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Ultra-processed food consumption and renal cell carcinoma incidence and mortality: results from a large prospective cohort

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Abstract

Background Growing evidence shows that ultra-processed food consumption is associated with the risk of cancer. However, prospective evidence is limited on renal cell carcinoma (RCC) incidence and mortality. In this study, we aimed to examine the association of ultra-processed food consumption and RCC incidence and mortality in a large cohort of US adults.

Methods A population-based cohort of 101,688 participants were included from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Ultra-processed food items were confirmed by using the NOVA food classification system. The consumption of ultra-processed food was expressed as a percentage of total food intake (g/day). Prospective associations were calculated using Cox regression. Restricted cubic spline regression was used to assess nonlinearity. Subgroup analyses were performed to investigate the potential effect modifiers on the incidence and mortality of RCC.

Results A total of 410 participants developed RCC during a total of 899,731 person-years of follow-up (median 9.41 years) and 230 RCC deaths during 1,533,930 person-years of follow-up (median 16.85 years). In the fully adjusted model, participants in the highest compared with the lowest quintiles of ultra-processed food consumption had a higher risk of RCC (HR quartile 4 vs 1:1.42; 95% CI: 1.06–1.91; $P_{trend} = 0.004$) and mortality (HR quartile 4 vs. quartile 1: 1.64; 95% CI: 1.10–2.43; $P_{trend} = 0.027$). Linear dose–response associations with RCC incidence and mortality were observed for ultra-processed food consumption (all $P_{nonlinearity} > 0.05$). The reliability of these results was supported by sensitivity and subgroup analyses.

Conclusion In conclusion, higher consumption of ultra-processed food is associated with an increased risk of RCC incidence and mortality. Limiting ultra-processed food consumption might be a primary prevention method of RCC.

Keywords Ultra-processed food, Renal cell cancer (RCC), Prospective cohort, Cancer prevention

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Introduction

Kidney and renal pelvis cancer, of which 90% is renal cell carcinoma (RCC), is the most common malignant cancer of the urinary system, accounting for > 80,000 new cancer diagnoses and > 14,000 deaths in the United States, with an increasing burden of disease continuously [1]. The incidence rates of RCC showed a steadily rising trend in the world, especially in the developed world. Since 1975, the incidence rate of RCC in the United States (US) has more than doubled [2]. This incidence rate is consistent with the growing epidemic of obesity [3] and hypertension [4, 5], alongside cigarette smoking [6], which collectively account for only approximately half of all diagnosed cases in the US population [7]. However, the incidence and mortality rate of RCC vary substantially across different countries and geographic locations, with the highest incidence and mortality rates observed in the developed countries [8], implying certain modifiable risk factors should be considered crucial for the primary prevention of RCC. Although the specific mechanisms of RCC remain poorly understood, epidemiological evidence suggested that a poor-quality and unhealthy dietary pattern change have been suggested as potential risk factors for increasing the incidence and mortality of RCC [9–12].

Over the past few decades, there was a substantial increase in the consumption of ultra-processed foods worldwide due to the fact that they were easily accessible, microbiologically safe, highly palatable, and affordable [13]. Some surveys examining intakes, household expenses, or supermarket sales showed that mean contribution of ultra-processed food products in total daily energy intake ranged from 25 to 60% in many countries [14–16]. Generally, ultra-processed foods have several nutritional features, including a higher content of total fat, and added sugar and salt, along with a lower fiber and vitamin density, which might lead to the detrimental influence of diet quality [17–19]. Beyond nutritional composition, ultra-processed foods contain neoformed compounds (such as acrylamide and heterocyclic amines) produced during processing [20, 21], compounds deriving from packaging and food additives used in processing [19, 22], which have shown potential carcinogenicity in animal or cellular experiments. This dietary trend is now receiving significant attention and interest to investigate the potential impact of ultra-processed foods on health outcomes [23, 24], such as cancer [25, 26]. Monteiro et.al established the NOVA classification system of foods according to their degree of processing, which promoted to investigate the relationship between ultra-processed foods and the potential health outcomes [23, 27], whereas epidemiological studies on the association between higher consumption of ultra-processed foods and cancer are still scarce and limited. Although some studies have linked cancer to ultra-processed foods, as far as we know, the present study is the first that associate ultra-processed foods and RCC. We hypothesize that the consumption of ultra-processed foods is an important and modifiable factor that increases the incidence and mortality of RCC. Therefore, based on a large prospective cohort, we evaluate whether the consumption of ultra-processed food was associated with the incidence and mortality of RCC in a large US population (Figs. 1 and 2).

Results

Baseline characteristics

A total of 101,668 participants (49,435 (48.6%) men and 52,233 (51.4%) women) were included in the study. The mean age of participants was 65.5 (SD 5.7) years. Table 1 describes the baseline characteristics of participants from the PLCO cohort study by sex-specific quartile of the proportion of ultra-processed foods in the diet. Compared with the first quarter, participants in the highest quartiles tended to be younger, be non-Hispanic White or non-Hispanic Black, less educated, and more likely to have history of diabetes and hypertension. They also had lower levels of physical activity levels, alcohol consumption, and Healthy Eating Index-2015 but have higher intakes of energy from diet and BMI levels. Furthermore, they had higher intakes of meats, fat, carbohydrates, protein, cholesterol, and sodium, along with lower fruits, vegetables, whole grain, and dietary fiber intake. The distribution of the proportion of ultra-processed food in the diet among our study population is shown in Additional file 1: Fig. S1.

Associations between ultra-processed foods intake and RCC incidence

During follow-up (899,731 person years, median follow-up time 9.41 years), a total of 410 RCC cases were observed, with an overall incidence rate of 456 per 100,000 person years in this whole population. Table 2 shows the results of the univariable and multivariable Cox regression analyses on the proportion of ultra-processed foods in the diet and incidence of RCC. The incidence rates for RCC were 35 per 100,000 person-years in the first quartile (low consumers) of ultra-processed food intake, 38 in the second quartile, 53 in the third quartile, and 56 in the fourth quartile (high consumers).

