,980 participants with 22821 (21.7%) men and 82159 (78.3%) women were included in the present study. Mean age of participants was 42.8 (SD=14.8) years. Mean number of dietary records per subject over their first two years of follow-up was 5.4 (SD=2.9). Main baseline characteristics of participants according to quartiles of the proportion of ultra-processed foods in the diet are described in Table 1. Participants among the highest quartile of ultra-processed food intake tended to be younger, current smokers, 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. Main food groups contributing to ultra-processed food intake were sugary products (26%), beverages (20%), starchy foods and breakfast cereals (16%), fruits and vegetables (15%) and dairy products (7%) (Figure 1).

TABLE 1 Baseline characteristics of the study population according to sex-specific quartiles of ultra-processed food consumption (n=104,980), NutriNet-Santé cohort, France, 2009-2017[a]

		Quartiles of ultra-processed food consumption[b]				
	All participants	**Quartile 1 (n=26,244)**	**Quartile 2 (n=26,245)**	**Quartile 3 (n=26,246)**	**Quartile 4 (n=26,245)**	**P-trend[c]**
Age, years	42.8 ± 14.8	47.9 ± 13.5	45.0 ± 14.0	42.0 ± 14.4	36.5 ± 13.6	<.0001
Sex, n (%)						
Female	82159 (78.3)	20,539 (78.3)	20,540 (78.3)	20,541 (78.3)	205,42 (78.3)	
Male	22821 (21.7)	5,705 (21.7)	5,706 (21.7)	5,707 (21.7)	5,708 (21.7)	
Height, cm	166.8 ± 8.1	166.3 ± 8.0	166.7 ± 8.0	167.0 ± 8.1	167.3 ± 8.2	<.0001
Body mass index, kg/m²	23.8 ± 4.6	23.8 ± 4.3	23.8 ± 4.4	23.8 ± 4.5	23.8 ± 5.0	0.9
Family history of cancer, yes[d]	35668 (34.0)	10,542 (40.2)	9,624 (36.7)	8,625 (32.9)	6,877 (26.2)	<.0001
Higher education, n (%)						0.01
No	19357 (18.4)	5,154 (19.6)	4,961 (18.9)	4,637 (17.7)	4,605 (17.6)	
Yes <2 years	18076 (17.2)	3,938 (15.0)	1,091 (15.6)	4,426 (16.9)	5,621 (21.4)	
Yes ≥2 years	67,547 (64.3)	17,152 (65.4)	17,193 (65.5)	17,183 (65.5)	16,019 (61.0)	
Smoking status, n (%)						<.0001
Current	17,763 (16.9)	4,127 (15.7)	4,065 (15.5)	4,266 (16.3)	5,305 (20.2)	
Never/former	87,217 (83.1)	22,117 (84.3)	22,180 (84.5)	21,980 (83.8)	20,940 (79.8)	
IPAQ Physical activity level, n (%)[e]						<.0001
High	29603 (28.2)	8,753 (33.4)	7,762 (29.6)	6,983 (26.6)	6,105 (23.3)	
Moderate	38874 (37.0)	9,620 (36.7)	9,953 (37.9)	9,814 (37.4)	9,487 (36.2)	
Low	21888 (20.9)	4,407 (13.8)	4,407 (16.8)	5,839 (22.3)	6,490 (24.7)	
Energy intake without alcohol, kcal/d	1879.0±473.7	1,810.6 ± 454.1	1,881.1 ± 457.7	1,908.5 ± 472.3	1,915.8 ± 501.8	<.0001
Alcohol intake, g/d	7.8 ± 11.9	9.3 ± 13.3	8.5 ± 11.9	7.5 ± 11.3	5.9 ± 10.5	<.0001
Total Lipid intake, g/d	80.5 ± 25.5	76.0 ± 24.3	80.3 ± 24.4	82.1 ± 25.3	83.4 ± 27.3	<.0001
Carbohydrate intake, g/d	195.4 ± 57.9	184.6 ± 57.8	193.9 ± 55.3	199.3 ± 56.6	203.6 ± 60.2	<.0001
Sodium intake, mg/d	2,700.1 ± 893.1	2,589.3 ± 881.6	2,731.8 ± 871.0	2,761.9 ± 884.1	2,717.7 ±	<.0001

					925.0	
Number of children	1.3 ± 1.2	1.6±1.2	1.4±1.2	1.3±1.2	1.0±1.2	
Menopausal status, n (%)[f]						<.0001
Premenopausal	57408 (69.9)	11,797 (57.4)	13,497 (65.7)	14,961 (728)	17,153 (83.5)	
Perimenopausal	4282 (5.2)	1,471 (7.16)	1,148 (5.6)	997 (4.9)	666 (3.2)	
Postmenopausal	20469 (24.9)	7,271 (35.4)	5,895 (28.7)	4,582 (22.3)	2,721 (13.3)	
Use of hormonal treatment	4324 (5.3)					
for menopause, yes n (%)[f]		1602 (7.8)	1242 (6.1)	932 (4.5)	548 (2.7)	<.0001
Oral contraception, yes n	23073 (22.0)					
(%)[f]		3,779 (14.4)	4,990 (19.0)	6,209 (23.7)	8,095 (30.8)	<.0001
Ultraprocessed food (%)	18.7 ± 10.1	8.5 ± 2.5	14.3 ± 1.4	19.8 ± 1.9	32.3 ± 9.8	<.0001

[a]Values are means ± SDs or n (%).

