Consumption of ultra-processed foods and drinks and colorectal, breast and prostate cancer

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Short running head: Ultra-processed foods and drinks and cancer risk

List of abbreviations:

Confidence interval (CI).

Estrogen receptor (ER)

Food frequency questionnaire (FFQ)

Generalized additive models (GAM)

Hazard ratio (HR)

Hormone replacement treatment use (HRT)

Human epidermal growth factor receptor (HER2)

International Classification of Diseases 10th Revision (ICD-10)

Multi-centric case-control Spanish study (MCC-Spain)

Non-steroidal anti-inflammatory drug use (NSAIDs)

Odds ratio (OR)

Oral contraceptive use (OC)

Progesterone receptor (PR)

Standard deviations (SD)

Triple negative tumours (TN)

Abstract

Aims: To study whether the consumption of ultra-processed foods and drinks is associated with breast, colorectal and prostate cancers.

Methods: Multicentric population-based case-control study (MCC-Spain) conducted in 12 Spanish provinces. Participants were men and women between 20-85 years of age with diagnoses of colorectal (n=1852), breast (n=1486) or prostate cancer (n=953), and population-based controls (n=3543) frequency-matched by age, sex and region. Dietary intake was collected using a validated food frequency questionnaire. Foods and drinks were categorized according to their degree of processing based on the NOVA classification. Unconditional multivariable logistic regression was used to evaluate the association between ultra-processed food and drink consumption and colorectal, breast and prostate cancer.

Results: In multiple adjusted models, consumption of ultra-processed foods and drinks was associated with higher risk of colorectal cancer (OR for an increment of 10% in consumption: 1.11; 95% CI 1.04 to 1.18). The corresponding odds for breast (OR 1.03; 95% CI 0.96 to 1.11) or prostate cancer (OR 1.02; 95% CI 0.93 to 1.12) were indicative of no association.

Conclusions: Results of this large population-based case-control study suggest an association between the consumption of ultra-processed foods and drinks and colorectal cancer. Food policy and public health should include a focus on food processing when formulating dietary guidelines.

Keywords: Ultra-processed foods and drinks, Colorectal cancer, Breast cancer, Prostate cancer, Case-control study

INTRODUCTION

Social, economic and industrial changes have driven to an increase in ultra-processed food and drink consumption [1], contributing to 25 - 50% of total energy intake in usual diets of individuals in Europe and other high- and middle- income countries [2,3]. According to the NOVA classification, which takes into account the degree of food processing, ultra-processed foods and drinks are defined as industrial formulations typically with five or more ingredients, including sugar, oils, fats, salt, anti-oxidants, stabilizers, and preservatives, but also additives that imitate or intensify the sensorial qualities of unprocessed foods [4].

Ultra-processed foods and drinks are known for being microbiologically safe, convenient, appealing, affordable, accessible and highly profitable for the food industry [5]; yet, the impact of ultra-processed foods and drinks on human health might be less desirable [6]. Beyond their poor nutritional composition, characterized by a high content in salt, sugar, saturated fat, energy density, glycemic load and low quantity of fiber and micronutrients [2,3,7], ultra-processed foods and drinks may

contain other substances including heterocycle amines, aromatics polycyclic hydrocarbons or acrylamide which are produced during transformation processing [8–10]. Likewise, in order to increase their longevity or enhance the colour, these foods may also contain sodium nitrites or titanium dioxide. In addition, packaging processes can use materials that are in contact with the ultra-processed foods, such as bisphenol A [11,12]. Some of these components, despite being allowed, have been linked to carcinogenesis, endocrine disruption, inflammation and dysbiosis [13–15].

Several epidemiological studies have applied the NOVA classification to their dietary data and have linked ultra-processed food and drink consumption to intermediate risk factors (i.e. body weight gain [16,17], high blood pressure [18], chronic inflammation [19], and the metabolic syndrome [20]) as well as disease outcomes, including type 2 diabetes [21], cardiovascular disease [22] and mortality [5,23–25]. Many of these studies have a prospective design [5,16,18,21–26].

Recently, a French study reported a link between the consumption of ultra-processed foods and the risk of developing cancer, specifically breast cancer [27]. Another recent study conducted in Canada, found an increased risk of developing prostate cancer with higher intake of processed foods, but not with ultra-processed foods [28]. Given the above, it is possible that this association is causal, but further evidence is needed. Considering this, the aim of the present study is to evaluate whether the consumption of ultra-processed foods and drinks is associated with breast, colorectal and prostate cancers in a multi-centric case-control Spanish study (MCC-Spain).

