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Drinking Water Disinfection Byproducts, Ingested Nitrate, and Risk of Endometrial Cancer in Postmenopausal Women

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Background: Disinfection byproducts (DBPs) and *N*-nitroso compounds (NOC), formed endogenously after nitrate ingestion, are suspected endometrial carcinogens, but epidemiological studies are limited.

Objectives: We investigated the relationship of these exposures with endometrial cancer risk in a large prospective cohort.

Methods: Among postmenopausal women in the Iowa Women's Health Study cohort, we evaluated two major classes of DBPs, total trihalomethanes (TTHM) and five haloacetic acids (HAA5), and nitrate-nitrogen (NO_3-N) in public water supplies (PWS) in relation to incident primary endometrial cancer (1986–2014). For women using their PWS >10 y at enrollment ($n = 10{,}501$; cases = 261), we computed historical averages of annual concentrations; exposures were categorized into quantiles and when possible ≥95th percentile. We also computed years of PWS use above one-half the U.S. maximum contaminant level (>½ MCL; 40 μg/L TTHM; 30 μg/L HAA5; 5 mg/L NO_3-N). Dietary nitrate/nitrite intakes were estimated from a food frequency questionnaire. We estimated hazard ratios (HR) and 95% confidence intervals (CI) via Cox models adjusted for age, endometrial cancer risk factors [e.g., body mass index, hormone replacement therapy (HRT)], and mutually adjusted for DBPs or NO_3-N. We evaluated associations for low-grade (cases = 99) vs. high-grade (cases = 114) type I tumors. We assessed interactions between exposures and endometrial cancer risk factors and dietary factors influencing NOC formation.

Results: Higher average concentrations of DBPs (95th percentile: TTHM ≥93 μg/L, HAA5 ≥49 μg/L) were associated with endometrial cancer risk (TTHM: $HR_{95vsQ1} = 2.19$, 95% CI: 1.41, 3.40; HAA5: $HR_{95vsQ1} = 1.84$, 95% CI: 1.19, 2.83; *p*trend <0.01). Associations were similarly observed for women greater than median years of PWS use with levels >½ MCL, in comparison with zero years (TTHM: $HR_{36+vs0y} = 1.61$, 95% CI: 1.18, 2.21; HAA5: $HR_{38+vs0y} = 1.85$, 95% CI: 1.31, 2.62). Associations with DBPs appeared stronger for low-grade tumors (TTHM: $HR_{Q4vsQ1} = 2.12$, 95% CI: 1.17, 3.83; *p*-trend = 0.008) than for high-grade tumors (TTHM: $HR_{Q4vsQ1} = 1.40$, 95% CI: 0.80, 2.44; *p*-trend = 0.339), but differences were not statistically significant (*p*-heterogeneity = 0.43). Associations with TTHM were stronger among ever HRT users than non-HRT users (*p*-interaction <0.01). We observed no associations with NO_3-N in drinking water or diet.

Discussion: We report novel associations between the highest DBP levels and endometrial cancer for our Iowa cohort that warrant future evaluation. https://doi.org/10.1289/EHP10207

Introduction

Endometrial cancer is the most common gynecological cancer in the United States, with most cases occurring among postmenopausal women.[1] Established risk factors include obesity, other components of metabolic syndrome, and certain types of hormone replacement therapy (HRT).[2] The shared etiological pathway of such risk factors is thought to be increased levels of estrogen unopposed by progesterone,[3] which can lead to endometrial cell proliferation and transformation.[4] Decreased risk of endometrial cancer has been associated with reproductive factors related to fewer menstrual cycles, including oral contraceptive use, parity, and younger age at menopause.[5,6] The role of drinking water contaminants in endometrial cancer risk is not well-characterized, despite evidence of carcinogenicity[7–9] and demonstrated endocrine disrupting properties for certain chemicals.[10,11]

Trihalomethanes (THMs) and haloacetic acids (HAAs) are classes of disinfection byproducts (DBPs) frequently present in chlorinated water, a standard disinfection method for public drinking water supplies.[12] Some of the common THMs (e.g., chloroform) and HAAs (e.g., bromochloroacetic) have been classified as probable human carcinogens based on animal studies demonstrating genotoxicity, mutagenicity, and cell proliferation.[7,8] Animal studies have reported measures of infertility,[13–17] disruption in estrous cycles,[18] persistent elevated levels of serum estradiol levels,[19,20] and suppression of progesterone[18] following ingestion of DBPs in drinking water. Although the toxicity of DBPs in the uterus has not been directly investigated, a growing body of literature suggest endocrine disruptors in the environment may play an important role in endometrial cancer.[21]

Epidemiological studies evaluating THMs have produced the strongest evidence for bladder cancer risk[22–24] and some evidence for colorectal cancers[7,8,25]; epidemiological evidence for HAAs and cancer is considerably more limited.[7] To our knowledge, the only analysis of endometrial cancer and DBPs, which was conducted in the Iowa Women's Health Study (IWHS), found a nonsignificant increased risk among postmenopausal women who used public supplies that were sourced from surface water vs. ground water, and for women using public water with the highest levels of chloroform.[26] However, these results were limited by 8 y of follow-up time and measurements from two short-term statewide water monitoring efforts in 1979, 1986, and 1987.[26]

Nitrate (NO_3) is a common drinking water contaminant in agricultural areas and has been classified by the International

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Agency for Research on Cancer (IARC) as a probable human carcinogen under conditions that increase endogenous formation of *N*-nitroso compounds (NOCs), such as low dietary antioxidant levels.[9,27] Dietary intake of vegetables, particularly leafy greens, is also a source of nitrate, but NOC formation is unlikely due to the co-ingestion of antioxidants like vitamin C.[9] Ingestion of nitrite (NO_2-), which is added to processed meats, is more likely to result in NOC formation.[9] Bladder,[28] kidney, stomach, and colorectal cancers have been associated with drinking water nitrate and dietary nitrite from red and processed meats.[9,27] An analysis of drinking water nitrate in early follow-up of the IWHS found a statistically significant inverse association at the highest quartile of nitrate for endometrial cancer, but this analysis was based on 32 exposed cases, and authors noted possible chance findings[29] One case–control study found a decreased risk of endometrial cancer and dietary nitrate mainly from vegetables, whereas nitrite from processed foods was not evaluated.[30]

In the present study, we aimed to evaluate the relationship between drinking water contaminants and risk of endometrial cancer in the IWHS. Our analysis enhances the two previous investigations in this cohort[26,29] and includes more than 15 y of additional follow-up and more than 90 additional endometrial cancer cases ($n = 261$) among women who reported using the same public water supply for >10 y. We employed an exposure assessment that estimated levels of THMs, HAAs, and nitrate in public drinking water for several decades prior to enrollment, averaged for each participant based on reported duration of use. We also explored associations between endometrial cancer and dietary nitrate and nitrite, for which there are limited epidemiological investigations. Our study considered relationships between classes of drinking water contaminants and potential interaction with established endometrial cancer risk factors and dietary intake of antioxidants known to influence endogenous nitrosation.

Methods

Study Population

The IWHS is a cohort of postmenopausal women 55–69 y of age enrolled in 1986 and followed prospectively for cancer incidence and mortality.[31] Briefly, 98,030 women were randomly selected from Iowa driver's license records and mailed a baseline survey that included questions about demographics, diet and lifestyle, reproductive and medical history, and family history of cancer. A total of 41,836 (42%) women responded and thereafter were enrolled in the study for follow-up. Additional questionnaires were mailed in 1987, 1989, 1992, 1997, and 2004 with high response rates (91%, 90%, 83%, 79%, and 70%, respectively among those alive at the time of each survey). Information about participants' primary drinking water source (municipal water system, rural water system, private well, bottled water, other, do not know) and duration of use (<1 y, 1–5 y, 6–10 y, 11–20 y, >20 y, do not know) were collected in the 1989 survey ($n = 36{,}127$). The institutional review boards of the University of Minnesota, the University of Iowa, and the National Institutes of Health approved the study. Return of the baseline questionnaire was considered to indicate informed consent to participate.