[b]Sex specific quartiles of the proportion of ultra-processed food intake in the total quantity of food consumed. Sex-specific cut-offs for quartiles of ultra-processed proportions were 11.8%, 16.8% and 23.3% in men and 11.8%, 16.8% and 23.4% in women.

[c] P_{value} for the comparison between sex-specific quartiles of ultra-processed food consumption, by Fisher test or x^2 test where appropriate.

[d]Among first-degree relatives

[e] Available for 14615 subjects. Subjects were categorized into the "high", "moderate" and "low" categories according to IPAQ guidelines[38]

[f]Among women

Between May 2009 and January 2017 (371,128 person-years), 2,228 first incident cancer cases were diagnosed, among which 739 breast cancers (n=264 pre-menopausal and n=475 post-menopausal), 281 prostate cancers and 153 cases of colorectal cancers. Associations between the proportion of ultra-processed foods in the diet and overall, breast, prostate and colorectal cancer risks are shown in Table 2. Corresponding cumulative incidence curves are shown in Figure 2. In model 1, ultra-processed food intake was associated with increased risks of overall cancer ($HR_{\text{for a 10-point increment in the proportion of ultra-processed foods in the diet}}$=1.12 (1.06, 1.18), P-trend<.0001) and breast cancer (HR=1.11 (1.02, 1.22), P-trend=0.02). The later association was more specifically observed for post-menopausal breast cancer (P=0.04) but not for pre-menopausal breast cancer (P=0.2).

TABLE 2 Associations between ultra-processed food intake and overall, prostate, colorectal and breast cancer risk, from multivariable Cox proportional hazard models, NutriNet-Santé cohort, France, 2009 – 2017 (n=104,980)[a]

	Proportion of ultra-processed food intake in the diet											
	Continuous[b]			Sex-specific quartiles[c]								
				Q1	Q2		Q3			Q4		
	HR	95% CI	*P*-trend	HR	HR	95% CI	HR	95% CI		HR	95% CI	*P*-trend
All cancers												
N for cases/non-cases	2228/102753			712/25532	607/25638		541/25705			368/25877		
Model 1	1.12	1.06 - 1.18	<.0001	1	0.99	0.89 - 1.11	1.10	0.99 - 1.24		1.21	1.06 - 1.38	0.002
Model 2	1.12	1.07 - 1.18	<.0001	1	1.00	0.90 - 1.11	1.11	0.99 - 1.25		1.23	1.08 - 1.40	0.001
Model 3	1.12	1.06 - 1.18	<.0001	1	0.99	0.89 - 1.11	1.01	0.98 - 1.23		1.21	1.06 - 1.38	0.002
Model 4	1.13	1.07 - 1.18	<.0001	1	1	0.90 - 1.11	1.11	0.99 - 1.24		1.23	1.08 - 1.40	0.001
Prostate cancer												
N for cases/non-cases	281/22540			96/5609	96/5609		59/5647			30/5675		
Model 1	0.98	0.83 - 1.16	0.8	1	1.18	0.89 - 1.57	0.95	0.69 - 1.32		0.93	0.61 - 1.40	0.6
Model 2	0.98	0.83 - 1.16	0.8	1	1.18	0.89 - 1.57	0.95	0.69 - 1.32		0.93	0.61 - 1.40	0.6
Model 3	0.98	0.83 - 1.15	0.8	1	1.18	0.89 - 1.56	0.95	0.68 - 1.31		0.92	0.61 - 1.39	0.6
Model 4	0.98	0.83 - 1.16	0.8	1	1.18	0.89 - 1.57	0.95	0.68 - 1.32		0.93	0.61 - 1.40	0.6
Colorectal cancer												
N for cases/non-cases	153/104827			48/26196	43/26202		36/26210			26/26219		
Model 1	1.13	0.92 - 1.38	0.2	1	1.10	0.72, 1.66	1.17	0.76 - 1.81		1.49	0.92 - 2.43	0.1
Model 2	1.16	0.95 - 1.42	0.1	1	1.12	0.74, 1.70	1.22	0.79 - 1.90		1.59	0.97 - 2.60	0.07
Model 3	1.13	0.92 - 1.38	0.2	1	1.09	0.92, 1.38	1.16	0.75 - 1.80		1.48	0.91 - 2.41	0.1
Model 4	1.16	0.95 - 1.42	0.1	1	1.12	0.74, 1.70	1.22	0.79 - 1.89		1.23	1.08 - 1.40	0.07
Breast cancer												
N for cases/non-cases	739/81420			247/20292	202/20338		179/20361			111/20429		
Model 1	1.11	1.02 - 1.22	0.02	1	0.97	0.81 - 1.17	1.10	0.90 - 1.34		1.14	0.91 - 1.44	0.2
Model 2	1.11	1.01 - 1.21	0.03	1	0.96	0.80 - 1.16	1.09	0.89 - 1.32		1.12	0.89 - 1.42	0.2
Model 3	1.11	1.02 - 1.22	0.02	1	0.97	0.80 - 1.17	1.09	0.90 - 1.33		1.14	0.91 - 1.44	0.2
Model 4	1.11	1.01 - 1.21	0.03	1	0.96	0.80 - 1.16	1.08	0.89 - 1.32		1.13	0.89 - 1.42	0.2
Pre-menopausal breast cancer												
N for cases/non-cases	264/57151			90/14263	70/14284		55/14299			49/14305		
Model 1	1.09	0.95 - 1.25	0.2	1.00	0.91	0.67 - 1.25	0.92	0.65 - 1.29		1.30	0.90 - 1.86	0.3
Model 2	1.07	0.93 - 1.23	0.4	1.00	0.90	0.66 - 1.24	0.90	0.64 - 1.27		1.25	0.87 - 1.80	0.4
Model 3	1.09	0.95 - 1.26	0.2	1.00	0.91	0.67 - 1.25	0.92	0.66 - 1.30		1.30	0.91 - 1.88	0.3

