Disinfection by-products in drinking water and colorectal cancer: a meta-analysis

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Background There is inconclusive evidence from observational studies that disinfection by-products (DBPs) in drinking water are associated with colorectal cancer.

Methods A literature search, without language or time limits, was performed to identify relevant case–control and cohort studies. Separate risk estimates for colon and rectal cancer were extracted from studies meeting the inclusion criteria. Relative risks (RRs) or odds ratios (ORs) comparing the highest exposure category with the lowest were pooled using random effects methods.

Results A total of 13 studies (3 cohort and 10 case–control) were analysed. For colon cancer, the pooled RR estimates were 1.11 [95% confidence interval (CI): 0.73–1.70] for cohort studies, 1.33 (95% CI: 1.12–1.57) for case–control studies and 1.27 (95% CI: 1.08–1.50) combining both study types. For rectal cancer, the corresponding RR estimates were 0.88 (0.57–1.35), 1.40 (1.15–1.70) and 1.30 (1.06–1.59). Sensitivity analysis showed these results were not importantly influenced by any single study. Publication bias was not evident for the colon cancer analysis but may have been a minor issue for the rectal cancer analysis. The results for rectal cancer may have been influenced by the quality of the studies.

Conclusions The study findings provide limited evidence of a positive association between colorectal cancer and exposure to DBPs in drinking water. The small number of studies and limitations in study quality prevent causal inference.

Keywords Disinfection by-products, colorectal cancer, meta-analysis, quality score

Introduction

Chlorine is often used to disinfect drinking water because of its low cost and ease of use. During the disinfection process, chlorine reacts with organic matter in the water to produce halogenated and non-halogenated by-products, the concentration and distribution of which vary with characteristics of the raw water and the treatment process.1 Treated surface water contains much higher levels of by-products than treated groundwater, owing to the higher concentrations of organic matter in untreated surface water.2 Rodent studies have shown liver, kidney and intestinal tumours following gavage administration of trihalomethanes (THMs), the main chlorination disinfection by-product (DBP). However, THMs were
not carcinogenic when administered through drinking water\(^3\) and the doses used in the animal studies were much higher than the doses seen in human studies included in this meta-analysis. Possible carcinogenic effects of human ingestion of DBPs were first investigated in ecological studies that related cancer incidence or mortality rates in different communities to their water sources.\(^4–7\) These studies suggested that people drinking chlorinated water, especially chlorinated surface water, might be at increased risk of bladder, colon and rectal cancers.\(^2,8\) Morris and co-workers\(^9\) concluded in their meta-analysis that higher exposure to DBPs in drinking water could be associated with a 10–40% excess risk of cancers of the bladder, colon and rectum. Since that meta-analysis, several other case–control and cohort studies have investigated the association between DBPs and colon and rectal cancers (CRCs), with inconsistent results.\(^2,10–14\)

We have conducted a meta-analysis that includes all relevant case–control and cohort studies of DBPs and CRCs. It provides greater precision for the estimates of risk than has been available hitherto and includes a careful assessment of the possible effects of study quality and publication and other biases on the meta-analysis results.

**Methods**

**Literature search**

We used a comprehensive search strategy to identify all relevant studies, including ‘grey literature’, pertaining to the association between colorectal cancer and DBPs in drinking water. The research question was defined as ‘What are the associations between disinfection by-products (both in general and for specific by-products) and colorectal cancer?’. This question was then broken down to cover specific search terms such as ‘colorectal cancer/colorectal neoplasm’, ‘disinfection by-products’, ‘water disinfection’, ‘chlorination by-products’, ‘water chlorination’, ‘trichloromethane’, ‘chloroform’ and ‘bromoform’. Each term was included in one or more searches. The search was first carried out in MEDLINE in July 2005, without limitation on the time of publication. We also replicated the search in EMBASE, PubMed, MediText, Toxline and CANCERLIT, but these databases did not identify any additional relevant references. Articles in the grey literature were also identified by reviewing the bibliographies of retrieved publications. The search was last updated in February 2009 to locate new studies published following the initial search. None of the studies was excluded on the basis of language (possibly relevant non-English language publications were translated into English). We contacted authors directly to obtain copies of reports of, or dissertations on, unpublished studies.

