Archives of Environmental & Occupational Health

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/vaeh20

Drinking-water nitrate and cancer risk: A systematic review and meta-analysis

Eno E. Essien , Kassim Said Abasse , André Côté , Kassim Said Mohamed , Mirza Muhammad Faran Ashraf Baig , Murad Habib , Muhammad Naveed , Xiaojin Yu , Weihua Xie , Sun Jinfang & Muhammad Abbas

To cite this article: Eno E. Essien , Kassim Said Abasse , André Côté , Kassim Said Mohamed , Mirza Muhammad Faran Ashraf Baig , Murad Habib , Muhammad Naveed , Xiaojin Yu , Weihua Xie , Sun Jinfang & Muhammad Abbas (2020): Drinking-water nitrate and cancer risk: A systematic review and meta-analysis, Archives of Environmental & Occupational Health, DOI: 10.1080/19338244.2020.1842313

To link to this article: https://doi.org/10.1080/19338244.2020.1842313

ARCHIVES OF ENVIRONMENTAL & OCCUPATIONAL HEALTH
https://doi.org/10.1080/19338244.2020.1842313

Drinking-water nitrate and cancer risk: A systematic review and meta-analysis

Eno E. Essien[a], Kassim Said Abasse[b], André Côté[b], Kassim Said Mohamed[b], Mirza Muhammad Faran Ashraf Baig[c], Murad Habib[d], Muhammad Naveed[e], Xiaojin Yu[a], Weihua Xie[a], Sun Jinfang[a], and Muhammad Abbas[f]

[a]Key Laboratory of Environmental Medicine Engineering, Ministry of Education, Global Health, School of Public Health, Southeast University, Nanjing, China; [b]Département de Management, Centre de Recherche en Gestion des Services de Sante, Faculté des sciences de l'administration (FSA), Université Laval (UL), Centre Hospitalière Universitaire (CHU) de Québec UL-IUCPQ-UL, Québec, Canada; [c]State Key Laboratory of Analytical Chemistry for Life Sciences, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, China; [d]Ayub Department of Surgery, Ayub Medical College, Abbottabad, Pakistan; [e]Key Laboratory of Cardiovascular & Cerebrovascular Medicine, School of Pharmacy, Nanjing Medical University, Nanjing, China; [f]State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing, China

ABSTRACT

Background: Nitrate is an inorganic compound that occurs naturally in all surface and groundwater, although higher concentrations tend to occur only where fertilizers are used on the land. The regulatory limit for nitrate in public drinking water supplies was set to protect against infant methemoglobinemia, but other health effects were not considered. Risk of specific cancers and congenital disabilities may be increased when the nitrate is ingested, and nitrate is reduced to nitrite, which can react with amines and amides by nitrosation to form N-nitroso compounds which are known animal carcinogens. This study aims to evaluate the association between nitrate ingested through drinking water and the risk of developing cancers in humans.

Methods: We performed a systematic review following PRISMA and MOOSE guidelines. A literature search was performed using PubMed, EMBASE, the Cochrane Library databases, Web of Science and Google Scholars in the time-frame from their inception to January 2020, for potentially eligible publications. STATA version 12.0 was used to conduct meta-regression and a two-stage meta-analysis.

Results: A total of 48 articles with 13 different cancer sites were used for analysis. The meta-regression analysis showed stomach cancer had an association with the median dosage of nitrate from drinking water ($t = 3.98$, $p = 0.0001$, and adjusted R-squared = 50.61%), other types of cancers didn't show any association. The first stage of meta-analysis showed there was an association only between the risk of brain cancer & glioma (OR = 1.15, 95% CI: 1.06, 1.24) and colon cancer (OR = 1.11, 95% CI: 1.04, 1.17) and nitrate consumption in the analysis comparing the highest ORs versus the lowest. The 2nd stage showed there was an association only between the risk colon cancer (OR = 1.14, 95% CI: 1.04, 1.23) and nitrate consumption in the analysis comparing all combined higher ORs versus the lowest.

Conclusion: This study showed that there is an association between the intake of nitrate from drinking water and a type of cancer in humans. The effective way of controlling nitrate concentrations in drinking water is the prevention of contamination (water pollution). Further research work on this topic is needed.

ARTICLE HISTORY
Received 29 August 2020
Accepted 21 October 2020

KEYWORDS
Cancer; drinking water; meta-analysis; nitrates; nitrites; systematic review

Introduction

Clean water interventions are constantly implemented worldwide and include various methods boreholes, like rock catchments, springs, kiosks, boreholes, etc. The use of nitrogen fertilizers (inorganic and manure), in agriculture to produce food is becoming increasingly common.[1,2] A fraction of the nitrogen-based fertilizers is converted to plant matter and used up. The remainder accumulates in the soil or is lost as run-off.[3] The major anthropogenic source of nitrogen in the environment is nitrogen fertilizers, animal waste, organic manure, poor sewerage system, combined with the higher water solubility of nitrate leads to contaminate surface and groundwater, nitrate

CONTACT Kassim Said Abasse kassim.said-abasse@fsa.ulaval.ca; Muhammad Abbas tanoliabbas7@yahoo.com
Supplemental data for this article is available online at https://doi.org/10.1080/19338244.2020.1842313

concentrations in our water resources have also increased.[4–6]

People who live close to farms or agricultural plantation and get drinking water from household private wells may be highly exposed or at risk of ingesting nitrates than people who drink from public water supplies or bottled water.[1,7–9] The continuous consumption of such water in these high-risk areas may pose serious health issues in residents.

In the last twenty-eight years, several cohort and case-control studies have evaluated historical nitrate levels in a community or public water supplies, bottled water and private wells (significantly below 10 mg/l)[10,11] and risk of several cancers even though the standard maximum contaminant level in public drinking water in the United States (U.S) is 10 mg/L as nitrate-nitrogen (NO_3-N) which was put in place to protect children from infant methemoglobinemia.[1,12,13] A couple of studies have taken measurements of nitrate intake from public water supplies and have measured as low as 0.19 mg/l15[14] to as high as 75 mg/l values of nitrates in the water.[15,16] Another study conducted in India measured nitrate level in drinking water supplies from some villages ranged from 7.1 mg/l to 162 mg/l.[6] It has been noted that in some areas of the world they have to be records of nitrate level in drinking water which exceeded 100 mg/l10. That said, data on levels and exposures to people who gather water from private wells are still scarce or not available.[9]

Nitrates in water are a significant problem because exposures can contribute to cancer. Some epidemiologic studies have tried to find an association between nitrate, nitrite, and N-nitroso compounds (NOCs) from water and cancers.[7,13,17–24] Once nitrate (NO3−) is ingested through water, it is metabolizing to bioactive nitrite (NO2−) and circulated through the bloodstream in humans.[25] In the oral cavity, commensal facultative anaerobic bacteria can reduce nitrate to nitrite by action of nitrate reductase enzymes; this is known as entering salivary pathway.[26] The produced nitrite enters the gastrointestinal tract when swallowed.[25,27–29] Nitrite in the body can react with amines and amides by nitrosation to form NOCs, which are known animal carcinogens in experimental studies.[30] Nitrosamines are produced by chemical reactions of nitrates, nitrites and other proteins (amino acids) in the stomach. N-nitroso dimethylamine (NDMA) is one of the most frequently occurring nitrosamines in dietary foods.[23,31,32] Approximately 300 NOCs have been tested carcinogenicity in laboratory experimental.[33–35] NOCs likes NDMA and nitroso pyrrolidine (NPYR) has been proven by researches and experiments to be a known carcinogen capable of inducing malignant tumors in various animal species in a variety of tissues including pancreas, liver, lung, cervix and stomach.[4,9,36–40] Scholars have found positive association between N-nitroso dimethylamine intake and esophageal cancer in humans.[2,31,38,41–48] There is also supporting evidence for a role of NOCs in the cause of certain cancers such as gastric, esophageal, rectal and colon cancer in humans.[30,40,42]

Other confounding factors like alcohol intake, smoking, fat intake, obesity, vegetable intake, fruit intake, age, gender, race, average body mass index (BMI), hypertension, education, exercise frequency, and cancer in the family (a particular type of cancer or cancer in any part of the body) have been known in some way to increase or reduce the risk of cancers in humans and they are sometimes adjusted when risk ratios (RR), odds ratios (OR) and hazard ratios (HR) are calculated.[17,19,24,31,36,49–56] Few studies have tried to evaluate interactions between nitrate intake from drinking water with magnesium and calcium in the risk of cancer, but these studies showed no evidence of a significant interaction.[22,57–59] Epidemiologic studies have tried to establish a relationship between nitrate, nitrite and NOCs compounds and cancer in humans from different exposures. Results have been mixed, with some studies showing positive associations,[7,16,27,60] many showing no association,[12,31,59,61] and a few showing inverse associations for humans.[21,62] Therefore, this systematic review and meta-analysis were mainly conducted to assess and clarify the strength of association between nitrate ingested through drinking water and risk of cancer in the human body.

Methods

Search methods for identifications of studies

We performed a systematic review following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines.[63] The study investigated the association of nitrite or nitrate ingested through drinking water with the risk of cancers in the human body. Two investigators (ENO and Cote) independently searched PubMed, EMBASE, the Cochrane Library databases, the Web of Science and Google Scholars in the time-frame from their inception to January 2020, for potentially eligible publications. The core search terms of (nitrate* OR

nitrite* OR N-nitroso compounds) AND (cancer OR neoplasm* OR tumor* OR carcinoma OR carcinogenesis OR malignant OR adenocarcinoma OR non-Hodgkin lymphoma OR glioma) AND (drinking water) were used. The full search strategy is detailed in the online supplementary Appendix 1. References lists and related citations of relevant articles were reviewed to identify any new eligible studies.

Inclusion and exclusion criteria

After duplicate citations were excluded, the PICOS (Population, Intervention, Comparison Outcomes) criteria[63] were used to identify any potential studies. Studies that met the following criteria were included in the meta-analysis: (1) the study was either a cohort or ecological studies; (2) the exposure of interest was nitrate or nitrite intake from drinking water; (3) the study reported the relationship between nitrite or nitrate intake and the risk of cancer incidence or mortality; and (4) the study reporting effect (relative risks (RRs) or odds ratios (ORs)) estimates and 95% confidence intervals (CIs) for comparisons of various categories and the lowest nitrite or nitrate intake. Six authors (Kassim, Faran, Murad, Naveed, Xiaojin, Weihua, Sun) screened titles, abstracts and, where necessary, full text, to create a list of potentially relevant full text articles. Discrepant views were resolved by a group discussion to create the final list of included articles based on the refined eligibility criteria. Exclusion criteria comprised: (1) reviews, papers not published in English, those for which the abstract or full text were not available (2) all articles with animal experiments; (3) reported only qualitative data derived from structured questionnaires; (4) articles with short commentary, short notes, no data or no records or incomplete results and letters were excluded.

