HHS Public Access
Author manuscript
Nutr Cancer. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:
Nutr Cancer. 2021 ; 73(2): 239–245. doi:10.1080/01635581.2020.1743870.

Dietary intakes of trace elements and the risk of kidney cancer: the Singapore Chinese Health Study

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Abstract

Background: Epidemiological studies have demonstrated separately that patients with kidney stone may have higher dietary intake of zinc and higher risk of developing kidney cancer. We prospectively assessed the associations of dietary zinc and other trace elements with kidney cancer risk for the first time.

Methods: We used data from the prospective Singapore Chinese Health Study that recruited 63,257 adult Chinese residing in Singapore between 1993 and 1998. A validated food frequency questionnaire and the Singapore Food Composition Database was used to compute the values of intake for zinc, copper and manganese. We identified incident cancer cases via linkage with nationwide cancer registry, and used Cox proportional hazard models to compute hazard ratio (HR) and 95% confidence interval (CI) for the association with kidney cancer risk.

Results: There were 229 incident kidney cancer cases after median follow-up of 20.1 years. Dietary zinc intake was positively associated with higher kidney cancer risk; the HR comparing the extreme quartiles of zinc intake was 1.74 (95% CI: 1.02–2.97; *P*-trend=0.033). Conversely, intakes of copper and manganese were not associated with kidney cancer risk.

Conclusions: The positive association between dietary zinc and risk of kidney cancer suggests that zinc may be implicated in renal carcinogenesis.

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Author's contributions:
WPK conceived the study, interpreted the data, and critically revised the reports. AZ analyzed the data. YW drafted and critically revised the reports. THJ critically revised the reports. JMY contributed to the acquisition of study materials and critically revised the reports. All authors revised and approved the final report.

Disclosure: No conflicts of interest declared.

Data availability:
Data are available upon reasonable request from the corresponding author subject to approval by the IRB.

Keywords

Epidemiology; Zinc; Cohort study

INTRODUCTION

According to the World Health Organization, kidney cancer was the 9th and 14th most common cancer in men (214,000 cases) and women (124,000 cases), and ranked as the 16th leading cause of cancer-related deaths (143,000 deaths) worldwide in 2012 [1]. As the most deadly urinary tract cancer, a quarter of the patients present with advanced disease (locally invasive or metastatic disease), and the median survival for patients with metastatic disease is about 13 months [2]. Hence, there is a need to identify risk factors of kidney cancer in order to understand the process of carcinogenesis for better prevention and control of this cancer.

Some known risk factors of kidney cancer include smoking [3], obesity [4], hypertension [4], and diabetes [5]. In addition, findings from epidemiological studies have shown that kidney stone may be associated with increased risk of kidney cancer [6]. A meta-analysis of seven case-control and retrospective cohort studies reported that a history of kidney stone was associated with a statistically significant 76% increase in risk of kidney cancer [6], and the positive association was further supported by a recent prospective study among 120,852 participants in the Netherlands [7]. Interestingly, observational studies have reported that dietary intakes of trace elements, such as zinc, could be associated with increased risk of kidney stone disease; while intake of manganese could be associated with reduced risk of kidney stone disease [8–10]. Moreover, in a study that examined malignant tumor samples from patients with kidney cancer, presence of heavy metals including copper were detected in tumor tissue but not in adjacent normal tissue [11], prompting the authors to suggest a possible role of trace elements in the oncogenic pathway of renal cell carcinoma. However, to our best knowledge, no epidemiological study has examined the prospective association between dietary intakes of trace elements and the risk of kidney cancer.

In this study, we examined intakes of dietary zinc, copper and manganese and their associations with incident kidney cancer in a prospective cohort study of Chinese living in Singapore.

