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Exposure to Drinking Water Trihalomethanes and Risk of Cancer: A Systematic Review of the Epidemiologic Evidence and Dose–Response Meta-Analysis

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Background: Chlorination is a widespread method for drinking water disinfection that has the drawback of introducing potentially carcinogenic chemical by-products to drinking water.

Objective: We systematically evaluated the epidemiologic evidence of exposure to trihalomethane (THM) disinfection by-products and risk of cancer.

Methods: We conducted a systematic review and meta-analysis of epidemiologic studies that assessed the association of exposure to residential concentrations of THMs with risk of cancer in adults. A protocol was preregistered in PROSPERO (CRD42023435491). PubMed, Embase, Web of Science, and Cochrane were searched for publications up to April 2024. Study selection and risk of bias appraisal using the National Toxicology Program Office of Health Assessment and Translation (NTP OHAT) tool was done in duplicate. Summary risk estimates were assessed using random effects meta-analysis and one-stage dose–response meta-analysis.

Results: The literature search resulted in 2,022 records, of which 29 publications assessing 14 different cancers were eligible for inclusion. Summary relative risks (RRs) were estimated for bladder cancer and colorectal cancer based on 5,860 and 9,262 cases and 84,371 and 90,272 participants, respectively. The summary RR of bladder cancer for the highest exposed compared with the lowest was 1.33 (95% CI: 1.04, 1.71), and in the dose–response analysis, RRs were statistically significant above THM concentrations of 41 μg/L. For colorectal cancer, the summary RR was 1.15 (95% CI: 1.07, 1.24).

Conclusion: According to the World Cancer Research Fund criteria, we found limited-suggestive evidence that THM in drinking water increases the risk of bladder and colorectal cancer at levels below current regulatory limits in the US and EU, indicating that these fail to protect against cancer in the general population. https://doi.org/10.1289/EHP14505

Introduction

Drinking water is an important part of our diet that, in some form, is consumed daily by essentially everyone in the population. Hence, assuring that the public drinking water maintains a high standard is important for public health. Chlorination is a cheap, effective, and readily available method for preventing waterborne infectious disease and is widely adopted across the globe.[1] Nevertheless, chemical drinking water disinfection may also give rise to disinfection by-products that are formed when chlorine or other chemical disinfectants react with natural organic matter in the raw water, and the most prevalent class of by-products in chlorinated drinking water is the trihalomethanes (THMs).[2] There are concerns that THMs may have carcinogenic properties. Animal and mechanistic studies have confirmed that three out of the four most common THMs (chloroform, bromoform, bromodichloromethane, and chlorodibromomethane) are genotoxic and that all four of them are rodent carcinogens.[3–5] Therefore, the sum of these four THMs is currently regulated in drinking water to not exceed 80 μg/L in the US and 100 μg/L in the EU, respectively.[6,7]

The existing epidemiologic evidence on the link between disinfection by-products and cancer in humans consists mainly of case–control studies and a small number of cohort studies, most of which have focused on bladder or colorectal cancer.[8–10] The findings of these studies have been mixed, which to some extent may be due to differences in the exposure assessment. Several pooled and meta-analyses using slightly different approaches have been published in an attempt to summarize the epidemiologic evidence on these two cancers, most recently in 2010 and 2011.[8,9] In the latest study of bladder cancer, it was found that men with the highest exposure to THM disinfection by-products had statistically significantly increased odds of bladder cancer compared with the lowest exposed after pooling data from 3 European case–control studies.[9] Similarly, a meta-analysis of 13 case–control and cohort studies reported a statistically significantly increased risk for both colon cancer and rectal cancer when comparing the highest category of disinfection by-product exposure with the lowest.[8] Nevertheless, since then, a number of new studies with prospective designs or improved methods for exposure assessment, or a combination of the two, have been published.[11–16] To our knowledge, none of the previous meta-analyses were preceded by a systematic review or summarized the evidence for cancer of other sites.[8–10]

The aim of this study was to summarize the current evidence on disinfection by-product exposure through drinking water and the risk of cancer, per cancer site, using a systematic review and meta-analysis design. To aid translation of results into practice and to increase comparability across individual studies, we focused our study on residential concentrations of THMs in drinking water. The THMs are frequently used as a surrogate for disinfection by-products exposure in epidemiologic studies assessing health effects of disinfection by-products.

Methods

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Prior to initiating any systematic review tasks, we wrote a study protocol that was registered in PROSPERO, an online database for prospectively registered systematic reviews (https://www.crd.york.ac.uk/prospero/), with the review identification (ID) CRD42023435491.

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Table 1. Summary of the study PI/ECOTSS statement that was used for specifying the research question.

PI/ECOTSS block	Definition
Population	Adults in the general population
Intervention/exposure	Quantitative measures (measured or predicted) of total THMs (the sum of chloroform, bromoform, dibromochloromethane, and bromodichloromethane)
Comparator	Higher concentrations of residential THM concentrations will be compared with lower or zero concentrations
Outcome	Cancer, overall, and per site
Timing	Minimum 2 y of follow-up (prospective studies) or 2 y measurements in case–control studies
Setting	Relevant for the general population
Study design	Observational studies with individual-level outcome data (cohort studies, case–control studies)

Note: PI/ECOTSS, Population, Intervention/Exposure, Control, Timing, Setting, and Study design; THM, trihalomethane.

Research Question and Study Eligibility Criteria

We formulated a focused research question using the Population, Intervention/Exposure, Control, Timing, Setting, and Study (PI/ECOTSS) design framework[17] that is summarized in Table 1. We included original research studies of the general adult population with cohort or case–control design that had individual outcome data. In drinking water studies, exposure is almost always measured at an aggregated level (because participants living in the same area are often supplied by the same drinking water treatment plant), and therefore ecological assessment of the exposure was accepted. To facilitate comparability across individual studies and enable dose–response analysis, we defined the exposure of interest as quantitative measures of concentrations of THMs in residential drinking water (both measured and predicted). The exposure information had to cover at least 2 y of the participants' lives (i.e., at least 2 y of follow-up in cohort studies or 2 y of prior measurements in case–control studies). We included studies that provided risk estimates [hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs)] with 95% confidence intervals (CIs) for units of increments or ordinal categories of the exposure. The outcome of interest was cancer incidence or mortality. Mortality is generally an acceptable proxy for incidence when survival is not related to the exposure under evaluation.[18] The primary cancer outcomes were bladder cancer and colorectal cancer, whereas other site-specific cancers and overall cancer were secondary outcomes.

Search Strategy

We carried out an extensive literature search in the following databases: US National Library of Medicine Medline database (using the PubMed interface), Embase, Web of Science, and Cochrane Central Register of Controlled Trials. Key search terms such as the following were used: "THM," "chloroform," "bromodichloromethane," "bromoform," "chlorodibromomethane," or "disinfection-byproducts," in combination with "tap water" or "drinking water" and "cancer," "colorectal cancer," or "bladder cancer." We included publications in English or Swedish. The initial search was conducted from database inception up through 1 June 2023 and updated on 2 April 2024 to identify additional papers published since the previous search (papers published between 2 June 2023 and 2 April 2024). The full search strategy is outlined in Table S1. In addition to the database searches, we checked the reference lists of included articles and previous meta-analyses for additional potentially eligible studies. We did not search gray literature or unpublished studies.

Record Screening and Data Extraction

Lists of records identified in the search were imported to the Rayyan online tool for systematic reviews (https://www.rayyan.ai/),[19] which automatically detected duplicates that were then manually removed. The remaining records were screened independently by two authors (E.H. and F.S.) and selected for inclusion or exclusion in two steps: title and abstract screening, followed by full-text screening. Any disagreements in decisions were solved through discussions with a senior team member (A.Å.). We included original research articles that adhered to the PI/ECOTSS statement outlined in Table 1 and reported relative risk estimates (i.e., HR, RR, or adjusted OR) with 95% CIs. When an outcome was published multiple times from the same cohort, we included the article with the longest follow-up time or the most recent publication. Articles that were excluded after full-text screening are outlined together with the reason for exclusion in Table S2. Data from papers that were included were extracted by one author (E.H.) using standardized extraction templates that asked for information on author and year, country, study design, study population, sample size (including number of cases), exposure (including method for assessment and categorization), outcome (including definition and method for ascertainment), effect size (HR/RR/OR for each exposure category), and confidence limits for the most adjusted model or by the authors specified primary model, confounding adjustments, and author conclusions. The accuracy of the extracted data was thoroughly checked by a second author (F.S.) and any disagreements were resolved.

Risk of Bias Assessment

Individual study quality was evaluated by two authors (E.H. and F.S.) using the National Toxicology Program's Office of Health Assessment and Translation (NTP OHAT) Risk of Bias Rating Tool for Human and Animal Studies.[20] Seven domains were evaluated: *a*) exposure assessment, *b*) outcome assessment, *c*) confounding bias, *d*) selection bias, *e*) attrition bias, *f*) selective reporting bias, and *g*) other threats to internal validity, with the first three being regarded as key domains. The possible ratings for each domain were "definitely low risk of bias," "probably low risk of bias," "not reported/probably high risk of bias," and "definitely high risk of bias." Ratings were made according to a modified version of the OHAT criteria, taking study design and important potential confounders for each outcome into consideration. The modified rating criteria for all domains assessed is outlined in Table S3. In brief, for the evaluation of the exposure assessment, studies were required to have had direct measurement of THM concentrations at the individual level (i.e., THM concentrations in tap water sampled at participant residences) to be rated "definitely low risk of bias," whereas indirect measurements (i.e., measurements of THM in samples taken at the drinking water treatment plant supplying the participants' residential addresses) were rated "probably low risk of bias," and predicted THM concentrations (direct or indirect) qualified for a "probably high risk of bias" rating.

Key covariates for each outcome were selected based on directed acyclic graphs. For all cancers, those covariates were *a*) age, *b*) sex (when applicable), *c*) smoking, and *d*) some proxy for socioeconomic status (SES). For studies on bladder cancer that included study participants using private wells, we additionally considered adjustment for concentrations of the well-established bladder cancer carcinogen arsenic[21] in drinking water important; for studies on colorectal cancer, alcohol consumption, physical activity, and overweight/obesity were regarded as key confounders.[22] Additional outcome-specific covariates were hormone replacement

therapy (HRT) and use of oral contraceptives (OC), alcohol consumption, physical activity, and overweight/obesity for breast cancer[23]; overweight/obesity and physical activity, HRT, and OC for endometrial cancer[24]; overweight/obesity, HRT, and OC for ovarian cancer[25]; overweight/obesity and alcohol consumption for kidney cancer[26]; overweight/obesity for pancreatic cancer and prostate cancer[27,28]; and sun habits for malignant melanoma.[29]

For the outcome assessment, outcomes had to have been assessed using well-established methods (i.e., gold standard diagnostic tools), participants had to have been followed for the same length of time in all study groups, and the assessors had to have been adequately blinded to the exposure for the outcomes to receive the highest ranking in this domain. Studies using cancer registers for case ascertainment were considered to fulfill these conditions. Given that the research questions were about disease etiology, studies were downgraded if they assessed cancer mortality rather than incidence.[18]

The overall quality of individual studies was determined by summarizing the ratings for each domain and classifying them according to tier 1, 2, or 3. To be classified as tier 1, studies had to be rated at least as "probably low risk of bias" for all three key domains and to have most other domains rated as "probably low risk of bias" or higher. Similarly, tier 3 studies were those that had "definitely high" or "probably high" risk of bias for key domains and had most other applicable items answered "definitely high" or "probably high" risk of bias. Tier 2 studies were those that met neither the criteria for the first nor the third tiers.

