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Drinking Water Contamination & Cancer in Canada and USA: A Review

Lars K. Hallstrom, Dareskedar W. Amsalu

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Executive Summary

The contamination of drinking water is a major cause of global public health problems including enteric disease, cancer (Meliker & Nriagu, 2007; Christoforidou et al., 2013) and acute gastrointestinal illness (OECD/WHO, 2003). In Canada, while both drinking water quality and supply are issues (Murphy et al., 2016), there is particular attention in western Canada to the implications of water-based contaminants for human health. The purpose of this report is to present the lessons learned from the peer-reviewed research that assessed health impacts of drinking water contamination in the United States and Canada.

We reviewed and analyzed 64 published articles (11 in Canada and 53 in the USA) to identify: (1) the most common water contamination indicators; (2) associated health risks; and (3) methods used in the studies. Arsenic contamination and bladder cancer were by far the most commonly used indicators. A second synthesis was then undertaken based on 7 articles to evaluate the studies that specifically assessed this association.

Population-based, case-control studies along with statistical regression was the most commonly applied approach for assessing the association between arsenic and bladder cancer. While studies (n=5) that considered large arsenic samples and/or controlled for the confounding risk factors found statistically significant associations between bladder cancer and exposure to low-to-medium levels (e.g., 10-100 μg/L) of arsenic in drinking water, studies (n=2) that considered relatively small arsenic samples and/or did not control for the confounding risk factors found insignificant associations.

Our review suggests that the association between bladder cancer and low-to-medium levels of arsenic in drinking water needs to be assessed by following appropriate quality criteria and using commonly applied study designs and methods. These include using population-based, case-control design, considering different arsenic exposure metrics, incorporating large sample size, controlling for confounding risk factors, and adjusting for demographic covariates.

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1. Background

The contamination of drinking water is a major cause of global public health problems including enteric disease, cancer (Meliker & Nriagu, 2007; Christoforidou et al., 2013) and acute gastrointestinal illness (OECD/WHO, 2003). In Canada, while both drinking water quality and supply are issues (Murphy et al., 2016), there is particular attention in western Canada to the implications of water-based contaminants for human health.

The purpose of this report is to present the lessons learned from the peer-reviewed research that assessed the risks of cancer associated with drinking water contamination in Canada and the United States. The selected studies were analyzed in two phases. A preliminary analysis was first conducted to identify: (1) the most common water contamination indicators; (2) associated health risks; (3) and methods used in the studies. A second synthesis was then undertaken to evaluate the studies that specifically assessed the association between arsenic contamination in drinking water and bladder cancer.

In the preliminary analysis, studies were analyzed to answer three questions:

1. What are the most commonly used drinking water contamination indicators associated with the risks of cancer?
2. What are the most common types of cancer associated with drinking water contamination? and
3. What are the most common methods used for measuring the indicators and assessing the relationship between drinking water contamination and risks of cancer?

In examining the relationship between arsenic in drinking water and bladder cancer, studies were analyzed to address three questions:

1. Is there a statistically significant association between bladder cancer and arsenic in drinking water? If so, what are the relevant results and/or thresholds?
2. What confounding factors affect arsenic levels and so the risk of bladder cancer? and
3. What demographic factors need to be considered in assessing the relationship between arsenic in drinking water and bladder cancers?

2. Literature Search

We searched peer-reviewed articles published from 1980 to 2017 in Canada and the United States using keywords “drinking water” and “cancer’. The search was done using Web Science and EBSCOHost databases generating a total of 279 articles (265 in the USA and 14 in Canada). However, only 64 most relevant and most recent articles (from 2000 to 2017) were selected for the purpose of the preliminary analysis. The selection criteria include availability of full text, consideration of risks of cancer related to drinking water contamination, and studies undertaken within the selected geographical domain[1]. A search was also conducted for “microbial” and “chemicals” in drinking water; however, no further attempt was made to review those articles (See Table 1).

[1] Studies conducted by the United States research institutions for other countries were not included.

