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Ingested nitrate, disinfection by-products, and kidney cancer risk in older women

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Abstract

Background—*N*-nitroso compounds formed endogenously after nitrate/nitrite ingestion are animal renal carcinogens. Previous epidemiologic studies of drinking water nitrate did not evaluate other potentially toxic water contaminants, including the suspected renal carcinogen chloroform.

Methods—In a cohort of postmenopausal women in Iowa (1986–2010), we used historical measurements to estimate long-term average concentrations of nitrate-nitrogen (NO_3-N) and disinfection byproducts (DBP) in public water supplies. For NO_3-N and the regulated DBP [total trihalomethanes (THM) and the sum of five haloacetic acids (HAA5)], we estimated the number of years of exposure above one-half the current maximum contaminant level (>½-MCL NO_3-N; >5mg/L). Dietary intakes were assessed via food frequency questionnaire. We estimated hazard ratios (HR) and 95% confidence intervals (CI) with Cox models, and evaluated interactions with factors influencing *N*-nitroso compound formation.

Results—We identified 125 incident kidney cancers among 15,577 women reporting using water from public supplies >10 years. In multivariable models, risk was higher in the 95th percentile of average NO_3-N ($HR_{P95vsQ1}$=2.3;CI:1.2–4.3;p_{trend}=0.33) and for any years of exposure >½-MCL; adjustment for total THM did not materially change these associations. There were no independent relationships with total THM, individual THMs chloroform and bromodichloromethane, or with haloacetic acids. Dietary analyses yielded associations with high nitrite intake from processed meats but not nitrate or nitrite overall. We found no interactions.

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Replication: Study data and code must be requested from the University of Minnesota and the National Cancer Institute and are subject to institutional data release policies.

The authors declare no conflicts of interest.

Conclusions—Relatively high nitrate levels in public water supplies were associated with increased risk of renal cancer. Our results also suggest that nitrite from processed meat is a renal cancer risk factor.

Keywords

nitrate; nitrite; kidney cancer; drinking water; disinfection by-products; trihalomethanes

Introduction

Kidney cancer is among the 10 most common adult malignancies in the United States.[1] Established risk factors for renal cell carcinoma, the predominant histologic type, include cigarette smoking, obesity, and hypertension.[2] Evidence is accumulating for low levels of physical activity, high alcohol consumption, and high parity as risk factors.[3] Certain occupations and exposure to industrial chemicals, such as trichloroethylene,[4] are also positively associated with renal cancer risk. Relationships with other occupational and environmental exposures are less well established.[3]

Drinking water may be a source of exposure to renal toxicants in the general population. Inorganic nitrate (NO_3-) is a common ground and surface water contaminant in agricultural areas, arising from synthetic fertilizers and livestock manure.[5,6] Nitrate is naturally present in plants, thus diet also contributes to exposure.[7] In the presence of nitrosatable precursors such as amines and amides, nitrite derived from nitrate by the oral microbiome and nitrite from processed meats and other dietary sources react endogenously to form *N*-nitroso compounds. Ingestion of nitrate or nitrite under conditions that result in such nitrosation is classified by the International Agency for Research on Cancer as a probable human carcinogen.[7] Several *N*-nitroso compounds, including ethylated and methylated nitrosoamines and ureas[7,8] and *N*-nitrosomorpholine administered in drinking water, cause kidney tumors in animals.[8] In human biomonitoring studies, *N*-nitroso compound formation in the gastrointestinal tract can be almost entirely inhibited by high intakes of antioxidants.[7,9] However, animal studies suggest that antioxidant inhibition of nitrosation is incomplete for some organ sites, including the kidney.[7]

The few epidemiologic studies of the relationship between kidney cancer and drinking water nitrate report inconsistent findings.[10–13] One ecologic study in Slovakia found no association with nitrate concentrations in public water supplies,[10] while another in Germany reported an elevated rate ratio for renal cell carcinomas among women in areas with high public water supply nitrate levels.[11] Early follow-up of a single prospective cohort with a small number of accrued cases, the Iowa Women's Health Study (IWHS), found no kidney cancer risks associated with long-term average nitrate levels >0.36 mg/L in public water supplies.[13] A case-control study in Iowa found no relationship with long-term average public water supply nitrate and renal cell carcinoma, except among subgroups with hypothesized greater potential for endogenous nitrosation.[12]

None of these studies of nitrate evaluated potentially carcinogenic co-contaminants, such as disinfection by-products (DBP) that are formed when organic matter and inorganic bromide react with disinfectants such as chlorine, chloramines, and ozone. The U.S. Environmental

Protection Agency requires routine measurement of several chlorinated DBP in drinking water, including the sums of four trihalomethanes (total THM) and five haloacetic acids (HAA5), which have maximum contaminant levels (MCLs) of 80 and 60μg/L, respectively.[14] Over 600 DBP chemical species have been characterized,[15] and regulated DBP are often considered surrogates for other toxic components of the complex drinking water mixture. Some DBP, such as chloroform,[16] are renal carcinogens in animals at high levels,[14] but corresponding epidemiologic evidence is limited. One case-control study of kidney cancer reported positive associations with water mutagenicity attributed to the levels of the chlorinated furanone MX.[17] An analysis in the IWHS found no association between chlorinated THM in PWS and RCC.[18] To our knowledge, no cohort studies have assessed both nitrate and DBP in drinking water in relation to kidney cancer.

While drinking water accounts for much of an individual's nitrate intake at high levels,[7] dietary sources constitute the bulk of daily nitrate/nitrite intakes in typical American diets.[19,20] The relationship between dietary nitrate and renal cancer has been evaluated in both case-control[21] and cohort[13,22,23] studies, including non-significant positive associations reported previously in the IWHS.[13] Several studies have implicated high consumption of processed meats,[22,23] which usually contain nitrite and/or nitrate salts as preservatives, as a kidney cancer risk factor.