**Selection of studies**

We included studies if: (i) they were case–control or cohort studies of DBPs and CRCs; (ii) a relative risk (RR) or odds ratio (OR) was reported, or one could be estimated from the data published; and (iii) the exposure was assessed by a method more specific for DBP exposure than just water source (whether surface water or ground water). When multiple publications reported results from the same population with the same study design over the same time period, we used the publication that reported most information on exposure assessment. A single investigator inspected the search results and excluded articles that, on the basis of their title, were clearly not relevant. The remaining studies were discussed by all four investigators, initially using the abstracts. Where the abstract showed clearly that the article was not relevant, it was excluded. For the remaining articles, a final decision on inclusion or exclusion was made on the basis of their full text.

**Data extraction**

We prepared a data extraction form to extract relevant information from the individual studies. The data items extracted from each study were:

(i) general information—first author’s name and affiliation, year of publication, country and region in which the study was conducted;

(ii) study design—population, number and sources of cases and controls, consent rate and participation rate, length of follow-up and loss to follow-up (for cohort studies), method of ascertainment of cases;

(iii) exposure assessment methods—water sources, type of treatment, status of disinfection, types of DBPs measured (total THMs, subspecies of THMs, other DBP species, etc.), and, for routinely collected exposure data, time, frequency and point in the water supply system for collecting the samples, analytical methods for measuring DBP, models used and all relevant information on individual-level exposure assessment; and

(iv) analysis—covariates for adjustment in multivariate models, adjusted and unadjusted or stratified effect estimates [i.e. OR, RR or standardized mortality ratio (SMR)] and 95% confidence intervals (CIs). If a study did not report CIs, we estimated the standard error and the resulting CI from the \(P\)-value\(^{15}\) where possible.

**Quality of the studies**

We developed separate scoring instruments for case–control and cohort studies based on standard critical appraisal principles and knowledge of the methodological issues that arise in studies of DBPs and cancer, taking into account instruments used to assess the quality of controlled trials and
The objective of this instrument was to evaluate in a standardized, though necessarily subjective manner, the quality of the studies included in the systematic review. The score assigned to each study (maximum value 100) summarized its overall quality. This score was the weighted sum of scores for four domains of quality: selection (weight 40), measurement (of exposure and outcome, weight 40), adjustment for confounding (weight 15) and analysis (weight 5). The analysis section was given the least weight because if the other three sections were of good quality but the analysis was not carried out properly, the data could often be re-analysed. The domain scores were, in turn, weighted sums of a number of individually scored sub-domains. For example, 65% of the measurement domain score was allocated to exposure assessment, since exposure assessment is critical in any study of DBP exposure, and the remaining 35% to outcome measurement. We developed written guidelines and structured forms for scoring.

Two independent readers (B.R. and T.D.) scored all the articles, blind to the other’s assessments. Any significant disagreement between the readers was resolved through discussion. For minor differences, the average score was used as the agreed score. This resulted in a single agreed score for each characteristic of each paper. Inter-observer agreement was assessed.

Statistical analysis

For cohort studies we extracted RRs, hazard ratio or SMRs, and for case–control studies ORs, as the effect estimates. When several measures of association were reported, we selected the measure obtained from the model with the highest number of categories of DBP exposure. If several models had used the same number of exposure categories, we chose the model that had adjusted for the most appropriate covariates. If any study provided only gender-specific risks, we calculated the overall risk estimate through a meta-analysis of male and female estimates. Some studies provided measures of THMs and some only of chloroform. These were considered equivalent for the purposes of the analysis presented here. Nearly all studies compared long-term consumption of THMs (or chloroform) with no consumption. Two studies compared high with very low concentrations of THMs and chloroform. The most recent study reported the OR for rectal cancer due to 1 U (THM2 and chloroform). The most recent study compared high with very low concentrations of chloroform. These were considered equivalent for the purposes of the analysis presented here. Nearly all studies compared long-term consumption of THMs and chloroform. The most recent study reported the OR for rectal cancer due to 1 U (THM2 and chloroform). The most recent study compared high with very low concentrations of chloroform. These were considered equivalent for the purposes of the analysis presented here. Nearly all studies compared long-term consumption of THMs and chloroform. The most recent study reported the OR for rectal cancer due to 1 U (THM2 and chloroform). The most recent study compared high with very low concentrations of chloroform. These were considered equivalent for the purposes of the analysis presented here. Nearly all studies compared long-term consumption of THMs and chloroform. The most recent study reported the OR for rectal cancer due to 1 U (THM2 and chloroform). 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The effect estimates from individual studies were pooled using the inverse-variance weighted random-effects methods described by DerSimonian and Laird. Between-studies heterogeneity was quantified with the I2 statistic, which describes the proportion of total variation in study estimates due to heterogeneity. The influence of each study on the combined risk estimate was examined by consecutively omitting each study from the meta-analysis. Finally, we tested for possible publication bias using Begg’s and Egger’s tests and by visual inspection for asymmetry of funnel plots of the natural logarithms of the effect estimates against their standard errors. Where asymmetry was identified, we adopted the ‘trim and fill’ method described by Duval and Tweedie to see the effect of correcting the publication bias. This method first identifies the asymmetry in the funnel plot and trims those studies that cause the asymmetry. The pooled estimate with the remaining studies is calculated and then the funnel plot is filled in by replacing the trimmed plots and adding their mirror images in the plot. The final pooled results come from an analysis using all the true estimates and the simulated mirror images. Meta-regressions of the logs of the effect measures, weighted by the inverse of their variances, on the total quality scores and their sub-categories were undertaken to assess the possible impact of study quality on the effect measures. These regressions fitted a random effects model with two additive variance components (within and between studies). We conducted a separate meta-analysis excluding studies that were of very poor quality (<25% of the total possible quality score).

