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Review article

Nitrate and nitrite contamination in drinking water and cancer risk: A systematic review with meta-analysis

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ABSTRACT

Background: Pollution of water sources, largely from wide-scale agricultural fertilizer use has resulted in nitrate and nitrite contamination of drinking water. The effects on human health of raised nitrate and nitrite levels in drinking water are currently unclear.
Objectives: We conducted a systematic review of peer-reviewed literature on the association of nitrate and nitrite in drinking water with human health with a specific focus on cancer.
Methods: We searched eight databases from 1 January 1990 until 28 February 2021. Meta-analyses were conducted when studies had the same exposure metric and outcome.
Results: Of 9835 studies identified in the literature search, we found 111 studies reporting health outcomes, 60 of which reported cancer outcomes (38 case-control studies; 12 cohort studies; 10 other study designs). Most studies were set in the USA (24), Europe (20) and Taiwan (14), with only 3 studies from low and middle-income countries. Nitrate exposure in water (59 studies) was more commonly investigated than nitrite exposure (4 studies). Colorectal (15 studies) and gastric (13 studies) cancers were the most reported. In meta-analyses (4 studies) we identified a positive association of nitrate exposure with gastric cancer, OR = 1.91 (95%CI = 1.09–3.33) per 10 mg/L increment in nitrate ion. We found no association of nitrate exposure with colorectal cancer (10 studies; OR = 1.02 [95%CI = 0.96–1.08]) or cancers at any other site.
Conclusions: We identified an association of nitrate in drinking water with gastric cancer but with no other cancer site. There is currently a paucity of robust studies from settings with high levels nitrate pollution in drinking water. Research into this area will be valuable to ascertain the true health burden of nitrate contamination of water and the need for public policies to protect human health.

1. Introduction

Water pollution in general, and from nitrate specifically, is an increasing problem threatening both human health and ecosystems (Mateo-Sagasta et al., 2018). Nitrogen is needed for the production of chlorophyll in plants (Evans and Clarke, 2019) and nitrogen compounds are widely used in agricultural fertilisers to increase crop yields. The use of nitrogen fertilisers has increased substantially over recent years, particularly in South Asia (FAO, 2015). While this has significantly benefitted global food production it has had a marked negative impact on the wider ecosystem (Sutton et al., 2013; Townsend et al., 2003). Nitrogen fertilisers are the major source of water-soluble nitrate and nitrite compounds in the soil that can be carried away via surface runoff into groundwater, rivers and drinking water (Beeckman et al., 2018; Mateo-Sagasta et al., 2018; Shukla and Saxena, 2020). Other important sources of nitrate contamination in freshwater systems are human, animal and industrial waste (Shukla and Saxena, 2020; WHO, 2016).

Nitrogen is an essential element for the human body to synthesise proteins and nucleic acids. Nitrate ingested through food and drinking water is absorbed by the stomach and small intestine. 75% of the ingested nitrate is excreted in urine and the remainder is reabsorbed from blood and ends up in salivary glands in the oral cavity where it is

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reduced to nitrite and absorbed systemically (Lundberg et al., 2018). In the stomach and other gastric organs nitrite can be transformed into nitric oxide that acts as a cell signaling modulator. Additionally, the body has means to endogenously synthesise nitric oxide which maintains and regulates many physiological functions including blood pressure and immune function (Carlstrom et al., 2020). Nitrite can also form nitroso compounds (NOCs), including N-nitrosamines that can be carcinogenic, in the stomach and intestine (Carlstrom et al., 2020; Kobayashi, 2018). According to the International Agency for Research on Cancer (IARC) classification, ingested nitrate and nitrite that can form NOCs are probably cancerogenic to humans and are included in group 2A (IARC, 2010).

The World Health Organisation (WHO) has issued guidelines on safe concentrations of nitrate and nitrite compounds in water for human use that are based on the absence of specific short-term health effects (methemoglobinemia and thyroid effects) (WHO, 2016). However, in many countries these safe limits are regularly exceeded, especially in shallow waters and wells both in developed and developing countries (Prakasa Rao et al., 2017; WHO, 2016; Tirado, 2007; EEA, 2018; Ouedraogo et al., 2016). An increasing number of observational studies have found associations between levels of nitrate in drinking water and human pathologies, including certain forms of cancer (Ward et al., 2018). Improving our understanding of these threats will help policy- and decision-makers to take actions to reduce nitrogen pollution.

We systematically review and synthesise peer-reviewed literature on the human health effects of nitrate and nitrite in drinking water. We examine the strength of available evidence on exposure to nitrate and nitrite in drinking water and the risk of any forms of cancer, with the aim of identifying knowledge gaps and supporting public health and environmental policy.

2. Methods

2.1. Search strategy

The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) updated guidelines (Page et al., 2021). The systematic review methods were published in advance of data collection on the PROSPERO register (protocol number CRD42020186945).

We performed a search of peer-reviewed literature to identify studies reporting health outcomes in people exposed to drinking water containing nitrate or nitrite. We systematically searched the following databases: OvidSP MEDLINE, OvidSP PubMed, OvidSP EMBASE, Global Health, Scopus, ISI Web of Science, GreenFILE, and AGRIS from 1 January 1990 until 28 February 2021.

The search strategy was developed initially in MEDLINE with the same search terms used with minor adjustments as required for the input to other databases. The search terms for exposure included nitrate, nitrite, nitrogen, and nitroso. The search terms for the sources of the exposure included river, lake, well water, drinking water, ground water, fresh water, aquifer, bottled water, surface water, public water, water supply, water pollutant, water pollution, and fertilizer. The search strategy was not restricted to specific outcomes and was conducted in parallel with a second systematic review evaluating the association of nitrate and nitrite in water and risks of non-cancer outcomes (to be published separately). The full search strategy for each database is detailed in supplementary material S1.

2.2. Selection criteria and data extraction

Titles and abstracts were screened by a single reviewer (RP) for relevance. A second reviewer (MD) screened a random sample of 20% of the publications found. Consensus on any discrepancies was reached through discussion with a third reviewer (RG). One reviewer assessed the full texts to confirm eligibility.

Studies were included in this review if they met the following criteria: published peer-reviewed papers (all languages with an abstract in English), human studies, randomized control trials or observational studies with any design (i.e., cohort, case-control, longitudinal, prospective, ecological, and cross-sectional studies), and studies reporting measured or modelled concentrations of nitrate or nitrite in drinking water and measured health outcomes.

Animal studies were excluded as were reviews and systematic reviews (the reference lists of which were searched for relevant studies). Here we report only on studies presenting data on cancer outcomes; studies reporting other health outcomes will be published separately.

Data were extracted by a single reviewer (RP), and a second reviewer (MD) extracted data from a random sample of 10% of the publications. Data included: health outcome, nitrate, nitrate-N, nitrite, nitrite-N concentrations, participants and study design, year of study and year of data collection, duration of exposure, exposure-outcome association measure (e.g. odds ratio, rate ratio with 95% confidence interval), other outcomes such as biomarkers, comparator, and country where the study was conducted. For consistency, all concentrations of nitrate or nitrite in the text, figures and tables are reported as ion concentrations, i.e. NO_3^- and NO_2^-, not as nitrate-nitrogen and nitrite-nitrogen concentrations. We used the following conversion formulae: nitrate = nitrate-N x 4.422664 and nitrite = nitrite-N x 3.28443 (Interconverting Nitrate as Nitrate and Nitrate as Nitrogen, 2011).

2.3. Quality assessment

We appraised study quality following an adapted appraisal tool based on the Critical Appraisal Skills Programme (CASP) Case-Control study and Cohort study Checklists (CASP). Appraisal criteria for cross-sectional studies were adapted from the STrengthening the Reporting of OBservational studies in Epidemiology checklist (STROBE) and Downes et al. (2016). Appraisal criteria for ecological studies were adapted from Marchevsky (2000). Our adjusted appraisal tool included 9 criteria, with studies scoring either “0” for not fulfilled, “1” for fulfilled, or “Not Reported”. Each study included in the review was graded based on its score and converted to a percentage, with <50% as low, 50–70% as medium, and >70% as high. Quality assessment was carried out by 2 independent researchers (RP and SP), and discrepancies resolved through consensus with a third researcher (RG).

2.4. Confounding variables

We screened the eligible cohort, case-control and cross-sectional studies for the confounding variables used in the models that generated the estimates extracted for our analyses. Where possible, the extracted confounders were grouped into a higher-order variable (for instance, urinary infections, gastric ulcers, previous cancer, and diabetes were grouped into “Other health data”). We generated a color-coded matrix with the number of times that each confounder or higher-order variable was used for each cancer type.

2.5. Data synthesis

Quantitative estimates (odds ratios [OR], relative risks [RR], hazard ratios, or other measures of association) and 95% confidence intervals (CIs; or other measures of variance) of the association between nitrate or nitrite levels and the health outcome were extracted from each study. For studies that reported multiple estimates, only the most fully adjusted estimate was extracted for inclusion in summary estimates. Some studies included additional chemicals (e.g. magnesium or calcium) in the most adjusted model to investigate the potential interaction with nitrate. For consistency with the studies that did not include additional chemicals, when the most adjusted estimate included other potential water pollutants, we extracted the second most adjusted estimate that included all the other confounders without the additional pollutant.

In line with previous reports, the epidemiological measures reported in included studies i.e. odds ratios, risk ratios, relative risks, hazard ratios and rate ratios, were considered approximately equal because absolute cancer risks are small (World Cancer Research Fund & American Institute for Cancer Research, 2007; Stare and Maucort-Boulch, 2016; Davies et al., 1998).