We ascertained incident endometrial cancers diagnosed from 1986 through 31 December 2014 from the State Health Registry of Iowa, including morphology and stage. We identified primary epithelial endometrial cancer cases using ICD-O-3 morphology codes; nonepithelial cases were recoded as noncases. Subtypes of endometrial cancer were classified as follows: type I (endometrioid, tubular, adenocarcinoma not otherwise specified, adenocarcinoma with squamous differentiation, and mucinous), type II (serous carcinoma, clear cell, and mixed cell adenocarcinoma), or other epithelial. Among type I cases (over 80% of cases), we classified tumor grade 1 as "low grade" and tumor grades 2 and 3 as "high grade."

Vital status was determined through linkages with the National Death Index and State Health Registry. Person-years of follow-up were calculated from enrollment date until the earliest date of the following events: endometrial cancer diagnosis, surgical removal of the uterus (self-reported in the 1992 and 2004 survey), death, loss to follow-up, or end of follow-up (2014). For those who emigrated or died outside of Iowa, the censored date was calculated as the midpoint between the last contact and the date of death.

Drinking Water Exposure Assessment

The exposure assessment approach used to estimate long-term levels of THMs, HAAs, and nitrate in public water supplies (municipal or rural water system, hereafter PWS) for the IWHS has been described, and key details are noted herein.[32,33] Annual average concentrations were computed for the historical exposure period of 1955 to 1988, leveraging historical water characteristics data collected by the University of Iowa Center for Health Effects of Environmental Contamination (CHEEC). Annual nitrate measurements were available for each PWS starting after the promulgation of the U.S. Environmental Protection Agency (U.S. EPA) 1992 Phase II rule.[34] Monitoring frequency prior to this rule depended on the size of the population served; therefore, our long-term average nitrate exposures were derived from a variable number of measurements per PWS. For some utilities, typically the larger PWS, multiple measurements were available per year, and we averaged these into annual values. Regulation of DBPs was not promulgated until the 1980s, and measurement data were limited prior to that time. Annual DBP concentrations for PWS with no data in earlier years were estimated based on available measurements and characteristics of supplies (e.g., water source and treatment).[35] The approach for estimating these historical levels was based on case studies and an understanding of the water quality and operational parameters that impact DBP formation. Each utility treating surface or groundwater was evaluated on a case-by-case basis and considered multiple treatment/disinfection scenarios and water quality parameters along with actual DBP measurements leveraged from various water surveys conducted since the 1970s. The bulk of the data supporting this effort came from 34 Iowa utilities representing 9 surface water systems, 8 mixed surface/groundwater systems, and 17 groundwater systems with a range (high and low) of brominated THMs. The estimation also considered changes in disinfection practices over time (e.g., moving from chlorination of raw water to settled water).

For our analyses, we computed the sum of the four regulated THMs, hereafter referred to as total trihalomethanes (TTHM; μg/L), and the sum of the five regulated haloacetic acids (HAA5; μg/L). We evaluated these summed classes of DBPs because they are regulated as a group and because of the high correlation between individual estimates of the THMs (e.g., chloroform, bromodichloromethane; Spearman's rho ($\rho = 0.95$), as well as the individual HAA5 chemicals (trichloroacetic, dichloroacetic, and bromochloroacetic acid; $\rho = 0.69$–0.82; Table S12). Frequency of nitrate-nitrogen (NO_3-N; mg/L) measurements for each utility ranged from every several years to multiple samples per year prior to regulation beginning in 1993. For those who reported using a PWS in the 1989 survey ($n = 25{,}251$; 60%), we linked annual average concentrations of TTHM, HAA5, and NO_3-N by matching the city name of the PWS and participant address. Some rural water supplies could not be matched by city name, and we received assistance in assigning participants to these sources from CHEEC, which has maintained water contaminant records in Iowa for decades.

There were 21,477 (51%) women who reported using their PWS for more than 10 y; these women selected the categorical survey responses of either 11–20 y or >20 y of PWS use. Because the questionnaire did not collect the exact years of PWS use, we estimated these years with data from a case–control study conducted in Iowa during a time period similar to that of IWHS enrollment in which complete drinking water histories were ascertained.[36] Using information from the female controls in that study, we estimated a median duration of 16 y for IWHS participants who responded 11–20 y and a median of 40 y for those who reported >20 y.[33] To investigate whether long-term exposure at levels one-half of the regulatory limit were associated with risk, we enumerated the number of years that annual concentrations were above half their respective U.S. EPA maximum contaminant levels (>½ MCL; 40 μg/L TTHM; 30 mg/L HAA5; 5 mg/L NO_3-N).[12,34] We were not able to evaluate risk above the MCLs due to the few women exposed at these levels. Characteristics of each participant's PWS were also included in the linkage, such as ever/never use of chloramination and primary water source (e.g., ground or surface) during the historical time period.

Dietary Assessment

As previously described, estimates of dietary macro- and micronutrients were derived from a food frequency questionnaire administered at enrollment, and they have shown good reproducibility in later surveys.[37] Total dietary nitrate (converted to NO_3-N for comparison with drinking water) and nitrite (mg/day) were calculated by multiplying dietary intakes of each food item and their contents derived from multiple studies that measured concentrations in foods.[38–40] Almost all dietary nitrate intake was from plant sources (97%), whereas nitrite intake was derived from plant (62%), animal (38%), and processed meat sources (2%). Total vitamin C (mg/day) was estimated from dietary sources and supplement use. All dietary exposures were standardized by total caloric intake (per 1,000 calories).

Statistical Analysis

Based on self-reported data at enrollment, we excluded women from our analyses who were premenopausal ($n = 547$), diagnosed with cancer (except nonmelanoma skin cancer) prior to enrollment or received cancer chemotherapy ($n = 3{,}830$), and those who reported unrealistic dietary information (<600 or >5,000 kcal/d) or left more than 30 dietary items blank ($n = 2{,}751$), leaving 34,708 women. We further excluded women who reported having their uterus removed (i.e., hysterectomy) at the time of enrollment ($n = 11{,}694$). The remaining 23,014 women eligible for analyses were similar to those excluded due to hysterectomy, except that the women who reported hysterectomies reported more HRT use and a younger age at menopause (Table S1).

Additionally, our drinking water analyses excluded women who did not respond to the 1989 survey, reported a drinking water source other than a PWS ($n = 7{,}844$) or who reported using a PWS at their home for <10 y ($n = 2{,}692$). Participants were further excluded if their PWS had no measurements of DBPs or NO_3-N during their historical exposure period ($n = 843$), were missing water source information or used the same water source (e.g., surface water, aquifer) for <75% of the study period ($n = 1{,}091$). The final group eligible for drinking water analyses included 10,544 women.

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between drinking water contaminants and risk of primary epithelial endometrial cases. We first considered relationships between natural logarithm continuous exposures and endometrial cancer using cubic splines and quadratic terms. Based on our observations, we categorized long-term average concentrations of TTHM, HAA5, and NO_3-N into quartiles and used the first quartile (Q1) as the reference. We further split the fourth quartile (Q4) at or above the 95th percentile (≥95th). We also categorized women based on the median number of years served by a PWS with levels above one-half the MCLs (less than median or greater than or equal to median years) in comparison with those with no years of exposure at this level. We evaluated linearity of relationships by deriving a Wald p-value for linear trend (p-trend) from a continuous variable parameterized from the median value of each exposure quartile. We repeated these models focusing only on type I endometrial cancers, high-grade type I cancers, and low-grade type I cancers, and censoring the other cancer types when conducting these analyses. Effect heterogeneity comparing low-grade and high-grade tumors was assessed by Wald tests where the covariance matrices were estimated by the bootstrap procedure (p-heterogeneity).

