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Ingested Nitrate, Disinfection By-products, and Risk of Colon and Rectal Cancers in the Iowa Women's Health Study Cohort

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Abstract

Background: *N*-nitroso compounds (NOC) formed endogenously after nitrate/nitrite ingestion and disinfection by-products (DBPs) are suspected colorectal carcinogens, but epidemiologic evidence of these associations is limited.

Objectives: We investigated the relationship between drinking water exposures and incident colorectal cancers in a cohort of postmenopausal women.

Methods: Using historical nitrate-nitrogen (NO_3-N) measurements and estimates of total trihalomethanes (TTHM), the sum of 5 or 6 haloacetic acids (HAAs), and individual DBPs in public water supplies (PWS), we computed average exposures and years of exposure above one-half the U.S. maximum contaminant level (>½-MCL; >5 mg/L NO_3-N and >40 μg/L TTHM). Nitrate/nitrite intakes from dietary sources were estimated using a food frequency questionnaire. We estimated hazard ratios (HR) and 95% confidence intervals (CI) from Cox regression models. We assessed NO_3-N interactions with DBPs and with factors influencing endogenous NOC formation.

Results: We identified 624 colon and 158 rectal cancers (1986–2010) among 15,910 women reporting PWS use >10 years. Ingestion of NO_3-N from drinking water was not associated with risk. Colon cancer risks were non-significantly associated with the average TTHM levels >17.7 μg/L (HR_{Q5vsQ1}=1.13,CI=0.89–1.44;p_{trend}=0.11) and were elevated for any duration of exposure >½ MCL. Rectal cancer risks were associated with the highest TTHM levels (HR_{Q5vsQ1}=1.71,CI=1.00–2.92;p_{trend}=0.22) but not with years >½ MCL. Bromodichloromethane

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(HR_{Q4vsQ1}=1.89,CI=1.17–3.00; p_{trend}=0.09) and trichloroacetic acid (HR_{Q4vsQ1}=1.92,CI=1.20–3.09; p_{trend}=0.18) levels were also associated with risk of rectal cancer. We found no evidence of interaction between TTHM and NO_3-N and risk of either cancer. Dietary analyses yielded a positive colon cancer association with red meat, but not with processed meat intake or estimated nitrate/nitrite from specific dietary sources.

Conclusions: Our results suggest that exposure to TTHM in drinking water is associated with increased risk of rectal cancer. Positive findings for individual THMs and HAAs for both colon and rectal cancers require replication in other studies. We found no associations for nitrate overall or in subgroups with presumed higher NOC exposure.

Keywords

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

INTRODUCTION

Colorectal cancer (CRC) is the 3rd most common cancer worldwide and is a major cause of cancer-related death (American Cancer Society (ACS) 2015). Established risk factors include consumption of red and/or processed meats (Domingo and Nadal 2017, International Agency for Research on Cancer (IARC) 2018) heavy alcohol use, obesity, physical inactivity, a personal history of inflammatory bowel disease, and first-degree family history of CRC (Chang, Chang et al. 2018, Wu, Keum et al. 2018). Evidence is mixed for specific dietary components, including fiber, certain fats, and consumption of meats cooked at high temperatures (Wu, Keum et al. 2018). Meat and meat components, including heme iron, may be involved in the endogenous formation of N-nitroso compounds (NOC), which are potent animal carcinogens (International Agency for Research on Cancer (IARC) 2010). Processed meat preserved with nitrate and nitrite, important NOC precursors, is classified as a human carcinogen largely based on evidence for CRC risk (International Agency for Research on Cancer (IARC) 2018). Nitrate is also a naturally occurring component of green leafy and root vegetables. While many studies have evaluated dietary sources of nitrite and nitrate in relation to CRC, few have included quantitative estimates of intakes (Weyer, Cerhan et al. 2001, Dellavalle, Xiao et al. 2014, Espejo-Herrera, Gracia-Lavedan et al. 2016) and associations have been inconsistently observed.

Drinking water is also a source of human exposure to several suspected colorectal carcinogens (Cantor, Steinmaus et al. 2018). In agricultural areas, water resources may be contaminated with nitrate from widespread use of nitrogen-containing fertilizers and manure storage (Ward 2009). Animal studies have shown CRC tumor development following ingestion of nitrate from both drinking water and diet (Bogovski and Bogovski 1981, Pour, Runge et al. 1981, International Agency for Research on Cancer (IARC) 2010). The epidemiologic evidence is more limited, and nitrate is classified as a probable human carcinogen when ingested under specific conditions favorable for endogenous nitrosation (Grosse, Baan et al. 2006, International Agency for Research on Cancer (IARC) 2010), such as in the presence of nitrosating agents (e.g., amines and amides) and low levels of antioxidants (Bartsch, Ohshima et al. 1988, Bartsch and Frank 1996). Positive associations between nitrate in drinking water and CRC have been observed in several ecologic studies

and investigations of cancer mortality (Ward, deKok et al. 2005, International Agency for Research on Cancer (IARC) 2010, Cantor, Steinmaus et al. 2018) in case-control studies (De Roos, Ward et al. 2003, McElroy, Trentham-Dietz et al. 2008, Espejo-Herrera, Gracia-Lavedan et al. 2016, Fathmawati, Fachiroh et al. 2017), and most recently in a large, registry-based cohort study (Schullehner, Hansen et al. 2018). Two case-control studies reported water nitrate-CRC associations among subgroups with high potential for endogenous NOC exposure (De Roos, Ward et al. 2003, Espejo-Herrera, Gracia-Lavedan et al. 2016). One U.S. cohort, the Iowa Women's Health Study (IWHS), found no increased CRC risk in relation to long-term average nitrate levels in public drinking water; however, effect modification by factors influencing NOC formation was not evaluated (Weyer, Cerhan et al. 2001).

Disinfection by-products (DBPs) commonly found in chlorinated drinking water, including trihalomethanes (THMs) and haloacetic acids (HAAs) - the predominant byproducts -, have been evaluated in relation to CRC in a small number of epidemiologic studies. Most investigations of CRC have shown null or differing patterns of association for colon and rectum sites separately, or heterogeneity in risks between men and women (Cantor, Ward et al. 2006, International Agency for Research on Cancer (IARC) 2013, Cantor, Steinmaus et al. 2018). Several studies evaluated individual DBP species; including case-control studies in Spain and New York that were suggestive of increased CRC risks in relation to brominated THMs (Bove, Rogerson et al. 2007, Villanueva, Gracia-Lavedan et al. 2017), as was an ecologic analysis in Australia (Rahman, Cowie et al. 2014). In early follow-up of the IWHS cohort, colon cancer risk was associated with chloroform levels in public water supplies (Doyle, Zheng et al. 1997).