In the fully adjusted model, participants in the highest quartile of ultra-processed food intake were significantly associated with an increased risk of RCC incidence ($HR_{\text{quartile 4 vs. quartile 1}}$: 1.42; 95% CI 1.06–1.91; $P = 0.004$) during a median follow-up of 9.41 years. The linearity assumption between ultra-processed food and the incidence of RCC was analyzed using restricted cubic spline regression ($P_{\text{nonlinearity}} = 0.74$) (Fig. 3). Similar associations

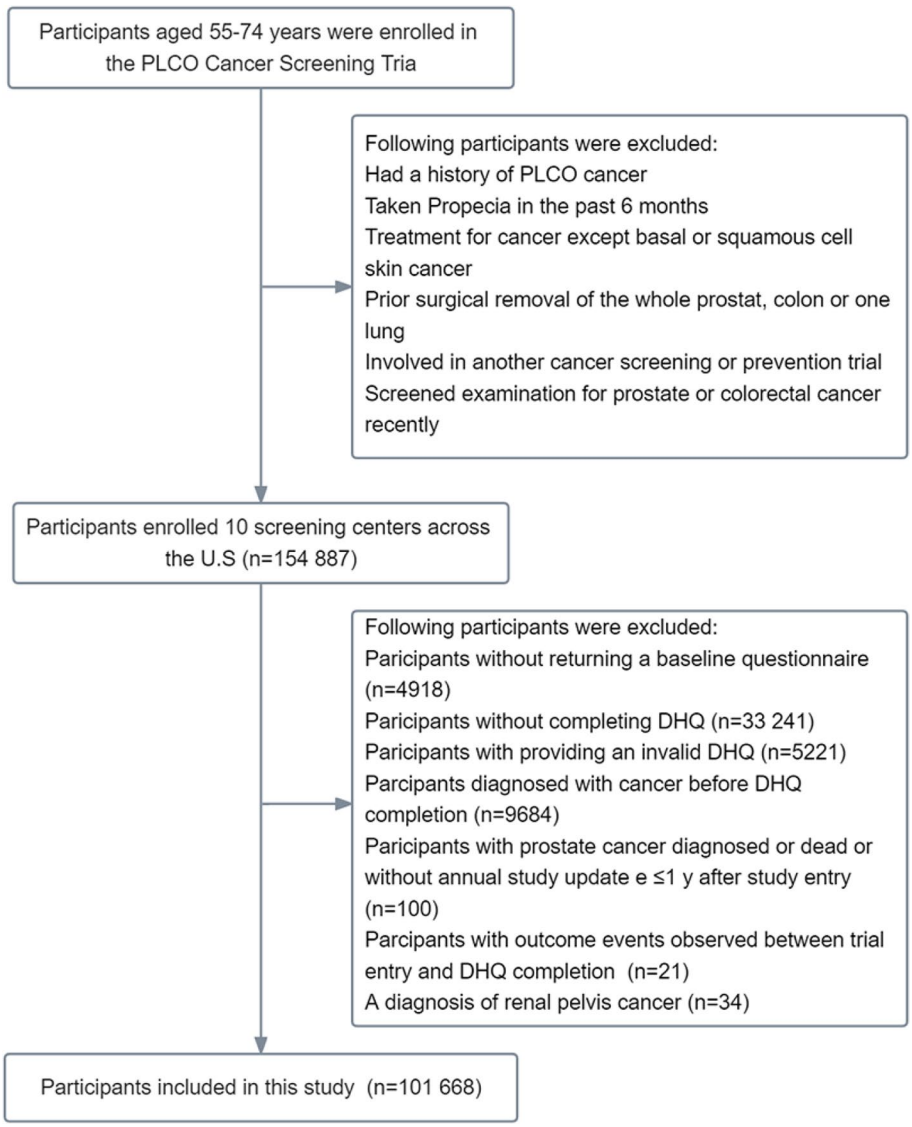

Fig. 1 The flow chart of identifying individuals eligible for our study

were observed when repeating the above analyses in 98,646 participants with complete covariate data (Additional file 1: Table S4).

Subgroup analyses showed a more significant association between ultra-processed food consumption and RCC incidence in participants with age < 65 (HR $_{\text{quartile 4 versus 1}}$: 2.28; 95% CI: 1.36, 3.83) than in those with age ≥ 65 (HR $_{\text{quartile 4 versus 1}}$: 1.07; 95% CI: 0.73, 1.55) ($P_{\text{interaction}} = 0.035$) (Additional file 1: Table S5). The initial association remained consistent in sensitivity analyses (Additional file 1: Table S6), confirming the reliability of the relationship between ultra-processed food consumption and RCC incidence.

In this study, main food groups contributing to ultra-processed food intake were soft drinks (48.14%) and cereals (16.27%), followed by ultra-processed fruits and vegetables (13.11%) and ultra-processed dairy products (7.05%) (Additional file 1: Fig. S2). Higher consumption of soft drinks (HR $_{\text{quartile 4 vs 1}}$:1.52; 95% CI: 1.14–2.03; $P_{\text{trend}} = 0.004$) and ultra-processed dairy products (HR $_{\text{quartile 3 vs 1}}$:1.35; 95% CI: 1.01–1.79) was significantly associated with a higher risk of RCC, while no significant associations were found for the remaining ultra-processed food groups (Additional file 1: Table S7).