We evaluated potential confounders based on information collected at enrollment, including: body mass index (BMI; normal, <25 kg/m^3, overweight, 25–29.9 kg/m^3, obese, ≥30 kg/m^3), age at menopause (<48, 48 to <52, ≥52 y), oral contraceptive (OC) use (ever/never), HRT use (ever/never), parity (ever/never), smoking status (never, former, current), and female family (biological mother/sister/daughter) history of any cancer and specifically any reproductive cancer or endometrial cancer (yes/no).

In addition to including *a priori* selected covariates that are established endometrial cancer risk factors (e.g., BMI, age at menopause, HRT and OC use, parity) in models, we evaluated the importance of covariates with backward elimination and a 10% change in the effect estimate of the exposure. Final models were adjusted for age, BMI, age at menopause, OC use, HRT use, parity, and smoking status. We did not mutually adjust TTHM and HAA5 exposures because these DBPs are highly correlated ($\rho = 0.90$). However, we adjusted DBP models for the continuous natural logarithm average concentration of NO_3-N and vice versa (ρ between TTHM and NO_3-N = 0.24). Dietary intakes of nitrate and nitrite were not correlated with NO_3-N in drinking water ($\rho \leq 0.01$) and therefore were not included as covariates in the final models.

We observed small percentages of missing data in our drinking water subgroup for the covariates parity (1%), age at menopause (2.6%), smoking status (1.1%), HRT use (0.26%), and oral contraceptive use (0.17%; proportions missing were similar in the dietary analysis group; Table S1). We found nonrandom patterns of missingness across exposure categories (Table 1) and prioritized the inclusion of as many participants and endometrial cancer cases by using a missing indicator category for parity, age at menopause, and smoking status variables. The small proportion of those with missing information for HRT use and OC use (<1%) were excluded from all analyses ($n = 43$ women; $n = 1$ case). Among the remaining 10,501 women in the drinking water analyses (Figure S1), there were 261 primary epithelial endometrial cancer cases, of which 223 were type I cases (Table S2).

In sensitivity analyses, we evaluated indicators of DBP exposure that have been used in previous IWHS analyses,[25,32,33] including whether a participant's PWS primarily used a surface water source (vs. ground) or ever used chloramination treatment (vs. never). Because domestic wells are not typically chlorinated[41] and private well users were presumed to have no DBP exposure, we also compared quartiles of TTHM and HAA5 among PWS users to participants who reported using a private well in the 1989 survey for 10 or more years ($n = 3{,}406$) as the reference group. In contrast, private wells in Iowa have higher NO_3-N levels in comparison

Table 1. Characteristics of IWHS participants eligible for the drinking water analysis ($n = 10{,}544$), by quartiles of TTHM and nitrate-nitrogen (NO_3-N) in PWS.

	TTHM (μg/L)				HAA5 (μg/L)			
	<0.90	0.90–<4.77	4.77–<14.50	14.50–200.88	<1.87	1.87–<3.52	3.52–<8.17	8.17–118.15
Age at baseline [y (mean ± SD)]	61.6 ± 4.2	61.9 ± 4.2	61.8 ± 4.1	61.6 ± 4.2	61.7 ± 4.2	61.9 ± 4.2	61.8 ± 4.2	61.6 ± 4.1
Race [*n* (%)]								
Non-Hispanic White	2,511 (98.6)	2,778 (98.5)	2,814 (98.4)	2,283 (98.5)	2,523 (98.5)	2,537 (98.5)	2,694 (98.4)	2,632 (98.6)
Non-Hispanic Black	1 (0)	9 (0.3)	12 (0.4)	5 (0.2)	1 (0)	7 (0.3)	13 (0.5)	6 (0.2)
Hispanic	2 (0.1)	5 (0.2)	11 (0.4)	6 (0.3)	4 (0.2)	5 (0.2)	5 (0.2)	10 (0.4)
American Indian or Alaskan Native	4 (0.2)	4 (0.1)	3 (0.1)	1 (0)	5 (0.2)	3 (0.1)	4 (0.1)	0
Asian or Pacific Islander	0	2 (0.1)	2 (0.1)	2 (0.1)	0	2 (0.1)	1 (0)	3 (0.1)
Missing	29 (1.1)	22 (0.8)	17 (0.6)	21 (0.9)	29 (1.1)	22 (0.9)	20 (0.7)	18 (0.7)
Education [*n* (%)]								
Less than high school	165 (6.5)	177 (6.3)	160 (5.6)	117 (5)	175 (6.8)	174 (6.8)	166 (6.1)	104 (3.9)
High school	1,333 (52.3)	1,392 (49.4)	1,441 (50.4)	1,235 (53.3)	1,339 (52.3)	1,337 (51.9)	1,316 (48.1)	1,409 (52.8)
More than high school	1,044 (41)	1,246 (44.2)	1,256 (43.9)	966 (41.7)	1,043 (40.7)	1,061 (41.2)	1,252 (45.7)	1,156 (43.3)
Missing	5 (0.2)	5 (0.2)	2 (0.1)	NA	5 (0.2)	4 (0.2)	3 (0.1)	0 (0)
Body mass index [*n* (%)]								
<25	1,077 (42.3)	1,223 (43.4)	1,256 (43.9)	1,017 (43.9)	1,059 (41.3)	1,082 (42)	1,267 (46.3)	1,165 (43.6)
25–29.9	925 (36.3)	992 (35.2)	1,038 (36.3)	823 (35.5)	950 (37.1)	914 (35.5)	953 (34.8)	961 (36)
≥30	545 (21.4)	605 (21.5)	565 (19.8)	478 (20.6)	553 (21.6)	580 (22.5)	517 (18.9)	543 (20.3)
Age at menopause [*n* (%)][a]								
<48	602 (23.6)	640 (22.7)	722 (25.3)	582 (25.1)	604 (23.6)	615 (23.9)	657 (24)	670 (25.1)
<52	869 (34.1)	1,018 (36.1)	982 (34.3)	825 (35.6)	873 (34.1)	917 (35.6)	962 (35.1)	942 (35.3)
≥52	1,014 (39.8)	1,079 (38.3)	1,073 (37.5)	860 (37.1)	1,020 (39.8)	972 (37.7)	1,035 (37.8)	999 (37.4)
Missing	62 (2.4)	83 (2.9)	82 (2.9)	51 (2.2)	65 (2.5)	72 (2.8)	83 (3)	58 (2.2)
Oral contraceptive use [*n* (%)][b]								
Never	2,041 (80.1)	2,269 (80.5)	2,311 (80.8)	1,795 (77.4)	2,042 (79.7)	2,094 (81.3)	2,187 (79.9)	2,093 (78.4)
Ever	499 (19.6)	546 (19.4)	544 (19)	521 (22.5)	510 (19.9)	480 (18.6)	545 (19.9)	575 (21.5)
Missing	7 (0.3)	5 (0.2)	4 (0.1)	2 (0.1)	10 (0.4)	2 (0.1)	5 (0.2)	1 (0)
HRT use [*n* (%)][b]								
Never	1,869 (73.4)	1,979 (70.2)	2,054 (71.8)	1,636 (70.6)	1,895 (74)	1,819 (70.6)	1,965 (71.8)	1,859 (69.7)
Ever	675 (26.5)	831 (29.5)	802 (28.1)	671 (28.9)	661 (25.8)	752 (29.2)	767 (28)	799 (29.9)
Missing	3 (0.1)	10 (0.4)	3 (0.1)	11 (0.5)	6 (0.2)	5 (0.2)	5 (0.2)	11 (0.4)
Parity [*n* (%)][a]								
Never	232 (9.1)	322 (11.4)	347 (12.1)	233 (10.1)	232 (9.1)	273 (10.6)	333 (12.2)	296 (11.1)
Ever	2,300 (90.3)	2,478 (87.9)	2,496 (87.3)	2,075 (89.5)	2,314 (90.3)	2,288 (88.8)	2,385 (87.1)	2,362 (88.5)
Missing	15 (0.6)	20 (0.7)	16 (0.6)	10 (0.4)	16 (0.6)	15 (0.6)	19 (0.7)	11 (0.4)
Smoking status [*n* (%)][a]								
Never	1,644 (64.5)	1,730 (61.3)	1,655 (57.9)	1,314 (56.7)	1,653 (64.5)	1,576 (61.2)	1,648 (60.2)	1,466 (54.9)
Former	666 (26.1)	818 (29)	918 (32.1)	774 (33.4)	674 (26.3)	749 (29.1)	829 (30.3)	924 (34.6)
Current	199 (7.8)	243 (8.6)	254 (8.9)	208 (9)	199 (7.8)	220 (8.5)	232 (8.5)	253 (9.5)
Missing	38 (1.5)	29 (1)	32 (1.1)	22 (0.9)	36 (1.4)	31 (1.2)	28 (1)	26 (1)
Family history of endometrial cancer[b] [*n* (%)]								
No	2,441 (95.8)	2,691 (95.4)	2,719 (95.1)	2,206 (95.2)	2,452 (95.7)	2,465 (95.7)	2,610 (95.4)	2,530 (94.8)
Yes	106 (4.2)	129 (4.6)	140 (4.9)	112 (4.8)	110 (4.3)	111 (4.3)	127 (4.6)	139 (5.2)
Family history of reproductive cancer[b] [*n* (%)]								
No	2,053 (80.6)	2,295 (81.4)	2,280 (79.7)	1,871 (80.7)	2,066 (80.6)	2,112 (82)	2,180 (79.6)	2,141 (80.2)
Yes	494 (19.4)	525 (18.6)	579 (20.3)	447 (19.3)	496 (19.4)	464 (18)	557 (20.4)	528 (19.8)
Family history of any cancer[b] [*n* (%)]								
No	1,558 (61.2)	1,753 (62.2)	1,774 (62)	1,418 (61.2)	1,575 (61.5)	1,626 (63.1)	1,673 (61.1)	1,629 (61)
Yes	989 (38.8)	1,067 (37.8)	1,085 (38)	900 (38.8)	987 (38.5)	950 (36.9)	1,064 (38.9)	1,040 (39)
Total calories [kcal/d (median)]	1,704	1,704	1,686	1,686	1,703	1,710	1,693	1,673
Dietary nitrate [mg/d (median)][c]	58.62	60.58	61.98	62.99	58.86	58.91	61.85	64.3
Dietary nitrite [mg/d (median)][c]	0.64	0.64	0.65	0.64	0.65	0.64	0.64	0.65
Vitamin C [mg/d (median)][c]	105	109	107	111	104	106	108	114
PWS primary water source [*n* (%)]								
Ground	2,547 (100)	2,644 (93.8)	1,987 (69.5)	887 (38.3)	2,562 (100)	2,575 (100)	1,642 (60)	1,286 (48.2)
Surface	0 (0)	176 (6.2)	872 (30.5)	1,431 (61.7)	0 (0)	1 (0)	1,095 (40)	1,383 (51.8)
PWS chloraminated[d] [*n* (%)]								
Never	2,470 (97)	2,390 (84.8)	1,889 (66.1)	942 (40.6)	2,553 (99.6)	1,579 (59.9)	2,012 (73.5)	670 (25.1)
Ever	77 (3)	430 (15.2)	970 (33.9)	1,376 (59.4)	9 (0.4)	1,059 (40.1)	725 (26.5)	1,999 (74.9)