With 12 additional years of follow-up, we conducted an updated analysis of kidney cancer in the IWHS to evaluate exposure to both nitrate and DBP in public water supplies in relation to kidney cancer risk. We also evaluated dietary nitrate and nitrite and factors that may inhibit or promote *N*-nitroso compound formation, including vitamins C and E and cigarette smoking.

METHODS

Study Population and Design

In 1986, the IWHS randomly selected a total of 98,030 women 55–69 years old from Iowa driver's license records; 41,836 (42%) completed the baseline survey on demographics, anthropometry, diet, physical activity, reproductive and medical histories, tobacco and alcohol consumption, and family history of cancer.[24] Five follow-up surveys have since been administered (1987,1989,1992,1997,2004). In 1989 (N=36,127;87% response), women reported the primary source of drinking water at their home (municipal water system; rural water system; private well; bottled water; other; don't know) and the duration using this source (<1;1–5;6–10;11–20;>20 years; don't know). Most (77%) had a municipal or rural water source (hereafter public water supply), and 19% a private well. Women reporting bottled water or other sources (<5%) were considered unlikely to have nitrate exposures through these sources and were excluded from drinking water analyses. The 1989 follow-up participants were demographically similar to the full cohort (data not shown).

We identified vital status through linkage with the National Death Index and incident kidney cancers diagnosed between January 1, 1986 and December 31, 2010 from the State Health Registry of Iowa. We calculated person-time from the enrollment date until the earliest of the dates of kidney cancer diagnosis, death, or December 31, 2010. For women who

emigrated out of Iowa (<0.5% annually), or died out-of-state (0.5% of all deaths), we censored participants at the midpoint between the date of last contact and the date the subject was located outside Iowa or their death, respectively. The IWHS and current analyses were approved by the Institutional Review Boards of the University of Iowa and the University of Minnesota. The current analyses were also approved by the Office of Human Subjects Research at the National Cancer Institute.

Drinking water exposure assessment

We obtained historical measurements (1955–1988)[25] of nitrate-nitrogen (mg/L NO_3-N) for finished water samples from Iowa public water utilities. Monitoring of nitrate was not required annually before 1993,[26] and utility-specific data ranged from periodic samples every several years to multiple samples per year. We also had limited DBP data prior to the promulgation of the THM Rule in the 1980s. We estimated historical DBP levels via expert assessment, using available measurements (including data from plants before they made changes to comply with the Rule) and other information such as water source, quality, treatment, and disinfectant type, accounting for changes in source water or treatment/disinfection processes over time.[27] Estimated DBP included total THM and two of the four specific THM (chloroform, bromodichloromethane), the sum of five haloacetic acids (HAA5: monochloroacetic, trichloroacetic, dichloroacetic, monobromoacetic, and dibromoacetic acids), and HAA6 (the sum of HAA5 and the unregulated species bromochloroacetic acid).[26] The majority (86%) of women reported using their drinking water source for >10 years; we limited our drinking water evaluation to this subgroup. In contrast to analyses by Weyer et al.[13] that used the 33-year average nitrate level for each city, we accounted for each woman's duration at her public water supply. Because duration was reported in categories, we estimated the medians within categories of 11–20 years and >20 years as 16 and 40 years, respectively, based on data from female general population controls in an Iowa case-control study with complete water source histories.[28] We computed 16- and 40-year averages (from 1989, when water source and duration were collected) of annual mean NO_3-N and individual DBP levels, and the number of years within these periods when annual means of NO_3-N, total THM, and HAA5 exceeded one-half the maximum contaminant level (>½-MCL;5mg/L,40μg/L, and 30μg/L, respectively). Since we lacked annual NO_3-N measurements for all public water supplies, nitrate exposure metrics reflect a variable number of years of data (range=1–28 years; median=8). We also examined whether a public water supply was served from a ground or surface water source, the latter which may reflect elevated DBP concentrations, and whether disinfection was by chloramination, a method that may produce the carcinogenic nitrosamine *N*-nitrosodimethylamine.[29,30] Supplemental details of the exposure assessment are published.[31,32]

Dietary Assessment

Usual intake of food items and dietary supplements over the prior 12 months[33] was assessed at enrollment via a semi-quantitative food frequency questionnaire (FFQ) previously validated in the IWHS.[34] We identified the nitrate and nitrite contents of foods from published U.S. and Canadian studies[35,36] and computed food-specific nitrate and nitrite means weighted by the number of samples analyzed in each study. To assign a nitrate and

nitrite level to the FFQ line items, we weighted food-specific values by female-specific intakes from the 1994–1996 Continuing Survey of Food Intake by Individuals, accounting for variation in nitrate levels by food preparation method (e.g., raw, cooked, canned).[37] A similar approach to estimate nitrate and nitrite levels from a FFQ found good correlations with 24 hour-based recalls for women.[38] For each participant, we estimated dietary nitrate and nitrite overall and separately for intakes from plant, animal, and processed meat (e.g., sausage, salami, bologna; bacon; and hot dogs) sources. We multiplied the frequency of consumption of vitamin C-containing foods and dietary supplements by their vitamin C levels to generate total intake, and similarly estimated intake of vitamin E, another antioxidant and potential inhibitor of endogenous nitrosation.

Statistical Analysis

Of 41,836 enrolled women, we excluded those with a cancer or chemotherapy history (N=3,830), who had illogical or extreme dietary intakes (<600 or >5000 kcal/day) or missing responses to >30 dietary questions (n=2,751), or who were not menopausal (N=547), for consistency with the cohort's target population of postmenopausal women and with the previous drinking water evaluation by Weyer et al.[13] This left 34,708 women available for dietary analyses. For drinking water analyses, we additionally excluded women who did not participate in the 1989 survey or were missing water source duration, were using a public water supply with <75% of the exposure period served by a single source, or were lacking measurement data for both nitrate and DBP in their public water supply (N=10,247). Women with <10 years at their water source (N=2,879) were excluded, leaving 15,910 on public water supplies and 5,035 on private wells (eTable 1). Lastly, we excluded women missing covariate data, retaining 33,964 in dietary analyses and 15,577 and 4,930 for analyses of public and private water supplies, respectively.

