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Ingested nitrate and nitrite, disinfection by-products, and pancreatic cancer risk in postmenopausal women

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Abstract

Nitrate and nitrite are precursors of *N*-nitroso compounds (NOC), probable human carcinogens that cause pancreatic tumors in animals. Disinfection by-products (DBP) exposures have also been linked with digestive system cancers, but few studies have evaluated relationships with pancreatic cancer. We investigated the association of pancreatic cancer with these drinking water contaminants and dietary nitrate/nitrite in a cohort of postmenopausal women in Iowa (1986-2011). We used historical monitoring and treatment data to estimate levels of long-term average nitrate and total trihalomethanes (TTHM; the sum of the most prevalent DBP class) and the duration exceeding one-half the maximum contaminant level (>½ MCL; nitrate-nitrogen 5mg/L, 40μg/L TTHM) among participants on public water supplies (PWS) >10 years. We estimated dietary nitrate and nitrite intakes using a food frequency questionnaire. We computed hazard ratios (HR) and 95% confidence intervals (CI) using Cox regression and evaluated nitrate interactions with smoking and vitamin C intake. We identified 313 cases among 34,242 women, including 152 with >10 years PWS use (N=15,710). Multivariable models of average nitrate showed no association with pancreatic cancer ($HR_{p95vs.Q1}$=1.16, 95%CI: 0.51-2.64). Associations with average TTHM levels were also null (HR_{Q4vsQ1}=0.70, 95%CI:0.42-1.18). We observed no

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trend with increasing years of exposure to either contaminant at levels >½ MCL. Positive associations were suggested in the highest dietary nitrite intake from processed meat ($HR_{p95vs.Q1}$=1.66, 95% CI 1.00-2.75;p_{trend}=0.05). We found no interactions of nitrate with known modifiers of endogenous NOC formation. Our results suggest that nitrite intake from processed meat may be a risk factor for pancreatic cancer.

Keywords

nitrate; drinking water contaminants; disinfection by-products; pancreatic cancer; dietary nitrate/nitrite

Background

Pancreatic cancer is the twelfth most common cancer in the U.S., with incidence rates slightly higher among men, and is the fourth leading cause of cancer-related death in both sexes.[1] Pancreatic cancer incidence rates overall have been rising over the past decade,[1,2] but apart from smoking and hereditary pancreatitis, few risk factors are established.[3,4] Several environmental and occupational exposures, including nitrosamines, organochlorine chemicals, and heavy metals, are hypothesized pancreatic carcinogens.[5]

Humans ingest nitrate and nitrite through their diet as well as from drinking water.[6] Because nitrate is found in fertilizers and manure, agricultural areas have high potential for nitrate contamination of drinking water sources.[7,8] Nitrate and nitrite are precursors in the formation of *N*-nitroso compounds (NOC), which are formed endogenously in the presence of amine sources simultaneous with nitrate or nitrite ingestion.[6] When ingested under conditions favorable to endogenous nitrosation, nitrate and nitrite are classified as probable human carcinogens,[9] and NOC cause pancreatic tumors in animals.[6,9-11]

Despite biologic plausibility, few epidemiologic studies have examined the association between ingested nitrate in drinking water and pancreatic cancer.[12-14] A mortality study in Taiwan found no increased risk of pancreatic cancer death associated with levels of nitrate in municipal water.[13] A case-control study in Iowa found no association between pancreatic cancer risk and increasing levels of nitrate in public water supplies.[12] In the only prospective analysis of this relationship, Weyer et al. also reported no association among participants of the Iowa Women's Health Study (IWHS), although estimates were based on small numbers of cases and a relatively short follow-up period.[14]

There have also been few studies of pancreatic cancer and other water contaminants, including disinfection by-products (DBP), some of which are probable or possible human carcinogens.[15,16] Exposure to high levels of halogenated DBP, such as the total trihalomethanes (TTHM) commonly found in chlorinated drinking water, has been associated most consistently with bladder cancer in epidemiologic studies.[16-18] There is limited animal evidence of dose-related effects of chlorinated DBP on pancreatic tumor formation in animals.[19] Some nitrogenous DBP, like the probable human carcinogen nitrosodimethylamine, may also be present in treated drinking water, especially if the water was chloraminated.[20,21] However, evaluations of the association between DBP and

pancreatic cancer are limited to a small number of case-control studies with varied exposure assessments, and evidence of associations is mixed.[17,18] A Finnish study found an elevated risk for pancreatic cancer associated with long term exposure to increased water mutagenicity,[22] but a later case-control study found reduced risk among individuals with chlorinated municipal drinking water from a surface source at the home compared with those without this drinking water source.[23] A case-control study in Washington County, Maryland found a significantly positive association with having a chlorinated municipal drinking water source compared to individuals using private wells, which are typically not disinfected.[24] In contrast, a Canadian case-control study found no association between pancreatic cancer and measured levels of chlorinated DBP.[25] An early investigation of chlorinated DBP and cancer in the IWHS did not evaluate a relationship with pancreatic cancer.[26] To our knowledge, the association between DBP and pancreatic cancer risk has not been evaluated in a cohort simultaneous with nitrate exposure.

Plant in the diet, especially vegetables, are the major dietary sources of nitrate, and many of these sources also contain antioxidants, such as vitamin C, which inhibit the formation of NOC.[27,28] Processed meats are typically cured or smoked and usually contain added nitrite or nitrate, which can result in the formation of carcinogenic NOC.[29] Red and processed meat also contain high levels of heme iron, which has been found to increase NOC formation.[30] Dietary intakes of red and processed meats have been inconsistently associated with increased risk of pancreatic cancer in previous studies.[29,31] However, most of these studies did not quantify nitrate and nitrite in the diet and did not consider vitamin C or other antioxidant intakes in their analysis.[6]

Our objective was to investigate the association between ingestion of nitrate from drinking water and nitrate and nitrite intake from diet, and pancreatic cancer risk among postmenopausal women in the IWHS. With an additional 13 years of follow-up, we extended the previous analysis of Weyer et al.,[14] which was based on a small number of pancreatic cancer cases and did not evaluate dietary nitrite intake. We also evaluated exposure to TTHM in relation to pancreatic cancer risk in the IWHS for the first time.