Data extraction and quality assessment

Data collection and quality assessment processes were performed by two authors (Kassim and Abbas), and any disagreement was settled by group discussion. The collected information included the first author's surname, publication year, study design, country, sample size, assessment of exposure (nitrite/nitrate intake mg/l) with the risk ratios (RR), odds ratios (OR) and hazard ratios (HR) and their 95% CIs for each category of exposure, cancer sites, and adjustment. The Newcastle–Ottawa Scale (NOS), based on selection (4 stars), comparability (2 stars), and outcome (3stars); was used to assess the quality of included studies in the analysis. Scores ranged from 0 to 9, studies with score ≥ 7 were seen as higher quality studies.[64]

Statistical analysis

The relationship between nitrite or nitrate intake and the risk of cancer were examined based on the effect estimate. All nitrate dosage, OR, RR, HR, with 95% CIs was extracted (both crude and adjusted OR, RR, HR,). The RRs and HRs were assumed to be the accurate estimates of ORs. The median intake of nitrate dosage was calculated from the range given, (formula = lowest dosage (lower limit) + highest dosage (upper limit) divided by 2 in each given quartile). When the median intake was given, the data was used directly. When the interval of a quartile of any category of nitrate dosage was not provided, the width of the class interval of quartile before this quartile was used to calculate and estimate the interval, (when the shortest or longest category was open-ended, the authors assumed that the open-ended interval length had the same length as the adjacent interval). Also, the logarithm of the ORs (Log OR) and standard error (SE) was calculated using Microsoft Office Excel. Mg/l was used as the standard unit for nitrate dosage from drinking water for meta-regression analysis because the majority of the selected studies have used this unit in their research.

Meta-regression analysis was conducted to figure out the associations between nitrate and nitrite exposure and cancer risk, and recognize a positive meta-regression coefficient ($p \leq 0.05$). The multiple categories of nitrite or nitrate intake within a single study were summarized into high or moderate nitrite/nitrate intake using a fixed-effects model. In contrast, the pooled results across included studies were evaluated using a random-effects model.[65,66] Heterogeneity test was performed using the I-square and Q-statistic, and significant heterogeneity was defined as $P < 0.010$.[67,68] A sensitivity analysis was conducted to assess the stability of the pooled results.[69]

Furthermore, any cancer site that had less than 3 studies was not included in the meta-regression. Two types of cancers that had similar sites or very close location in the human body were merged together for analysis (these included; brain cancer & glioma, ovarian cancer & uterus corpus). Publication biases for high or moderate nitrite/nitrate intake and the risk of cancer were evaluated using funnel plots, Egger test[70] and Begg test.[71] The inspective levels for pooled results are 2-sided, and p-values less than 0.05 were

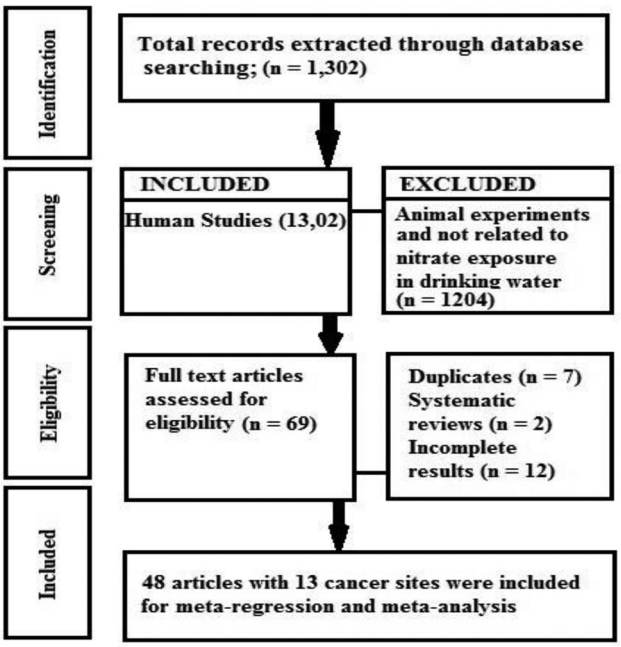


Figure 1. Flow chart of the studies selection.

regarded as statistically significant. Stata software was employed for all statistical analyses (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Selection of the studies

The total records identified through database searching are 1,302 articles, there were none from any other sources. Total records gotten after excluding articles that are not related to nitrate exposure from drinking water intake and cancer or that had animal experiments and included only human studies by evaluating titles and abstracts were 98 articles. Full-text articles assessed for eligibility were 69 articles. After excluding 22 articles because they didn't meet the inclusion criteria, 48 articles with 13 different cancer sites were used for quantitative analysis. The process of selection of studies can be seen in Figure 1.

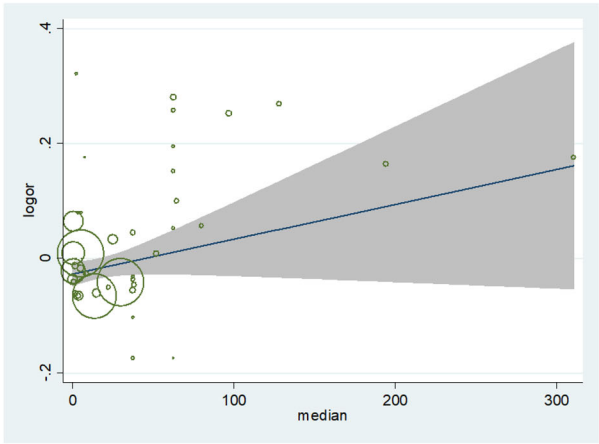
Meta-regression

The meta-regression analysis demonstrated the effect size of stomach cancer had a statistically significant association with the median dosage of nitrate from drinking water ($t = 3.98$, $p = 0.0001$, and adjusted R^2=50.61%; Figure 2a). There was no association between the effect size of reproductive organs (ovarian cancer and uterine corpus) and median dosage of nitrate in the meta-regression analysis, ($t = 1.55$, $p = 0.152$, and adjusted R^2=30.95%; Figure 2b). In the meta-regression for breast, brain & glioma, non-Hodgkin's lymphoma, pancreatic, esophageal, bladder, kidney, colon, and rectal cancer, there was no association between the risk of cancer and median dosage of nitrate from drinking water, because had very poor adjusted R-squared and p-value was greater than 0.05. A sensitivity analysis was conducted by removing one study after another and analyzed to see if it will yield different results or show a positive association, but it didn't (Table 1).

Meta-analysis

The first stage of meta-analysis showed that there was an evidence in the association between the risk of brain cancer & glioma (OR = 1.15, 95% CI: 1.06, 1.24) as shown in the Figure 3a & Table 2, and similarly with the colon cancer (OR = 1.11, 95% CI: 1.04, 1.17; **2**) and nitrate consumption in the analysis comparing the highest versus lowest category of dosage of nitrate consumption from drinking water, as shown in Figure 3b & Table 2. Little heterogeneity was observed (I^2 = 0.0%, $p = 0.551$ and I^2 = 37.3%, $p = 0.072$, respectively). There was no evidence in the association between the risk of cancer of the reproductive organs (ovary and uterine corpus) (OR = 1.57, 95% CI: 0.38, 2.76), with a large heterogeneity (I^2 = 77.1%, $p = 0.013$); breast cancer (OR = 1.06, 95% CI: 0.94, 1.17) with little or no heterogeneity (I^2 = 0.0%, $p = 0.739$); non-Hodgkin's lymphoma (OR = 0.98, 95% CI: 0.81, 1.16), with moderate heterogeneity (I^2 = 62.8%, $p = 0.004$); stomach cancer (OR = 1.09, 95% CI: 0.97, 1.21) with moderate heterogeneity (I^2 = 63.8%, $p = 0.001$); pancreatic cancer (OR = 1.08, 95% CI: 0.94, 1.22) with little or no heterogeneity (I^2 = 1.1%, $p = 0.386$); esophageal cancer (OR = 1.06, 95% CI: 0.99, 1.13) with little or no heterogeneity (I^2 = 0.0%, $p = 0.936$); bladder cancer (OR = 0.94, 95% CI: 0.70, 1.17) with moderate heterogeneity (I^2 = 69.3%, $p = 0.0001$); cancer of the kidney (OR = 1.03, 95% CI: 0.78, 1.28) with little heterogeneity (I^2 = 8.2%, $p = 0.352$) and rectal cancer (OR = 1.07, 95% CI: 0.86, 1.28) with a large heterogeneity (I^2 = 76.6%, $p = 0.0001$) and nitrate consumption in the analysis comparing the highest versus lowest category of dosage of nitrate consumption from drinking water, as reported in the Table 2.

The second stage of meta-analysis showed that there was an evidence in the association between the risk colon cancer (OR = 1.14, 95% CI: 1.04, 1.23) and nitrate consumption in the analysis comparing all combined higher dosages versus the lowest category

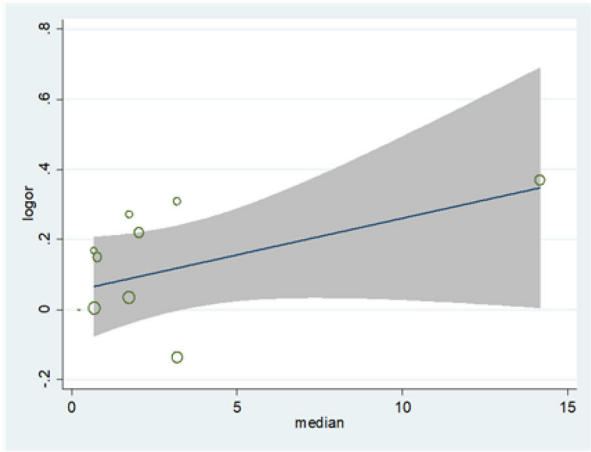



```
. metareg logor median, wsse(selogor) bsest(reml) graph

Meta-regression                                 Number of obs   =        47
REML estimate of between-study variance         tau2            =  .002086
% residual variation due to heterogeneity       I-squared_res   =  58.93%
Proportion of between-study variance explained  Adj R-squared   =  50.61%
With Knapp-Hartung modification

------------------------------------------------------------------------------
       logor |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      median |   .0010877   .0002736     3.98   0.000     .0005367    .0016387
       _cons |  -.0162263   .0150015    -1.08   0.285    -.0464409    .0139882
------------------------------------------------------------------------------
```

a) Stomach cancer




```
Meta-regression                                 Number of obs   =        12
REML estimate of between-study variance         tau2            =   .01106
% residual variation due to heterogeneity       I-squared_res   =  19.93%
Proportion of between-study variance explained  Adj R-squared   =  30.95%
With Knapp-Hartung modification

------------------------------------------------------------------------------
       logor |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      median |   .0197597   .0127577     1.55   0.152    -.0086662    .0481856
       _cons |   .0711925   .0666259     1.07   0.310    -.0772592    .2196441
------------------------------------------------------------------------------
```

b) Reproductive organs (Ovary and Uterine corpus)

Figure 2. Meta- regression; the association between the risk of logarithm ORs and median dosage of nitrate consumption from drinking water for each type of cancer.

of nitrate consumption from drinking water, as shown in the Figure 4 & Table 2. Moderate heterogeneity was observed (I^2 = 54.4%, p = 0.006). There was no evidence in the association between the risk of cancer of reproductive organs (ovarian cancer and uterine corpus) (OR = 1.38, 95% CI: 0.75, 2.01) with a large heterogeneity (I^2 = 80.6%, p = 0.006); breast cancer (OR = 1.00, 95% CI: 0.94, 1.06) with little or no heterogeneity (I^2 = 0.0%, p = 0.523); brain cancer & glioma (OR = 0.98, 95% CI: 0.80, 1.17) with moderate heterogeneity (I^2 = 64.4%, p = 0.010); non-Hodgkin's lymphoma (OR = 1.02, 95% CI: 0.90, 1.13) with moderate heterogeneity (I^2 = 65.0%, p = 0.002); stomach cancer (OR = 1.02, 95% CI: 0.94, 1.10) with moderate heterogeneity (I^2 = 65.2%, p = 0.000); pancreatic cancer (OR = 0.99, 95% CI: 0.77, 1.21) with a large heterogeneity (I^2 = 72.4%, p = 0.012); esophageal cancer (OR = 1.03, 95% CI: 0.99, 1.07) with little or no heterogeneity (I^2 = 0.0%, p = 0.631); bladder cancer (OR = 0.95, 95% CI: 0.78, 1.11) with a large heterogeneity (I^2 = 75.1%, p = 0.000); cancer of the kidney (OR = 0.99, 95% CI: 0.84, 1.13) with little or no heterogeneity (I^2 = 0.0%, p = 0.547); and rectal cancer (OR = 0.99, 95% CI: 0.81, 1.17) with a large heterogeneity (I^2 = 82.9%, p = 0.0001) and nitrate consumption in the analysis comparing all combined higher dosages versus the lowest category of nitrate consumption from drinking water. The remaining Figures are shown in the supplementary file Appendix 2 for the two stages.