We computed Spearman rank correlations to describe relationships between water contaminants. We created quartile-based average NO_3-N and DBP exposure categories and compared participant characteristics across NO_3-N and total THM (the most abundant DBP class) levels and private well use. For multivariable analyses, we further split NO_3-N at the 95th percentile; this value corresponded to ½-MCL (>5 mg/L). Case numbers were too small to allow a 95th percentile split for all individual DBP. We estimated hazard ratios (HR) and 95% confidence intervals (95% CI) with Cox regression, using the lowest quartile (Q1) as the referent group. We divided the number of years of exposure >½-MCL at the median and compared to those with no years of exposure at this level. Without measurements for private wells, we compared women on private well water to women with low (Q1) average nitrate in the public water supply. We similarly estimated associations with dietary nitrate and nitrite, for total intakes and separately for those from plant, animal, and processed meat sources. Non-parametric analyses did not indicate non-linear associations, so we present natural log-transformed (ln-transformed) results for continuous models in addition to categorical analyses.

We evaluated potential confounders from baseline data, including sociodemographic (e.g., age, education), health (e.g., hypertension, obesity), and lifestyle characteristics (e.g., smoking, physical activity), reproductive history (e.g., parity, estrogen use), and family

history of cancer, for model inclusion based on a ≥10% change in the exposure parameter estimate. Smoking status (never, former, current smoker) was reported at enrollment and in three follow-up surveys; results were similar regardless of which was used for adjustment. A hypertension diagnosis was positively associated with risk, as in the full cohort,[39] but was not strongly correlated with nitrate in drinking water and diet (ρ=0.20–0.22). Final drinking water nitrate models (Model 1) were adjusted for age, the most recent available smoking status, pack-years of smoking (0,≤1–19, 20–39, ≥40), and body mass index (BMI), and were further adjusted by continuous total THM concentration (Model 2). Dietary models were adjusted for smoking, age, BMI, and total calorie intake (Model 1), and were mutually adjusted for continuous dietary nitrate or nitrite intakes (Model 2).

We tested for linear trend in categorical exposures using continuous variables derived from the median of each category. We used stratified analyses with common referent groups assumed to have the lowest risk of endogenous nitrosation to assess nitrate interactions, including with smoking (common referent Q1 and non-smokers) and vitamins C and E (common referent Q1 and ≥median of the vitamin). We also evaluated DBP interactions with NO_3-N and smoking. We used likelihood ratio tests to compare fit between models with and without product interaction terms of the exposure and modifier and to derive global interaction p-values.

We used sensitivity analyses to evaluate the consistency of our results, such as by excluding cities contributing the top 10% of person-time or exposure levels to the analyses. We also repeated analyses restricting to women with >20 years at their water source and whose long-term NO_3-N exposure estimates were based on ≥8 years (≥median) of annual measurements, and to renal cell carcinomas only (90% of cases). We conducted all analyses in SAS v.9.3 (Cary, NC) with p≤0.05 the threshold for statistical significance.

RESULTS

We observed 266 kidney cancers over an average of 21 years (median=25) of follow-up. Among women >10 years at their water source, there were 125 cases on PWS and 38 cases on a private well. The percentile distribution of drinking water contaminants among women on PWS is shown in eTable 2. We observed few substantive differences in follow-up, lifestyle, and medical history characteristics across quartiles of NO_3-N or total THM (Table 1). However, smoking status varied across total THM quartiles, and surface water and chloramination percentages varied across levels of both contaminants. Public water supply and private well users also differed; the latter were less likely to smoke, consumed more calories and red meat, had lower vitamin C intakes, and higher BMIs. Approximately 5% of women on public water supplies lived on farms or in non-farm rural areas, versus 91% on private wells. Average NO_3-N was only moderately correlated with total THM (ρ=0.24) and uncorrelated with HAA5 (ρ=0.06). Individual THMs chloroform and bromodichloromethane were strongly correlated (ρ=0.95), as were individual haloacetic acids (trichloroacetic, dichloroacetic, and bromochloroacetic acid; ρ=0.71–0.82).

Women in the 95th percentile of average public water supply nitrate had higher risks of kidney cancer compared to those in Q1, but we observed no trend with increasing levels

(Model 1 $HR_{p95vsQ1}$=2.3,95%CI:1.2–4.3;p_{trend}=0.33;Table 2). Total THM adjustment had little impact on these associations (Model 2). The association with >5 mg/L NO_3-N remained in sensitivity analyses of women at their water source for >20 years and whom had exposures estimated based on ≥8 years of data; approximately 55% of women from 147 cities (Model 2 $HR_{p95vsQ1}$=3.6,95%CI:1.3–10.5;p_{trend}=0.17). It also held when we excluded women from the city with the largest person-time contribution to the analysis (N=1,340), or with the highest average NO_3-N exposure (25.3mg/L;N=17;data not shown). Associations with continuous nitrate levels showed an imprecisely measured elevation (Model 2 HR=1.1,95%CI:0.97–1.3;Table 2). Risks were higher among women exposed to 1–4 years (Model 2 HR=1.6,95%CI:0.99–2.4) or ≥4 years (range 4–36) >½-MCL NO_3-N (HR=1.5,95%CI:0.97,2.4) compared to women with zero years of exposure, and there was no trend (p=0.09). We observed no association among private well users compared to women on public water supplies with low (Q1) nitrate (HR=0.96,95%CI:0.59–1.58).

We found no associations between long-term average total THM or HAA5 and kidney cancer risk (Table 2). Similarly, we found no associations between HAA6 (data not shown) or individual THMs or HAAs and kidney cancer (eTable 3). Further adjustment for nitrate (Model 2) did not substantively change these results. We found no association with the number of years >½-MCL for total THM or HAA5 (Table 2). Using a public water supply with surface water sources or that disinfected by chloramination was also not associated with kidney cancer (data not shown).

We found no evidence for multiplicative interaction between drinking water nitrate or total THM and vitamins C or E on risk of kidney cancer. Models stratified by smoking status were imprecise, but likewise did not show interactions between smoking and either nitrate or total THM. We also found no interactions for women on private wells (data not shown).

