The Association between Fish Consumption and Risk of Renal Cancer: A Meta-Analysis of Observational Studies

Hong-wei Bai, Ye-yong Qian, Bing-yi Shi, Gang Li, Yu Fan, Zhen Wang, Ming Yuan, Lu-peng Liu

Department of Urology, Institute of Organ Transplantation of PLA, 309th Hospital of PLA, Beijing, China

Abstract

Background: Several case-control studies and cohort studies have investigated the association between fish intake and renal cancer risk, however, they yielded conflicting results. To our knowledge, a comprehensive assessment of the association between fish consumption and risk of renal cancer has not been reported. Hence, we conducted a systematic literature search and meta-analysis to quantify the association between fish consumption and renal cancer.

Methods: A systematic search was performed using the PubMed, Embase, and Cochrane Library Central database for case-control and cohort studies that assessed fish intake and risk of renal cancer. Two authors independently assessed eligibility and extracted data. Fixed-effect and random-effect models were used to estimate summary relative risks (RR) and the corresponding 95% confidence intervals (CIs). Subgroup analyses, sensitivity analysis and cumulative meta-analysis were also performed.

Results: A total of 12 case-control studies and three cohort studies published between 1990 and 2011 were included in the meta-analysis, involving 9,324 renal cancer cases and 608,753 participants. Meta-analysis showed that fish consumption did not significantly affect the risk of renal cancer (RR=0.99, 95% CI [0.92,1.07]). In our subgroup analyses, the results were not substantially affected by study design, region, gender, and confounder adjustments. Furthermore, sensitivity analysis confirmed the stability of results.

Conclusions: The present meta-analysis suggested that there was no significant association between fish consumption and risk of renal cancer. More in-depth studies are warranted to report more detailed results, including stratified results by fish type, preparation method, and gender.

Introduction

Renal cancer accounts for almost 2% of all cancers worldwide, which consists of malignant tumors arising from the renal parenchyma and renal pelvis [1,2]. Renal cell carcinoma (RCC) accounts for about 90% of adult renal cancer and 3% of adult malignancies. The incidence of renal cancer has been steadily increasing worldwide in males and females, doubling over the past three decades[1-3]. Although cigarette smoking, obesity, and hypertension are established risk factors, the etiology of renal cancer is largely unknown[1,4].

Renal cancer is a multifactorial disease, with both hereditary and environmental components playing a role[5]. It has been found that diet is an important factor in the development of renal cancer[1,5]. Increased consumption of meat, especially red meat and processed meat were found to be associated with an increased risk of renal cancer[6]. As we know, fish is an important aspect of diet, and previous meta-analyses have investigated the association between fish consumption and the risk of several cancers. It was found that fish consumption could reduce the risk of colorectal cancer (OR=0.88; 95% CI, 0.80-0.95). However, there was no significant association between fish consumption and the risk of other cancers, such as pancreatic cancer, bladder cancer, prostate cancer, or esophageal cancer[7-12]. There are several case-control and cohort studies investigating the association between fish intake and renal cancer risk, however, they yielded conflicting results. To our knowledge, there has not been any quantitative attempt to summarize the results on the possible fish–renal cancer risk association. Thus, we conducted a quantitative meta-analysis of currently available epidemiologic studies to verify this putative association.
Methods

Study identification

This meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA) [13], as well as the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [14]. A literature search was carried out using Pubmed (www.ncbi.nlm.nih.gov/sites/entrez) (1966 to May 2013), Embase (www.embase.com) (1947 to May 2013), and Cochrane Library Central database (http://onlinelibrary.wiley.com/cochranelibrary/search/) (1967 to May 2013). There was no restriction of origin and language. Search terms included: “fish” or “seafood” and “cancer(s)” or “neoplasm(s)” or “malignancy(ies)” and “renal” or “kidney”. Furthermore, the reference lists of each comparative study included in this meta-analysis and previous reviews were manually examined to identify additional relevant studies.