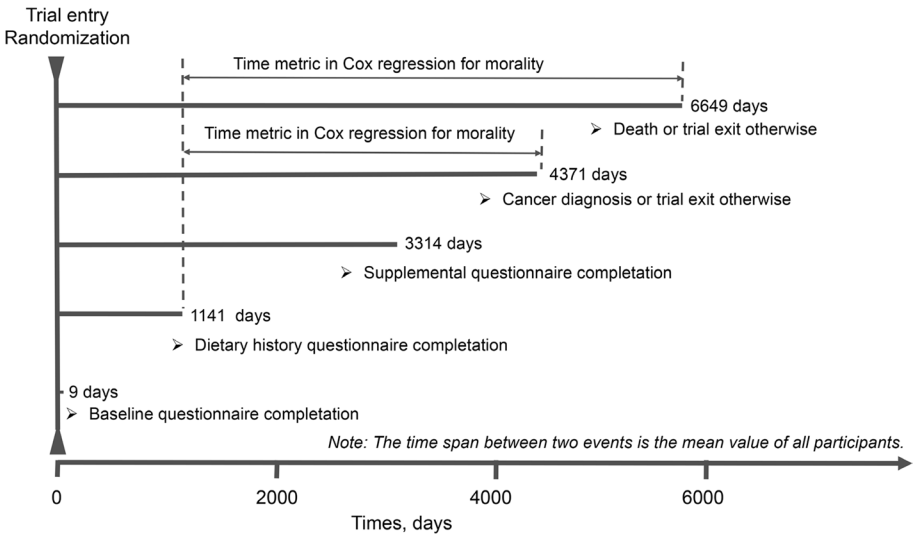

Fig. 2 The timeline and follow-up scheme of our study. The baseline point in this study was set at the date of diet history questionnaire completion

Associations between ultra-processed foods intake and RCC mortality

During 1,533,930 person-years of follow-up (median follow-up time 16.85 years), 230 RCC deaths were ascertained, with an overall mortality rate of 15 deaths per 100,000 person-years. After fully adjusting for confounding factors, compared with subjects in the lowest quartile of ultra-processed food intake, the HR for RCC mortality was 1.64 (95% CI: 1.10–2.43; *P* trend = 0.027) for those in the highest quartile (Table 3). In addition, similar results were observed for the association between ultra-processed foods intake and RCC mortality in 98,646 participants with complete covariate data (Additional file 1: Table S8). A linear dose–response association with ultra-processed foods intake was demonstrated for RCC mortality ($P_{\text{nonlinearity}} = 0.69$) (Fig. 4) based on restricted cubic spline functions.

The significant association between ultra-processed food intake and RCC mortality could be not modified by predefined stratification factors (all $P_{\text{interaction}} > 0.05$; Additional file 1: Table S9). In sensitivity analyses, this association of ultra-processed food intake with RCC mortality remained significant (Additional file 1: Table S10). Intriguingly, no significant associations between ultra-processed food groups and RCC mortality were found in this large population (Additional file 1: Table S11), implying that the complexity of the carcinogenic mechanism of ultra-processed foods.

Discussion

In this large, prospective, multicenter cohort involving 101,668 participants from US population, higher consumption of ultra-processed food consumption was significantly associated with an increased risk of RCC incidence and mortality in a linear dose–response manner. In subgroup analyses, this association was more pronounced among participants aged < 65 years. These results remained stable in sensitivity analyses using the quantity (g/day), using the complete covariate data or using the daily percentage contribution in energy (% kcal/day). The results were still consistent even after additional adjusting for physical activity and several markers of the nutritional quality of the diet. Therefore, our results support the hypothesis that consumption of ultra-processed foods could be an important and modifiable factor that increased the incidence and mortality of RCC.

Interpretation and comparison with other studies

NOVA classification system was a standardized tool to characterize foods based on their level of processing and NOVA was using to estimate relationships between ultra-processed foods consumption and diet quality or health outcomes [23]. Although the NOVA classification system does not truly reflect the intensity of the processes used, it can associate technological dimensions with formulation considerations, such as the use of specific ingredients or the total number of ingredients in a recipe [36]. Therefore, NOVA classification system could help better understand whether the links observed between ultra-processed food consumption and health are mainly due to the food structure or the food composition (specific ingredients and additives).

Ultra-processed foods have been shown to accounts for up to 50% of the total energy intake in many middle- and high-income countries [37, 38]. During the period of increasing ultra-processed foods consumption, there has

Table 1. Baseline characteristics of the PLCO study population according to sex specific quartile of ultra-processed food consumption ($n = 101\,668$) . *Values are mean ± SD or numbers (percentages)