Dietary nitrate intakes came almost exclusively from plants, thus we present results only for total nitrate, whereas nitrite came from plant, animal, and processed meat sources.[31] We observed no association between dietary nitrate intake and kidney cancer risk, or for dietary nitrite overall (Table 3). However, a higher risk was evident for the 95th percentile of dietary nitrite from processed meats ($HR_{p95vs.Q1}$=1.8,95%CI:1.1–3.0;p_{trend}=0.54). Red meat consumption was not associated with kidney cancer, and we observed no modification of dietary associations by vitamin C or E intake or smoking (data not shown).

DISCUSSION

We found a higher risk of kidney cancer among postmenopausal Iowa women with >5mg/L average nitrate levels in their public drinking water. Use of water with lower average NO_3-N concentrations was not positively associated with risk, and the pattern of associations lacked monotonic trend. Total THM adjustment did not substantially change risk estimates, and no individual DBP were associated with kidney cancer. Our analyses also indicated greater relative risk associated with high nitrite intakes from processed meat. Factors shown to influence intragastric *N*-nitroso compound formation -- vitamins C and E and cigarette smoking -- did not modify kidney cancer risk associated with nitrate from either drinking water or diet.

This study extends a prior analysis of 55 renal cancer cases conducted in the IWHS[13] that found imprecise associations in the top three quartiles of 33-year averaged drinking water nitrate. With improved exposure assessment that accounted for duration and DBP co-exposures, we found associations with relatively high average NO_3-N and that risk was marginally higher for any duration of exposure to levels >½-MCL. While our average and ½-MCL nitrate metrics were correlated (ρ=0.74), only 32% of women were classified into high exposure categories by both metrics. Results held among women with >20 years at their public water supply, somewhat expected as they comprised 87% of the group. Restriction to renal cell carcinoma or exclusion of participants contributing high exposure levels or proportions of person-time also yielded similar results. Few studies are available for comparison with our findings. A German study found an elevated rate ratio for renal cell carcinoma among women exposed to higher levels of nitrate (60 mg/L as NO_3, equivalent to 13.6 mg/L as NO_3-N).[11] A population-based case-control study in Iowa reported associations with long duration of use of a public water supply with >5 mg/L NO_3-N among subgroups with low vitamin C and high red meat intakes, who would be expected to have greater potential for endogenous nitrosation.[12]

Global indicators of toxicity have been applied as drinking water exposures in epidemiologic investigations,[40] as in a Finnish case-control study that reported associations between water mutagenicity (based on historical water quality and treatment information) and kidney cancer risk in men, but not among women.[17] However, apart from previous efforts in the IWHS, no analytic studies have evaluated specific disinfection by-products and renal cancer risk. Chlorinated DBP were of *a priori* interest because chloroform causes renal tumors in rats and mice and is a possible human carcinogen,[16] although this may only be a high-dose phenomenon.[14] Unregulated chlorinated DBP,[15] such as furanones, are renal carcinogens in rats;[15,41] public water supplies high in total THM may also have higher levels of such other chlorinated byproducts. Additionally, bromide reactions with ozone can form bromate, and bromide and organic matter reactions with chlorine can form brominated and mixed chloro-bromo by-products, such as bromodichloromethane and bromochloroacetic acid, all of which are renal carcinogens in animals.[15] Natural bromide sources such as salt water intrusion or bromide dissolution from rocks are not prevalent in Iowa,[42] and ozonation was not historically used for disinfection.[26] We observed no relationship between kidney cancer and average concentration of any DBP examined. Average total THM exposures (median=4.6μg/L, IQR=0.9–14.3) were generally below the MCL and were mostly all below 40μg/L, the level at or above which associations with other cancer sites, such as bladder, have been observed.[43] There were also no relationships with years >½-MCL of total THM or HAA5, but fewer than 10% of cases were ever exposed at these levels. Over 90% of participants had chloroform exposures below the maximum contaminant level goal (MCLG) of 70μg/L, at which there is no expected health risk to sensitive populations,[44] and only 6% were exposed above the MCL (80μg/L). A prior IWHS analysis also found no association for renal cell cancer and chloroform measured during a 1986–1987 sampling campaign, nor with public water supplies sourced by surface waters, a crude surrogate for the presence of DBP.[18] However, we acknowledge that nitrate associations in our study could reflect unmeasured DBP or other contaminants more highly correlated with nitrate than total THM.[15]

We found a positive association with estimated nitrite intakes from processed meats, consistent with other published studies. An exogenous source of *N*-nitroso compounds in U.S. diets is processed meats,[7] which are classified as a Group 1 human carcinogen based on evidence for colorectal cancer.[20] The large, prospective NIH-AARP cohort reported higher risks of renal cell carcinoma associated with high meat-derived nitrate and nitrite intakes[22] and with processed red meat consumption.[21] An older meta-analysis of case-control studies identified a higher pooled risk estimate for renal cancer with intakes of all meat, red meat, and processed meat.[23] Associations in our data were limited to those with nitrite intakes from processed meats, not with nitrite from animal sources overall or with red meat intake specifically. A European cohort reported a processed meat-renal cell carcinoma association in pre-menopausal, but not in post-menopausal, women.[45] Both animal and human studies suggest such meat-related associations may be driven by nitrate and/or nitrite. Simultaneous intake of sodium nitrite and fish meal (an amine source) induces renal epithelial tumors in rats.[46] Human feeding studies have characterized how oral bacteria reduce ingested nitrate to nitrite, which reacts in the stomach with available amines sources to form *N*-nitroso compounds[7,46] that can ultimately be absorbed into the bloodstream and filtered through the kidneys.