Data Synthesis and Statistical Analyses

When more than five studies per outcome were available, effect estimates for the highest exposed group compared with the lowest exposed were pooled using random effect meta-analysis with the restricted maximum likelihood (REML) method.[30] Two cancer outcomes were meta-analyzed: bladder cancer and colorectal cancer. Outcomes not amenable to a meta-analysis were tabulated and qualitatively summarized. Given that there are large disparities in bladder and colorectal cancer incidence between men and women, analyses were performed by sex for both outcomes, combining cohort and case–control studies.

The effect estimate most frequently reported in the included studies was OR, although some cohort studies provided HRs. For this meta-analysis, we considered OR and HR to be effectively interchangeable, given that both measures are estimates of relative risk when the outcome is rare. All studies reported risk estimates comparing exposure categories, except one study on rectal cancer in which the effect estimate was expressed as per unit increase in residential THM concentration. In that study, we recalculated the OR and 95% CI to correspond to a mean 35-μg/L increase (the average residential THM concentration in that study).[31]

The presence of between-study heterogeneity was assessed using Cochran's Q test with $p < 0.05$ set as the threshold for statistical significance, and the extent of heterogeneity was quantified using I^2 statistics.[32] When significant heterogeneity was present, we explored potential causes by conducting meta-regression, adjusting for potential moderators, and by performing subgroup analyses. Moreover, to assess the impact of individual studies on the overall results, we performed leave-one-out analyses by excluding one study at a time. Publication bias was assessed graphically using funnel plots and Egger regression-based tests.[33]

Linear and nonlinear dose–response meta-analyses were performed to estimate associations of residential drinking water THM concentrations up to 100 μg/L (the highest concentration reported in the included studies) and risk of bladder and colorectal cancer and to assess evidence of nonlinearity in the exposure–response relationship. The linear estimations were assessed using one-stage random effects dose–response models, assuming linear trends, whereas the nonlinear estimations were obtained using one-stage random effects dose–response models with restricted cubic splines and three knots (at 10th, 50th, and 90th percentiles).[34] RRs and corresponding 95% CIs were estimated based on model equations. Departure from linearity was examined graphically and through chi-square tests of that the second spline coefficient was equal to zero,[35] with the significance level set at 0.05. Because incidence is the most appropriate measure of disease occurrence when studying disease etiology, we performed sensitivity analyses in which we excluded mortality studies. Moreover, given that colorectal cancer is a heterogeneous disease with subtypes that may have different sensitivity toward environmental risk factors, we also performed separate analyses for colon and rectal cancer. All statistical analyses were made in Stata/SE (version 16; StataCorp LLC) using the metan and drmeta packages.

Results

We identified a total of 2,020 records in the literature search, and of the 1,353 records that remained after removal of duplicates, 91 were selected for full-text review. Of these, 7 were not possible to retrieve, and 55 were deemed ineligible. Two additional potentially eligible records were identified from reference lists of included articles, as well as previous meta-analyses, but which could not be retrieved.[36,37] A list of all records excluded from full-text review, together with the rationale for exclusions, and records that could not be retrieved is provided in Table S2. In total, we identified 29 papers evaluating residential THM concentrations in relation to the risk of cancer that fulfilled the eligibility criteria for inclusion in our study (Figure 1).

Study Characteristics

The 29 papers represented 12 unique studies that assessed residential THM concentrations in relation to cancer of 14 different organs: 8 on bladder cancer,[11,14,16,38–42] 8 on colorectal cancer (including separate studies on colon or rectal cancer),[12,13,15,31,43–46] 3 on pancreatic cancer,[47,48] 2 on kidney cancer,[49–51] 2 on female breast cancer,[52,53] 2 on leukemia,[54,55] and 1 each on endometrial cancer,[56] ovarian cancer,[57] prostate cancer,[58] lung cancer, cancer of the upper digestive tract, non-Hodgkin's lymphoma, and malignant melanoma.[53] Nine publications used data from the prospective cohorts the Iowa Women's Health Study (IWHS; $n = 7$)[12,16,49,51,56,57] or the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM) ($n = 2$).[13,14] The remaining 20 were case–control studies, of which 5 were based on the Spanish Multicase–Control Study on Cancer (MCC-Spain) study,[11,15,52,55,58] and 2 on the Canadian National Enhanced Cancer Surveillance System (NECSS).[48,54] The earliest study was published in 1987[46] and the latest in 2024,[55] with the start of baseline data collection ranging between 1986 and 2010. The number of participants in the cohort studies ranged between 10,501 and 58,672, and in case–control studies, between 381 (128 cases) and 5,291 (1,837 cases). Seven publications from the IWHS included only women,[12,16,49,51,53,56,57] and one case–control study included only men.[31] All studies were conducted in North America, Europe, or Taiwan. Characteristics of the included studies are summarized in Table 2 (bladder cancer), Table 3 (colorectal cancer), and Table 4 (cancer of other organs).

Risk of Bias Assessment

In the risk of bias assessment, 6 studies were rated as overall "low" risk of bias (tier 1)[11–14,49,51] and the remaining 23 were

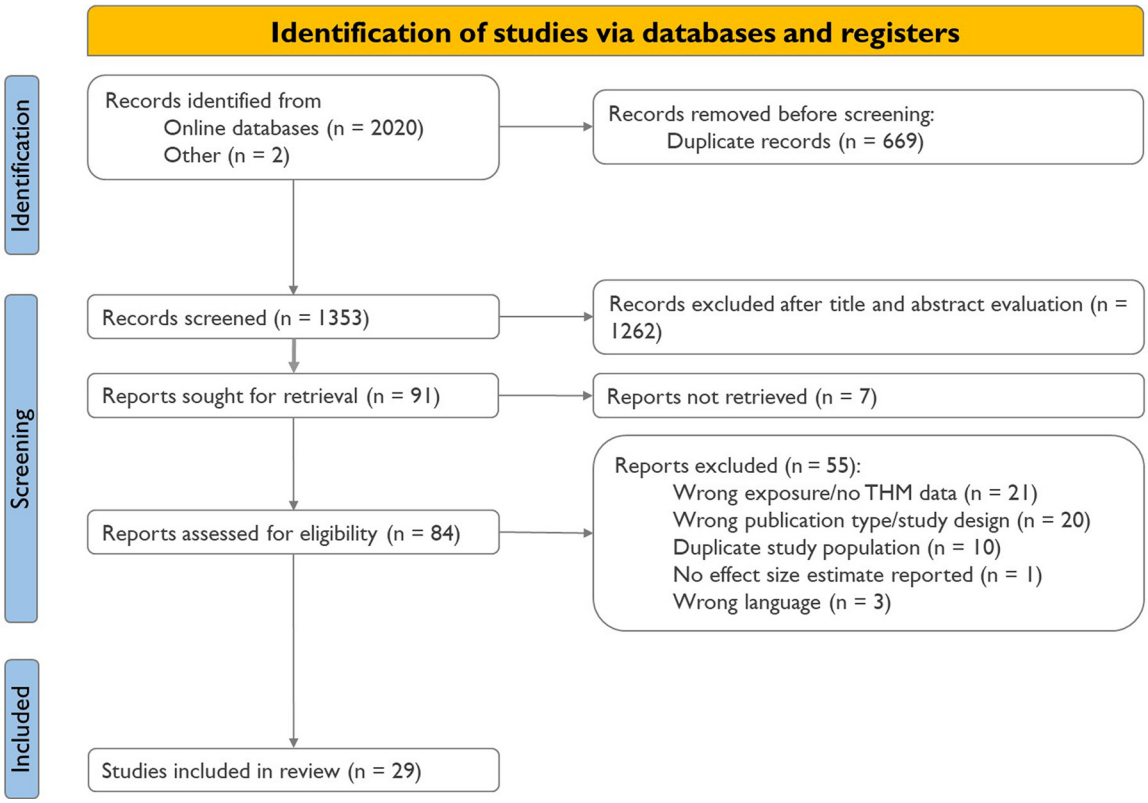

Figure 1. Flow diagram showing the literature search, screening, and study selection process for epidemiologic studies relevant to the research question of drinking water exposure to trihalomethanes (THMs) and risk of cancer.

rated as "moderate" risk of bias (tier 2). No studies fulfilled the criteria for "high" risk of bias (tier 3) (Figure 2).

All studies used indirect methods for the exposure assessment, with most using THM monitoring data or directly collected drinking water samples from drinking water treatment plants in the study area that were linked to individual information on study participants' residences (e.g., addresses, municipality, or locality of residence). The spatial resolution for residences was exact addresses in 4 studies,[11,31,48,54] and city, town, locality, or municipality in the remaining studies. A number of publications did not report the exact level of granularity for residential history (Tables 2–4). All but 1 study[31] assigned the same THM concentration to all residences supplied by the same water utility. The exception was the study by Bove et al.,[31] in which measured THM concentrations from four different sample points were used in kriging, a method of interpolation, to provide a range of estimated THM values throughout the distribution network. Based on this, the authors extracted THM estimates at the exact locations of the study participants. In addition to the study by Bove et al.,[31] 6 studies used predicted THM concentrations rather than using measured levels (or a combination of the two), based on modeling of known raw water characteristics and drinking water treatment practices.[40,41,44,46,48,54] All studies relied on exposure data that was collected over a period of at least 2 y, and a number of case–control studies estimated lifetime average residential THM concentrations.[11,15,38,40,42,43,58,59] No studies received the highest ranking on the exposure assessment because none assessed personal exposure to THMs directly (i.e., THM concentrations in the tap water at individual residences). Eighteen studies were rated as "probably low risk of bias" in the exposure assessment. The remaining 11 were downgraded because assigned THM concentrations were based on predictions or because the information used to identify the drinking water source was deemed to be imprecise (Figure 2).

Most studies were ranked as "definitely low" or "probably low" risk of bias in the outcome assessment domain because cancer cases were histologically confirmed and diagnosed at participating hospitals or ascertained from registers. Four studies assessed mortality rather than incidence.[39,45,47,50]

All studies made some attempt to control for confounding, and six studies were rated as "definitely low" or "probably low" risk of bias in this domain. The remaining studies were either lacking information on key covariates or did not make explicit considerations or proper adjustments for these in their final analyses. Four studies were register-based and lacked individual risk factor data, other than age, sex, and SES.[39,45,47,50] Studies were also downgraded if they included participants on private wells in the referent category because private well water is often uncontrolled with respect to other exposures (e.g., arsenic, nitrite, minerals) that could potentially confound the association under evaluation (Figure 2).

Twenty-four studies were rated as "definitely low" or "probably low" risk of bias with respect to selection bias. The remaining 5 studies were case–control studies and downgraded because they either used hospital controls or the response rate in controls was low/not reported.[15,31,40,42,46] All studies were rated as "definitely low" or "probably low" risk of bias in the attrition/exclusion from analysis domain. Only 1 study was rated as "high risk of bias" in the selective reporting domain, because the risk estimates in that study were insufficiently reported.[16] The remaining studies were all rated as "probably low risk of bias" because no study protocols could be found for any of the studies. Twenty-six studies were deemed to have no other threats to internal validity, and 3 studies were downgraded because the controls were originally matched to cases on residences or because a large proportion of the interviews were completed by proxy respondents.[31,48,59] A heatmap summarizing the results of the risk of bias assessment is provided in (Figure 2).