METHODS

Study population and data collection

We used data from the Multi Case Control (MCC)-Spain study [29]. MCC-Spain is a population-based multicenter case-control study that assesses risk factors of the most common cancers in Spain (prostate, breast, colorectal, gastric tumours, and chronic lymphocytic leukaemia) in adults.

Patients aged between 20 - 85 years with histology-confirmed newly-diagnoses cancer of colon or rectum (International Classification of Diseases 10th Revision (ICD-10): C18, C19, C20, D01.0, D01.1, and D01.2), breast (C50, D05.1, and D05.7-9), and prostate (C61, D07.5), from 23 different hospitals (in 12 different Spanish provinces) were recruited between September 2008 and December 2013. Simultaneously, population-based controls frequency-matched to cases, by age, sex and region were randomly selected from primary care centres within hospitals' catchment areas. This ensured that, for each case, there was at least one control from the same region with the same sex and within the same 5-year age interval. Response rates (subjects interviewed/ all subjects including refusals) were 68% for colorectal cancer cases, 71% for breast and 72% for prostate. In controls, participation rate was 53% and varied by region. All the participants signed an informed consent. The study was approved by the Ethics Committee of all participating centres.

As shown in **Supplemental Figure 1**, all 9054 participants from the MCC-Spain study with breast, colorectal and prostate cancer and their respectively controls were included. After excluding participants with no nutritional data available (those who did not fill out the diet questionnaire) and those within the 1% top and bottom distribution of total energy intake, the final sample size was 7834.

Trained personnel carried out face-to-face interviews using a questionnaire, which included questions on socio-demographics, lifestyle, environmental exposure, residential history, personal/family medical history, drug use, and weight information at different ages (Questionnaire available at http://www.mccspain.org).

Dietary data was assessed using a validated 140-item semi-quantitative food frequency questionnaire (FFQ) [30,31]. The FFQ included portion sizes and photos and it evaluated the usual food intake from the previous year. For cancer cases, the FFQ was administered close after cancer diagnosis (median time between diagnosis and FFQ administration: 2.1 months). The FFQ was self-administered or filled out in face-to-face interviews (global response rate 88%). Total energy, nutrients, and ethanol intake were calculated using the Spanish food composition tables and other specific sources [32,33] .

Ultra-processed food and drink consumption

We used the NOVA definition to classify the food and drink items of the MCC-Spain FFQ based on the degree of industrial food processing [4,34]. This definition distinguishes four food (including drinks) groups: Unprocessed or minimum processed foods (G1) are natural foods or foods altered, at most, by processes applied to increase shelf life or storage (such as refrigerating, freezing and pasteurizing) and which contain no added ingredients (such as salt, sugar, oils or fats). Some examples are: seeds, fruits, leaves, roots or food directly extracted from animals like milk or eggs; Processed culinary ingredients (G2) are obtained from group 1 foods (or from nature) and are used in the preparation, seasoning and cooking of group 1 foods or as food preservatives. Examples are salt, sugar and oil; Processed foods (G3) are industrial products characterized by the addition of salt, sugar, oil or fat (or other group 2 foods) aimed at improving their sensorial qualities or durability. Some examples are canned or bottled vegetables, canned fish and cheeses. Ultra-processed foods (G4) are formulations of ingredients, mostly of exclusive industrial use, frequently added of substances such

as sugar, oils and fats, and salt, and of cosmetic additives. Examples are sweet or savoury packaged snacks, sweetened beverages and ready to eat foods. This study is mainly focused on G4, the ultra-processed food and drink group.

We classified the foods based on the consensus of a group of nutrition specialists and based on the literature. Further details and underlying assumptions are described in **Supplemental Table 1**.

We classified each food and drink item into one of the four groups and added up their consumption expressed in daily grams. We calculated the percentage of consumption of each category of food processing of the total daily diet (daily g within each group/total daily g, multiplied by 100). We categorized the food processing groups into tertiles based on the sex-specific distribution in the control group.

Tumour subtypes

Tumour subtypes were determined from pathology records for most cancer cases. Colorectal were divided into colon and rectal cancer. Breast cancer cases were classified according to the estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor (HER2), in the following sub-types: hormone receptor positive tumours (HR+: ER+ or PR+ with HER2–); human epidermal growth factor receptor positive tumours (HER2+: independent of ER or PR), and triple negative tumours (TN: ER–, PR– and HER2–) [35]. Prostate cancer cases were classified according to tumour aggressiveness (Gleason score) as moderately/well differentiated (Gleason score <7) and poorly differentiated/undifferentiated (Gleason score ≥7) [36].