We evaluated vitamins C and E as modifiers of the relationship between nitrate ingestion and kidney cancer risk based on evidence that these antioxidants can inhibit intragastric *N*-nitroso compound formation.[7,9] We found no evidence of a vitamin C interaction with nitrate in drinking water, in contrast to the aforementioned case-control study in Iowa.[12] Our dietary analyses also found no such interaction. Another prospective study similarly found no effect of vitamin C intakes on the association between dietary nitrite and risk of renal cell carcinoma,[22] and an analysis of meat intake and renal cell carcinoma did not evaluate effect modification by vitamin C.[21] The lack of interaction is supported by at least one animal study demonstrating that vitamin C's ability to protect against tumor formation, observed at other sites, is incomplete in the kidney.[48] Inhibition of endogenous nitrosation by vitamin E was suggested in an older case-control study of gastric cancer in Sweden and is inconsistently shown in animals,[7] but we found no evidence for this interaction in our data.

This study represents to our knowledge the only evaluation of kidney cancer in relation to both drinking water nitrate and DBP exposures in a cohort, and the IWHS is a residentially stable study population with historical water quality data. We lacked information on drinking water and other fluid intake, but restricted drinking water analyses to women with long duration at their water source and addressed variability in the nitrate sampling frequency across public water supplies with sensitivity analyses that supported our main findings. We had little DBP data prior to their initial regulation, but estimates were based on expert assessment with available measurement data and known treatment/disinfection characteristics of the public water supplies. We had no quantitative exposures for women on private wells or information to predict their nitrate levels, such as well depth.[48] We acknowledge possible misclassification of dietary exposures arising from use of a food frequency questionnaire. We also note potential etiologic heterogeneity for different renal cancer cell types; however, the small number of cases of types other than renal cell carcinoma precluded examining them separately. The generalizability of our drinking water

findings may be limited to other agriculturally-intensive areas or to public water supplies with similar DBP or precursors.

Conclusion

Our results suggest that ingesting nitrate at high levels from drinking water is associated with increased kidney cancer risk. A relationship with average nitrate levels >5 mg/L in public water supplies was not explained by the co-occurrence of DBP, which were not associated with kidney cancer at levels observed in this population. These results add to a limited literature of the association between drinking water contaminants and kidney cancer. We also observed higher intakes of nitrite-processed meats as a renal cancer risk factor, consistent with findings from other studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. American Cancer Society. Cancer Facts and Figures 2016. American Cancer Society; Atlanta, Ga: 2016.
2. McLaughlin, JK., Lipworth, L., Tarone, RE., Blot, WJ. Renal cancer. In: Schottenfeld, DF., JF, editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 2006. p. 1087-1100.
3. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol. 2010; 7(5):245–57. [PubMed: 20448658]
4. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. Cancer J. 2008; 14(5): 288–301. [PubMed: 18836333]
5. Nolan BT, Stoner JD. Nutrients in groundwaters of the conterminous United States, 1992–1995. Environ Sci Technol. 2000; 34:1156–1165.
6. Ward MH. Too much of a good thing? Nitrate from nitrogen fertilizers and cancer. Rev Environ Health. 2009; 24(4):357–63. [PubMed: 20384045]
7. IARC. IARC Monographs on the Evaluation of Carcionogenic Risks to Humans. Vol. 94. Lyon: 2010. Ingested Nitrate and Nitrite and Cyanobacterial Peptide Toxins.
8. National Toxicology Program (NTP). Report on Carcinogens, Thirteenth Edition. U.S. Department of Health and Human Services, Public Health Service; 2014.
9. Mirvish SS. Effects of vitamins C and E on N-nitroso compound formation, carcinogenesis, and cancer. Cancer. 1986; 58(8 Suppl):1842–50. [PubMed: 3756808]
10. Gulis G, Czompolyova M, Cerhan JR. An ecologic study of nitrate in municipal drinking water and cancer incidence in Trnava District, Slovakia. Environ Res. 2002; 88(3):182–7. [PubMed: 12051796]
11. Volkmer BG, Ernst B, Simon J, Kuefer R, Bartsch G Jr, Bach D, Gschwend JE. Influence of nitrate levels in drinking water on urological malignancies: a community-based cohort study. BJU Int. 2005; 95(7):972–6. [PubMed: 15839916]