Methods

Study Population (IWHS)

As described in detail previously, the IWHS is a large prospective cohort study of postmenopausal women in Iowa.[32] In 1986, a questionnaire was mailed to 98,030 women, aged 55-69, randomly selected from Iowa driver's license records. Of these, 41,836 (42%) responded to the baseline questionnaire and formed the initial cohort. The women were queried about their dietary intake, demographics, family history of cancer, and medical and reproductive history. Five follow-up questionnaires (1987,1989,1992,1997,2004) were mailed and completed, with high response rates (91%, 90%, 83%, 79%, and 70%, respectively). The Institutional Review Boards of the University of Minnesota and the University of Iowa approved the IWHS.

For the current analyses, we obtained information on incident pancreatic cancers diagnosed between 1986-2011 from the State Health Registry of Iowa. Rare histologic types (N=7;

leiomyosarcoma, malignant pancreatic endocrine tumor, carcinoid tumor, neuroendrocrine carcinoma, small cell carcinoma) were excluded from our case definition because these rare sub-types may have different etiology. Vital status was also ascertained through the State Health Registry of Iowa, supplemented by the National Death Index. Person-years of follow-up were calculated from enrollment date until the date of incident pancreatic cancer diagnosis, death, emigration from Iowa, or the midpoint of last contact date and December 31, 2011.

Exposure Assessment

Drinking Water—Participants' main source of current drinking water (municipal water system, rural water system, bottled water, private well water, other, don't know) was obtained in the 1989 follow-up questionnaire and reported by 36,127 participants. The women also reported how long they had used the reported water source in categories: <1, 1–5, 6–10, 11–20, >20 years. The majority (76.7%) indicated that they used a public water supply (municipal or rural water system), 18.5% were served by a private well, and fewer than 5% reported using bottled or other water sources. Ninety percent of follow-up participants indicated they had used their drinking water source for >10 years; we focused our drinking water analyses on these residentially stable women.

We previously described the assessment of contaminants in public water supplies (PWS) and report the key elements herein.[14,33] Nitrate-nitrogen (NO_3-N) measured in water samples from municipal water supplies in Iowa were used to calculate annual average NO_3-N (mg/L) levels for each PWS year with measurements across the 33-year historical exposure period (1955-1988). Historical annual estimates of total trihalomethanes (TTHM; in μg/L), which included chloroform, bromoform, bromodichloromethane and dibromochloromethane, were also available ; concentrations before promulgation of TTHM regulations in the 1980s were estimated by experts based on known characteristics of the PWS, including treatment practices and water source measurements.[34] We used TTHM, the sum of the most prevalent DBP class and a surrogate for the presence of other halogenated DBP in our drinking water analyses to evaluate potential confounding by DBP. Estimates for the sum of six haloacetic acids, which included trichloroacetic, dichloroacetic, monochloroacetic, dibromoacetic, monobromoacetic, and bromochloroacetic acid, were also available. We estimated the median years within the women's reported drinking water source duration categories from complete water source histories obtained from similarly aged women in Iowa during the same timeperiod.[35] For the long-duration categories of 11-20 and >20 years used in our analyses, we assigned medians of 16 and 40 years, respectively. Long-term nitrate averages were based on the period of available measurements available for each utility, with a maximum of 33 years. We therefore calculated two nitrate exposure metrics based on duration: 1) 16- and 33-year averages from the annual averages of NO_3-N levels, and 2) the number of years in these time periods when the annual average NO_3-N level was greater than one-half the maximum contaminant level (>½-MCL; NO_3-N= 5mg/L). DBP estimates were available for the full 40-year period, so we generated 16- and 40-year average TTHM exposures and the number of years these averages were >½-MCL (40μg/L). Additionally, because the relative concentrations and types of DBP (e.g., nitrosamines and THM, respectively)[20] may differ depending on the treatment methods of chloramination versus

chlorination, we evaluated whether each PWS had ever used chloramination (yes/no) during the study period. Because private wells are not regulated and routine measurement of contaminants uncommon, we did not have sufficient data for private wells to generate quantitative estimates of exposure for women who reported using a private well as their drinking water source.

Diet—An adapted version of the Harvard food frequency questionnaire (FFQ),[36] consisting of 127 questions about foods participants consumed in the past 12 months, was used to assess dietary intake at baseline. The reproducibility of the FFQ was demonstrated for most macro- and micronutrients, including vitamin C, by re-administering it to a sample of the cohort two years following enrollment.[37] Nitrate and nitrite were not evaluated in this effort, but a calibration study in another large cohort found good performance of a FFQ that asked about a similar list of foods for assessing nitrate and nitrite intakes as compared to 24-hour dietary recalls.[38] We estimated total intakes of nitrate and nitrite overall and from plant, animal, and processed meat sources by multiplying reported intakes of food items by estimates of the nitrate and nitrite contents of the food obtained from the published literature.[39,40] We also calculated red meat intake (g/day) and total vitamin C (mg/day) intake from foods and dietary supplements combined.

Statistical analysis

Based on self-reported data, we excluded women at study enrollment who were premenopausal (N=547), who had been diagnosed with prior cancer (apart from non-melanoma skin cancer) or received cancer chemotherapy (N=3,830). For consistency with previous investigations, we also excluded those who reported unrealistic dietary intakes (<600 or >5,000 kcal/day), responded to ≤30 dietary questions (N=2,723) on the baseline survey or were missing covariate information (N=466). After these exclusions (N=7,135), a total of 34,242 women remained in the dietary analyses. Excluded women were similar to women included in the dietary analyses with respect to demographic and other characteristics collected at study enrollment (data not shown).

For the drinking water analyses, an additional 4,718 women were excluded because they had not participated in the 1989 follow-up survey. We then excluded women who reported use of their water supply for ≤10 years (N=5,718) or for an unreported period of time (N=74), those who reported drinking only bottled or other water (N=138), and women on PWS with no nitrate or TTHM measurements (N=6,535). To reduce sources of uncertainty in the exposure assessment, we further excluded women from cities for which we lacked adequate PWS source detail, or that had a single surface water source or groundwater aquifer for <75% of the study period (N=1,615). After these additional exclusions, 15,910 women on PWS and 5,035 women on private wells remained eligible for analysis. Participants with missing final model covariates were excluded (N=200), leaving a sample size of 15,710 for women on PWS. After similarly excluding N=80 women on private wells, N=4,955 of these women remained for analysis of women on private well water. We previously demonstrated that women eligible for drinking water analyses were similar to those excluded in regard to demographic and other characteristics.[41]

We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) of the association between drinking water and dietary nitrate and nitrite and incident pancreatic cancer. In drinking water analyses, we compared risks in average nitrate exposure quartiles and in the 95th percentile to risks in the lowest exposure quartile (Q1). We evaluated categories of years >½ MCL based on the median duration for such exposure (<4 years, ≥4 years) compared to women with no years of exposure >½ MCL. We transformed continuous variables using natural logarithms to achieve normality. No nitrate data were available for private wells, therefore we compared risks among women on private well water to women on PWS in Q1 of the average nitrate level. We used the same exposure metrics and analytic approach for TTHM, except that we only evaluated quartiles of average TTHM due to sparse numbers of cases in the 95th percentile.