Table 1: Literature search results [Databases: Web Science & EBSCOHost; Peer-reviewed article; Year of publication: 1980-2017]

Search targets	Total Search Results		Reviewed for Preliminary Analysis*	
	Canada	**USA**	**Canada**	**USA**
Drinking water and cancer	14	265	11	53
Drinking water and microbial	34	162	Not Reviewed	
Drinking water and chemical	83	410	Not Reviewed	

* Note: Only most recent studies (from 2000 to 2017) that had full text and considered risks of cancer related to drinking water contamination were selected.

The results of the preliminary analysis indicated that arsenic contamination and bladder cancer were by far the most common indicators (See Table 2). Population-based, case-control studies along with statistical regression was the most commonly applied approach for assessing the association between drinking water contamination and cancer. Other methods such as correlational and spatial analysis were also used in some cases. There were relatively few studies that considered other types of drinking water indicators such as disinfection bi-products (mainly nitrates, trihalomethanes, and tetrachloroethylenes) and other types of cancer (such as lung, breast and bone). The selected studies were then categorized into different themes and majority of them were focused on investigating the relationship between drinking water contamination and risk of cancer, and some studies were focused merely on water quality assessment (see Appendix Table 9).

Table 2: Total number of studies for major drinking water indicators, cancer types, and study design/methods

Water contaminants	Number of Studies (Out of 64)	Cancer types	Number of studies (Out of 64)	Methods/ design	Number of Studies (Out of 64)
Arsenic	26	Bladder	17	Population case-control	22
Nitrates	7	Lung	6	Regression analysis	31
Trihalomethanes	6	Skin	2	Correlation analysis	8
Tetrachloroethylenes	2	Prostate	2	Spatial analysis	8

Table 3 indicates that the arsenic studies are highly correlated with the bladder cancer studies, indicating that the majority of the selected studies considered the impact of arsenic in drinking water on bladder cancer. There are also some studies that considered the effect of arsenic on other types of cancers such as lung (Celik et al., 2008; Gibb et al., 2011; Dauphine et al., 2013; Lamm et al. 2015; Ferdosi et al., 2016; Mendez et al., 2017), prostate (Bulka et al., 2016; Roh et al., 2017) and skin (Knobeloch et al., 2006; Mayer & Goldman, 2016).

Table 3: Number of studies for major cancer types by major drinking water indicators

Major cancer types	**Major drinking water indicators**					
	Arsenic	Nitrates	Trihalomethanes	Bromide	Radium	**Total**
Bladder cancer	12	2	2	1		**17**
Lung cancer	6					**6**
Skin cancer	2					**2**
Prostate cancer	2					**2**
Bone cancer					2	**2**
Stomach cancer		2				**2**
Colon cancer		1				**1**

In 2002, the International Agency for research on Cancer (IARC) has concluded that arsenic in drinking water is the cause for an increased risk of cancer of bladder, lung, and skins in humans. Particularly, bladder cancer is known to be the seventh most frequent type of cancer in men in the world, with the highest incidence occurring in the United Sates and Western Europe (Meliker & Nriagu, 2007).

Further examining only the arsenic studies from Table 2, major arsenic indicators and methods used for measuring the indicators were identified (See Table 4). The arsenic indicators can be grouped into three major categories: arsenic in drinking water, urinary arsenic and toenails arsenic.

Table 4: Number of studies by arsenic indicators and measurement methods

Arsenic (As) indicators		**Arsenic measurement methods**	
1. Drinking water As:	**Count**	**1. Secondary data source:**	**Count**
As concentration (µg/L)	22	Drinking water arsenic data	11
As intake (µg/Day)	7	**2. Direct measurement (laboratory analysis):**	
As cumulative intake (mg)	2	Inductively coupled plasma-mass spectrometry	10
2. Urinary As:		Hydride generation atomic absorption spectroscopy	2
As concentration (µg/L)	4	Graphite furnace atomic absorption	1
Arsenite (As[III])	3	Instrumental neutron activation analysis	1
Dimethylarsenic acid (DMA)	3	**3. Prediction (modelling):**	
Methylarsenic acid (MMA)	3	Statistical modelling	3
Arsenate (As[V])	2	Spatial modelling	1
Arsenobetaine (AsB)	1		
3. Toenails As:			
As concentration (µg/L)	6		
4. Other indicators:			
Blood sample	1		
Other elements (Ca, Fe, Se, Zn)	1		
Number of years arsenic exceeds current limit	1		