Participants and Methods

Study population—The baseline recruitment of the current cohort study was conducted between April 1993 and December 1998, and a total of 63,257 Chinese adults (27,954 men and 35,303 women) aged between 45 and 74 years old were recruited. The detailed design of the Singapore Chinese Health Study has been described previously [12]. Briefly, participants were from two major dialect groups (Cantonese and Hokkien), who originated from Guangdong and Fujian provinces in southern China. The participants were residents in government housing estates, where 86% of Singaporean residents lived at the period of recruitment. At recruitment, a face-to-face interview was conducted to collect information on demographics, habitual dietary and lifestyle habits, and medical history by using structured questionnaires. Informed consents were obtained from all participants, and the study protocol was approved by the Institutional Review Board at the National University of Singapore and the University of Pittsburgh.

Assessment of exposures and covariates—We used a semi-quantitative food frequency questionnaire (FFQ), which included 165 common food items in Singapore, to measure dietary intake at baseline interviews. The FFQ included eight categories of food intake frequencies (ranged from “never or hardly ever” to “two or more times a day”) and three portion sizes (small, medium and large) for participants to choose from. In addition, total energy intake and intakes of selected nutrients were derived using information from the FFQ and the Singapore Food Composition Database, which was developed for this cohort and listed values for 98 nutritive components from 849 food items in this cohort. Briefly, the development of this database relied heavily on data published by the US Department of Agriculture, supplemented with multiple resources for other foods and components. We also selected items from published food composition tables of the People’s Republic of China, Malaysia and Taiwan. For several cooked items, we began with the raw values from the Chinese food composition table and developed item-specific formulas to adjust the published raw values to the cooked state before inclusion in this Singapore database [12].

This FFQ was subsequently validated using 24-hour recalls conducted on a subset of 810 (332 men and 478 women) cohort subjects. The validation study showed that most mean values of energy and selected nutrients assessed using the FFQ and the 24-hour recalls were very comparable and within 10% of each other [12]. The correlation coefficient for energy intake and selected nutrients from the FFQ versus the 24-hour recalls ranged from 0.24 to 0.79, which is comparable with previous validation study in diverse populations [12].

We also asked about the use of supplements of specific vitamins and trace elements, including vitamin A, beta-carotene, vitamin C, vitamin E, calcium, selenium and zinc. However, only about 875 participants (1.43%) took zinc supplements in this population. Nevertheless, the intake of zinc included supplements for these participants. Using baseline questionnaires, we also collected self-reported information on age, sex, dialect group, education levels, body weight and height, smoking status, and physician-diagnosed history of hypertension and diabetes. Body mass index (BMI) was calculated by the following equation: BMI = body weight (kg)/(height [m])^2.

Identification of kidney cancer—We identified incident kidney cancer cases and deaths through record linkage with the Singapore Cancer Registry and the Singapore Registry of Births and Deaths. We used the 10th version of the International Classification of Diseases (ICD-10) code C64 for the diagnosis of kidney cancer. We excluded 1936 participants with cancer at baseline identified through either self-report or linkage with the Singapore Cancer Registry. Thus, the final sample size for the current analysis was 61,321 participants.

Statistical analysis—Person-year for each participant was counted from the date of baseline interview to the date of death, cancer diagnosis or the end of follow-up (31 December 2016), whichever happened first. We adjusted nutrients intake (zinc, copper, manganese and protein) for total energy using the residual method [13]. For the multivariable analyses, participants were divided in quartiles based on their intake and the lowest quartile intake served as the reference group. We used Cox proportional hazards models to assess the hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for the associations between trace elements (zinc, copper and manganese) and kidney cancer risk. In model 1, we adjusted for age of recruitment (years), year of recruitment (1993–1995, 1996–1998), sex (men, women), dialect group (Hokkien, Cantonese), and education levels (no formal education, primary school, secondary and above). In model 2, we further included total energy (Kcal/day), BMI categories (<18.5, 18.5-<23.0, 23.0-<27.5, ≥27.5 kg/m^2), history of hypertension (yes, no), history of diabetes (yes, no), and smoking status (never, former and current smokers). We additionally adjusted for protein intake to be consistent with a previous study that showed an association between dietary zinc and protein [8]. In the final model (model 3), we simultaneously included all three trace elements in the same model. After finding zinc intake to be associated with kidney cancer risk, we further studied the association between major sources of dietary zinc and risk of kidney cancer. Since we had information on the use of zinc supplementation, in the sensitivity analyses, we repeated the above-mentioned analysis with the exclusion of participants taking zinc supplementation (n =875), as well as participants with extreme energy intake (<700 or >3700 kcal/day for men and <600 or >3000 kcal/day for women; n =1023) and kidney cancer cases that were not confirmed by histology (n =45). To examine the potential changes of dietary zinc intake due to preclinical symptoms or diagnosis of kidney cancer, we repeated the analysis after excluding all participants with less than 2 years of follow-up. We used SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) for all analyses, and considered 2-sided P values <5% as statistically significant.