Covariates

We considered several variables: age at the time of the interview (in years); study area (12 regions); educational level; body mass index (kg/m^2) one year before recruitment; physical activity over the last 10 years; smoking status; family history of any cancer as well as colorectal, breast, and prostate

cancer in first degree relatives; total energy intake (in kcal/day); ethanol intake (g/day); fiber intake (g/day); saturated fatty acids intake (% total energy intake); simple carbohydrates (% total energy intake); energy density (calculated as energy (kcal) from foods (solid foods and semisolid or liquid foods such as soups) divided by the weights (g) of these foods, excluding drinks such as water, tea, coffee, juice, soft drinks, alcoholic drinks and milk); consumption of fruits & vegetables (g/day). For colorectal cancer cases and controls, sex and non-steroidal antiinflammatory drug use were also taken into account. For breast cancer cases and controls: hormone replacement treatment use; oral contraceptive use; age at menarche; age at first pregnancy; number of children (continuous); menopausal status. For categorical variables, missing values (ranging between 1.28% to 4.30%) were coded as a separate category (for more information on number of missing and categories of categorical variables, see **Supplemental Table 2**).

Statistical analysis

We performed descriptive analyses of baseline dietary and sociodemographic characteristics using means and standard deviations (SD) for continuous variables and percentages for categorical variables. Differences between cases and controls and across ultra-processed food and drink categories (tertiles) in controls were assessed using Student's t-test (or ANOVA test, when appropriate) and Pearson χ^2 test.

Generalized additive models (GAM) were used and visual inspection of the graphs revealed linear associations between the ultra-processed food and drink consumption and colorectal, breast and prostate cancer.

We used unconditional multivariable logistic regression to evaluate the association between ultra-processed food and drink consumption and colorectal, breast and prostate cancer. We obtained the odds ratio (OR) and the 95% confidence interval (CIs). Ultra-processed food and drink consumption was analysed as a continuous variable (per 10% increment) and as a categorical variable (low,

371 medium, high consumption, based on the sex-specific tertiles of the control group). The first tertile
372 (low consumption) was considered as a reference category. P for trend was calculated including the
373 categorical variable as continuous ordinal (scored from 1 to 3) in our models.

374 Two models with two levels of adjustments were used for each cancer. Model 1 included as
375 covariates: age, educational level, study area and sex (the latter for colorectal models only). Model 2
376 was further adjusted for family history of each cancer, smoking status, body mass index one year
377 before the recruitment, physical activity over the last 10 years, total energy intake, and ethanol intake.
378 In analyses of colorectal cancer, model 2 was also adjusted for NSAIDs use; in breast cancer analyses,
379 model 2 was further adjusted for menopausal status, OC use, HRT use, age at menarche, age at first
380 pregnancy, and number of children.

381 Model 2 was also run after stratification according to a series of key variables that might influence
382 the association between the ultra-processed food intake and cancer, including tumour sub-type, sex
383 (for colorectal), and menopausal status (for breast cancer). The *p* for interaction was calculated by
384 modelling cross-product terms between ultra-processed food intake (as continuous variables) and sex
385 (for colorectal cancer) or menopausal status (for breast cancer).

386 We performed complementary analyses for all the cancers, by further adjusting model 2 for dietary
387 factors that could act as potential confounders or mediators (fiber intake (g/day), fruit and vegetable
388 consumption (g/day)), energy density (kcal/g), sugar intake (% total energy intake), saturated fatty
389 acid intake (% total energy intake)) of the association between ultra-processed foods and drinks and
390 cancer. Also, as complementary analyses, we evaluated the effect modification by age groups (in
391 tertiles: 22 to 59 years vs 59 to 69 years vs 69 to 85 years) and several lifestyle variables, such as
392 smoking status (never vs former/current), educational level (less than secondary vs secondary or
393 more), physical activity level (inactive vs active), and fruit & vegetable consumption (below vs above
394 the median) on the association between ultra-processed food and drink consumption and cancer.

To ensure that results were not biased due to changes in the diet of participants as a consequence of cancer diagnosis, we repeated all analyses excluding cases (237 colorectal, 321 breast and 191 prostate) with >6 months between cancer diagnosis and the date of interview. Results were similar to the main models, therefore are not displayed.

All statistics were performed using software R (version 3.5). Statistical hypotheses were tested using a two-tailed $p<0.05$ level of significance.

RESULTS

After exclusions, a total of 1852 colorectal cases, 1486 breast cancer cases, 953 prostate cancer cases, and 3543 healthy controls were included. Included and excluded individuals showed some differences (**Supplemental Table 2**). Excluded individuals had slightly higher mean BMI value, lower educational level and a higher proportion were smokers. Comparison of cancer cases with controls can be found in **Supplemental Table 3**. As expected, there were statistically significant differences in main risk factors for cancer between cases and controls. Breast and colorectal (but not prostate) cancer cases exhibited a less healthy diet compared to controls, in terms of their intake of energy, fiber, energy density and saturated fatty acids. Consumption of unprocessed and minimally processed foods was lower and consumption of ultra-processed foods and drinks was higher in colorectal and breast cancer cases compared to controls (all p-values <0.05).