Most studies have reported estimates based on quantiles of the distribution of nitrate concentrations with different ranges and numbers of quantiles. Some studies provided an OR for a dichotomous concentration of nitrate, i.e. above and below a cut-off. To standardize the method of expressing the results of the individual studies, we estimated the overall measure of association across quantiles, and the continuous relative risk for dichotomous results by following the methods detailed elsewhere (World Cancer Research Fund & American Institute for Cancer Research, 2007; Orsini et al., 2006), and assuming a linear increase in the log-odds of the outcome per unit increase of nitrate concentration. If RRs reported in primary studies were generated comparing private well sources to public water sources, or comparing top to bottom quantile without showing the intermediate quantiles, these RRs were not included in meta-analyses, but were mentioned in the text. Meta-analyses were conducted using log-transformed values, and a random-effects model to allow for heterogeneity between studies (restricted maximum likelihood method, or REML). The minimum number of studies for a meta-analysis was two (Valentine et al., 2010; World Cancer Research Fund & American Institute for Cancer Research, 2007). When both cohort and case-control studies were available for the same cancer type, meta-analysis estimates stratified by study design and overall estimates were performed. Types of cancer with similar locations (e.g., brain cancer, glioma, and meningioma) or that are often combined in the literature (e.g., colon and rectum cancer) were combined in the same analysis. Estimates were calculated per 10 mg/L increments of nitrate. Meta-analyses with estimates per 1 mg/L increments of nitrate are available in Fig. 1S. Statistical heterogeneity was estimated by the I^2 statistic (Higgins and Thompson, 2002). All meta-analyses were performed using estimates of associations between cancer and nitrate from public water sources and private wells if the nitrate concentration in the specific water source was provided.

A p value < 0.05 was considered statistically significant for all analyses. Statistical analyses were performed with Stata statistical software: Release 17.0 (College Station, Texas, USA).

3. Results

3.1. Literature search

The initial search identified 16,527 studies and three additional records were obtained through citation searches. After removing duplicates, 8680 unique records were screened based on title and abstract, and 269 were included for full text review. The disagreement rate between the two screeners was 2.8%. Most studies excluded at this stage were ineligible due to their study design (i.e. case studies, reviews, studies on animals, n = 109), with smaller numbers being ineligible due to inappropriate exposures or outcomes (n = 23) or because the full text could not be retrieved despite repeated attempts (n = 26). We identified 111 records reporting on exposure to nitrate or nitrite in drinking water and health outcomes in humans (Fig. 1). Of these eligible studies, 60 had cancer as a health outcome and are included in this review.

3.2. Study characteristics

All included studies were observational in design (38 case-control, 12 cohort, 2 cross sectional and 8 ecological studies) (Table 1). All studies reported on nitrate in drinking water and four studies also reported on nitrite in drinking water, with local municipalities (n = 56) and private wells (n = 28) being the most common sources (Table 2). Two studies did not specify the source of drinking water. Most studies (n = 45) reported drinking water nitrate concentrations stratified by quantiles, 21 studies reported average nitrate concentrations, and three reported nitrate ingestion (in mg) from drinking water (Table 2). Table 2 shows measures of association relative to the top quantiles. Association measures for all quantiles are shown in Supplementary Table 5S. Average drinking water nitrate concentrations varied greatly depending on country and water source (Table 5S). Generally, the nitrate average levels were below 50 mg/L, but in a few studies the concentration range included values above 50 mg/L. Included studies were conducted in the USA (n = 24), Europe (n = 20), Taiwan (n = 14). Only 4 studies were conducted in other parts of Asia (outside Taiwan) and no included studies were conducted for Africa or other parts of the world (Table 1).

Cancer risks were reported for 17 different sites; the majority were in the gastrointestinal tract (n = 37) and the urinary tract (n = 14), and 10 studies reported on cancers in the central nervous system (Table 1). Of the 60 studies included here, 57 studies were graded as high quality and

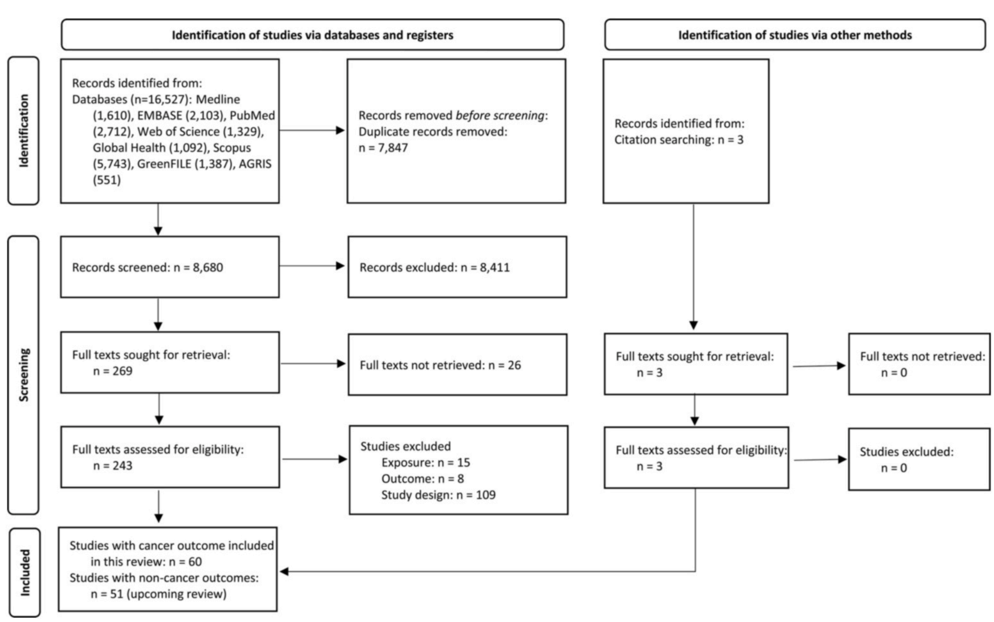

Fig. 1. Flow diagram of search. Modified from Page et al. (2021).

Table 1
Basic characteristics of the included studies. For some of the characteristics the total number of studies may not be 60 because some studies showed data from more than one country or more than one type of cancer.

Characteristics	No. of studies
Study design	
Cohort	12
Case-control	38
Cross-sectional	2
Ecological	8
Country	
Australia	1
Canada	3
China	1
Denmark	1
France	1
Germany	3
Hungary	1
India	1
Indonesia	1
Israel	1
Italy	3
Netherlands	3
Slovakia	1
Spain	5
Taiwan	14
UK	2
USA	24
Type of cancer	
Bladder	8
Bone	1
Brain	10
Breast	3
Colorectal	15
Esophagus	4
Gastric	13
Gastrointestinal and urinary	1
Kidney	4
Leukemia	3
Non-Hodgkin lymphoma	9
Ovaries	2
Pancreas	4
Penis	1
Prostate	2
Testis	1
Thyroid	1
Urinary	1

three as medium quality (Tables 1S–4S).

3.3. Nitrate and cancer to digestive/gastrointestinal organs

3.3.1. Stomach

13 studies (two cohort, six case-control, one cross-sectional, four ecological) reported the association of nitrate in drinking water with gastric cancer. Meta-analysis of four case-control studies on gastric cancer with a total included population of 19,874 participants (Chiu et al., 2012; Taneja et al., 2017; Ward et al., 2008; Yang et al., 1998) demonstrated a positive association per 10 mg/L increment in nitrate concentrations (RR = 1.91, 95% CI = 1.09–3.33) (Fig. 2A). Heterogeneity was high, $I^2 = 76.64\%$, but the estimates of the individual studies were all in the same direction. Two further case-control studies were not included in the meta-analysis because one (Rademacher et al., 1992) used different statistical methods, and the other (Yang et al., 1997) reported estimates that were used in a subsequent study as crude estimates (Yang et al., 1998). Two further cohort studies were not meta-analyzed as the exposure could not be expressed per 10 mg/L (van Loon et al., 1997, 1998). The two case-control and two cohort studies not included in the meta-analysis found no evidence of an association.

The effect of nitrate in water from private wells was reported in two studies, but neither found a significant association with stomach cancer (Rademacher et al., 1992; Ward et al., 2008) (Tables 2 and 5S).

One cross-sectional study found a significant positive association of nitrate with gastric cancer only among those aged 55–75 (Morales-Suarez-Varela et al., 1995) (Table 2). One ecological study found a positive association of nitrate and gastric cancer in the general Hungarian population (Sandor et al., 2001), one ecological study in Canada found an inverse association (Van Leeuwen et al., 1999) and the final two ecological studies found no association (Barrett et al., 1998; Gulis et al., 2002).

3.3.2. Esophagus

Four studies (two case-control, two ecological) reported the association of nitrate in drinking water and esophageal cancer. Meta-analysis of two case control studies with 6453 participants (Liao et al., 2013; Ward et al., 2008) found no significant association (RR = 1.08, 95%CI = 0.85–1.37, Fig. 2B). Of the studies not included in meta-analysis, one ecological study reported no association (Barrett et al., 1998) and the other ecological study, conducted in a Chinese county with a high incidence of esophageal squamous cell carcinoma and water collected from wells, rivers and cisterns, found a highly positive association (Zhang et al., 2012) (Table 2).

One case-control study reported a protective effect of nitrate, but it was not significant and the population was very small (Ward et al., 2008) (Tables 2 and 5S).

3.3.3. Colorectal cancer

15 studies (three cohort, nine case-control, two cross-sectional, one ecological) reported the association of nitrate in drinking water with colorectal cancer (Table 2). Meta-analysis of three cohort studies with a population of 1,774,166 people (Schullehner et al., 2018; Weyer et al., 2001; Jones et al., 2019), and seven case-control studies with 21,344 participants (Chang et al., 2010a; Chiu et al., 2010; De Roos et al., 2003; Fathmawati et al., 2017; Kuo et al., 2007; McElroy et al., 2008; Yang et al., 2007) found no significant association, although the confidence interval barely crossed 1 (RR = 1.052, 95%CI = 0.995–1.111) (Fig. 2C). One case-control study (Chiu et al., 2011) was not included in the meta-analysis because the results had been reported in an earlier (included) study (Chiu et al., 2010). The separate meta-analysis of two case-control studies that reported results on well water only revealed a significant association of nitrate and colorectal cancer, RR = 1.10 per 10 mg/L increase of nitrate (95%CI = 1.02–1.18, $I^2<0.01\%$) (Fathmawati et al., 2017; McElroy et al., 2008).

The separate analyses of colon and rectal cancers did not show any significant associations. The meta-analysis of studies on colon cancer included four case-control reports with a population of 15,302 participants (Chiu et al., 2010; De Roos et al., 2003; McElroy et al., 2008; Yang et al., 2007), and three cohort studies with 1,774,229 participants (Jones et al., 2019; Schullehner et al., 2018; Weyer et al., 2001) (Fig. 2D). The meta-analysis of studies on rectal cancer included four case-control papers with a population of 9037 participants (Chang et al., 2010a; De Roos et al., 2003; Kuo et al., 2007; McElroy et al., 2008), and three cohort studies with 1,774,328 participants (Jones et al., 2019; Schullehner et al., 2018; Weyer et al., 2001) (Fig. 2E). Of the studies reporting on well water, only one reported a significant association of nitrate and cancer to the proximal region of the colon at concentrations above 44 mg/L, but not at lower concentrations and to the distal region of the colon (McElroy et al., 2008). One cohort study showed no association between nitrate in well water and colon and rectum cancers (Weyer et al., 2001).