We evaluated potential confounders assessed in the baseline questionnaire, including smoking status (current smoker, former smoker, non-smoker), number of pack-years smoked, body mass index (BMI), prevalent diabetes (yes/no), estrogen use (ever/never), age at menopause, occupation, (homemaker, professional, clerical/craft, farmer, other) and place of residence (rural/farm vs. city/town), as well as aspirin and NSAID use obtained from a 1992 follow-up survey. After a stepwise selection process, we included age and smoking status in all multivariable-adjusted models based on a ≥10% change in the parameter estimates.

Nitrate and TTHM levels in public drinking water were weakly correlated (ρ=0.24). We evaluated PWS nitrate, TTHM, and pancreatic cancer associations through multivariable models adjusted for both age and smoking status (Model 1), and in models further mutually adjusted for either natural log-transformed TTHM or NO_3-N concentrations (Model 2).

In the dietary analyses, we estimated hazard ratios for categories of overall dietary nitrate and nitrite as well as nitrite intake from plant, animal, and processed meat sources separately. Dietary nitrate from animal and plant sources were not analyzed separately because most dietary nitrate (median proportion=97%) was derived from plant sources.[33] We adjusted final dietary models for age, categorical smoking status, total calorie intake, and mutually adjusted for either dietary nitrate or nitrite; the last three variables were natural log-transformed. For analyses of nitrate from animal sources and from processed and red meats, we additionally adjusted models for log-transformed continuous saturated fat intake. We also computed associations for intakes of red and processed meats (g/day), separate from their nitrate and nitrite content. Due to the limited range in processed meat intakes, we split this variable at the median value for regression models.

We tested for linear trend by modeling continuous variables derived from median values of each exposure category. We assessed effect modification by TTHM, smoking status, chloramination, and vitamin C with stratified analyses using exposure quartiles; there were too few cases to further evaluate at the 95th percentile as in the main analyses. HRs were estimated in relation to a common reference group of the lowest quartile of average nitrate exposure and the assumed lowest risk group of the modifier (<median TTHM, nonsmokers, no chloramination, ≥median vitamin C). We used likelihood ratio tests from comparison of models with and without product interaction terms to obtain global interaction p-values.

We conducted sensitivity analyses to evaluate the potential influences of sparse measurement data and large person-time contributions from particular cities on associations with drinking water nitrate. Specifically, we restricted analyses to participants whose long-term average PWS nitrate level was based on eight or more years of data (the median number of years of data available) and excluded women from the top ten cities contributing person-time to the analysis. SAS® version 9.3 was used for all analyses (SAS Institute Inc., Cary, NC), and $p<0.05$ was the criterion for statistical significance.

Results

We identified 313 pancreatic cancer cases after baseline exclusions; and 189 with exposure data suitable for analysis of PWS nitrate or TTHM levels (N=153 on PWS and N=36 on private wells). Participants in our analyses were followed up for an average of 20 years (median=25). The mean age of participants at baseline was 61.6 years. The percent of participants on a PWS sourced from surface water varied across average nitrate categories, from a low of 5.2% in the 1st quartile to a high of 55.7% in the 4th quartile (Table 1). Chloramination treatment also varied by nitrate category. There was no pattern in mean concentration of TTHM across nitrate categories. We observed few other differences in demographic and lifestyle characteristics across nitrate categories in PWS. Participants on private well water were more likely to live on a farm and to be homemakers than those on PWS (Table 1). Women on private wells were also less likely to smoke, consumed more calories, and had a lower median intake of vitamin C.

In multivariable-adjusted models, we found no association between mean drinking water nitrate concentrations and pancreatic cancer (Table 2, Model 1 $HR_{P95\ vs.\ Q1}$=1.18, 95% CI=0.52, 2.67). No monotonic trend was observed with increasing categories of exposure or with average nitrate as a continuous variable. We observed a significant positive association with exposure to one to four years >½ MCL (Model 1 $HR_{1\text{-}4\ vs.\ 0\ years}$=1.66, 95% CI=1.22, 2.44) compared to no years of exposure above this level; however, longer duration of exposure to PWS with >½ MCL nitrate was not associated with risk. Mutual adjustment for TTHM did not materially change these associations (Table 1; Model 2), and models of several individual DBP (including 2 individual trihalomethanes and 3 haloacetic acids) did not indicate associations with pancreatic cancer (data not shown). In sensitivity analyses among women with >20 years at their water source and exposure based on ≥8 years of data, the nitrate association for one to four years >½ MCL was both attenuated and no longer statistically significant (Model 1 $HR_{1\text{-}4\ vs.\ 0\ years}$=1.35, 95% CI=0.71, 2.58; Table S1). Adjustment of nitrate models for TTHM did not materially change these associations (Table S1; Model 2). We also found no associations for women on private well water compared to women in the lowest quartile of average nitrate in public water (Table 2, Model 1 HR=0.92, 95% CI= 0.56, 1.52). Analyses excluding the top ten cities of residence in the study population were consistent with all of these results (data not shown).

TTHM concentrations showed no association with pancreatic cancer risk, in models both not adjusted or mutually adjusted for nitrate concentrations; associations with categories of years >½ MCL TTHM were similarly null. The lack of association held among women with >20 years at their water source and exposure based on ≥8 years of data; the association was

significantly inverse in the highest exposure quartile, but without trend (Table S1). We also found no evidence of interaction between nitrate and TTHM on pancreatic cancer risk in analyses of nitrate quartiles stratified by < or ≥ median TTHM levels (data not shown).

Models of nitrate from drinking water stratified by smoking status and additionally adjusted for pack-years of smoking showed no significant interactions with either average nitrate (Table S3, $p_{interaction}$=0.83) or years >½ MCL ($p_{interaction}$=0.22) on pancreatic cancer risk. We similarly observed no significant interactions in nitrate models stratified by vitamin C intake (Table S2).