Most studies of CRC and nitrate and DBP ingestion through drinking water have not examined these exposures simultaneously, and epidemiologic investigations of risks associated with individual THMs and HAAs are limited. In this updated analysis in the IWHS cohort, we estimated the association between CRC risk and nitrate exposures from drinking water and diet, included assessment of DBPs, and evaluated potential effect modification by factors known to influence NOC formation.

METHODS

Study Population

The IWHS is a large prospective cohort study of postmenopausal women in Iowa (Folsom, Kaye et al. 1989). 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 mailed follow-up questionnaires (1987,1989,1992,1997,2004) had 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.

We ascertained incident colon and rectum cancers diagnosed between 1986–2011 from the State Health Registry (SHR) of Iowa. Vital status was also ascertained through the

SHR, supplemented by the National Death Index. Person-years of follow-up were calculated from enrollment date until the date of incident colon or rectum cancer diagnosis, death, emigration from Iowa, or the midpoint of last contact date and December 31, 2011. Six individuals were diagnosed with both colon and rectum cancers; we assigned case status based on the diagnosis date of the first cancer.

Drinking Water Exposure Assessment

We previously described the updated IWHS drinking water exposure assessment (Jones, Weyer et al. 2016) and report key elements herein. Nitrate-nitrogen (NO_3-N) concentrations (mg/L) measured in water samples from municipal water supplies in Iowa were used to calculate annual average NO_3-N levels for each PWS across the historical exposure period (1955–1988). Annual DBP concentrations (μg/L) 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, and current and historical DBP measurements (Krasner, Cantor et al. 2017). Estimated DBPs included TTHM and two of the four specific THMs (chloroform, bromodichloromethane), the sum of five and six HAAs (HAA5 [including mono, di, and trichloroacetic acids, and mono and dibromoacetic acids], and HAA6 [which included the unregulated species bromochloroacetic acid], respectively), and three specific HAAs (trichloroacetic, dichloroacetic, and bromochloroacetic acid). High correlations were observed between long-term averages levels of the two THMs (Spearman's rho>0.95) and between HAAs (rho>0.71); TTHM levels were weakly correlated with nitrate (rho<0.24) (Jones, Weyer et al. 2016).

The main source of drinking water (municipal water system, rural water system, bottled water, private well water, other, don't know) was obtained in a 1989 follow-up questionnaire and was reported by 36,127 participants. The majority (76.7%) indicated that they used a public water supply (municipal or rural water system, hereafter PWS), 18.5% were served by a private well, and fewer than 5% reported using bottled or other water sources. IWHS participants reported the duration at their drinking water source in categories (<1, 1–5, 6–10, 11–20, >20 years); we estimated the median years within these categories from a population with complete water source histories as described previously (Jones, Weyer et al. 2016). Most women (~80%) indicated using their drinking water source for 11–20 years (median=16 years) or >20 years (median=40 years); we limited drinking water analyses to these women with >10 years at their water source. For women on PWS, we calculated two exposure metrics for each participant based on the median duration at their water source prior to 1989 by linking the annual NO_3-N and TTHM concentrations for each participant's PWS: 1) a long-term average based on duration of use, and 2) the number of years of use with NO_3-N or TTHM concentrations greater than one-half the maximum contaminant level (>½-MCL; 5mg/L and 40μg/L for NO_3-N and TTHM, respectively). Additionally, we estimated long-term average concentrations of individual THMs and HAAs. Because the relative concentrations and types of DBP (e.g., nitrosamines and THMs) may differ depending on the use of chloramination versus chlorination treatment (Krasner, Mitch et al. 2013), we evaluated ever/never use of chloramination for each PWS during the study period. Because private wells are not regulated and nitrate measurement data were sparse for these sources, we were unable to generate quantitative nitrate exposures for women who reported

using a private well. Private wells are typically not chlorinated and would be expected to have low or no DBPs.

Dietary Nitrate and Nitrite Intake

A modified version of the Harvard food frequency questionnaire (FFQ), (Willett, Sampson et al. 1988) 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 (Munger, Folsom et al. 1992). 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 (Inoue-Choi, Virk-Baker et al. 2016). 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 (Ward, Cantor et al. 2003, Ward, Cerhan et al. 2006). We also calculated red and processed meat intakes (g/day) and estimated total vitamin C intake (mg/day) from foods and dietary supplements combined. The amount of vitamin C from supplements was reported separately (<400 mg, 400–700 mg, 750–1250 mg, ≥1300 mg, don't know), and the recommended daily allowance (60 mg) was assigned as the amount of vitamin C from reported multivitamin intake.

Statistical Analysis

Based on self-reported data at enrollment, we excluded women 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). 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). A total of 34,708 women remained in dietary analyses.

For the drinking water analyses, an additional 4,718 women were excluded from the dietary analysis subset because they had not participated in the 1989 survey when drinking water source was reported. We excluded women who reported use of their water source for ≤10 years (N=5,718) or for an unspecified period (N=74), those who drank only bottled or other water source (N=138), and women on PWS for which we had no nitrate measurements or TTHM estimates (N=6,535). To reduce other sources of uncertainty, 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 exclusions, 15,910 women on PWS and 5,862 women on private wells remained eligible for drinking water analyses; participants retained for analysis were similar to those excluded in regard to demographic and other characteristics (Jones, Weyer et al. 2017).

We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between drinking water NO_3-N and DBPs and dietary exposures and colon and rectal cancer risk. In drinking water analyses, we compared

risks in average nitrate or TTHM exposure quintiles to risks in the lowest exposure quintile (Q1). We evaluated categories of years >½ MCL based on the median duration for such exposure compared to women with no years of exposure >½ MCL. We compared risks among women on private well water to the women in Q1 of average nitrate levels in PWS; assuming no DBP exposure through private wells precluded a similar comparison to women in Q1 of TTHM. We evaluated dietary nitrate and nitrite intakes in quartiles or at the median for more limited intakes and estimated HRs for total nitrate and nitrite, and nitrite intakes from plant, animal, and processed meat sources separately (dietary nitrate was derived almost exclusively from plant sources (Jones, Weyer et al. 2016). We also computed associations for intakes of red and processed meats separate from their nitrate and nitrite content. We evaluated the linearity of relationships by modeling exposures using cubic splines and quadratic terms; as there was no evidence of non-linearity, we present natural log-transformed results for continuous variables.