In controls, average consumption of ultra-processed foods and drinks was about 13% (SD 10%) of total food intake **(Table 1)**. Those control participants with high ultra-processed food and drink consumption (those in Tertile 3, with an average intake of ultra-processed foods of nearly 25% (SD 9.7%) of total food) were on average younger, with higher educational level, smokers, and physically inactive, compared to those with the low consumption (Tertile 1, average consumption of ultra-processed foods and drinks of 4% (SD 1.8%)) (all p values <0.05). High consumption of ultra-processed foods and drinks was significantly associated with higher total energy, energy density, saturated fatty acids, as well as with lower fiber intake, lower fruit & vegetable consumption, and lower consumption of other categories of food processing (**Table 1)**. The food groups contributing in greater proportion to ultra-processed food intake were beverages (35.14%), sugary products (19.27%), ready-to-eat foods (15.75%) and processed meats (12.50%) (**Supplemental Figure 2**).

Table 2 shows the association of ultra-processed food and drink consumption with colorectal, breast and prostate cancer. In minimally adjusted models (Model 1), high consumption of ultra-processed

foods and drinks (T3) was associated with a 44% higher odds of having colorectal cancer (OR 1.44; 95% CI 1.24 to 1.67; P for trend<0.001) and with a 24% higher odds of having breast cancer (OR 1.24; 95% CI 1.03 to 1.49; P for trend=0.023), compared to low consumption (T1). After adjusting for potential confounders (Model 2) the OR of colorectal cancer in T3 vs T1 was 1.30 (95% CI 1.11 to 1.51; P for trend=0.001) and the OR of breast cancer in T3 vs T1 was 1.15 (95% CI 0.95 to 1.40; P for trend=0.166). Consumption of ultra-processed foods and drinks was not associated with prostate cancer (Model 2, T3 vs T1, OR 1.06 (95% CI 0.84 to 1.34; P for trend=0.589). When the exposure variable was entered as a continuous variable in Model 2, a 10% increment in ultra-processed food and drink consumption was associated with an 11% increase in colorectal cancer (OR 1.11, 95% CI 1.04 to 1.18). In multiple adjusted models, non-significant associations were also observed between continuous increments of ultra-processed food and drink consumption and breast or prostate cancer.

Table 3 shows the association of ultra-processed food and drink consumption with different cancer sub-types, as well as after stratifying by sex (for colorectal cancer) and menopausal status (for breast cancer). There was no evidence of heterogeneity by sex in the association between ultra-processed food consumption and colorectal cancer risk (P for interaction=0.108). Both colon and rectal cancer were similarly associated with higher ultra-processed food intake. No evidence of effect modification by menopausal status or hormonal receptor status were observed in the association between ultra-processed food intake and breast cancer, but a borderline significant association was observed in pre-menopausal women when comparing high vs low consumption of ultra-processed food and drink (OR 1.47, 95% CI 1.00 to 2.17; P for trend=0.060). Consumption of ultra-processed food was not associated with prostate cancer after stratification by Gleason score.

Figure 1 shows the association between ultra-processed food and drink consumption (per 10% increments) and colorectal, breast and prostate cancer using Model 2 further adjusted for several nutritional variables. The association between ultra-processed food and drink consumption and colon cancer was attenuated and loss statistical significance after further adjustment for dietary fiber and

fruit and vegetable consumption, but did not change after adjustment for saturated fat, simple carbohydrates or energy density. Associations with breast and prostate cancers continued to be null.

In **Supplemental Table 4**, effect modification and stratified analyses by age and common lifestyle factors are shown (i.e. smoking, physical activity, educational level). Most p-values for interaction were non-statistically significant, indicative of no effect-measure modification. The exceptions were: the interaction between fruit & vegetable intake and ultra-processed foods and drinks on colorectal cancer (P=0.003) and the interaction between smoking status and ultra-processed foods and drinks on breast cancer (P=0.004): in stratified analyses, ultra-processed food and drink consumption was significantly associated to colorectal cancer in those with high fruit & vegetable consumption, and with breast cancer in former and current smokers.

DISCUSSION

In the present case-control study, consumption of ultra-processed foods and drinks was associated with increased odds of colorectal cancer. Overall, no association was observed between consumption of ultra-processed foods and drinks and breast cancer after adjusting for confounding factors; however, some associations emerged in some sub-groups of women, i.e. former and current smokers. No association was observed with prostate cancer.