In multivariable dietary analyses, we found no association between total dietary nitrate intake and pancreatic cancer (Table 3). We similarly found no association for dietary nitrite overall or from plant sources, but observed a suggestive positive association with high nitrite intake from all animal sources in models additionally adjusted for saturated fat ($HR_{P95\ vs.\ Q1}$=1.65, 95% CI= 0.84, 3.2, p=0.13). We also found a positive association with the 95th percentile (>0.18 mg/day) of nitrite intake from processed meat, with a significant trend ($HR_{P95\ vs.\ Q1}$=1.73, 95% CI=1.05, 2.85; p_{trend}=0.03; data not shown). However, this association was attenuated and only borderline statistically significant when the model was additionally adjusted for saturated fat (Table 3, $HR_{P95\ vs.\ Q1}$=1.66, 95% CI=1.00, 2.75, p_{trend}=0.05). We found no association between red meat intake and pancreatic cancer ($HR_{P95\ vs.\ Q1}$=1.00, 95% CI=0.47, 1.85); p_{trend}=0.72). Likewise, we saw no association with average daily intake of processed meat split at the median (data not shown). In stratified analyses, we found no interactions between vitamin C and any of these dietary intakes on risk (data not shown).

Discussion

In this updated analysis of the IWHS cohort, we found no associations between nitrate in drinking water and pancreatic cancer risk. Adjustment for TTHM, a hypothesized risk factor for pancreatic cancer, did not change these results. Although vitamin C inhibits the endogenous formation of NOC from nitrate,[28] and thiocyanate from cigarettes promotes NOC formation,[42] we saw no differences in nitrate associations within strata of vitamin C or smoking. We observed a positive association between dietary intake of nitrite from processed meat and pancreatic cancer risk.

Our drinking water results are consistent with the prior analysis of the IWHS that found no association between nitrate in drinking water and pancreatic cancer risk using a single 33-year long-term average exposure metric.[14] Our updated water analysis added 13 years of follow-up and 91 additional pancreatic cancer cases, for a total of N=152. We also improved the drinking water exposure assessment by incorporating both average exposure duration and the duration of exposure to levels >½ MCL. The lack of association between average nitrate exposure from drinking water and pancreatic cancer is consistent with the small number of other epidemiologic studies evaluating this relationship. A population-based case-control study in Iowa with comparable nitrate levels to the IWHS (median=1.27 mg/L) reported no association among men or women.[12] Similarly, a matched case-control study in

Taiwan found no association between municipality-level average nitrate exposures in drinking water and pancreatic cancer mortality.[13]

Our improved drinking water exposure metrics aimed to capture both long-term average exposure as well as exposure intensity, as these features may have meaningfully different effects on risk. We did observe a positive association between short-duration (<4 years) exposure to nitrate in drinking water at levels >½ MCL, but no monotonic increase with the number of years of exposure. This finding was likely explained by chance, as the association was attenuated and no longer significant when we restricted our analyses to the more limited number of PWS with at least eight years of measurement data and to women with longer duration at their water source.

Our analysis represents the first study to examine the association between both drinking water nitrate and TTHM co-exposure and pancreatic cancer. There have been limited studies of the relationship between DBP and pancreatic cancer to-date in spite of animal evidence linking exposure to the chlorinated furanone MX, a mutagenic DBP, with pancreatic tumors in rats.[16,19] However, our data did not indicate an association of pancreatic cancer risk with TTHM, either with average exposure levels or with duration of exposure to levels >½ MCL. A meta-analysis of six studies in the U.S. and Europe found no elevation in pooled relative risks for pancreatic cancer incidence or mortality in relation to chlorinated drinking water exposure.[43] Two later case-control studies found elevated pancreatic cancer risk in association with surrogates for exposure to chlorinated DBP in drinking water: increased mutagenicity (estimated from historical water quality and treatment information) in Finland, [22] and using a municipal chlorinated drinking water source versus a non-chlorinated, non-municipal source in a U.S. study in Maryland.[24] The only previous study that estimated levels of exposure to chlorinated DBP as we did, a case-control study in Canada, found no association with pancreatic cancer risk.[25] Thus, our findings contribute to what remains inconsistent evidence for the association between DBP and pancreatic cancer risk. Moreover, it is not known if the levels of TTHM and other DBP observed in our population adequately reflect the concentrations and/or mixture of compounds that are potentially relevant to pancreatic cancer risk.

Our analyses yielded a positive association between nitrite from processed meat and pancreatic cancer risk, but no association with red meat intake. These findings add new information to the inconsistent observations of other prospective cohort studies, many of which have found null or weak associations between red and processed meat and pancreatic cancer.[31,44-47] A previous dietary analysis in the IWHS with 16 years of follow-up found no association between pancreatic cancer risk and dietary intakes of red meat, but did not evaluate a relationship with processed meat.[47] A large, prospective, multi-ethnic cohort study in Hawaii and Los Angeles found a significant association between high intakes of both processed meat (RR=1.68, 95% CI=1.35-2.07) and red meat (RR=1.45, CI=1.19-1.76) and increased pancreatic risk (N=482 cases).[48] Neither of these previous studies specifically examined nitrate or nitrite intakes derived from these meat sources. However, the multi-ethnic cohort found higher pancreatic cancer risk among those in the highest quintile of dietary nitrosamine intake, the major source of which was processed meat.[48] That cohort study also found no associations with saturated fat intake overall or from dairy products

specifically, but a significant risk associated with saturated fat intakes from red and processed meat. In the NIH-AARP Diet and Health Study cohort (N=1,417 cases), a positive association between processed meat and pancreatic cancer was no longer significant in women after adjustment for saturated fat, although it remained among men.[49] Two meta-analyses reported an overall association between high consumption of red meat[50,51] and processed meats[51] and increased pancreatic cancer risk from case-control studies, but no such associations in cohort studies. In the cohort studies, an association between red meat intake and pancreatic cancer risk was observed in men but not women, possibly because men have been demonstrated to have greater meat intake than women.[51] The only previous prospective study that evaluated dietary nitrite from processed meat, as we did, found no association with pancreatic cancer in women and a non-significantly elevated risk in men.[52]