Model 4	1.08	0.94 - 1.24	0.3	1.00	0.91	0.66 - 1.24	0.91	0.64 - 1.28	1.27	0.88 - 1.83	0.4
Post-menopausal											
breast cancer											
N for cases/non-cases		475/29191		107/7309		128/7289		123/7294		117/7299	
Model 1	1.13	1.01 - 1.27	0.04	1.00	1.23	0.95 - 1.60	1.28	0.98 - 1.66	1.39	1.07 - 1.82	0.02
Model 2	1.13	1.00 - 1.27	0.05	1.00	1.23	0.95 - 1.60	1.27	0.98 - 1.65	1.39	1.05 - 1.81	0.02
Model 3	1.13	1.00 - 1.27	0.04	1.00	1.23	0.95 - 1.59	1.27	0.98 - 1.65	1.38	1.06 - 1.81	0.02
Model 4	1.13	1.00 - 1.27	0.05	1.00	1.23	0.95 - 1.59	1.27	0.97 - 1.65	1.38	1.05 - 1.81	0.02

CI, confidence interval, HR, Hazard ratio

[a] Model 1 is a multivariable Cox proportional hazard model adjusted for age (timescale), sex, energy intake without alcohol, number of 24h-dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, and family history of cancers. Breast cancer models were additionally adjusted for menopausal status, hormonal treatment for menopause, oral contraception and number of children.

Model 2 = Model 1 + lipid intake, sodium intake, carbohydrate intake

Model 3 = Model 1 + Western dietary pattern (derived by factor analysis)

Model 4 = Model 1 + lipid intake, sodium intake, carbohydrate intake, Western dietary pattern (derived by factor analysis)

[b] HR for an increase of 10% of the proportion of ultra-processed food intake in the diet

[c] Sex-specific cut-offs for quartiles of ultra-processed proportions were 11.8% ; 16.8% and 23.3% in men and 11.8% ; 16.8% and 23.4% in women.

In premenopausal group : Cut-offs for quartiles of ultra-processed proportions were 12.8% ; 18.1% and 25.0%. In postmenopausal group : Cut-offs for quartiles of ultra-processed proportions were 10.1% ; 14.3% and 19.5%.

Further adjustment for several indicators of the nutritional quality of the diet (lipid, sodium and salt intakes – model 2; Western pattern – model 3; or both – model 4) did not modify these findings. Consistently, analyses performed according to the method proposed by Lange et al. [48] to assess a potential mediation of the relationship between ultra-processed food and cancer risk by these nutritional factors showed no statistically significant mediation effect of any of the factors tested (all P>0.05, data not tabulated).

No association was statistically significant for prostate and colorectal cancers. However, a borderline non-significant trend of increased colorectal cancer risk associated with ultra-processed food intake was observed ($HR_{Q4 \text{ versus } Q1}$=1.23 (1.08, 1.40), P-trend=0.07 in model 4).