Table 2. Selected characteristics of epidemiologic studies included in the review on THM and bladder cancer.

Author, year	Outcome	Study design	Country	Study population	Exposure	THM (μg/L) range, categorization, and effect size (95% CI)	Overall RoB
Beane Freeman et al. 2017[11]	Bladder cancer (including *in situ*)	Population-based case–control study	New England, USA	2,158 (974 cases, 1,184 controls) men and women 30–79 years of age with THM data available for at least 70% of their lifetime.	Lifetime average residential THM concentrations estimated based on lifetime residential history (GPS coordinates for exact addresses), history of work locations, and primary source of drinking water in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0 to >45.73 μg/L Total: 0–6.83: 1.00 (Ref) >6.83–15.73: 0.86 (0.66, 1.11) >15.73–26.75: 0.96 (0.74, 1.25) >26.75–37.14: 0.97 (0.72, 1.30) >37.14–45.73: 0.92 (0.59, 1.44) >45.73: 1.27 (0.83, 1.96) Men: 0–6.83: 1.00 (Ref) >6.83–15.73: 0.83 (0.61, 1.11) >15.73–26.75: 0.94 (0.69, 1.26) >26.75–37.14: 0.92 (0.65, 1.30) >37.14–45.73: 0.80 (0.49, 1.32) >45.73: 1.20 (0.73, 2.06) Women: 0–6.83: 1.00 (Ref) >6.83–15.73: 0.92 (0.54, 1.57) >15.73–26.75: 1.08 (0.63, 1.87) >26.75–37.14: 1.01 (0.56, 1.82) >37.14–45.73: 1.70 (0.59, 4.88) >45.73: 1.66 (0.74, 3.70)	Low (tier 1)
Cantor et al. 1998[38]	Bladder cancer (including *in situ*)	Population-based case–control study	Iowa, USA	3,106 (1,123 cases, 1,983 controls) men and women, 40–85 years of age with THM data available for at least 70% of their lifetime.	Lifetime average residential THM concentrations estimated based on lifetime residential history (name of city or town), history of work locations, and primary source of drinking water in combination with survey data on THM concentration at the corresponding water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0–46.3 μg/L Total: <0.7: 1.00 (Ref) 0.8–2.2: 1.2 (1.0, 1.5) 2.3–8.0: 1.1 (0.8, 1.4) 8.1–32.5: 1.1 (0.8, 1.4) 32.6–46.3: 1.3 (0.9, 1.8) >46.4: 1.2 (0.8, 1.8) Men: <0.7: 1.00 (Ref) 0.8–2.2: 1.3 (1.0, 1.6) 2.3–8.0: 1.1 (0.9, 1.5) 8.1–32.5: 1.1 (0.8, 1.5) 32.6–46.3: 1.7 (1.1, 2.6) ≥46.4: 1.5 (1.0, 2.4) Women: <0.7: 1.00 (Ref) 0.8–2.2: 0.9 (0.6, 1.3) 2.3–8.0: 0.8 (0.5, 1.3) 8.1–32.5: 0.9 (0.6, 1.5) 32.6–46.3: 0.6 (0.3, 1.3) ≥46.4: 0.6 (0.3, 1.3)	Moderate (tier 2)
Chang et al. 2007[39]	Bladder cancer mortality	Register-based mortality case–control study	Taiwan	806 deceased residents in 65 municipalities of Taiwan (403 cases and 403 controls), 50 and 69 years of age at time of death and who died between 1996 and 2005.	Two years' average residential THM concentrations at participant residence at the time of their death. The spatial resolution for participant residences as well as THM concentrations in public drinking water was municipality.	Range: 0 to >31 μg/L 3.9: 1.00 (Ref) 13.9–21.1: 1.80 (1.18, 2.74) ≥21.2: 2.11 (1.43, 3.11)	Moderate (tier 2)
Chevrier et al. 2004[40]	Bladder cancer	Hospital-based case–control study	France	553 (281 cases, 272 controls) patients admitted to any of 7 participating hospitals in	Predicted[a] lifetime average residential THM concentrations estimated based on lifetime residential history	Range: 1–78 <1: 1.00 (Ref) 1–5: 1.09 (0.6, 2.0)	Moderate (tier 2)

Table 2. (*Continued.*)

Author, year	Outcome	Study design	Country	Study population	Exposure	THM (μg/L) range, categorization, and effect size (95% CI)	Overall RoB
				France 1985–1987, 30–80 years of age and with THM data available for at least 70% of their lifetime.	(municipality, town or within Paris–arrondissements) in combination with predicted THM concentration at the corresponding water utilities. The same THM level was assigned to all locations within one distribution network.	6–50: 1.2 (0.5, 2.4) >50: 1.28 (0.5, 3.0)	
Helte et al. 2022[14]	Bladder cancer (including *in situ*)	Population-based prospective cohort study	Sweden	58,672 men and women (831 cases; 699 men and 132 women) 45–83 years of age at enrollment in 1997, on public drinking water (Swedish Mammography Cohort and Cohort of Swedish Men)	Average multiannual residential THM concentrations that were estimated based on residential history (name of locality) in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0–63 μg/L Total: Non-chlorinated: 1.00 (Ref) <15 μg/L: 0.83 (0.69, 0.99) ≥15 μg/L: 0.90 (0.73, 1.11) Men: Non-chlorinated: 1.00 (Ref) <15 μg/L: 0.83 (0.68, 1.01) ≥15 μg/L: 0.91 (0.72, 1.15) Women: Non-chlorinated: 1.00 (Ref) <15 μg/L: 0.78 (0.18, 1.26) ≥15 μg/L: 0.79 (0.47, 1.32)	Low (tier 1)
Jones et al. 2016[16]	Bladder cancer	Population-based prospective cohort study	Iowa, USA	15,577 postmenopausal women (130 cases) 55–69 years of age at enrollment who were on public drinking water and who reported use of their drinking water source for at least 10 y prior to study (IWHS).	Long-term average residential THM concentrations estimated based on reported water source and city of residence in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: not known Quartiles of exposure: Q4 vs. Q1: 0.93 (0.55, 1.58)	Moderate (tier 2)
King and Marrett 1996[41]	Bladder cancer (including *in situ*)	Population-based case–control study	Canada	1,009 (312 cases, 697 controls) men and women, 25–74 years of age with known water history and homogeneous exposure to water source characteristics for ≥30 of the 40 y before the study.	Predicted[a] long-term average residential THM concentrations estimated based on residential history (unknown spatial resolution), primary source of drinking water, in combination with survey data on parameters used to predict THM concentrations from supplying water utilities.	Range: 0 to >75 μg/L 0–24: 1.00 (Ref) 25–74: 1.43 (1.00, 2.03) ≥75: 1.66 (1.11, 2.51)	Moderate (tier 2)
Villanueva et al. 2007[42]	Bladder cancer	Multicenter, hospital-based case–control study	Spain	1,479 (707 cases and 772 controls) patients admitted to any of 18 participating hospitals in five geographic areas of Spain during 1998–2001, who were 20–80 years of age with exposure information available for at least 70% of the exposure window.	Lifetime average residential THM concentrations that were estimated based on residential history (municipality) and primary water source, in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations with public drinking water within one municipality.	Range: 0 to >49 μg/L ≤8.0: 1.00 (Ref) 8.0–26.0: 1.25 (0.80, 1.93) 26.0–49.0: 1.98 (1.21, 3.24) >49.0: 2.10 (1.09, 4.02) Men: ≤8.0: 1.00 (Ref) >8.0–26.0: 1.53 (0.95, 2.48) >26.0–49.0: 2.34 (1.36, 4.03) >49.0: 2.53 (1.23, 5.20) Women: ≤8.0: 1.00 (Ref) >8.0–26.0: 0.40 (0.13, 1.27) >26.0–49.0: 1.14 (0.31, 4.10) >49.0: 1.50 (0.26, 8.61)	Moderate (tier 2)

Note: CI, confidence interval; GPS, Global Positioning System; IWHS, Iowa Women's Health Study; Ref, reference; RoB, risk of bias; THM, trihalomethane.
[a]Predicted refers to that THM concentrations were predicted based on other known drinking water parameters that are known to impact THM formation (i.e., estimations were not made/only partially made based on actual THM measurements).

Table 3. Selected characteristics of epidemiologic studies included in the review on THM and colorectal cancer.

Author, year	Outcome	Study design	Country	Study population	Exposure	THM (μg/L) range, categorization, and effect size (95% CI)	Overall RoB
Bove et al. 2007[31]	Rectal cancer	Population-based case–control study	Western New York State, USA	381 (128 cases and 253 controls) men 35–90 years of age in Monroe County (a subset of the Upstate New York Diet Case–Control Study).	Predicted[a] average residential THM concentration estimated based on residential history (geocoded addresses) in combination with monitoring data from different locations throughout the distribution system.	Range not known (mean concentration: 35.07 μg/L) Continuous per-unit increment in THM (μg/L): 1.01 (0.98, 1.03)	Moderate (tier 2)
Helte et al. 2023[13]	Colorectal cancer (excluding appendiceal cancer)	Population-based prospective cohort study	Sweden	58,672 men and women (1,913 cases; 1,176 men and 746 women) 45–83 years of age at enrollment in 1997, on public drinking water (Swedish Mammography Cohort and Cohort of Swedish Men)	Average multiannual residential THM concentrations that were estimated based on residential history (name of locality) in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0–63 μg/L Men: Non-chlorinated: 1.00 (Ref) <15 μg/L: 1.23 (1.03, 1.47) ≥15 μg/L: 1.26 (1.05, 1.51) Women: Non-chlorinated: 1.00 (Ref) <15 μg/L: 0.93 (0.74, 1.17) ≥15 μg/L: 0.97 (0.77 to 1.23)	Low (tier 1)
Hildesheim et al. 1998[43]	Colon and rectal cancer	Population-based case–control study	Iowa, USA	3,080 (560 colon cancer cases, 537 rectal cancer cases, and 1,983 controls) men and women 40–85 years of age with identifiable drinking water data for at least 70% of their lifetime.	Lifetime average residential THM concentrations estimated based on residential history (unknown spatial resolution), in combination with survey data on parameters used to predict THM concentrations from supplying water utilities.	Range: 0 to ≥46.4 Colon cancer: ≤0.7: 1.00 (Ref) 0.8–2.2: 1.01 (0.8, 1.3) 2.3–8.0: 0.93 (0.7, 1.3) 8.1–32.5: 1.07 (0.8, 1.4) 32.6–46.3: 0.93 (0.6, 1.5) ≥46.4: 1.06 (0.7, 1.6) Rectal cancer: ≤0.7: 1.00 (Ref) 0.8–2.2: 1.05 (0.8, 1.4) 2.3–8.0: 1.24 (0.9, 1.7) 8.1–32.5: 1.23 (0.9, 1.7) 32.6–46.3: 1.66 (1.1, 2.6) ≥46.4: 1.66 (1.1, 2.6)	Moderate (tier 2)
Jones et al. 2019[12]	Colon and rectal cancer	Population-based prospective cohort study	Iowa, USA	15,532 postmenopausal women (738 colon cancer cases and 186 rectal cancer cases) 55–69 years of age at enrollment who were on public drinking water and who reported use of their drinking water source for at least 10 y prior to study (IWHS).	Long-term average residential THM concentrations estimated based on reported water source and city of residence in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0 to >17.7 Colon cancer: ≤0.68: 1.00 (Ref) 0.69–2.17: 0.87 (0.67, 1.12) 2.18–7.82: 1.10 (0.85, 1.41) 7.83–17.7: 0.87 (0.67, 1.13) >17.7: 1.13 (0.89, 1.44) Continuous: 1.01 (0.98, 1.05) Rectal cancer: ≤0.68: 1.00 (Ref) 0.69–2.17: 1.28 (0.73, 2.20) 2.18–7.82: 1.63 (0.94, 2.84) 7.83–17.7: 1.83 (1.06, 3.16) >17.7: 1.71 (1.00, 2.92) Continuous: 1.06 (0.99, 1.14)	Low (tier 1)
King et al. 2000[44]	Colon and rectal cancer	Population-based case–control study	Ontario, Canada	1,282 (345 colon cases, 286 rectal cases, and 651 controls) men and women 30–74 years of age with known	Predicted[a] average residential THM concentration at least 30 y prior to the study estimated based on residential history	Range: 0 to >75 μg/L Colon cancer: Men: 0–24: 1.00 (Ref)	Moderate (tier 2)