Processed meat is classified by IARC as a human carcinogen based on epidemiologic data for colorectal cancer, and evidence is accumulating for other cancers.[29] There are several constituents of a meat-containing diet potentially linked to pancreatic cancer. In addition to nitrate, meat cooked at high temperatures has heterocyclic amines and polycyclic aromatic hydrocarbons, which are mutagenic and have been associated with increased pancreatic cancer risk.[29] Our finding of a suggestive increased risk of pancreatic cancer among those with the highest dietary intake of nitrite from processed meats should be interpreted cautiously because of its borderline significance. Average intakes of processed meat in this population (3 g/day) were not high relative to average intakes for American women, which were approximately 18 g/day in 2003-2004.[53] Processed meats are usually cured with nitrite or nitrate salts to inhibit the growth of bacteria, to add flavor, and to obtain a red color. However, our FFQ had limited questions about processed meat, and most dietary nitrate and nitrite intakes in the IWHS came from plant sources, which unlike meats also contain vitamin C, a known inhibitor of nitrosation.[27,28]

A key strength of this study includes our assessment of exposure to both drinking water nitrate and TTHM, which had not previously been examined together in relation to pancreatic cancer risk. Moreover, only one other epidemiologic study evaluated estimated nitrite and nitrate intakes from diet in relation to incident pancreatic cancer. That we observed an association with estimated nitrite from processed meat but no association with intakes of processed meat itself may indicate the importance of estimating nitrate/nitrite levels in these dietary sources, especially since processed meat intakes were low with limited variability in intake.

Our analyses had some additional limitations, including the lack of detailed lifetime smoking history in the cohort. However, we observed only weak correlations between smoking and drinking water NO_3-N or dietary nitrate in our data, and model results were unchanged when further adjusted for pack-years of smoking. We also did not have nitrate measurements for private wells, or information on well depth, which can be used to estimate nitrate levels.[54] Thus, we were unable to assess the relationship between nitrate levels in private wells, which may be higher than in regulated PWS, and pancreatic cancer risk. However, our analyses of PWS included a large number of participants and a range of nitrate levels. This study also lacked information on participants' water consumption, which could have been used to better estimate cumulative drinking water exposures. Another source of

likely non-differential exposure misclassification in our study was the FFQ used to estimate dietary intakes, but a previous validation effort in the cohort indicated good accuracy and reliability to support its usage to assess macronutrients in our analyses.[37,38] The occupational data collected in the IWHS was limited to broad groups, thus we were unable to examine if women were employed in manufacturing or other jobs where they might have had exposure to nitrosamines or other factors associated with pancreatic cancer. In the Agricultural Health Study, Andreotti et al. (2009) found associations between occupational exposure to nitrosatable herbicides and pancreatic cancer risk.[56] Only 4% of women in the IWHS reported their occupation as farmers, but many lived near agricultural fields[55]; therefore, residential pesticide exposure and pesticide drift were also potential sources of exposure to nitrosamine precursors. However, given the high prevalence of agricultural activity throughout Iowa (>90% of land area), we believe it unlikely that environmental pesticide exposure was a major source of uncontrolled confounding in our analyses.

Conclusion

We found no association between historical nitrate levels in Iowa public water utilities and pancreatic cancer risk in postmenopausal women, and no evidence of confounding by or interaction with TTHM. Our observed positive association between relatively high dietary intakes of nitrite from processed meat and pancreatic cancer risk is consistent with the limited existing literature, but was imprecise and based on a small number of cases. We did not find evidence of interactions between drinking water contaminants, or between nitrate levels in drinking water or diet with factors shown to inhibit or promote NOC formation, on associations with pancreatic cancer risk. These findings should be interpreted as part of a limited number of epidemiologic evaluations of nitrate and nitrite in drinking water and diet and pancreatic cancer, with consideration of the potential limited generalizability of our drinking water findings to other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. SEER Cancer Stats Facts: Pancreatic Cancer 1992-2013. National Cancer Institute; https://seer.cancer.gov/statfacts/html/pancreas.html Accessed April 17, 2017
2. Bjerregaard JK, Mortensen MB, Pfeiffer P, Academy of Geriatric Cancer R. Trends in cancer of the liver, gall bladder, bile duct, and pancreas in elderly in Denmark, 1980-2012. Acta Oncol. 2016; 55(Suppl 1):40–5. [PubMed: 26767397]
3. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg. 2008; 393(4):535–45. [PubMed: 18193270]

4. Nitsche C, Simon P, Weiss FU, Fluhr G, Weber E, Gartner S, Behn CO, Kraft M, Ringel J, Aghdassi A, Mayerle J, Lerch MM. Environmental risk factors for chronic pancreatitis and pancreatic cancer. Dig Dis. 2011; 29(2):235–42. [PubMed: 21734390]
5. Barone E, Corrado A, Gemignani F, Landi S. Environmental risk factors for pancreatic cancer: an update. Arch Toxicol. 2016; 90(11):2617–2642. [PubMed: 27538405]
6. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 94. Lyon: 2010. Ingested Nitrate and Nitrite and Cyanobacterial Peptide Toxins.
7. Zirkle KW, Nolan BT, Jones RR, Weyer PJ, Ward MH, Wheeler DC. Assessing the relationship between groundwater nitrate and animal feeding operations in Iowa (USA). Sci Total Environ. 2016; 566-567:1062–8. [PubMed: 27277210]
8. Ward MH. Too much of a good thing? Nitrate from nitrogen fertilizers and cancer. Rev Environ Health. 2009; 24(4):357–63. [PubMed: 20384045]
9. Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Cogliano V. Carcinogenicity of nitrate, nitrite, and cyanobacterial peptide toxins. Lancet Oncology. 2006; 7(8):628–629. [PubMed: 16900606]
10. Pour PM, Runge RG, Birt D, Gingell R, Lawson T, Nagel D, Wallcave L, Salmasi SZ. Current knowledge of pancreatic carcinogenesis in the hamster and its relevance to the human disease. Cancer. 1981; 47(6 Suppl):1573–89. [PubMed: 6456057]
11. Bogovski P, Bogovski S. Animal Species in which N-nitroso compounds induce cancer. Int J Cancer. 1981; 27(4):471–4. [PubMed: 7275353]
12. Coss A, Cantor KP, Reif JS, Lynch CF, Ward MH. Pancreatic cancer and drinking water and dietary sources of nitrate and nitrite. Am J Epidemiol. 2004; 159(7):693–701. [PubMed: 15033647]
13. Yang CY, Tsai SS, Chiu HF. Nitrate in drinking water and risk of death from pancreatic cancer in Taiwan. J Toxicol Environ Health A. 2009; 72(6):397–401. [PubMed: 19199146]
14. 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]
15. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 52. Lyon: 1991. Chlorinated drinking-water, chlorination by-products; some other halogenated compounds; cobalt and cobalt compounds.
16. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 101. Lyon: 2013. Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-Water.
17. Cantor, KP., Ward, MH., Moore, LE., Lubin, JE. Water Contaminants. In: Schottenfeld, D., Fraumeni, JF., editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 2006. p. 382-404.
18. Villanueva CM, Cordier S, Font-Ribera L, Salas LA, Levallois P. Overview of Disinfection By-products and Associated Health Effects. Curr Environ Health Rep. 2015; 2(1):107–15. [PubMed: 26231245]
19. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 84. Lyon: 2004. Some Drinking-water Disinfectants and Contaminants, including Arsenic.
20. Krasner SW, Mitch WA, McCurry DL, Hanigan D, Westerhoff P. Formation, Precursors, Control, and Occurrence of Nitrosamines in Drinking Water: A Review. Water Research. 2013; 47:4433–4450. [PubMed: 23764594]
21. Mitch WA, Sharp JO, Trussell RR, Valentine RL, Alvarez-Cohen L, Sedlak DL. N-nitrosodimethylamine (NDMA) as a drinking water contaminant: A review. Environmental Engineering Science. 2003; 20(5):389–404.
22. Koivusalo M, Vartiainen T, Hakulinen T, Pukkala E, Jaakkola JJ. Drinking water mutagenicity and leukemia, lymphomas, and cancers of the liver, pancreas, and soft tissue. Arch Environ Health. 1995; 50(4):269–76. [PubMed: 7677425]
23. Kukkula M, Lofroth G. Chlorinated drinking water and pancreatic cancer: A population-based case-control study. Eur J Public Health. 1997; 7(3):297–301.