Since the development of the NOVA classification of foods and drinks according to the degree of processing [4], numerous epidemiological studies have evaluated the association between ultra-processed food and drink consumption and adverse health outcomes [6], such as cardiovascular disease [22] and mortality [5,23–25]. In 2018, based on the French NutriNet-Santé prospective cohort of approximately 105,000 participants of median age 42.8 years, the first study on ultra-processed food and drink consumption and cancer risk was published. In that study, a 10% increase in the consumption of ultra-processed foods and drinks, was significantly associated with an increased risk of total cancer (Number of cases 2228, hazard ratio (HR) 1.12, 95% CI 1.06 to 1.18) and breast cancer

(Number of cases 739, HR 1.11, 95% CI 1.02 to 1.22). The HR for colorectal cancer (Number of cases 153) was 1.13 (95% CI 0.92 to 1.38), not reaching the standard threshold for statistical significance, maybe due to the low number of incident cases. The HR for prostate cancer was closer to 1. In 2020, a case control study conducted in Canada was published [28]. In this study with 1919 incident cases, the OR for prostate cancer was 1.29 (95% CI 1.05 to 1.59) when comparing the highest quantile of processed foods vs the lowest quantile. However, there was no association with ultra-processed food consumption.

In the MCC study, ultra-processed food and drink consumption was significantly associated with colorectal and the OR (per 10% increase in ultra-processed food and drink consumption OR 1.11, 95% CI 1.04 to 1.18) was of similar magnitude to the HR observed in the NutriNet-Santé cohort, but statistically significant, maybe due to the larger number of cases (1842). The association was observed for both colon and rectal cancer. Further adjustment for nutritional characteristics of diets rich in ultra-processed foods and drinks, i.e. daily energy density, total saturated fat or simple carbohydrate intake, did not attenuate the association, indicating that the association may be driven by factors beyond the diet quality of such foods and drinks, such as food additives [13]. On the other hand, when fiber intake, or fruit and vegetable consumption, well-known protective factors against colorectal cancer [37], were included in the model, the association was attenuated losing statistical significance. This could indicate that the association between ultra-processed foods and drinks and colorectal cancer may be partly explained by the low intake of fiber, fruit and vegetables in high consumers of ultra-processed foods; nevertheless, when analyses were stratified by low versus high consumption of fruit and vegetables, the association between ultra-processed foods and drinks and colorectal cancer was only significant in the group of high consumers of fruit and vegetables. This possible interaction between fruit and vegetable consumption and ultra-processed foods and drinks on colorectal cancer, deserves further investigation, but may indicate that, in low fruit & vegetable consumers, other factors such as low fiber or folate intake, might be more relevant for the

development of colorectal cancer than other characteristics of the diet related to food processing[38,39].

For breast cancer, results of our study differ from those in the French cohort as we did not find evidence for an association between ultra-processed food and drink consumption and breast cancer, in the overall sample. Reasons for such discrepancies in results are difficult to elucidate and could be explained by differences in study design or study population. For instance, participants in the NutriNet-Santé cohort were younger on average than participants in the MCC-Spain study, and in our study there was some evidence that the association was stronger in younger population sub-groups (i.e. premenopausal women). Of note, in minimally adjusted models, the association between ultra-processed food and drink consumption and breast cancer was statistically significant; further adjustment by total energy intake and/or ethanol intake resulted in an attenuation of the association and loss of statistical significance. This could indicate that the effect of ultra-processed foods on breast cancer risk, if any, would be mediated through alterations in the energy balance [40], or its contribution to ethanol intake, well known risk factors for breast cancer [41]. Lastly, in the subgroup of former and current smokers, the association between ultra-processed food and drink consumption and breast cancer was statistically significant. Smoking is a risk factor for breast cancer [42], and it is known that smoking and some dietary factors might have some synergetic effects on the development of cancer [43], as it might be the case with the consumption of ultra-processed foods and drinks and smoking on breast cancer; however, this finding needs confirmation.

In this study, ultra-processed food and drink consumption was not associated with prostate cancer. This is not surprising given that the evidence linking dietary factors to prostate cancer risk is indicative of no association [37].