All statistical analyses were carried out in Stata Version 10.1 SE and RevMan version 5.26

Results

Literature search

Our search yielded 35 articles, of which 18 reported data from 17 separate case–control or cohort studies of CRCs and thus met the study selection criteria (two papers described the same study). Five of these articles were excluded for the following reasons: point estimates of the effect measure were reported without P-values, CIs or raw data
from which they could be calculated;\textsuperscript{28} the risk estimate was reported using as the exposed group—those exposed to chlorinated water—and the unexposed group—those exposed to chloraminated water;\textsuperscript{35} duplicate papers\textsuperscript{16,32} and the use of water mutagenicity not DBPs as the exposure variable.\textsuperscript{37}

Thus, our final meta-analysis comprised 13 studies: 3 cohort studies and 10 case–control studies (Table 1). In total, 10 of these studies considered colon cancer and 10 considered rectal cancer; 7 considered both colon cancer and rectal cancer.

**Quality scoring**

The total and domain-specific quality scores are summarized in Table 2 and sub-domain scores are referred to below when particularly informative. Percentages shown are the percentages of the highest possible scores for specific quality sub-domains or domains, or total quality. Cohort studies scored a little higher for total quality than case–control studies (Table 2). Cohort studies scored higher on selection (57% of highest possible score) than case–control studies (49%). All but three of the case–control studies had a well-defined study base but selection of cases (48%) and controls (35%) was relatively poor, particularly because the selection of cases was likely to have been biased (when the studies did not include all cases or a representative sample of cases) or information about non-participants was lacking. Comparability of exposed and unexposed cohorts (60%) and losses to follow-up (53%) in the cohort studies were acceptable.

Both case–control (39%) and cohort (33%) studies scored poorly on measurement (Table 2), mainly because of poor measurement of DBP exposure (26 and 23%, respectively). One study\textsuperscript{2} estimated DBP concentration in tap water and duration of exposure; four\textsuperscript{1,14,32,36} estimated only DBP concentration in water and one estimated duration of exposure only.\textsuperscript{34} The remaining studies determined only whether tap water was chlorinated or not. Outcome ascertainment, the other main measurement issue, was good (sub-domain scores of 65% in case–control and 62% in cohort studies).

We assessed quality with respect to confounding by listing all confounders relevant to studies of DBP and CRCs and counting how many were adjusted for, or shown not to be confounders, in each study. Both study types performed poorly in this aspect (cohort studies 28%; case–control studies 20%; Table 2). Analysis was better conducted in case–control studies, as none of the cohort studies estimated a hazard ratio or RR with CIs in categories of age, sex or other relevant variables.

There was good inter-observer agreement on the total quality scores: intraclass correlation coefficient (ICC) 0.75, 95% CI 0.22–0.92 (Table 2). ICCs for the quality scoring categories ranged from 0.56 to 0.94. Comparatively poor agreement on selection (ICC of 0.56) appeared to be due to the poor reporting of the way participants were selected, particularly in the older studies.

There was no obvious pattern of association between the total quality of individual studies and their year of publication (plot not shown).

**Risk estimates and meta-analysis**

Pooled estimates of RRs (or their equivalent) comparing the highest exposure category with the lowest, along with the relevant Forest plots, are shown in Figures 1 and 2. In these plots, the centre of each rectangle represents the point estimate for one study, the rectangle’s size corresponds to the point estimate’s weight in the pooled estimate and the horizontal line through the rectangle represents the 95% CI about the point estimate. Each diamond represents a pooled estimate; its vertical axis marks the point estimate and its horizontal extremes the upper and lower 95% confidence bounds.