24. IJsselmuiden C, Gaydos C, Feighner B, Novakoski WL, Serwadda D, Caris LH, Vlahov D, Comstock GW. Cancer of the pancreas and drinking water: a population-based case-control study in Washington County, Maryland. Am J Epidemiol. 1992; 136(7):836–42. [PubMed: 1442749]
25. Do MT, Birkett NJ, Johnson KC, Krewski D, Villeneuve P, Group CCRER. Chlorination disinfection by-products and pancreatic cancer risk. Environ Health Perspect. 2005; 113(4):418–24. [PubMed: 15811832]
26. 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]
27. Bartsch H, Frank N. Blocking the endogenous formation of N-nitroso compounds and related carcinogens. IARC Sci Publ. 1996; (139):189–201.
28. Bartsch H, Ohshima H, Pignatelli B. Inhibitors of endogenous nitrosation. Mechanisms and implications in human cancer prevention. Mutat Res. 1988; 202(2):307–24. [PubMed: 3057363]
29. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, Guha N, Mattock H, Straif K. Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 2015; 16(16):1599–600. [PubMed: 26514947]
30. Cross AJ, Pollock JR, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. Cancer Res. 2003; 63(10):2358–60. [PubMed: 12750250]
31. Food, Nutrition, Physical Activity, and the Prevention of Pancreatic Cancer. World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project Report. 2012
32. Folsom AR, Kaye SA, Potter JD, Prineas RJ. Association of incident carcinoma of the endometrium with body weight and fat distribution in older women: early findings of the Iowa Women's Health Study. Cancer Res. 1989; 49(23):6828–31. [PubMed: 2819722]
33. Jones RR, Weyer PJ, DellaValle CT, Inoue-Choi M, Anderson KE, Cantor KP, Krasner S, Robien K, Freeman LE, Silverman DT, Ward MH. Nitrate from Drinking Water and Diet and Bladder Cancer Among Postmenopausal Women in Iowa. Environ Health Perspect. 2016; 124(11):1751–1758. [PubMed: 27258851]
34. Krasner SW, Cantor KP, Weyer PJ, Hildesheim M, Amy G. Case study approach to modeling historical disinfection by-product exposure in Iowa drinking waters. J Env Sci. 2017 in press.
35. Cantor KP. Drinking water and cancer. Cancer Causes Control. 1997; 8(3):292–308. [PubMed: 9498894]
36. 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]
37. 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]
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. 2016; 19(11):1934–43. [PubMed: 26626817]
39. 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]
40. 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]
41. Jones RR, Weyer PJ, DellaValle CT, Robien K, Cantor KP, Krasner S, Beane Freeman LE, Ward MH. Ingested nitrate, disinfection by-products, and kidney cancer risk in older women. Epidemiology. 2017 in press.
42. Preston-Martin S, Correa P. Epidemiological evidence for the role of nitroso compounds in human cancer. Cancer Surv. 1989; 8(2):459–73. [PubMed: 2696590]
43. Morris RD, Audet AM, Angelillo IF, Chalmers TC, Mosteller F. Chlorination, chlorination by-products, and cancer: a meta-analysis. Am J Public Health. 1992; 82(7):955–63. [PubMed: 1535181]