Of the studies not included in the meta-analysis, one cross-sectional study (Morales-Suarez-Varela et al., 1995) showed no association between nitrate in public drinking water and colorectal cancer in men and women in any of the age strata. However, there was a possible protective effect of nitrate on colon cancer in women over the age of 75 exposed to a nitrate concentration between 25 and 50 mg/L (RR = 0.32, 95% CI = 0.11–0.95). One cross-sectional study (Leclerc et al., 1991) reported no

Table 2
Studies on nitrate in drinking water and types of cancer.

Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
Stomach cancer	Barrett et al., 1998	Ecological 15,544 cases	Age and sex, allowing for SES	UK (Yorkshire) 1975–1994	Water from 148 water supply zones	Highest vs. lowest quartile (mean NO3 29.8 mg/L vs. 2.4) RR = 0.96 (0.89–1.05), p = 0.08 (unordered categorical)
	Chiu et al., 2012	Case-control 2832 cases - 2832 controls	Age, gender, marital status, and urbanization level of residence.	Taiwan 2006–2010	Municipality provided drinking water	Higher vs. lower level (NO3 ≥ 1.68 mg/L vs. < 1.68) OR = 1.16 (1.05–1.29)
	Gulis et al., 2002	Ecological 197,854 total population	n/a	Slovakia (Trnava district) 1986–1995	Municipality provided drinking water	Highest tertile (>20) Total - SIR = 1.08 (0.87–1.35), p trend 0.012 Men - SIR = 0.96 (0.70–1.30), p trend 0.18 Women - SIR = 1.24 (0.91–1.70), p trend 0.10
	Morales-Suarez-Varela et al. (1995)	Cross-sectional About 1.5 million people	Age, sex	Spain (Valencia) 1975–1980	Public water supply	Higher vs. lower tertile (>50 vs < 25 mg/L) Age Men Women <55 1.57 (0.75–3.30) 1.67 (0.17–2.67) 55-75 1.91 (1.36–2.67) 1.81 (1.15–2.87) >75 1.13 (0.56–2.27) 1.42 (0.81–2.51)
	Rademacher et al., 1992	Case-control 471 pairs for which control was exposure-negative and case was exposure-positive 476 pairs for which control was exposure-positive and case was exposure-negative.	Matched pairs (criteria not specified)	USA (Wisconsin) 1982–1985	Public water supply	Matched-pair analysis. Highest quartile (>44.22 mg/L) OR = 1.50 (0.12–18.25) Private wells: OR = 1.09 (0.82–1.47)
	Sandor et al., 2001	Ecological 108,000 people in 192 settlements	Age-, year- and sex-standardised specific mortality ratios	Hungary (Baranya county)	Water sources not specified	Log-transformed nitrate levels b = 5.48 × 10ˆ-2, 95% CI=(1.11–9.85)×10ˆ-2, p = 0.014
	Taneja et al., 2017	Case-control 78 cases 156 controls	Age, gender, and tobacco consumption	India (Nagpur) 2000–2014	Participants had to choose among a wide selection of sources for sampling. 91% of the participants resided in the same place for ≥10 years	OR = 1.20 (1.04–1.34)
	Van Leeuwen et al., 1999	Ecological Data from the Ontario Cancer Registry	n/a	Canada (Ontario) 1987–1991	Municipal water, Farm wells	Variable: Ln(NO3) mg/L Parameter: 0.136, 95% CI = −0.151, −0.122
	van Loon et al., 1997	Cohort study	Age, sex, smoking status, education, intake of vitamin C and beta- carotene, family history of stomach cancer, prevalence of stomach	The Netherland	Municipality provided drinking water.	Higher vs. lower quintile

(continued on next page)

Table 2 (*continued*)

Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
		3500 subcohort members, 177 cases	disorders and use of refrigerator or freezer	Sept. 1986–Dec. 1990		RR = 1.02 (0.62–1.68), p trend = 0.89
	van Loon et al., 1998	Cohort study 3123 subcohort members, 282 cases	Age, sex, smoking status, education, intake of vitamin C and beta- carotene, family history of stomach cancer, prevalence of stomach disorders and use of refrigerator or freezer	The Netherland Sept. 1986–Dec. 1992	Municipality provided drinking water	Higher vs. lower quintile (mean, 16.5 vs. 0.02 mg/day): RR = 0.88 (0.59–1.32), p trend = 0.73
	Ward et al., 2008	Case-control Public water 79 distal stomach, 321 controls Private wells 11 cases, 31 controls	Gender, year of birth, education, smoking, alcohol	USA (Nebraska) 1992–1994	Public water supply Private wells	Public water supply. Higher vs. lower quartile (>19.11 vs. <10.84) OR = 1.2 (0.5–2.7), p trend = 0.95 Private wells. Higher vs. lower quartile (>19.9 vs. <2.21): OR = 5.1 (0.5–52)
	Yang et al., 1997	Case-control 6766 cases - 6766 controls	Age and sex	Taiwan 1987–1991	Municipality provided drinking water	Higher vs. lower tertile (≥1.99 vs. ≤0.97) OR = 1.02 (0.93–1.11), p trend = 0.44
	Yang et al., 1998	Case-control 6766 cases - 6766 controls	Age, sex, urbanization level of residence, calcium, and magnesium levels	Taiwan 1987–1991	Municipality provided drinking water	Higher vs. lower tertile (≥1.99 vs. ≤0.97) OR = 1.14 (1.04–1.25)
Esophageal cancer	Barrett et al., 1998	Ecological 5399 cases	Age and sex, allowing for SES	UK (Yorkshire) 1975–1994	Water from 148 water supply zones	Highest vs. lowest quartile (mean NO3 29.8 mg/L vs. 2.4): RR = 1.06 (0.98–1.14)
	Liao et al., 2013	Case-control 3024 cases - 3024 controls	Age, gender, marital status, and urbanization level of residence.	Taiwan 2006–2010	Municipality provided drinking water	Higher vs. lower tertile (≥2.92 vs. <1.98) OR = 1.05 (0.91–1.19), p trend = 0.79
	Ward et al., 2008	Case-control Public water 84 cases, 321 controls Private wells 8 cases, 13 controls (highest quartile)	Gender, year of birth, smoking, alcohol, body mass index)	USA (Nebraska) 1992–1994	Public water supply Private wells	Public water supply. Higher vs. lower quartile (>19.11 vs. <10.84) OR = 1.2 (0.6–2.7), p trend = 0.52 Private wells. Higher vs. lower quartile (>19.9 vs. <2.21) OR = 0.5 (0.1–2.9)
	Zhang et al., 2012	Ecological 661 adults with cancer 54,055 non-cancer subjects	n/a	China (Shexian county) Jan. to Dec. 2010	Wells, rivers, cisterns	OR = 46.29 (3.16–667.39), p = 0.01
Colorectal cancer	Chang et al., 2010a	Case-control (rectal cancer) 1838 cases, 1838 controls	Age, gender, marital status, and urbanization level of residence	Taiwan 2003–2007	Municipality provided drinking water	NO3 categories ≥1.68 vs. <1.68 OR = 1.15 (1.01–1.32)
	Chiu et al., 2010	Case-control (colon cancer) 3707 cases, 3707 controls	Age, gender, marital status, and urbanization level of residence	Taiwan 2003–2007	Municipality provided drinking water	Higher vs. lower tertile (>2.67 vs. <1.67)

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Table 2 (*continued*)

Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
						OR = 1.16 (1.04–1.30), p trend = 0.001
	Chiu et al., 2011	Case-control (colon cancer)	Age, gender, marital status, and urbanization level of residence	Taiwan	Municipality provided drinking water	Higher vs. lower tertile (≥2.65 vs. <1.68)
		3707 cases, 3707 controls		2003–2007		OR = 1.16 (1.04–1.30), p trend = 0.001
	De Roos et al., 2003	Case-control	Age and sex. Estimates for rectum cancer are additionally adjusted for years served with chlorinated surface water	USA (Iowa)	Public water supplies	Higher vs. lower quartile (>22.11 vs. ≤4.42)
		376 colon cancer cases 338 rectum cancer cases 1244 controls		1986–1989	Bottled water	Colon cancer OR = 1.2 (0.8–1.7) Rectum cancer OR = 1.2 (0.8–1.8)
	Espejo-Herrera, 2016a, .	Case-control	Sex, age, education, body mass index, physical activity, non-steroidal anti-inflammatories use, family history of colorectal cancer and intake of energy. Analyses for women were also adjusted for oral contraceptives use	Spain (9 provinces)	Municipal water	Higher vs. lower tertile (>10 vs. ≤5 mg/day ingested)
		1869 colorectal cancer cases		Italy (2 provinces)	Bottled water	All Men Women
		1285 colon cancer cases		2008–2013	Springs and wells water	Colorectal 1.49 (1.24–1.38) 1.50 (1.21–1.87) 1.41 (1.04–1.91)
		557 rectum cancer cases				Colon 1.52 (1.24–1.86) 1.51 (1.17–1.94) 1.46 (1.04–2.05)
		3530 controls				Rectum 1.62 (1.23–2.14) 1.55 (1.16–2.08) 1.49 (0.89–2.48)
	Fathmawati et al., 2017	Case-control (colorectal cancer)	Protein intake, smoking history, age, family history of cancer, and diabetes	Indonesia (Yogyakarta province)	Well water	NO3 categories >50 vs. ≤50
		75 cases, 75 controls		Jan. 2014–Feb. 2016	Samples measured during rainy season	OR = 2.820 (1.075–7.395)
	Gulis et al., 2002	Ecological	Standardized incidence ratios (SIR), indirect standardization using age (10-year) and calendar year strata and sex-specific incidence rate.	Slovakia (Trnava district)	Municipality provided drinking water	Highest tertile (>20)
		197,854 total population		1986–1995		Total: SIR = 1.18 (1.04–1.34), p trend <0.001 Men: SIR = 1.07 (0.89–1.29), p trend 0.051 Women: SIR = 1.29 (1.08–1.55), p trend <0.001
	Jones et al., 2019	Cohort	Age, smoking status, pack-years of smoking, and body mass index, alcohol intake, estrogen use, other dietary intakes.	USA (Iowa)	Public water supply	Higher vs. lower quartile (>15.52 vs. <1.59)
		15,532 women		1986–2010		Colon: HR = 0.97 (0.75–1.26), p trend = 0.18
		612 colon cancer cases				Rectum: HR = 0.64 (0.38–1.07), p trend = 0.69
		155 rectum cancer cases				Continuous variables analysis Colon: HR = 0.97 (0.90–1.05) Rectum: HR = 0.93 (0.80–1.08)
	Kuo et al., 2007			Taiwan		