Publication bias

Majority of the funnel plot didn't show asymmetry except the Egger's test showed statistical evidence of bias for stomach (p = 0.013) and rectal cancer (p = 0.017), as shown in Figure 5 & Table 2. The Begg's test didn't show any bias for stomach (p = 0.567) and rectal cancer (p = 0.080). Other cancers didn't show any bias in the two test, ovary & uterine corpus (Egger, p = 0.097; Begg, p = 0.297), breast (Egger, p = 0.217; Begg, p = 0.069), brain & glioma (Egger, p = 0.060; Begg, p = 0.284), non-Hodgkin's lymphoma (Egger, p = 0.370; Begg, p = 0.221), pancreatic (Egger, p = 0.595; Begg, p = 0.337), esophagus (Egger, p = 0.113; Begg, p = 0.216), bladder (Egger, p = 0.659; Begg, p = 0.568), kidney (Egger, p = 0.319; Begg, p = 0.464), and colon cancer (Egger, p = 0.766; Begg, p = 0.173). The remaining figures are shown in the supplementary file Appendix 2.

Table 1. Characteristics of the included studies from association nitrate (mg/l) intake from drinking water and cancer.

First Author, Year, Country	Study Design	Exposure Categories Nitrate intake mg/l)	Reported OR/RR/HR 95% CI	Cancer sites	Adjustment	NOS
Maki Inoue-Choi *et al,* 2015, USA[1]	Cohort study, from 1986 to 2010.	0.01–0.472 0.473–1.08 1.09–2.97 2.98–25.34	1 (Reference) 1.41 (0.82–2.41) 1.66 (1–2.76) 2.34 (1.42–3.84)	Ovary	Age-adjusted	8
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36 0.36–1 1.01–2.46 2.46–3.91	1 (Reference) 1.47 (0.73–2.98) 1.87 (0.95–3.68) 2.04 (1.05–3.96)	Ovary	Unadjusted	7
		0–0.36 0.36–1 1.01–2.46 2.46–3.91	1(Reference) 1.01 (0.66–1.52) 1.08 (0.72–1.63) 0.73 (0.46–1.15)	Uterine corpus		
* Maki Inoue-Choi *et al,* 2012, USA[3]	Prospective cohort study, from 1986 to 2008	0–1.4 1.5–3.95 4.0–7.05 7.15–16.65 16.75–72.65	1(Reference) 1.07 (0.89–1.28) 0.96 (0.80–1.16) 1.05 (0.88–1.27) 1.14 (0.95–1.36)	Breast	Age, total energy intake, BMI, WHR, education, smoking, physical activity level, alcohol intake, family history of breast cancer, education, smoking status, age at menopause, age at first live birth, estrogen use, total intake of folate, vitamin C and E intake and flavonoids, intake of cruciferae and red meat.	8
* Nadia Espejo-Herrera *et al,* 2016, Spain[4]	Multicase–Control study, from 2008 to 2013.	0–1.1 1.1–1.9 1.9–4.05 4.05–6.2	1 (Reference) 0.96 (0.77–1.19) 1.04 (0.8–1.31) 1.09 (0.83–1.43)	Breast	Study area, age and education	7
Julia Green Brody *et al,* 2006, USA[5]	Case-control study, from 1988–1995	0–0.3 0.3–0.6 0.6–0.9 0.9–1.2 1.2–1.5	1 (Reference) 1 (0.7–1.3) 0.9 (0.6–1.2) 0.9 (0.6–1.2) 0.9 (0.5–1.7)	Breast	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.	7
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36 0.36–1 1.01–2.46 2.46–3.91	1 (Reference) 1.01 (0.83–1.22) 0.9 (0.74–1.09) 1 (0.83–1.22)	Breast	Unadjusted	7
Jennifer Barrett et al, 1998, England[6]	Ecological study from 1975 to 1994.	2.4 5 13.7 29.8	1 (Reference) 1.14 (1.04–1.26) 1.13 (1.03–1.25) 1.18 (1.08–1.3)	Brain	Age and gender	6
Beth A. Mueller, *et al,* 2001, USA[7]	Case-control study from 1984 to 1991.	0 10–24.9 25–49.9 50–100	1 (Reference) 0.4 (0.1–1) 0.6 (0.2–2.4) 1.4 (0.1–15)	Brain	Child sex and child age	6
Beth A Mueller, *et al,* 2004, USA[8]	Case-control study from 1976 to 1994	0 10–25 25–50 50–75	1 (Reference) 0.7 (0.5–1.1) 0.5 (0.3–1.0) 0.8 (0.4–1.5)	Brain	Centre, age, sex and diagnosis year	7
Hsu-Huei Weng, *et al,* 2011, Taiwan[9]	Matched case-control study, from 1999 to 2008.	0–0.31 0.31–0.62	1 (Reference) 1.4 (1.07–1.84)	Brain	Age, gender, and urbanization level of residence.	8
Steindorf, K., *et al,* 1994, Germany[10]	Case-control study, from 1987 to 1988.	0–2 2–11.3 11.3–25.2 25.2–39.1	1(Reference) 0.99 (0.6–1.63) 1.12 (0.69–1.83) 1 (0.61–1.64)	Brain	Age, and sex.	7
Chi-Kung Ho, *et al,* 2011, Taiwan[11]	Case-control, from 2003 to 2008.	0–0.38 0.38–0.76	1(Reference) 1.04 (0.85–1.27)	Brain	Age, gender, marital status, and urbanization level of residence.	8
Mary H. Ward, *et al,* 2005, USA[12]	Case-control study from 1983 to 1994.	0–2.38 2.38–2.57 2.58–4.32 4.32–6.06	1 (Reference) 1.4 (0.7–2.7) 1.2 (0.6–2.3) 1.3 (0.7–2.6)	Glioma	Age, gender, respondent type, education, and ever live/work on a farm.	7
					Age, and gender	6

(*Continued*)

Table 1. Continued.

First Author, Year, Country	Study Design	Exposure Categories Nitrate intake mg/l)	Reported OR/RR/HR 95% CI	Cancer sites	Adjustment	NOS
Chih-Ching Chang, *et al,* 2010, Taiwan[13]	Case-control study from 2000 to 2006.	0–0.18 0.19–0.45 0.48–2.86	1 (Reference) 1.05 (0.89–1.23) 1.08 (0.91–1.27)	Non-hodgkin's lymphoma		
Michal Freedman, D., *et al,* 2000, USA[14]	Case-control study from 1947- 1982.	0–0.5 0.5–1.5 1.5–2.5	1 (Reference) 1.4 (0.7–2.5) 0.3 (0.1–0.9)	Non-hodgkin's lymphoma	Not described	6
Mary H. Ward, *et al,* 2006, USA[15]	Case-control study from 1998 to 2000.	0–0.63 0.63–1.36 1.37–2.89 2.9–4.42	1 (Reference) 0.9 (0.5–1.7) 0.8 (0.4–1.4) 0.9 (0.5–1.6)	Non-hodgkin's lymphoma	Age, education, and sex	7
* Mary H. Ward, *et al,* 1996, USA[16]	Case-control study, from 1950 to 1987.	0–1.25 1.25–1.95 2.0–3.1 3.15–4.25	1 (Reference) 1.5 (0.7–3.0) 1.6 (0.8–3.2) 1.9 (1.0–3.9)	Non-hodgkin's lymphoma	Age, gender, and family history of cancer.	7
Graham Law, *et al,* 1999, United Kingdom[17]	Population-based study, from 1984 to 1993.	0–3.24 3.24–14.85 14.85–26.46 0–3.24 3.24–14.85 14.85–26.46	1 (Reference) 1.17 (1.01–1.35) 1.21 (1.04–1.41) 1 (Reference) 1.069 (0.92–1.25) 0.917 (0.78–1.08)	Non-hodgkin's lymphoma	Not described	5
Gabriel Gulis, *et al,* 2002, Slovakia[18]	Ecologic study from 1985 – 1995.	0–10 10.1–20 20–29.9	0.36 (0.11–1.11) (Ref) 1.26 (0.82–1.93) 1.22 (0.76–1.96)	Non-hodgkin's lymphoma	Not described	6
P Cocco, *et al,* 2003, Italy[17]	Cohort study, from 1974 to 1993	0–2 2.01–3 3.01–4 4.01–5 5.01–7 7.01–10 10.01–15 15.01–26.64	1 (Reference) 1.13 (0.87–1.47) 1.21 (0.91–1.61) 1.15 (0.88–1.49) 1.01 (0.76–1.33) 1.4 (0.99–1.99) 1 (0.74–1.36) 1.32 (0.88–1.97)	Non-hodgkin's lymphoma	Not described	6
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36 0.36–1 1.01–2.46 2.46–3.91	1 (Reference) 0.88 (0.52–1.47) 0.75 (0.44–1.29) 0.78 (0.46–1.33)	Non-hodgkin's lymphoma	Not described	7
Martha G. Rhoades *et al,* 2013, USA[19]	Case-control study, from 1999 to 2002.	0–1.99 2–8	1(Reference) 0.9 (0.5–1.4)	Non-hodgkin's lymphoma	Age	6
Janos Sandor, *et al,* 2001, Hungary[20]	Ecological study, from 1980 to 1993.	5.58 22.26 38.19 51.98 64.61 79.95 97 127.94 194.16 310.64	1(Reference) 0.89 (0.56–1.43) 0.9 (0.6–1.35) 1.02 (0.7–1.49) 1.26 (0.81–1.97) 1.14 (0.69–1.87) 1.79 (1.26–2.55) 1.86 (1.18–2.93) 1.46 (0.96–2.23) 1.5 (0.95–2.37)	Stomach	Not described	6
* A. J. M. van Loon, *et al,* 1998, The Netherlands[21]	Cohort Study, from 1986 to 1992.	0.01 0.83 1.93 3.46 8.25	1(Reference) 0.91(0.62–1.34) 0.87 (0.59–1.28) 0.86 (0.59–1.27) 0.94 (0.64–1.38)	Stomach	Age, and sex.	6
John J. Rademacher, *et al,* 1992, USA[22]	Case-control study, from 1982 to 1985.	0–0.5 0.6–2.5 2.6–5 5.1–10	0.92 (0.75–1.12) (Ref) 0.97 (0.74–1.35) 0.86 (0.69–1.08) 1.5 (0.12–18.25)	Stomach	Not described	6
Hui-Fen Chiu, *et al,* 2012, Taiwan[23]	Case-control study, from 2006 to 2010.	0–0.38 0.38–0.76	1 (Reference) 1.16 (1.05–1.29)	Stomach	Age, gender, marital status, and urbanization level of residence.	6
Chun-Yuh Yang, *et al,* 1998, Taiwan[24]	Case-control study, from 1987 to 1991.	0–0.22 0.23–0.44 0.45–0.65	1 (Reference) 0.95 (0.87–1.03) 1.02 (0.93–1.11)	Stomach	Not described	6
Jennifer Barrett et al, 1998, England[6]	Ecological study, from 1975 to 1994.	2.4 5 13.7 29.8	1(Reference) 1.02(0.98–1.07) 0.86(0.82–0.9) 0.91(0.87–0.95)	Stomach	Age and gender	6
				Stomach	Not described	6

(*Continued*)

Table 1. Continued.