Note: The IWHS is a cohort of postmenopausal women 55–69 y of age in Iowa and were enrolled in 1986 by completing a mailed survey and followed for cancer incidence and mortality until 2014 ($N = 41{,}836$). $n = 10{,}544$ is the group of women restricted to those with >10 y at their drinking water source and with no hysterectomy reported at baseline. $n = 43$ women were missing information on oral contraceptive or hormone replacement therapy use and were excluded from all subsequent drinking water analyses. HRT, hormone replacement therapy; IWHS, Iowa Women's Health Study; PWS, public water supplies; TTHM, total trihalomethanes.

[a]Determined using information collected at baseline and follow-up surveys.

[b]Among biological mother, sister, and daughter.

[c]Per 1,000 kcal per day of energy intake.

[d]During the study period.

with PWS[42]; therefore, we assessed risk for women on private wells in comparison with PWS users in the first quartile of average NO_3-N concentrations (<0.48 mg/L). We also evaluated associations with quartiles of individual THMs (chloroform, bromodichloromethane) and HAAs (dichloroacetic, trichloroacetic, and bromochloroacetic acid).

We used stratified models to explore differences in associations for drinking water contaminants by factors associated with

endometrial cancer: HRT use, BMI, and smoking status. We also stratified NO_3-N quartiles by levels of dietary intake of vitamin C and red meat, both of which may influence endogenous nitrosation in the gastrointestinal tract (less than median or greater than or equal to median). We tested for multiplicative interaction (p-interaction) using likelihood ratio tests that compared nested and full models with and without an interaction term. Because we observed differences in associations for DBP classes when stratified by HRT use, we conducted *a posteriori* sensitivity analyses by individual THM and HAA compounds. We also further stratified HRT users by ≤ 1 y or >1 y of use prior to study enrollment.

Dietary analyses included the aforementioned 23,014 women satisfying inclusion criteria minus those with $<1\%$ missing covariate information (OC and HRT use; $n=117$), leaving 22,897 women for analysis (Figure S1). We used Cox proportional hazards regression to evaluate quartiles of total dietary nitrate and nitrite; nitrite intakes from plant, animal, and processed meat sources; and risk of endometrial cancer. Models were adjusted for covariates included in the drinking water analyses and mutually adjusted for dietary nitrate or nitrite. We also evaluated dietary nitrate and nitrite stratified by low/high vitamin C intake (less than median or greater than or equal to median). All analyses were conducted in R (version 4.0.2; R Development Core Team). We considered results statistically significant at the p-value threshold of <0.05.

Results

Demographics, lifestyle characteristics, reproductive history, family history of cancer, and dietary intakes of micronutrients among the 10,544 women in the drinking water analysis were similar across quartiles of TTHM and HAA5 (Table 1). We observed a larger proportion of current and former smokers in the highest quartiles of TTHM and HAA5 levels. A greater proportion of women in the highest quartiles of TTHM and HAA5 had a PWS that used a surface water source. Women using a PWS that was ever chloraminated had higher TTHM and HAA5 levels. The mean total follow-up time was 21 y and included 221,036 total person-years at risk.

Crude models (adjusted only for age) for the drinking water analyses are presented in Tables S3–S5. In multivariable models, average concentrations of DBPs in drinking water $\geq$95th percentile in comparison with Q1 were significantly associated with endometrial cancer risk (TTHM: $HR_{95vsQ1}=2.19$, 95% CI: 1.41, 3.40;

Table 2. Association between drinking water TTHM, HAA5, and NO_3-N and incident epithelial endometrial cancer overall and restricted to type I cases in the Iowa Women's Health Study ($n=10{,}501$).