Different exposure metrics were used in each type of arsenic. Arsenic concentration in drinking water injection was the most common exposure metric. Other exposure metrics such as arsenic intake, and cumulative lifetime arsenic intake were also used in some cases. The use of urinary arsenic and toenails arsenic concentrations was relatively limited. The urinary arsenic are breakdown into five arsenic species: Arsenite (As[III]), Dimethylarsenic acid (DMA), Methylarsenic acid (MMA), Methylarsenic acid (MMA), Arsenate (As[V]), and Arsenobetaine (AsB). Other indicators and metrics of arsenic exposure (e.g., blood sample, DNA repair, elements, and exposure year) were also used in a few cases.

The methods used for measuring the arsenic level can be categorized into three major groups: (1) use of secondary data; (2) direct measurement; and (3) data modelling. Secondary data sources are a cost-effective way of gathering arsenic data, where researchers simply gather the arsenic measurement data from previously collected databases. Direct measurement involves collection of samples from study participants (e.g., water samples, urine samples, toenail samples) and analysis of the samples for the arsenic levels using laboratory facilities. In the data modelling approach, the arsenic levels are predicted based on historical arsenic data by using modelling software (e.g., statistical analysis, spatial analysis). This approach was rarely used in the reviewed studies.

Secondary data sources and direct measurements were the most commonly used approaches. The secondary data sources were merely used for the arsenic concentration in drinking water. The direct measurement approach was used to measure the arsenic levels in drinking water as well as in urine and toenails. Different analytical methods were used to determine arsenic. The most commonly used method is inductively coupled plasma-mass spectrometry. Other laboratory analysis (e.g., hydride generation atomic absorption spectroscopy, graphite furnace atomic absorption spectroscopy, and neutron activation analysis) were also used in few cases. Assessment of arsenic in the laboratory involves three stages: extraction, arsenic determination, and detection (see Table 5). A detailed description of the analytical methods used in the three stages can be found in Sankararamakrishnan & Mishra (2018).

The major arsenic detection methods used in the reviewed studies are briefly described below.

- In the inductively coupled plasma technique, plasma is used to atomize and ionize all forms of arsenic in the acidified samples. This technique is used in conjunction with mass spectrometry (MS) or atomic emission spectrometry (AES) detectors. MS ionizes all forms of arsenic based on of their mass-to-charge ratio. AES measures characteristic of atomic-line emission spectra by optical spectroscopy and this technique provides a higher precision than the AES technique.
- In the hydride generation atomic absorption spectroscopy, arsenic is vaporized by converting it into volatile hybrids.
- In graphite furnace atomic absorption spectroscopy, a small sample is injected into a graphite tube and then heated using electric furnace to atomize arsenic.
- In neutron activation analysis, arsenic is bombarded with neutrons to form radioactive nuclides which further decay via *beta* (β) and/or *gamma* (γ) emission.

Table 5: Analytical methods used for determination of arsenic

	Phases	Methods
1.	Arsenic extraction in environmental samples (e.g., water, food, soils) and biological samples (e.g., nails, urine, blood)	• Liquid-Liquid • Microwave • Ultrasound • Cloud point • Enzymatic
2.	Arsenic determination	• Anion Exchange Chromatographic • Cation Exchange Chromatographic • Reversed-Phase Chromatographic • Ion Exchange Chromatographic • Solid-Phase Extraction • Hydride Generation • Capillary Electrophoresis
3.	Arsenic detection	• Atomic Absorption Spectroscopy • Graphite Furnace Atomic Absorption Spectroscopy* • Hydride Generation Atomic Absorption Spectroscopy * • Inductively Coupled Plasma Atomic Emission Spectrometry • Inductively Coupled Plasma Atomic Mass Spectrometry* • Neutron Activation Analysis* • X-ray Absorption Near Edge Spectroscopy • X-ray Fluorescence • Cathodic Stripping Voltammetry • Anodic Stripping Voltammetry • Sensors