Sensitivity analyses excluding cancer cases diagnosed during the first year of follow-up provided similar results ($HR_{\text{for a 10-point increment in the proportion of ultra-processed foods in the diet}}$=1.10 (1.05, 1.18), P-trend=0.0003 for overall cancer risk, n=1791 cases/102752 non cases included; HR=1.13 (1.02, 1.25), P-trend=0.02 for breast cancer risk, n=588 cases/81420 non cases included, data not tabulated).

DISCUSSION

In this large prospective cohort, a 10% increase in the proportion of ultra-processed foods in the diet was associated with a 12% and 11% significant increase in overall and breast cancer risks, respectively. While a few studies previously suggested that ultra-processed foods may contribute to increase the risk of cardiometabolic disorders - such as obesity [32], hypertension [33], and dyslipidaemia [31] - no prior prospective epidemiological study evaluated the association between food processing and cancer risk.

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. Indeed, 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 [11;13-21]. Ultra-processed foods have also been associated with a higher glycaemic response and a lower satiety effect [49]. Although not being the unique

determinant, excessive energy, fat, and sugar intakes contribute to weight gain and obesity risk, the latter being recognized as a major risk factor for the following cancers: post-menopausal breast, stomach, liver, colorectal, oesophagus, pancreas, kidney, gallbladder, endometrium, ovary, liver, prostate (advanced) and hematological malignancies [50]. For instance, body fatness in post-menopausal women is estimated to contribute to 17% of the breast cancer burden [2]. Besides, most of ultra-processed foods, such as dehydrated soups, processed meats, biscuits and sauces, have a high salt content. Salt-preserved foods are associated with increased gastric cancer risk [50]. Conversely dietary fiber intake decreases colorectal cancer risk with a convincing level of evidence [3;50] and may also reduce breast cancer risk [3]. However, the association between ultra-processed food intake and cancer risk observed in this study were statistically significant despite adjustment for BMI, and remained significant after further adjustment for a Western-type dietary pattern and/or energy, fat, sugar and salt content of the diet. Besides, mediation analyses did not support a strong effect of the "nutritional quality" component in this association, thereby suggesting that other bioactive compounds contained in ultra-processed food may contribute to explain the observed relationships.

A second interpretation track concerns the wide range of additives contained in ultra-processed foods. While maximum authorized levels normally protect the consumers against adverse effects of each individual substance in a given food product, health impact of the cumulative intake across all ingested foods and potential cocktail/interaction effects remain largely unknown. More than 250 different additives are authorized for an adjunction to food products in Europe and in the US [24;51]. For some of them, experimental studies on animal or cellular models have suggested carcinogenic properties that deserve further investigation in humans. For instance, this is the case for titanium dioxide (TiO_2), a common food additive that contains nanoscale particules and that is used as a whitening agent or in packaging in contact with food or beverages to provide a better texture and anti-microbial properties. Experimental studies, mainly conducted in rodent models, suggested that this additive could initiate or promote the development of colon preneoplastic lesions, as well as chronic intestinal inflammation, thus, TiO_2 was evaluated as "possibly carcinogenic to humans" (Group 2B) by the World Health Organization - International Agency for Research on Cancer (WHO-IARC) [26]. The effects of intense artificial sweeteners such as aspartame on human metabolism and gut microbiota composition/functioning are also controversial [52]. Although previous

experimental studies on animals confirmed the safety of aspartame, their relevance to human health outcomes has been questioned, particularly regarding a potential long-term carcinogenicity [53]. Moreover, another concern about sodium nitrite 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 the etiology of colorectal cancer [25;54].

Next, food processing and particularly heat treatments produce neoformed contaminants (e.g.acrylamide) in ultraprocessed products such as fried potatoes, biscuits, bread or coffee. A recent meta-analysis underlined a modest association between dietary acrylamide and both kidney and endometrial cancer risks, in non-smokers [55]. In addition, the European Food Safety Agency (EFSA) judged that proofs from animal studies were sufficient to classify acrylamide as genotoxic [22].

Lastly, bisphenol A (BPA) is another contaminant suspected of migrating from plastic packaging of ultra-processed foods. Its endocrine disruptor properties made it judged as "a substance of very high concern" by the European Chemicals Agency (ECHA)[56]. There is increasing evidence for involvement in the development of several non-communicable diseases, including cancer [23] linked to endocrinal disruptors.

Strengths of this study pertained to its prospective design and large sample size, along with a detailed and up-to-date dietary intake assessment. Repeated 24h-dietary records (including 3300 different food items) are more accurate than food frequency questionnaires with aggregated food groups and than household purchasing data. However, some limitations should be acknowledged. First, as it is generally the case in volunteer-based cohorts, this study overrepresented women, health-conscious behaviours and higher socio-professional and educational levels as compared to the general French population [57]. Consequently, underrepresentation of unhealthy behaviours (and thus, of the proportion of ultra-processed food in their diet) may have weakened the observed associations. Second, some misclassification in the NOVA 'ultra-processed food' category cannot be ruled out. Furthermore, statistical power was limited for some cancer locations (such as colorectal cancer), which may have impaired our ability to detect hypothesized associations. Last, although a large range of confounding factors was included in the analyses, the hypothesis of residual confounding cannot be entirely excluded.