Advantages of the study include the substantial sample size of histologically-confirmed incident cancer cases. Foods and drinks in the validated FFQ were carefully classified using the NOVA

system, according to the degree of processing, by a panel of nutritionists. We performed several sensitivity analyses to test the robustness of our results. Main limitations are inherent to the case-control design of the study, i.e. recall bias and selection bias. Regarding recall bias, the dietary data collected at recruitment referred to the preceding year, and was collected early after cancer diagnosis, reflecting mostly the habitual diet before cancer. Thus, if recall bias exists, it would probably be non-differential, thus implying underestimation of the studied effects. For a small percentage of participants, the period between cancer diagnosis and completion of the FFQ was longer and the disease or treatment could have influenced dietary habits; for this reason we decided to exclude in sensitivity analyses, those with >6 months between cancer diagnosis and the date of interview, with no change in results. Another limitation of using data about dietary habits close to cancer incidence, is that this diet may not be the same as the diet consumed years before cancer – the most relevant given the latency period of cancer: nevertheless, there is some evidence that diet in adulthood tend to be stable over time [44]. Regarding selection bias, the MCC-study was designed with the goal of minimizing selection biases by recruiting population-based controls, and all cases with a first diagnosis of cancer in the selected health areas, ensuring few incident cases were missed in the study. Another limitation is related to the use of the NOVA classification to assign FFQ food items to different NOVA groups: for some food items, the FFQ does not provide enough information of food processing to determine if the food items belongs to one food group or another, which may have resulted in some degree of misclassification; nevertheless, we discussed each food item within a team of nutritionist and used information on food composition and food system in Spain to classify all foods items. Also, the NOVA methodology/classification has limitations that have been criticized by some [45], but it is the most used method for classifying ultra-processed foods and drinks today [46]. Dietary data might be also subject to measurement error; nevertheless, we used a previously validated FFQ for Spanish population. When interpreting results of analyses carried out in certain sub-group, we need to bear in mind the potential lack of statistical power due to small sample sizes. These associations should be interpreted in the context of multiple comparisons and possibility of chance

findings. Finally, although we adjusted for a range of potential confounders, residual confounding cannot be totally ruled out.

CONCLUSIONS

In conclusion, results of this study suggest an association between the consumption of ultra-processed foods and drinks and cancer, namely colorectal cancer. The association with breast cancer is less robust and limited to certain population sub-groups. These results need confirmation from other epidemiological and mechanistic studies. Given the above, and the existing evidence on the association between ultra-processed foods and drinks and health, food and public health policies and dietary guidelines should include a focus on food processing.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All the participants signed an informed consent prior to their enrolment. The study was approved by the Ethics Committee of all participating centres and followed national and international directives on ethics and data protection.

AVAILABILITY OF DATA AND MATERIALS

Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

DR, SFB and PA conceived the presented study design. DR, SFB, EV, MA and PA were the members of a working group to classify the foods groups following the NOVA classification. EGL conducted the statistical analysis. DR and SFB drafted the manuscript. All authors contributed to the interpretation of the results and revised the manuscript.

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Figure 1: Associations between 10% increment in ultra-processed food and drink consumption and colorectal, breast and prostate cancer.

Colorectal cancer: Logistic regression adjusted for sex, age, area and educational level, body mass index, physical activity, smoking, nonsteroidal anti-inflammatory drugs, family history of colorectal cancer, total energy intake, and ethanol intake.

Breast cancer: Logistic regression adjusted for age, area and educational level, body mass index, physical activity, smoking, hormone replacement therapy use, oral contraceptive use, family history of breast cancer, age at menarche, age first pregnancy, number of children, menopausal status, total energy intake, and ethanol intake.

Prostate cancer: Logistic regression adjusted for age, area and educational level, body mass index, physical activity, smoking, family history of prostate cancer, total energy intake, and ethanol intake.

Supplemental files:

Supplemental_material_clinicalnut.docx contains Supplemental Tables 1, 2 and 3 and Supplemental Figures 1 and 2

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Table 1. Characteristics of controls according to their ultra-processed foods and drinks consumption in the MCC-Study (based on their distribution in categories)[a]