Study selection

Two of the authors independently selected eligible case-control and cohort studies investigating the association between fish intake and renal cancer risk. Disagreement between the two reviewers was settled by discussing with the third reviewer. Inclusion criteria were: (i) used a case-control or cohort study design; (ii) evaluated the association between fish intake and renal cancer risk; (iii) presented odds ratio (OR), relative risk (RR), or hazard ratio (HR) estimates with its 95% confidence interval (CI). When there were multiple publications from the same population, only data from the most recent report was included in the meta-analysis and the remaining were excluded. Studies reporting different measures of RR like risk ratio, rate ratio, hazard ratio, and odds ratio were included in the meta-analysis. In practice, these measures of effect yield a similar estimate of RR, since the absolute risk of renal cancer is low.

Data extraction

Two of the authors independently extracted the relevant data from each included study by using a unified data form. The items included in the data form were as follows: name of first author, publishing time, country of the population studied, study design, study period, number of cancer cases and subjects, dietary assessment method, type of fish, quantity of intake, the study-specific adjusted ORs, RRs, or HRs with their 95% CIs for the highest category of fish consumption versus the lowest, confounding factors for matching or adjustments. The 2 lists from the authors were compared, and disagreements were resolved by consensus.

Methodological quality assessment

To assess the study quality, a 10-star system on the basis of the Newcastle-Ottawa Scale was used in which a study was judged on 3 broad perspectives as follows: selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each). A “star” presents a “high-quality” choice of individual study. With consideration that there is a correlation between caloric intake and nutrient consumption, and possibly a direct or indirect causal relation between caloric intake and renal cancer risk, the scoring system was modified by adding an item in which a study with data analysis that used an energy-adjusted residual or nutrient-density model received an additional star [15]. Hence, the full score was 10 stars, and the high-quality study was defined as a study with ≥7 awarded stars.

Data synthesis and analysis

Heterogeneity was assessed using the Cochran Q and I² statistics. For the Q statistic, a P value ≤ 0.10 was considered statistically significant for heterogeneity; for the I² statistic, heterogeneity was interpreted as absent (I²: 0%–25%), low (I²: 25.1%–50%), moderate (I²: 50.1%–75%), or high (I²: 75.1%–100%) [16]. To better investigate the possible sources of between-study heterogeneity, a meta-regression analysis was performed [17]. Some studies presented individual risk estimates according to the different types of fish, and did not report the effect of total fish consumption. In this situation, the study-specific effect size in overall analysis was calculated by pooling the risk estimates of the various fish types, using the inverse-variance method [18]. For studies that reported results separately for males and females, but not combined, we pooled the results using a fixed-effect model to obtain an overall combined estimate before combining with the rest of the studies [19]. Subgroup analyses were carried out according to (i) study design (cohort study versus population based case-control study versus hospital based case-control study), (ii) geographic location (Europe versus North America versus others), (iii) gender (male versus female), (iiii) number of adjustment factors (n ≥ 7 versus n ≤ 6), adjustment for alcohol intake (yes versus no), adjustment for total energy intake (yes versus no). Pooled RR estimates and their corresponding 95% CIs were calculated using the inverse variance method. When substantial heterogeneity was detected (I² ≥ 50%), the summary estimate based on the random-effect model (DerSimonian-Laird method) [20] was reported, which assumed that the studies included in the meta-analysis had varying effect sizes. Otherwise, the summary estimate based on the fixed-effect model (the inverse variance method) [21] was reported, which assumed that the studies included in the meta-analysis had the same effect size. We carried out sensitivity analysis by excluding one study at a time to explore whether the results were significantly influenced by a specific study. Cumulative meta-analysis was also performed to identify the change in trend of reporting risk over time. In cumulative meta-analysis, studies were chronologically ordered by publication year, then the pooled RRs were obtained at the end of each year. Publication bias was assessed using Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test [22,23]. All analyses were performed using Stata version 11.0 (StataCorp, College Station, TX).
Results