*Note: methods that were used in the reviewed studies in Table 4 above.
Source: Adopted from (Sankararamakrishnan & Mishra, 2018, p. 23)

The choice of the method for detection of arsenic depends on several factors including detection limit, precision, cost-effectiveness, etc. The most commonly used arsenic detection methods in the United States are inductively coupled plasma mass spectrometry, graphite furnace atomic absorption spectrophotometer, and hydride generation atomic absorption spectrophotometer (Sankararamakrishnan & Mishra, 2018). The findings of our review confirmed that inductively coupled plasma mass spectrometry was the most commonly used method.

Given the high interest in arsenic and bladder cancer, we further evaluated the studies that specifically considered the association between bladder cancer and arsenic in drinking water by selecting only 7 articles from Table 3 that closely match our selection criteria of using statistical analysis methods for assessing the association. The remaining 5 studies did not consider the association between bladder cancer and arsenic, and hence excluded from the analysis.

3. Bladder Cancer and Arsenic

There is evidence that bladder cancer has a strong association with exposure to arsenic in drinking water at high concentrations (e.g., exceeding 300-500 μg/L) (Meliker & Nriagu, 2007; Christoforidou et al., 2013). However, the evidence at low-to-medium levels (e.g., 10-100 μg/L) is uncertain (Mink et al., 2008). This is, in part, because other sources of arsenic exposure (e.g., food, occupational hazards, and tobacco) and other potential causes of bladder cancer in drinking water (e.g., nitrates) can also affect bladder cancer. High arsenic concentration is largely prevalent in developing countries, where drinking water sources are exposed to high levels of arsenic through natural and anthropogenic sources, and there is lack of drinking water regulations (Christoforidou et al., 2013).

All of the selected 7 studies used in our review were focused on the low-to-medium levels (<100 μg/L) of arsenic. Only one study (Saint-Jacques et al., 2018) was conducted in Canada while the remaining six studies were undertaken in the USA (Steinmaus et al., 2003; Lamm et al., 2004; Meliker et al., 2010; Rivera-Núñez et al., 2012; Baris et al., 2016; Mendez et al., 2017). In the USA, studies used the Environmental Protection Agency's current regulatory limit (10 µg/L) as a reference point. All studies used population-based, case-control of bladder cancer except Lamm et al. (2004) that used martality rate of bladder cancer. The cases were patients primarily diagnosed with bladder cancer and identified from hospitals or cancer registries. Controls were selected in such a way that the frequency matched to the cases by race, age, gender, etc. Data from cases and controls were collected through interviews, questionnaires and home visits.

The major arsenic-related determinants of bladder cancer and their effects on bladder cancer are summarized in Table 6. The factors include both arsenic in drinking water and non-drinking water arsenic sources. The association between bladder cancer and exposure to the low-to-medium arsenic in drinking water is inconsistent across studies. While studies that considered relatively large samples of arsenic (e.g., 10,498 and 31,000 samples) in drinking water found a statistically significant association between 1.5 and 10 µg/L (e.g., Mendez et al., 2017; Saint-Jacques et al., 2018), other studies that considered relatively small arsenic samples (e.g., based on 181 cases and 320 controls of bladder cancer participants) found insignificant associations between 10-100 µg/L (e.g., Lamm et al., 2004; Meliker et al., 2010).

Apart from the differences in the sample size, differences in the method of data analysis might contribute to the inconsistency of the findings. Methods range from a simple univariate analysis, considering only arsenic in drinking water (Lamm et al., 2004), to a complex multivariate analysis also considering confounding factors that influence the level of urinary arsenic and so bladder cancer (Steinmaus et al., 2003; Meliker et al., 2010; Rivera-Núñez et al., 2012; Baris et al., 2016; Mendez et al., 2017; Saint-Jacques et al., 2018). The studies that found significant associations used spatially structured Poisson regression analysis and/or controlled for the effects of confounding factors (e.g., Baris et al., 2016; Mendez et al., 2017; Saint-Jacques et al., 2018) while the studies that found insignificant associations used simple regression analysis and/or did not incorporate the effects of confounding factors (e.g., Lamm et al., 2004).