First Author, Year, Country	Study Design	Exposure Categories Nitrate intake mg/l)	Reported OR/RR/HR 95% CI	Cancer sites	Adjustment	NOS
Maria M. Morales-Suarez-Varela, *et al,* 1995, Spain[25]	Cross-sectional study, from 1975 to 1980.	25–50 50–75	0.93 (0.5–1.75) (Ref.) 1.57(0.75–3.3)			
		25–50 50–75	0.79 (0.32–1.91) (Ref.) 0.67 (0.17–2.67)			
			25–50 50–75 0.88 (0.64–1.23) (Ref) 1.91 (1.36–2.67) 25–50 50–75 1.11 (0.74–1.66) (Ref) 1.81 (1.15–2.87)			
25–50 50–75 25–50 50–75	0.67 (0.37–1.22)(Ref) 1.13 (0.56–2.27) 0.92 (0.57–1.49) (Ref) 1.42 (0.81–2.51)					
Gabriel Gulis, *et al,* 2002, Slovakia[18]	Ecologic study, from 1985 to 1995.	0–10 10.1–20 20–29.9	0.96 (0.71–1.3) (Ref) 0.87 (0.69–1.1) 1.08 (0.87–1.35)	Stomach	Not described	6
Mary H. Ward, *et al,* 2008, USA[26]	Case-control study, from 1965 to 1984	0–2.45 2.45–2.58 2.58–4.32 4.32–5.97	1 (Reference) 2.1 (1–4.4) 1.2 (0.5–2.6) 1.2 (0.5–2.7)	Stomach	Year of birth, gender, education, smoking, and alcohol.	6
Chun-Yuh Yang, *et al,* 2009, Taiwan[27]	Case-control study, from 2000 to 2006.	0–0.18 0.19–0.45 0.48–2.86	1(Reference) 1.05 (0.92–1.2) 1.13 (0.98–1.29)	Pancreas	Age and gender	6
Arbor J.L. Quist, *et al,* 2018, USA[28]	Cohort study, from 1986 to 2011.	0–0.47 0.47–1.08 1.09–2.97 2.98–5.69 5.69–8.4	1(Reference) 1.4 (0.88–2.24) 1.51 (0.96–2.37) 1.14 (0.67–1.93) 1.18 (0.52–2.67)	Pancreas	Age and smoking status	5
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36 0.36–1 1.01–2.46 2.46–3.91	1 (Reference) 0.77 (0.37–1.58) 1.2 (0.63–2.28) 0.65 (0.31–1.39)	Pancreas	Unadjusted	7
Angela Coss, *et al,* 2004, USA[29]	Case-control study, from 1960 to 1987.	0–0.6 0.6–1.3 1.3–2.8 2.8–4.3	1(Reference) 1.2 (0.79–1.8) 0.54 (0.33–0.89) 0.99 (0.64–1.5)	Pancreas	Age, gender, and cigarette use	6
Jennifer Barrett et al, 1998, England[6]	Ecological study, from 1975 to 1994.	2.4 5 13.7 29.8	1(Reference) 1.01 (0.93–1.09) 1.01 (0.94–1.09) 1.06 (0.98–1.14)	Esophagus	Age and gender	6
Yen-Hsiung Liao, *et al,* 2013, Taiwan[30]	Case-control study, from 2006 to 2010.	0–0.38 0.39–0.65 0.66–0.92	1(Reference) 0.99 (0.88–1.12) 1.04 (0.91–1.19)	Esophagus	Age, and gender	6
Mary H. Ward, *et al,* 2008, USA[26]	Case-control study, from 1965 to 1984	0–2.45 2.45–2.58 2.58–4.32 4.32–5.97	1(Reference) 2.1 (1–4.6) 1.2 (0.5–2.7) 1.2 (0.6–2.7)	Esophagus	Year of birth, gender, body mass index, smoking, and alcohol.	6
Maria M. Morales-Suarez-Varela, *et al,* 1995, Spain[25]	Cross-sectional study, from 1975 to 1980.	25–50 25–50 50–75 25–50 50–75	0.83 (0.2–3.41) 0.85 (0.52–1.37) (Ref) 1.4 (0.8–2.48) 0.69 (0.31–1.54) (Ref) 0.53 (0.14–2.07)	Bladder	Not described	6
Nadia Espejo-Herrera *et al,* 2015, Spain[31]	Case–Control study, from 1998 to 2001.	0–2.5 2.5–8 8–13.5 0–2.5 2.5–8 8–13.5	1(Reference) 0.84 (0.56–1.26) 0.66 (0.4–1.07) 1(Reference) 0.79 (0.54–1.17) 0.63 (0.39–1.03)	Bladder	Age, sex and area of residence	6
Hui-Fen Chiu, *et al,* 2007, Taiwan[32]	Case-control study, from 1999 to 2003.	0–0.18 0.19–0.45 0.48–2.86	1 (Reference) 1.75 (1.27–2.41) 1.96 (1.41–2.73)	Bladder	Age and gender	6
Rena R. Jones, *et al,* 2016, USA[33]	Cohort study from 1986 to 2010.	0–0.47 0.47–1.07	1 (Reference) 1.16 (0.7–1.91)	Bladder	Age	6

(*Continued*)

Table 1. Continued.

First Author, Year, Country	Study Design	Exposure Categories Nitrate intake mg/l)	Reported OR/RR/HR 95% CI	Cancer sites	Adjustment	NOS
		1.08–2.97	1 (0.6–1.67)			
		2.97–4.86	1.49 (0.92–2.41)			
* Maurice P. Zeegers, *et al,* 2006, Netherlands[34]	Cohort Study, from 1986 to 1995.	0–0.45	1 (Reference)	Bladder	Age, and sex	5
		0.45–1.2	0.86 (0.66–1.1)			
		1.2–2.2	1.1 (0.86–1.4)			
		2.2–3.85	1.05 (0.82–1.34)			
		3.85–46.35	1.11 (0.87–1.41)			
Mary H. Ward, *et al,* 2003, USA[35]	Case-control study from 1986 to 1989.	0–0.6	1 (Reference)	Bladder	Age, education, and cigarette smoking, years chlorinated surface water and study period	6
		0.6–1.4	0.9 (0.6–1.2)			
		1.4–3.09	0.8 (0.6–1.1)			
		3.09–4.78	0.5 (0.4–0.8)			
		0–0.67	1 (Reference)			
		0.67–1.18	0.7 (0.4–1.2)			
		1.18–2.48	0.6 (0.3–1.1)			
		2.48–3.78	0.8 (0.4–1.3)			
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36	1 (Reference)	Bladder	Unadjusted	7
		0.36–1	2.01 (0.81–4.98)			
		1.01–2.46	1.16 (0.42–3.19)			
		2.46–3.91	2.59 (1.08–6.21)			
Gabriel Gulis, *et al,* 2002, Slovakia[18]	Ecologic study from 1985 to 1995.	0–10	1.22 (0.9–1.64) (Ref)	Bladder	Not described	6
		10.1–20	1.01 (0.8–1.28)			
		20–29.9	0.93 (0.71–1.2)			
Mary H. Ward, *et al,* 2007, USA[36]	Case-control study, from 1986 to 1989.	0–0.62	1 (Reference)	Kidney	Age, gender, body mass index and average population size residences	6
		0.62–1.27	0.88 (0.56–1.38)			
		1.27–2.78	0.83 (0.53–1.3)			
		2.78–4.29	0.89 (0.57–1.39)			
Rena R. Jones, *et al,* 2017, USA[37]	Cohort study, from 1986 to 2010.	0–0.47	1 (Reference)	Kidney	Age, smoking status, pack-years of smoking, and body mass index.	6
		0.47–1.07	0.98 (0.58–1.7)			
		1.08–2.97	1.3 (0.81–2.1)			
		2.97–5	0.76 (0.41–1.4)			
		5–7.03	2.3 (1.2–4.3)			
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36	1 (Reference)	Kidney	Unadjusted	7
		0.36–1	1.23 (0.51–2.97)			
		1.01–2.46	1.46 (0.63–3.43)			
		2.46–3.91	1.35 (0.57–3.19)			
Gabriel Gulis, *et al,* 2002, Slovakia[18]	Ecologic study from 1985 to 1995.	0–10	0.81 (0.51–1.29) (Ref)	Kidney	Not described	6
		10.1–20	1.05 (0.78–1.4)			
		20–29.9	1.05 (0.77–1.44)			
Maria M. Morales-Suarez-Varela, et al, 1995, Spain[25]	Cross-sectional study, from 1975 to 1980.	25–50	1.3 (0.47–3.58)	Colon	Not described	6
		25–50	0.24 (0.04–1.49) (Ref)			
		50–75	1.05 (0.4–2.25)			
		25–50	0.98 (0.58–1.66) (Ref)			
		50–75	0.66 (0.25–1.75)			
		25–50	1.19 (0.74–1.9) (Ref)			
		50–75	1.15 (0.57–2.31)			
		25–50	0.65 (0.24–1.75) (Ref)			
		50–75	1.13 (0.36–3.53)			
		25–50	0.32 (0.11–0.95) (Ref)			
		50–75	0.94 (0.35–2.52)			
Anneclaire J. De Roos *et al,* 2003, USA[38]	Case-Control study, from 1986 to 1990	0–1	1 (Reference)	Colon	Age, sex, and chlorinated surface water.	7
		1–3	1 (0.8–1.3)			
		3–5	0.7 (0.4–1.1)			
		5–7	1.2 (0.8–1.7)			
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36	1 (Reference)	Colon	Unadjusted	7
		0.36–1	1.49 (1.07–2.08)			
		1.01–2.46	1.61 (1.16–2.24)			
		2.46–3.91	1.11(0.78–1.59)			
Nadia Espejo-Herrera *et al,* 2016, Spain[39]	Case-control study, from 2008 to 2013.	0–5	1 (Reference)	Colon	Sex, age, education, body mass index, physical activity, non-steroidal anti-inflammatories use, family history of colorectal cancer, intake of energy and oral contraceptives use.	7
		5–10	1.28 (1.06–1.55)			
		10–15	1.52 (1.24–1.86)			
Chun-Yuh Yang, *et al,* 2007, Taiwan[40]	Case-control study, from 1999 to 2003.	0–0.22	1 (Reference)	Colon	Age, and sex	6
		0.23–0.45	0.98 (0.85–1.12)			
		0.48–2.86	0.92 (0.79–1.06)			

(*Continued*)

Table 1. Continued.