Characteristics	Quartile of ultra-processed food consumption[1]				
	All participants	Q1($n = 25\,418$)	Q2($n = 25\,417$)	Q3($n = 25\,416$)	Q4($n = 25\,417$)
Age, years	65.5 (5.7)	66.2 (5.7)	65.9 (5.8)	65.5 (5.7)	64.5 (5.6)
Body mass index (kg/m^2)	27.2 (4.8)	26.2 (4.3)	26.9 (4.5)	27.4 (4.7)	28.4 (5.2)
Physical activity (min/week)[4]	125.1 (123.6)	134.1 (128.1)	125.8 (121.6)	122.3 (120.9)	118.4 (123.2)
Males	49 435 (48.6%)	12 359 (48.6%)	12 359 (48.6%)	12 358 (48.6%)	12 359 (48.6%)
Family history of renal cancer, n (%)	1543 (1.5%)	414 (1.6%)	348 (1.4%)	391 (1.5%)	390 (1.5%)
History of diabetes, n (%)	6790 (6.7%)	1308 (5.1%)	1346 (5.3%)	1678 (6.6%)	2458 (9.7%)
History of hypertension, n (%)	33 002 (32.5%)	7373 (29.0%)	7926 (31.2%)	8347 (32.8%)	9356 (36.8%)
Aspirin user, n (%)	47 756 (47.0%)	11 941 (47.0%))	12 089 (47.6%)	11 941 (47.0%)	11 785 (46.4%)
Body mass index, n (%)					
Underweight (<18.5 kg/m^2)	675 (0.7%)	258 (1.0%)	175 (0.7%)	127 (0.5%)	115 (0.5%)
Normal (18.5-24.9 kg/m^2)	33 744 (33.2%)	10 496 (41.3%)	9005 (36%)	7832 (31%)	6411 (26%)
Overweight (25-29.9 kg/m^2)	44 112 (43.4%)	10 574 (41.6%)	10 854 (43%)	11 387 (44.8%)	10 959 (43.1%)
Obese(>30 kg/m^2)	23 137 (22.8%)	4090 (16.1%)	5045 (20%)	6070 (24%)	7932 (32%)
Racial/ethnic group, n (%)					
Non-Hispanic White	92 497 (91.0%)	22 827 (89.8%)	23 415 (92.1%)	23 329 (91.8%)	22 926 (90.2%)
Non-Hispanic Black	3349 (3.3%)	418 (1.6%)	568 (2.2%)	880 (3.5%)	1483 (5.8%)
Hispanic	1495 (1.5%)	383 (1.5%)	382 (1.5%)	356 (1.4%)	374 (1.5%)
Other race/ethnicity[3]	4327 (4.3%)	1790 (7.0%)	1052 (4.1%)	851 (3.3%)	634 (2.5%)
Educational degree, n (%)					
College below	64 886 (63.8%)	15 261 (60.0%)	15 932 (62.7%)	16 426 (64.6%)	1 767 (67.9%)
College graduate	17 838 (17.5%)	4746 (18.7%)	4675 (18.4%)	4389 (17.3%)	4028 (15.8%)
Postgraduate	18 944 (18.6%)	5411 (21.3%)	4810 (18.9%)	4601 (18.1%)	4122 (16.2%)
Smoking status, n (%)					
Never	48 553 (47.8%)	10 713 (42.1%)	11 993 (47.2%)	12 708 (50.0%)	13 139 (51.7%)
Current	9390 (9.2%)	2720 (10.7%)	2332 (9.2%)	2031 (8.0%)	2307 (9.1%)
Former	43 725 (43.0%)	11 985 (47.2%)	11 092 (43.6%)	10 677 (42.0%)	9971 (39.2%)
Alcohol intake, g/d	9.5 (25.2)	15.4 (38.3)	9.7 (20.5)	7.6 (17.3)	5.6 (17.5)
Energy intake from diet, kcal/day	1738.4 (736.2)	1586.9 (693.4)	1725.0 (691.8)	1805.6 (735.4)	1836.1 (794.1)
Healthy Eating Index-2015	66.5 (9.7)	71.1 (9.1)	67.8 (8.9)	65.5 (9.0)	61.9 (9.4)
Food consumption					
Whole grain (g/day)	61.1 (59.9)	68.2 (69.0)	62.7 (57.9)	60.4 (56.1)	53.2 (54.7)
Vegetable (g/day)	284.0 (186.3)	304.2 (216.8)	289.8 (179.7)	283.8 (175.6)	258.3 (165.9)
Fruit (g/day)	273.9 (217.9)	305.4 (252.8)	279.5 (206.3)	271.2 (206.5)	239.7 (196.3)
Red Meats (g/day)	61.5 (52.4)	47.2 (42.1)	61.5 (50.8)	66.8 (53.7)	70.5 (58.6)
White Meats (g/day)	51.1 (47.9)	48.2 (47.1)	51.8 (47.3)	53.1 (48.1)	51.1 (49.1)
Nutrient intake					
Fat (g/day)	62.4 (33.6)	51.3 (26.9)	62.4 (31.9)	67.0 (34.6)	69.1 (37.1)
Carbohydrate (g/day)	221.2 (91.5)	203.5 (83.9)	217.2 (83.7)	228.9 (90.2)	236.4 (103.4)
Protein (g/day)	66.6 (30.3)	61.8 (27.5)	67.6 (29.8)	69.4 (31.1)	67.8 (32.2)
Cholesterol (mg/day)	208.6 (134.3)	176.9 (119.1)	209.8 (129.9)	222.0 (136.5)	225.5 (145.1)
Dietary fiber (g/day)	18.0 (8.5)	18.5 (9.4)	18.2 (8.3)	18.3 (8.2)	17.1 (7.9)
Sodium (mg/day)	2732.5 (1216.1)	2419.3 (1042.5)	2743.5 (1162.7)	2885.8 (1254.9)	2881.6 (1,325.9)

[1] Quarters of proportion of ultra-processed food intake in total quantity of food consumed. Sex specific cut-offs for quarters of ultra-processed proportions were 7.8%, 12.5%, and 19.5% in men and 6.6%, 10.9%, and 17.9% in women.

[2] *P* value for comparison between sex specific quarters of ultra-processed food consumption, by Kruskal-Wallis rank sum test or pearson's Chi-squared test

[3] Other race/ethnicity = Asian, Pacific Islander or American Indian.

[4] Total time of moderate-to-vigorous physical activity per week.

Table 2. Association between the proportion of ultra-processed food consumption and the RCC incidence[1]

Categories	Sex specific quartile of proportion of ultra-processed food consumption				
	Q1(n = 25,418)	Q2(n = 25,417)	Q3(n = 25,416)	Q4(n= 25,417)	P_{trend}
No of cases	78	86	120	126	
Person-years	225,263.11	226,197.26	225,142.33	223,128.23	
Incidence rate[2]	35	38	53	56	
Unadjusted	1.00 (reference)	1.10 (0.81-1.49)	1.54 (1.16-2.05)	1.63 (1.23-2.16)	<0.001
Model 1[3]	1.00 (reference)	1.08 (0.80-1.47)	1.53 (1.15-2.04)	1.65 (1.25-2.20)	<0.001
Model 2[4]	1.00 (reference)	1.04 (0.76-1.42)	1.42 (1.06-1.90)	1.42 (1.06-1.91)	0.004

[1] Values are hazard ratios (95% confidence intervals).

[2] Crude incidence rate per 100 000 person-years.

[3] age (years), sex (male, female), and race (non-Hispanic White, non-Hispanic Black, Hispanic, and other race/ethnicity)

[4] Adjusted for covariates in model 1 plus smoking status [current (>20 cigarettes/day, 10-20 cigarettes/day, <10 cigarettes/day), former (stop smoking >15 years, stop smoking ≤15 years), never], alcohol consumption (g/day), body mass index (kg/m^2), aspirin use (yes, no), history of diabetes and hypertension (yes, no), family of renal cancer (yes, no), energy intake from diet (kcal/day), physical activity, and educational level.