The point estimates of the pooled RRs ranged from 0.88 to 1.40. For all meta-analyses containing more than three studies, the point estimates were above one and the 95% CI did not include one. The meta-analyses for cohort studies of colon cancer displayed moderately high heterogeneity (63%) but Cochrane’s Q test for heterogeneity was not significant for any of the pooled estimates.

**Meta-regression and sensitivity analysis**

The logs of the studies’ effect measures weighted by the inverse of their variances were regressed on the studies’ scores for the five major indicators of study quality (selection, measurement, adjustment for confounding, analysis and total study quality) (Table 3). For colon cancer, RR increased with increasing scores for analysis and adjustment for confounding and fell, very weakly, with increasing measurement and selection scores. None of these associations was statistically significant. For rectal cancer, the RR increased with an increase in selection score, and was inversely associated, though not statistically significantly, with all other sub-group quality scores, some quite strongly. Only for measurement was the $P$-value <0.05. The total quality score was not significantly associated with either of the effect measures.

Three studies of colon cancer\textsuperscript{29,30,33} and four of rectal cancer\textsuperscript{27,30,31,33} had scores <10 (out of a possible 40) for measurement. To examine the influence of those poorer quality studies, the meta-analyses were repeated excluding them. Their exclusion had minimal effect on the pooled analysis for colon cancer: the RR was 1.25 (95% CI 1.06–1.46), compared with 1.27 (1.08–1.50). For rectal cancer, however, their exclusion reduced the RR and its significance to 1.11 (0.88–1.39) from 1.30 (1.06–1.59).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design and sample size</th>
<th>Location and population</th>
<th>Exposure assessment</th>
<th>Outcome assessment</th>
<th>Variables adjusted for</th>
<th>Findings: OR/RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alavanja M, 1978</td>
<td>Population-based case-control study, number of cases not known; controls: 3444</td>
<td>New York state counties, USA</td>
<td>Subject's residence served by chlorinated vs non-chlorinated water supply</td>
<td>Death certificates</td>
<td>Age</td>
<td>Chlorinated vs non-chlorinated water.</td>
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<td>Rectal cancer: Calculated based on separate male/female results</td>
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<tr>
<td>Wilkins JR, 1981</td>
<td>Retrospective cohort study. Exposed: 23,727. Moderately exposed: 2,231. Unexposed: 4,842. Follow-up period: 12 years</td>
<td>Washington county, USA</td>
<td>Residential sources of drinking water categorized as chlorinated surface water; chlorinated ground and surface water and non-chlorinated ground water</td>
<td>Death certificate and cancer registry</td>
<td>Age, marital status, education, smoking history, frequency of church attendance, adequacy of housing and persons per room</td>
<td>High chloroform and THM exposure compared with ground water exposure</td>
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<td>Colorectal cancer: RR = 0.89 (0.57–1.43)</td>
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</table>
| Young TB, 1981    | Death-certificate-based case-control study. Total sample: 3,202; colon cancer death: 510     | Wisconsin, USA (White females only) | Chlorination status at subject’s residence classified as high, medium and low as determined from water supply system’s information | Death certificates              | Urbanicity, marital status and site-specific high-risk occupation | ORs for chlorine doses (p.p.m.) categorized into high (1.71–7.0), medium (1.0–1.7) and low (0.01–0.99) vs no chlorination | Colon cancer: Low: OR = 1.53 (1.11–2.11). Medium: OR = 1.53 (1.08–2.00). High: OR = 1.51 (1.06–2.14). 
Rectal cancer: Low: OR = 1.13 (0.61–2.08). Medium: OR = 1.16 (0.58–2.32). High: OR = 1.39 (0.67–0.86)

Reference level was no chlorination. 
Rectal cancer: OR = 1.21 (0.93–1.79) chlorination ≤ 1.09 p.p.m.; OR = 1.68 (1.17–2.42) chlorination > 1.09 p.p.m.; OR = 1.53 (1.13–2.04) chlorination of surface water; OR = 1.04 (0.72–1.50) chlorination of ground water