To our knowledge, this large prospective cohort was the first to investigate and highlight an increase in overall – and more specifically, breast – cancer risk associated with ultra-processed food intake. Further studies are needed to better understand the relative impact of nutritional composition, food additives, contact materials, and neoformed contaminants in this relationship. 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;10]. Several countries have already introduced this aspect in their official nutritional recommendations in the name of the precautionary principle [58;59].

Acknowledgements

The authors sincerely thank all the volunteers of the NutriNet-Santé cohort. We also thank Véronique Gourlet, Nathalie Arnault, Stephen Besseau, Laurent Bourhis, Yasmina Chelghoum, Than Duong Van, Younes Esseddik, Paul Flanzy, Julien Allègre, Mac Rakotondrazafy, Régis Gatibelza, Fabien Szabo, Roland Andrianasolo, Fatoumata Diallo, Ludivine Ursule, Cédric Agaesse, Claudia Chahine, Anne-Elise Dussoulier and Marion Genest for their technical contribution to the NutriNet-Santé study.

The authors' contributions were as follows – TF, CJ, EKG, CM, BA and MT: designed the research; SH, MT, CJ, EKG: conducted the research; TF: performed statistical analysis; MT: supervised statistical analysis; TF and MT: wrote the paper; TF, BS, LS, MD, PF, PLM, EKG, BA, MB, SH, PG, CL, CM, CJ, and MT: contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. MT had primary responsibility for the final content. None of the authors reported a conflict of interest related to the study. The funders had no role in the design, implementation, analysis, or interpretation of the data.

REFERENCES

(1) Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136(5):E359-E386.

(2) World Cancer Research Fund International/American Institute for Cancer Research. Cancer preventability estimates. Available at: wcrf.org/cancer-preventability-estimates accessed on 03-07-2017. 2017.

(3) Latino-Martel P, Cottet V, Druesne-Pecollo N, Pierre FH, Touillaud M, Touvier M et al. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence. *Crit Rev Oncol Hematol* 2016; 99:308-323.

(4) ANSES (French Agency for Food,Environmental and Occupational Health & Safety). Individual national study for dietary intakes 3 (INCA 3) [Étude individuelle nationale des consommations alimentaires 3 (INCA 3)] (in French). 17-7-2017.

(5) Monteiro CA, Moubarac JC, Cannon G, Ng SW, Popkin B. Ultra-processed products are becoming dominant in the global food system. *Obes Rev* 2013; 14 Suppl 2:21-28.

(6) Moodie R, Stuckler D, Monteiro C, Sheron N, Neal B, Thamarangsi T et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet* 2013; 381(9867):670-679.

(7) Moubarac JC, Batal M, Martins AP, Claro R, Levy RB, Cannon G et al. Processed and ultra-processed food products: consumption trends in Canada from 1938 to 2011. *Can J Diet Pract Res* 2014; 75(1):15-21.

(8) PAHO. Ultra-processed food and drink products in Latin America: Trends, impact on obesity, policy implications. 2015.

(9) Venn D, Banwell C, Dixon J. Australia's evolving food practices: a risky mix of continuity and change. *Public Health Nutr* 2016;1-10.

(10) Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada ML, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr* 2017;1-13.

(11) Luiten CM, Steenhuis IH, Eyles H, Ni MC, Waterlander WE. Ultra-processed foods have the worst nutrient profile, yet they are the most available packaged products in a sample of New Zealand supermarkets. *Public Health Nutr* 2016; 19(3):539.

(12) Slimani N, Deharveng G, Southgate DA, Biessy C, Chajes V, van Bakel MM et al. Contribution of highly industrially processed foods to the nutrient intakes and patterns of middle-aged populations in the European Prospective Investigation into Cancer and Nutrition study. *Eur J Clin Nutr* 2009; 63 Suppl 4:S206-S225.

(13) Martinez SE, Baraldi LG, Louzada ML, Moubarac JC, Mozaffarian D, Monteiro CA. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open* 2016; 6(3):e009892.

(14) Poti JM, Mendez MA, Ng SW, Popkin BM. Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households? *Am J Clin Nutr* 2015; 101(6):1251-1262.

(15) Adams J, White M. Characterisation of UK diets according to degree of food processing and associations with socio-demographics and obesity: cross-sectional analysis of UK National Diet and Nutrition Survey (2008-12). *Int J Behav Nutr Phys Act* 2015; 12:160.

(16) Moubarac JC, Batal M, Louzada ML, Martinez SE, Monteiro CA. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite* 2017; 108:512-520.