Literature search and study characteristics

A flow diagram that shows how we located relevant studies is presented in Figure 1. A total of 1,283 citations were identified from the three databases. On the basis of the title and abstract, we identified 17 papers. After reviewing the full text, three studies were excluded, because they were from the same population[24-26]. One study was identified from reference lists[27]. At last, the remaining 15 studies published between 1990 and 2011 were included in the meta-analysis, involving a total of 608,753 participants and 9,324 renal cancer cases. Of these 15 studies, seven were population-based case-control studies[28-34], five were hospital-based case-control studies[35-39], and the remaining three were cohort studies[27,40,41]. Four studies were conducted in North America[27,28,33,34], nine in Europe [29,30,32,35-37,39-41], one in Asia[38], and the remaining one study was a multi-center study which was conducted in Australia, Denmark, Sweden and the United States[31]. Almost all studies adjusted for smoking status and body mass index(BMI), and about half of the included studies adjusted for alcohol drinking status (Baseline data and other details are shown in Table 1). Table S1 summarizes the quality scores of cohort studies and case-control studies. The Newcastle-Ottawa Scale scores for the included studies ranged from 6 to 10, with a median 7. The median scores of cohort studies and case-control studies were 8 and 7, respectively. 11 studies were deemed to be of a high quality (≥7).

Main analysis

Because of statistically significant heterogeneity was not observed ($I^2 =23.8\%$, $p = 0.19$), a fixed-effects model was chosen over a random-effects model, and we found that fish consumption did not significantly affect renal cancer risk(RR=0.99, 95% CI [0.92,1.07]). Both multivariable adjusted RR estimates with 95 % CIs of each study and combined RR are shown in Figure 2.

Subgroup analyses, sensitivity analysis, cumulative meta-analysis, and meta-regression analysis

No statistically significant association was detected between fish consumption and renal cancer risk among cohort studies(RR=1.03, 95% CI [0.80, 1.33]), population based case-control studies (RR=0.94, 95% CI [0.82, 1.07]), or hospital based case–control studies (RR=0.96, 95% CI [0.83, 1.12]), presented in Table 2.

When stratified the various studies by study population, we found no significant association among studies conducted in Europe (RR= 0.98, 95%CI [0.86, 1.10]), North America (RR=...
Table 1. Characteristics of studies included in the meta-analysis.

| Author       | Publication year | Country                  | Study design                     | Study period       | Methods used for dietary assessment | Cases/Subjects | Type of fish | Units and comparison groups | Confounders for adjustment                                                                 |
|--------------|------------------|--------------------------|----------------------------------|--------------------|--------------------------------------|----------------|--------------|-----------------------------|---------------------------------------------------------------------------------------------|
| Daniel CR    | 2011             | USA                      | cohort study                     | 1995–1996          | FFQ 124 items                        | 2,065/492,186 | Total fish   | Q5 vs Q1                    | meat intake, age, sex, education, marital status, family history of cancer, race, BMI, smoking status, frequency of vigorous physical activity, menopausal hormone therapy in women, intake of alcohol, fruit, vegetables, and total energy |
| Wilson RT    | 2009             | Finland                  | cohort study                     | 1985-2002          | FFQ 203 items                        | 228/27,111    | Total fish, salted/canned fish | g/day ≤ 21.0 vs >50.7  | hypertension, smoking, and BMI, education and place of residence                             |
| Hu J         | 2008             | Canada                   | population based case-control study | 1994-1997          | FFQ 69 items                         | 1,345/6,384   | Total fish, smoked fish       | 4Q vs 1Q                     | age, province, education, BMI, sex, alcohol use, smoking, total of vegetable and fruit intake, and total energy intake |
| Hsu CC       | 2007             | Eastern and Central Europe | hospital based case-control study | 1999-2003          | FFQ 23 items                         | 1,065/2,574   | Total fish                | Tertile 3 vs Tertile 1 | age, country, gender, tobacco smoking, education, BMI, hypertension medication use, alcohol consumption, and vegetable consumption |
| Bravi F      | 2007             | Italy                    | hospital based case-control study | 1992-2004          | FFQ 40 items                         | 767/2,301     | Total fish                | 3Q vs 1Q                     | sex, age, period of interview, education, tobacco smoking, alcohol drinking, BMI, family history of kidney cancer, and total energy intake |
| Wolk A       | 2006             | Sweden                   | cohort study                     | 1987-1990          | FFQ 67 items                         | 150/61,433    | Total fish, fatty fish, and lean fish | Servings/ week1 vs 0 | education, BMI, intakes of total energy, alcohol, total meat, fruits, and vegetables, fatty fish and lean fish were mutually adjusted |
| Fernandez E  | 1999             | Italy                    | hospital based case-control study | 1983-1996          | FFQ 37 items                         | 190/8,180     | Total fish                | Servings/ week2 vs <1 | age, sex, area of residence, education, smoking, alcohol consumption, and BMI               |
| Lindblad P   | 1997             | Sweden                   | population based case-control study | 1989-1991          | FFQ 63 items                         | 379/729       | Total fish                | 3Q vs 1Q                     | age, sex, BMI, cigarette smoking, and educational level                                     |
| Boeing H     | 1997             | Germany                  | population based case-control study | 1989-1991          | FFQ 122 items                        | 277/563       | Total fish                | high vs low                  | age, gender, educational status, tobacco smoking and alcohol consumption                  |
| Wolk A       | 1996             | Australia, Denmark, Sweden and the United States | population based case-control study | 1989-1991          | FFQ 63-205 items                     | 1,185/2,711   | Total fish                | 4Q vs 1Q                     | age, sex, study center, BMI and smoking                                                   |
and RR=0.94, 95% CI [0.81, 1.09], respectively)(shown in Table 1 (continued).