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<table>
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<th>Findings: OR/RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Kanarek MS, 198233</td>
<td>Population-based case–control study. Colon cancer: 2350 subjects. Rectal cancer: 778 subjects. No separate information provided on the numbers of cases and controls</td>
<td>Wisconsin, USA (females only)</td>
<td>Mean values of chlorination variables (chlorination status, surface or ground source, etc.) from waterworks reports were assigned as exposure</td>
<td>Death registry</td>
<td>Urbanicity, marital status and site-specific high-risk occupation</td>
<td>OR calculated for chlorinated surface water vs unchlorinated water</td>
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<td></td>
<td>Wisconsin, USA</td>
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<td>Colon cancer: OR = 2.81 (1.28–6.17) Rectal cancer: OR = 1.59 (0.78–3.23)</td>
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<tr>
<td>Cragle et al., 198534</td>
<td>Population-based case–control study. Cases: 200; controls: 407</td>
<td>North Carolina, USA</td>
<td>Exposure categorized: ground water, no chlorination; ground water, chlorination; and surface water chlorination. Length of exposure estimated between 1953 and 1978</td>
<td>Tumour registry</td>
<td>Age, sex, diet, family history of colon cancer, alcohol, smoking, number of pregnancies. Age was found to be an effect modifier</td>
<td>OR: length of exposure (years) for chlorinated vs non-chlorinated water. There was no risk &lt; 60 years of age Colon cancer: OR = 1.18 (0.94–1.47) for age 60 years and length &lt; 15 years OR = 1.38 (1.10–1.72) for age 60 years and length &gt; 15 years</td>
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<tr>
<td>Young et al., 198736</td>
<td>Population-based case–control study. Cases: 347. Cancer-controls: 639.; Population-controls: 611.</td>
<td>Wisconsin, USA</td>
<td>Predicted THM from routine survey combined with water use questionnaire to estimate period-specific and cumulative exposure</td>
<td>Wisconsin cancer reporting system</td>
<td>Age, sex and urbanicity</td>
<td>Reference level was &lt;10 µg/l THM Colon cancer: With population controls OR = 0.73 (0.44–1.21) for 10–40 µg/l; OR = 1.10 (0.68, 1.78) for &gt; 40 µg/l</td>
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<td>Doyle et al., 199711</td>
<td>Prospective cohort. Exposed: 27339 (municipal water). Unexposed: 6618 (private well) plus 2170 (bottled water); follow-up time: 3–8 years.</td>
<td>Iowa, USA</td>
<td>Questionnaire survey for residential and water consumption history combined with historical water treatment data for chloroform</td>
<td>State health registry</td>
<td>Smoking, pack-years smoked, BMI, waist-to-hip ratio, fruit and vegetable intake, total caloric intake, age and education</td>
<td>Reference level: non-detectable chloroform concentration compared with the following low, medium and high concentration Colon cancer: Low: RR = 1.06 (0.68–1.66) for 1–2 µg/l; Medium: RR = 1.39 (0.89–2.15) for 3–13 µg/l; High: RR = 1.68 (1.11–2.53) for 14–287 µg/l Rectal cancer: Low: RR = 0.80 (0.44–1.48) for 1–2 µg/l; Medium: RR = 0.75 (0.39–1.46) for 3–13 µg/l; High: RR = 1.07 (0.60–1.93) for 14–287 µg/l</td>
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<tr>
<td>Hildesheim et al., 1998²</td>
<td>Population-based case-control study. Colon-cancer cases: 560. Rectal-cancer cases: 537. Controls: 1983.</td>
<td>Iowa, USA</td>
<td>Routinely collected THM data combined with water use questionnaire</td>
<td>Cancer registry</td>
<td>Age, sex and urbanicity for rectal cancer only</td>
<td>Reference level was lifetime average THM concentration ≤ 0.7 µg/l. Colon cancer: Low: OR = 1.07 (0.8–1.4) for 8.1–32.5 µg/l, Medium: OR = 0.93 (0.6–1.5) for 32.6–46 µg/l. High: OR = 1.06 (0.7–1.6) for ≥ 46.4 µg/l. Rectal cancer: Low: OR = 1.23 (0.9–1.7) for 8.1–32.5 µg/l, Medium: OR = 1.66 (1.1–2.6) for 32.6–46 µg/l, High: OR = 1.66 (1.1–2.6) for ≥ 46.4 µg/l, Dose-response relationship was found with rectal cancer and lifetime average THM concentration (P = 0.01) ≥ 35 years of exposure vs &lt; 10 years to chlorinated water. Colon cancer: OR = 1.63 (1.07–2.48) for ≥ 75 µg/l, Rectal cancer: OR = 0.91 (0.55–1.51) for ≥ 75 µg/l, SMR (calculated CI): Reference level is total THM 0.2 µg/l vs 39 – 70 µg/l. Colon cancer: SMR = 0.90 (0.58–1.41) Rectal cancer: SMR = 0.70 (0.39-1.31)</td>
</tr>
<tr>
<td>King et al., 2000¹²</td>
<td>Population-based case-control. Cases: 1428; Controls: 1545.</td>
<td>Southern Ontario, Canada</td>
<td>Exposure assigned from water consumption history over 2 years before interview and modeled and measured THM in water</td>
<td>Ontario cancer registry</td>
<td>Age, sex, education, BMI, intake of energy, cholesterol, calcium, alcohol, and coffee</td>
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<tr>
<td>Vinceti et al., 2004¹³</td>
<td>Retrospective cohort study. Exposed: 5144, 59 430 person-years of follow-up</td>
<td>Exposed from Guastalla, Italy, Reference population from Emilia Romana</td>
<td>Chloroform and total THM concentration in the exposed region was linked to the residential history of the participants</td>
<td>Health department death registry</td>
<td>Not mentioned</td>
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<tr>
<td>Bove et al., 2007¹⁴</td>
<td>Case-control study. Cases: 128; Controls: 253</td>
<td>Western New York, USA</td>
<td>Individual DBP concentrations measured in about 65 sampling sites, 7–10 times per year, from 1998 to 2003, with spatial interpolation of average levels assigned to geocoded addresses of the participants. Mean DBP concentration was assumed as exposure</td>
<td>Hospitals in the area collected for another study²⁶</td>
<td>Caloric intake, alcohol, socio-economic status, age, smoking</td>
<td>Rectal cancer: Calculated OR for 35 µg/l (mean) increase in total THM OR = 1.42 (0.49 to 2.82)</td>
</tr>
</tbody>
</table>