12. Ward MH, Rusiecki JA, Lynch CF, Cantor KP. Nitrate in public water supplies and the risk of renal cell carcinoma. Cancer Causes Control. 2007; 18(10):1141–51. [PubMed: 17717631]
13. Weyer PJ, Cerhan JR, Kross BC, Hallberg GR, Kantamneni J, Breuer G, Jones MP, Zheng W, Lynch CF. Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study. Epidemiology. 2001; 12(3):327–38. [PubMed: 11338313]
14. U.S. Environmental Protection Agency (EPA). National Primary Drinking Water Regulations: Stage 2 Disinfectants and Disinfection Byproducts Rule. 2006; 71
15. Richardson SD, Plewa MJ, Wagner ED, Schoeny R, Demarini DM. Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: a review and roadmap for research. Mutat Res. 2007; 636(1–3):178–242. [PubMed: 17980649]
16. IARC. IARC Monographs on the Evaluation of Carcionogenic Risks to Humans. Vol. 73. Lyon; 1999. Some Chemicals the Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances.
17. Koivusalo M, Hakulinen T, Vartiainen T, Pukkala E, Jaakkola JJ, Tuomisto J. Drinking water mutagenicity and urinary tract cancers: a population-based case-control study in Finland. Am J Epidemiol. 1998; 148(7):704–12. [PubMed: 9778177]
18. Doyle TJ, Zheng W, Cerhan JR, Hong CP, Sellers TA, Kushi LH, Folsom AR. The association of drinking water source and chlorination by-products with cancer incidence among postmenopausal women in Iowa: a prospective cohort study. Am J Public Health. 1997; 87(7):1168–76. [PubMed: 9240108]
19. Hord NG, Tang Y, Bryan NS. Food sources of nitrates and nitrites: the physiologic context for potential health benefits. Am J Clin Nutr. 2009; 90(1):1–10. [PubMed: 19439460]
20. IARC. IARC Monographs on the Evaluation of Carcionogenic Risks to Humans. Vol. 114. Lyon; 2015. Red Meat and Processed Meat.
21. Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: meta-analysis of case-control studies. Cancer Causes Control. 2007; 18(2): 125–33. [PubMed: 17242980]
22. Daniel CR, Cross AJ, Graubard BI, Park Y, Ward MH, Rothman N, Hollenbeck AR, Chow WH, Sinha R. Large prospective investigation of meat intake, related mutagens, and risk of renal cell carcinoma. Am J Clin Nutr. 2012; 95(1):155–62. [PubMed: 22170360]
23. Dellavalle CT, Daniel CR, Aschebrook-Kilfoy B, Hollenbeck AR, Cross AJ, Sinha R, Ward MH. Dietary intake of nitrate and nitrite and risk of renal cell carcinoma in the NIH-AARP Diet and Health Study. Br J Cancer. 2013; 108(1):205–12. [PubMed: 23169285]
24. Folsom AR, Zhang S, Sellers TA, Zheng W, Kushi LH, Cerhan JR. Cancer incidence among women living on farms: findings from the Iowa Women's Health Study. J Occup Environ Med. 1996; 38(11):1171–6. [PubMed: 8941908]
25. CHEEC. Historical community water supply and treatment data for the State of Iowa. 6. Center for Health Effects of Environmental Contamination, University of Iowa; Iowa City, IA: 2013.
26. U.S. Environmental Protection Agency (EPA). National Primary Drinking Water Regulations: Final Rule. Fed Register. 1991; 56:3526–3597.
27. Amy, G., Graziano, N., Craun, G., Krasner, S., Cantor, KP., Hildesheim, M., Weyer, PJ., King, W. Improved Exposure Assessment on Existing Cancer Studies. AWWA Research Foundation; Denver, CO: 2005.
28. Cantor KP, Lynch CF, Hildesheim ME, Dosemeci M, Lubin J, Alavanja M, Craun G. Drinking water source and chlorination byproducts. I. Risk of bladder cancer. Epidemiology. 1998; 9(1):21–8. [PubMed: 9430264]
29. Krasner SW, Mitch WA, McCurry DL, Hanigan D, Westerhoff P. Formation, precursors, control, and occurrence of nitrosamines in drinking water: a review. Water Res. 2013; 47(13):4433–50. [PubMed: 23764594]
30. Mitch WA, Sharp JO, Rhoades Trussell R, Valentine RL, Alvarez-Cohen L, DSedlak DL. *N*-Nitrosodimethylamine (NDMA) as a Drinking Water Contaminant: A Review. Environmental Engineering Science. 2003; 20(5):389–404.

31. Jones RR, Weyer PJ, Dellavalle CT, Inoue-Choi M, Anderson KE, Cantor KP, Krasner S, Robien K, Beane Freeman LE, Silverman DT, Ward MH. Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. Environ Health Perspect. In press.
32. Inoue-Choi M, Jones RR, Anderson KE, Cantor KP, Cerhan JR, Krasner S, Robien K, Weyer PJ, Ward MH. Nitrate and nitrite ingestion and risk of ovarian cancer among postmenopausal women in Iowa. Int J Cancer. 2015; 137(1):173–82. [PubMed: 25430487]
33. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol. 1988; 127(1):188–99. [PubMed: 3337073]
34. Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am J Epidemiol. 1992; 136(2):192–200. [PubMed: 1415141]
35. Ward MH, Cantor KP, Riley D, Merkle S, Lynch CF. Nitrate in public water supplies and risk of bladder cancer. Epidemiology. 2003; 14(2):183–90. [PubMed: 12606884]
36. Ward MH, Cerhan JR, Colt JS, Hartge P. Risk of non-Hodgkin lymphoma and nitrate and nitrite from drinking water and diet. Epidemiology. 2006; 17(4):375–82. [PubMed: 16699473]
37. Subar AF, Midthune D, Kulldorff M, Brown CC, Thompson FE, Kipnis V, Schatzkin A. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. Am J Epidemiol. 2000; 152(3):279–86. [PubMed: 10933275]
38. Inoue-Choi M, Virk-Baker MK, Aschebrook-Kilfoy B, Cross AJ, Subar AF, Thompson FE, Sinha R, Ward MH. Development and calibration of a dietary nitrate and nitrite database in the NIH-AARP Diet and Health Study. Public Health Nutr. 2015:1–10.
39. Prineas RJ, Folsom AR, Zhang ZM, Sellers TA, Potter J. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. Epidemiology. 1997; 8(1):31–6. [PubMed: 9116091]
40. Villanueva CM, Kogevinas M, Cordier S, Templeton MR, Vermeulen R, Nuckols JR, Nieuwenhuijsen MJ, Levallois P. Assessing exposure and health consequences of chemicals in drinking water: current state of knowledge and research needs. Environ Health Perspect. 2014; 122(3):213–21. [PubMed: 24380896]
41. Komulainen H. Experimental cancer studies of chlorinated by-products. Toxicology. 2004; 198(1–3):239–48. [PubMed: 15138047]
42. Davis SN, Fabryka-Martin JT, Wolfsberg LE. Variations of Bromide in Potable Ground Water in the United States. Ground Water. 42(6):902–909. 20014.
43. Costet N, Villanueva CM, Jaakkola JJ, Kogevinas M, Cantor KP, King WD, Lynch CF, Nieuwenhuijsen MJ, Cordier S. Water disinfection by-products and bladder cancer: is there a European specificity? A pooled and meta-analysis of European case-control studies. Occup Environ Med. 2011; 68(5):379–85. [PubMed: 21389011]
44. EPA. [Accessed May 10, 2016] How EPA Regulates Drinking Water Contaminants. https://www.epa.gov/dwregdev/how-epa-regulates-drinking-water-contaminants
45. Rohrmann S, Linseisen J, Overvad K, Lund Wurtz AM, Roswall N, Tjonneland A, Boutron-Ruault MC, Racine A, Bastide N, Palli D, Agnoli C, Panico S, Tumino R, Sacerdote C, Weikert S, Steffen A, Kuhn T, Li K, Khaw KT, Wareham NJ, Bradbury KE, Peppa E, Trichopoulou A, Trichopoulos D, Bueno-de-Mesquita HB, Peeters PH, Hjartaker A, Skeie G, Weiderpass E, Jakszyn P, Dorronsoro M, Barricarte A, Santiuste de Pablos C, Molina-Montes E, de la Torre RA, Ericson U, Sonestedt E, Johansson M, Ljungberg B, Freisling H, Romieu I, Cross AJ, Vergnaud AC, Riboli E, Boeing H. Meat and fish consumption and the risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. Int J Cancer. 2015; 136(5):E423–31. [PubMed: 25258006]
46. Furukawa F, Nishikawa A, Ishiwata H, Takahashi M, Hayashi Y, Hirose M. Renal carcinogenicity of concurrently administered fish meal and sodium nitrite in F344 rats. Jpn J Cancer Res. 2000; 91(2):139–47. [PubMed: 10761700]
47. Vermeer IT, Pachen DM, Dallinga JW, Kleinjans JC, van Maanen JM. Volatile N-nitrosamine formation after intake of nitrate at the ADI level in combination with an amine-rich diet. Environ Health Perspect. 1998; 106(8):459–63.