44. Vrieling A, Verhage BA, van Duijnhoven FJ, Jenab M, Overvad K, Tjonneland A, Olsen A, Clavel-Chapelon F, Boutron-Ruault MC, Kaaks R, Rohrmann S, Boeing H, Nothlings U, Trichopoulou A, John T, Dimosthenes Z, Palli D, Sieri S, Mattiello A, Tumino R, Vineis P, van Gils CH, Peeters PH, Engeset D, Lund E, Rodriguez Suarez L, Jakszyn P, Larranaga N, Sanchez MJ, Chirlaque MD, Ardanaz E, Manjer J, Lindkvist B, Hallmans G, Ye W, Bingham S, Khaw KT, Roddam A, Key T, Boffetta P, Duell EJ, Michaud DS, Riboli E, Bueno-de-Mesquita HB. Fruit and vegetable consumption and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2009; 124(8):1926–34. [PubMed: 19107929]
45. Michaud DS, Skinner HG, Wu K, Hu F, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary patterns and pancreatic cancer risk in men and women. J Natl Cancer Inst. 2005; 97(7): 518–24. [PubMed: 15812077]
46. Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA. Meat and fat intake and pancreatic cancer risk in the Netherlands Cohort Study. Int J Cancer. 2009; 125(5):1118–26. [PubMed: 19452526]
47. Inoue-Choi M, Flood A, Robien K, Anderson K. Nutrients, food groups, dietary patterns, and risk of pancreatic cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2011; 20(4): 711–4. [PubMed: 21278328]
48. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. J Natl Cancer Inst. 2005; 97(19):1458–65. [PubMed: 16204695]
49. Taunk P, Hecht E, Stolzenberg-Solomon R. Are meat and heme iron intake associated with pancreatic cancer? Results from the NIH-AARP diet and health cohort. Int J Cancer. 2016; 138(9): 2172–89. [PubMed: 26666579]
50. Paluszkiewicz P, Smolinska K, Debinska I, Turski WA. Main dietary compounds and pancreatic cancer risk. The quantitative analysis of case-control and cohort studies. Cancer Epidemiol. 2012; 36(1):60–7. [PubMed: 22018953]
51. Zhao Z, Yin Z, Pu Z, Zhao Q. Association Between Consumption of Red and Processed Meat and Pancreatic Cancer Risk-a Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2016
52. Aschebrook-Kilfoy B, Cross AJ, Stolzenberg-Solomon RZ, Schatzkin A, Hollenbeck AR, Sinha R, Ward MH. Pancreatic cancer and exposure to dietary nitrate and nitrite in the NIH-AARP Diet and Health Study. Am J Epidemiol. 2011; 174(3):305–15. [PubMed: 21685410]
53. Daniel CR, Cross AJ, Koebnick C, Sinha R. Trends in meat consumption in the USA. Public Health Nutr. 2011; 14(4):575–83. [PubMed: 21070685]
54. Wheeler DC, Nolan BT, Flory AR, DellaValle CT, Ward MH. Modeling groundwater nitrate concentrations in private wells in Iowa. Sci Total Environ. 2015; 536:481–8. [PubMed: 26232757]
55. Jones RR, Yu CL, Nuckols JR, Cerhan JR, Airola M, Ross JA, Robien K, Ward MH. Farm residence and lymphohematopoietic cancers in the Iowa Women's Health Study. Environ Res. 2014; 133:353–61. [PubMed: 25038451]
56. Andreotti G, Freeman LE, Hou L, Coble J, Rusiecki J, Hoppin JA, Silverman DT, Alavanja MC. Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. Int J Cancer. 2009; 124(10):2495–500. [PubMed: 19142867]

Novelty and impact

N-nitroso compounds formed endogenously after nitrate/nitrite ingestion are suspected pancreatic carcinogens. This is the first study to examine concomitant exposure to both drinking water nitrate and disinfection by-products (DBP), some of which are also probable or possible human carcinogens. We found no association between nitrate or DBP in public water supplies and pancreatic cancer risk. A positive association between intakes of dietary nitrite from processed meats and pancreatic cancer is consistent with limited epidemiologic studies.

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Table 1

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

	Public water supplies (N=15,910)					Private wells (N=5035)
	Mean NO_3-N[a] (mg/L)					
Characteristic	**<0.47**	**0.47-1.08**	**1.09-2.97**	**2.98-5.69**	**>5.69**	
n	4064	3913	4211	2912	810	5035
Mean length of follow-up, years	21.2	21.0	21.1	21.2	20.9	21.9
Mean age at baseline, years	61.7	61.6	61.6	61.6	61.5	61.2
White race, %	99.5	99.2	99.2	98.6	99.3	99.6
PWS chloraminated, %	17.7	37.9	38.3	8.6	2.8	NA
Surface water as source for PWS, %	5.2	28.1	15.9	55.7	11.7	NA
Mean TTHM[a], µg/L	7.3	35.0	17.5	14.9	7.9	NA
Smoking status, %						
Never	62.6	61.9	59.9	61.5	64.1	78.5
Former	21.2	22.5	23.1	22.6	21.0	12.3
Current	16.2	15.6	17.0	15.9	14.9	9.2
Pack-years smoking, %[b]						
1-19	40.6	41.5	38.2	39.0	39.6	45.0
20-39	33.3	33.6	35.2	34.0	35.3	34.4
≥40	26.1	24.9	26.6	27.0	25.1	20.6
Occupation, %						
Homemaker	33.1	33.4	32.5	31.9	35.4	52.5
Professional	16.3	16.9	15.1	16.6	15.7	12.0
Clerical/craft	48.8	48.1	50.9	50.6	46.7	25.7
Farmer	1.5	1.2	0.9	0.6	1.8	9.4
Other	0.4	10.5	0.7	0.3	0.4	0.4
Residence, %						
Farm	3.2	3.3	2.1	2.2	4.2	71.3
Rural area (non-farm)	1.8	2.2	1.5	2.8	3.2	19.3
City/town	95.0	94.5	96.4	95.1	92.6	9.4

	Public water supplies (N=15,910)					Private wells (N=5035)
	Mean NO_3-N[a] (mg/L)					
Characteristic	**<0.47**	**0.47-1.08**	**1.09-2.97**	**2.98-5.69**	**>5.69**	
Body mass index (BMI), %						
<25	40.8	42.5	42.8	43.3	35.9	35.7
25-29.9	37.3	36.2	35.9	36.3	37.9	38.0
≥30	22.0	21.3	21.4	20.4	26.2	26.3
Education, %						
Less than high school	6.8	6.1	6.6	5.0	7.2	10.1
High school	53.3	52.0	54.0	47.4	55.4	52.2
More than high school	39.9	42.0	39.5	47.7	37.4	37.8
Diabetes, %	5.9	5.8	5.6	5.3	5.6	4.9
Physical activity level,%						
Low	46.4	47.1	48.1	46.2	49.3	47.7
Moderate	28.3	27.5	26.3	26.5	25.5	28.4
High	25.4	25.4	25.6	27.3	25.2	24.0
Oral contraceptive use, ever, %	20.8	20.9	19.3	18.7	20.6	18.9
Estrogen use	40.4	39.7	40.7	43.3	34.4	34.9
Insulin use, %						
No	98.0	97.8	98.1	97.9	97.3	98.3
Yes, but not currently	0.6	0.3	0.4	0.5	0.7	0.5
Yes, currently	1.5	1.7	1.5	1.6	1.9	1.1
Mean age at menopause, years	47.6	47.7	47.6	47.5	48.0	48.3
Nitrate in diet, mg/day (median)[c]	61.2	61.3	61.8	63.1	59.2	59.1
Nitrite in diet, mg/day (median)[c]	0.64	0.64	0.65	0.65	0.65	0.66
Nitrite in diet from processed meat, mg/day (median)[c]	0.03	0.03	0.03	0.03	0.04	0.04
Vitamin C in diet, mg/day (median)[c]	108.0	111.8	108.7	114.9	106.3	99.9

NA= not applicable

[a] Exposures assigned to individuals based on their reported duration at drinking water source. Categories include quartiles 1-3; 75th-95th percentile, and 95th percentile.

[b] Among current or former smokers at baseline.