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Table 2 (*continued*)

Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
		Case-control (rectal cancer) 1118 cases, 1118 controls	Age, gender, marital status, and urbanization level of residence	1999–2003	Municipality provided drinking water	Higher vs. lower tertile (2.12–12.60 vs. ≤0.49) OR = 1.36 (1.08–1.70)
	McElroy et al., 2008	Case-control (all women) 475 cases 1447 controls	Age, interview period, family history of colorectal cancer, and smoking status.	USA (Wisconsin) 1990–1992 and 1999–2001	Private well water.	Higher vs. lower quintile (≥44.23 vs. <2.21) Colorectal cancer OR = 1.57 (0.97–2.52) Proximal colon cancer OR = 2.76 (1.42–5.38) Distal colon cancer OR = 1.23 (0.59–2.56) Rectal cancer OR = 1.26 (0.47–3.43)
	Morales-Suarez-Varela et al. (1995)	Cross-sectional About 1.5 million people	Age, sex	Spain (Valencia) 1975–1980	Public water supply	Higher vs. lower tertile (>50 vs < 25 mg/L) Age Men Women <55 0 1.05 (0.40–2.25) 55-75 0.66 (0.25–1.75) 1.15 (0.57–2.31) >75 1.13 (0.36–3.53) 0.94 (0.35–2.52)
	Schullehner et al., 2018	Cohort Colorectal N = 1,742,093 cases = 5944 Colon N = 1,742,156 cases = 3700 Rectum N = 1,742,255 cases = 2308	Age, sex, year of birth, previous cancer diagnosis, education	Denmark 1 Jan. 1978 to 31 Dec. 2011.	Public water supply Private wells	Higher vs. lower decile (≥16.75 vs < 0.69 mg/L) Colorectal HR = 1.14 (1.06–1.23) Colon HR = 1.14 (1.04–1.26) Rectum HR = 1.13 (1.00–1.27)
	Weyer et al., 2001	Cohort (all women) Public water supply Colon: N = 16,541 cases = 300 Rectum: N = 16,541 cases = 106 Private wells Colon: N = 5436 cases = 85 Rectum: N = 5436 cases = 23	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply Colon cancer RR = 1.01 (0.70–1.48) Rectum cancer RR = 0.50 (0.27–0.93) Private wells Colon cancer RR = 1.14 (0.80–1.62) Rectum cancer RR = 0.65 (0.37–1.12)
	Yang et al., 2007	Case-control 2234 cases - 2234 controls	Age, sex, calcium levels in drinking water, level of residence.	Taiwan 1999–2003	Municipality provided drinking water	Higher vs. lower tertile (≥2.12 vs. ≤0.97) OR = 0.98 (0.83–1.16), p trend = 0.22
Gastrointestinal and urinary cancer	Leclerc et al., 1991	Cross-sectional 3.5 million people	n/a	France (Pas-de-Calais) 1983	Municipality provided drinking water	Age standardized relative risk (>45 vs. <45 mg/L) Men: RR = 0.94 (0.87–1.02), Women: RR = 0.88 (0.77–1.02)
Other digestive tract cancers	Gulis et al., 2002	Ecological 197,854 total population	n/a	Slovakia (Trnava district) 1986–1995	Municipality provided drinking water	Highest tertile (>20) Total: SIR = 1.13 (1.03–1.25), p trend 0.001

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Table 2 (*continued*)

Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
						Men: SIR = 1.06 (0.92–1.21), p trend 0.051 Women: SIR = 1.28 (1.12–1.47), p trend <0.001
	Weyer et al., 2001	Cohort (all women) Public water supply N = 16,541 cases = 55 Private wells N = 5436 cases = 21	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply: RR = 1.70 (0.74–3.88) Private wells: RR = 1.69 (0.75–3.82)
Pancreatic cancer	Coss et al., 2004	Case-control 189 cases - 1244 controls	Age, gender, and cigarette use	USA (Iowa) 1985–1987	Community water supplies	Higher vs. lower quartile (>12.38 vs. <2.65) OR = 0.99 (0.64–1.5)
	Quist et al., 2018	Cohort study Post-menopausal women Wells 4955 women - 34 cases Public water 15,710 women - 152 cases	Age and smoking status	USA (Iowa) 1986–2011	Public water supply Private wells	Higher vs. lower quartile (>25.16 vs. <2.08) HR = 1.18 (0.52–2.67), p trend = 0.97 Continuous variables analysis: HR = 1.07 (0.92, 1.25) Private wells: HR = 0.92 (0.56, 1.52) compared to first quartile of public supply
	Yang et al., 2009	Case-control 2412 cases - 2412controls	Age, gender, and urbanization level of residence	Taiwan 2000–2006	Municipality provided drinking water	Higher vs. lower tertile (2.12–12.65 vs. ≤0.80) OR = 1.10 (0.96–1.27), p trend = 0.08
	Weyer et al., 2001	Cohort (all women) Public water supply N = 16,541 cases = 61 Private wells: N = 5436 cases = 14	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply: RR = 0.52 (0.22–1.22) Private wells: RR = 0.66 (0.31–1.41)
Bladder cancer	Barry et al., 2020	Case-control 987 cases 1180 controls	Age, sex, race, Hispanic ethnicity, study state (New Hampshire, Maine, Vermont), smoking, and high-risk occupation, average total trihalomethanes	USA (Maine, Vermont 2001–2004) (New Hampshire 2002–2004)	Public water supply Private wells	NO3 concentration in water (mg/L) Higher vs. lower quintile (>9.15 vs. ≤0.93) OR = 1.5 (0.97–2.3), p trend = 0.01 NO3 ingested (mg/day) Higher vs. lower quintile (>20.30 vs. ≤1.33)

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Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
						OR = 1.4 (0.89–2.2), p trend = 0.06
	Chiu et al., 2007	Case-control	Age, gender, and urbanization level of residence	Taiwan	Municipality provided drinking water	Higher vs. lower tertile (2.12–12.65 vs. <.080)
		513 cases - 513 controls		1999–2003		OR = 1.96 (1.41–2.72), p trend <0.001
	Espejo-Herrera et al., 2015	Case-control	Age, sex and area of residence smoking status, NSAIDs use, night-time urinary frequency, time working in farm/ agriculture activities, tap water and vitamin C daily intake, and urinary infections, intake of vitamin E, processed meat, red meat, alcohol, and gastric ulcer diagnosis	Spain (5 regions)	Public water supply system	NO3 concentration in water (mg/L)
		531 cases - 556 controls		June 1998–June 2001	Bottled water	Higher vs. lower tertile (≥44.23 vs. ≤22.11) OR = 1.04 (0.60–1.81) NO3 ingested (mg/ day) Higher vs. lower tertile (>35.38 vs. ≤17.69) OR = 0.65 (0.41–1.02)
	Jones et al., 2016	Cohort	Age, smoking status, and pack-years of smoking	USA (Iowa)	Public water supply	Higher vs. lower quartile (>13.14 vs. <2.08)
		Public water:		1986–2010	Private wells	HR = 1.48 (0.92–2.40), p trend = 0.11
		15,577 women - 130 cases				Continuous variables analysis: HR = 1.12 (0.95–1.32)
		Private wells:				Private wells: HR = 1.16 (0.70, 1.91) compared to first quartile of public supply
		4930 women – 36 cases				
	Morales-Suarez-Varela et al. (1995)	Cross-sectional	Age, sex	Spain (Valencia)	Public water supply	Higher vs. lower tertile (>50 vs < 25 mg/L), men
		About 1.5 million people		1975–1980		Age RR <55 0 55-75 1.4 (0.8–2.48) >75 0.53 (0.14–2.07)
	Ward et al., 2003	Case-control	Age, cigarette smoking, years of education, duration of chlorinated surface water use and study period	USA (Iowa)	Public water supply (data used in analyses)	Higher vs. lower quartile (≥13.67 vs. <2.65)
		Men: 622 cases - 788 controls Women: 186 cases - 471 controls		1986–1989	Private wells, Bottled water	Men: OR = 0.5 (0.4–0.8) Women: OR = 0.8 (0.4–1.3)
	Weyer et al., 2001	Cohort (all women)	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa)	Public water supply	Higher vs. lower quartile (>10.88 vs. <1.59)
		Public water supply		1986–31 December 1998	Private wells	Public water supply: RR = 2.43 (1.01–5.88)
		N = 16,541 cases = 47 Private wells N = 5436 cases = 10				Private wells: RR = 1.01 (0.83–1.22)
	Zeegers et al., 2006	Cohort study	Age, sex, current smoking, smoking amount, smoking duration, and nitrate exposure from food	The Netherland	Pumping stations	Higher vs. lower quintile (>7.7 vs. <0.9)