		Ultra-processed food and drink consumption[b]			
	Total	**Low**	**Medium**	**High**	***p*-value**
	N=3543	**N=1170**	**N=1169**	**N=1204**	
	mean (sd) / N (%)	**mean (sd) / N (%)**	**mean (sd) / N (%)**	**mean (sd) / N (%)**	
Age (years)	62.9 (12.0)	65.9 (10.4)	63.0 (11.5)	59.7 (13.0)	<0.001
Sex					1.000
Male	1792 (50.6%)	592 (50.6%)	591 (50.6%)	609 (50.6%)	
Female	1751 (49.4%)	578 (49.4%)	578 (49.4%)	595 (49.4%)	
Body Mass Index					0.276
< 25 (kg/m^2)	1390 (39.2%)	472 (40.3%)	460 (39.3%)	458 (38.0%)	
25-30 (kg/m^2)	1455 (41.1%)	488 (41.7%)	481 (41.1%)	486 (40.4%)	
≥ 30 (kg/m^2)	698 (19.7%)	210 (17.9%)	228 (19.5%)	260 (21.6%)	
Education level					<0.001
Less than primary	615 (17.4%)	249 (21.3%)	180 (15.4%)	186 (15.4%)	
Primary	1134 (32.0%)	388 (33.2%)	399 (34.1%)	347 (28.8%)	
High school	1036 (29.2%)	314 (26.8%)	339 (29.0%)	383 (31.8%)	
University	758 (21.4%)	219 (18.7%)	251 (21.5%)	288 (23.9%)	
Tobacco smoking					<0.001
Never smoker	1575 (44.6%)	578 (49.6%)	502 (43.1%)	495 (41.3%)	
Former smoker	1226 (34.7%)	397 (34.0%)	426 (36.6%)	403 (33.6%)	
Current smoker	729 (20.7%)	191 (16.4%)	237 (20.3%)	301 (25.1%)	
Physical activity					<0.001
Inactive	1352 (38.6%)	406 (34.9%)	434 (37.5%)	512 (43.2%)	
Moderately active	522 (14.9%)	150 (12.9%)	193 (16.7%)	179 (15.1%)	
Active	426 (12.1%)	153 (13.1%)	143 (12.3%)	130 (11.0%)	
Very active	1207 (34.4%)	455 (39.1%)	388 (33.5%)	364 (30.7%)	
Energy intake (kcal/day)	1893 (560)	1720 (457)	1926 (540)	2029 (622)	<0.001
Ethanol intake (g/day)	10.9 (15.8)	10.4 (14.5)	11.2 (16.8)	11.1 (16.0)	0.419
Fiber (g/1000 kcal)	12.1 (4.00)	13.6 (4.18)	12.0 (3.68)	10.8 (3.66)	<0.001
Energy density (kcal/g)	1.41 (0.31)	1.28 (0.27)	1.43 (0.28)	1.52 (0.32)	<0.001

Saturated fatty acids (% total EI)[c]	11.0 (2.39)	10.1 (2.25)	11.2 (2.19)	11.5 (2.47)	<0.001
Simple carbohydrate (% total EI)	22.5 (6.02)	23.0 (6.23)	21.8 (5.33)	22.6 (6.38)	<0.001
Fruit consumption (g/day)	345 (212)	393 (223)	344 (205)	298 (199)	<0.001
Vegetable consumption (g/day)	189 (117)	209 (126)	193 (118)	166 (104)	<0.001
G1: Unprocessed or minimally processed food consumption (%)[d]	68.6 (13.5)	76.6 (11.2)	70.7 (10.9)	58.7 (11.5)	<0.001
G2: Processed culinary ingredient consumption (%)	1.73 (1.13)	1.86 (1.18)	1.79 (1.17)	1.56 (1.03)	<0.001
G3: Processed food consumption (%)	16.4 (10.3)	17.4 (11.0)	17.1 (10.7)	14.9 (8.94)	<0.001
G4: Ultra-processed food and drink consumption (%)	13.2 (10.5)	4.14 (1.76)	10.4 (2.18)	24.8 (9.68)	0.000

[a]MCC, Multi-case-control Spain study.

[b]Categories based on sex-specific tertiles of ultra-processed processed foods and drinks (%) (Men: Low (T_1 0-6.93); Medium ($T_2$6.93-14.55); High ($T_3$14.55 – 70.28); Women: Low (T_1 0 – 7.01); Medium ($T_2$7.01-14.56); High ($T_3$14.56-83.54)).Based on the NOVA definition.

[c]EI; Total daily energy intake.

[d]Calculated as daily g within each group/total daily g, multiplied by 100.

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Table 2. Association between ultra-processed food and drink consumption and colorectal, breast and prostate cancer in the MCC-Spain Study

		Ultra-processed food and drink consumption				
		10% increase	**Low**	**Medium**	**High**	
Control/Cases	**Control/Cases**	**OR (95% CI)**		***OR* (95% CI)**	***OR* (95% CI)**	***P for trend***
Colorectal cancer						
Model 1[a]	3447/1852	1.16 (1.09,1.22)	Ref	1.17 (1.00,1.35)	1.44 (1.24,1.67)	<0.001
Model 2[b]	3399/1842	1.11 (1.04,1.18)	Ref	1.09 (0.94,1.28)	1.30 (1.11,1.51)	0.001
Breast cancer						
Model 1[a]	1652/1486	1.07 (1.00,1.15)	Ref	1.14(0.95,1.37)	1.24 (1.03,1.49)	0.023
Model 2[c]	1628/1471	1.03 (0.96,1.11)	Ref	1.12 (0.93,1.35)	1.15 (0.95,1.40)	0.166
Prostate cancer						
Model 1[a]	1283/953	1.04 (0.95,1.14)	Ref	0.98 (0.78,1.22)	1.10 (0.88,1.37)	0.379
Model 2[d]	1262/951	1.02 (0.93,1.12)	Ref	0.95 (0.76,1.19)	1.06 (0.84,1.34)	0.589

MCC, Multi-case-control Spain study; Categories based on sex-specific tertiles of ultra-processed processed foods and drinks (%) (Men: Low (T_1 0-6.93); Medium ($T_2$6.93-14.55); High ($T_3$14.55 – 70.28); Women: Low (T_1 0 – 7.01); Medium ($T_2$7.01-14.56); High ($T_3$14.56-83.54)).