First Author, Year, Country	Study Design	Exposure Categories Nitrate intake mg/l)	Reported OR/RR/HR 95% CI	Cancer sites	Adjustment	NOS
Jörg Schullehner, *et al,* 2018, Denmark[41]	Cohort study from 1978 to 2011.	9.25–14.63	1.15 (1.05–1.26)	Colon	Age, sex, year of birth and previous cancer diagnosis.	7
* Hui-Fen Chiu *et al,* 2010, Taiwan[42]	Case-control study, from 2003 to 2007	0–4.86 5.04–7.38 7.74–10.08	1 (Reference) 1.07 (0.94–1.2) 1.22 (1.01–1.36)	Colon	Age and gender	6
* Jane A. McElroy, *et al,* 2008, USA[43]	Case-control of two studies, from 1990 to 1992 and 1999–2001.	0–0.5 0.5–1.9 2–5.9 6–9.9 10–13.9 0–0.5 0.5–1.9 2–5.9 6–9.9 10–13.9	1 (Reference) 1.6 (1.05–2.43) 1.42 (0.96–2.11) 1.41 (0.85–2.37) 1.18 (0.57–2.44) 1 (Reference) 1.35 (0.82–2.24) 1.43 (0.91–2.27) 1.33 (0.73–2.44) 2.91 (1.52–5.56)	Colon	Age, and interview period.	6
Rena R. Jones, *et al,* 2019, USA[44]	Cohort study, from 1986 to 2010.	0–0.36 0.37–0.8 0.81–1.35 1.36–3.51 3.51–5.66	1 (Reference) 1.13 (0.88–1.45) 1.32 (1.03–1.69) 0.98 (0.76–1.27) 0.97 (0.75–1.26)	Colon	Age, physical activity, smoking status, and NO_3-N or TTHM	7
Anneclaire J. De Roos *et al,* 2003, USA[38]	Case-Control study, from 1986 to 1990	0–1 1–3 3–5 5–7	1 (Reference) 0.8 (0.6–1.1) 0.7 (0.5–1.2) 1.2 (0.8–1.8)	Rectum	Age, sex, and chlorinated surface water.	7
Peter J. Weyer, et al, 2001, USA[2]	Cohort study, from 1986 to 1998.	0–0.36 0.36–1 1.01–2.46 2.46–3.91	1 (Reference) 0.76 (0.45–1.28) 0.98 (0.61–1.6) 0.49 (0.27–0.89)	Rectum	Unadjusted	7
Nadia Espejo-Herrera *et al,* 2016 Spain[39]	Case-control study, from 2008 to 2013.	0–5 5–10 10–15	1 (Reference) 0.93 (0.7–1.23) 1.62 (1.23–2.14)	Rectum	Sex, age, education, body mass index, physical activity, non-steroidal anti-inflammatories use, family history of colorectal cancer, intake of energy and oral contraceptives use.	7
Hsin-Wei Kuo *et al,* 2007 Taiwan[45]	Case-control study, from 1999 to 2003	0–0.18 0.19–0.45 0.48–2.85	1 (Reference) 1.13 (0.92–1.39) 1.27 (1.04–1.56)	Rectum	Age, and gender	6
Jörg Schullehner *et al,* 2018 Denmark[41]	Cohort study, from 1978 to 2011.	3.87–9.25	1.17 (1.04–1.32)	Rectum	Age, sex, year of birth and previous cancer diagnosis.	7
Chih-Ching Chang *et al,* 2010 Taiwan[13]	Case-control study, from 2003 to 2007.	0–0.38 0.38–0.76	1 (Reference) 1.15 (1.01–1.32)	Rectum	Age, gender, marital status, and urbanization level of residence.	6
Rena R. Jones *et al,* 2019, USA[44]	Cohort study, from 1986 to 2010.	0–0.36 0.37–0.8 0.81–1.35 1.36–3.51 3.51–5.66	1 (Reference) 0.48 (0.28–0.84) 0.86 (0.53–1.38) 0.94 (0.6–1.48) 0.64 (0.38–1.07)	Rectum	Age, physical activity, smoking status, and NO_3-N or TTHM	7
* Jane A. McElroy, *et al,* 2008, USA[43]	Case-control of two studies, from 1990 to 1992 and 1999–2001.	0–0.5 0.5–1.9 2–5.9 6–9.9 10–13.9	1 (Reference) 1.32 (0.74–2.33) 1.21 (0.7–2.07) 1.03 (0.49–2.17) 1.14 (0.43–3.05)	Rectum	Age, and interview period.	6

Discussion

This is likely the first research work to evaluate the relationship between nitrate exposure from drinking water and all types of cancers using meta-regression and meta-analysis. In this systematic review, a total of 48 articles were used for quantitative analysis after proper selection. The meta-regression analysis showed there was an association between nitrate exposure from drinking water and stomach cancer ($p = 0.0001$). All other types of cancers didn't show any association even after the sensitivity analysis. The meta-analysis showed there was an evidence of the association between the risk of brain cancer & glioma (OR = 1.15, 95% CI: 1.06, 1.24), and colon cancer (OR =1.10, 95% CI: 1.03, 1.17), and nitrate consumption in the analysis comparing the highest versus the lowest category of dosage of nitrate consumption from drinking water, other types of cancers didn't show any

Table 2. Meta-analysis of pooled ORs (95% CI) of the highest versus lowest category & all combined higher versus the lowest category of nitrate consumption from drinking water for each type of cancer.

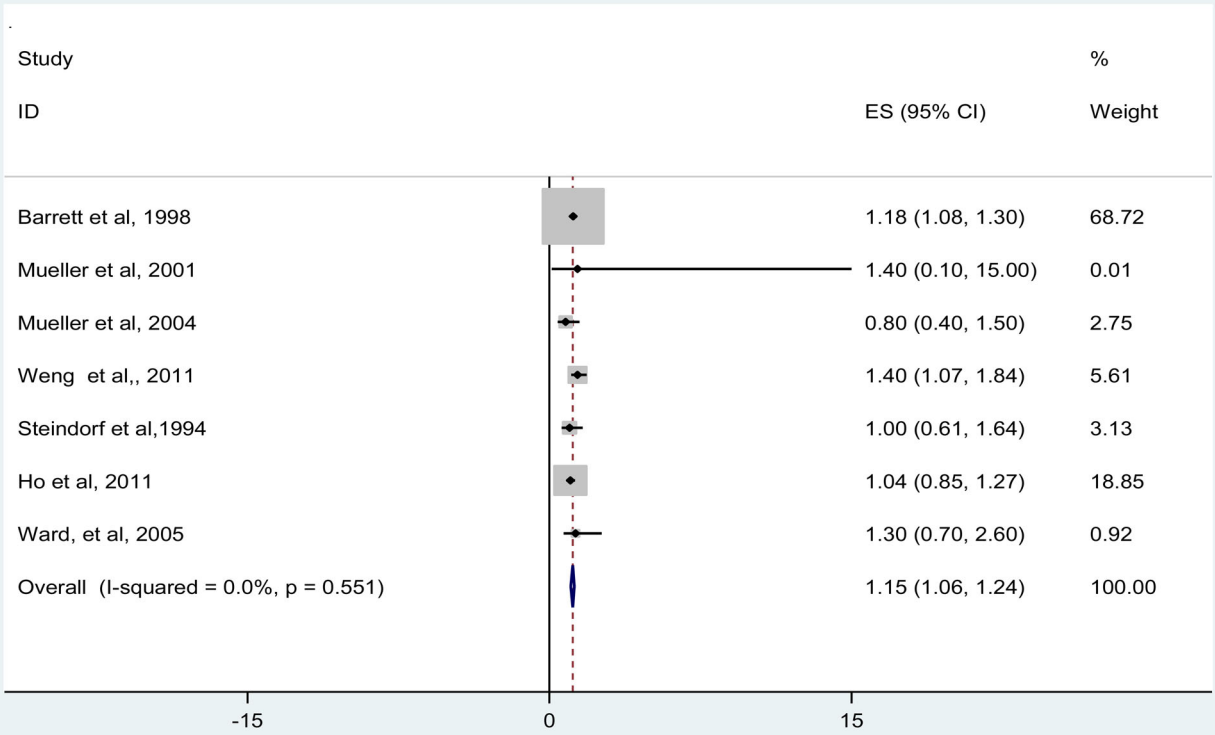
	highest versus the lowest		all combined higher versus the lowest		Publication Bias	
Cancer site	Pooled OR (95 % CI)	I-squared (I^2) and *p*-value	Pooled OR (95 % CI)	I-squared (I^2) and *p*-value	Egger's test *p*-value	Begg's test *p*-value
Ovary & Uterine corpus	1.57, (0.38, 2.76)	77.1%, p = 0.013	1.38, (0.75, 2.01)	80.6%, p = 0.006	0.097	0.297
Breast	1.06, (0.94, 1.19)	0.0%, p = 0.739	1.00, (0.94, 1.06)	0.0%, p = 0.523	0.217	0.069
Brain & Glioma	1.15, (1.06, 1.24)	0.0%, p = 0.551	0.94, (0.73, 1.15)	64.4%, p = 0.010	0.060	0.284
Non-Hodgkin's Lymphoma	0.98, (0.81, 1.16)	62.8%, p = 0.004	1.02, (0.90, 1.13)	65.0%, p = 0.002	0.370	0.221
Stomach	1.09, (0.97, 1.21)	63.8%, p = 0.001	1.02, (0.94, 1.10)	65.2%, p = 0.000	0.013	0.567
Pancreas	1.08, (0.94, 1.22)	1.1%, p = 0.386	0.99, (0.77, 1.21)	72.4%, p = 0.012	0.595	0.337
Esophagus	1.06, (0.99, 1.13)	0.0%, p = 0.936	1.03, (0.99, 1.07)	0.0%, p = 0.631	0.113	0.216
Bladder	0.94, (0.70, 1.17)	69.3%, p = 0.000	0.95, (0.78, 1.11)	75.1%, p = 0.000	0.659	0.568
Kidney	1.03, (0.78, 1.28)	8.2%, p = 0.352	0.99, (0.84, 1.13)	0.0%, p = 0.547	0.319	0.464
Colon	1.11, (1.04, 1.17)	37.3%, p = 0.072	1.14, (1.04, 1.23)	54.4%, p = 0.006	0.766	0.173
Rectum	1.07, (0.86, 1.28)	76.6%, p = 0.000	0.99, (0.81, 1.17)	82.9%, p = 0.000	0.017	0.080

I-squared (I^2), a statistic representing the amount of total variation attributed to heterogeneity; *p*-value of Cochran's Q test for heterogeneity.