Table 3. (*Continued.*)

Author, year	Outcome	Study design	Country	Study population	Exposure	THM (μg/L) range, categorization, and effect size (95% CI)	Overall RoB
				water history and homogeneous exposure to water source characteristics for ≥30 of the 40 y before the study.	(unknown spatial resolution), primary source of drinking water, in combination with survey data on parameters used to predict THM concentrations from supplying water utilities.	25–74: 1.53 (0.99, 2.38) ≥75: 1.87 (1.15, 3.05) Women: 0–24: 1.00 (Ref) 25–74: 0.46 (0.26, 0.81) ≥75: 0.92 (0.49, 1.71) Rectal cancer: Men: 0–24: 1.00 (Ref) 25–74: 1.27 (0.81, 2.00) ≥75: 0.98 (0.56, 1.72) Women: 0–24: 1.00 (Ref) 25–74: 0.62 (0.34, 1.13) ≥75: 0.72 (0.34, 1.53)	
Kuo et al. 2011[45]	Colon cancer mortality	Register-based mortality case–control study	Taiwan	4,360 deceased residents in 65 municipalities of Taiwan (2,180 cases and 2,180 controls) 50–69 years of age at time of death and who died between 1998 and 2007.	Two years' average residential THM concentrations at participant residence at the time of their death. The spatial resolution for participant residences as well as THM concentrations in public drinking water was municipality.	Range not known (median concentration: 4.9 μg/L). <4.9: 1.00 (Ref) ≥4.9: 1.14 (1.01–1.28)	Moderate (tier 2)
Villanueva et al. 2017[15]	Colorectal cancer	Hospital- and population-based multicenter case–control study	Spain and Italy	5,291 (1,837 cases and 3,454 controls) men and women 20–85 years of age with available exposure data for ≥70% of the years between 18 years of age and 2 y before the interview (MCC-Spain and HIWATE).	Lifetime average residential THM concentrations estimated based on residential history (unknown spatial resolution) in combination with monitoring data from supplying water utilities. The same THM concentration was assigned to all locations in the same water zone.	Range: 0 to >62 Total: <16.2: 1.00 (Ref) 16.2–29.5: 0.57 (0.45, 0.72) 29.5–62: 0.44 (0.33, 0.58) >62: 0.92 (0.66, 1.28) Men: <16.2: 1.00 (Ref) 16.2–29.5: 0.56 (0.41, 0.77) 29.5–62: 0.38 (0.27, 0.55) >62: 1.04 (0.68, 1.60) Women: <16.2: 1.00 (Ref) 16.2–29.5: 0.62 (0.41, 0.93) 29.5–62: 0.60 (0.38, 0.93) >62: 0.68 (0.39, 1.20)	Moderate (tier 2)
Young et al. 1987[46]	Colon cancer	Case–control study (population and cancer controls)	Wisconsin, USA	1,597 (347 cases and 1,250 controls) White male and female residents of Wisconsin 35–90 years of age at enrollment.	Predicted[a] average residential THM concentrations at different time points estimated based on residential history (unknown spatial resolution) and information on primary water source in combination with survey data from supplying utilities that was used to predict THM in finished drinking water.	Range: 0 (non-chlorinated) to 113 μg/L Population controls (in 1981): <10: 1.00 (Ref) 10–40: 1.06 (0.63, 1.77) >40: 1.01 (0.36, 2.84) Cancer controls (in 1981): <10: 1.00 (Ref) 10–40: 1.38 (0.84, 2.28) >40: 0.66 (0.26, 1.67)	Moderate (tier 2)

Note: CI, confidence interval; HIWATE, Health Impacts of long-term exposure to disinfection byproducts in drinking WATEr; IWHS, Iowa Women's Health Study; MCC-Spain, Spanish Multicase–Control Study on Cancer; Ref, reference; RoB, risk of bias; THM, trihalomethane.

[a]Predicted refers to that THM concentrations were predicted based on other known drinking water parameters that are known to impact THM formation (i.e., no actual measurements were made).

Table 4. Selected characteristics of epidemiologic studies included in the review on THM and cancer of sites other than the bladder and the colorectum.

Author, year	Outcome	Study design	Country	Study population	Exposure	THM (μg/L) range, categorization, and effect size (95% CI)	Overall RoB
Cantor et al. 1999[59]	Glioma	Population-based case–control study	Iowa, USA	2,274 (291 cases and 1,983 controls) male and female residents of Iowa, 40–85 years of age, with no history of cancer and with identifiable drinking water data for at least 70% of their lifetime.	Lifetime average residential THM concentrations estimated based on lifetime residential history (name of city or town), history of work locations, and primary source of drinking water in combination with survey data on THM concentration at the corresponding water utilities. The same THM level was assigned to all locations within one distribution network.	Range: <0.7 to >32.6 <0.7: 1.00 (Ref) 0.8–2.2: 0.9 (0.6, 1.3) 2.3–32.5: 0.9 (0.6, 1.4) >32.6: 1.1 (0.7, 1.8) Women: <0.7: 1.00 (Ref) 0.8–2.2: 0.9 (0.5, 1.5) 2.3–32.5: 0.8 (0.5, 1.5) >32.6: 0.9 (0.4, 1.8) Men: <0.7: 1.00 (Ref) 0.8–2.2: 0.9 (0.6, 1.6) 2.3–32.5: 1.0 (0.6, 1.8) >32.6: 1.4 (0.7, 2.9)	Moderate (tier 2)
Chiu et al. 2010[47]	Pancreatic cancer mortality	Register-based mortality case–control study	Taiwan	2,112 deceased residents in 65 municipalities of Taiwan (1,056 cases and 1,056 controls) 50–69 years of age at time of death and who died between 1998 and 2007.	Two years' average residential THM concentrations at participant residence at the time of their death. The spatial resolution for participant residences, as well as THM concentrations in public drinking water, was municipality.	Range not known (median concentration: 4.9 μg/L). <4.9: 1.00 (Ref) ≥4.9: 1.01 (0.85, 1.21)	Moderate (tier 2)
Do et al. 2005[48]	Pancreatic cancer	Population-based case–control study	Canada	3,985 men and women (476 cases and 3,509 controls) 30–75 years of age living in one of six provinces in Canada (Nova Scotia, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia) at enrollment.	Predicted[a] average residential TTHM concentrations during a 30-y exposure time window ending 3 y before interview. The exposure was estimated based on lifetime residential histories (exact addresses) in combination with monitoring data on THM levels in municipal water supplies and survey data that were used to predict THM concentrations in water from other water utilities. The same THM level was assigned to all locations within one distribution network	Range: 0 (non-chlorinated) to >50. <10: 1 (Ref) 10–20: 0.88 (0.67, 1.17) 20–50: 1.07 (0.83, 1.39) >50: 0.86 (0.58, 1.28)	Moderate (tier 2)
Donat-Vargas et al. 2023[58]	Prostate cancer	Population-based case–control study	Spain	1,624 (697 cases and 927 controls) men 20–85 years of age with available exposure data for ≥70% of the years between 18 years of age and 2 y before the interview (MCC-Spain).	Lifetime average residential THM concentrations estimated based on residential history (unknown spatial resolution) in combination with monitoring data from supplying water utilities. The same THM concentration was assigned to all locations in the same water zone.	Range: <LOD to >64.4 <32.5: 1.00 (Ref) 32.5–64.4: 1.06 (0.75, 1.51) >64.4: 0.78 (0.49, 1.24) Continuous (per 5 μg/L): 0.92 (0.89, 0.95)	Moderate (tier 2)
Donat-Vargas et al. 2024[55]	Chronic lymphocytic leukemia	Population-based case–control study	Spain	1,374 (144 cases and 1,230 controls) men 20–85 years of age with available exposure data for ≥70% of the years between 18 years of age and 2 y before the interview (MCC-Spain).	Lifetime average residential THM concentrations estimated based on residential history (unknown spatial resolution) in combination with monitoring data from supplying water utilities. The same THM concentration was assigned to all locations in the same water zone.	Range: <LOD to >83.3 <52.2: 1.00 (Ref) 52.2–83.2: 0.57 (0.22, 1.48) >83.3: 2.22 (0.90, 5.48) Continuous (per 10 μg/L): 1.24 (1.16, 1.34)	Moderate (tier 2)

Table 4. (*Continued.*)

Author, year	Outcome	Study design	Country	Study population	Exposure	THM (μg/L) range, categorization, and effect size (95% CI)	Overall RoB
Doyle et al. 1997[53]	Cancer of the upper digestive tract, lung cancer, malignant melanoma, non-Hodgkin's lymphoma, breast cancer (some other cancers were also assessed, but later publications are available for those outcomes)	Population-based prospective cohort	Iowa, USA	19,199 postmenopausal women 55–69 years of age at enrollment who were on public drinking water and who reported use of their drinking water source for at least 10 y prior to study (IWHS).	Residential chloroform concentrations 2 y prior to baseline. The exposure was estimated based on residential history (city or town) in combination with survey data on chloroform levels in public drinking water. All women who lived in the same community and reported drinking municipal water were assigned the same exposure level of chloroform.	Range: <LOD to 287 μg/L (chloroform) Cancer of the upper digestive tract: <LOD: 1.00 (Ref) 1–2: 1.93 (0.73, 5.16) 3–13: 1.01 (0.31, 3.31) 14–287: 1.59 (0.56, 4.47) Lung cancer: <LOD: 1.00 (Ref) 1–2: 1.24 (0.75, 2.07)3–13: 1.81 (1.11, 2.97)14–287: 1.59 (0.97, 2.59) Malignant melanoma: <LOD: 1.00 (Ref) 1–2: 2.55 (0.99, 6.58)3–13: 1.28 (0.41, 3.98)14–287: 3.37 (1.33, 8.56)Non-Hodgkins lymphoma: <LOD: 1.00 (Ref) 1–2: 0.82 (0.39, 1.70) 3–13: 0.85 (0.40, 1.84) 14–287: 0.99 (0.48, 2.02) Breast cancer: <LOD: 1.00 (Ref) 1–2: 1.06 (0.84, 1.33) 3–13: 1.18 (0.93, 1.49) 14–287: 1.08 (0.85, 1.37)	Moderate (tier 2)
Font-Ribera et al. 2018[52]	Breast cancer	Population-based case–control study	Spain	2,461 (1,003 cases and 1,458 controls) women 20–85 years of age with available exposure data for ≥70% of the years between 18 years of age and 2 y before the interview (MCC-Spain).	Lifetime average residential THM concentrations estimated based on residential history (unknown spatial resolution) in combination with monitoring data from supplying water utilities. The same THM concentration was assigned to all locations in the same water zone.	Range: 0.8–145.7 ≤21.7: 1.00 (Ref) >21.7–30.5: 1.15 (0.88, 1.49) >30.5–48.3: 1.09 (0.81, 1.46) >48.3: 1.14 (0.83, 1.57) Continuous (per 10 μg/L): 1.01 (0.97, 1.05)	Moderate (tier 2)
Inoue-Choi et al. 2015[57]	Ovarian Cancer	Population-based prospective cohort	Iowa, USA	13,051 postmenopausal women (145 cases) 55–69 years of age at enrollment who were on public drinking water and who reported use of their drinking water source for at least 10 y prior to study (IWHS).	Long-term average residential THM concentrations. The exposure was estimated based on reported water source and city of residence in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0–200.88 μg/L. Quartiles of exposure: <0.89: 1.00 (Ref) 0.9–4.59: 1.08 (0.64, 1.82) 4.77–14.31: 1.64 (1.00, 2.70) 14.50–200.88: 1.24 (0.73, 2.13)	Moderate (tier 2)
Jones et al. 2017[49]	Kidney cancer	Population-based prospective cohort	Iowa, USA	15,577 postmenopausal women (125 cases) 55–69 years of age at enrollment who were on public drinking water and who reported use of their drinking water source for at least 10 y prior to study (IWHS).	Long-term average residential THM concentrations. The exposure was estimated based on reported water source and city of residence in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0–200.88 μg/L Quartiles of exposure: <0.90: 1.00 (Ref) 0.90–4.58: 0.87 (0.54, 1.4) 4.59–14.30: 0.84 (0.51, 1.4) >14.30: 0.70 (0.41, 1.2) Continuous: 0.95 (0.90, 1.0)	Low (tier 1)