²The bold estimates were used in the meta-analysis.

BMI = body mass index.
Influence analysis
Omitting each study in turn from the analysis showed that no single study importantly influenced the pooled estimate for either colon or rectal cancer (data not shown).

Publication bias
There was no evidence of publication bias for colon cancer. The funnel plot for colon cancer was symmetrical (Figure 3); Egger’s test gave a P-value of 0.82 for bias.

For rectal cancer, the funnel plot appeared to have a hole in the lower middle portion, although the Egger’s test P-value was 0.92 (Figure 4). It appeared that some negative non-significant results were missing below the lower arm of the funnel. The pooled estimate became 1.23 (1.00–1.51) after correcting for apparent publication bias using the trim and fill method (only one mirror-image point was added).

Dose–response
Although six studies reported RRs for CRCs in ordered categories of exposure to DBPs, only two provided sufficient information to allow dose–response to be estimated. Thus we did not perform a dose–response meta-analysis as this would not be informative with only two studies. Among the six studies that provided some dose–response data, three (of five) studies that reported on colon cancer and three (of four) studies that reported on rectal cancer found an increasing risk with increasing DBP exposure.

Table 2 Average quality scores and inter-observer agreement on quality scores for studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Categories of quality scoring (maximum points value)</th>
<th>Case–control studies (n = 10)</th>
<th>Cohort studies (n = 3)</th>
<th>ICCs for inter-observer agreement (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection (40 points)</td>
<td>49 (12–87)</td>
<td>57 (50–60)</td>
<td>0.56 (–1.0 to 0.84)</td>
</tr>
<tr>
<td>Measurement (40 points)</td>
<td>39 (12–78)</td>
<td>33 (20–45)</td>
<td>0.65 (–0.09 to 0.89)</td>
</tr>
<tr>
<td>Adjustment for confounding (15 points)</td>
<td>20 (0–61)</td>
<td>28 (9–48)</td>
<td>0.94 (0.86 to 0.98)</td>
</tr>
<tr>
<td>Analysis (5 points)</td>
<td>48 (0–100)</td>
<td>23 (20–30)</td>
<td>0.60 (–0.24 to 0.87)</td>
</tr>
<tr>
<td>Total quality score (100 points)</td>
<td>40 (26–56)</td>
<td>41 (38–44)</td>
<td>0.75 (0.22 to 0.92)</td>
</tr>
</tbody>
</table>

Figure 1 Forest plots of meta-analysis of colon cancer in cohort and case–control studies with exposure to chlorination DBPs in water
Discussion

This meta-analysis found similar, statistically significant, but weakly increased risks of colon cancer and rectal cancer associated with exposure to DBPs after pooling estimates from 10 case-control and 3 cohort studies. There were, however, important differences between the analyses of CRCs, particularly with respect to study quality and publication bias. Therefore, they are considered separately in this discussion.