Maclure M et al reported an effect estimate of 1.13 (95% CI [0.81, 1.58]). Between 1991 and 1999, seven studies were carried out by excluding studies one-by-one and analyzing the homogeneity and effect size for all of rest studies. Sensitivity analysis indicated that no significant association was observed in both male(RR= 0.72, 95%CI [0.47, 1.10]) or female population(RR= 0.78, 95%CI [0.58, 1.03]). When we examined whether the associations differed by adjustment for alcohol intake, or total energy intake status, the associations did not vary by these factors. Further, it was observed that studies with higher control for potential confounders ( n ≥ 7) as well as studies with lower control (n ≤ 6) presented no significant association between fish intake and renal cancer risk (RR=0.97, 95% CI[0.86, 1.09] and RR=0.94, 95% CI[0.81, 1.09], respectively)(shown in Table 2). To test the robustness of association and characterize possible sources of statistical heterogeneity, sensitivity analysis were carried out by excluding studies one-by-one and analyzing the homogeneity and effect size for all of rest studies. Sensitivity analysis indicated that no significant variation in combined RR by excluding any of the study, confirming the stability of present results. A cumulative meta-analysis of total 14 studies was carried out to evaluate the cumulative effect estimate over time. In 1990, Talamini R and Maclure M et al reported an effect estimate of 1.13 (95% CI [0.81, 1.58]). Between 1991 and 1999, seven studies were published, with a cumulative RR being 0.91(95% CI [0.79, 1.05]). Between 1999 and 2009, five more publications were added cumulatively, resulting in an overall effect estimate of 0.99 (95% CI [0.92, 1.07])(Figure 3). To better investigate the possible sources of between-study heterogeneity, a meta-regression analysis was performed. Study design, geographic area, control source, publication year, control for confounding factors, which may be potential sources of heterogeneity, were tested by a meta-regression method. However, meta-regression revealed that none of the above factors were responsible for the between-study heterogeneity.

Publication bias

In the present meta-analysis, no publication bias was observed among studies using Begg's P value (P = 0.40); Egger's (P = 0.38) test, which suggested there was no evidence of publication bias (Figure 4).