Table 4. (*Continued.*)

Author, year	Outcome	Study design	Country	Study population	Exposure	THM (μg/L) range, categorization, and effect size (95% CI)	Overall RoB
Kasim et al. 2006[54]	Leukemia	Population-based case–control study	Canada	2,525 men and women (419 cases and 2,106 controls) 20–74 years of age living in 1 of 8 provinces in Canada (Prince Edward Island, Newfounland, Nova Scotia, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia), with water quality information available for at least 30 y prior to study and who were exposed to chlorinated water (Canadian National Enhanced Cancer Surveillance System; NECSS).	Predicted[a] average residential TTHM concentrations during a 30-y exposure time window ending 3 y before interview. The exposure was estimated based on lifetime residential histories (exact addresses) in combination with monitoring data on THM levels in municipal water supplies and survey data that were used to predict THM concentrations in water from other water utilities. The same THM level was assigned to all locations within one distribution network.	Range: non-chlorinated to >40 μg/L Leukemia (all types): <20: 1 (Ref) 20–40: 0.80 (0.55, 1.17) >40: 0.90 (0.70, 1.10) Acute myelocytic leukemia: <20: 1 (Ref) 20–40: 0.90 (0.42, 1.80) >40: 1.03 (0.68, 1.60) Acute lymphocytic leukemia: <20: 1 (Ref) 20–40: 1.45 (0.30, 7.26) >40: 1.42 (0.50, 4.10) Chronic myelocytic leukemia: <20: 1 (Ref) 20–40: 0.90 (0.32, 2.58) >40: 1.76 (1.01, 3.10) Chronic lymphocytic leukemia: <20: 1 (Ref) 20–40: 0.63 (0.36, 1.10) >40: 0.73 (0.51, 0.97) Hairy cell leukemia: <20: 1 (Ref) 20–40: 0.85 (0.23, 3.16) >40: 0.31 (0.10, 0.80)	Moderate (tier 2)
Liao et al. 2012[50]	Kidney cancer mortality	Register-based mortality case–control study	Taiwan	1,000 deceased residents in 53 municipalities of Taiwan (500 cases and 500 controls) 50–69 years of age at time of death and who died between 1998 and 2007.	Two years' average residential THM concentrations at participant residence at the time of their death. The spatial resolution for participant residences as well as THM concentrations in public drinking water was municipality.	Range not known (median concentration: 4.9 μg/L) <4.9: 1.00 (Ref) >4.9: 0.98 (0.77–1.25)	Moderate (tier 2)
Medgyesi et al. 2022[56]	Endometrial cancer	Population-based prospective cohort	Iowa, USA	10,501 postmenopausal women (261 cases) 55–69 years of age at enrollment who were on public drinking water and who reported use of their drinking water source for at least 10 y prior to study (IWHS).	Long-term average residential THM concentrations (4th quartile is split into 2 categories). The exposure was estimated based on reported water source and city of residence in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: <0.9 to 200.88 <0.90: 1.00 (Ref) 0.90–4.76: 1.11 (0.77, 1.61) 4.77–14.49: 1.40 (0.96, 2.04) 14.50–93.19: 1.38 (0.90, 2.11) 93.2–200.88: 2.19 (1.41, 3.40)	Moderate (tier 2)
Quist et al. 2018[51]	Pancreatic cancer (excluding leiomyosarcoma, endocrine tumors, carcinoid tumors, neuroendocrine carcinoma, and small cell carcinoma)	Population-based prospective cohort study	Iowa, USA	15,710 postmenopausal women (152 cases) 55–69 years of age at enrollment who were on public drinking water and who reported use of their drinking water source for at least 10 y prior to study (IWHS).	Long-term average residential THM concentrations estimated based on reported water source and city of residence in combination with monitoring data from the supplying water utilities. The same THM level was assigned to all locations within one distribution network.	Range: 0 to >14.31 <0.9: 1.00 (Ref) 0.9–4.58: 1.22 (0.8, 1.86) 4.59–14.31: 0.88 (0.55, 1.4) >14.31: 0.7 (0.42, 1.18) Continuous: 0.98 (0.94, 1.04)	Low (tier 1)

Note: CI, confidence interval; IWHS, Iowa Women's Health Study; LOD, limit of detection; MCC-Spain, Spanish Multicase–Control Study on Cancer; Ref, reference; RoB, risk of bias; THM, trihalomethane; TTHM, total trihalomethanes.
[a]Predicted refers to that THM concentrations were predicted based on other known drinking water parameters that are known to impact THM formation (i.e., no actual measurements were made).

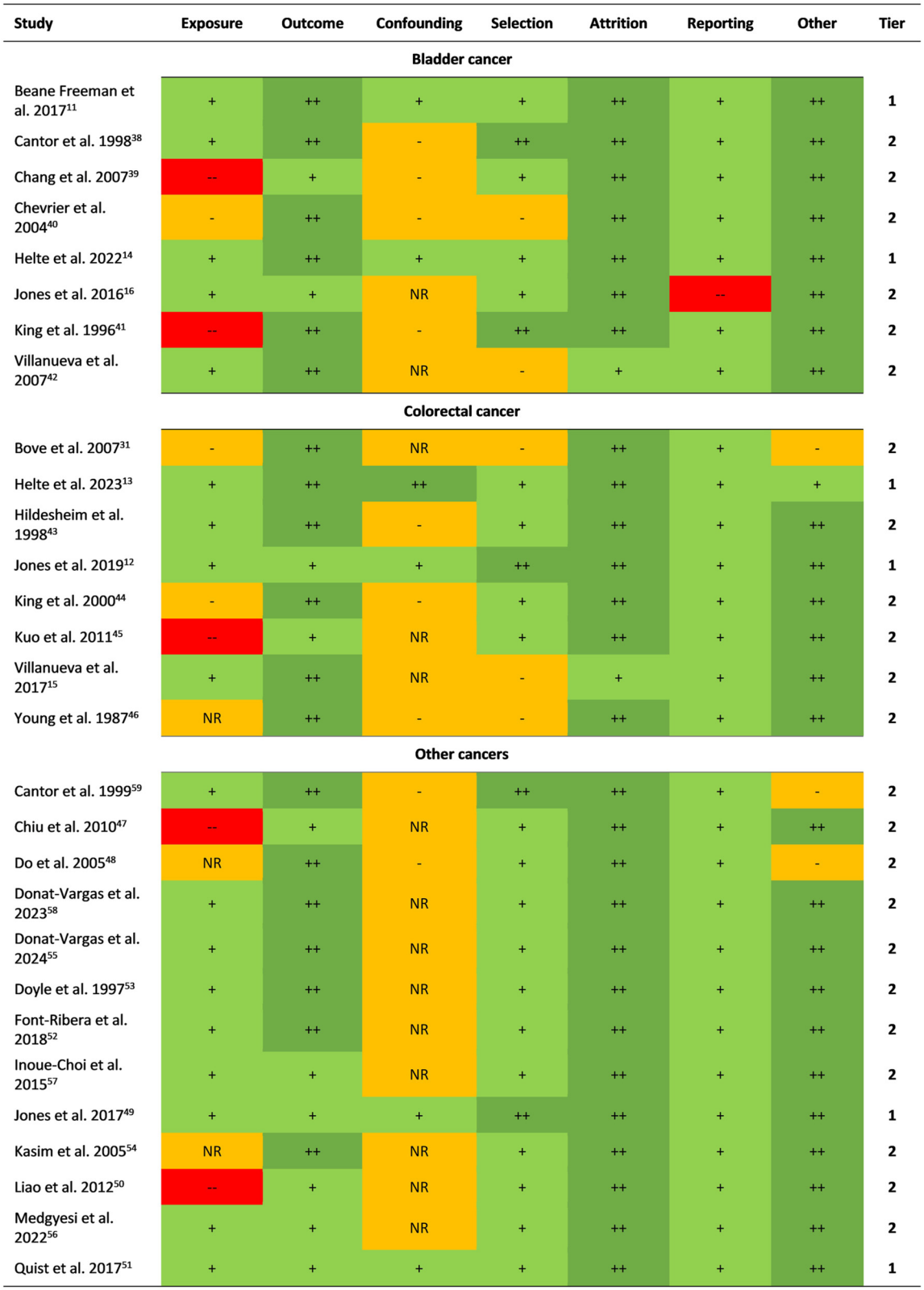

Figure 2. Heatmap of individual study quality ratings evaluated using the National Toxicology Program Office of Health Assessment and Translation (NTP OHAT) Risk of Bias Rating Tool for Human and Animal Studies. A thorough description along with the full assessment criteria are outlined in Table S3. Note: NR, not reported.