We evaluated potential confounding based on data collected at enrollment, including smoking status (current smoker, former smoker, non-smoker) and pack-years smoked, body mass index, alcohol intake, estrogen use (ever/never), and various dietary intakes that were either relevant to nitrate formation or had been previously associated with colon or rectum cancers in the IWHS (e.g., fiber, saturated fat, calcium, vitamins C and E (Bostick, Potter et al. 1993, Bostick, Potter et al. 1993, Gapstur, Potter et al. 1994, Steinmetz, Kushi et al. 1994). Covariates were selected separately for colon and rectum cancers and for drinking water and dietary analyses based on univariate associations and when their retention in backward stepwise regression resulted in a ≥10% change in the exposure parameter estimate. Levels of NO_3-N and TTHM were not associated with most of these factors, and final drinking water models for both sites were adjusted for age, smoking category, and physical activity level, and were mutually adjusted for TTHM or NO_3-N. Final dietary models were at minimum adjusted for age and mutually adjusted for either dietary nitrate or nitrite. The median value of each exposure quintile was parameterized as a continuous variable for tests of linear trend.

We assessed multiplicative interactions between drinking water nitrate and several exposures, including TTHM levels, smoking status, and specific dietary intakes. Stratified associations were estimated by comparing to a common reference group of the lowest quintile of drinking water nitrate exposure and the lowest risk group for the potential effect modifier (e.g., <median TTHM, nonsmokers, ≥median vitamin C, and <median fiber, vitamin E, heme iron, and red meat). P-heterogeneity for these models was derived from likelihood ratio tests that compared fit between models including and excluding product interaction terms. We used $p<0.05$ as the criterion for statistical significance.

RESULTS

Among women >10 years at their PWS, with 87% reporting >20 years drinking from this source, we observed 612 colon cancers and 155 rectal cancer cases. PWS characteristics varied across levels of NO_3-N and TTHM (Table 1). Specifically, nitrate and TTHM levels were higher in PWS served by surface water sources. The proportion of PWS ever using chloramination treatment varied without clear pattern. Apart from smoking status, few

differences in lifestyle and dietary characteristics were observed across exposure categories (Table 1). A total of 212 colon and 54 rectal cancer cases were observed among private well users. As described previously, these women were less likely to smoke, consumed more calories and red meat, had lower vitamin C intakes, and higher BMIs than women on PWS (Quist, Inoue-Choi et al. 2018).

In multivariable models, we observed no consistent associations between average PWS nitrate or years >½-MCL for either colon or rectal cancer risk (Table 2). A positive association for colon cancer in the third exposure quintile was statistically significant ($HR_{Q3vs.Q1}$=1.32; CI=1.03–1.69; Table 2), however, risks were not evident in other quintiles and there was no association with continuous nitrate levels (HR per 1 mg/L ln-NO_3-N=1.04,95%CI:0.89–1.21). Average TTHM levels were not associated with colon cancer risk (HR_{Q5vsQ1}=1.13,95%CI:0.89–1.44;p-trend=0.11;Table 2). Rectal cancer risks were significantly higher for women in the top two quintiles of average TTHM compared to Q1 (HR_{Q5vsQ1}=1.71,95%CI:1.00–2.92; p-trend =0.22;Table 2). Associations with the number of years of exposure >½ MCL TTHM suggested increased risks for colon cancer both among women exposed 1–35 years (HR=1.26,95%CI:1.01–1.58) and ≥36 years (HR=1.23,95%CI:0.97,1.56; p-trend=0.07) compared with women with 0 years of exposure at this level. We observed no association with years >½ MCL TTHM and rectal cancer (Table 2). Chloramination of the PWS was not associated with risk of either cancer (data not shown).

Compared with women on PWS with low (Q1) nitrate, we observed no associations for either cancer site among women on private wells. We found no evidence of multiplicative interaction between drinking water nitrate and vitamin C or smoking status on risk of either cancer (data not shown). Nitrate models stratified by TTHM level similarly did not suggest a statistical interaction (Table S1).

In quartile analyses of individual DBPs, we observed no associations for THMs and colon cancer risk (Table 3). Risk of colon cancer was significantly higher for women in the top category of BCAA exposure compared to Q1 (HR=1.26, 95%CI=1.01–1.57; p-trend=0.03) and for continuous BCAA, and was non-significantly elevated in the highest exposure quartiles of the two other HAAs and the summed HAAs (p-trend=0.01–0.05). Rectal cancer risk was positively associated with estimated concentrations of THMs. For BDCM, these risks were elevated across exposure quartiles (p-trend=0.09) and the association with continuous levels was statistically significant (HR per 1 μg/L ln-BDCM=1.16, 95%CI=1.04–1.28). For chloroform, the association with continuous levels was statistically significant (HR=1.12, 95% CI=1.03–1.22). Rectal cancer risks were also observed in association with the top two quartiles of TCAA with no monotonic trend (HR=1.92, 95%CI=1.20–3.09; p-trend=0.18). An increased rectal cancer risk with BCAA was suggested, but the pattern of association was inconsistent. Risks were significantly increased in association with continuous summed HAAs.

Associations between total estimated dietary nitrate intake and both colon and rectal cancer risk were null, as were associations with dietary nitrite overall and with intakes from plant, animal, and processed meat sources evaluated separately (Table 4). We observed

no modification of these associations by smoking status or by intakes of vitamins C and E, fiber, heme iron, and red meat (data not shown). Relatively high intakes of red meat were associated with increased colon cancer risk (HR_{Q5vsQ1}=1.18, 95%CI:1.01–137; p-trend=0.04), but associations for rectal cancer were not statistically significant (Table 4). Processed meat intakes were not associated with risk of colon or rectal cancer.

DISCUSSION

In this analysis among postmenopausal women in Iowa, we found no association between average NO_3-N concentrations in PWS and colon or rectum cancer risk. Factors shown to influence endogenous NOC formation did not modify colon or rectal cancer risks associated with nitrate from either drinking water or diet. We found a significantly higher risk of rectal cancer among women exposed to average estimated TTHM levels >7.83 μg/L in public drinking water, as well as positive associations for individual THMs and HAAs. Modest positive associations between DBPs and colon cancer were also suggested, although not all statistically significant.