(17) Costa Louzada ML, Martins AP, Canella DS, Baraldi LG, Levy RB, Claro RM et al. Ultra-processed foods and the nutritional dietary profile in Brazil. *Rev Saude Publica* 2015; 49:38.

(18) Martinez SE, Popkin BM, Swinburn B, Monteiro CA. The share of ultra-processed foods and the overall nutritional quality of diets in the US: evidence from a nationally representative cross-sectional study. *Popul Health Metr* 2017; 15(1):6.

(19) Moubarac JC, Martins AP, Claro RM, Levy RB, Cannon G, Monteiro CA. Consumption of ultra-processed foods and likely impact on human health. Evidence from Canada. *Public Health Nutr* 2013; 16(12):2240-2248.

(20) Cediel G, Reyes M, da Costa Louzada ML, Martinez SE, Monteiro CA, Corvalan C et al. Ultra-processed foods and added sugars in the Chilean diet (2010). *Public Health Nutr* 2017;1-9.

(21) Louzada ML, Martins AP, Canella DS, Baraldi LG, Levy RB, Claro RM et al. Impact of ultra-processed foods on micronutrient content in the Brazilian diet. *Rev Saude Publica* 2015; 49:45.

(22) EFSA (European Food Safety Agency). EFSA Panel on Contaminants in the Food Chain (CONTAM). «Scientific Opinion on Acrylamide in Food». *EFSA Journal* 13, n° 6 (1 juin 2015): n/a-n/a. doi:10.2903/j.efsa.2015.4104. 2015.

(23) Muncke J. Endocrine disrupting chemicals and other substances of concern in food contact materials: an updated review of exposure, effect and risk assessment. *J Steroid Biochem Mol Biol* 2011; 127(1-2):118-127.

(24) European Union (EU) - List of authorized food additives. 2008.

(25) Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol* 2015; 16(16):1599-1600.

(26) Carbon black, titanium dioxide, and talc. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC Monogr Eval Carcinog Risks Hum. 2010; 93:1-413. 2017.

(27) Canella DS, Levy RB, Martins AP, Claro RM, Moubarac JC, Baraldi LG et al. Ultra-processed food products and obesity in Brazilian households (2008-2009). *PLoS One* 2014; 9(3):e92752.

(28) Juul F, Hemmingsson E. Trends in consumption of ultra-processed foods and obesity in Sweden between 1960 and 2010. *Public Health Nutr* 2015; 18(17):3096-3107.

(29) Louzada ML, Baraldi LG, Steele EM, Martins AP, Canella DS, Moubarac JC et al. Consumption of ultra-processed foods and obesity in Brazilian adolescents and adults. *Prev Med* 2015; 81:9-15.

(30) Tavares LF, Fonseca SC, Garcia Rosa ML, Yokoo EM. Relationship between ultra-processed foods and metabolic syndrome in adolescents from a Brazilian Family Doctor Program. *Public Health Nutr* 2012; 15(1):82-87.

(31) Rauber F, Campagnolo PD, Hoffman DJ, Vitolo MR. Consumption of ultra-processed food products and its effects on children's lipid profiles: a longitudinal study. *Nutr Metab Cardiovasc Dis* 2015; 25(1):116-122.

(32) Mendonca RD, Pimenta AM, Gea A, Fuente-Arrillaga C, Martinez-Gonzalez MA, Lopes AC et al. Ultraprocessed food consumption and risk of overweight and obesity: the University of Navarra Follow-Up (SUN) cohort study. *Am J Clin Nutr* 2016; 104(5):1433-1440.

(33) Mendonca RD, Lopes AC, Pimenta AM, Gea A, Martinez-Gonzalez MA, Bes-Rastrollo M. Ultra-Processed Food Consumption and the Incidence of Hypertension in a Mediterranean Cohort: The Seguimiento Universidad de Navarra Project. *Am J Hypertens* 2017; 30(4):358-366.

(34) Hercberg S, Castetbon K, Czernichow S, Malon A, Mejean C, Kesse E et al. The Nutrinet-Sante 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.

(35) Vergnaud AC, Touvier M, Mejean C, Kesse-Guyot E, Pollet C, Malon A et al. Agreement between web-based and paper versions of a socio-demographic questionnaire in the NutriNet-Sante study. *Int J Public Health* 2011; 56(4):407-417.

(36) Lassale C, Peneau S, Touvier M, Julia C, Galan P, Hercberg S et al. Validity of web-based self-reported weight and height: results of the Nutrinet-Sante study. *J Med Internet Res* 2013; 15(8):e152.

(37) Touvier M, Mejean C, Kesse-Guyot E, Pollet C, Malon A, Castetbon K et al. Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. *Eur J Epidemiol* 2010; 25(5):287-296.

(38) Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35(8):1381-1395.

(39) Touvier M, Kesse-Guyot E, Mejean C, Pollet C, Malon A, Castetbon K 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(7):1055-1064.