RESULTS

A total of 229 kidney cancer cases were documented during an average of 20.1 years of follow-up (1,125,296 person-years). The mean age at recruitment was 56.9 (8.02) years. Among the 229 kidney cancer cases, 184 were confirmed with histology and majority of the confirmed cases (87%) had renal cell carcinoma.

Baseline characteristics of participants in the first and fourth quartiles of dietary intakes of trace elements are shown in Table 1. Compared to participants in the lowest quartiles of zinc, copper and manganese intakes, those in the highest quartiles had higher BMIs and education levels, and were more likely to be never smokers and to have medical histories of hypertension and diabetes. In the multivariable analysis, dietary zinc intake was positively associated with higher risk of kidney cancer in a dose-dependent manner (P-trend=0.033). In the fully adjusted model, the HR of kidney cancer risk when comparing the highest versus lowest quartile of dietary zinc was 1.74 (95% CI: 1.02–2.97). Conversely, dietary intakes of copper and manganese were not associated with kidney cancer risk; the corresponding HRs were 1.10 (95% CI: 0.71–1.72; P-trend=0.65) and 1.26 (95% CI: 0.83–1.91; P-trend=0.31), respectively (Model 3; Table 2). Similarly, the results remained unchanged when we excluded 875 subjects who took zinc supplements and only studied the intake of zinc from food. In the sensitivity analyses that excluded people with extreme calorie intake or cases not confirmed with histology, we observed similar results that only the intake of zinc was positively associated with kidney cancer risk (data not shown). When we excluded the first 2 years of follow-up to reduce the possibility of reverse causality for the observed association between dietary zinc and kidney cancer risk, the result remained materially unchanged (data not shown).

The major food sources of zinc in this study population were rice, red meat, noodle, all fish and shellfish, poultry, green vegetables and bread (Table 3). We further studied the association between these food sources of zinc and risk of kidney cancer to investigate if zinc intake was only the surrogate marker of a specific food that was associated with reduced risk of kidney cancer. In the analysis, none of these food items was associated with the risk of kidney cancer. Although the P-trend was significant ($P = 0.03$) for the association between increasing quartile intake of red meat and the risk of kidney cancer, compared to the lowest quartile, none of the risk estimates for the higher quartiles reached statistical significance (Table 3).

DISCUSSION

In this large-scale prospective cohort study in Singapore Chinese men and women, we found that dietary zinc was significantly associated with kidney cancer risk when comparing the mean intakes of 8.67 (SD: 4.08) mg/day in the highest quartile versus 6.34 (SD: 2.31) mg/day in the lowest quartile. To the best of our knowledge, this is the first epidemiological study that has shown an association between dietary zinc and kidney cancer risk.

We compared the median intake in this cohort to the US Recommended Daily Allowances (USRDA) and found that this study population had slightly lower intake of zinc (6.51 mg for men and 6.72 mg for women in this study versus 11 mg for men and 8 mg for women in the USRDA recommendation), but comparable intake of copper (0.97 mg in this study versus 0.90 mg in the USRDA recommendation) and higher intake of manganese (3.67 mg for men and 3.61 mg for women in this study versus 2.30 mg for men and 1.80 mg for women in the USRDA recommendation). The main food sources for zinc with the highest bioavailability are red meat and poultry, and those for copper and manganese are grain products and seafood [14]. Compared to the US population, this cohort ate less red meat and poultry, and more seafood and grain products [12]. Therefore, the observed lower intake of zinc, comparable intake of copper and higher intake of manganese in this study compared to the USRDA recommendation could be due to the differences in dietary pattern between this Chinese cohort in Singapore and US populations.