Ingested drinking water contaminants are an exogenous CRC risk factor of interest due to relevant contact between these compounds and colorectal tissues. Human feeding studies demonstrate increased levels of total NOC in feces following ingestion of nitrate from drinking water in combination with red meat (Rowland, Granli et al. 1991, Hughes, Cross et al. 2001). Nitrate in drinking water at levels near or above the MCL can supersede diet as a primary exposure source in communities with nitrate contamination of either surface or groundwater (Ward 2009), as is common in Iowa. A prior investigation in the IWHS assessed drinking water nitrate exposure as a single long-term average level for each PWS (Weyer, Cerhan et al. 2001); in the current analysis, we accounted for the duration of exposure to elevated levels, concomitant DBP exposures, and added 12 years of follow-up. Like a case-control study of colon and rectum cancers in Iowa (De Roos, Ward et al. 2003), we observed no association with average drinking water nitrate exposure levels or with the duration of exposure to nitrate levels > 5 mg/L (De Roos, Ward et al. 2003). In contrast to our findings, a large registry-based cohort study in Denmark found increased risk of CRC at average levels >17.1 mg/L as NO_3 (3.86 mg/L as NO_3-N) (Schullehner, Hansen et al. 2018). A multi-center case-control study in Spain and Italy found positive associations with estimated daily water NO_3-N intake >2.3 mg/day for both colon and rectal cancers (Espejo-Herrera, Gracia-Lavedan et al. 2016). Differences in exposure levels in these studies do not fully explain the lack of consistency with our findings, as long-term average NO_3-N concentrations in the IWHS population (mean=1.83; median=1.07 mg/L) were comparable. Two small case-control studies observed positive CRC associations at higher levels above the U.S. MCL, including with long-term exposure to nitrate >50 mg/L (>11.3 mg/l NO_3-N) in well water in Indonesia (Fathmawati, Fachiroh et al. 2017), and with >10 mg/L on private wells in Wisconsin (McElroy, Trentham-Dietz et al. 2008). Different patterns of association between colon and rectal cancer and nitrate in drinking water could indicate etiologic heterogeneity, but evidence remains limited. While the two European studies found a consistent positive association for both colon and rectal cancers separately, the study in Wisconsin observed an increased risk for only proximal colon cancer, but not distal colon cancer or rectal cancer, in relation to estimated nitrate levels (McElroy, Trentham-Dietz et al.

2008). The previous investigation in the IWHS found no association with colon cancer, and a statistically significant inverse association with rectal cancer, with nitrate levels >2.5 mg/L in PWS (Weyer, Cerhan et al. 2001). We did not observe an inverse association for rectal cancer in our updated analysis.

We hypothesized that women with greater exposure to nitrosation precursors from diet or cigarette smoking would have higher risk of colorectal cancer due to higher endogenous formation of NOC. Antioxidants have been shown to inhibit this reaction in the gastrointestinal tract (Mirvish 1986, Bartsch, Ohshima et al. 1988, Bartsch, Pignatelli et al. 1993, Bartsch and Frank 1996). A protective effect of antioxidant intake has been observed for gastric cancers, possibly due to this reduction in NOC exposure. In contrast, diets rich in heme iron and thiocyanate in cigarette smoke may promote NOC formation (International Agency for Research on Cancer (IARC) 2010). The case-control study in Iowa reported significant interactions between long-term consumption of public drinking water with average levels >5 mg/L NO_3-N with low vitamin C and high red meat intakes. Increased risk was observed only among those with higher water nitrate intake and lower vitamin C or high red meat intake (De Roos, Ward et al. 2003). The case-control study in Spain and Italy also found that drinking water nitrate-colorectal cancer associations varied by intakes of red meat, vitamins C and E, and fiber, although none of these interactions were statistically significant (Espejo-Herrera, Gracia-Lavedan et al. 2016). We did not observe evidence of these interactions in the IWHS. Thus, our findings contribute to a literature inconsistently demonstrating that ingestion of NOC precursors may influence the association between drinking water nitrate and CRC (Ward, deKok et al. 2005, Ward, Jones et al. 2018).

We observed a positive association between long-term average TTHM and individual THMs and HAAs in relation to rectal cancer, a finding for which existing epidemiologic evidence remains limited. Several ecologic studies and investigations of cancer mortality suggested non-significantly elevated risks of CRC in association with THM levels or years of exposure to chlorinated drinking water (Cantor, Steinmaus et al. 2018). Subsequent case-control studies examined levels of TTHM, the most abundant DBP class and the most routinely measured regulated contaminant, as a marker of DBPs in chlorinated drinking water. A Canadian population-based case-control study reported an increased risk of colon cancer in association with long duration of exposure to drinking water with levels ≥50 μg/L THMs among men, but no such association was observed among women and no increased risks were observed for rectal cancer (King, Marrett et al. 2000). A case-control study in Iowa found a positive association for rectal cancer, but not colon cancer, with duration of chlorinated water use and with several measures of estimated lifetime TTHM exposure (Hildesheim, Cantor et al. 1998). Average TTHM levels >62 μg/L were not associated with CRC overall in a case-control study in Spain and Italy where risk of combined colon and rectal cancers were evaluated (Villanueva, Gracia-Lavedan et al. 2017). This study also reported an inverse association with chloroform and a positive association with the highest exposure to brominated THMs (median=9 μg/L), although the latter was observed only among men. An ecologic analysis in Australia observed an elevated incidence rate ratio for CRC among men, but not women, in relation to bromoform levels (Rahman, Cowie et al. 2014). A case-control study in New York found that increasing bromoform levels (mean; median=1.30; 0.45 μg/L) were associated with rectal cancer

(Bove, Rogerson et al. 2007). All four of the structurally-related THMs comprising TTHM (chloroform, bromoform, bromodichloromethane, and dibromochloromethane) are carcinogenic in rodents. Toxicological studies have shown development of preneoplastic rectal lesions in rats following drinking water exposure to bromodichloromethane and bromoform, both of which are genotoxic (National Toxicology Program 1989, DeAngelo, Geter et al. 2002). The plausibility of increased colon cancer risk associated with BCAA exposure suggested in our analysis is also supported by animal data that demonstrate increased incidence of rare adenomas of the large intestine of rats (International Agency for Research on Cancer (IARC) 2013). Thus, both epidemiologic and experimental studies provide some evidence that brominated DBPs may be more important than chlorinated DBPs to CRC etiology. However, mechanisms for the carcinogenicity of DBPs individually or as part of a mixture, which is more reflective of actual human exposure, are still being explored (Richardson, Plewa et al. 2007).