Table 6: Association between bladder cancer and arsenic in drinking water and confounding factors

	Factors	Effects on bladder cancer	Studies
1.	Arsenic concentration in drinking water	• No association between bladder cancer and exposure to arsenic levels 10-100 µg/L. • Bladder cancer risk increased with exposure to water arsenic levels <10 µg/L.	(Lamm et al., 2004); (Meliker et al., 2010) (Mendez et al., 2017); (Saint-Jacques et al., 2018)
2.	Water intake	• No association between bladder cancer and arsenic water intake >80 µg/Day. • Bladder cancer risk increased with arsenic water intake >2.2 µg/L.	(Steinmaus et al., 2003) (Baris et al., 2016)
3.	Age of wells	• Dug wells used pre-1960s have positive effect on bladder cancer.	(Baris et al., 2016)
4.	Water sources	• Private wells have positive effect.	(Baris et al., 2016); (Steinmaus et al., 2003)
5.	Depth of well	• Shallow wells have more apparent effect on bladder cancer than deep wells.	(Baris et al., 2016)
6.	Smoking	• No association with bladder cancer. • Bladder cancer risk associated with smoking.	(Meliker et al., 2010) (Steinmaus et al., 2003)
7.	Diet	• Seafood intake correlated with urinary As. • Drinking water is important predictor of urinary As.	(Rivera-Núñez et al., 2012)
8.	Exposure duration	• Cumulative exposure to arsenic for 40+ years has a positive effect on bladder cancer.	(Baris et al., 2016); (Steinmaus et al., 2003)

The amount of water intake from tap water and beverages made with tap water (e.g., coffee, hot or iced tea) was found to be positively associated with bladder cancer; heavier water consumers have higher risks than that of lighter water consumer. In rural areas where arsenical pesticides (e.g., agricultural chemicals) were used historically, the age of the wells was found to be an important factor in predicting the arsenic levels in drinking water and so bladder cancer (Baris et al., 2016). The study of Baris et al. (2016) also indiciated that other attributes of drinking water such as source and depth of the wells play important role. Among private well users, the risk of bladder cancer was significant if well water was derived exclusively from shallow dug wells but not if well water was supplied only by deeper drilled wells (Baris et al., 2016).

Smoking is an important confounding factor that contributes to the risk of bladder cancer but there is inconsistency among studies on the effect of smoking on bladder cancer. The study of Steinmaus et al. (2003) indicated that smokers exposed to drinking water arsenic for a long period are more likely to have higher risk of bladder cancer than non-smokers. On the other hand, Meliker et al. (2010) found no statistically significant correlation between smoking and bladder cancer. The study of Rivera-Núñez et al. (2012) predicted the determinants of urinary arsenic and found that arsenic intake from food items (e.g., seafood) was statistically significant in predicting urinary arsenic. Exposure to arsenic for a long period over lifetime (e.g., 40+ years) was significantly correlated with bladder cancer in the studies of Steinmaus et al. (2003) and Baris et al. (2016).

The studies analyzed also varied in terms of considering the heterogeneity of the risk of bladder cancer associated with arsenic exposure across different demographic factors. The major demographic factors used in the studies and their associations with bladder cancer are provided in Table 7. These demographic factors were collected from the population cases-controls of bladder cancer participants through interviews, questionnaires and home visits.