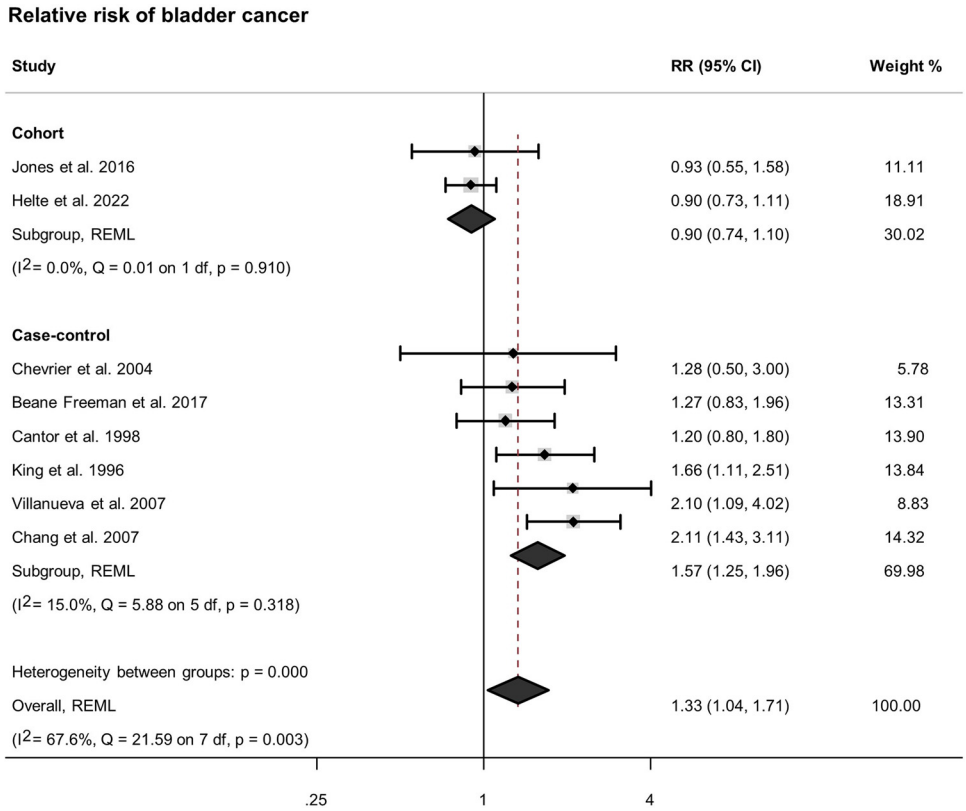

Figure 3. Forest plot and meta-analysis of the eight included epidemiologic studies for the highest vs. lowest exposed category with RR of bladder cancer in men and women, stratified by study design. *N* total cases = 3,920, *n* total controls/person-years = 9,379/965,590. Reported effect estimates (95% CI) from individual studies, and overall pooled estimate from random effect model. Studies referenced: Jones et al.,[16] Helte et al.,[14] Chevrier et al.,[40] Beane Freeman et al.,[11] Cantor et al.,[38] King et al.,[41] Villanueva et al.,[42] Chang et al.[39] Note: CI, confidence interval; df, degrees of freedom; REML, restricted maximum likelihood; RR, relative risk.

Synthesis of Results

Of the 29 included studies, 16 were included in meta-analyses of two outcomes: bladder cancer[11,14,16,38–42] and colorectal cancer,[12,13,15,31,43–46] comprising in total 5,860 and 9,262 cases and 84,371 and 90,272 participants, respectively. The results for other cancer outcomes were tabulated and summarized qualitatively.

Bladder cancer. The summary RR for bladder cancer obtained from the meta-analysis comparing the highest category of residential drinking water THM exposure to the lowest exposed was significantly increased (RR = 1.33; 95% CI: 1.04, 1.72), but there was substantial heterogeneity present ($I^2 = 67.6\%$, $Q = 21.59$ on 7 degrees of freedom (df), $p = 0.003$) (Figure 3). Potential sources of heterogeneity, explored in meta-regression, included study design, sex, and overall risk of bias as moderators. The model output suggested that a large part of the between-study variability could be explained by these three factors ($R^2 = 71.5$, remaining $I^2 = 25.7\%$). Further, we explored the impact by overall study quality, and the association with increased risk was more pronounced, although not statistically significantly different, in the studies with a higher risk of bias score [summary RR in low risk of bias = 1.01 (95% CI: 0.74, 1.40); summary RR in moderate of bias = 1.50 (95% CI: 1.14, 1.98); $p_{\text{subgroup heterogeneity}} = 0.07$; Figure S1]. In the leave-one-out analysis, we obtained RRs that ranged between 1.21 and 1.46, and the greatest difference in results was observed when excluding the study by Helte et al.[14] (RR = 1.46; 95% CI: 1.16, 1.71; Figure S2). Graphical evaluation of funnel plots and Egger's tests did not indicate publication bias (Figure S3).

To explore potential sex differences, we performed stratified analyses by sex that were limited to the four studies that reported effect estimates separately for men and women[11,14,16,38,42] and one additional study that included only women. Although there was no statistically significant between-group heterogeneity ($p_{\text{heterogeneity}} = 0.13$), the results showed a stronger association in men than in women, with a RR of 1.31 (95% CI: 0.89, 1.94) in men and 0.90 (95% CI: 0.67, 1.21) in women (Figure 4).

The results of the dose–response analyses are illustrated in Figure 5. In men and women, a 10-μg/L increase in residential THM concentration was associated with a borderline statistically significant increased risk of bladder cancer, RR = 1.08 (95% CI: 1.00, 1.17), with no evidence of nonlinearity. In the stratified analysis by sex, the corresponding results were RR = 1.05 (95% CI: 0.99, 1.12) in men and 0.99 (95% CI: 0.90, 1.10) in women. The predicted RRs were statistically significant at THM concentrations of ≥41 μg/L and higher. The corresponding results for each spline knot are outlined in Table S4.

In the sensitivity analysis, after excluding one study that assessed mortality rather than incidence,[39] the association in the highest vs. lowest random effect meta-analysis was attenuated to a statistically nonsignificant increased risk with increasing THM exposure and a summary RR of 1.21 (95% CI: 0.96, 1.54; Figure S4). The results of the corresponding dose–response analysis only changed marginally with the THM concentration associated with a statistically significant increased risk increasing from 41 to 44 μg/L (Figure S5). According to the World Cancer Research Fund (WCRF) criteria for judging the evidence,[60] we conclude the evidence for the association of THMs in drinking water with risk of bladder cancer to be limited-suggestive.

Colorectal cancer. The summary RR of colorectal cancer for the highest vs. the lowest concentration of residential THM concentrations was statistically significantly increased (RR = 1.15;

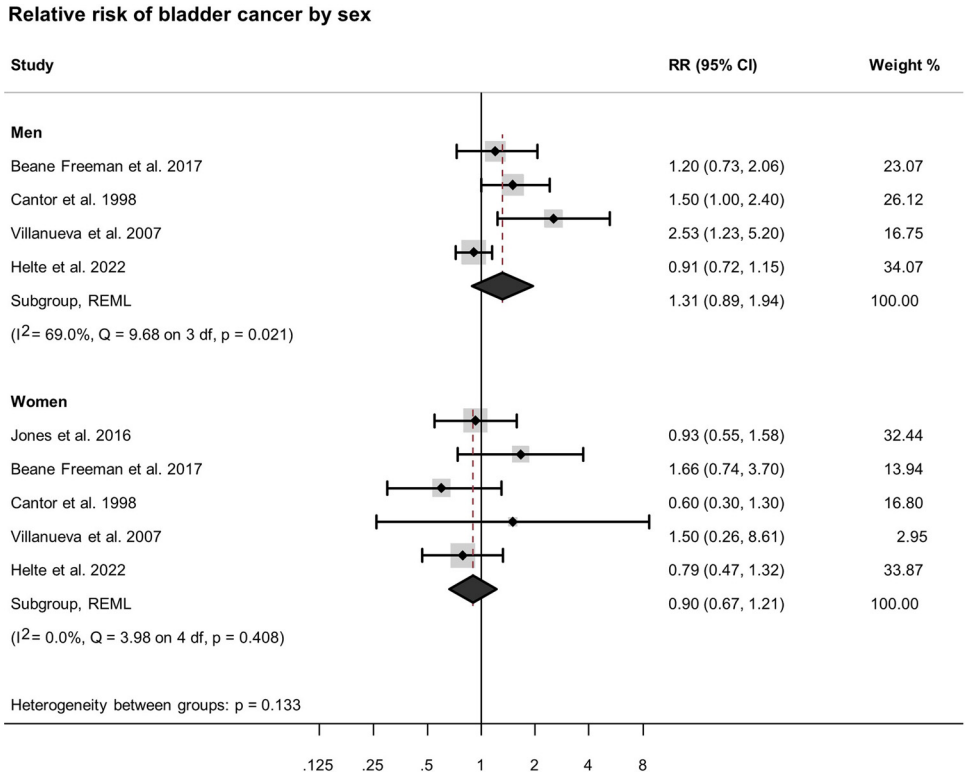

Figure 4. Forest plot and meta-analysis of the eight included epidemiologic studies for the highest vs. lowest exposed category with relative risk of bladder cancer, stratified by sex. In men: *N* total cases = 2,929, *n* total controls/person-years = 5,375/523,558. In women: *N* total cases = 706, *n* total controls/person-years = 2,906/442,030. Reported effect estimates (95% CI) from individual studies, and overall pooled estimate from random effect model. Studies referenced: Beane Freeman et al.,[11] Cantor et al.,[38] Villanueva et al.,[42] Helte et al.,[14] Jones et al.[16] Note: CI, confidence interval; df, degrees of freedom; REML, restricted maximum likelihood; RR, relative risk.

95% CI: 1.07, 1.24), and there was no evidence of significant heterogeneity ($I^2 = 19.9\%$, $Q = 16.2$ on 13 df, $p = 0.24$) (Figure 6). There were no major differences across groups in the subgroup analysis by overall risk of bias score ($p_{\text{subgroup heterogeneity}} = 0.27$; Figure S6). Excluding one study at the time did not have any major impact on the obtained results, with RRs ranging between 1.13 and 1.17 (Figure S7). Funnel plots and Egger's tests showed no clear evidence of small-study effects (Figure S8).

Because there are large disparities in colorectal cancer incidence, and, to some degree, sensitivity toward external risk factors in men and women, stratified analyses by sex were performed (Figure 7). These analyses were limited to three studies that reported effect estimates separately for men and women,[13,15,44] and two studies that only included one sex.[12,31] The results, although not statistically significant ($p_{\text{subgroup heterogeneity}} = 0.07$), revealed that the overall association was stronger in men (RR = 1.26; 95% CI: 1.08, 1.46) than in women (RR = 1.03; 95% CI: 0.87, 1.21).

The results of the dose–response analysis are illustrated in Figure 5. When combining men and women, a 10-μg/L increase in residential THM concentration (assuming a linear relationship) corresponded to a RR of 1.03 (95% CI: 1.00, 1.06), although predicted RRs did not reach statistical significance at any THM concentration modeled. In men, the linear association was RR = 1.04 (95% CI: 0.99, 1.08), and in women, 0.99 (95% CI: 0.95, 1.02) per 10-μg/L increment in THM. For the spline model, the results for each spline knot are outlined in Table S4. There was no evidence of departure from linearity in any of the analyses.