	Epithelial endometrial cancer cases			Type I endometrial cancer cases		
	n	Cases	HR (95% CI)[a,b]	n	Cases	HR (95% CI)[a,b]
Average TTHM (μg/L)						
<0.90	2,537	52	Ref	2,537	45	Ref
0.90–<4.77	2,805	63	1.11 (0.77, 1.61)	2,805	54	1.10 (0.74, 1.65)
4.77–<14.50	2,853	75	1.40 (0.96, 2.04)	2,853	64	1.40 (0.94, 2.10)
14.50–<93.2	1,494	38	1.38 (0.90, 2.11)	1,494	34	1.44 (0.91, 2.26)
≥95th (93.2–200.88)	812	33	2.19 (1.41, 3.40)	812	26	1.99 (1.22, 3.24)
p-trend[c]	—	—	0.001	—	—	0.006
Years >40 μg/L TTHM						
0	7,857	178	Ref	7,857	155	Ref
<36	1,171	33	1.23 (0.85, 1.79)	1,171	28	1.20 (0.80, 1.80)
≥36	1,473	50	1.61 (1.18, 2.21)	1,473	40	1.49 (1.04, 2.10)
p-trend[c]	—	—	0.004	—	—	0.032
Average HAA5 (μg/L)						
<1.87	2,547	55	Ref	2,547	48	Ref
1.87–<3.52	2,569	58	1.01 (0.70, 1.48)	2,569	52	1.05 (0.71, 1.55)
3.52–<8.17	2,727	65	1.18 (0.82, 1.69)	2,727	55	1.15 (0.77, 1.70)
8.17–<48.5	1,775	50	1.36 (0.93, 2.00)	1,775	42	1.31 (0.86, 1.99)
≥95th (48.5–118.15)	883	33	1.84 (1.19, 2.83)	883	26	1.64 (1.02, 2.65)
p-trend	—	—	0.002	—	—	0.024
Years >30 μg/L HAA5						
0	8,729	203	Ref	8,729	175	Ref
<38	817	20	1.09 (0.69, 1.73)	817	19	1.20 (0.75, 1.92)
≥38	955	38	1.85 (1.31, 2.62)	955	29	1.64 (1.10, 2.43)
p-trend	—	—	0.001	—	—	0.013
Average NO_3-N (mg/L)						
<0.48	2,640	70	Ref	2,640	64	Ref
0.48–<1.09	2,628	63	0.92 (0.66, 1.30)	2,628	50	0.80 (0.55, 1.15)
1.09–<2.98	2,807	70	0.93 (0.66, 1.29)	2,807	60	0.86 (0.61, 1.23)
2.98–<5.71	1,898	45	0.92 (0.63, 1.34)	1,898	37	0.83 (0.55, 1.24)
≥95th (5.71–25.34)	528	13	0.96 (0.53, 1.73)	528	12	0.97 (0.52, 1.79)
p-trend	—	—	0.814	—	—	0.798
Years >5 mg/L NO_3-N						
0	7,427	190	Ref	7,427	161	Ref
<4	1,494	33	0.85 (0.59, 1.23)	1,494	30	0.91 (0.62, 1.35)
≥4	1,580	38	0.97 (0.69, 1.38)	1,580	32	0.96 (0.66, 1.41)
p-trend	—	—	0.897	—	—	0.852

Note: The IWHS is a cohort of postmenopausal women 55–69 y of age who lived in Iowa and were enrolled in 1986 by completing a mailed survey and followed for cancer incidence and mortality until 2014 ($N=41{,}836$). —, no data; CI, confidence interval; HR, hazard ratio; IWHS, Iowa Women's Health Study; Ref, reference; TTHM, total trihalomethanes.

[a]A total of $n=43$ women were missing information on oral contraceptive or hormone replacement therapy use and were excluded from analyses. Participants missing information for other covariates were included in models with missing coded as a separate category.

[b]Adjusted for age, body mass index, menopause age, oral contraceptive use, hormone replacement therapy use, parity, smoking status, and mutually adjusted for ln-transformed concentrations of NO_3-N (for TTHM/HAA5 models) or TTHM (for NO_3-N models).

[c]Modeled as a continuous variable derived from the median of each exposure category.

Table 3. Association between individual trihalomethane and haloacetic acid compounds and incident epithelial endometrial cancer in the Iowa Women's Health Study ($n = 10{,}501$).

	Epithelial endometrial cancer cases		
	n	Cases	HR (95% CI)[a,b]
Individual trihalomethanes			
Chloroform (μg/L)			
<0.6	2,610	54	Ref
0.6– < 1.85	2,532	57	1.10 (0.75, 1.59)
1.85– < 8.41	2,371	68	1.52 (1.06, 2.20)
8.41–185.6	2,988	82	1.50 (1.05, 2.15)
p-trend[c]	—	—	0.081
Bromodichloromethane (μg/L)			
<0.25	2,145	42	Ref
0.25– < 1.16	2,981	75	1.35 (0.93, 1.98)
1.16– < 3.78	2,730	61	1.26 (0.83, 1.89)
3.78–33.0	2,645	83	1.81 (1.24, 2.64)
p-trend	—	—	0.003
Individual haloacetic acids			
Dichloroacetic (μg/L)			
<1.6	2,572	57	Ref
1.6– < 2.27	2,651	63	1.04 (0.72, 1.49)
2.27– < 5.24	2,570	55	1.02 (0.70, 1.48)
5.24–53.5	2,708	86	1.53 (1.09, 2.14)
p-trend	—	—	0.002
Trichloroacetic (μg/L)			
<0.25	2,090	42	Ref
0.25– < 0.63	2,327	54	1.22 (0.81, 1.82)
0.63– < 1.69	3,448	82	1.32 (0.90, 1.94)
1.69–52.1	2,636	83	1.77 (1.22, 2.59)
p-trend	—	—	0.003
Bromochloroacetic (μg/L)[d]			
<0.88	5,231	118	Ref
0.88– < 1.89	2,574	71	1.34 (0.98, 1.83)
1.89–10.4	2,696	72	1.24 (0.91, 1.67)
p-trend	—	—	0.237

Note: The IWHS is a cohort of postmenopausal women 55–69 y of age who lived in Iowa and were enrolled in 1986 by completing a mailed survey and followed for cancer incidence and mortality until 2014 ($N = 41{,}836$). —, no data; CI, confidence interval; HR, hazard ratio; IWHS, Iowa Women's Health Study; Ref, reference.
[a]A total of $n = 43$ women were missing information on oral contraceptive or hormone replacement therapy use and were excluded from analyses. Participants missing information for other covariates were included in models with missing coded as a separate category.
[b]Adjusted for age, body mass index, menopause age, oral contraceptive use, hormone replacement therapy use, parity, smoking status, and ln-transformed concentrations of NO_3-N.
[c]Modeled as a continuous variable derived from the median of each exposure category.
[d]Analyzed as tertiles, given the limited distribution.

HAA5: $HR_{95vsQ1} = 1.84$, 95% CI: 1.19, 2.83), and trends across increasing categories were significant for both contaminants (TTHM: p-trend = 0.001; HAA5: p-trend = 0.002); Table 2. Cubic splines of continuous log-transformed average estimated concentrations illustrate this increased risk at the high exposure levels (Figure S2). Associations between DBP exposures and type I cases were similar (TTHM: $HR_{95vsQ1} = 1.99$, 95% CI: 1.22, 3.24; HAA5: $HR_{95vsQ1} = 1.64$, 95% CI: 1.02, 2.65). Women with TTHM and HAA5 levels >½ the MCL for 36 and 38 y, respectively, in comparison with no years of exposure at these levels, had significantly increased risk of endometrial cancer (TTHM: $HR_{\geq medianvs0y} = 1.61$, 95% CI: 1.18, 2.21; HAA5: $HR_{\geq medianvs0y} = 1.85$, 95% CI: 1.31, 2.62).

When DBPs were categorized in quartiles, risks were similarly observed at the highest exposure levels (Q4); Table S6. Risk for those using a surface water source or chloraminated PWS were higher in comparison with their complementary reference groups (i.e., groundwater source and never chloraminated PWS), but associations were not statistically significant. We also compared quartiles of DBPs in reference to private well users and found significant trends in risk (TTHM: p-trend = 0.011; HAA5: p-trend = 0.009), and risks in the highest quartiles were elevated but not statistically significant (TTHM: $HR_{Q4vsPrivate} = 1.32$, 95% CI: 0.96, 1.81; HAA5: $HR_{Q4vsPrivate} = 1.31$, 95% CI: 0.97, 1.78). Associations with quartiles of individual THMs and HAAs were similar to the respective summed classes and highest for bromodichloromethane ($HR_{Q4vsQ1} = 1.81$, 95% CI: 1.24, 2.64) and trichloroacetic acid ($HR_{Q4vsQ1} = 1.77$, 95% CI: 1.22, 2.59); Table 3.