Discussion

The present meta-analysis included 15 observational studies currently available (12 case–control studies and three cohort studies), involving a total of 608,753 participants and 9,324 renal cancer cases. There was no statistically significant heterogeneity among the 15 studies, so a fixed-effects model was chosen over a random-effects model. Finally, we found that fish consumption did not significantly affect the risk of renal cancer(comparing the highest with the lowest category). In our subgroup analyses, the results were not substantially affected by study design, geographic location, gender, or confounder adjustments. Cohort and case–control studies alone showed no significant association between fish consumption and the risk of renal cancer. However, we should notice that there were only three cohort studies investigating the association between fish intake and renal cancer risk. That number was rather low to draw firm conclusions. Furthermore, most of the included studies didn’t reported results separately for males and females. So, future studies should reported results separately for males and females. Sensitivity analysis indicated that an omission of any studies did not alter the magnitude of observed heterogeneity.
effect, suggesting a stability of our findings. Cumulative meta-
analyses showed that the estimates gradually became
consistent, and the corresponding CIs narrowed down with the
increase of the number of included studies in the order of
publication year. Moreover, the results of Begg’s test and
Egger’s test did not support the existence of significant
publication bias.

Fish consumption has both anticarcinoma and carcinogenic
effects. As we know, fish oil is rich source of n-3 fatty acids.
Previous animal model studies have shown that n-3
polyunsaturated fatty acids were linked to the reduction of the
progression of cancer cells [42,43]. Multiple mechanisms are
involved in this chemopreventive activity, including suppression
of neoplastic transformation, cell growth inhibition and
enhanced apoptosis, and antiangiogenicity [44-46]. On the
other hand, fish consumption is positively correlated with blood
levels of dioxin, polychlorinated biphenyls, cadmium, mercury,
and lead[47-49]. Cadmium, mercury, and lead are known
nephrotoxicants which will induce oxidative stress and damage
to the proximal renal tubule, the location where nearly renal
cancer arises [50,51]. Previous studies have shown that
cadmium, mercury, and lead were associated with an
increased risk of renal cancer[50,52]. Maybe the combination
of anticarcinoma and carcinogenic effect leads to the
nonsignificant association between fish consumption and renal
cancer risk found in our meta-analysis.

Although we haven’t found significant association between
processed fish intake and increased renal cancer risk, we
should notice that there were only two studies investigating
processed fish and renal cancer risk, that number was rather
low to draw firm conclusion. As we know, processed fish is rich
in chemical carcinogens, such as nitrites, heterocyclic amines,
2-chloro-4-methylthiobutanoic acid, and so on, which may be
associated with an increased risk of renal cancer. So more
studies are needed to confirm the association between
processed fish consumption and the risk of renal cancer in the
future.

A study of women in Sweden by Wolk et al. [41]reported a
reduced risk of renal cancer with higher fatty fish (salmon,
herring, sardines, and mackerel) consumption. The possible
reason is that there are large differences between fatty fish and
lean fish in the content of omega-3 fatty acids and vitamin D.
Lower serum vitamin D levels have been found to be
associated with development and progression of renal

---

**Figure 2. Forest plot: overall meta-analysis of fish consumption and renal cancer risk.** Squares indicated study-specific risk estimates (size of square reflects the study-statistical weight, i.e. inverse of variance); horizontal lines indicate 95% confidence intervals; diamond indicates summary relative risk estimate with its corresponding 95% confidence interval.

doi: 10.1371/journal.pone.0081939.g002
cancer[53]. This was the only study investigating the association between fatty fish and the risk for development of renal cancer, so the association is needed to be confirmed by more studies in the future, especially in male population.

The strength of the present meta-analysis lies in a large sample size (608,753 participants and 9,324 renal cancer cases) and no significant evidence of publication bias. Two investigators independently performed the article identification, data extraction, and verification and resolved all discrepancies. Most studies adjusted for some important potential confounders, including age, sex, smoking status, and BMI. Furthermore, our findings were stable and robust in sensitivity analysis. However, several limitations to this meta-analysis should be noted. Firstly, as a meta-analysis of observational data, the possibility of recall and selection biases can’t be ruled out. Compared with case-control studies, cohort studies are less susceptible to bias due to their nature. However, the present meta-analysis included only three cohort studies, so more prospective cohort studies are need to confirm the association in the future. Secondly, we haven’t searched for unpublished studies, so only published studies were included in our meta-analysis. Therefore, publication bias may have occurred although no publication bias was indicated from both visualization of the funnel plot and Egger’s test. Thirdly, most of the included studies haven’t adjusted for hypertension, red and processed meat consumption, which are associated with an increased risk of renal cancer[6,54]. Lastly, different types of fish (lean fish and fatty fish, fresh fish and processed fish) may have different effects on renal cancer, however, we can’t do detailed subgroup meta-analysis for a lack of data. Although we assessed processed fish and renal cancer risk, the number of included studies was rather low to draw firm conclusion. Further, different processing methods may influence the effect on renal cancer.