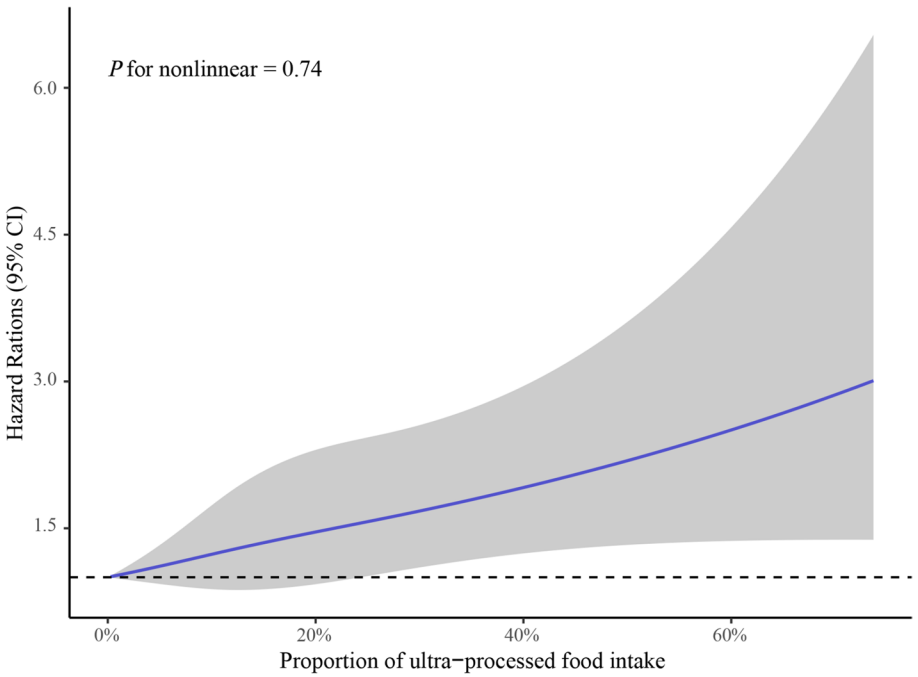

Fig. 3 Spline plot for linearity assumption of association between proportion of ultra-processed food in diet and incidence of RCC

been a greater risk of overweight and adiposity in both adolescents and adults [39, 40]. Meanwhile, an increasing number of observational studies have previously suggested that ultra-processed foods contribute to increasing the risk of hypertension [41], type 2 diabetes [42], and cardiovascular diseases [33]. In recent years, although some prospective studies have evaluated the association between ultra-processed foods and cancer risk [25, 43, 44], epidemiological evidence on this association remains limited. In the NutriNet-Santé prospective cohort, Fiolet et.al showed a significant positive association between the consumption of ultra-processed foods and the risk of cancer, especially postmenopausal breast cancer [25]. However, participants in the NutriNet-Santé cohort were more often women, which may limit the generalizability of population. Subsequently, another European prospective cohort study found that consumption of processed food was associated with the risk of colorectal cancer and postmenopausal breast cancer. What is more, increased intake of minimally processed foods (wholegrains, nonstarchy vegetables, and coffee) was identified as a protective factor for reducing the incidence of overall cancer,

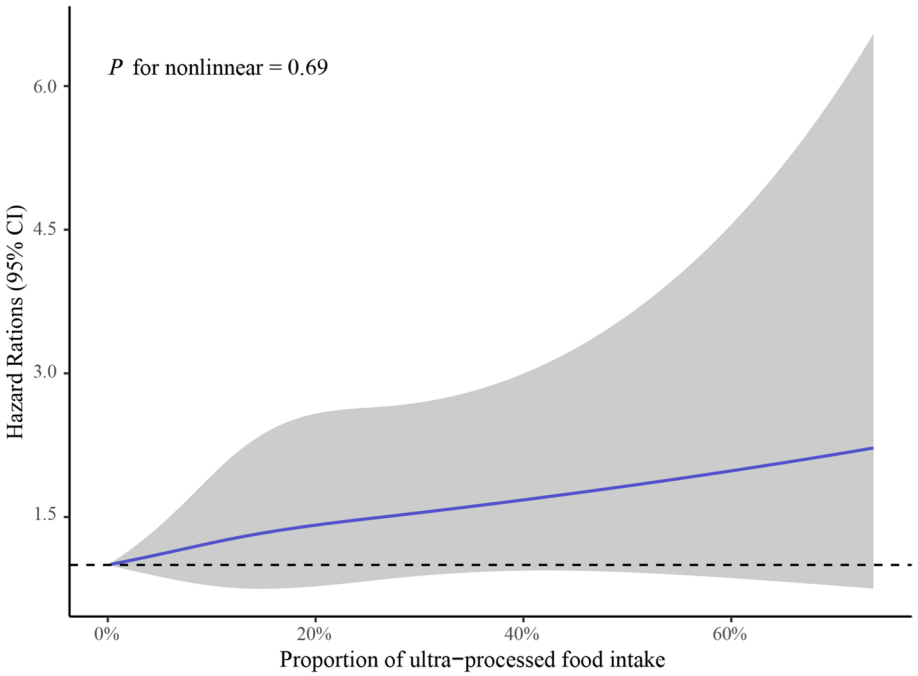

Fig. 4 Spline plot for linearity assumption of association between proportion of ultra-processed food in diet and mortality of RCC

Table 3 Association between the proportion of ultra-processed food consumption and the RCC mortality[1]

Models	Quartile of proportion of ultra-processed food intake				
	Q1 ($n = 25,418$)	Q2 ($n = 25,417$)	Q3 ($n = 25,416$)	Q4 ($n = 25,417$)	P_{trend}
RCC-related death					
No. of events	43	58	54	75	
Person-years	384,752.01	385,271.80	383,209.48	380,697.20	
Incidence rate[2]	11	15	14	20	
Unadjusted	1.00 (reference)	1.35 (0.91-2.00)	1.26 (0.85-1.89)	1.77 (1.22-2.58)	0.006
Model 1[3]	1.00 (reference)	1.32 (0.89-1.96)	1.25 (0.84-1.87)	1.81 (1.24-2.65)	0.006
Model 2[4]	1.00 (reference)	1.32 (0.89-1.97)	1.22 (0.81-1.84)	1.64 (1.10-2.43)	0.027