We observed no significant relationships between average NO_3-N in PWS (p-trend = 0.860) or years >½ MCL (p-trend = 0.923) and endometrial cancer, or among type I cases (average NO_3-N p-trend = 0.858); Table 2. Likewise, risk was not elevated for private well users in comparison with PWS users in the lowest quartile of NO_3-N exposure ($HR_{PrivatevsQ1} = 0.96$; 95% CI: 0.69, 1.34); Table S6. We found no evidence of effect modification by dietary intakes of vitamin C or red meat (p-interaction = 0.593 and 0.689, respectively; Table S7).

In separate models of type I cancers by grade, risk at the highest quartile of DBP exposure was significant for low-grade tumors (TTHM: $HR_{lowgradeQ4} = 2.12$, 95% CI: 1.17, 3.83; HAA5: $HR_{lowgradeQ4} = 1.86$, 95% CI: 1.03, 3.38) but not for high-grade tumors (TTHM: $HR_{highgradeQ4} = 1.40$, 95% CI: 0.80, 2.44; HAA5: $HR_{highgradeQ4} = 1.27$, 95% CI: 0.77, 2.11); Table 4. However, the tests for heterogeneity were not statistically significant (TTHM: p-heterogeneity = 0.428; HAA5: p-heterogeneity = 0.507).

In stratified analyses, we observed greater risk of endometrial cancer in the highest quartile of TTHM exposure for women who had ever used HRT ($HR_{Q4HRTusers} = 2.16$, 95% CI: 1.21, 3.84; p-trend = 0.005) vs. nonusers ($HR_{Q4NonUsers} = 1.40$, 95% CI: 0.86, 2.27; p-trend = 0.262); p-interaction = 0.007; Table 5. Trends for HAA5 exposure were the same in both HRT groups (p-trends = 0.048 and 0.046 for never and ever, respectively) and no interaction was observed (p-interaction = 0.997). Results by duration of HRT use showed the risk estimate for highest TTHM quartile was stronger among HRT users >1 y ($HR_{Q4HRT>1y} = 2.42$, 95% CI: 1.26, 4.64; p-trend <0.001) than HRT users ≤1 y ($HR_{Q4HRT\leq 1y} = 1.54$, 95% CI: 0.40, 5.89; p-trend = 0.802); Table S8. In similarly stratified analyses for individual THMs and HAAs, we observed significant trends for bromodichloromethane (p-trend = 0.002) and trichloroacetic acid (p-trend = 0.004) among participants who had ever used HRT, but not among those who had never used HRT (bromodichloromethane: p-trend = 0.250; ttrichloroacetic acid: p-trend = 0.194); however, interactions were not statistically significant (bromodichloromethane: p-interaction = 0.216; trichloroacetic acid: p-interaction = 0.375); Table 6.

Tests for interaction did not suggest differences in associations between DBPs and categories of BMI, although risk was significantly increased in the highest quartile of HAA5 for women who were obese ($HR_{Q4vsQ1} = 1.76$, 95% CI: 1.04, 2.98), but not for those who were overweight or normal weight (Table S9). Stratified analyses and evaluation of interaction terms between DBPs and smoking status (less than median or greater than or equal to median) did not suggest differences in associations with endometrial cancer (Table S10).

Analyses of dietary intakes of nitrate and nitrite included 566 epithelial endometrial cancer cases among 22,897 women followed for a mean of 23 y and included 467,193 person-years at risk (Table 7). We did not observe any statistically significant associations or trends across quintiles of dietary nitrate (p-trend = 0.357) or nitrite (p-trend = 0.871). Associations with intakes of nitrite from plant or animal sources were similarly null, but we observed a non-statistically significant increased risk in the fourth and fifth quintiles of nitrite intake from processed meats ($HR_{Quin4vsQuin1} = 1.19$; 95% CI: 0.92, 1.55) and ($HR_{Quin5vsQuin1} = 1.11$; 95% CI: 0.85, 1.45). In a stratified analysis, increased risk was observed for women with below median vitamin C intake in the fourth quintile of nitrite from processed meat ($HR_{Quin4vsQuin1} = 1.73$; 95% CI: 1.14, 2.62),

Table 4. Association between TTHM and HAA5 and risk of low- and high-grade type I endometrial cancer in the Iowa Women's Health Study ($n = 10{,}501$).

		Low grade		High grade		
	n	Cases	HR (95% CI)[a,b]	Cases	HR (95% CI)[a,b]	p-Heterogeneity[c]
Average TTHM (μg/L)						
<0.90	2,537	18	Ref	24	Ref	—
0.90–<4.77	2,805	20	1.04 (0.55, 1.97)	33	1.25 (0.73, 2.12)	—
4.77–<14.50	2,853	30	1.66 (0.89, 3.08)	29	1.16 (0.66, 2.06)	—
14.50–<200.88	2,306	31	2.12 (1.17, 3.83)	28	1.40 (0.80, 2.44)	—
p-trend[d]	—	—	0.008	—	0.339	0.428
Average HAA5 (μg/L)						
<1.87	2,547	17	Ref	27	Ref	—
1.87–<3.52	2,569	23	1.33 (0.71, 2.50)	29	1.02 (0.60, 1.73)	—
3.52–<8.17	2,727	28	1.65 (0.90, 3.06)	23	0.84 (0.48, 1.48)	—
8.17–118.15	2,658	31	1.86 (1.03, 3.38)	35	1.27 (0.77, 2.11)	—
p-trend	—	—	0.097	—	0.174	0.507

Note: The IWHS is a cohort of postmenopausal women 55–69 y of age who lived in Iowa and were enrolled in 1986 by completing a mailed survey and followed for cancer incidence and mortality until 2014 ($N = 41{,}836$). —, no data; CI, confidence interval; HR, hazard ratio; IWHS, Iowa Women's Health Study; Ref, reference; TTHM, total trihalomethanes.
[a]A total of $n = 43$ women were missing information on oral contraceptive or hormone replacement therapy use and were excluded from analyses. Participants missing information for other covariates were included in models with missing coded as a separate category; grade unknown for 10 type I cases.
[b]Adjusted for age, body mass index, menopause age, oral contraceptive use, hormone replacement therapy use, parity, smoking status, and ln-transformed NO_3-N levels.
[c]Computed using Wald tests where the covariance matrices were estimated by the bootstrap procedure.
[d]Modeled as a continuous variable derived from the median of each exposure category.

and the interaction was borderline statistically significant (p-interaction = 0.0465); Table S11.

Discussion

In a cohort of postmenopausal women living in Iowa, we found a novel association between relatively high levels of TTHM and HAA5 in drinking water and endometrial cancer risk. We observed a suggestive stronger association between these contaminants and risk of low-grade in comparison with high-grade type I tumors. Stratified analyses suggested risk associated with TTHM may be greater for those who had ever used HRT. We did not observe associations with NO_3-N in drinking water or total intakes of dietary nitrate or nitrite.

To our knowledge, no other epidemiological studies besides the IWHS cohort have evaluated the association between exposure to DBPs and endometrial cancer risk. An IWHS analysis conducted in 1997 found a suggestive association with endometrial cancer among women using a surface in comparison with a groundwater drinking water source, and those with high levels of chloroform measured during a short-term campaign effort in 1979 and 1986–1987.[26] Our study sought to reexamine this research question with additional follow-up time and ascertained cases and an improved exposure assessment estimating long-term historical concentrations of two regulated classes of DBPs. In doing so, we found a trend of elevated risk with increasing levels of average TTHM and HAA5 in PWS used by women in this cohort for more than 10 y. Some of the common chemicals in TTHM and HAA5 are probable human carcinogens based on animal studies demonstrating genotoxicity, mutagenicity, and cell proliferation at high levels of exposure.[7,8] DBPs have been associated with several noncancer reproductive outcomes in men and women, including infertility, which suggests they play a role in hormonal dysfunction.[43] Animal studies suggest DBPs may increase estradiol levels[19,20] and suppress progesterone levels[18]; elevated levels of estrogen unopposed by progesterone is a known risk factor for endometrial cancer.[3,4] However, we are not aware of any mechanistic studies specifically evaluating the toxicity or carcinogenicity of DBPs in the uterus.