The results were robust to the sensitivity analyses that explored the impact of excluding mortality studies (Figures S9 and S10). Similarly, the analyses that assessed differences in the association by tumor location suggested similar associations for colon cancer and rectal cancer in the highest vs. lowest random effect meta-analysis, although the association only reached statistical significance for colon cancer [summary RR colon cancer = 1.17 (1.07, 1.27) and not for rectal cancer = 1.18 (0.94, 1.48); Figures S11 and S12]. In the dose–response analyses, the association with colon cancer was statistically significant at THM concentrations >19 μg/L up to 47 μg/L, whereas for rectal cancer, it never reached statistical significance (Figures S13 and S14). Overall, we concluded the evidence for the association of THMs in drinking water with risk of colorectal cancer to be limited-suggestive according to the WCRF criteria.[60]

Cancer of other organs. Following bladder cancer and colorectal cancer, the third most common outcome to be evaluated in relation to residential THM concentrations was pancreatic cancer. In total, three studies of drinking water THM and pancreatic cancer were identified, and all of them reported findings close to null for the highest exposed category compared with the lowest.[47,48,51] For kidney cancer, leukemia, and breast cancer, two studies were identified each. The results of the studies on kidney cancer were either nonstatistically significantly inverse or null when comparing the highest exposed to the lowest.[49,50] One study of those that assessed the relationship with leukemia reported a nonstatistically significant inverse association with residential THM exposure,[54] whereas the other found nonstatistically significant associations with increased risk chronic lymphocytic leukemia among the highest exposed.[55] Both studies that assessed breast cancer in relation to residential THM exposure reported increased, although nonstatistically significant, risk estimates.[52,53] Other hormone-related cancers assessed were ovarian cancer, endometrial cancer, and prostate cancer.[56–58] The reported risk estimates for both female cancers comparing the highest exposed to the lowest were increased but only statistically significant for endometrial cancer (RR = 2.19; 95% CI: 1.41, 3.40).[56] In contrast, there was no clear

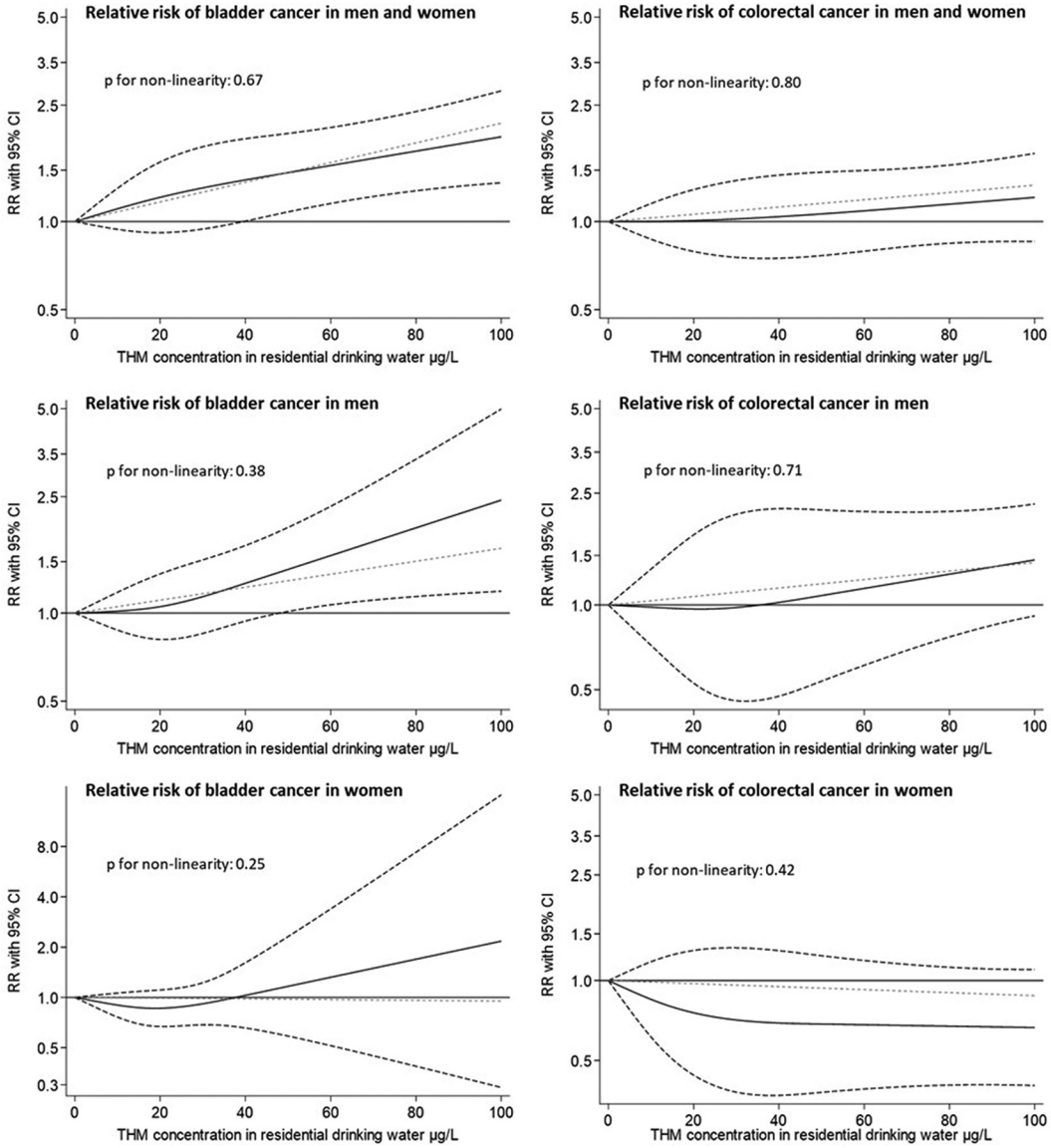

Figure 5. Linear (light gray dashed lines represent RRs), and nonlinear dose–response (black lines represent RRs, with black dashed lines representing CIs) relationship per unit increase (in µg/L) in residential drinking water THM concentrations and risk of bladder cancer and colorectal cancer in men and women, derived from dose–response meta-analyses. Bladder cancer: *n* total cases = 3,920, *n* total controls/person-years = 9,379/965,590, men: *n* cases = 2,929, *n* total controls/person-years = 5,375/523,558, women: *n* cases = 706, *n* total controls/person-years = 2,906/442,030. Colorectal cancer: *n* total cases = 8,582, *n* total controls/person-years = 16,286/1,019,274, men: *n* cases = 2,714, *n* controls/person-years = 4,198/536,622, women: *n* cases = 2,589, *n* controls/person-years = 3,022/482,652. The numeric results for each spline knot are outlined in Table S4. Note: CI, confidence interval; RR, relative risk; THM, trihalomethane.

association of residential THM concentrations and prostate cancer.[58] One study assessed residential chloroform levels in relation to several different cancers: cancer of the upper digestive tract, lung cancer, malignant melanoma, and non-Hodgkin's lymphoma.[53] The point estimate was positive for all these outcomes, except non-Hodgkin's lymphoma, but only statistically significant for malignant melanoma (RR = 3.37; 95% CI: 1.33, 8.56). Finally, one study evaluated the relationship with brain tumors and reported no clear association with increasing residential THM concentrations.[59] According to the WCRF criteria, we concluded the overall evidence for cancer of sites other than the bladder and colorectum to be limited-no conclusion.[60]

Discussion

In this comprehensive systematic review and meta-analysis of observational studies, we summarized the evidence of exposure to THMs in drinking water with risk of 14 different cancers. Of the cancers evaluated, bladder cancer and colorectal cancer were eligible for meta-analysis. The overall results showed a statistically significant 33% and 15% increased risk of bladder cancer and colorectal cancer, respectively, when comparing the highest with the lowest category of THM exposure. In the dose–response meta-analysis, the RRs for bladder cancer were statistically significant at THM concentrations of 41 µg/L and higher. Lack of power may have affected the ability to detect significant associations at lower levels. Subgroup analyses by sex suggested potential sex differences, particularly for colorectal cancer where the association seemed to be driven mainly by an increased risk in men.

In comparison to previous meta- and pooled analyses of disinfection by-product exposure and cancer that we are aware of, our review is a systematic review that also includes a larger number and more recent publications. Yet, the results are broadly in line

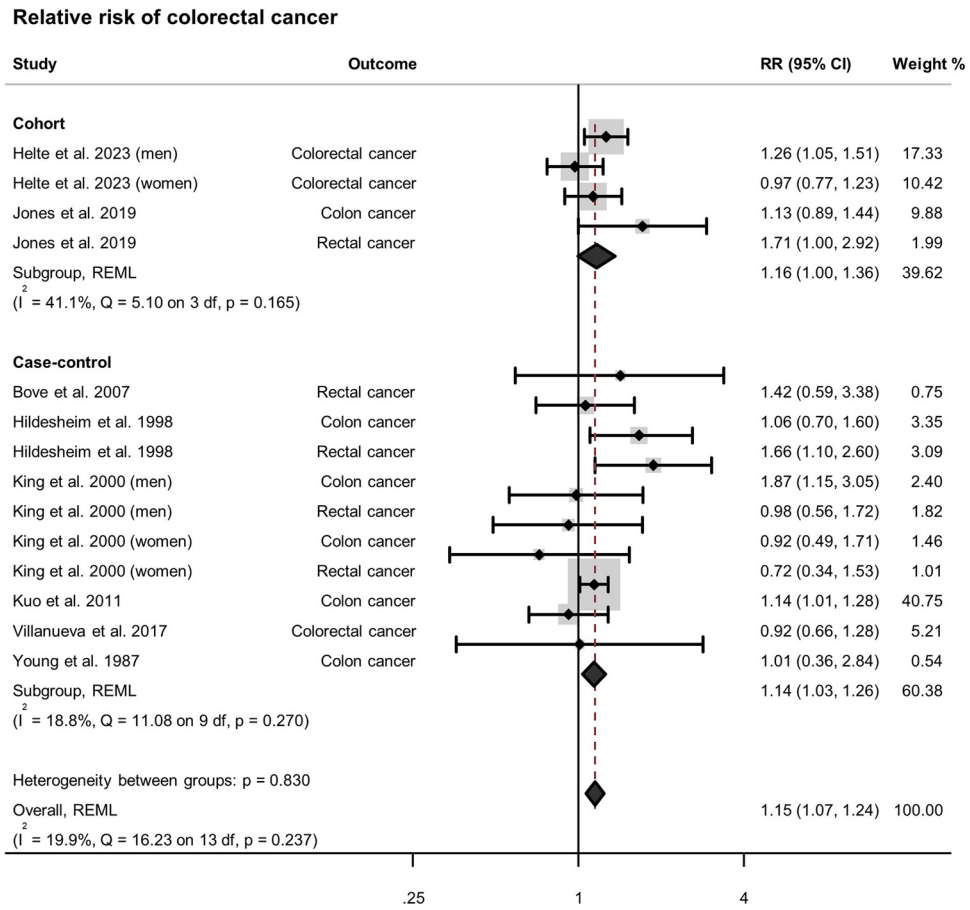

Figure 6. Forest plot and meta-analysis of the eight included epidemiologic studies for the highest vs. lowest exposed category with RR of colorectal cancer stratified by study design. *N* total cases = 8,582, *n* total controls/person-years = 16,286/1,019,274. Reported effect estimates (95% CI) from individual studies, and overall pooled estimate from random effect model. Studies referenced: Helte et al.,[13] Jones et al.,[12] Bove et al.,[31] Hildesheim et al.,[43] King et al.,[44] Kuo et al.,[45] Villanueva et al.,[15] Young et al.[46] Note: CI, confidence interval; df, degrees of freedom; REML, restricted maximum likelihood; RR, relative risk.

with the results of those previous pooled efforts.[8–10] In 2004, a pooled analysis of six North American and European case–control studies that used THMs as a marker of disinfection by-product exposure found an association with 44% increased odds of bladder cancer in men at concentrations >50 μg/L, whereas the association in women was close to null.[10] A later pooled analysis of only European studies came to a similar conclusion.[9] Moreover, a meta-analysis published in 2010 that evaluated the association of disinfection by-product exposure both in terms of residential THM concentrations and by chlorination status with colorectal cancer found 27% and 30% increased odds of colon and rectal cancer, respectively, when comparing the highest exposed to the lowest. The authors, however, did not perform any dose–response analyses or address any potential sex differences.[8]

There are discrepancies in which publications were included in the present work and previous pooled analyses,[8–10] which are mainly due to differences in the inclusion criteria and, in some cases, due to the studies included being unpublished or not possible to retrieve. Moreover, we included additional studies published after 2011 in our work. In contrast to the two latest pooled efforts on bladder cancer,[9,10] we excluded three studies because they did not report THM concentrations in drinking water,[61–63] and one study because it was unpublished. Similarly, of the studies included in the meta-analysis on colorectal cancer, we did not include five studies[64–68] because they did not report THM concentrations, one study because a more recent publication from the same study was included in the present work,[53] one study because it reported only standardized mortality rates that were calculated by comparing rates in the exposed cohort to rates in a reference population,[69] and two that were not identified in the literature search and could not be retrieved following manual search.[36,37]

In the association with bladder cancer, we identified a threshold of 41 μg/L for drinking water THM concentrations above which the risk was statistically significantly increased. The dose–response analysis was based on data from eight publications with varying exposure contrasts. All studies assessed bladder cancer in relation to THM concentrations up to ∼20 μg/L,[11,14,16,38–42] five studies up to at least 50 μg/L,[11,38,40–42] and only one study up to 100 μg/L,[41] reducing the certainty in the findings at higher exposures. Still, it is important to note that THMs are currently regulated not to exceed 80 μg/L in the US and 100 μg/L in the EU,[6,7] and our results suggest that these limits may not be sufficient to protect against bladder cancer in the general population.