In conclusion, the present meta-analysis suggested that there was no significant association between fish consumption and renal cancer risk. More in-depth studies are warranted to report more detailed results, including stratified results by fish type, preparation method, and gender.

| Table 2. Meta-analysis of fish consumption and renal cancer risk. |
|---------------------------------|-----|-----|-----|-----|
| No. of studies | Pooled estimate | Tests of heterogeneity | |
| | RR | 95% CI | P value | I^2(|%| |
| All studies | 15 | 0.99 | 0.92-1.07 | 0.19 | 23.80 |
| Study design | | | | | |
| Cohort | 3 | 1.03 | 0.80-1.33 | 0.03 | 79.80 |
| Population based case–control | 8 | 0.94 | 0.82-1.07 | 0.40 | 4.10 |
| Hospital based case–control | 4 | 0.96 | 0.83-1.12 | 0.31 | 15.80 |
| Geographic location | | | | | |
| Europe | 9 | 0.98 | 0.86-1.10 | 0.36 | 8.70 |
| North America | 4 | 1.01 | 0.84-1.20 | 0.29 | 19.40 |
| Other | 2 | 0.83 | 0.66-1.04 | 0.09 | 66.40 |
| Gender | | | | | |
| Male | 3 | 0.72 | 0.47-1.10 | 0.10 | 56.30 |
| Female | 4 | 0.78 | 0.58-1.03 | 0.73 | 0.00 |
| Adjusted for confounders | | | | | |
| Number of adjustment factors | | | | | |
| n ≥ 7 confounders | 7 | 0.97 | 0.86-1.09 | 0.21 | 30.00 |
| n ≤ 6 confounders | 8 | 0.94 | 0.81-1.09 | 0.25 | 22.30 |
| Major confounders adjusted | | | | | |
| Alcohol | | | | | |
| yes | 7 | 0.96 | 0.85-1.07 | 0.41 | 0.30 |
| no | 8 | 0.97 | 0.83-1.12 | 0.13 | 37.40 |
| Total energy intake | | | | | |
| yes | 4 | 0.90 | 0.77-1.04 | 0.31 | 14.80 |
| no | 11 | 1.00 | 0.89-1.12 | 0.24 | 21.00 |
| Processed fish | 2 | 0.91 | 0.70-1.19 | 0.25 | 25.30 |

RR= relative risks; CI=confidence intervals
doi: 10.1371/journal.pone.0081939.t002
Figure 3. Forest plot: cumulative meta-analysis of fish consumption and renal cancer risk.

doi: 10.1371/journal.pone.0081939.g003
Figure 4. Funnel plot for publication bias in the studies investigating risk for renal cancer associated with fish intake. doi: 10.1371/journal.pone.0081939.g004
Supporting Information

Table S1. Methodologic quality of observational studies included in the meta-analysis.