The IWHS population is served primarily by ground water sources. DCAA accounts for the majority (~43%) of HAA5 across groundwater systems in the U.S. (Environmental Protection Agency (EPA) 2005), and estimated average DCAA exposures (mean; median=5.3; 2.3) were low in the cohort compared to levels in large groundwater systems nationally (Environmental Protection Agency (EPA) 2005). Few study participants (<1%) were exposed to HAA5 at levels above the regulatory limit (60 μg/L) and only 13% at levels >½ MCL. No studies have reported an association between HAAs and CRC; our data allowed investigation of BCAA, an unregulated HAA for which epidemiologic evaluation is limited. Natural bromide sources are uncommon in Iowa, and average BCAA levels (1.47 μg/L) in the IWHS population were comparable to national groundwater occurrence estimates (International Agency for Research on Cancer (IARC) 2013). Levels of BDCM (mean; median=3.3; 1.2 μg/L) were also lower than the lifetime residential tap water concentrations of brominated THMs observed in Villanueva et al. (2017) (Villanueva, Gracia-Lavedan et al. 2017). The positive rectal cancer association with TCAA and suggestive association with BCAA require replication in other study populations with a greater range of exposure to these HAAs.

Our analyses using estimates of individual DBPs should be interpreted cautiously due to their high correlations and the complex nature of drinking water mixtures arising from variation in disinfection practices, organic matter composition, natural bromide sources, and other hydrogeological characteristics of the water supplies which complicate comparisons to other studies. However, our results indicate some associations between DBPs and rectal cancer that should be further explored. Because of the intensity of agricultural land use and high nitrogen inputs into source waters in Iowa, unregulated nitrogenous DBPs (e.g., N-nitroso-dimethylamine [NDMA]) could be more abundant than in other regions, but we were not able to estimate these species in the IWHS. Chloramination treatment of the PWS is a crude surrogate for exposure to higher levels of certain nitrogenous DBPs (e.g., NDMA); however, it was not associated with increased risk of CRC. We did not confirm the positive association between chloroform and colon cancer in the IWHS previously observed by Doyle et al. (1997) in follow-up through 1993, for which exposure assessment relied only on measurement data from short-term drinking water measurement campaigns in 1979 and 1986/1987 (Doyle, Zheng et al. 1997). However, our DBP estimates likely represent a better

assessment of historical exposure (Krasner, Cantor et al. 2017), therefore these different findings may be explained by poor correlation between cross-sectional measures and long-term average exposures. Our updated analyses are also comparatively well-powered, as the previous evaluation included only 79 rectal cancer cases.

Processed meat is classified by IARC as carcinogenic to humans, with the weight of evidence driven by epidemiologic studies of CRC risk (International Agency for Research on Cancer (IARC) 2018). Processed meats are a common source of NOC in U.S. diets, but in contrast to the findings of multiple case-control and prospective studies (International Agency for Research on Cancer (IARC) 2018), we found no associations with estimated dietary nitrate/nitrite intakes overall or with nitrite intakes from processed meats. Another large cohort of women, the Shanghai Women's Health Study, reported higher CRC risks associated with dietary nitrate among women with low vitamin C intakes (Dellavalle, Xiao et al. 2014). In the EPIC cohort, dietary NDMA was associated with increased gastrointestinal cancer risk overall and rectal cancer specifically, and risk was similarly higher among individuals with low vitamin C intakes (Loh, Jakszyn et al. 2011). However, few other studies had comparable quantitative estimates of nitrate/nitrite intake and instead use processed meat consumption as a proxy since most processed meats contain added nitrate and nitrite (International Agency for Research on Cancer (IARC) 2018). Our finding of an increased colon cancer risk in association with red meat intake has been observed in several other prospective investigations, but the putative carcinogenic components of meat have not been identified. Both animal and human studies suggest that meat-related CRC may be driven from nitrate and/or nitrite used as a preservative of processed meats, which are an NOC source. Red processed meats may be especially important, as human feeding studies have demonstrated that red, but not white, processed meat increases fecal NOC (Bingham, Hughes et al. 2002). However, meats cooked at high temperatures are also a source of dietary heterocyclic amines and polycyclic aromatic hydrocarbons, which have been associated with dose-dependent DNA adducts and risk of colorectal adenoma, respectively (International Agency for Research on Cancer (IARC) 2018). Because of the inconsistency in how these dietary exposures are assessed in previous studies, we explored main effects of red meat intake, as well as potential modification of drinking water and dietary nitrate associations by intakes of heme iron and red and processed meat. Two studies reported suggestive, but non-statistically significant relationships between CRC and dietary nitrate among individuals with red meat intake (Dellavalle, Xiao et al. 2014, Espejo-Herrera, Gracia-Lavedan et al. 2016). The null associations observed with processed meat in our data are inconsistent with most studies (International Agency for Research on Cancer (IARC) 2018). We note that average intakes of red meat were higher in the IWHS at enrollment in 1986 compared to intakes in the general female U.S. population in 2003–2004 (mean=90 vs. 53 g/day) (Daniel, Cross et al. 2011), although processed meat intakes were considerably lower in the IWHS (mean=3 vs. 18 g/day).

Strengths of this study include the availability of historical water quality data, long period of follow-up, and low rates of residential mobility among cohort participants. We restricted drinking water analyses to women with long duration at their water source, which allowed latent periods of >20 years for >85% of the population and supports the general plausibility for our findings. Associations for women using private wells were of interest due to the

potential for these women to have high nitrate (and theoretically, no DBP) exposure through their drinking water source, but we were unable to estimate exposures for these women as we lacked information on well depth. Instead, we compared women on private wells to those on PWS exposed to the lowest quartile of average nitrate (≤0.36 mg/L), based on published data showing average nitrate concentrations in private wells across Iowa were higher (3.2 mg/L) (Wheeler, Nolan et al. 2015). While our analyses of TTHM indicated associations with estimated long-term average levels, a relationship with the duration of exposure was not clear. This is likely due to limited variation in historical TTHM estimates, as measurement data were sparse. Average TTHM levels in our population were low compared to levels associated with bladder cancer in other studies (>~50 μg/L), the site for which the epidemiologic associations with DBPs are most consistent (Cantor, Steinmaus et al. 2018). While the top TTHM exposure category in our data included estimated average exposure levels >17.7 μg/L, the mean and median concentrations in this group were 72 and 76 μg/L, respectively, indicating that some women had estimated exposure levels comparable to other studies. However, the number of rectal cancer cases was too small to evaluate whether associations were stronger among women in the >95th percentile (>93 μg/L) of exposures. Misclassification of drinking water nitrate exposure was also a concern. Levels were low and there was variability in the number of available measurements, which historically were required of PWS under specific conditions relating to nitrate contamination and the size of the population served. Women living in areas with high nitrate concentrations in their drinking water may also choose to drink bottled water, but very few women reported drinking bottled water. We acknowledge further potential misclassification of all drinking water exposures due to a lack of information on total water intake. We were also limited by use of a FFQ to estimate dietary intakes, which was based on diet for the past 12 months and may not sufficiently reflect past dietary exposure.