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Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
		4359 subcohort members 871 cases		Sept. 1986–Dec. 1995		RR = 1.06 (0.82–1.38), p trend = 0.24 Increment per 10 mg/day RR = 1.09 (0.96–1.24)
Kidney cancer	Jones et al., 2017	Cohort Public water 15,577 women - 125 cases Private wells: 4930 women – 38 cases	Age, smoking status, pack-years of smoking, and body mass index	USA (Iowa) 1986–2010	Public water supply (data used in analyses) Private wells	Higher vs. lower quartile (>12.30 vs. <2.74) HR = 2.3 (1.2–4.3), p trend = 0.33 Continuous variables analysis: HR = 1.3 (0.96–1.3) Private wells: HR = 0.96 (0.59, 1.58) compared to first quartile of public supply
	Volkmer et al., 2005	Cohort Group A: 57,253 inhabitants Incidence renal cell carcinoma (per 100,000 inhabitants): Male = 10.0, Female = 6.8, Total = 8.3 Group B: 10,037 inhabitants Incidence RCC (per 100,000 inhabitants): Male = 16.5, Female = 2.3, Total = 9.5	Stratified by sex	Germany (Bocholt) 1986–1997	Municipality provided drinking water	Male RR = 0.61 (0.28–1.33) Female RR = 2.96 (0.66–13.18) Total RR = 0.87 (0.34–2.22)
	Ward et al., 2007	Case-control Public water 201 cases – 1244 controls Private wells: 406 cases - 2434 controls	Age, gender, current body mass index, and average population size of towns where subjects resided over their lifetime in Iowa	USA (Iowa) 1986–1989	Public water supply (data used in analyses) Private wells, Bottled water	Higher vs. lower quartile (>12.3 vs. <2.74) OR = 0.89 (0.57–1.39) Private wells (20+ years use private wells vs. use public water sources): OR = 0.89 (0.59–1.34)
	Weyer et al., 2001	Cohort (all women) Public water: N = 16,541 cases = 45 Private wells: N = 5436 cases = 13	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supplyPrivate wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply: RR = 1.06 (0.42–2.68) Private wells: RR = 1.07 (0.45–2.57)
Brain cancer	Barrett et al., 1998	Ecological 3441 cases	Age and sex, allowing for SES	UK (Yorkshire) 1975–1994	Water from 148 water supply zones	Highest vs. lowest quartile (mean NO3 29.8 mg/L vs. 2.4): RR = 1.20 (1.08–1.33)
	Boeing et al., 1993	Case-control 115 gliomas, 81 meningiomas 418 controls	Age, gender and tobacco-smoking	Germany (Rhein-Neckar-Odenwald) 1987–1988	Drinking water	NO3 ≥50 mg/L (NO3 levels were higher for controls than cases, but not specified) Glioma RR = 0.1 (95% CI 0.0–1.0)

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Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
						Meningioma RR = 0.2 (95%CI 0.0–1.2)
	Ho et al., 2011	Case-control 787 cases - 787 controls	Age, gender, marital status, and urbanization level of residence	Taiwan 2003–2008	Municipality provided drinking water	$NO_3 \geq 1.68$ mg/L OR = 1.04 (0.85–1.27)
	Mueller et al., 2001	Case-control Public water 119 cases - 191 controls(<20 years old) All sources of water: 540 cases - 801 controls	Age and sex	USA (WA and CA) Jan 1984–Dec 1990 (WA) Jan 1984–Dec 1991 (CA)	Public water supply Wells	Higher vs. lower quartile (50–100 vs. not detected) OR = 1.4 (0.1–15) Well water (vs public water): OR = 1.2 (0.8–2.2)
	Mueller et al., 2004	Case-control 283 cases - 537 controls (children)	Centre, age, sex and diagnosis year	USA (CA, WA), France, Italy, Spain, Israel, Canada (Winnipeg), Australia 1976–1994	Public water supply Wells	Higher vs. lower quartile (>50 vs. none) OR = 0.8 (0.4–1.5)
	Steindorf et al., 1994	Case-control 173 cases - 418 controls	Age and sex	Germany (Rhein-Neckar-Odenwald region) Jan. 1987 to Dec. 1988	Public water supply, wells	Higher vs. lower quartile (>25.2 vs. <2) RR = 1.00 (0.61–1.64)
	Thorpe and Shirmohammadi (2005)	Ecological 262 cases (Children 0–17)	None	USA (Maryland) 1992–1998	Public water supply, wells	Crude OR for exposure to all detectable concentrations of NO_3: OR = 1.23 (0.86–1.75)
	Ward et al. (2005b)	Case-control (≥21 years age) Public water: 130 gliomas - 319 controls Private wells: 63 gliomas - 72 controls	Age, gender, respondent type, education, and ever live/work on a farm	USA (Nebraska) 1988–1990 1991 to June 1993.	Public water supply Private wells, Bottled water	Higher vs. lower quartile (>19.11 vs. <10.53) OR = 1.3 (0.7–2.6) Well water (≥44.2 vs < 44.2 mg/ml): OR = 1.2 (0.4–4.1)
	Weng et al., 2011	Case-control (0–19 years old) 457 cases - 457 controls	Age, gender, and urbanization level of residence	Taiwan 1999–2008	Municipality provided drinking water	$NO_3 > 1.37$ mg/L OR = 1.40 (1.07–1.84)
Non-Hodgkin lymphoma	Chang et al., 2010b	Case-control 1716 cases - 1716 controls	Age, gender, and urbanization level of residence	Taiwan 2000–2006	Municipality provided drinking water	Higher vs. lower tertile (2.12–12.65 vs. ≤0.80) OR = 1.05 (0.89–1.24), p trend = 0.39
	Cocco et al., 2003	Ecological 737 cases 7,756,474 person years	Gender, age, and population size	Italy (Sardinia) 1974–1993	Municipality provided drinking water	Higher vs. lower quantile (8 quantiles, 15.01–26.64 vs. ≤2.0) Total: IRR = 1.32 (0.88–1.97) Men: IRR = 1.64 (0.92–2.91), Women: IRR = 1.10 (0.63–1.93)
	Freedman et al., 2000	Case-control 73 cases - 147 controls	Age	USA (Minnesota) 1980–1982	Community water supplies, Bottled water	Higher vs. lower tertile (>6.6 vs. ≤2.21) OR = 0.3 (0.1–0.9)
	Gulis et al., 2002	Ecological 197,854 total population	n/a	Slovakia (Trnava district) 1986–1995	Municipality provided drinking water	Higher vs. lower tertile (>20 vs. ≤10)

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Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
						Total: SIR = 1.22 (0.76–1.96), p trend 0.021 Men: SIR = 1.09 (0.52–2.28), p trend 0.17 Women: SIR = 1.35 (0.72–2.50), p trend 0.13
	Law et al., 1999	Ecological 160 million person years	n/a	UK (Yorkshire, North Humberside) 1984–1993	Municipality provided drinking water 148 water supply zones	Higher vs. lower tertile (>14.85 vs.<3.24) 1984–1988: IRR = 1.210 (1.04, 1.41) 1989–1993: IRR = 0.917 (0.78, 1.08)
	Rhoades et al., 2013	Case-control 140 cases - 192 controls	Unspecified covariates	USA (Nebraska) 1999–2002	Public water supplies	NO_3 > 8.85 mg/L OR = 0.6 (0.3–1.1)
	Thorpe and Shirmohammadi (2005)	Ecological 71 cases (Children 0–17)	None	USA (Maryland) 1992–1998	Public water supply, Wells	Crude OR for exposure to all detectable concentrations of NO_3: OR = 1.41 (0.74–2.68)
	Ward et al., 1996	Public Water: Case-control 156 cases - 527 controls Private wells: 46 cases - 136 controls	Age, gender, family history of cancer	USA (Nebraska) 1 July 1983–30 June 1986	Public water supply (data reported here) Private wells Bottled water	Higher vs. lower quartile (≥17.69 vs. <7.08) Total: OR = 2.0 (1.1–3.6), P trend = 0.03 Men: OR = 1.9 (0.7–4.9), P trend = 0.3 Women: OR = 2.1 (1.0–4.4), P trend = 0.04 Intake - Total (mg/day) Higher vs. lower quartile (≥27.86 vs. <11.06) OR = 1.9 (1.0–3.9), P trend = 0.07 Private wells: 44.2 vs < 4.42 mg/l OR = 1.5 (0.6–3.8)
	Ward et al., 2006	Case-control Public supplies 181 cases - 142 controls Public supplies and private wells 211 cases - 165 controls	Age, gender and education	USA (Iowa) 1998–2000	Public water supply Private wells	Higher vs. lower quartile (≥12.83 vs. <2.79) Public supplies: OR = 1.2 (0.6–2.2) Public supplies + private wells: OR = 0.9 (0.5–1.6)
	Weyer et al., 2001	Cohort (all women) Public water: N = 16,541 cases = 105 Private wells: N = 5436, cases = 38	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply: RR = 0.71 (0.39–1.28) Private wells: RR = 0.88 (0.52–1.47)
Breast cancer	Brody et al., 2006	Case-control 824 cases - 745 controls	Diagnosis/reference year, age at diagnosis/reference year, birth decade, study, vital status, previous breast cancer diagnosis, age at first birth, family history of breast cancer, and education	USA (Cape Cod) 1988–1995	Public water supply	Higher vs. lower quintile (≥5.31 vs. <1.33 mg/L) OR = 0.9 (0.5–1.7)
	Espejo-Herrera et al., 2016b	Case-control	Study area, age, education, body mass index, family history	Spain (8 provinces)	Municipal water	

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Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
		1245 cases - 1520 controls	of breast cancer, age at first birth, age at menopause, use of oral contraceptives, and energy intake	2008–2013	Bottled water Springs and wells water	Higher vs. lower quartile (>8.8 vs. <2.3 mg/day) Pre- and post-menopausal OR = 1.08 (0.8–1.43), p for trend = 0.64 Post-menopausal OR = 1.29 (0.92–1.81), p for trend = 0.20 Pre-menopausal OR = 1.14 (0.67–1.94), p for trend = 0.80
	Weyer et al., 2001	Cohort (all women) Public water: N = 16,541 cases = 810 Private wells: N = 5436 cases = 275	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply: RR = 1.00 (0.82–1.23) Private wells: RR = 1.01 (0.83–1.22)
Leukemia	Infante-Rivard et al., 2001	Case-control (0–9 years of age) prenatal: 8 cases, 11 controls postnatal: 7 cases, 11 controls	Maternal age and level of schooling	Canada (Quebec) 1980–1993	Tapwater	>95th percentile vs ≤ 95th percentile Prenatal: OR = 0.68 (0.27–1.70) Postnatal: OR = 0.59 (0.23–1.55)
	Thorpe and Shirmohammadi (2005)	Ecological 293 cases (Children 0–17)	None	USA (Maryland) 1992–1998	Public water supply Wells	Crude OR for exposure to all detectable levels of NO3 OR = 1.81 (1.35–2.42)
	Weyer et al., 2001	Cohort (all women) Public water: N = 16,541 - cases = 94 Private wells: N = 5436 - cases = 27	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply: RR = 0.92 (0.52–1.63) Private wells: RR = 0.82 (0.47–1.43)
Cancers to reproductive organs	Inoue-Choi et al., 2015	Cohort Public water: N = 13,051 - cases = 145 Private wells: N = 4165 - cases = 45	Age, BMI, family history of ovarian cancer, number of live births, age at menarche, age at menopause, age at first live birth, oral contraceptive use, estrogen use, and history of unilateral oophorectomy	USA (Iowa) 1986–2010	Public water Private wells	Ovarian cancer Higher vs. lower quartile (≥13.18 vs. ≤2.09) Public water supply HR = 2.14 (1.30–3.54), p trend = 0.002 Private wells (comparison with lower public water quartile): HR = 1.53 (0.93–2.54)
	Morales-Suarez-Varela et al. (1995)	Cross-sectional About 1.5 million people	Age, sex	Spain (Valencia) 1975–1980	Public water supply	Prostate cancer Higher vs. lower tertile (>50 vs < 25 mg/L) Age Men <55 RR = 3.07 (0.45–21.17) 55-75 RR = 1.86 (1.20–2.88) >75 RR = 1.80 (1.15–2.82)
	Volkmer et al., 2005	Cohort Group A: 57,253 inhabitants	Stratified by sex	Germany (Bocholt) 1986–1997		Prostate cancer: RR = 1.06 (0.76–1.48)