[1] Values are hazard ratios (95% confidence intervals)

[2] Crude incidence rate per 100,000 person-years

[3] age (years), sex (male, female), and race (non-Hispanic White, non-Hispanic Black, Hispanic, and other race/ethnicity)

[4] Adjusted for covariates in model 1 plus smoking status [current (>20 cigarettes/day, 10-20 cigarettes/day, <10 cigarettes/day), former (stop smoking >15 years, stop smoking ≤15 years), never], alcohol consumption (g/day), body mass index (kg/m2), aspirin use (yes, no), history of diabetes and hypertension (yes, no), family of renal cancer (yes, no), energy intake from diet (kcal/day), physical activity, and educational level

including colon cancer, rectal cancer, and postmenopausal breast cancer [43]. However, a prospective UK-based cohort study reported that a 10% increase in ultra-processed foods in the diet was associated with an increased incidence of overall cancer by 2% and ovarian cancer by 19% but not with breast cancer or colorectal cancer [45]. Although consumption of ultra-processed food has been associated with an increased incidence of pancreatic cancer in the PLCO cohort [29], and increased risks of overall cardiovascular and heart disease mortality [46], no prospective epidemiological study had evaluated the association between the proportion of ultra-processed foods in the diet and risk of RCC in the US population. In this study, our findings extend the harmful association between the intake of ultra-processed food and cancers, particularly RCC.

Several potential mechanisms could be put forward to explain this association. Firstly, the high ultra-processed food intake might drive the incidence of RCC because of obesogenic properties and low nutritional value. Dietary

patterns with a high proportion of ultra-processed food generally have a higher energy density and a poorer nutritional quality, including higher components of sodium, fat, and sugar and lower components of fiber and micronutrients [17, 19, 37, 47–51]. Sugar sweetened beverages might impair the internal satiety and leaded to excessive energy intake [52]. These excessive intakes of energy, fat, and sugar promote the incidence of metabolic disorders (e.g., obesity and diabetes), which are risk factors for many cancers including RCC [53]. Diets rich in ultra-processed food tend to have a low dietary quality and leaded to a lower Healthy Eating Index-2015. When dietary quality was additionally adjusted in our model, the association between consumption of ultra-processed food and RCC decreased, suggesting that dietary quality probably drove this association.

In addition, even when accounting for BMI and nutritional quality of the diet, including protein, fat, sodium, carbohydrates, and dietary fiber in the diet, ultra-processed food intake was significantly associated with RCC risk. Emerging studies have suggested non-nutritional compounds of ultra-processed food that be implicated in cancer outcomes, including through the wide use of controversial food additives (e.g., preservatives) and cosmetic additives (e.g., flavors and emulsifiers) [27]. For example, sodium nitrate, widely used by manufacturers to preserve ultra-processed meat, may increase the risk of RCC [9]. Aspartame, an intense artificial sweetener, was classified as "possibly carcinogenic to humans" (Group 2B) [54]. In this study, when we considered the interaction of different food group, our results showed that the intake of soft drinks may be a risk factor for RCC incidence. However, a European prospective cohort study found soft drinks were not associated with RCC incidence after adjusting for obesity (HR = 1.01, 0.98–1.05) [55]. Therefore, the association between soft drinks still are also controversial, particularly regarding potential long-term carcinogenicity.

Lastly, toxic contaminants migrated from ultra-processed food packaging, such as phthalates [56] and bisphenol A (BPA) [57], may additionally increase cancer risk. Although these available data on endocrine-disrupting chemicals are mainly experimental, they have consistently shown obvious toxic effects including for increasing damage to DNA in cancer cells and impairing immune systems [58]. Food processing may induce neoformed contaminants in ultra-processed products, such as acrylamide. These contaminants may induce the incidence of cancer. Indeed, a modest association between acrylamide and RCC risk was confirmed in a meta-analysis [59].

Our results using energy contributions found a higher number of significant associations than results using gram contributions. This finding supports the strength of using gram contributions as a measure index because it considers the effect of non-nutritional compounds on the incidence of RCC, which would not otherwise be captured. Importantly, our results using gram contributions also remained stable even after further adjusting the models for the nutritional quality of the diet (Additional file 1: Table S7).

Strengths and limitations of this study

The strengths of this study lie in its prospective design with a high follow-up rate, along with large number of RCC cases and deaths and detailed and repeated assessment of dietary intake and other covariates to minimize measurement errors. Furthermore, the confirmed diagnosis of RCC through medical record review enhances the reliability of the findings. However, several limitations should be considered. First, although the established risk factors were robustly adjusted, potential residual and unmeasured confounding cannot be completely excluded due to the observational design of this study. Moreover, the observational design precludes establishing causality. Second, there may be misclassification of food items owing to lacking to enough information and data on food processing required for the NOVA food classification, and DHQ used in this cohort was not specifically designed to classify foods. Nevertheless, this study is prospective and the nondifferential misclassification of the exposure likely could have biased our effect size toward the null. Third, the assessment of physical activity level and all sociodemographic characteristics except age were obtained by the supplemental questionnaire and baseline questionnaire in this study, respectively. Therefore, during the period of DHQ completion and completion of supplemental or baseline questionnaire, the changes in physical activity level and sociodemographic characteristics might cause nondifferential bias to some degree. Fourth, due to the lack of the histological subtypes of RCC in the PLCO cohort, the association between ultra-processed food and different subtypes of RCC risk cannot be determined. Finally, the majority of included participants were non-Hispanic White, over 60% had educational levels of some college or less, and approximately half were ever smokers or aspirin users, which may lead to protentional selection bias. However, our study aims to investigate the association between an exposure and an outcome. Thus, the representative population is not vital to estimate disease prevalence and incidence.