| References |
|--------------------------|
| 1. Chow WH, Dong LM, Devesa SS (2010) Epidemiology and risk factors for kidney cancer. Nat. Rev Urol 7: 245-257. doi:10.1038/nrurol.2010.46. |
| 2. Jemal A, Bray F, Center MM, Ferlay J, Ward E et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90. doi:10.3322/caac.20107. PubMed: 21296855. |
| 3. Mathew A, Devesa SS, Fraumeni JF Jr., Chow WH (2002) Global increases in kidney cancer incidence, 1973-1992. Eur J Cancer Prev 11: 171-178. doi:10.1097/00006849-200204000-00010. PubMed: 11984136. |
| 4. Dhôte R, Pellicer-Coeuret M, Thiounn N, Debré B, Vidal-Trecan G (2000) Risk factors for adult renal cell carcinoma: a systematic review and implications for prevention. BJU Int 86: 20-27. PubMed: 10896077. |
| 5. Curti BD (2004) Renal cell carcinoma. JAMA 292: 97-100. doi:10.1001/jama.292.1.97. PubMed: 15238597. |
| 6. Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y (2007) Consumption of different types of meat and the risk of renal cancer: meta-analysis of case-control studies. Cancer Causes Control 18: 125-133. doi:10.1007/s10552-006-0104-9. PubMed: 17249280. |
| 7. Szymanski KM, Wheeler DC, Mucci LA (2010) Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr 92: 1223-1233. doi:10.3945/ajcn.2010.29530. PubMed: 20844069. |
| 8. Salehi M, Moradi-Lakeh M, Salehi MH, Nojimi M, Kolahdooz F (2013) Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. Nutr Rev 71: 257-267. doi:10.1111/nure.12028. PubMed: 23587003. |
| 9. Li Z, Yu J, Miao Q, Sun S, Sun L et al. (2011) The association of fish consumption with bladder cancer risk: a meta-analysis. World J Surg 8: 336-341. doi: 10.1016/j.ijsu.2010.02.007. PubMed: 15238597. |
| 10.果合 M, Davey Smith G, Schneider M, Mindar C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634. doi: 10.1136/bmj.315.7109.629. PubMed: 9310563. |
| 11. Grieb SM, Theis RP, Burr D, Benardot D, Siddiqui T et al. (2009) Food groups and renal cell carcinoma: results from a case-control study. J Am Diet Assoc 109: 656-667. doi:10.1016/j.jada.2008.12.020. PubMed: 19328261. |
| 12. Hu J, Mao Y, White K, Canadian Cancer Registries Epidemiology Research G (2003) Diet and vitamin or mineral supplements and risk of renal cell carcinoma in Canada. Cancer Causes Control 14: 705-714. |
| 13. Rashidkhan B, Akesson A, Lindblad P, Wolk A (2005) Major dietary patterns and risk of renal cell carcinoma in a prospective cohort of Swedish women. J Nutr 135: 1575-1762. PubMed: 15987861. |
| 14. Daniel CR, Cross AJ, Graubard BI, Hollenbeck AR, Park Y et al. (2011) Prospective investigation of poultry and fish intake in relation to cancer risk. Cancer Prev Res (Phila) 4: 1903-1911. doi:10.1158/1940-6207.CAPR-11-0241. PubMed: 21600207. |
| 15. Hu J, La Vecchia C, DesMeules M, Negri E, Mery L et al. (2008) Meat and fish consumption and cancer in Canada. Nutr Cancer 60: 313-324. doi:10.1080/01694080701759724. PubMed: 18444165. |
| 16. Lindblad P, Wolk A, Bergström R, Adami HO (1997) Diet and meat intake based on meta-analysis of prospective studies. Gastroenterology 114: 106-118. doi:10.1053/gastro.2011.04.013. PubMed: 21600207. |
| 17. DenSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177-198. doi:10.1016/0197-2456(86)90046-2. PubMed: 3802833. |
| 18. Woolf B (1955) On estimating the relation between blood group and disease. Ann Hum Genet 19: 251-253. doi:10.1111/j.1469-1809.1955.tb01348.x. PubMed: 14388528. |
| 19. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088-1101. doi:10.2307/2533446. PubMed: 7786990. |
| 20. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634. doi: 10.1136/bmj.315.7109.629. PubMed: 9310563. |
| 21. Grieb SM, Theis RP, Burr D, Benardot D, Siddiqui T et al. (2009) Food groups and renal cell carcinoma: results from a case-control study. J Am Diet Assoc 109: 656-667. doi:10.1016/j.jada.2008.12.020. PubMed: 19328261. |
| 22. Hu J, Mao Y, White K, Canadian Cancer Registries Epidemiology Research G (2003) Diet and vitamin or mineral supplements and risk of renal cell carcinoma in Canada. Cancer Causes Control 14: 705-714. |

Author Contributions

Conceived and designed the experiments: HWB YYQ. Performed the experiments: ZW GL. Analyzed the data: YF LPL. Contributed reagents/materials/analysis tools: MY HWB. Wrote the manuscript: HWB YYQ.
39. Talamini R, Bartón AE, Barra S, Bidoli E, La Vecchia C et al. (1990) A case-control study of risk factor for renal cell cancer in northern Italy. Cancer Causes Control 1: 125-131. doi: 10.1007/BF00053163. PubMed: 2102282.