(40) Lassale C, Castetbon K, Laporte F, Camilleri GM, Deschamps V, Vernay M et al. Validation of a Web-based, self-administered, non-consecutive-day dietary record tool against urinary biomarkers. *Br J Nutr* 2015; 113(6):953-962.

(41) Lassale C, Castetbon K, Laporte F, Deschamps V, Vernay M, Camilleri GM 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(3):427-438.

(42) Le Moulenc N, Deheeger M, Preziozi P, Montero P, Valeix P, Rolland-Cachera M et al. Validation du manuel photo utilisé pour l'enquête alimentaire de l'étude SU.VI.MAX. [Validation of the food portion size booklet used in the SU.VI.MAX study] (in French).

(43) Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. *Int J Obes Relat Metab Disord* 2000; 24(9):1119-1130.

(44) Arnault N, Caillot L, Castetbon Keal. Table de composition des aliments, étude NutriNet-Santé. [Food composition table, NutriNet-Santé study] (in French). Paris: Les éditions INSERM/Economica. 2013.

(45) Julia C, Martinez L, Alles B, Touvier M, Hercberg S, Mejean C et al. Contribution of ultra-processed foods in the diet of adults from the French NutriNet-Sante study. *Public Health Nutr* 2017;1-11.

(46) Carlos A. Monteiro, Geoffrey Cannon, Renata Levy, Jean-Claude Moubarac, Patricia Jaime, Ana Paula Martins, et al. NOVA. The star shines bright. [Food classification.
Public health].World Nutrition.Mars 2016;7(1-3):28-38. 2017.

(47) Moubarac JC, Parra DC, Cannon G, Monteiro CA. Food Classification Systems Based on Food Processing: Significance and Implications for Policies and Actions: A Systematic Literature Review and Assessment. *Curr Obes Rep* 2014; 3(2):256-272.

(48) Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. *Am J Epidemiol* 2012; 176(3):190-195.

(49) Fardet A. Minimally processed foods are more satiating and less hyperglycemic than ultra-processed foods: a preliminary study with 98 ready-to-eat foods. *Food Funct* 2016; 7(5):2338-2346.

(50) WCRF/AICR. Cancer prevention and survival: Diet, nutrition, physical activity, and cancer. Continuous Update Project. 2016.

(51) US Food & Drug Administration FDA **Food Additive Status List. Available :** https://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm091048.htm [Accessed 03 July 2017]. 2017.

(52) Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 2014; 514(7521):181-186.

(53) EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2013. Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. EFSA Journal 2013;11(12):3496, 263 pp. doi:10.2903/j.efsa.2013.3496.

(54) Santarelli RL, Vendeuvre JL, Naud N, Tache S, Gueraud F, Viau M et al. Meat processing and colon carcinogenesis: cooked, nitrite-treated, and oxidized high-heme cured meat promotes mucin-depleted foci in rats. *Cancer Prev Res (Phila)* 2010; 3(7):852-864.

(55) Virk-Baker MK, Nagy TR, Barnes S, Groopman J. Dietary acrylamide and human cancer: a systematic review of literature. *Nutr Cancer* 2014; 66(5):774-790.

(56) European CHemical Agency (ECHA). Member State Committee support document for identification of 4,4'-isopropylidenediphenol (bisphenol a) as a substance of very high concern because of its toxic for reproduction (Article 57 c) properties. Adopted on 2 December 2016.

(57) Andreeva VA, Salanave B, Castetbon K, Deschamps V, Vernay M, Kesse-Guyot E et al. Comparison of the sociodemographic characteristics of the large NutriNet-Sante e-cohort with French Census data: the issue of volunteer bias revisited. *J Epidemiol Community Health* 2015; 69(9):893-898.

(58) Ministry of Health of Brazil. Dietary Guidelines for the Brazilian population. 2014.

(59) Haut Conseil de la Santé Publique. Avis relatif à la révision des repères alimentaires pour les adultes du futur Programme National Nutrition Santé 2017-2021. 16-2-2017.