Significant risks at the highest quartiles of exposure (e.g., TTHM ≥14.5 μg/L; HAA5 ≥8.17 μg/L), and even greater risk at the 95th percentile (TTHM ≥93.2; HAA5 ≥48.5), suggest associations are

Table 5. Association between drinking water TTHM and HAA5 and risk of endometrial cancer, stratified by HRT use in the Iowa Women's Health Study ($n = 10{,}501$).

	Never HRT use			Ever HRT use			
	n	Cases	HR (95% CI)[a,b]	n	Cases	HR (95% CI)[a,b]	p-Interaction[c]
Average TTHM (μg/L)							
<0.90	1,867	34	Ref	670	18	Ref	—
0.90–<4.77	1,977	28	0.86 (0.52, 1.42)	828	35	1.50 (0.84, 2.67)	—
4.77–<14.50	2,051	53	1.79 (1.13, 2.86)	802	22	0.98 (0.51, 1.86)	—
14.50–<200.88	1,636	35	1.40 (0.86, 2.27)	670	36	2.16 (1.21, 3.84)	—
p-trend[d]	—	—	0.262	—	—	0.004	0.007
Average HAA5 (μg/L)							
<1.87	1,892	34	Ref	655	21	Ref	—
1.87–<3.52	1,819	33	1.04 (0.64, 1.67)	750	25	0.98 (0.54, 1.75)	—
3.52–<8.17	1,961	38	1.22 (0.76, 1.96)	766	27	1.10 (0.62, 1.97)	—
8.17–118.15	1,859	45	1.53 (0.98, 2.39)	799	38	1.53 (0.89, 2.61)	—
p-trend	—	—	0.048	—	—	0.046	0.997

Note: The IWHS is a cohort of postmenopausal women 55–69 y of age who lived in Iowa and were enrolled in 1986 by completing a mailed survey and followed for cancer incidence and mortality until 2014 ($N = 41{,}836$). —, no data; BMI, body mass index; CI, confidence interval; HR, Hazard ratio; HRT, hormone replacement therapy; IWHS, Iowa Women's Health Study; Ref, reference; TTHM, total trihalomethanes.
[a]A total of $n = 43$ women were missing information on oral contraceptive or hormone replacement therapy use and were excluded from analyses. Participants missing information for other covariates were included in models with missing coded as a separate category.
[b]Adjusted for age, BMI, menopause age, oral contraceptive use, parity, smoking status, and ln-transformed NO_3-N levels.
[c]Interaction terms: Exposure quartiles and never/ever HRT use.
[d]Modeled as a continuous variable derived from the median of each exposure category.

Table 6. Association between individual trihalomethane and haloacetic acid compounds and risk of endometrial cancer, stratified by HRT use in the Iowa Women's Health Study ($n = 10{,}501$).

	Never HRT use			Ever HRT use			
	n	Cases	HR (95% CI)[a,b]	*n*	Cases	HR (95% CI)[a,b]	*p*-Interaction[c]
Individual trihalomethanes							
Chloroform (μg/L)							
<0.6	1,921	36	Ref	689	18	Ref	—
0.6– < 1.85	1,771	25	0.81 (0.48, 1.35)	761	32	1.60 (0.89, 2.86)	—
1.85– < 8.41)	1,708	44	1.68 (1.06, 2.66)	663	24	1.39 (0.75, 2.59)	—
8.41–185.6	2,131	45	1.34 (0.85, 2.13)	857	37	1.84 (1.02, 3.31)	—
p-trend[d]	—	—	0.316		—	0.131	0.105
Bromodichloromethane (μg/L)							
<0.25	1,595	28	Ref	550	14	Ref	—
0.25– < 1.16	2,109	41	1.28 (0.79, 2.07)	872	34	1.54 (0.82, 2.89)	—
1.16– < 3.78	1,926	39	1.39 (0.83, 2.30)	804	22	1.12 (0.56, 2.23)	—
3.78–33	1,901	42	1.48 (0.91, 2.41)	744	41	2.40 (1.29, 4.44)	—
p-trend	—	—	0.25	—	—	0.002	0.216
Individual haloacetic acids							
Dichloroacetic (μg/L)							
<1.6	1,920	37	Ref	652	20	Ref	—
1.6– < 2.27	1,914	36	0.99 (0.62, 1.57)	737	27	1.14 (0.64, 2.03)	—
2.27– < 5.24	1,804	31	1.00 (0.62, 1.62)	766	24	1.06 (0.58, 1.92)	—
5.24–53.5	1,893	46	1.45 (0.94, 2.24)	815	40	1.69 (0.99, 2.91)	—
p-trend	—	—	0.037	—	—	0.021	0.961
Trichloroacetic (μg/L)							
<0.25	1,558	28	Ref	532	14	Ref	—
0.25– < 0.63	1,665	29	1.09 (0.64, 1.83)	662	25	1.47 (0.76, 2.83)	—
0.63– < 1.69	2,405	49	1.43 (0.88, 2.32)	1,043	33	1.26 (0.66, 2.39)	—
1.69–52.1	1,903	44	1.51 (0.93, 2.44)	733	39	2.25 (1.21, 4.18)	—
p-trend	—	—	0.194	—	—	0.004	0.375
Bromochloroacetic (μg/L)							
<0.88	3,847	72	Ref	1,384	46	Ref	—
0.88– < 1.89	1,849	42	1.36 (0.90, 2.04)	725	29	1.29 (0.79, 2.11)	—
1.89–10.4	1,835	36	1.18 (0.78, 1.77)	861	36	1.31 (0.83, 2.06)	—
p-trend	—	—	0.515	—	—	0.291	0.846

Note: The IWHS is a cohort of postmenopausal women 55–69 y of age who lived in Iowa and were enrolled in 1986 by completing a mailed survey and followed for cancer incidence and mortality until 2014 ($N = 41{,}836$). —, no data; CI, confidence interval; HR, Hazard ratio; HRT, hormone replacement therapy; IWHS, Iowa Women's Health Study; Ref, reference.

[a]A total of $n = 43$ women were missing information on oral contraceptive or hormone replacement therapy use and were excluded from analyses. Participants missing information for other covariates were included in models with missing coded as a separate category.

[b]Adjusted for age, body mass index, menopause age, oral contraceptive use, parity, smoking status, and ln-transformed NO_3-N levels.

[c]Interaction terms: Exposure quartiles and never/ever HRT use.

[d]Modeled as a continuous variable derived from the median of each exposure category.

driven by the highest levels in Iowa, despite some of these levels being below their U.S. EPA MCLs (TTHM = 80; HAA5 = 60).[44] Risks at similar levels have been observed in this cohort for colon and rectal[25] but not bladder[33] or kidney[32] cancers. Exposure to DBP concentrations above half the regulatory limits over a period of more than 30-y resulted in similar risks observed at the highest average concentrations, suggesting that both duration and intensity of exposure could be important factors in the development of endometrial cancer. However, the interpretation of these findings should consider the uncertainty in historical DBP levels because estimates for years prior to regulation were based on relatively fewer measurements.[35] Individual DBPs were highly correlated in our data, which limited our ability to mutually adjust for different compounds and to draw inferences for individual species. However, analyses of some individual compounds showed that risk estimates were highest for bromodichloromethane and trichloroacetic acid among their respective classes. Brominated compounds are hypothesized to drive TTHM-associated risks for other cancer sites, such as the bladder.[22] Studies of adverse birth outcomes have reported stronger associations with bromodichloromethane than other THM species.[45,46] Studies on specific HAA compounds are limited.