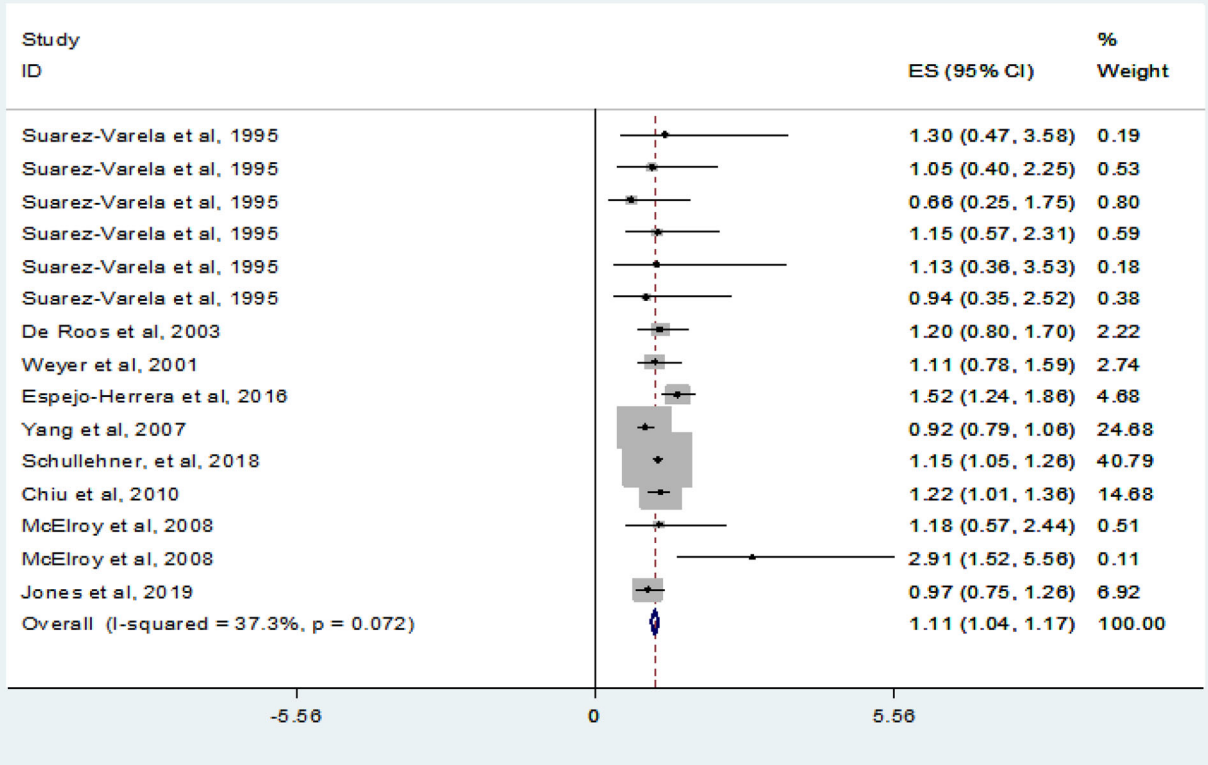
association. There was evidence of the association between the risk of colon cancer (OR = 1.14, 95% CI: 1.04, 1.23) and nitrate consumption in the analysis comparing all combined higher dosages versus the lowest category of nitrate consumption from drinking water, other types of cancers didn't show any association. Furthermore, the intake of nitrate/nitrite from drinking water for a while, can be associated with the possibility of getting a type of cancer in humans.

Different ranges of dosages of nitrates intake showed a relationship with the risk of having cancer. Weyer et al,[10] showed an association with nitrates intake as low as 0.36 to 1 mg/l and colon cancer in a cohort study, RR: 1.49 (95% CI: 1.07, 2.08) for women, between the ages of 55–69 years, while Morales-Suarez-Varela et al[15] showed an association at high nitrates intake level 50 to 75 mg/l and stomach cancer in a cross-sectional study, RR:1.91 (95% CI: 1.36–2.67); RR:1.81 (95% CI: 1.15–2.87) for males and females between the ages of 55–75 years respectively. It will be better if all studies can show the association with several different ranges of dosages of nitrates without so much gap or missing data for a better understanding. In some studies, researchers did not find any association between nitrate and cancer but some studies have tried to observe if the duration of exposure (number of years) combined with certain nitrate levels in drinking water showed a significant association or not (some articles have reported for 4 or 5 years and above). Ward et al[72] observed a positive association between nitrate concentrations level at $>$ 5 mg/l in public drinking water for $\geq$ 5 years and incident thyroid cancer (RR = 2.59, 95% CI = 1.09–6.19) but not for $\leq$4 years. A cohort study of postmenopausal women in Iowa from 1986 to 2011, who consumed water from public water supplies for 1 to 4 years to exposure levels $>1/2$ MCL, $>$5mg/l NO_3-N showed a significant positive association for pancreatic cancer (HR = 1.66, 95% CI = 1.22, 2.44) but it was not significant for $\geq$4 years.[39] This was completely contradictory with the case-control study on pancreatic cancer in Iowa, from 1960 – 1987, which showed no association for the few individuals exposed to community water supply with nitrate level at 7.5 mg/l and 10 mg/l for $>$4 years and $>$2 years respectively.[41] This is similar to a study done for adult glioma and year of using Nebraska public water supply with nitrate level at $\geq$ 5 and $\geq$ 10 mg/l from 1947 to 1984. There was no positive association between the number of years of exposure, including more 9 and 10 years.[73] All studies need to include the number of years of exposure together with nitrate levels, age, race, BMI, physical activity and gender to help with early diagnosis and detection of each type of cancer.

Other studies have tried to evaluate if the presence of calcium and magnesium in drinking water combined with nitrate intake can increase the risk of cancer. Liao et al[57] conducted a case-control study in Taiwan which showed no evidence of a significant interaction between drinking water nitrate and calcium (high and low) intake and esophageal cancer. The study also suggested individuals with the highest nitrate exposure (1.16 mg/l median intake) and low magnesium intake ($<$9.3 mg/l) have a 1.27 fold increased risk of esophageal cancer (OR= 1.27; 95% CI = 1.03–1.57), but those with the same nitrate exposure and high magnesium intake ($\geq$9.3 mg/l) showed no association. Chiu et al[74] conducted a case-control study in Taiwan which showed individuals with nitrate exposure (both high = $\geq$0.38 mg/l and low = $<$0.38 mg/l) and low calcium $<$34.6 mg/l intake from drinking water (OR: 1.70, 95% CI = 1.43–2.03) and (OR: 1.30, 95% CI = 1.11–1.52) respectively had a statistically significant risk of having gastric cancer. These results were also similar to that with nitrate exposure (both high = $\geq$0.38 mg/l, and low =



a) Brain cancer & Glioma



b) Colon Cancer

Figure 3. pooled ORs (95% CI) of the highest dosage versus lowest category of dosage of nitrate consumption from drinking water for each type of cancer.

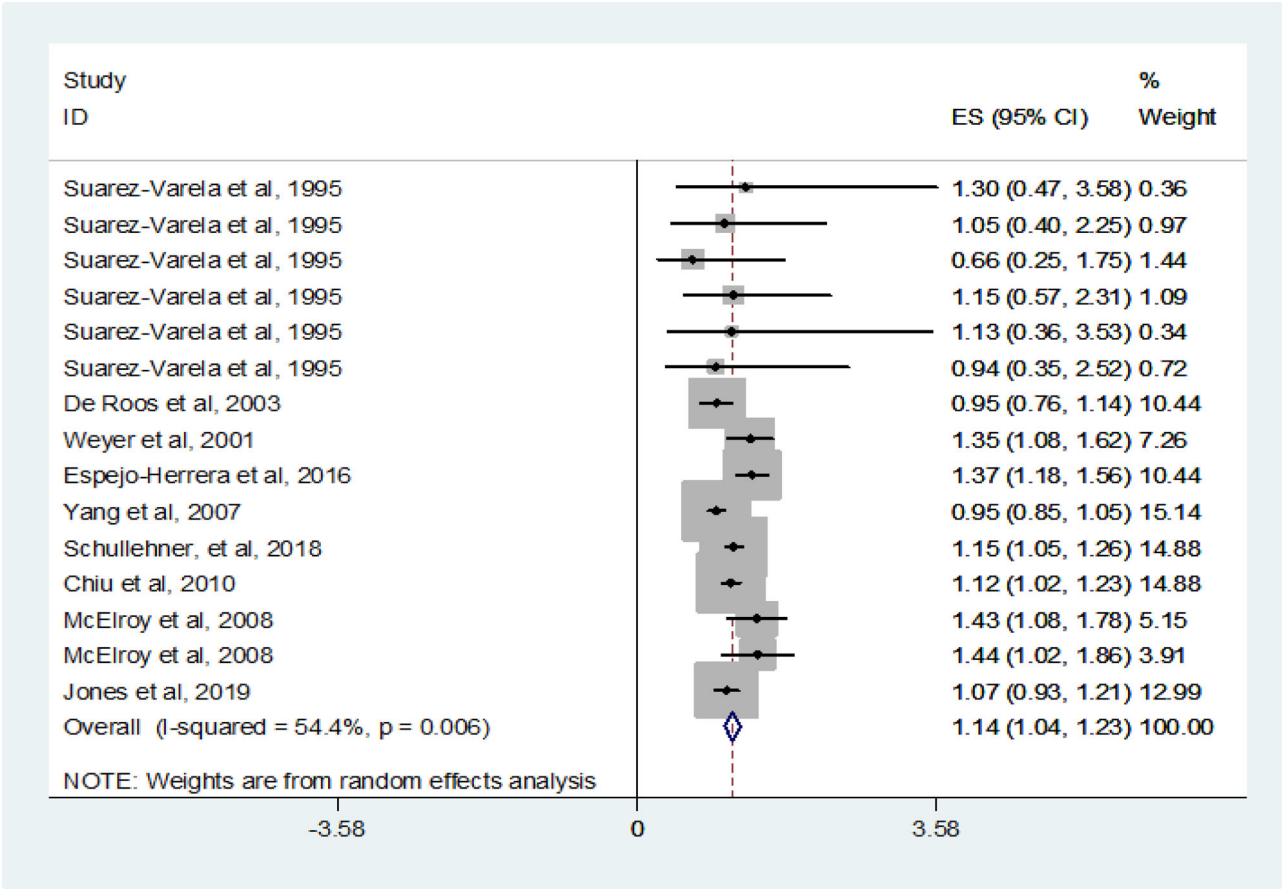
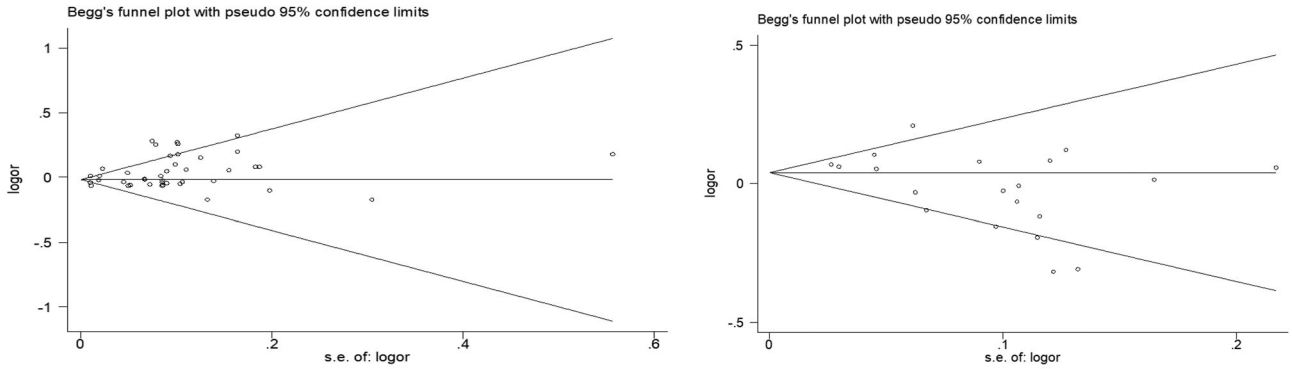


Figure 4. pooled ORs (95% CI) of all combined higher dosages versus the lowest category of nitrate consumption from drinking water for Colon Cancer.



a) Stomach cancer **b) Rectal Cancer**

Figure 5. Funnel plot of nitrates and **(a)** Stomach cancer risk; and **(b)** Rectal Cancer risk for publication bias.