CONCLUSION

Ingested nitrate from drinking water at levels below the MCL was not associated with colon or rectal cancer risk in the IWHS. However, our results suggest that ingestion of the highest average DBP levels, as estimated for our study, is a risk factor for rectal cancer. Positive associations with individual haloacetic acids and trihalomethanes, most consistent for rectal cancer, require further investigation in study populations with higher exposures. Our data did not support a relationship between dietary nitrate and nitrite and colon or rectal cancer, adding to the mixed associations observed from a limited number of studies with quantitative exposure estimates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Nitrate in drinking water was not associated with risk of colon or rectal cancers.
- Exposure to total trihalomethanes in drinking water is associated with the risk of rectal cancer.
- Increased risks of both colon and rectal cancers associated with other disinfection byproducts are plausible and require replication in larger studies.
- Red meat intake was associated with colon cancer risk.

Table 1.

Characteristics of Iowa Women's Health Study participants at their reported public drinking water source >10 years (N=15,910), by quintiles of long-term average nitrate-nitrogen (NO_3-N) and total trihalomethanes (TTHM)

	NO_3-N (mg/L)					TTHM (μg/L)				
	<0.38	**0.38–0.80**	**0.81–1.35**	**1.36–3.50**	**>3.50**	**<0.68**	**0.68–2.17**	**2.18–7.52**	**7.53–17.70**	**>17.70**
	n=3,317	**n=3,133**	**n=3,085**	**n=3,316**	**n=3,059**	**n=3,226**	**n=3,279**	**n=3,041**	**n=3,202**	**n=3,162**
Age, years [mean(sd)]	61.7 ± 4.2	61.7 ± 4.2	61.6 ± 4.1	61.6 ± 4.2	61.7 ± 4.1	61.5 ± 4.2	61.8 ± 4.2	61.1 ± 4.2	61.8 ± 4.2	61.5 ± 4.1
Race, %										
White	98.3	98.6	98.4	98.3	97.8	98.7	98.2	98.1	98.3	98.3
Non-white	0.6	0.3	1.1	0.6	1.5	0.4	0.6	0.1	1.1	0.8
missing	1.1	1.1	0.6	0.1	0.8	0.9	1.2	0.8	0.6	0.9
Education, %										
Less than high school	6.8	6.0	5.6	7.7	5.0	7.3	7.2	4.6	6.8	5.1
High school	52.8	51.7	53.8	52.2	50.0	52.6	50.7	53.1	50.9	53.4
<More than high school	40.3	42.2	40.6	39.9	44.9	39.9	41.9	42.3	42.2	41.4
missing	0.2	0.2	0.1	0.2	0.1	0.2	0.2	0.1	0.1	0.1
Smoking status, %										
Current	16.9	14.0	17.7	15.4	15.8	15.1	14.6	17.0	15.8	17.4
Former	21.6	20.2	24.0	22.4	21.8	18.9	19.5	24.2	22.7	24.8
Never	60.1	64.6	57.3	61.3	60.7	64.6	64.5	57.5	60.3	56.8
missing	1.4	1.2	1.0	1.0	1.6	1.4	1.5	1.3	1.2	1.0
Body Mass Index, %										
<25	22.0	21.5	20.9	21.3	22.1	22.4	22.0	21.6	20.5	21.4
25–30	36.8	37.3	35.4	37.2	35.6	36.3	36.6	36.9	36.7	26.1
≥30	41.1	41.1	43.7	41.4	42.3	41.3	41.5	41.6	42.8	42.6
Physical activity, %										
Low	46.2	45.7	46.8	47.0	46.9	45.3	46.5	46.8	47.4	46.6
Medium	27.5	27.6	26.8	26.6	25.5	28.1	26.8	26.9	25.6	26.6
High	25.0	25.3	25.4	25.2	26.6	25.3	25.4	25.3	26.9	25.6
missing	1.4	1.4	1.1	1.1	1.1	1.3	1.3	1.1	1.2	1.2
PWS, %										

	NO_3-N (mg/L)					TTHM (μg/L)				
	<0.38	**0.38–0.80**	**0.81–1.35**	**1.36–3.50**	**>3.50**	**<0.68**	**0.68–2.17**	**2.18–7.52**	**7.53–17.70**	**>17.70**
	n=3,317	**n=3,133**	**n=3,085**	**n=3,316**	**n=3,059**	**n=3,226**	**n=3,279**	**n=3,041**	**n=3,202**	**n=3,162**
Ground water	96.9	92.5	65.9	76.6	52.1	100	99.2	92.7	57.6	36.0
Surface water source	3.1	7.5	34.1	23.4	47.9	0	0.8	7.3	42.4	64.0
Chloraminated[a]	18.5	27.5	61.6	20.9	0.8	0.5	11.2	40.9	17.3	60.5
Dietary intakes (median) [b]										
Calories, kcal/d	1676.7	1705.5	1668.9	1684.0	1702.6	1682.0	1672.2	1677.7	1718.0	1696.2
Vitamin C, mg/d	84.7	83.4	84.9	82.9	82.8	85.0	83.9	83.4	82.9	83.8
Vitamin E, mg/d	5.2	4.9	5.1	5.1	5.0	5.2	5.1	5.2	4.9	4.9
Red meat, g/d	41.7	44.1	43.4	45.1	43.8	43.0	41.9	42.4	45.1	45.1
Processed meats, g/d	2.3	2.4	2.5	2.4	2.5	2.6	2.3	2.4	2.3	2.5
Heme iron, mg/d	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Nitrate, mg/d	61.2	61.8	63.4	60.2	61.4	63.0	62.4	63.6	60.7	59.4
Nitrate processed meats, mg/d	0.1	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.1	0.2
Nitrite, mg/d	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Calcium, mg/d	607.5	580.0	570.9	569.4	559.9	576.4	588.6	594.2	564.7	565.5
Fat (total), g/d	37.3	37.6	37.5	37.8	37.7	37.7	37.4	37.4	37.6	37.8
Fiber (soluble), g/d	3.3	3.3	3.3	3.4	3.3	3.3	3.3	3.3	3.3	3.3
Fiber (insoluble), g/d	8.2	8.0	8.1	8.2	8.0	8.1	8.1	8.1	8.1	8.0

[a] PWS ever used chloramine treatment during study period.