[a]Model 1: Logistic regression adjusted for sex (only for colorectal), age, study area and educational level.

[b]Model 2: Model 1 further adjusted for body mass index, physical activity, smoking, nonsteroidal anti-inflammatory drugs, family history of colorectal cancer, total energy intake, and ethanol intake.

[c]Model 2: Model 1 further adjusted for body mass index, physical activity, smoking, hormone replacement therapy use, oral contraceptive use, family history of breast cancer, age at menarche, age first pregnancy, number of children, menopausal status, total energy intake, and ethanol intake.

[d]Model 2: Model 1 further adjusted for body mass index, physical activity, smoking, family history of prostate cancer, total energy intake, and ethanol intake.

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Table 3. Association between ultra-processed food and drink consumption and colorectal, breast and prostate cancer in the MCC-Spain Study (stratified analysis)

		10% increase		Low	Medium	High	
	Control/Case	OR (95% CI)	*P for interaction*	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P for trend*
Colorectal cancer							
Sex[a]			0.108				
Men	1748/1174	1.12 (1.03, 1.21)		Ref	1.18 (0.96,1.44)	1.34 (1.10,1.65)	0.005
Women	1651/668	1.10 (1.10, 1.21)		Ref	1.01 (0.78,1.30)	1.24 (0.96,1.59)	0.100
Colorectal cancer subtypes[b]							
Colon cancer	3399/1122	1.11 (1.04, 1.19)		Ref	1.06 (0.88,1.27)	1.25 (1.04,1.50)	0.017
Rectal cancer	3399/700	1.10 (1.01,1.19)		Ref	1.15 (0.92,1.43)	1.41 (1.13,1.75)	0.002
Breast cancer							
Menopausal status[c]			0.737				
Premenopausal	469/526	1.09 (0.97,1.23)		Ref	1.32 (0.0.90,1.95)	1.47 (1.00,2.17)	0.060
Postmenopausal	1159/945	1.04 (0.94, 1.14)		Ref	1.09 (0.88,1.36)	1.12 (0.89,1.42)	0.332
Breast cancer subtypes[d]							
HR+[e]	1628/986	1.04 (0.96,1.13)		Ref	1.21 (0.98,1.49)	1.22 (0.98,1.52)	0.086
HER2+[e]	1628/251	0.96 (0.84,1.10)		Ref	0.81 (0.57,1.16)	0.79 (0.54,1.14)	0.216
TN[e]	1628/105	0.93 (0.75,1.15)		Ref	1.26 (0.74,2.15)	1.14 (0.64,2.02)	0.709
Prostate cancer							
Prostate cancersubtypes[f]							
Gleason < 7	1262/437	0.99 (0.88,1.12)		Ref	0.84 (0.62,1.13)	0.99 (0.73,1.33)	0.975
Gleason >=7	1262/499	1.04 (0.93,1.17)		Ref	0.98 (0.74,1.29)	1.11 (0.83,1.48)	0.459

[a]Logistic regression adjusted for age, study area, educational level, body mass index, physical activity, smoking, nonsteroidal anti-inflammatory drugs, family history of colorectal cancer, total energy intake, and ethanol intake.

[b]Logistic regression adjusted for sex, age, study area, educational level, body mass index, physical activity, smoking, nonsteroidal anti-inflammatory drugs, family history of colorectal cancer, total energy intake, and ethanol intake.

[c]Logistic regression adjusted forage, study area, educational level, body mass index, physical activity, smoking, hormone replacement therapy use, oral contraceptive use, family history of breast cancer, age at menarche, age first pregnancy, number of children, total energy intake, and ethanol intake.

[d]Logistic regression adjusted for age, study area, educational level, body mass index, physical activity, smoking, hormone replacement therapy use, oral contraceptive use, family history of breast cancer, age at menarche, age first pregnancy, number of children, menopausal status, total energy intake, and ethanol intake.

[e]HR+: hormone receptor positive tumors (ER+ or PR+ with HER2-); HER2+: human epidermal growth factor receptor positive tumors, independent of ER or PR; TN: triple negative tumors (ER-, PR- and HER2-).

[f]Logistic regression adjusted for age, study area, educational level, for body mass index, physical activity, smoking, family history of prostate cancer, total energy intake, and ethanol intake.

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