As zinc is essential for human physiological growth and immune system [15], zinc deficiency may give rise to health problems such as stunting and depressed immunity [16]. However, excessive zinc intake is also toxic to cell and has been shown to impair immune responses in adults [17]. Food groups with high zinc content (such as red meat, poultry, and shellfish [18]) are also rich in protein. The current study observed a strong and positive association between zinc and kidney cancer after adjusting for protein intakes, and thus suggested that the association between zinc and kidney cancer is unlikely to be explained by protein intake. In addition, none of the major food source of zinc has shown association with the risk of kidney cancer. Although the underlying mechanism is not known yet, several lines of evidence suggest that the association between dietary zinc and kidney cancer risk could be mediated via zinc deposits in the kidney leading to the formation of kidney stones [8–10]. In turn, kidney stone disease, which may cause inflammation in the urinary tract [19], has been linked to an increased risk of kidney cancer [6,7]. Zinc has been found to be present in kidney stone [20], and four case-control studies conducted in Turkey, Italy and India among kidney stone formers and healthy controls showed that patients with kidney stone had higher urinary zinc excretion compared to healthy controls [21–24]. Cross-sectional data from 15,444 participants in the NHANES III showed that higher intake of zinc was associated with higher risk of kidney stone disease [8], while a randomized trial of 3,640 subjects on high dose supplemental zinc or non-zinc placebo showed that a higher risk of admissions for urinary lithiasis approached significance in men on zinc compared to placebo [10]. However, a recent prospective study of three US cohorts (Health Professional Follow-up Study, Nurses' Health Study [NHS], and NHS II) did not report any association between zinc intake and risk of kidney stone disease [9]. Two other case-control studies also did not observe higher urinary zinc levels in patients with kidney stone compared to controls [25,26]. Hence, the role of zinc in urolithiasis remains controversial.

An alternative mechanism underlying the observed association between zinc and kidney cancer in our study may be via the role of zinc as a co-factor for enzymes involved in cancer cell proliferation and metastasis [27]. In support of this hypothesis, the expression of zinc transporters, which tightly regulate zinc homeostasis in its influx and efflux processes [27], has been shown to be upregulated in renal cell carcinoma and to correlate with tumor aggressiveness [28]. Further studies are needed to elucidate these mechanisms in renal carcinogenesis.

A strength of the current study is its prospective study design to minimize the error from temporal bias by recording dietary intake prior to kidney cancer diagnosis. In addition, we had a long follow-up duration and comprehensive capture of all kidney cancer cases in the cohort via linkage with the nationwide Singapore Cancer Registry, which has been in place since 1968 and shown to be comprehensive in its recording of cancer cases [29]. Moreover, we used a FFQ that was developed and validated in this population to measure dietary intake of trace elements. However, the present study had some limitations. First, dietary intakes of trace elements were computed from self-reported food intake and were not included in the validation study, thus some measurement errors may exist. However, this may likely lead to non-differential misclassification of dietary intake and an underestimation of the observed association. Second, diet was only assessed once at baseline; therefore, we lack information about potential changes in exposures occurred during the follow-up period. Third, 19.7% of the kidney cancer cases did not have histology confirmation. However, sensitivity analysis among histologically confirmed kidney cancer cases showed similar results to the ones observed in all cases. Fourth, we do not have information on the presence of kidney stones in the current study, and thus could not investigate whether kidney stones mediate the association between dietary zinc and risk of kidney cancer. Finally, residual confounding cannot be completely ruled out in our study due to the limitation of the observational design.

In conclusion, the present study demonstrated a positive dose-dependent association between dietary zinc intake and risk of kidney cancer. Further epidemiological studies are warranted to validate our findings, and mechanistic studies are needed to investigate the underlying mechanism by which dietary zinc may increase kidney cancer risk.