<0.38 mg/l) and low magnesium intake (<9.3 mg/l), (OR: 1.49, 95% CI = 1.24–1.80) and (OR: 1.21, 95% CI = 1.02–1.43) respectively. A study done on nitrates in drinking water and the risk of death from brain cancer by Ho et al[22] showed the risk of adult brain cancer development with both high (≥ 0.38 mg/l) and low intake (<0.38 mg/l) of nitrate levels (OR: 1.43, 95% CI = 1.04–1.97) and (OR: 1.43, 95% CI = 1.07–1.92) respectively from drinking water was seen among individuals with lower calcium levels (<34.6 mg/l). There was no significant evidence of interaction of drinking water nitrate levels with and low magnesium intake (<9.3 mg/l). Further studies are needed to understand and control the intake of these chemical elements both from drinking water and food.

The combined effect with endogenous nitrosation factors and other dietary covariables with nitrate

intake from drinking water is extremely important in this kind of study to see if they can influence the outcome or not. It was seen in some cases people who take in high Vitamin C, high Vitamin E, folate intake, alpha-tocopherol and low intake of red meat (or any meat) while being exposed to nitrate at the same time had a lower risk of having cancer.[26,75] Ward et al[76] observed the highest ORs for distal stomach cancer among those with higher water nitrate ingestion and higher processed meat intake compared with low intakes of both; however, the test for interaction was not significant ($p = 0.213$). Espejo-Herrera et al[7] observed individual with high red meat intake (>29 g/day) together with high nitrate intake from drinking water (>4.4 mg/day) were at risk of getting colon cancer (OR = 1.66, 95% CI: 1.30, 2.12) compared to those who with low red meat intake together with high nitrate intake from drinking water. This result was the same for rectal cancer. Individuals with high vitamin C intake (>137 mg/day) together with high nitrate intake from drinking water (>4.4 mg/day) were not at risk of getting colon cancer (OR = 0.92, 95% CI: 0.73, 1.15) compared to those who with low vitamin C intake together with high nitrate intake from drinking water (OR = 1.36, 95% CI: 1.08, 1.71). These results were similar to the analysis for vitamin E and fiber for colon cancer. This result wasn't the same for rectal cancer, ORs were low for all the combination (both for vitamin C E, and fiber). Inoue-Choi et al[12] observed in a large prospective cohort study among women with adequate or higher total folate intake (≥400 μg/d), breast cancer risk was statistically significantly increased among those using public water with the highest quintile of (HR = 1.40, 95%CI = 1.05–1.87) and private well users (HR = 1.38, 95%CI = 1.05– 1.82) compared to public water users with the lowest nitrate quintile; in contrast, there was no association among those with lower folate intake. Many studies didn't show any analysis about the joint effect with endogenous nitrosation factors and other dietary covariables when studying nitrate intake. Further studies need to add this analysis so that it can be better understood in a larger population to see if these factors can be protective factors against cancer since some results are contradictory.

Cancer of different parts of the digestive system (stomach, gastric, bladder, colon, and rectum) had the highest number of studies and showed more risk compared to other types of cancer. Majority of these studies were done in Europe and the U.S., with reported nitrate levels from private wells, and community or public drinking water supply. Very few or no studies have been conducted in other countries, especially in South America, Africa, Australia and Asia. A proper and comprehensive assessment of nitrate and even nitrite from drinking water including bottled water and private wells as well as confounders, including inhibitors of endogenous nitrosation, and intakes of antioxidants are needed in future studies. Many studies lacked information about study participants' water consumption from bottled water and private wells, which may be an essential determinant of exposure to drinking water contaminants.[22] Future studies should also pay close attention to the different duration or length (years) of usage from various sources of drinking water with nitrate or nitrite levels, especially to understand the effects from the duration of exposure. There is still no precise standard maximum contaminant level for nitrate-nitrogen (NO_3-N) in drinking water put in place to protect people from non-communicable diseases like cancer. This might be because, non-communicable diseases like cancer can take a long time to occur and the casualty hasn't yet been fully established, significantly since other factors can increase or reduce the risk of having said disease. Few articles have tried to find the association between the nitrate from drinking water, and thyroid cancer, prostate cancer, lung and bronchus cancer, cancer of other parts of the digestive tract, skin cancer (melanoma), leukemia, nasophargeal carcinoma, and cancer in the neck region with epidemiological studies of humans.

Limitations of this study

Using two different statistical analysis for each cancer sites is the strength of this research work, and it can help to understand the association better using other methods and see if the results will be same or not. However, the limitations of the study are followed; first, only very few articles were available for each type of cancer, some with 3 or fewer studies, and so the results for this analysis should be treated with caution. More detailed, well-designed studies with accurate and precise information about study participants' water consumption, which may be an essential determinant of exposure to drinking water contaminants is needed to show a true association. Secondly, this research work couldn't evaluate if other confounders could affect the outcome of the disease. Pertinent details, records of analysis of the intake of other compounds (especially the dosage) or nutrients, from food and drinking water which could affect the process of nitrosation in the body should be added and shown in all studies. Thirdly, there was a wide range of

dosage of nitrate intake values from different studies for the lowest and highest categories and also incomplete results (especially for private wells) which might pose an issue for the meta-regression analysis or to conduct dose-response analysis. At the same time this might pose a problem to set a limit or precise standard maximum contaminant level put in place to protect people from having cancer.

Conclusion

In summary, the results from the meta-regression and meta-analysis showed that there is an association between nitrate from drinking water and a type of cancer. Even though pollution (especially water pollution) is a severe problem around the world today, not so much work and research has been done between the exposure of nitrates and nitrites from drinking water and risk of getting different types of cancers. The most appropriate means of controlling nitrate concentrations particularly in groundwater is the prevention of contamination. This means forms of proper management of agricultural practices should be encouraged, the careful siting of pit latrines and septic tanks, sewer leakage control, as well as management of fertilizer and manure application and storage of animal manures.

A lot of well-designed and large-sample epidemiological studies (especially cohort studies) in different parts of the world are essential to clarify better, understand, and interpret the association between nitrate or nitrite consumption from drinking water and the risk of cancer in humans.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Muhammad Naveed http://orcid.org/0000-0002-2193-9266

References

1. Ward MH, Jones RR, Brender JD, et al. Drinking water nitrate and human health: an updated review. *IJERPH*. 2018;15(7):1557.
2. Beyer CH, Bergfeld WF, Berndt WO, et al. Final report on the safety assessment of triethanolamine, diethanolamine, and monoethanolamine. *J Am Coll Toxicol*. 1983;2(7):183–235.
3. Callisto M, Molozzi J, Barbosa JLE. Eutrophication of lakes. In: *Eutrophication: Causes, Consequences and Control*. Dordrecht: Springer; 2014:55–71.
4. Rosen CJ, Horgan B. *Preventing Pollution Problems from Lawn and Garden Fertilizers*. USA: Minnesota Extension Service; 2005.
5. Sekhon G. Fertilizer-N use efficiency and nitrate pollution of groundwater in developing countries. *J Contam Hydrol*. 1995;20(3–4):167–184.
6. Suthar S, Bishnoi P, Singh S, Mutiyar PK, Nema AK, Patil NS. Nitrate contamination in groundwater of some rural areas of Rajasthan, India. *J Hazard Mater*. 2009;171(1–3):189–199. doi:10.1016/j.jhazmat.2009.05.111.
7. Espejo-Herrera N, Gràcia-Lavedan E, Boldo E, et al. Colorectal cancer risk and nitrate exposure through drinking water and diet. *Int J Cancer*. 2016;139(2):334–346. doi:10.1002/ijc.30083.
8. Rhoades MG, Meza JL, Beseler CL, et al. Atrazine and nitrate in public drinking water supplies and non-Hodgkin lymphoma in Nebraska, USA. *Environ Health Insights*. 2013;7:S10629.
9. Sandor J, Kiss I, Farkas O, Ember I. Association between gastric cancer mortality and nitrate content of drinking water: ecological study on small area inequalities. *Eur J Epidemiol*. 2001;17(5):443–447. doi:10.1023/A:1013765016742.
10. Weyer PJ, Cerhan JR, Kross BC, et al. Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study. *Epidemiology*. 2001;12(3):327–338.
11. Jones RR, Weyer PJ, DellaValle CT, et al. Ingested nitrate, disinfection by-products, and kidney cancer risk in older women. *Epidemiology (Cambridge, Mass.)*. 2017;28(5):703.
12. Inoue-Choi M, Ward MH, Cerhan JR, Weyer PJ, Anderson KE, Robien K. Interaction of nitrate and folate on the risk of breast cancer among postmenopausal women. *Nutr Cancer*. 2012;64(5):685–694. doi:10.1080/01635581.2012.687427.
13. Inoue-Choi M, Jones RR, Anderson KE, et al. Nitrate and nitrite ingestion and risk of ovarian cancer among postmenopausal women in Iowa. *Int J Cancer*. 2015;137(1):173–182.
14. Yang C-Y, Tsai S-S, Chiu H-F. Nitrate in drinking water and risk of death from pancreatic cancer in Taiwan. *J Toxicol Environ Health A*. 2009;72(6):397–401. doi:10.1080/15287390802647229.
15. Morales-Suarez-Varela MM, Llopis-Gonzalez A, Tejerizo-Perez ML. Impact of nitrates in drinking water on cancer mortality in Valencia, Spain. *Eur J Epidemiol*. 1995;11(1):15–21. doi:10.1007/BF01719941.
16. Fathmawati Fachiroh J, Gravitiani E, Sarto Husodo AH. Nitrate in drinking water and risk of colorectal cancer in Yogyakarta, Indonesia. *J Toxicol Environ Health, Part A*. 2017;80(2):120–128. doi:10.1080/15287394.2016.1260508.
17. Cross AJ, Freedman ND, Ren J, et al. Meat consumption and risk of esophageal and gastric cancer in a large prospective study. *Am J Gastroenterol*. 2011;106(3):432.
18. De Roos AJ, Ward MH, Lynch CF, Cantor KP. Nitrate in public water supplies and the risk of colon and rectum cancers. *Epidemiology*. 2003;14(6):640–649.
19. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. *J*