For colon cancer (Figure 1) there was reasonable coherence between results of cohort and case-control studies, only weak evidence of between-study heterogeneity, and little evidence of publication bias. The pooled estimate of RR (95% CI) was 1.40 (1.15, 1.70).

Table 3 Results of meta-regression of RR of developing CRCs with exposure to chlorination DBPs in drinking water on quality scores of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Item in quality score</th>
<th>Regression coefficient (95% CI)</th>
<th>P-value</th>
<th>Percentage change in RR (95% CI) with 1-U change in the quality scorea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>Total score</td>
<td>−0.003 (−0.020 to 0.015)</td>
<td>0.77</td>
<td>−0.26 (−2.02 to 1.52)</td>
</tr>
<tr>
<td></td>
<td>Adjustment for confounding</td>
<td>0.037 (−0.012 to 0.085)</td>
<td>0.14</td>
<td>3.74 (−1.15 to 8.87)</td>
</tr>
<tr>
<td></td>
<td>Measurement</td>
<td>−0.011 (−0.032 to 0.010)</td>
<td>0.32</td>
<td>−1.06 (−3.13 to 1.05)</td>
</tr>
<tr>
<td></td>
<td>Analysis</td>
<td>0.058 (−0.003 to 0.120)</td>
<td>0.06</td>
<td>6.03 (−0.35 to 12.81)</td>
</tr>
<tr>
<td></td>
<td>Selection</td>
<td>−0.002 (−0.022 to 0.019)</td>
<td>0.89</td>
<td>−0.16 (−2.18 to 1.90)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>Total score</td>
<td>−0.015 (−0.035 to −0.004)</td>
<td>0.13</td>
<td>−1.52 (−3.43 to 0.44)</td>
</tr>
<tr>
<td></td>
<td>Adjustment for confounding</td>
<td>−0.038 (−0.104 to −0.07)</td>
<td>0.25</td>
<td>−3.78 (−9.90 to −2.74)</td>
</tr>
<tr>
<td></td>
<td>Measurement</td>
<td>−0.023 (−0.044 to −0.003)</td>
<td>0.03</td>
<td>−2.30 (−4.28 to −0.27)</td>
</tr>
<tr>
<td></td>
<td>Analysis</td>
<td>−0.055 (−0.189 to −0.079)</td>
<td>0.42</td>
<td>−5.33 (−17.20 to 8.24)</td>
</tr>
<tr>
<td></td>
<td>Selection</td>
<td>0.013 (0.023 to 0.050)</td>
<td>0.48</td>
<td>1.35 (−2.31 to 5.14)</td>
</tr>
</tbody>
</table>

*Obtained by subtracting 1 from the exponentiated coefficient and then multiplying it by 100. A negative sign means the RR decreased.
heterogeneity and little evidence of impact of study quality on, or of study selection bias in, the results. There was, in addition, evidence of a dose–response relationship in six studies. We consider that this meta-analysis provides only limited evidence that exposure to DBPs in water increases the risk of colon cancer. In making this ‘limited evidence’ assessment, we used the criteria adopted by the International Agency for Research on Cancer (IARC) for its assessments of carcinogenic risk in humans. The results for rectal cancer are superficially similar to those for colon cancer, but there are important differences. The positive association was completely dependent on the case–control study results; the pooled estimate from only two cohort studies showed a non-significant negative association (Figure 2). Although there was evidence that poor-study quality affected results for rectal cancer, removal of the four studies with very low scores on measurement only reduced the pooled RR a little. Correction for apparent publication bias also only reduced the pooled RR a little. There was evidence of a dose–response relationship in three studies. Overall, we consider this meta-analysis to show limited evidence (as defined by the IARC) of an association between rectal cancer and exposure to DBPs, and that the evidence for this association is weaker for rectal cancer than it is for colon cancer.