There are mechanistic and animal data that support the relationship between THM exposure and cancer. Of the four most common THMs, the three brominated ones are genotoxic *in vitro* following glutathione *S*-transferase theta 1 (GSTT-1) activation.[2] Chloroform is not genotoxic but has been shown to induce renal and liver tumors in both rats and mice through a nongenotoxic mode of action. Relating to colorectal cancer, bromoform and bromodichloromethane cause aberrant crypts and otherwise rare tumors of the large intestine in rats.[2] There is little evidence from animal data supporting an association with increased risk of bladder cancer.[2] Nevertheless, the translation of findings in laboratory animals to humans is not straightforward and is generally recognized as a complex challenge to toxicologists.

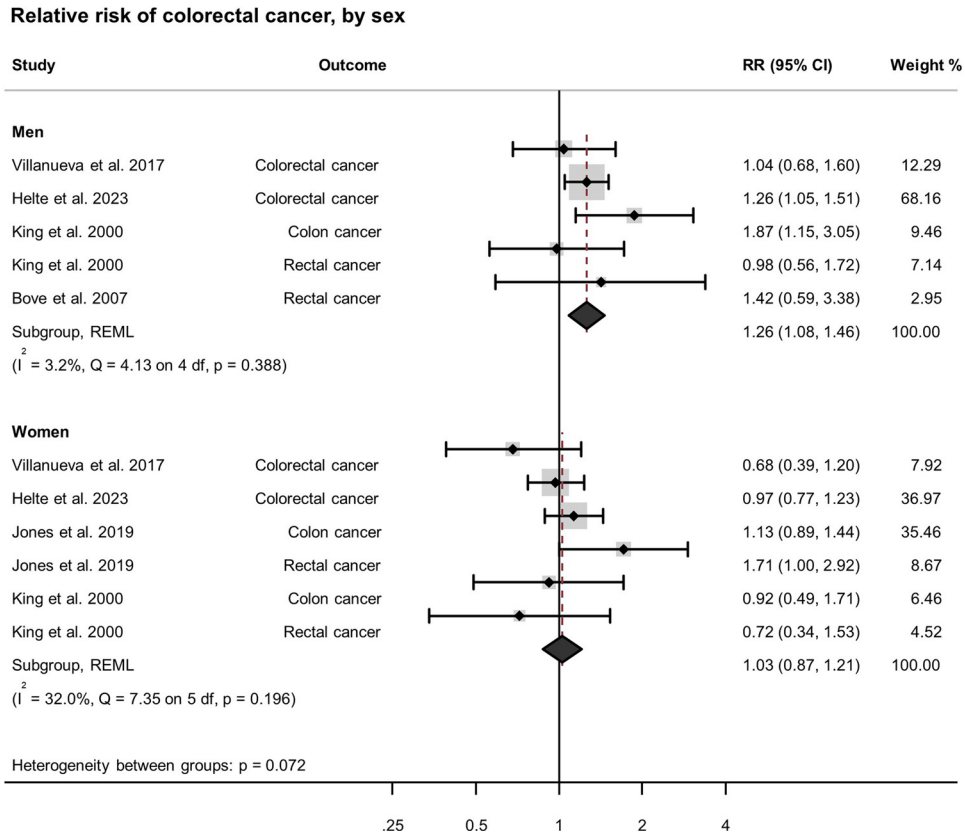

Figure 7. Forest plot and meta-analysis of the eight included epidemiologic studies for the highest vs. lowest exposed category with RR of colorectal cancer stratified by sex. In men: *N* total cases = 2,714, *n* total controls/person-years = 4,198/536,622. In women: *N* total cases = 2,589, *n* total controls/person-years = 3,022/482,652. Reported effect estimates (95% CI) from individual studies, and overall pooled estimate from random effect model. Studies referenced: Villanueva et al.,[15] Helte et al.,[13] King et al.,[44] Bove et al.,[31] Jones et al.[12] Note: CI, confidence interval; df, degrees of freedom; REML, restricted maximum likelihood; RR, relative risk.

In this review, we observed some indications of sex differences in the association of THMs with bladder cancer and colorectal cancer, with the overall increased risk of bladder cancer being more pronounced in men and the increased risk of colorectal cancer present only in men. The incidence rate of bladder cancer is about four times higher in men than in women,[70] and differences observed could be explained by the lower power in the analyses of women. With respect to colorectal cancer, men, compared with women, have been proposed to be more strongly influenced by environmental than genetic factors, which is also supported by migration studies.[71] Moreover, although men have a higher overall risk of colorectal cancer, women are more often diagnosed with right-sided colon cancer. Colorectal cancer is a heterogeneous disease, and tumors in the right and left sides of the colon and in the rectum exhibit different molecular characteristics, have different prognoses, and are treated differently.[71] We performed sensitivity analyses separately for colon and rectal cancer but observed only slight differences, with the association being more pronounced for colon cancer than rectal cancer. Ideally, we would have liked also to separate colon cancer into right- and left-sided colon cancer given that studies have previously reported differences in the association with THM exposure for these subtypes,[13] but the number of studies that made this distinction were too few to allow such analyses.

We focused our work in this review on studies using THMs as a marker of disinfection by-product exposure. However, disinfection by-products do not only consist of THMs but, rather, comprise a complex mixture of >800 known substances with distinct chemical and physical properties and toxicological profiles.[2] The degree to which different substances are formed in drinking water depends on a variety of factors, including, for example, the type of disinfectant used, the amount and composition of natural organic matter and bromide or iodide present in the raw water, pH, temperature, and retention time in the distribution system.[2] Hence, finding a single marker that is representative of all the by-products in the entire mixture is not easy, and one should bear in mind that any association observed for THMs may in part be due to other coexisting by-product substances.

Strengths of this study include the systematic review design, which minimizes bias arising from subjective or incomplete inclusion of studies. The work was conducted adhering to the PRISMA guidelines and based on what was outlined in our preregistered protocol. Moreover, the review was guided by our focused research question, which was formulated using the PI/ECOTSS framework. Study screening and selection were done in duplicate, and data extraction was checked thoroughly by a second reviewer. Rigorous risk of bias assessment was done for all studies eligible for inclusion in the review using the OHAT risk of bias tool. When applicable, we performed dose–response analyses to aid translation into policy.

Some limitations also need to be considered. We used the OHAT tool to assess the risk of bias of individual studies, which gave some insight into the overall quality of studies composing the body of evidence in this research question, and performed subgroup analyses by overall risk of bias score that showed no statistically significant differences across subgroups. The OHAT tool does, however, only address the risk of bias and not the direction and magnitude of bias. It should be noted that several studies on

bladder cancer were downgraded in the confounding domain because they either included private wells in the reference category or did not report differences in arsenic concentration across exposure groups. If private wells are included in the reference category and these contain other harmful substances that may increase bladder cancer risk, the association between increasing THM concentrations in drinking water will be biased toward the null. Similarly, arsenic is more commonly found in groundwater than in surface water, which in turn is less likely to be chlorinated. Hence, in these studies, bias due to uncontrolled confounding likely underestimated any real association. In addition, another domain in which none of the studies in this review received the highest ranking was exposure assessment; the main reason for downgrading was the use of indirect methods. Although indirect methods are less precise than direct methods, the resulting measurement error is likely both independent and nondifferential, which generally biases results toward the null, at least in the highest exposed categories. Another consideration regarding the exposure domain in the risk of bias assessment is that in some cases, predicted THM concentrations, which were made based on sophisticated models that, for example, take treatments along the distribution networks into account may actually better reflect the THM concentration at the recipient than actual measurements of THM concentrations sampled at the drinking water treatment plant. Yet according to our predefined criteria, all studies that used predictions were downgraded with respect to detection bias. Nevertheless, updating the criteria for the exposure assessment domain in an unbiased way so that it correctly distinguishes between sophisticated and more simple prediction models is difficult. Furthermore, in the assessment of overall risk of bias, the criteria for studies to be classified as "high risk of bias" were rather strict (all key domains had to be rated "definitely high" or "probably high" as well as most other domains), and therefore no study included in this review fulfilled that criterion. This resulted in a rather heterogeneous tier 2 group, with study quality ranging from rather high to relatively low.

We found significant differences in the results between case–control studies and cohort studies for bladder cancer in the highest vs. lowest random effect meta-analysis. Although this at first glance may reflect inherent differences in quality between study designs, the less pronounced findings of cohort studies may as well be attributed to a lower THM exposure in those studies or that the study populations mainly consisted of females who had an overall lower risk for bladder cancer, which in turn compromises the statistical power. Moreover, we did not consider the timing or duration of exposure in the quality assessment of the exposure assessment, which is a limitation of our review. A final methodological consideration is that we, in the random effect meta-analysis of bladder cancer comparing the highest to the lowest exposed category, observed significant between-study heterogeneity. According to the meta-regression, a large part of this variability could be explained by sex, study design, and risk of bias.

In conclusion, in this systematic review and dose–response meta-analysis, we found limited-suggestive evidence that exposure to THMs in drinking water increases the risk of bladder cancer and colorectal cancer. The summary RR estimate for bladder cancer in men and women was statistically significant at THM concentrations >41 μg/L. THMs are currently regulated not to exceed 80 μg/L in the US and 100 μg/L in the EU,[6,7] and our findings suggest that these limits may fail to protect against cancer in the general population. For other cancer outcomes evaluated, there were insufficient data available to draw any firm conclusions. Our review highlights the need for further research on disinfection by-products and cancer, particularly some cancers for which the few studies available indicated associations with increased risk, such as female hormone-related cancers[52,56] and malignant melanoma.[53] To further advance the field, future studies should focus on improving exposure assessment by increasing the precision of the assessment of personal THM exposure and confounding control. In addition, assessment of individual THM compounds, other classes of disinfection by-products, and mixture effect analyses could provide further insight into the presumed relationship between disinfection by-products and cancer.

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