Associations for endometrial cancer overall and restricted to type I cases, the predominant type, were similar. Our study did not have enough type II cases to examine associations restricted to this group. We observed a suggestive stronger association for both TTHM and HAA5 and low-grade type I tumors in comparison with high-grade cases. Previous studies have suggested differences in risk factors by endometrial cancer grade, such as stronger associations between unconjugated estradiol and low-grade tumors.[47]

Stratified analyses showed modestly greater risk associated with the highest quartile of TTHM among women who had ever used HRT in comparison with those who had never used HRT. However, there was no evidence of an interaction between HRT use and HAA5, despite the high correlation between these two DBP classes in our data. The reduced number of cases when accounting for both DBP exposure and HRT use could have contributed to the inconsistent patterns we observed between DBP classes. When we repeated stratified analyses using individual DBP compounds, we found trends were significant for bromodichloromethane and trichloroacetic acid among HRT users but not among nonusers. A few studies have demonstrated that DBP chemicals exhibit some estrogenic activity[48] and affinity for the estrogen receptor.[49] Unopposed estrogen therapy is associated with endometrial cancer risk, whereas continuous estrogen plus progestin formulations have been shown to be protective.[50] Although detailed information about HRT formulation was not available for our study population, data collected around the time of enrollment estimated that <20% of users were prescribed combination HRT; therefore, most women were likely using unopposed estrogen.[51] When further stratified by duration of HRT use, we found risk at the highest quartile of TTHM was strongest

Table 7. Quintiles of dietary nitrate and nitrite intake and risk of epithelial endometrial cancer in the Iowa Women's Health Study ($n = 22{,}897$).

	n	Cases	HR (95% CI)[a,b]
Dietary nitrate (mg/d)[c]			
1.01– < 8.88	4,576	100	Ref
8.88– < 12.11	4,573	100	0.95 (0.72, 1.26)
12.11– < 15.53	4,580	127	1.18 (0.91, 1.54)
15.53– < 20.72	4,585	124	1.17 (0.90, 1.53)
20.72–205.55	4,583	115	1.09 (0.83, 1.44)
p-trend[d]	—	—	0.357
Dietary nitrite (mg/d)			
0.06– < 0.55	4,573	103	Ref
0.55– < 0.62	4,574	104	0.94 (0.71, 1.23)
0.62– < 0.68	4,581	117	1.01 (0.77, 1.32)
0.68– < 0.76	4,583	131	1.13 (0.87, 1.48)
0.76–2.76	4,586	111	0.96 (0.72, 1.26)
p-trend	—	—	0.871
Nitrite from plant source (mg/d)			
0.05– < 0.31	4,577	109	Ref
0.31– < 0.37	4,584	108	0.92 (0.71, 1.21)
0.37– < 0.43	4,579	109	0.89 (0.68, 1.17)
0.42– < 0.51	4,572	124	1.04 (0.79, 1.36)
0.51–2.61	4,585	116	0.96 (0.73, 1.27)
p-trend	—	—	0.904
Nitrite from animal sources (mg/d)			
0.00– < 0.18	4,571	112	Ref
0.18– < 0.22	4,582	99	0.83 (0.64, 1.09)
0.22– < 0.26	4,581	110	0.90 (0.69, 1.17)
0.26– < 0.31	4,580	128	1.06 (0.82, 1.36)
0.31–1.41	4,583	117	0.98 (0.75, 1.27)
p-trend	—	—	0.552
Nitrite from processed meats (mg/d)			
0.000– < 0.003	4,575	101	Ref
0.003– < 0.014	4,579	109	1.05 (0.80, 1.38)
0.014– < 0.026	4,580	112	1.07 (0.81, 1.40)
0.026– < 0.044	4,582	126	1.19 (0.92, 1.55)
0.044–1.189	4,581	118	1.11 (0.85, 1.45)
p-trend	—	—	0.392

Note: The IWHS is a cohort of postmenopausal women 55–69 y of age who lived in Iowa and were enrolled in 1986 by completing a mailed survey and followed for cancer incidence and mortality until 2014 ($N = 41{,}836$). —, no data; CI, confidence interval; HR, hazard ratio; IWHS, Iowa Women's Health Study; Ref, reference.

[a]A total of $n = 117$ women were missing information on oral contraceptive or hormone replacement therapy use and were excluded from analyses. Participants missing information for other covariates were included in models with missing coded as a separate category. All dietary variables per 1,000 kcal per day of energy intake.

[b]Adjusted for age, body mass index, menopause age, oral contraceptive use, hormone replacement therapy use, parity, smoking status, and mutually adjusted for ln-transformed total dietary NO_3-N or nitrite.

[c]NO_3^- converted to NO_3-N.

[d]Modeled as a continuous variable derived from the median of each exposure category.

among long-term users (>1 y) in comparison with short-term users (≤1 y) and nonusers. The elevated risk among those with the highest TTHM levels and a history of HRT might be explained by the plausible shared effect of increased estrogen levels.

We found no associations between endometrial cancer and nitrate in drinking water, overall, by morphology and grade, or in stratified analyses. To our knowledge, the IWHS is the only cohort in which this relationship has ever been investigated. Inverse associations between drinking water nitrate and endometrial cancer were reported in a previous analysis in this cohort.[29] Our current, more comprehensive analysis with extended follow-up time, an additional 90 cases, and enhanced exposure assessment did not confirm an inverse association with NO_3-N in drinking water for endometrial cancer. Total dietary nitrate or nitrite intakes were also not associated with risk. A suggestive association with nitrite intake from processed meat was observed in both the main effect analysis and stratified analysis among those with low vitamin C intake. In a U.K. cohort, processed meat intake was associated with endometrial cancer risk among postmenopausal women,[52] whereas null findings were reported in a Swedish cohort.[53] Endogenous NOC formation, such as in the presence of low antioxidants, is thought to play a role in carcinogenesis.[9,27] A meta-analysis found antioxidant vitamins, including vitamin C, were associated with a decreased risk of endometrial cancer.[54] Whether risk is associated with processed meat intake and by what mechanism is not clear.

In our detailed evaluation between drinking water contaminants and endometrial cancer risk, we examined whether risk differed by etiological characteristics and established risk factors, afforded by available information on reproductive health and lifestyle factors collected at baseline. Although we tested for interaction between endometrial cancer risk factors and DBP exposures, mediation analyses were outside the scope of our study, given we report novel findings of uncertain mechanisms. We did not have prospective information about hysterectomies that occurred after enrollment; therefore, we were not able to censor women based on the date of surgery. Similarly, we did not evaluate changes in certain risk factors, like BMI, during the prospective period of follow-up. Although our exposure assessment entailed assigning participants long-term average exposures prior to follow-up, our approach was limited by reliance on estimated concentrations in earlier years. We used an ever/never indicator for use of chlorine or ammonia as disinfectant during the historical exposure period as a crude surrogate for the presence of chloraminated DBPs, which lacks temporal specificity; however, for most PWS, these treatments began in the 1980s or earlier and continued over time. Our exposure assessment did not capture potential variation in contaminant levels at the household level because we relied on samples collected at PWS distribution systems for compliance with the Safe Drinking Water Act rather than measurements taken directly from participants' home taps. Information regarding tap water consumption habits, including quantity, temperature, filtration use, and showering habits, was not collected from participants, which limited our ability to account for individual factors that may influence exposure levels. The previously established residential stability of the IWHS participants before and after enrollment was a study strength[55]; therefore, exposure misclassification due to mobility was likely minimal and mitigated by the restriction to women living at their addresses for more than a decade.

Our study reports a novel association between relatively high levels of DBPs in drinking water and endometrial cancer risk among postmenopausal women living in Iowa. With extended follow-up time and improved long-term exposure assessment in comparison with an earlier analysis in this cohort, we did not observe associations with nitrate in drinking water. Likewise, total dietary nitrate/nitrate were not associated with this cancer type. Our findings add to the limited literature about drinking water contaminants and endometrial cancer risk. Future research is warranted to examine underlying mechanisms and replicate epidemiological studies in other populations.

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