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

Table 2

Association between nitrate-nitrogen (NO_3-N) and total trihalomethanes (TTHM) in public water supplies and pancreatic cancer among Iowa Women's Health Study participants > 10 years at their drinking water source.[a]

			Model 1[b]	Model 2[c]
Drinking water nitrate	**Cases**	**N**	**HR (95% CI)**	**HR (95% CI)**
Private well[d]	34	4,955	0.92 (0.56, 1.52)	-
Average NO_3-N (mg/L)				
< 0.47	31	4,007	1.00 (Ref.)	1.00 (Ref.)
0.47 – 1.08	41	3,875	1.40 (0.88, 2.24)	1.44 (0.90, 2.30)
1.09 – 2.97	48	4,163	1.51 (0.96, 2.37)	1.56 (0.99, 2.46)
2.98-5.69	25	2,868	1.14 (0.67, 1.93)	1.16 (0.69, 1.98)
>5.69[e]	7	797	1.18 (0.52, 2.67)	1.16 (0.51, 2.64)
p_{trend}			0.97	0.97
Continuous [f]	152	15,710	1.07 (0.92, 1.25)	1.08 (0.93, 1.25)
Years >½ MCL (>5mg/L NO_3-N)				
0	99	11,026	1.00 (Ref.)	1.00 (Ref.)
1-4	34	2,318	1.66 (1.12, 2.44)	1.65 (1.12, 1.48)
≥4	19	2,366	0.90 (0.55, 1.47)	0.90 (0.55, 1.48)
p_{trend}			0.59	0.62
Continuous[g]	152	15,710	0.99 (0.93, 1.06)	0.99 (0.93, 1.06)
Average TTHM (µg/L)				
<0.90	37	3,781	1.00 (Ref.)	1.00 (Ref.)
0.90-4.58	52	4,339	1.24 (0.81-1.90)	1.22 (0.80-1.86)
4.59-14.31	39	4,182	0.95 (0.61-1.49)	0.88 (0.55-1.40)
>14.30	24	3,408	0.73 (0.44-1.22)	0.70 (0.42-1.18)
p_{trend}			0.07	0.06
Continuous [f]	152	15,710	0.99 (0.94-1.04)	0.98 (0.94-1.04)
Years >½ MCL (>40 µg/L TTHM)				
0	116	11,909	1.00 (Ref.)	1.00 (Ref.)
1-36	17	1,696	1.02 (0.62-1.70)	1.02 (0.62-1.69)
≥ 36	19	2,105	0.94 (0.58-1.52)	0.94 (0.58-1.52)
p_{trend}			0.79	0.79
Continuous [h]	152	15,710aa	1.00 (0.98-1.01)	1.00 (0.98-1.01)

[a] After excluding 200 women with missing covariate data.

[b] Adjusted for age and smoking status.

[c] Adjusted for age, smoking status, and mutually adjusted for natural log-transformed TTHM or NO_3-N.

[d] Compared to women in the 1st quartile (< 0.47 mg/L) of nitrate exposure in public water supplies.

[e] 95th percentile.

[f]HR per 1 natural log increase in concentration.

[g]HR per year increase in exposure >5 mg/L NO_3-N.

[h]HR per year increase in exposure >40 μg/L TTHM.

Table 3

Association between dietary nitrate and nitrite and red meat and pancreatic cancer among participants in the Iowa Women's Health Study (N=34,242[a]).

	Cases	N	HR[b] (95% CI)
Dietary nitrate (mg NO_3-N/day)			
All sources			
<16.2	78	8,558	1.00 (Ref.)
16.2-23.9	80	8,552	1.08 (0.78, 1.48)
24.0-34.2	73	8,568	0.99 (0.70, 1.39)
34.3-58.5	60	6,849	1.05 (0.72, 1.52)
>58.5	17	1,715	1.25 (0.71, 2.21)
p_{trend}			0.55
Continuous[c]	308		1.02 (0.92, 1.14)
Dietary nitrite (mg/day)			
All sources			
<0.86	88	8,501	1.00 (Ref.)
0.86-1.11	67	8,505	0.85 (0.59, 1.22)
0.12-1.43	70	8,753	0.94 (0.62, 1.42)
1.44-2.05	68	6,761	1.30 (0.79, 2.14)
>2.05	15	1,722	1.28 (0.59, 2.76)
p_{trend}			0.18
Continuous[c]	308		1.10 (0.94, 1.29)
Plant sources			
<0.51	94	8,731	1.00 (Ref.)
0.51-0.67	62	8,355	0.68 (0.48, 0.96)
0.68-0.90	83	8,615	0.89 (0.62, 1.28)
0.91-1.39	59	6,823	0.80 (0.52, 1.24)
>1.39	10	1,718	0.55 (0.25, 1.17)
p_{trend}			0.29
Continuous[c]	308		0.94 (0.83, 1.08)
Animal sources[d]			
<0.29	80	8,765	1.00 (Ref.)
0.29-0.40	71	8,021	1.06 (0.75, 1.50)
0.41-0.56	77	9,023	1.08 (0.74, 1.57)
0.57-0.84	62	6,697	1.27 (0.81, 1.99)
>0.84	18	1,736	1.65 (0.84, 3.22)
p_{trend}			0.13
Continuous[c]	308		1.09 (0.96, 1.25)
Processed meats[d]			
<0.01	78	8,803	1.00 (Ref.)

	Cases	N	HR[b] (95% CI)
0.01-0.03	75	8,644	0.98 (0.72, 1.35)
0.04-0.06	72	8,130	1.02 (0.73, 1.41)
0.07-0.18	61	6,937	1.06 (0.74, 1.51)
>0.18	22	1,728	1.66 (1.00, 2.75)
p_{trend}			0.05
Continuous[c]	308		1.06 (0.96, 1.18)
Red Meat (g/day)[d]			
<45.47	84	8581	1.00 (Ref.)
45.47-79.10	62	8536	0.75 (0.53, 1.05)
79.11-120.17	84	8559	1.03 (0.73, 1.47)
120.18-198.56	64	6947	1.00 (0.65, 1.50)
>198.57	14	1712	1.00 (0.47, 1.85)
p_{trend}			0.72
Continuous	308		1.00 (1.00, 1.00)

[a] After excluding 466 participants with missing smoking data.

[b] Adjusted for age, smoking category, calories, and mutually adjusted for either natural log-transformed nitrate or nitrite.

[c] HR per 1 natural log increase in intake.

[d] Additionally adjusted for natural log-transformed saturated fat.