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Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
		Incidence cancer (per 100,000 inhabitants): Penis = 2.7, Prostate = 71.7, Testis = 10.3 Group B: 10,037 inhabitants Incidence cancer (per 100,000 inhabitants): Penis = 4.3, Prostate = 67.6, Testis = 23.8				Penis cancer: RR = 0.66 (0.14–2.88) Testis cancer: RR = 0.43 (0.21–0.90)
	Weyer et al., 2001	Cohort (all women) Public water supply,N = 16,541 Cases: ovarian = 82, uterine = 168 Private wells, N = 5436 Cases: ovarian = 25, uterine = 70	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa) 1986–31 Dec. 1998	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply Ovarian RR = 2.03 (1.01–4.07), Uterine RR = 0.65 (0.40–1.06) Private wells Ovarian RR = 1.55 (0.77–3.13), Uterine RR = 1.09 (0.74–1.61)
Other types of cancer	Gulis et al., 2002	Ecological - all cancers 197,854 total population 4051 cases (1938 men and 2113 women)	n/a	Slovakia (Trnava district) 1986–1995	Municipality provided drinking water	Higher vs. lower tertile (>20 vs. ≤10) Total: SIR = 1.03 (0.97–1.08), p trend <0.001 Men: SIR = 0.94 (0.88–1.02), p trend <0.001 Women: SIR = 1.38 (1.28–1.47), p trend <0.001
	Thorpe and Shirmohammadi (2005)	Ecological - bone 63 cases (Children 0–17)	None	USA (Maryland) 1992–1998	Public water supply, wells	Crude OR for exposure to all detectable concentrations of NO3: OR = 1.28 (0.63–2.59)
	Volkmer et al., 2005	Cohort Group A: 57,253 inhabitants Incidence transitional cell carcinoma of the urinary tract (per 100,000 inhabitants): Male = 46.7, Female = 21,7, Total = 33.8 Group B: 10,037 inhabitants Incidence transitional cell carcinoma of the urinary tract (per 100,000 inhabitants): Male = 20.7, Female = 14.3, Total = 17.1	Stratified by sex	Germany (Bocholt) 1986–1997	Municipality provided drinking water	Male RR = 2.26 (1.34–3.79) Female RR = 1.52 (0.78–2.96) Total RR = 1.98 (1.10–3.54)
	Ward et al., 2010	Cohort (all women) - thyroid Public water supply	Age, vitamin C intake, and residence location.	USA (Iowa) 1986–31 Dec. 2004	Public water supply Private wells	Higher vs. lower quartile (>10.88 vs. <1.59) Public water supply: RR = 2.18 (0.83–5.76), P trend = 0.02

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Table 2 (*continued*)

Type of cancer	Reference	Design and population	Adjustment for confounders	Location and years	Exposure	Findings (95% CI)
		N = 16,541 cases = 28			Bottled water	Private wells (comparison with lowest public water quartile): RR = 1.13 (0.83–3.66)
		Private wells: N = 5436 cases = 12				
	Weyer et al., 2001	Cohort (all women)	Age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, dietary nitrate, and fruits and vegetables	USA (Iowa)	Public water supply	Higher vs. lower quartile (>10.88 vs. <1.59)
		Public water supply, N = 16,541 Lung + bronchus = 237, melanoma = 68 Private wells, N = 5436 Lung + bronchus = 43, melanoma = 25		1986–31 Dec. 1998	Private wells	Public water supply Lung and bronchus RR = 0.83 (0.55–1.26) Melanoma RR = 0.92 (0.59–1.42) Private wells Lung and bronchus RR = 0.97 (0.86–1.09) Melanoma RR = 1.01 (0.90–1.17)

association of nitrate in water with mortality risk from gastrointestinal and urinary cancers combined (Table 2). Analyzing the quantity of daily ingested nitrate through water, one case-control study (Espejo-Herrera et al., 2016a) reported positive associations with colorectal and colon cancers in both men and women (Table 2). With rectal cancer, the association was positive for all participants and men only, but there was no association in women alone.

One ecological study (Gulis et al., 2002) found a positive association of nitrate with both colorectal cancer and with all digestive tract cancers combined (Table 2). Stratification by sex showed no association in men, but a positive association in women in both estimates.

3.3.4. Pancreas

Four studies (two cohort, two case-control) reported the association of nitrate in water with pancreatic cancer. Meta-analyses of two cohort studies with 32,251 participants (Quist et al., 2018; Weyer et al., 2001) and meta-analysis of two case-control studies with 6257 participants (Coss et al., 2004; Yang et al., 2009) found no significant association (Fig. 2F, Table 2).

Two cohort studies reported no association of nitrate from private well water and pancreas cancer (Quist et al., 2018; Weyer et al., 2001) (Tables 2 and 5S).

3.4. Nitrate and cancer to the genitourinary organs

3.4.1. Bladder

Eight studies (three cohort, four case-control, one cross-sectional) reported the association of nitrate in drinking water and bladder cancer (Table 2). Meta-analysis of two cohort studies with 32,118 participants (Jones et al., 2016; Weyer et al., 2001) identified a significant increase in bladder cancer for a 10 mg/L increase in nitrate, RR = 1.31 (95% CI = 1.03–1.66, I^2 = 1.95%) (Fig. 2E). Meta-analysis of four case-control studies (Barry et al., 2020; Chiu et al., 2007; Espejo-Herrera et al., 2015; Ward et al., 2003) found no significant association (Fig. 2G). Similarly, meta-analysis of cohort and case-control studies combined showed no association (Fig. 2G). One cross-sectional study (Morales-Suarez-Varela et al., 1995) also found no association in men (Table 2).

Two cohort studies reported no association of nitrate from private well water and bladder cancer (Jones et al., 2016; Weyer et al., 2001) (Tables 2 and 5S).

Analyzing the relationship between the daily ingested amount of nitrate in water (mg/day) with bladder cancer, one cohort study (Zeegers et al., 2006) and two case-control studies (Barry et al., 2020; Espejo-Herrera et al., 2015) reported no association (Table 2).

3.4.2. Kidney

Four studies (three cohort, one case-control) reported the association of nitrate in water with kidney cancer (Table 2). Meta-analysis of two cohort studies with 32,118 participants (Jones et al., 2017; Weyer et al., 2001) found no significant association (Fig. 2H). The remaining cohort study (Volkmer et al., 2005) not included in the meta-analysis because of differences in statistical method used, and one case-control study (Ward et al., 2007) also reported no association (Table 2).

Two cohort studies reported no association of nitrate from private well water and kidney cancer (Jones et al., 2017; Weyer et al., 2001) (Tables 2 and 5S). One case-control study reported no association after more than 20 years of exposure to nitrate from private wells (Ward et al., 2007) (Table 2).

3.4.3. Reproductive organs

Four studies (three cohort and one cross-sectional) reported on the association of nitrate in water and cancers of reproductive organs (Table 2). Meta-analysis of two cohort studies (Inoue-Choi et al., 2015; Weyer et al., 2001) found no significant association with ovarian cancer (Fig. 2I). One cohort study (Volkmer et al., 2005) not included in the meta-analysis because of differences in statistical method used reported no association with cancers of the prostate or penis, and a potential protective effect on testicular cancer (Table 2). One cohort study (Weyer et al., 2001) reported no association with uterine cancer. One cross-sectional study (Morales-Suarez-Varela et al., 1995) reported a positive association with prostate cancer in men older than 55 years of age (Table 2). Two cohort studies reported no association of nitrate from private well water and cancer to the ovaries and uterine corpus (Inoue-Choi et al., 2015; Weyer et al., 2001) (Tables 2 and 5S).