48. Chan WC, Fong YY. Ascorbic acid prevents liver tumour production by aminopyrine and nitrite in the rat. Int J Cancer. 1977; 20:268–270. [PubMed: 892935]

49. Wheeler DC, Nolan BT, Flory AR, Dellavalle CT, Ward MH. Modeling groundwater nitrate concentrations in private wells in Iowa. Sci Total Environ. 2015; 536:481–488. [PubMed: 26232757]

Table 1

Characteristics of Iowa Women's Health Study participants with >10 years at their drinking water source, by private well use and nitrate-nitrogen (NO_3-N) and total trihalomethanes (total THM) concentrations in public water supplies (PWS)

	Private wells (N=4,930)	Public water supplies (N=15,577)							
		Mean[a] NO_3-N (mg/L)				Mean[a] total THM (μg/L)			
Characteristic		**<0.47**	**0.47–1.07**	**1.08–2.97**	**>2.97**	**<0.90**	**0.90–4.59**	**4.59–14.31**	**>14.31**
Mean length of follow-up, years	21	21	21	21	21	21	21	21	21
Mean age at baseline, years	61	62	62	62	62	62	62	62	62
Surface water as source for PWS, %	NA	5.3	28	16	46	0	6.0	32	61
PWS chloraminated, %	NA	18	38	38	7.4	2.9	14	32	58
Total caloric intake, kcal/day (median)	1830	1697	1682	1693	1685	1705	1698	1668	1682
Vitamin C in diet, mg/day (median)[b]	99.8	108	112	108	113	106	108	113	114
Vitamin E in diet, mg/day (median)[b]	4.7	5.0	5.1	5.0	5.1	4.8	5.0	5.1	5.2
Red meat intake, g/day (median)[b]	53	44	44	44	42	45	44	42	43
Nitrate in diet, mg/day (median)[b]	59	61	61	62	62	59	61	63	63
Nitrite in diet, mg/day (median)[b]	0.66	0.64	0.64	0.65	0.65	0.65	0.64	0.65	0.65
Alcohol intake, g/day (median)[e]	2.5	3.4	3.3	4.3	3.6	3.3	3.4	4.2	3.6
Smoking status[c], %									
Never	79	63	62	60	63	66	63	60	59
Former	17	29	30	32	29	27	29	32	32
Current	4.5	8.2	8.3	8.2	8.2	7.8	7.9	8.4	8.7
Pack-years of smoking[d], %									
1–19	45	41	42	38	39	41	40	39	40
20–39	34	33	34	35	34	33	35	34	35
≥40	21	26	25	27	27	26	26	28	25
Residence, %									
Farm or non-farm rural area	91	4.9	5.5	3.6.	5.5	7.4	4.3	3.3	4.5
Towns ≥1000 residents	9.0	95	95	96	95	93	96	97	96
BMI (kg/m^2), %									
<25	36	41	43	43	42	41	42	42	43

	Private wells (N=4,930)	Public water supplies (N=15,577)						
		Mean[a] NO_3-N (mg/L)				Mean[a] total THM (μg/L)		
Characteristic		**<0.47**	**0.47–1.07**	**1.08–2.97**	**>2.97**	**<0.90**	**0.90–4.59**	**4.59–14.31**	**>14.31**
25–29.9	38	37	36	36	37	37	36	37	36
≥30	26	22	21	21	22	22	22	21	21
Hypertension diagnosis, %	36	38	37	37	36	37	38	37	38
Physical activity level, low %	48	47	47	48	47	46	48	47	47
Education, %									
Less than high school	9.9	6.8	6.1	6.6	5.4	7.0	6.2	5.6	5.6
High school	52	53	52	54	49	53	52	51	53
More than high school	38	40	42	40	45	40	42	43	42
Number of live births, %									
Nulliparous	6.6	11	9.2	11	9.6	8.5	10	12	9.6
1–2	28	32	34	35	35	32	32	35	36
3–4	42	39	40	39	40	41	40	37	39
≥5	24	19	17	16	15	18	17	16	16

NA indicates not applicable.

[a]Exposure assigned to individuals based on their reported duration at drinking water source.

[b]Adjusted for 1,000 kcal per day of total energy intake.

[c]Determined based on most recent follow-up participation; otherwise from baseline report.

[d]Among current or former smokers at baseline.

[e]Among those reporting > 0 g/day of intake.