Acknowledgements:

We thank the Singapore Cancer Registry for the identification of cancer and mortality outcomes via database linkages. We also thank Siew-Hong Low of the National University of Singapore for supervising the fieldwork of the Singapore Chinese Health Study, and Renwei Wang for the maintenance of the cohort study database. In addition, we thank the founding principal investigator of the Singapore Chinese Health Study, Mimi C. Yu as well as all the cohort participants.

Funding:

This work was supported by the National Institutes of Health, USA [RO1 CA144034 and UM1 CA182876]. W-P Koh is supported by the National Medical Research Council, Singapore (NMRC/CSA/0055/2013).

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Table 1.

Participant characteristics according to extreme quartiles of dietary intakes of trace elements, the Singapore Chinese Health Study (n=61,321)[a]

	Zinc[a]		*Copper*		*Manganese*	
Characteristics	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**
Age at recruitment (SD) (years)	56.0 (7.75)	56.5 (8.10)	56.5 (7.90)	56.0 (7.96)	55.4 (7.81)	57.1 (8.03)
Men (%)	9,133 (59.3)	5,975 (39.2)	9,534 (61.9)	5,467 (35.9)	7,203 (47.0)	7,725 (50.5)
Dialect group (%)						
Hokkien	7,358 (47.8)	7,306 (47.9)	7,746 (50.3)	6,748 (44.3)	6,938 (45.3)	7,531 (49.2)
Cantonese	8,053 (52.2)	7,948 (52.1)	7,648 (49.7)	8,487 (55.7)	8,388 (54.7)	7,774 (50.8)
Body mass index (SD) (kg/m^2)	23.0 (3.24)	23.2 (3.35)	23.0 (3.28)	23.2 (3.29)	22.9 (3.24)	23.3 (3.26)
Level of education (%)						
No formal education	3,787 (24.6)	3,710 (24.3)	3,902 (25.4)	3,870 (25.4)	3,840 (25.1)	3,492 (22.8)
Primary school	7,420 (48.2)	6,371 (41.8)	7,571 (49.2)	6,283 (41.2)	6,964 (45.4)	6,673 (43.6)
Secondary and above	4,204 (27.2)	5,173 (33.9)	3,921 (25.4)	5,082 (33.4)	4,522 (29.5)	5,140 (33.6)
Cigarette smoking (%)						
Never smokers	9,234 (59.9)	11,189 (73.4)	8,678 (56.4)	11,750 (77.2)	10,071 (65.7)	10,570 (69.1)
Former smokers	2,100 (13.6)	1,584 (10.4)	2,110 (13.7)	1,528 (10.0)	1,646 (10.7)	1,964 (12.8)
Current smokers	4,077 (26.5)	2,481 (16.2)	4,606 (29.9)	1,957 (12.8)	3,609 (23.6)	2,771 (18.1)
History of hypertension (%)	3,437 (22.3)	3,796 (24.9)	3,347 (21.7)	3,831 (25.2)	3,116 (20.3)	4,092 (26.7)
History of diabetes (%)	876 (5.68)	1,978 (13.0)	1,175 (7.63)	1,463 (9.60)	1,128 (7.36)	1,788 (11.7)
Mean intake of protein (SD) (g/day)	55.8 (21.1)	73.0 (27.7)	61.1 (23.8)	66.5 (26.5)	66.7 (26.8)	61.9 (23.8)
Mean intake of zinc (SD) (mg/day)	6.34 (2.31)	8.67 (4.08)	6.93 (2.84)	7.79 (3.31)	7.23 (3.22)	7.44 (3.11)
Mean intake of copper (SD) (mg/day)	0.95 (0.38)	1.21 (0.47)	0.85 (0.34)	1.34 (0.44)	1.00 (0.43)	1.14 (0.46)
Mean intake of manganese (SD) (mg/day)	3.97 (1.47)	4.24 (1.64)	3.91 (1.47)	4.33 (1.64)	3.23 (1.27)	5.08 (1.53)

[a]Intake of zinc included both diet and use of supplement.