3.5. Nitrate and neurologic cancer

Nine studies (seven case-control, two ecological) reported the

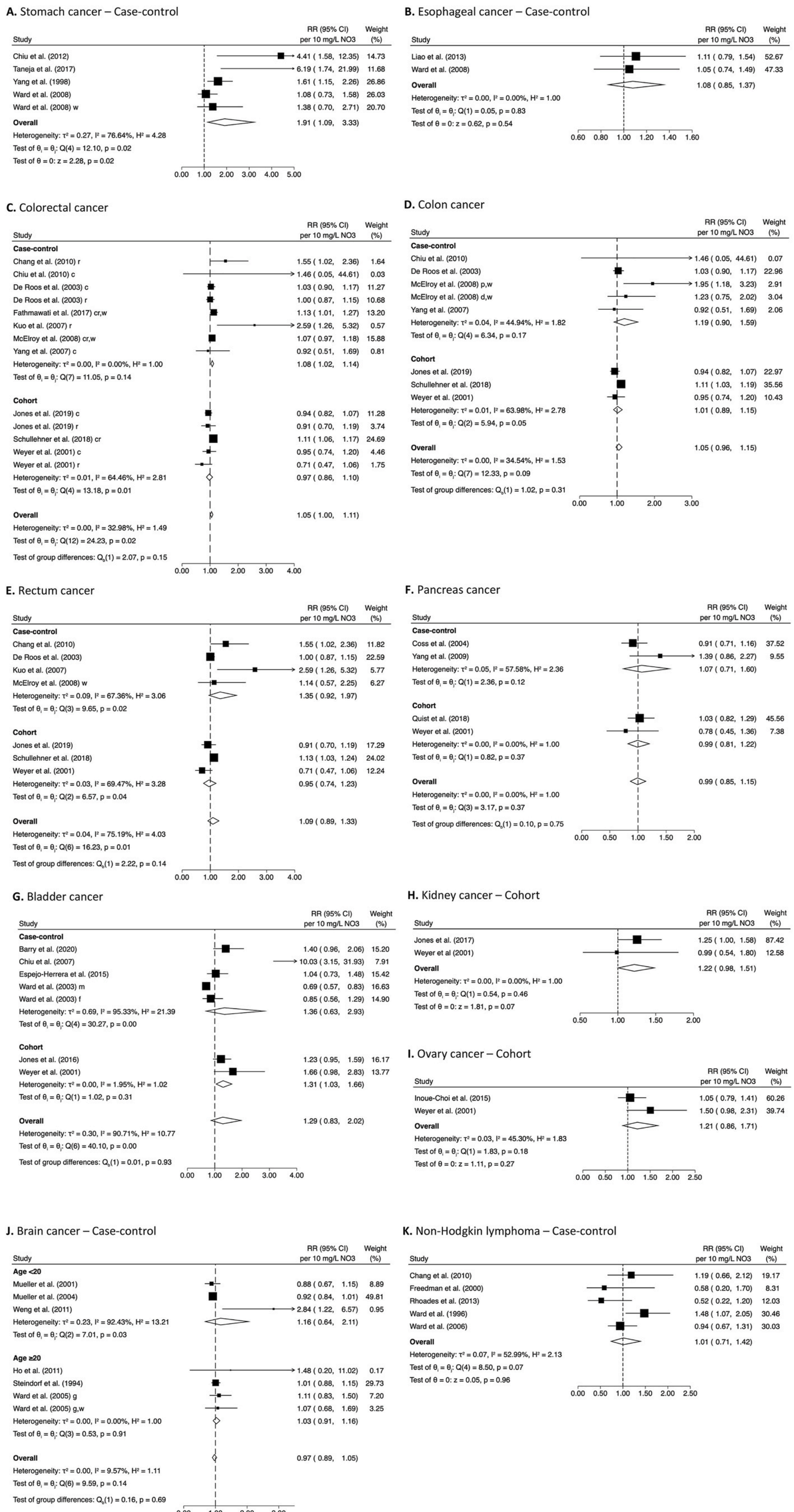

Fig. 2. Pooled risk ratios of nitrate in drinking water and specific types of cancer (A to K). Meta-analyses stratified by study design are shown for colorectal, pancreas, and bladder cancers. The point estimate (black squares), statistical weight (area of each square), and 95% confidence interval for each study (horizontal line) are shown. Overall summary estimates are displayed (diamonds). Estimates are shown per 10 mg/L increase of nitrate.

Abbr.: c = colon, cr = colorectal, d = distal, f = female, g = glioma, m = male, p = proximal, r = rectum, w = well water.

association of nitrate in water with brain cancer (Table 2). Meta-analysis including six case-control studies and 4776 participants (Ho et al., 2011; Mueller et al., 2001, 2004; Steindorf et al., 1994; Ward et al., 2005b; Weng et al., 2011) found no significant association (Fig. 2J). The subgroup analysis by age separating participants under 20 years of age from those 20 years old or older showed a possible higher risk in the younger subgroup, but the confidence interval was wide and the heterogeneity was very high, $I^2 = 92.43\%$. One case-control study (Boeing et al., 1993) reported no association, but was not included in the meta-analysis because it was not possible to determine the sample size (Table 2). One case-control study in young people under 20 years of age (Mueller et al., 2001) and one in adults over 20 (Ward et al., 2005b) showed no association of brain tumors with nitrate from private wells (Tables 2 and 5S).

One ecological study (Barrett et al., 1998) reported a positive association between nitrate and brain cancer for nitrate concentration above 30 mg/L, and one ecological study (Thorpe and Shirmohammadi, 2005) found no association (Table 2).

3.6. Nitrate and breast cancer

Three studies (one cohort, two case-control) reported the association of nitrate with breast cancer. All three studies found no significant association (Weyer et al., 2001; Espejo-Herrera et al., 2016b; Brody et al., 2006) (Table 2). Meta-analysis of the two case-control studies was not performed because of the different types of exposures (i.e., concentration of nitrate in water vs. ingested nitrate). One cohort study showed no association with nitrate in water from private wells (Weyer et al., 2001) (Tables 2 and 5S).

3.7. Nitrate and hematologic cancers

3.7.1. Non-Hodgkin lymphoma

Nine studies (one cohort, five case-control, three ecological) reported on the association of nitrate in water and non-Hodgkin lymphoma (NHL). Meta-analysis including five case-control studies with 5033 participants (Chang et al., 2010b; Freedman et al., 2000; Rhoades et al., 2013; Ward et al., 1996, 2006) found no significant association (Fig. 2K). One cohort study (Weyer et al., 2001) and all four ecological studies (Cocco et al., 2003; Gulis et al., 2002; Thorpe and Shirmohammadi, 2005; Law et al., 1999) also reported no association (Table 2). One cohort study (Weyer et al., 2001) and one case-control study (Ward et al., 1996) showed no association of NHL with nitrate from private wells (Tables 2 and 5S).

3.7.2. Leukemia

Three studies (one cohort, one case-control, one ecological) reported the relationship of nitrate in water with leukemia. One cohort study (Weyer et al., 2001) and one case-control (Infante-Rivard et al., 2001) reported no significant association. One ecological study (Thorpe and Shirmohammadi, 2005) reported a positive association (crude OR = 1.81, 95%CI = 1.35–2.42, Table 2). One cohort study showed no association with nitrate in water from private wells (Weyer et al., 2001) (Tables 2 and 5S).

3.8. Nitrate and other types of cancer

Five studies (three cohort, two ecological) reported on associations of nitrate in water with "combined" cancers or cancers in other areas of the body (Table 2). One cohort study reported no association of nitrate from public water sources and private wells with thyroid cancer in women (Ward et al., 2010). One cohort study (Weyer et al., 2001) reported no association of neither public water sources nor private wells with lungs and bronchus cancers, melanoma, and all types of cancer combined. One cohort study reported an association with transitional cell carcinoma of the urinary tract in men (Volkmer et al., 2005). One ecological study (Gulis et al., 2002) reported an association with all cancers combined in women (Table 2). One ecological study (Thorpe and Shirmohammadi, 2005) reported no association with bone cancer.

3.9. Nitrite and cancer

Four studies (three case-control, one ecological) reported on the association of nitrite in drinking water with cancer (Table 6S). One case control study (Boeing et al., 1993) reported no association of nitrite with gliomas or meningiomas. One case control study (Mueller et al., 2001) reported that nitrite concentrations of 1 mg/L were associated with a higher risk of brain cancer, whilst another reported no association (Mueller et al., 2004). One ecological study (Zhang et al., 2012) reported no association of nitrite with esophageal cancer.

3.10. Confounding variables

The two confounders adjusted for in almost all models were age and sex, 56 (18.8%) and 43 (14.4%) times, respectively (Figs. 3 and 2S). Nitrate intake from food was controlled in 14 models (4.7%, Figs. 3 and 2S).

The types of cancer with models that were adjusted with the highest number of confounders were breast and colorectal cancers (both with 17 confounders), and bladder cancer (16 confounders) (Fig. 2S). However, it was very rare that any two studies included the same confounders.

Four case-control studies studying colorectal cancer, stomach cancer, leukemia and NHL matched their populations on sex and age. One case-control study on NHL did not clearly describe the covariates included in the final model. One cohort study on cancers to the kidney, urinary tract and reproductive organs did not report on any confounders used in their models.

4. Discussion

4.1. Summary of findings

This systematic review assessed the evidence of association between nitrate or nitrite in drinking water and several types of cancer. Our meta-analyses found that a 10 mg/L increase in nitrate was associated with a doubled risk of gastric cancer, but no significant relationship with colorectal, esophagus, pancreatic, brain cancers and non-Hodgkin

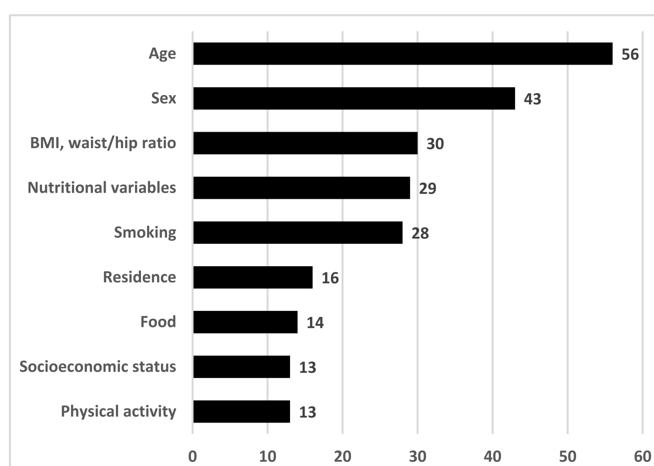

Fig. 3. The most common confounders controlled for in the included studies. Higher order confounders in this graph were: "Nutritional variables" including vitamins, energy intake, protein intake; "Residence" including level of urbanization of the residence and urban/rural location; "Socioeconomic status" including education level and occupation. Numbers on bars and on the x axis refer to the number of models that included a given confounder.

lymphoma. A significant association of between nitrate and bladder cancer was found in a meta-analysis of two cohort studies, but this was not confirmed by the meta-analysis of five estimates from case-control studies. The two individual cohort studies showed estimates in the same direction, and the heterogeneity of the summary analysis was very low. In contrast, the individual case-control studies showed estimates in opposing directions, and the heterogeneity of the meta-analysis was very high. The combined meta-analysis of cohort and case-control studies did not reveal an association between nitrate and bladder cancer. This latter result is in agreement with a systematic review in 2012 that included fewer studies (Wang et al., 2012).