Table 2

Hazard ratios (HR) and 95% confidence intervals (CI) for kidney cancer associations with drinking water nitrate-nitrogen (NO_3-N) and total trihalomethanes (total THM) and sum of five haloacetic acids (HAA5) in public supplies among Iowa Women's Health Study participants >10 years at their drinking water source

			Model 1[a]		Model 2[b]	
	Cases	**N**	**HR**	**95% CI**	**HR**	**95% CI**
NO_3-N (mg/L)						
<0.47	29	3,973	1.0	Ref.	1.0	Ref.
0.47–1.07	27	3,853	0.98	0.58–1.7	1.0	0.61–1.7
1.08–2.97	39	4,130	1.3	0.81–2.1	1.4	0.85–2.3
2.97–5.00	15	2,727	0.76	0.41–1.4	0.80	0.43–1.5
>5.00[c]	15	894	2.3	1.2–4.3	2.2	1.2–4.2
p_{trend}			0.33		0.35	
Continuous[d]	125	15,577	1.3	0.96–1.3	1.1	0.97–1.3
Years >5 mg/L NO_3-N[e]						
0	76	10,947	1.0	Ref.	1.0	Ref.
< 4	25	2,295	1.6	1.0–2.5	1.6	0.99–2.4
≥ 4	24	2,335	1.5	0.93–2.3	1.5	0.97–2.4
p_{trend}			0.13		0.09	
Continuous	125	15,577	1.0	0.96–1.1	1.0	0.97–1.10
Total THM (µg/L)						
<0.90	34	3,752	1.00	Ref.	1.0	Ref.
0.90–4.58	34	4,308	0.89	0.55–1.4	0.87	0.54–1.4
4.59–14.30	35	4,139	0.95	0.59–1.5	0.84	0.51–1.4
>14.30	22	3,378	0.74	0.43–1.3	0.70	0.41–1.2
p_{trend}			0.29		0.26	
Continuous	125	15,577	0.95	0.90–1.0	0.95	0.90–1.0
Years >40 µg/L total THM[e]						
0	97	11,804	1.00	Ref.	1.0	Ref.
< 36	15	1,683	1.1	0.63–1.9	1.1	0.62–1.8

			Model 1[a]		Model 2[b]	
	Cases	**N**	**HR**	**95% CI**	**HR**	**95% CI**
≥ 36	13	2,090	0.76	0.43–1.4	0.76	0.43–1.4
p_{trend}			0.34		0.35	
Continuous	125	15,577	0.99	0.97–1.0	0.99	0.97–1.0
HAA5 (µg/L)						
<1.89	38	3,882	1.00	Ref.	1.00	Ref.
1.89–3.48	27	3,197	0.87	0.53–1.4	0.84	0.51–1.4
3.49–6.43	35	4,581	0.81	0.51–1.3	0.78	0.49–1.2
>6.43	25	3,917	0.66	0.40–1.1	0.65	0.39–1.1
p_{trend}			0.17		0.18	
Continuous	125	15,577	0.99	0.98–1.00	0.99	0.98–1.0
Years >30 µg/L HAA5[e]						
0	109	13,016	1.0	Ref.	1.0	Ref.
< 16	8	1,275	0.75	0.37–1.5	0.76	0.37–1.6
≥ 16	8	1,286	0.74	0.36–1.5	0.74	0.36–1.5
p_{trend}			0.32		0.32	
Continuous	125	15,577	0.99	0.95–1.0	0.99	0.95–1.0

[a] Adjusted for age, smoking status (current/former/never), pack-years of smoking, and body mass index.

[b] NO_3-N models are adjusted for ln-transformed total THM concentrations, and total THM and HAA5 models are adjusted for ln-transformed NO_3-N.

[c] 95th percentile of exposure.

[d] HR per 1 mg/L increase in the ln-transformed value.

[e] Number of years the annual average level was >½ the MCL value.

Table 3

Hazard ratios (HR) and 95% confidence intervals (CI) for kidney cancer associations with dietary nitrate and nitrite in the Iowa Women's Health Study (N=33,964[a])

	Cases	N	HR[b]	95% CI
Dietary nitrate (mg NO_3-N/day[c])				
All sources				
<16.2	67	8,467	1.0	Ref
16.2–23.90	65	8,489	0.96	0.68–1.4
23.91–34.27	66	8,506	0.95	0.67–1.4
34.28–58.64	43	6,803	0.78	0.51–1.2
>58.6[d]	15	1,699	1.1	0.59–2.00
p_{trend}			0.49	
Continuous		33,964	0.92	0.72–1.2
Dietary Nitrite (mg/day)				
All sources				
<0.86	57	8,450	1.0	Ref
0.86–1.12	68	8,514	1.3	0.87–1.9
1.13–1.43	69	8,487	1.4	0.89–2.3
1.44–2.06	49	1,704	1.4	0.77–2.5
>2.06	13	6,809	1.6	0.70–3.8
p_{trend}			0.80	
Continuous		33,964	1.1	0.62–2.1
Plant nitrite (mg/day)				
<0.51	68	8,461	1.0	Ref
0.51–0.67	59	8,507	0.86	0.59–1.3
0.68–0.90	71	8,490	1.1	0.70–1.6
0.91–1.39	45	6,830	0.84	0.51–1.4
>1.39	13	1,676	1.0	0.48–2.0
p_{trend}			0.80	
Continuous		33,964	1.1	0.71–1.60
Animal nitrite (mg/day)				

	Cases	N	HR[b]	95% CI
<0.29	64	8,474	1.0	Ref
0.29–0.41	62	8,443	0.95	0.65–1.4
0.42–0.57	68	8,533	1.0	0.69–1.5
0.58–0.84	48	6,839	0.90	0.56–1.5
>0.84	14	1,675	1.1	0.55–2.3
p_{trend}			0.83	
Continuous		33,964	1.6	0.78–3.3
Processed meat nitrite (mg/day)				
<0.01	62	8,718	1.0	Ref
0.01–0.03	62	8,579	1.0	0.70–1.4
0.04–0.07	58	8,246	0.96	0.67–1.4
0.07–0.18	53	6,713	1.1	0.75–1.6
>0.19	21	1,708	1.8	1.1–3.0
p_{trend}			0.54	
Continuous		33,964	1.1	0.97–1.1

[a] After excluding women with missing covariates.

[b] Adjusted for age, smoking status, pack-years of smoking, ln-transformed total energy intake, body mass index, and mutually adjusted for ln-transformed total dietary nitrate or nitrite.

[c] NO_3 converted to NO_3-N. 97% of NO_3-N was derived from plant sources.

[d] 95^{th} percentile of exposure.