[b] All micronutrients are adjusted per 1000kcal/day of total energy intake.

Table 2.

Associations between nitrate and total trihalomethanes (TTHM) in public water supplies and incident colon and rectal cancers, Iowa Women's Health Study participants >10 years at their drinking water source (N=15,532[a])

		Colon		Rectum	
	N	**Cases**	**HR[b], 95%CI**	**Cases**	**HR[b], 95%CI**
Average NO_3-N (mg/L)					
≤0.36	3,226	118	1.00 (Ref.)	39	1.00 (Ref.)
0.37–0.80	3,055	126	1.13 (0.88, 1.45)	18	0.48 (0.28, 0.84)
0.81–1.35	3,020	146	1.32 (1.03, 1.69)	35	0.86 (0.53, 1.38)
1.36–3.51	3,251	116	0.98 (0.76, 1.27)	39	0.94 (0.60, 1.48)
>3.51	2,980	106	0.97 (0.75, 1.26)	24	0.64 (0.38, 1.07)
p_{trend}			0.18		0.69
Continuous[c]			0.97 (0.90, 1.05)		0.93 (0.80, 1.08)
Years >5 mg/L NO_3-N					
0		447	1.00 (Ref.)	111	1.00 (Ref.)
1–4	10,891	96	0.91 (0.73, 1.13)	25	0.97 (0.63, 1.50)
≥4	2,613	69	0.82 (0.63, 1.06)	19	0.86 (0.53, 1.41)
p_{trend}	2,028		0.10		0.60
Private well [d]		246	1.04 (0.89, 1.21)	64	1.08 (0.80, 1.45)
Average TTHM (µg/L)					
≤0.68	3,143	189	1.00 (Ref.)	37	1.00 (Ref.)
0.69–2.17	3,191	149	0.87 (0.67, 1.12)	33	1.28 (0.73, 2.20)
2.18–7.82	2,973	135	1.10 (0.85, 1.41)	35	1.63 (0.94, 2.84)
7.83–17.7	3,130	118	0.87 (0.67, 1.13)	41	1.83 (1.06, 3.16)
>17.7	3,095	147	1.13 (0.89, 1.44)	40	1.71 (1.00, 2.92)
p_{trend}			0.11		0.22
Continuous[c]			1.01 (0.98, 1.05)		1.06 (0.99, 1.14)
Years >40 µg/L TTHM					
0	11,768	440	1.00 (Ref.)	110	1.00 (Ref.)
1– 35	1,946	91	1.26 (1.01, 1.58)	26	1.43 (0.93, 2.20)

			Colon		Rectum
	N	**Cases**	**HR[b], 95%CI**	**Cases**	**HR[b], 95%CI**
≥36	1,818	81	1.23 (0.97, 1.56)	19	1.13 (0.69, 1.84)
p_{trend}			0.07		0.36

[a] After excluding 378 participants with missing covariate data.

[b] All models adjusted for age, physical activity, smoking status, and mutually adjusted for NO_3-N or TTHM.

[c] HR per 1 unit increase in the natural log-transformed value.

[d] Reference group is women in Q1 of average NO_3-N.

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Table 3.

Associations between average trihalomethanes and haloacetic acids in public water supplies and incident colon and rectal cancers, Iowa Women's Health Study participants >10 years at their drinking water source (N=15,532[a])

		Colon		Rectum	
	N	Cases	HR[b], 95% CI	Cases	HR[b], 95% CI
$CHCl_3$(μg/L)					
0.60	3,358	157	1.00 (Ref.)	30	1.00 (Ref.)
0.60–1.85	3,659	134	0.90 (0.72, 1.4)	32	1.13 (0.70, 1.87)
1.86–8.41	3,623	137	0.94 (0.75, 1.19)	45	1.68 (1.05, 2.70)
>8.41	4,392	184	1.08 (0.86, 1.34)	48	1.52 (0.95, 2.45)
p_{trend}			0.17		0.25
Continuous[c]			1.03 (0.99, 1.08)		1.12 (1.03, 1.22)
BDCM (μg/L)					
<0.25	4,741	178	1.00 (Ref.)	31	1.00 (Ref.)
0.25–1.16	3,328	139	1.14 (0.92, 1.43)	38	1.76 (1.10, 2.84)
1.17–3.78	3,793	141	1.03 (0.81, 1.30)	44	1.99 (1.22, 3.25)
>3.78	3,670	154	1.16 (0.94, 1.45)	42	1.87 (1.17, 3.00)
p_{trend}			0.30		0.09
Continuous			1.03 (0.98, 1.09)		1.16 (1.04, 1.28)
DCAA (μg/L)					
<1.65	4,206	169	1.00 (Ref.)	35	1.00 (Ref.)
1.65–2.27	2,864	97	0.83 (0.65, 1.07)	27	1.11 (1.67, 1.84)
2.28–4.84	4,259	153	0.90 (0.73, 1.13)	46	1.31 (0.84, 2.03)
>4.84	4,203	193	1.17 (0.95, 1.44)	47	1.34 (0.87, 2.08)
p_{trend}			0.01		0.32
Continuous			1.07 (1.00, 1.16)		1.13 (0.98, 1.31)
TCAA (μg/L)					
<0.25	4,673	181	1.00 (Ref.)	30	1.00 (Ref.)
0.25–0.63	1,900	68	0.94 (0.71, 1.25)	21	1.70 (0.99, 2.98)
0.64–1.69	5,249	199	1.02 (0.82, 1.25)	61	1.94 (1.24, 3.05)
>1.69	3,710	164	1.20 (0.97, 1.49)	43	1.92 (1.20, 3.09)