Figure Legends

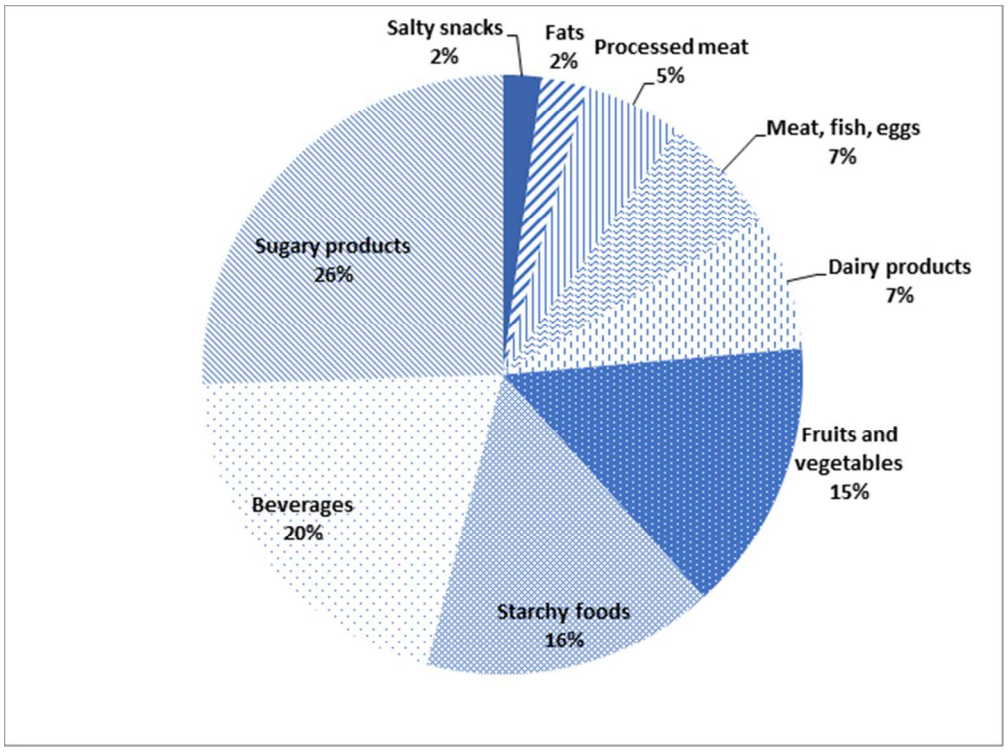
Figure 1:

Title: Relative contribution of each food group to ultra-processed consumption in the diet

Figure 2:

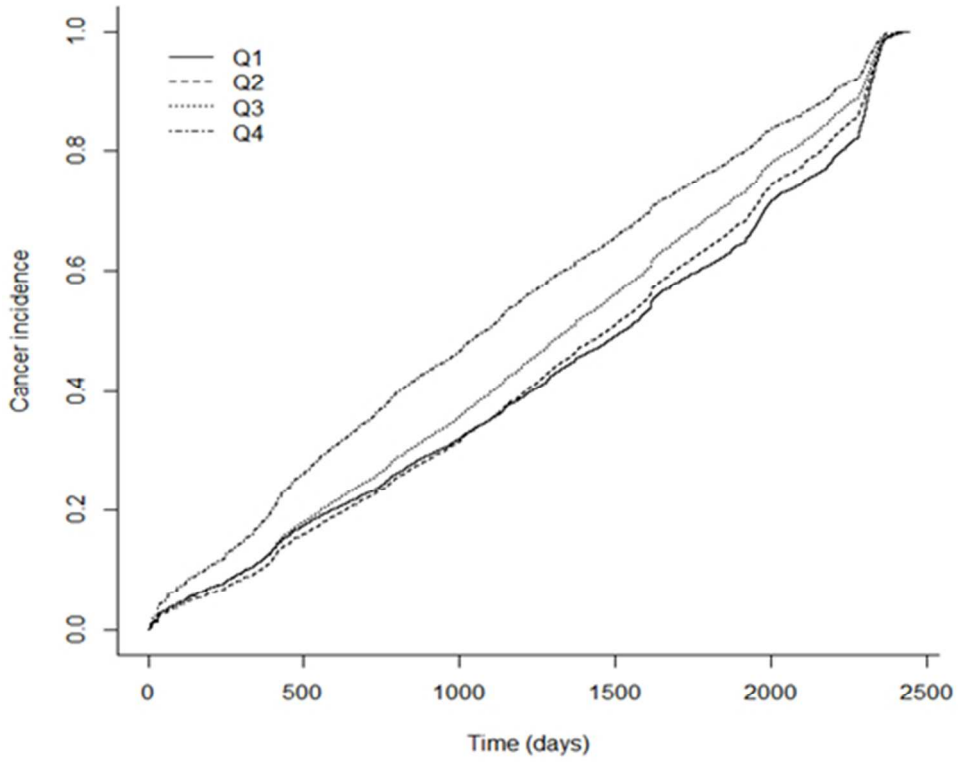
Title: Cumulative cancer incidence (overall cancer risk) according to quartiles of ultra-processed food intake

Legend: Q=quartile (1 to 4) of the proportion of ultra-processed food in the diet



Title: Relative contribution of each food group to ultra-processed consumption in the diet

166x123mm (96 x 96 DPI)



Title: Cumulative cancer incidence (overall cancer risk) according to quartiles of ultra-processed food intake

Legend: Q=quartile (1 to 4) of the proportion of ultra-processed food in the diet

141x115mm (96 x 96 DPI)

Supplemental file1. Flow chart