Table 7: Major demographic factors and their associations with bladder cancer

Factor	Description	Association with bladder cancer
1. Gender	• Male • Female	• Risk of bladder cancer is higher in men than women (e.g., Baris et al., 2016; Mendez et al., 2017; Saint-Jacques et al., 2018)
2. Education	• Less than high school • College diploma • Bachelor degree or higher	• Negatively associated with bladder cancer (Meliker et al., 2010; Baris et al., 2016; Mendez et al., 2017)
3. Occupation	• High risk occupation • Low risk occupation	• High risk occupation is positively associated with bladder cancer (Meliker et al., 2010; Baris et al., 2016)
4. Age	• <55 • 65-74 • 55-64 • 75+	• Population older than 65 years are most strongly associated with bladder cancer rate (Mendez et al., 2017)
5. Race	• American Indian • Asian • Black • Hispanic • White	• The risk of bladder cancer is lower in Hispanic than other races (Mendez et al., 2017)
6. Groundwater dependence	• Proportion of population served by public groundwater & domestic wells	• Negatively associated with bladder cancer (Mendez et al., 2017)
7. Income	• Median family/household income	• Positively associated with bladder cancer (Mendez et al., 2017)
8. Residential mobility	• Proportion of residents living in the same house for 5+years	• Positively associated with bladder cancer (e.g., Mendez et al., 2017)
9. Family history	• Family history with cancer • Any French ancestry	• Positively associated with bladder cancer (Meliker et al., 2010)
10. Body mass index	• <25 • 25-30 • 30+	• No significant difference in urine arsenic level among different body masses (Rivera-Núñez et al., 2012)
11. Rural-urban indicator	• Population density • Degree of urbanization	• No significant effect on bladder cancer (Mendez et al., 2017)
12. Material deprivation	• Average income • Proportion of people with no high school diploma • Employment rate	• No significant effect on bladder cancer (Saint-Jacques et al., 2018)
13. Social deprivation	• Proportion of separated/divorced/widowed • Proportion of persons living alone/single-parents	• No significant effect on bladder cancer (Saint-Jacques et al., 2018)

The risk of bladder cancer was consistently higher in males than in females across studies (e.g., Baris et al., 2016; Mendez et al., 2017; Saint-Jacques et al., 2018). This evedince is consistent with the general studies in the world. The review of Meliker & Nriagu (2007) indicates that the worldwide ratio of occurrence of bladder cancer in men to women is around 7:2. The number of years spent on education was negatively correlated with risk of bladder cancer (e.g., Meliker et al., 2010; Baris et al., 2016; Mendez et al., 2017), suggesting that people with fewer years of schooling are more likely to have high risk of bladder cancer.

The study of Meliker et al. (2010) and Baris et al. (2016) also indicated that exposure to high risk occupations (e.g., painting, aromatic amine manufacturing, working in leather factories, driving trucks) is strongly associated with the risk of bladder cancer. The study of Mendez et al. (2017) found that population older than 65 years are most strongly associated with bladder cancer. The study also found that the risk of bladder cancer is significantly lower in Hispaic than in whites or African Americans and for popluation that are largely dependent on groundwater, but higher for households with higher income and for people who live in the same house for five years or more. According to Meliker et al. (2010), people who have a family member diagosed with bladder cancer are also more likely to have a high risk of baldder cancer. The was no a statistically significant association discovered for the remaing demographic factors: body masss index (Rivera-Núñez et al., 2012), degree of urbanization (Mendez et al., 2017), and materical and social deprivation (Saint-Jacques et al., 2018).

4. Lessons Learned

The precision of the measurement of the association between bladder cancer and exposure to low-to-medium levels of arsenic in drinking water depends on the quality of the data and model specification considering:

- sample sizes of arsenic measurements and case-control participants,
- arsenic exposure metrics and measurement methods,
- associated confounding factors, and
- demographic factors.

The quality of the related studies can theoretically be assessed using the criteria given in Table 8.

Table 8: Quality criteria for evaluating case-control epidemiological studies

1.	Was the exposure assessed at the individual level?
2.	Was exposure assessed using a biomarker?
3.	Was the outcome based on objective tests in ≥90% of the study participants?
4.	Did the authors present internal comparisons within study participants?
5.	Did the authors control for potential confounding risk factors in addition to age?
6.	Did the authors control for the healthy worker effect?
7.	Was the data collected in a similar manner for all participants?
8.	Were the same exclusion criteria applied to all participants?
9.	Was the time period over which cases and non-cases were interviewed the same?
10.	Was the interviewer blinded with respect to the case status of the person interviewed?
11.	Was the response rate among non-cases at least 70%?
12.	Were all cases interviewed within 6 months of diagnosis?
13.	Was the study based on incident cases of disease?
14.	Were non-cases individuals who, had they developed the disease, been cases?