The only previous meta-analysis of DBP exposure and colorectal cancer risk gave a pooled RR estimate for all relevant studies of 1.11 (0.91–1.37) for colon cancer and 1.38 (1.01–1.87) for rectal cancer. For studies with a high overall quality score the RR estimates from that analysis were 1.10 (0.79–1.53) and 1.91 (1.56–2.35) for CRCs respectively, and for studies having overall low-quality scores the RR estimates were 1.13 (0.86–1.48) and 1.07 (0.89–1.70). These RR estimates are somewhat lower for colon cancer and higher for rectal cancer than we obtained in the present analysis. The effects of study quality on the results of Morris and co-workers are also at variance with ours, suggesting that higher-quality studies had higher ORs for rectal cancer than lower-quality studies, and the opposite for colon cancer. This difference between the results of the previous meta-analysis and ours is due to our inclusion of studies published after the previous meta-analysis. Three case–control studies and one cohort study that examined rectal cancer, and two case–control studies and two cohort studies that examined colon cancer, were published. The quality of these recent studies is better than that of the earlier ones. That we could analyse more and, on average, better studies than Morris et al. could probably make our pooled RRs closer to the true values for the associations studied.

Some 800 different species of DBPs have been identified to date and it is not clear which, if any, might result in carcinogenicity. This study considered mainly total THMs as the exposure measure, which includes chloroform, bromoform, chlorodibromomethane, bromodichloromethane and related compounds. Since chloroform is usually the dominant species of THMs, it might be reasonable to assume that chloroform is the species responsible for any identified association. However, relative toxicity of different species does not necessarily relate to their relative concentrations and a recent study found a statistically significant association between rectal cancer and bromoform (OR 1.85, 95% CI 1.25–1.74) but not chloroform, suggesting bromoform, or related bromine-containing compounds, might have carcinogenic effects. THM concentrations in water are generally correlated with a range of other DBPs in water, including haloacetic acids. Thus it is not possible, on present evidence, to attribute the associations observed in this analysis to any particular THM...
species or even, necessarily, to THMs at all. THMs may simply be a surrogate measure of one or more other DBP that has adverse health effects. It is worth noting that other studies have suggested a relationship between exposure to THMs and increased risk of adverse birth outcomes (e.g. still birth, low birth weight), \(^41-43\) bladder cancer, \(^5,44\) various gastrointestinal cancers and other cancers (breast, lung and brain), \(^9\) and skin cancer, \(^45\) but except for bladder cancer the evidence for causation is not strong.

It is an unavoidable weakness of our analysis that there were relatively few articles that had sufficiently specific exposure measures to allow them to be included. Moreover, only 3 of the 11 studies estimated individual exposure to DBPs using recall of water use behaviour and in none of these was non-ingestion routes of exposure to DBPs considered; there is good evidence that exposure to DBPs occurs more through inhalation and dermal absorption than through ingestion. \(^40\) The main strengths of our analysis are the inclusion of ‘grey’ and foreign language literature in our search, the comprehensive assessment of quality, the comprehensive analysis and the use of the quality score in a meta-regression and sub-group analysis to investigate the effect of quality scores on the study findings.

The previous meta-analysis \(^9\) used the same quality scoring instrument for cohort and case–control studies. We developed a quality scoring instrument that is different for case–control and cohort studies. It assessed all the quality issues important for the associations in question in more detail than has been previously attempted. There was, though, unavoidable subjectivity in the scoring and in the relative weighting given to the various aspects of study quality in the calculation of an overall quality score. To that extent, separate analyses for each major aspect of study quality are probably more useful than reliance on a single overall quality score, and it was on this basis that we chose to use the measurement quality score when assessing the impact of exclusion of poor-quality studies on the pooled RRs.

**Conclusions**

This meta-analysis points to an association between exposure to DBPs and an increase in the risk of colorectal cancer. The small number of studies and problems with study quality, however, prevent us from inferring causation. However, since most people drink water containing DBPs and colorectal cancer is common, a possible small association could translate into a large population-attributable risk and a large number of cases. Therefore, the association requires further investigation. Probably the best approach would be to conduct cohort studies using better methods of exposure assessment than have been used to date.

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**Conflict of interest:** T.D., C.C. and B.A. were recipients of a contract from the Sydney Water Corporation to study the health of sewer workers and B.R. worked on the contract. Sydney Water Corporation is currently assisting their research by giving them access to results of routine measurements of water quality, including concentrations of DBPs.

**KEY MESSAGES**

- Meta-analysis suggests an association between exposure to DBPs and an increase in the risk of colorectal cancer.
- The small number of relevant studies has important methodological limitations.
- A possible small association could translate into a large population-attributable risk and a large number of cases. Therefore, the association requires further investigation using improved methodology.

**References**