Natl Cancer Inst. 2003;95(18):1404–1413. doi:10.1093/jnci/djg047.
20. Espejo-Herrera N, Gracia-Lavedan E, Pollan M, et al. Ingested nitrate and breast cancer in the Spanish Multicase-Control Study on Cancer (MCC-Spain). *Environ Health Perspect*. 2016;124(7):1042–1049.
21. Gulis G, Czompolyova M, Cerhan JR. An ecologic study of nitrate in municipal drinking water and cancer incidence in Trnava District, Slovakia. *Environ Res*. 2002;88(3):182–187.
22. Ho C-K, Yang Y-H, Yang C-Y. Nitrates in drinking water and the risk of death from brain cancer: does hardness in drinking water matter? *J Toxicol Environ Health, Part A*. 2011;74(12):747–756.
23. Jakszyn P, Agudo A, Berenguer A, et al. Intake and food sources of nitrites and N-nitrosodimethylamine in Spain. *Public Health Nutr*. 2006;9(6):785–791.
24. Kilfoy BA, Zhang Y, Park Y, et al. Dietary nitrate and nitrite and the risk of thyroid cancer in the NIH-AARP Diet and Health Study. *Int J Cancer*. 2011;129(1):160–172.
25. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nat Rev Drug Discov*. 2008;7(2):156–167. doi:10.1038/nrd2466.
26. Jones RR, Weyer PJ, DellaValle CT, et al. Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. *Environ Health Perspect*. 2016;124(11):1751–1758. doi:10.1289/EHP191.
27. Hyde ER, Andrade F, Vaksman Z, et al. Metagenomic analysis of nitrate-reducing bacteria in the oral cavity: implications for nitric oxide homeostasis. *PLoS One*. 2014;9(3):e88645. doi:10.1371/journal.pone.0088645.
28. Duncan C, Dougall H, Johnston P, et al. Chemical generation of nitric oxide in the mouth from the enterosalivary circulation of dietary nitrate. *Nat Med*. 1995;1(6):546–551.
29. Li H, Duncan C, Townend J, et al. Nitrate-reducing bacteria on rat tongues. *Appl Environ Microbiol*. 1997;63(3):924–930. doi:10.1128/AEM.63.3.924-930.1997.
30. Mirvish SS. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. *Cancer Lett*. 1995;93(1):17–48. doi:10.1016/0304-3835(95)03786-V.
31. Keszei AP, Goldbohm RA, Schouten LJ, Jakszyn P, van den Brandt PA. Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. *Am J Clin Nutr*. 2013;97(1):135–146. doi:10.3945/ajcn.112.043885.
32. Tricker A, Pfundstein B, Theobald E, Preussmann R, Spiegelhalder B. Mean daily intake of volatile N-nitrosamines from foods and beverages in West Germany in 1989–1990. *Food Chem Toxicol*. 1991;29(11):729–732.
33. Cooper CS, Grover PL. *Chemical Carcinogenesis and Mutagenesis II*. Berlin, Heidelberg: Springer; 1990.
34. Lijinsky W. In vivo testing for carcinogenicity. In: *Chemical Carcinogenesis and Mutagenesis I*. Berlin, Heidelberg: Springer; 1990:179–209.
35. Schoental R, Magee P. Induction of squamous carcinoma of the lung and of the stomach and oesophagus by diazomethane and N-methyl-N-nitroso-urethane, respectively. *Br J Cancer*. 1962;16(1):92–100. doi:10.1038/bjc.1962.9.
36. Palli D, Russo A, Decarli A. Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy. *Cancer Causes Control*. 2001;12(2):163–172.
37. Pobel D, Riboli E, Cornée J, Hémon B, Guyader M. Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case-control study in Marseille, France. *Eur J Epidemiol*. 1995;11(1):67–73. doi:10.1007/BF01719947.
38. Pour PM, Runge RG, Birt D, et al. Current knowledge of pancreatic carcinogenesis in the hamster and its relevance to the human disease. *Cancer*. 1981;47(S6):1573–1587.
39. Quist AJ, Inoue-Choi M, Weyer PJ, et al. Ingested nitrate and nitrite, disinfection by-products, and pancreatic cancer risk in postmenopausal women. *Int J Cancer*. 2018;142(2):251–261. doi:10.1002/ijc.31055.
40. Schullehner J, Hansen B, Thygesen M, Pedersen CB, Sigsgaard T. Nitrate in drinking water and colorectal cancer risk: A nationwide population-based cohort study. *Int J Cancer*. 2018;143(1):73–79. doi:10.1002/ijc.31306.
41. Coss A, Cantor KP, Reif JS, Lynch CF, Ward MH. Pancreatic cancer and drinking water and dietary sources of nitrate and nitrite. *Am J Epidemiol*. 2004;159(7):693–701. doi:10.1093/aje/kwh081.
42. Tricker A, Preussmann R. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. *Mutat Res Genet Toxicol*. 1991;259(3–4):277–289.
43. Anderson LM, Souliotis VL, Chhabra SK, Moskal TJ, Harbaugh SD, Kyrtopoulos SA. N-nitrosodimethylamine-derived O6-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol. *Int J Cancer*. 1996;66(1):130–134.
44. Bogovski P, Bogovski S. Animal Species in which N-nitroso compounds induce cancer. *Int J Cancer*. 1981;27(4):471–474. doi:10.1002/ijc.2910270408.
45. Carmella SG, Han S, Fristad A, Yang Y, Hecht SS. Analysis of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. *Cancer Epidemiol Prev Biomarkers*. 2003;12(11):1257–1261.
46. Baris D, Waddell R, Beane Freeman LE, et al. Elevated bladder cancer in Northern New England: the role of drinking water and arsenic. *JNCI: J National Cancer Institute*. 2016;108(9):1–9.
47. Burnett CL, Bergfeld WF, Belsito DV, et al. Final amended report on the safety assessment of ammonium thioglycolate, butyl thioglycolate, calcium thioglycolate, ethanolamine thioglycolate, ethyl thioglycolate, glyceryl thioglycolate, isooctyl thioglycolate, isopropyl thioglycolate, magnesium thioglycolate, methyl thioglycolate, potassium thioglycolate, sodium thioglycolate, and thioglycolic acid. *Int J Toxicol*. 2009;28(4 Suppl):68–133. doi:10.1177/1091581809339890.
48. Xie L, Li J, Zhang Y, et al. Inhibitors of differentiation-1 promotes nitrosopyrrolidine-induced transformation of HPV 16-immortalized cervical epithelial cell. *Cancer Sci*. 2014;105(5):506–511. doi:10.1111/cas.12398.
49. Ward MH, Rusiecki JA, Lynch CF, Cantor KP. Nitrate in public water supplies and the risk of renal

cell carcinoma. *Cancer Causes Control*. 2007;18(10): 1141–1151. doi:10.1007/s10552-007-9053-1.
50. Abbas M, Kassim SA, Wang ZC, Shi M, Hu Y, Zhu HL. Clinical evaluation of plasma coagulation parameters in patients with advanced-stage non-small cell lung cancer treated with palliative chemotherapy in China. *Int J Clin Pract*. 2020;e13619.
51. Abbas M, Kassim SA, Habib M, et al. Clinical evaluation of serum tumor markers in patients with advanced-stage non-small cell lung cancer treated with palliative chemotherapy in China. *Front Oncol*. 2020;10:800.
52. Kassim SA, Tang W, Abbas M, et al. Clinicopathologic and epidemiological characteristics of prognostic factors in post-surgical survival of colorectal cancer patients in Jiangsu Province, China. *Cancer Epidemiol*. 2019;62:101565.
53. Kassim SA, Abbas M, Tang W, et al. Retrospective study on melanosis coli as risk factor of colorectal neoplasm: a 3-year colonoscopic finding in Zhuhai Hospital, China. *Int J Colorectal Dis*. 2020;35(2): 213–222. doi:10.1007/s00384-019-03435-7.
54. Li X, Abbas M, Li Y, et al. Comparative effectiveness of pemetrexed-platinum doublet chemotherapy with or without bevacizumab as first-line therapy for treatment-naive patients with advanced nonsquamous non-small-cell lung cancer in China. *Clin Ther*. 2019; 41(3):518–529. doi:10.1016/j.clinthera.2019.02.004.
55. Li X, Zhao X, Abbas M, et al. Comparative effectiveness study of single high-dose cisplatin with fractionated doses cisplatin in first-line therapy for treatment-naive Chinese patients with advanced non–small-cell lung cancer. *Curr Problems Cancer*. 2019;43(6):100466.
56. Abbas M, Ahmed A, Khan GJ, et al. Clinical evaluation of carcinoembryonic and carbohydrate antigens as cancer biomarkers to monitor palliative chemotherapy in advanced stage gastric cancer. *Curr Probl Cancer*. 2019;43(1):5–17. doi:10.1016/j.currprobl-cancer.2018.08.003.
57. Liao Y-H, Chen P-S, Chiu H-F, Yang C-Y. Magnesium in drinking water modifies the association between nitrate ingestion and risk of death from esophageal cancer. *J Toxicol Environ Health A*. 2013; 76(3):192–200. doi:10.1080/15287394.2013.752324.
58. Weng H-H, Tsai S-S, Wu T-N, Sung F-C, Yang C-Y. Nitrates in drinking water and the risk of death from childhood brain tumors in Taiwan. *J Toxicol Environ Health A*. 2011;74(12):769–778. doi:10.1080/15287394.2011.567951.
59. Vecchia Ferraroni LC, D'Avanzo M, Decarli B, Franceschi AS. Selected micronutrient intake and the risk of gastric cancer. *Cancer Epidemiol Prev Biomarkers*. 1994;3(5):393–398.
60. Espejo-Herrera N, Cantor KP, Malats N, et al. Nitrate in drinking water and bladder cancer risk in Spain. *Environ Res*. 2015;137:299–307. doi:10.1016/j.envres.2014.10.034.
61. Kor YY, Prabhu J, Esposito M. How large food retailers can help solve the food waste crisis. *Harvard Business Review*. December 19, 2017.
62. Freedman DM, Cantor KP, Ward MH, Helzlsouer KJ. A case-control study of nitrate in drinking water and non-Hodgkin's lymphoma in Minnesota. *Arch Environ Health*. 2000;55(5):326–329. doi:10.1080/00039890009604024.
63. Asar S, Jalalpour S, Ayoubi F, Rahmani M, Rezaeian M. PRISMA; preferred reporting items for systematic reviews and meta-analyses. *J Rafsanjan Univ Med Sci*. 2016;15(1):68–80.
64. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010; 25(9):603–605. doi:10.1007/s10654-010-9491-z.
65. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45(Pt A): 139–145. doi:10.1016/j.cct.2015.09.002.
66. Ades A, Lu G, Higgins J. The interpretation of random-effects meta-analysis in decision models. *Med Decis Making*. 2005;25(6):646–654. doi:10.1177/0272989X05282643.
67. Deeks JJ, Higgins JP, Altman DG, Group CSM. Analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. UK: Wiley; 2019:241–284.
68. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327(7414):557–560. doi:10.1136/bmj.327.7414.557.
69. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11(2): 193–206. doi:10.1037/1082-989X.11.2.193.
70. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634. doi:10.1136/bmj.315.7109.629.
71. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088–1101.
72. Ward MH, Kilfoy BA, Weyer PJ, Anderson KE, Folsom AR, Cerhan JR. Nitrate intake and the risk of thyroid cancer and thyroid disease. *Epidemiology (Cambridge, Mass.)*. 2010;21(3):389.
73. Ward MH, Heineman EF, McComb RD, Weisenburger DD. Drinking water and dietary sources of nitrate and nitrite and risk of glioma. *J Occup Environ Med*. 2005;47(12):1260–1267. doi:10.1097/01.jom.0000184879.67736.ae.
74. Chiu H-F, Kuo C-H, Tsai S-S, et al. Effect modification by drinking water hardness of the association between nitrate levels and gastric cancer: Evidence from an ecological study. *J Toxicol Environ Health, Part A*. 2012;75(12):684–693.
75. Ward MH. Too much of a good thing? Nitrate from nitrogen fertilizers and cancer: President's cancer panel-October 21, 2008. *Rev Environ Health*. 2009; 24(4):357–363. 2009doi:10.1515/reveh.2009.24.4.357.
76. Ward MH, Heineman EF, Markin RS, Weisenburger DD. Adenocarcinoma of the stomach and esophagus and drinking water and dietary sources of nitrate and nitrite. *Int J Occup Environ Health*. 2008;14(3): 193–197. doi:10.1179/oeh.2008.14.3.193.