Source: Adapted from (Celik et al., 2008)

The criteria were not directly applied in our analysis to systematically assess the quality of the selected studies. However, the following major lessons were learned from the reviewed studies.

1. Finding as many representative samples of arsenic measurements and study participants as possible and correctly aligning the As measurements with the population case-control study participants. For example, as indicated in Table 8 (criterion # 11), the response rate among controls needs to be at least 70%.
2. Considering different metrics of lifetime exposures to As in drinking water and analyzing their relationship with bladder cancer. The major exposure metrics used in the reviewed studies were:
    - Arsenic concentration in drinking water at home, work, and other places;
    - Arsenic intake in drinking water at home, work, and other places;
    - Cumulative arsenic intake; and
    - Number of years arsenic in drinking water exceed 10 µg/L.
3. Incorporating other attributes of drinking water such as sources (surface, groundwater, public, private), depth of the wells, age of the well, change in water sources over time, use of filtration, mobility, etc.
4. Finding appropriate data for non-drinking water sources of arsenic exposure (i.e., smoking, food and occupation) and controlling for their effects is also equally important. Controlling for the potential confounding risk factors is one of the quality criteria in Table 8 (criterion #5). Food intake questionnaire (FIQ) is an important source of data used in the USA studies.
5. Collection and analysis of urine samples and toenail samples from participants (cases-controls of bladder cancer incidence) is a common practice of measuring the level of arsenic in the human body.
6. Assessing the heterogeneity of the risk of bladder cancer across different demographic factors is a common practice in the epidemiological studies. There is evidence that bladder cancer occurs more often in men than women and the incidence rate among whites is higher than among Hispanic (see Table 7).
7. The population case-control design was conducted using the incidence of bladder (recently diagnosed patients) and there was only one study that considered mortality rate of bladder cancer.
8. The relationship between bladder cancer and arsenic was assessed using different types of regression analysis (linear, unconditional logistic, and poisson), where the dependent variables are odds ratio (RR), relative risk (RR), and standardized mortality ratio (SMR); and the independent variables are the different arsenic metrics and covariates (i.e., confounding variables and demographic variables). The following were the common practices:
    - Applying natural logarithm transformation;
    - Stratification for confounding factors;
    - Adjustment for demographic factors and heterogeneity test;
    - Considering arsenic as a continuous as well as a categorical variable especially to compare the effect between low and medium levels;
    - Use SAS and R software for data analysis; and
    - Few recent studies applied spatial analysis (e.g., Bayesian spatially structured model) and used ArcGIS for geocoding the residence/occupation address of cases and controls to link with As data.

5. Conclusion

Our review indicates that arsenic contamination and bladder cancer were the most commonly used operators for chemical contaminants and cancer in this research area. The association between bladder cancer and exposure to low-to-medium levels (e.g., 10-100 μg/L) of arsenic in drinking water was found to be inconsistent across studies. Studies that considered large arsenic samples and/or controlled for the confounding risk factors (e.g., smoking, high risk occupation) found statistically significant associations even in below 10 µg/L. On the other hand, studies that considered relatively small arsenic samples and/or did not control for the confounding factors found statistically insignificant associations in the range of 10-100 µg/L. In general, our review suggests that the association between bladder cancer and low-to-medium levels of arsenic in drinking water needs to be assessed by following appropriate quality criteria and using commonly applied study designs and methods. These include using population-based, case-control design, considering different arsenic exposure metrics, incorporating large sample size, controlling for confounding risk factors, and adjusting for demographic covariates.

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7. Appendix

Table 9: Number of reviewed studies by research topic/theme

Study themes	Number of studies
Relationship between water quality and cancer	50
Water quality assessment	8
Guidelines for drinking water and cancer	2
Relationship between water sources and cancer	1
Relationship between wells and water quality	1
Relationship between livestock operation and water quality	1
Health and environmental impact assessment	1
Total	**64**