Conclusion

In this study, our results indicated that greater intake of ultra-processed food was associated with higher incidence and mortality of RCC in this US population. While

causality cannot be inferred due to the observational nature of the study, these findings emphasize the importance of considering the degree of food processing in dietary assessments. In addition, these findings warrant confirmation through additional epidemiological and mechanistic studies, particularly large-scale observational studies in different populations and settings. In the future, if these findings are further confirmed, limiting the intake of ultra-processed foods may be beneficial in the primary prevent of RCC.

Methods

Study population

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which was a randomized multicenter controlled study, was aimed to determine whether screening exams or tests could reduce the risk of mortality from prostate, lung, colorectal and ovarian cancers. Study design and methodology of the PLCO trial have been reported in detail elsewhere [28]. Briefly, participants were aged 55–74 years in this trial during the period from 1993 to 2001 from 10 screening centers (St Louis, Denver, Detroit, Salt Lake City, Minneapolis, Marshfield, Birmingham, Pittsburgh, Washington, and Honolulu). Based on the predefined eligible criteria, approximately 155,000 individuals were enrolled and randomly assigned to the screening arm and control arm in equal proportions. Individuals in control arm received the usual care, whereas those in screening arm received a cancer screening intervention. Specifically, male participants received prostate-specific antigen (PSA) testing and digital rectal exams for prostate cancer screening, while female participants received the cancer antigen 125 testing and transvaginal ultrasounds for ovarian cancer screening. Besides, both men and women received the posteroanterior chest X-ray to screen lung cancer, and the flexible sigmoidoscopy to screen colorectal cancer. The PLCO trial was approved by the US National Cancer Institute and the Institutional Review Board of each screening center. All of the participants provided their informed consents.

In this study, the following participants were further excluded: (1) overall, 4918 participants without returning a baseline questionnaire; (2) overall, 33,241 participants without completing a Dietary History Questionnaire (DHQ); (3) overall, 5221 with providing an invalid DHQ; a valid DHQ referred to the presence of having a DHQ completion date, DHQ completion date before death date, < 8 missing DHQ items, and the absence of extreme values of calorie intake (lowest or highest 1%); notably, the above-mentioned criteria were jointly defined by nutritionists, epidemiologists, and statisticians from the US National Cancer Institute; (4) overall, 9684 participants diagnosed with cancer before DHQ completion; (5) those with RCC diagnosed or dead or without annual study update ≤ 1 year after study entry ($n = 100$); (6) overall, 21 participants with outcome events observed between trial entry and DHQ completion (outcome events referred to loss to follow-up, death or incident RCC); and (7) 34 participants with a diagnosis of renal pelvis cancer. These exclusions resulted in the analytic cohort of 101,668 participants (Fig. 1). Moreover, we compared the populations between inclusion and exclusion; the standardized differences were found to be < 0.1, which indicated that the possibility of non-participation bias was small because of the exclusion of numerous participants (Additional file 1: Table S1) [29].

Outcome ascertainment

In this PLCO Cancer Screening Trial, cancer cases were mainly ascertained via an annual study update form that was mailed to all study participants. This form collected information on whether the participant received a cancer diagnosis, the date and location of diagnosis, and the contact information of their physicians. A standardized form was used to extract relevant medical records for further confirming confirm the diagnosis, clinical stage, and grade. The indication of cancer on the death certificate and family report was additional sources for the ascertainment of cancer. In this study, only participants diagnosed with RCC (ICD-O-2 codes: C649) were considered for reducing the heterogeneity of renal cancer cases [30]. Data on cancer diagnoses were collected through 2009. Death information was ascertained mainly through the annual study update form, and causes of death were obtained from death certificates. Data on morality were collected through 2018 .(https://cdas.cancer.gov/learn/plco/trial-summary/).

Data collection

A sex-specific baseline questionnaire solicited information on age, race, weight, height, marital status, education, physical activity, smoking status, family history of RCC and history of diabetes and hypertension, and other factors. DHQ, a food frequency questionnaire including the portion size and frequency of intake of 124 food items and supplement use during the past year, was used to collect dietary information [31]. Age at DHQ completion and alcohol intake were collected through this questionnaire. The amount of daily food consumption was estimated by multiplying food frequency by portion size; the amount of daily energy and nutrient intake was calculated by the detailed analysis file of DietCalc (National Cancer Institute, Bethesda, MD), which determined frequency of consumption and serving size question and used nutrient values based on national dietary

data. Healthy Eating Index-2015 was index reflecting an individual's diet quality and was calculated as stated previously [32]. Physical activity level referred to the total time of moderate-to-vigorous activity per week, which was evaluated by a self-administered supplemental questionnaire.

Assessment of ultra-processed food consumption

All food and drink items of the DHQ composition table were allocated into one of the four food groups in NOVA by two researchers (YDL and ZJR) using the method described in the literature [29]. The NOVA was a food classification system based on the extent and purpose of industrial food processing, which was divided into the four food groups (unprocessed or minimally processed foods, processed culinary ingredients, processed foods and ultra-processed foods) [27]. In this study, we focused on the "ultra-processed foods" NOVA group, for example, beverage, sauce, and fast-food hamburgers. All ultra-processed foods were further divided into nine food groups, which is soft drinks, cereals, ultra-processed fruits and vegetables, ultra-processed dairy products, meat and fish, sauces and dressings, salty snacks, sugary products, and margarine [29]. Definitions and examples are presented in Additional file 1: Table S2.