Looking at individual studies, there may be a higher risk of colorectal cancer associated with nitrate in drinking water because eight out of 15 studies reported a positive association in the highest quantile analyzed. The summary analysis of two studies investigating nitrate in private wells alone revealed a significantly positive association with colorectal cancer. The analyses of colon and rectal cancers separately show possible higher risks at both sites. Two studies on ovarian cancers reported a positive association in the highest quartile of nitrate concentration.

Study designs and methodologies were heterogeneous, which may explain the different results between individual studies. Possible causes of the high heterogeneity observed in some of the meta-analyses (i.e., gastric, colorectal and bladder cancers) may be due to different country settings and population groups, nitrate ranges, different methods to assess nitrate concentration and difficulty of estimating intake in people. The variety of confounders used in the models may also have contributed to the heterogeneity. Except for age and sex that were used in almost all studies, the other confounders were used less consistently. Notably, nitrate from food was adjusted only in 4.7% of the models.

Except for brain cancer, all the associations between nitrate in water and cancer in our meta-analyses were in the direction of an increased risk of disease. However, when brain cancer studies were analyzed separately based on the age of the participants, the point estimates indicated a possible higher risk in both subgroups.

4.2. Research in context

Over the years, the number of epidemiological studies on nitrate in drinking water and cancer has been increasing, with 10 studies reviewed in Ward et al. (2005a), 18 in Ward et al. (2018), 3 in Zumel-Marne et al. (2019), 48 in Essien et al. (2020), and 59 in this review. Most studies focused on different organs of the gastrointestinal tract. Despite the growing body of evidence synthesized here, it is not possible to reach a definitive conclusion on the risk of cancer associated with nitrate in drinking water, since most cancer types were investigated by four studies or less. The degree of uncertainty was high, with wide confidence intervals. However, even though most studies do not show statistically significant associations between nitrate in water and cancer, the point estimates reported suggest that there may be a higher risk, with few exceptions. The evidence for the carcinogenicity of nitrate in animals remains inadequate (WHO, 2016).

Several reasons may explain the inconsistent findings and the uncertainty. The formation of NOCs from nitrate and nitrite depends on the microbiota composition, stomach acidity, and on the amount of nitrate, nitrite and nitrosamines ingested through diet and water (Carlstrom et al., 2020; Kobayashi, 2018). Diet is important also because antioxidants inhibit the formation of NOCs (Carlstrom et al., 2020; Kobayashi, 2018; Ward et al., 2005a) and should ideally be included in the analyses (Fan, 2019). The variability between individuals because of the above reasons may be wide, and the effect of nitrate and nitrite in water on vulnerable individuals may be diluted in studies without individual data (i.e. ecological studies), or if the number of vulnerable individuals is small the effect may be underestimated in cohort studies (Powlson et al., 2008). Differences in diets may also explain some of the contradictory findings for population subgroups in some of the included studies.

Our analysis confirmed the lack of association between nitrate in drinking water and the non-Hodgkin lymphoma as reported by a recent systematic review (Yu et al., 2020). Likewise, another systematic review did not find an association between nitrate in water and bladder cancer (Hosseini et al., 2020). A recent systematic review summarizing the evidence on the association between nitrate in water and cancer risks found a positive association only with the risk of colon cancer, and no association with gastric cancer, although there was an association with the median dose of nitrate (Essien et al., 2020). The discrepancy with our results may be due to several reasons. First, for gastric cancer we conducted the meta-analysis on case-control studies only. Second, our meta-analysis for colon cancer included only case-control and cohort studies. Although the point estimate in our study was very similar to that found by Essien et al. (2020), i.e. 1.17 vs 1.14 respectively, the 95% confidence interval in our analysis was wider, including the value of 1. Third, where the original studies provided rates stratified by quantiles, we estimated an overall rate across quantiles. This method avoids the need to run meta-analyses with data from categories with different scales and uses the information from intermediate quantiles that would be otherwise ignored.

Although a few individual studies have reported possible associations between nitrate in drinking water and brain cancer at specific levels of nitrate, as reviewed by Zumel-Marne et al. (2019), our meta-analysis showed no association.

The level of nitrate in municipal water reported in most of the included studies was below the WHO recommended limit of 50 mg/L, but we have very limited evidence of the levels in private wells, which may have higher levels of nitrate (IARC, 2010). Routine measurement of nitrate concentrations in private well water may be less common, so that the analyses were performed either on public water only, or the reference level for public water was used for well water. Well water can be an especially important source of drinking water and nitrate contamination in rural areas. In 2015, 13% of the population in the USA provided their own water, mostly from groundwater sources (Dieter et al., 2018). The concentration of nitrate in these sources varies with seasons (WHO, 2016), so it would be important to monitor these sources, especially in regions where the percentage of people collecting drinking water from wells or surface sources may be high.

We found only four studies on the health effect of nitrite contamination in water, and all of them showed a high level of uncertainty. Nitrite in solutions is an unstable molecule and is oxidized to nitrate, which may explain why nitrite concentration in drinking water is very low. The difficulty in detecting nitrite in drinking water may explain the low number of studies that included it. It is likely that nitrite in drinking water contributes negligibly to cancer development, unlike nitrite ingested through food which may a cancerogenic risk factor (IARC, 2010; IARC, 2015; Crowe et al., 2019).

4.3. Strength and limitations

This review employed a thorough and systematic search of eight databases to find relevant peer-reviewed studies, and use of an analysis method to estimate the continuous risk rate in papers that provided rates per quantiles only. This method avoids the comparison of rates from quantiles with different scales of nitrate concentration in water.

The main limitation of our conclusions is the number of studies available for some cancers, with 10 cancer types being investigated in less than five studies each. Additionally, because of the heterogeneous study designs and the unsuitability of combining these in a single analysis, five of our meta-analyses included just two studies. The limited number of studies per cancer type and study design meant that we did not fulfil at least one of the four conditions for reliably using asymmetry tests for publication bias, i.e. $\geq$ 10 studies (Ioannidis and Trikalinos, 2007), or a minimum of 10 studies per moderator to run a meta-regression (Deeks et al., 2019). Another limitation is the geographical locations of the studies, with most of them being carried out in the USA, Europe and Taiwan where nitrate levels in drinking water are generally low compared to many other settings. The absence of studies from Africa, Latin America, and very few studies from Asia and Australia, does not allow us to draw firm conclusions on the dose-outcome relationship or adequately predict the true impact of high nitrate levels that can be observed. We excluded papers without an abstract in English, potentially missing papers in other languages. Most studies did not take into account the intake of nitrate and nitrite from diet, which could be an important confounder given the association of red and processed meat consumption with the risk of developing several types of cancer, e.g. colorectal cancer (IARC, 2015). Regarding private well water, the evidence about the impact of nitrate was limited to few studies, direct measurements of its concentration of nitrate was rarely provided and the degree of uncertainty around the relative risks was generally high. We also bear in mind the potential for publication bias in that smaller studies with non-significant associations may not have been published in the peer-reviews literature of the 8 databases we searched.

Finally, only four studies investigated the exposure to nitrite in drinking water, possibly due to the difficulty of detecting it because of the low levels, making it difficult to reach a conclusion. Additionally, these studies had wide uncertainties around the estimates reported.

4.4. Further research needs and policy relevance

Our review of the evidence suggests a possible association of nitrate in drinking water and gastric cancer was derived studies were mostly conducted in high-income countries. However, the incidence rate of gastric cancer in Eastern Asia is more than three times higher than in Southern Europe, and six times higher than in Northern America (Sung et al., 2021). Incidence rates in Western Asia and South America are slightly higher than in Southern Europe (Sung et al., 2021). It is important to conduct more research in low- and middle-income countries where nitrogen-based fertilizers are frequently used in large quantities.

The use of fertilizers is often coupled with the use of herbicides and pesticides, which can also runoff into water bodies (Ryberg and Gilliom, 2015; Hansen et al., 2019; McKenzie et al., 2020). Very little is known about the effects on cancer risk of the interaction of nitrate and these other chemicals. Only two studies included in this review reported on the statistical interaction of nitrate and the herbicide atrazine. Rhoades et al. (2013) reported that nitrate or atrazine alone had no association with non-Hodgkin lymphoma, but exposure to both together was accompanied by a high risk of lymphoma (OR = 2.5; 95%CI = 1.0–6.2). An ecological study showed that children potentially exposed to nitrate and two herbicides may have a very high risk (crude OR = 7.56; 95%CI = 4.16–13.73) of developing one of the four cancer types studied in the paper (Thorpe and Shirmohammadi, 2005). Only three studies reported on the possible interaction of nitrate with disinfectant products like trihalomethanes and found no interaction (Jones et al., 2016, 2019; Quist et al., 2018). Thus, little is known about the possible interaction between nitrate, and its derivative N-nitrosamines, and disinfectant products in water (Diana et al., 2019). A few studies from Taiwan reported on the possible interaction of calcium and magnesium with nitrate. They found interactions between nitrate and calcium for rectal, colon and gastric cancers (Chang et al., 2010a; Chiu et al., 2011, 2012), and magnesium for colon, gastric and esophageal cancers (Chiu et al., 2010, 2012; Liao et al., 2013). There was no interaction of nitrate with magnesium for rectal and brain cancers (Weng et al., 2011; Chang et al., 2010a; Ho et al., 2011), and magnesium for brain cancer (Ho et al., 2011; Weng et al., 2011). Interaction with dietary factors such as meat consumption or vitamin C intake was investigated in 14 studies with mixed results. Because of the possible impact of hard water on health (Sengupta, 2013) and of diet on development of cancer (Key et al., 2020), more research is needed on these interactions in other countries. In general, a more consistent and homogeneous investigation of confounders would be beneficial.

Well-designed studies should also consider the timeframe of the exposure in relation to the time required to develop a particular cancer.

More evidence is needed on the impact of nitrate from private wells, which may be an important source of water in rural areas and may have a higher level of contamination compared to public water provided by municipalities.

In 2010, IARC concluded that "There is inadequate evidence in humans for the carcinogenicity of nitrate in drinking-water" (IARC, 2010). Over the past few years, the evidence of possible associations between nitrate in drinking water and risk of cancer to organs of the digestive apparatus has increased, but a firm conclusion is still not possible. Research using study designs that can establish a clear causality between exposure to nitrate and cancer and consider relevant confounders like diet should be prioritized, as well as research in regions where nitrate contamination in drinking water may be high because of increasing use of nitrogen-fertilizers.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.112988.

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