40. Wilson RT, Wang J, Chinchilli V, Richie JP, Virtamo J et al. (2009) Fish, vitamin D, and flavonoids in relation to renal cell cancer among smokers. Am J Epidemiol 170: 717-729. doi: 10.1093/aje/kwp178. PubMed: 19651663.

41. Wolk A, Larsson SC, Johansson JE, Ekman P (2006) Long-term fatty fish consumption and renal cell carcinoma incidence in women. JAMA 296: 1371-1376. doi:10.1001/jama.296.11.1371. PubMed: 16985229.

42. Hilakivi-Clarke L, Olivo SE, Shajahan A, Khan G, Zhu Y et al. (2005) Mechanisms mediating the effects of prepubertal (n-3) polyunsaturated fatty acid diet on breast cancer risk in rats. J Nutr 135: 2946S-2952S. PubMed: 16317153.

43. Ford JH (2010) Saturated fatty acid metabolism is key link between cell division, cancer, and senescence in cellular and whole organism aging. Age (Dordr) 32: 231-237.

44. Chapkin RS, Davidson LA, Ly L, Weeks BR, Lupton JR et al. (2007) Immunomodulatory effects of (n-3) fatty acids: putative link to inflammation and colon cancer. J Nutr 137: 2005S-204S. PubMed: 17162826.

45. Stoll BA (2002) N-3 fatty acids and lipid peroxidation in breast cancer inhibition. Br J Nutr 87: 193-198. doi:10.1079/BJN2002537. PubMed: 12064327.

46. Cerchietti LC, Navigante AH, Castro MA (2007) Effects of eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. Nutr Cancer 59: 14-20. doi: 10.1080/01635580701356088. PubMed: 17927497.

47. Risher JF, Murray HE, Prince GR (2002) Organic mercury compounds: human exposure and its relevance to public health. Toxicol Ind Health 18: 109-160. doi:10.1191/0748233702th138oa. PubMed: 12974562.

48. Bates CJ, Prentice A, Birch MC, Delves HT, Sinclair KA (2006) Blood indices of selenium and mercury, and their correlations with fish intake, in young people living in Britain. Br J Nutr 96: 523-531. PubMed: 16925858.

49. Wennberg M, Lundh T, Bergdahl IA, Hallmans G, Jansson JH et al. (2006) Time trends in burdens of cadmium, lead, and mercury in the population of northern Sweden. Environ Res 100: 330-338. doi: 10.1016/j.envres.2005.08.013. PubMed: 16221471.

50. Barbier O, Jacquillet G, Tauc M, Cougnon M, Poujeol P (2005) Effect of heavy metals on, and handling by, the kidney. Nephron Physiol 99: 105-110. doi:10.1159/0000833981. PubMed: 15722646.

51. Zalups RK (2000) Molecular interactions with mercury in the kidney. Pharmacol Rev 52: 113-143. PubMed: 10699157.

52. Dobrowolski Z, Drewniak T, Kwiatek W, Jakubik P (2002) Trace elements distribution in renal cell carcinoma depending on stage of disease. Eur Urol 42: 475-480. doi:10.1016/S0302-2838(02)00400-1. PubMed: 12429157.

53. Fujikawa T, Suzuki Y, Okamoto T, Mastushita N, Hasegawa M et al. (2000) Prevention of renal cell carcinoma by active vitamin D3. World J Surg 24: 1205-1210. doi:10.1007/s002680102026. PubMed: 11071463.

54. Corrao G, Scotti L, Bagnardi V, Sega R (2007) Hypertension, antihypertensive therapy and renal-cell cancer: a meta-analysis. Curr Drug Saf 2: 125-133. doi:10.2174/157488607780598296. PubMed: 18690958.