		Colon		Rectum	
	N	Cases	HR[b], 95% CI	Cases	HR[b], 95% CI
p_{trend}			0.05		0.18
Continuous			1.03 (0.99, 1.08)		1.14 (1.04, 1.25)
BCAA (μg/L)					
<0.1	6,289	230	1.00 (Ref.)	49	1.00 (Ref.)
0.1–0.94	2,449	83	0.96 (0.74, 1.23)	33	1.79 (1.15, 2.79)
0.95–1.89	4,012	161	1.17 (0.94, 1.46)	43	1.52 (0.97, 2.38)
>1.89	3,160	138	1.26 (1.01, 1.57)	30	1.30 (0.81, 2.08)
p_{trend}			0.03		0.87
Continuous			1.10 (0.99, 1.23)		0.92 (0.76, 1.11)
HAA5 (μg/L)					
<0.1	3,869	163	1.00 (Ref.)	34	1.00 (Ref.)
0.1–0.94	3,178	104	0.78 (0.61, 1.00)	26	0.95 (0.57, 1.59)
0.95–1.89	4,539	164	0.86 (0.70, 1.08)	51	1.30 (0.84, 2.01)
>1.89	3,946	181	1.12 (0.91, 1.39)	44	1.29 (0.82, 2.03)
p_{trend}			0.05		0.33
Continuous			1.06 (0.99, 1.13)		1.14 (1.01, 1.29)
HAA6 (μg/L)					
<0.1	3,921	159	1.00 (Ref.)	32	1.00 (Ref.)
0.1–0.94	4,878	166	0.84 (0.68, 1.05)	50	1.27 (0.81, 1.99)
0.95–1.89	2,795	108	0.98 (0.76, 1.27)	27	1.26 (0.74, 2.14)
>1.89	3,938	179	1.16 (1.16, 1.43)	46	1.46 (0.93, 2.31)
p_{trend}			0.02		0.18
Continuous			1.06 (1.00, 1.13)		1.15 (1.02, 1.29)

[a] After excluding 378 participants with missing covariate data.

[b] All models adjusted for age, physical activity, smoking status, and mutually adjusted for NO_3-N.

[c] Per 1-unit change in natural log-transformed value.

$CHCl_3$, chloroform; BDCM, bromodicholoromethane; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid; HAA5 and HAA6, haloacetic acids; BCAA, bromochloroacetic acid.

Table 4.

Associations between energy-adjusted dietary nitrate (NO_3-N) and nitrite and meat intakes and incident colon and rectal cancers (N=34,708)

		Colon		Rectum	
	N	Cases	HR[b], 95% CI	Cases	HR[c], 95% CI
Dietary NO_3-N[a](mg/day)					
≤9.80	8,676	324	1.00 (Ref.)	79	1.00 (Ref.)
9.81–13.80	8,674	324	0.98 (0.84, 1.15)	81	1.03 (0.76, 1.41)
13.81–19.29	8,685	321	0.97 (0.83, 1.13)	71	0.91 (0.66, 1.26)
>19.29	8,673	355	1.11 (0.94, 1.30)	94	1.27 (0.93, 1.74)
P_{trend}			0.17		0.09
Continuous[d]			1.07 (0.96, 1.20)		1.15 (0.92, 1.45)
Dietary Nitrite (mg/day)					
≤0.57	8,588	345	1.00 (Ref.)	93	1.00 (Ref.)
0.58–0.65	8,655	342	0.93 (0.80, 1.08)	74	0.75 (0.55, 1.02)
0.66–0.74	8,974	320	0.83 (0.71, 0.97)	91	0.88 (0.65, 1.18)
>0.74	8,491	317	0.87 (0.74, 1.02)	67	0.68 (0.49, 0.94)
P_{trend}			0.05		0.04
Continuous			0.82 (0.63, 1.07)		0.66 (0.39, 1.12)
Plant sources					
≤0.32	8,225	309	1.00 (Ref.)	73	1.00 (Ref.)
0.33–0.39	9,618	368	0.97 (0.83, 1.13)	102	1.12 (0.83, 1.52)
0.40–0.48	7,889	308	0.99 (0.85, 1.18)	75	1.00 (0.72, 1.39)
>0.48	8,976	339	0.96 (0.81, 1.14)	75	0.86 (0.61, 1.21)
P_{trend}			0.72		0.33
Continuous			0.95 (0.79, 1.14)		0.89 (0.61, 1.30)
Animal sources					
≤0.19	9,151	361	1.00 (Ref.)	82	1.00 (Ref.)
0.20–0.24	8,387	326	0.92 (0.79, 1.08)	97	1.26 (0.94, 1.69)
0.25–0.30	8,581	345	0.94 (0.80, 1.09)	80	1.02 (0.75, 1.38)
>0.30	8,264	292	0.82 (0.70, 0.97)	66	0.89 (0.64, 1.23)

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		Colon		Rectum	
	N	Cases	HR[b], 95% CI	Cases	HR[c], 95% CI
p_{trend}			0.03		0.11
Continuous			0.87 (0.74, 1.02)		0.75 (0.55, 1.01)
Processed meats [e]					
0	5,966	220	1.00 (Ref.)	58	1.00 (Ref.)
≤0.02	9,712	351	0.97 (0.82, 1.15)	86	0.88 (0.63, 1.23)
0.02–0.04	9,400	392	1.11 (0.94, 1.31)	99	1.03 (0.74, 1.43)
>0.04	9,630	361	1.03 (0.86, 1.22)	82	0.84 (0.59, 1.19)
p_{trend}					
Continuous			1.03 (0.99, 1.07)		0.98 (0.90, 1.05)
Red meat (g/day) [f]					
≤30.1	8,690	303	1.00 (Ref.)	70	1.00 (Ref.)
30.2–49.1	8,679	326	1.09 (0.93, 1.27)	86	1.24 (0.91, 1.70)
49.2–63.4	8,664	346	1.14 (0.98, 1.34)	90	1.29 (0.94, 1.76)
>63.4	8,675	349	1.18 (1.01, 1.37)	79	1.15 (0.83, 1.59)
p_{trend}			0.04		0.48
Continuous			1.09 (1.02, 1.16)		1.08 (0.95, 1.24)
Processed meat (g/day) [f]					
≤0.74	11,565	315	1.00 (Ref.)	85	1.00 (Ref.)
0.75–2.44	6,028	338	1.08 (0.92, 1.26)	77	0.92 (0.67, 1.25)
2.45–4.59	8,794	346	1.10 (0.94, 1.28)	84	0.99 (0.74, 1.35)
>4.59	8,321	325	1.07 (0.91, 1.25)	79	0.97 (0.71, 1.32)
p_{trend}			0.55		0.15
Continuous			1.07 (1.00, 1.15)		0.98 (0.85, 1.12)

[a] NO_3^- converted to NO_3-N. Dietary nitrate was derived almost exclusively from plant sources, therefore results are presented only for total dietary nitrate.

[b] Models adjusted for age, heme iron, red meat, and mutually adjusted for total dietary nitrate or nitrite.

[c] Models adjusted for age and mutually adjusted for total dietary nitrate or nitrite.

[d] Per 1-unit change in natural log-transformed value.

[e] Not mutually adjusted for nitrate from processed meat sources due to high correlation.

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[f] Models adjusted for age and total dietary nitrate.