[b]Data are reported as mean ± standard deviation for continuous variables and number (percentage) for categorical variables.

Table 2.

Dietary intake of trace elements in relation to kidney cancer risk, the Singapore Chinese Health Study

	Number of cases	Person-years	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)	Model 3[c] RR (95% CI)
Total	229	1,125,296			
Zinc (mg/day)[d]					
Quartile 1 (<6.17)	47	283,560	1.00	1.00	1.00
Quartile 2 (6.17–6.64)	53	283,210	1.30 (0.87–1.93)	1.38 (0.91–2.08)	1.32 (0.86–2.01)
Quartile 3 (6.64–7.13)	64	281,907	1.64 (1.12–2.40)	1.83 (1.18–2.83)	1.70 (1.07–2.69)
Quartile 4 (>7.13)	65	276,619	1.71 (1.17–2.50)	1.96 (1.20–3.19)	1.74 (1.02–2.97)
P for trend			0.003	0.005	0.033
Copper (mg/day)					
Quartile 1 (<0.85)	46	277,400	1.00	1.00	1.00
Quartile 2 (0.85–0.97)	60	280,596	1.51 (1.03–2.22)	1.48 (1.00–2.20)	1.38 (0.92–2.06)
Quartile 3 (0.97–1.11)	68	283,618	1.81 (1.23–2.64)	1.74 (1.18–2.58)	1.52 (1.01–2.28)
Quartile 4 (>1.11)	55	283,682	1.49 (1.00–2.23)	1.39 (0.92–2.09)	1.10 (0.71–1.72)
P for trend			0.030	0.09	0.65
Manganese (mg/day)					
Quartile 1 (<3.28)	41	282,849	1.00	1.00	1.00
Quartile 2 (3.28–3.63)	55	283,179	1.39 (0.93–2.09)	1.41 (0.93–2.12)	1.35 (0.89–2.04)
Quartile 3 (3.63–4.13)	66	280,561	1.61 (1.09–2.38)	1.61 (1.08–2.39)	1.49 (0.99–2.23)
Quartile 4 (>4.13)	67	278,709	1.52 (1.03–2.24)	1.45 (0.98–2.15)	1.26 (0.83–1.91)
P for trend			0.032	0.06	0.31

[a]Model 1 adjusted for age of recruitment (years), year of recruitment (1993–1995, 1996–1998), sex (men, women), dialect group (Hokkien, Cantonese), and education levels (no formal education, primary school, secondary and above);

[b]Model 2: Model 1 plus additional adjustment for energy (Kcal/day), body mass index (<18.5, 18.5-<23.0, 23.0-<27.5, ≥27.5 kg/m^2), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (never, former and current smokers), and protein intake (g/day; quartile).

[c]Model 3: Model 2 plus additional adjustment for the other two trace elements of zinc (mg), copper (mg) and manganese (mg; all in quartiles).

[d]Intake of zinc included both diet and use of supplement.

Table 3.

Daily intake, zinc concentration, and percent contribution to total zinc for selected food groups

Food item/group	Median daily intake (g)[a]	Percent contribution of each food group to total zinc intake	Crude model[c] RR (95% CI) for quartile 4 vs. 1 of the food group	*P* for trend
All red meat	28.7	11.9	1.46 (0.95–2.26)	0.03
Poultry	18.2	4.62	0.98 (0.66–1.44)	0.81
All fish and shellfish	52.6	8.36	1.04 (0.67–1.63)	0.94
All vegetables	102.1	8.16	1.16 (0.76–1.77)	0.29
Green vegetables	60.8	4.37	1.04 (0.69–1.56)	0.57
All grain products	525.0	34.8	1.17 (0.77–1.77)	0.81
Rice	404.7	20.3	1.30 (0.84–2.01)	0.42
Noodle	46.8	8.72	1.18 (0.80–1.74)	0.47
Bread	29.2	4.07	0.76 (0.50–1.14)	0.19

[a]These values were derived from intake among all cohort subjects (*n*=61,321).