Statistical analysis

For each participant, we calculated the proportion (%) of ultra-processed foods in the total weight of food and beverages consumed (g/day). The consumption of ultra-processed food was determined by calculating a weight ratio rather than energy ratio to consider ultra-processed foods that do not provide any energy (in particular soft drinks) and non-nutritional factors related to food processing (e.g., neoformed contaminants and food additives) [25, 33]. We expressed continuous variables as means with standard deviation (SD), and categorical variables are expressed as percentages. Education was categorized as postgraduate, college, and college below. Race/ethnicity was categorized as categorical variable of non-Hispanic White, non-Hispanic Black, Hispanic, and Asian. Other categorical variables included smoking status, classified as current, former and never, family history of RCC, and history of diabetes and hypertension. Continuous variables included age, BMI (kg/m^2), energy intake (kcal/day), alcohol consumption (g/day), food consumption, nutrient intake, physical activity (min/week), and Healthy Eating Index-2015. For all covariates except physical activity, 5% or less of values were missing and were imputed to the modal value (for categorical variables) or median (for continuous variables) [33]. For physical activity, the proportion of missing values was higher (25.56%), and these values were considered as missing at random, and then multiple imputation with chained equations was used to impute them (the number of imputations set at 25) [34]. A missing data was included into the models for this variable because massive imputation for a non-negligible number of participants and risk of selection bias were considered. We further conduct main analyses in participants with complete data for comparison. The corresponding distribution of variables with missing values before and after data imputation was present in Additional file 1: Table S3. The differences in participants' baseline characteristics between quarters of the ultra-processed food consumption were examined by using analysis of Kruskal–Wallis rank sum test or χ^2 tests wherever appropriate. We used Cox proportional hazards models with person-year as the primary timescale to evaluate the association between the proportion of ultra-processed foods in the diet (coded as a continuous variable or as sex-specific quarters) and incidence and mortality of RCC. In these models, for the follow-up time of RCC incidence, participants contributed person time from the date of DHQ completion to the date of diagnosis of RCC, the date of death, or 31 December 2009, whichever occurred first. For the follow-up time of RCC mortality, the end of mortality follow-up was 2018, which was detailed on the PLCO website (https://cdas.cancer.gov/learn/plco/early-qx/) (Fig. 2). Ultra-processed food consumption was divided into quartile. We estimated hazard ratios and 95% confidence intervals with the lowest quarter as the reference category. In models based on sex quarters of ultra-processed foods consumption, we tested for linear trend by coding the median value of each quarter of ultra-processed food as ordinal variable.

Covariates were selected on the basis of our causal knowledge from previous literature instead of the statistical criteria [35]. Model 1 was adjusted for age at DHQ completion and race/ethnicity; model 2 was adjusted for established variables for RCC incidence including age at DHQ completion, race/ethnicity, body mass index (BMI, continuous), alcohol consumption (g/day, continuous), energy intake (kcal/day, continuous), family history of RCC, and history of diabetes and hypertension.

Subgroup analyses were conducted to determine whether the observed associations between ultra-processed food consumption and incidence and mortality of RCC were modified by age at DHQ completion (≥ 65 vs. < 65 years), BMI (≥ 25 vs. < 25), smoking status (current or former smokers stopping smoking ≤ 15 years vs never or former smokers stopping smoking > 15 years), trial group (screening compared with control groups), and alcohol consumption ($\geq$ median vs $<$ median). A P value for interaction was obtained by comparing

models with and without interaction terms before performing the above-mentioned subgroup analyses to avert the possibly spurious subgroup differences.

Restricted cubic spline regression with three knots (i.e., 10th, 50th, and 90th percentiles) was used to accurately describe the association between ultra-processed food consumption and incidence and mortality of RCC with 0% of ultra-processed foods in the diet as the reference category. It is worth noting that number of knots was ascertained according to the Akaike's information criterion (AIC) and the Bayesian information criterion (BIC), with the lowest values representing the best-fitted model.

We did sensitivity analyses based on model 2 by excluding RCC cases diagnosed within the first 2, 3, or 5 years of follow-up to avoid reverse causality bias and excluding individuals with extreme ultra-processed food consumption (top 2.5% or bottom 2.5%). We assessed ultra-processed food consumption in relation to RCC incidence and mortality with additional adjustment for (1) trial group, physical activity, and Healthy Eating Index-2015 on model 2 and (2) physical activity and intakes of fruit, vegetable, red and white meat, and whole grain on model 2. To test for the potential influence of the nutritional quality of the diet in the association between intake of ultra-processed food and risk of RCC, model 2 was additionally adjusted for physical activity and intakes of protein, fat, sodium, carbohydrates, and dietary fiber. We examined associations between the quartiles of proportion of ultra-processed food consumption and risk of RCC and used daily percentage energy intake of ultra-processed food consumption to conduct main analysis.

We did an analysis to examine the association between the aforementioned nine individual food groups of ultra-processed food consumption and RCC incidence and mortality, and the main contributor(s) to this association could be determined. All statistical analyses were performed using R software (version 4.3.1) and STATA (version 16.0). Two-sided $P < 0.05$ was considered statistically significant.

Abbreviations

AIC	Akaike's information criterion
BIC	Bayesian information criterion
BMI	Body mass index
BPA	Bisphenol A
CI	Confidence interval
DHQ	Dietary History Questionnaire
HR	Hazard ratio
NCI	National Cancer Institute
PLCO	Prostate, Lung, Colorectal, and Ovarian
PSA	Prostate-specific antigen
RCC	Renal cell carcinoma
US	United States
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03677-5.

Additional file 1: Figures S1-S2 and Table S1-S11

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Authors' contributions
YD-L, YX-F, and LL-G contributed equally to this work. YD-L, ZJ-R, and CL conceived this study's ideas and design, and other authors made useful suggestions. YD-L and LL-G applied and acquired the original data from the US National Cancer Institute. YD-L, YX-F, LL-G, ZJ-R, and CL wrote the initial manuscript, and the other authors made critical comments and revisions; YD-L, TX, TW, and HH were responsible for the statistical analyses, and all authors interpreted the corresponding results together. All authors read and approved the final manuscript.

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Availability of data and materials
Data described in this study are from the PLCO, Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Data can be made available upon the application and approval (https://cdas.cancer.gov/plco/).

Declarations

Ethics approval and consent to participate
All procedures performed in the PLCO Trial involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. All participants provided written informed consent to participate in the PLCO Trial study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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