National Trends of Bladder Cancer and Trihalomethanes in Drinking Water: A Review and Multicountry Ecological Study

Joseph A. Cotruvo[1] and Heather Amato[2]

Abstract

We examined trends in incidence of bladder cancer in 8 countries in the 45+ years since trihalomethanes (THMs) were detected in chlorinated drinking water. Total trihalomethanes (TTHMs) are the principal regulated disinfection by-products (DBPs) along with halogenated acetic acids (HAAs). Numerous epidemiological studies have examined exposure to TTHMs and associations with bladder cancer. Concentrations of TTHM have declined in most of the 8 countries that were studied as has smoking prevalence. Incidences of bladder cancer have usually stayed relatively flat, especially for females, with some variations. Since THMs are not carcinogens in whole animal tests, they may not be appropriate surrogates for studying potential cancer risks in drinking water. Etiology of bladder cancer is complex; incidence correlates with age. Previously identified risk factors include smoking, type 2 diabetes, sex, ethnicity, arsenic, aromatic amines, and occupations. As a predominant risk factor, smoking trends may dominate incidence rates, but additional time might be required to determine whether a DBP risk exists due to long latency periods. Causal drinking water-related bladder cancer risks remain questionable and likely small compared to other factors, although surrogate-based DBP management is an appropriate strategy for maintaining drinking water quality as long as it does not compromise microbial disinfection.

Keywords

Highlights

- Numerous disinfection by-products (DBPs) are generated by chlorine and other disinfectants in drinking water.
- Some epidemiology studies have associated a possible risk of bladder cancer with trihalomethane (THM) exposures.
- Bladder cancer etiology is complex, and there are multiple risk factors.
- Trihalomethanes are not carcinogens in whole animal bioassays in water, so if there is a true correlation with bladder cancer it could be a secondary correlation with other DBPs present in much lower concentrations but with high potency.
- Lifetime DBP exposure is extremely difficult to quantify, and it requires numerous assumptions that might determine the outcomes.
- Observed national bladder cancer rate trends over 45+ years could be mostly smoking related, and they do not seem to parallel THM reductions in most cases at this time.

Introduction

Drinking water chlorination, introduced in the early 20th century, remains one of the greatest public health benefits of science and engineering. Chlorination is a simple, low-cost, and broadly effective technique for disinfecting drinking water and reducing risks of waterborne disease. Chlorination and water filtration technologies provide remarkable reductions in waterborne disease such that source water-related waterborne disease outbreaks have virtually disappeared when they are functioning as designed.

[1] Joseph Cotruvo & Associates LLC, Washington, DC, USA
[2] Public Health Institute, Oakland, CA, USA

Corresponding Author:
Joseph A. Cotruvo, Joseph Cotruvo & Associates LLC, 5015 46th St NW, Washington, DC 20016, USA.
Email: joseph.cotruvo@verizon.net

Chlorine is chemically reactive and an oxidizing and halogenating agent. In the early 1970s, studies indicated that chlorinated water produced halogenated disinfection by-products (DBPs), as a function of the levels of natural total organic carbon (TOC) and contact time, pH, and temperature.[1,2] Monochloramine use increased as a secondary disinfectant.

Four trihalomethanes (THMs), trichloromethane (TCM, chloroform), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and tribromomethane (TBM, bromoform), have been subjects of concern since their discovery in drinking water. Brominated DBPs are produced by the competing chlorine oxidation of bromide to $HOBr/OBr^-$ a brominating agent. The mixed halogen THMs result from the precursor concentrations and relative rates of the reactions. The THMs and HAAs comprise the major portion of the mass of halogenated DBPs and have been regulated in numerous countries. The THMs were originally regulated in the United States[3] by the US Environmental Protection Agency (USEPA) as a readily analyzed indicator of many other DBPs present in much greater numbers but in lower concentrations. The maximum contaminant level (MCL) of 0.10 mg/L (100 μg/L) applied to total trihalomethanes (TTHM), the sum of the 4 THMs, and compliance was measured by a drinking water system-wide annual average of quarterly samples. The TTHM MCL was based upon treatment feasibility while protecting chlorination disinfection, controlling waterborne microbial disease risks. The MCL initially applied only to larger water systems. The TTHMs were used as indicators to drive treatment to concurrently reduce other DBPs, analogous to requiring reduction in coliforms and *Escherichia coli* bacterial indicators for pathogenic microorganisms.

Disinfectant chemistry is complex, and different disinfectants produce arrays of different DBPs. Noting the efficacy of chloramines to reduce DBP formation, many water suppliers shifted from chlorine to chloramine residuals in distribution. Some water suppliers initiated the use of ozone or chlorine dioxide as primary disinfectants, often supplemented with chlorine or chloramine for distribution system residuals.

Chloroform (TCM) is always present in chlorinated drinking water and usually at the highest concentrations; other THM contributions vary. The MCL was technologically feasible, and it would not jeopardize essential chlorine disinfection practice. It was later reduced to 0.08 mg/L (80 μg/L), and 5 haloacetic acids (HAAs) were added.[4] The HAAs represent a substantial portion of the DBPs, have their own potential health risk issues, and may be indicators of other DBPs. The MCLs for TTHMs and HAAs have since been reaffirmed.[5]

Carcinogenicity History of TTHMs

The 1979 THM regulation was initiated from bioassay results that chloroform was carcinogenic in rats and mice tested at high doses by corn oil gavage. The numerical MCL was not based upon quantitative toxicology but by water treatment feasibility. The other 3 THMs were included by structural analogy and common formation chemistry, with only limited data from then new cellular mutagenicity tests.

Subsequently, other tested THMs showed some level of carcinogenicity under similar testing conditions. However, TCM[6] and BDCM[7] were not carcinogenic when retested in water rather than corn oil. The USEPA concluded that TCM and DBCM were not likely to be carcinogenic below a dose threshold.[4] The World Health Organization (WHO) Guidelines for Drinking Water Quality[8] do not treat TCM, DBCM, and TBM as genotoxic nonthreshold carcinogens and state that "as BDCM was negative for carcinogenicity in a recent NTP bioassay in which it was dosed in drinking water, exceedances of the guideline value (which is 0.06 mg/L) are not likely to result in an increased risk of cancer".[8] The International Agency for Research on Cancer (IARC) determined that TCM, DBCM, and TBM did not have sufficient evidence to be classified as possible carcinogens in humans.

Chloroform has been evaluated for inhalation toxicology in male and female mice in 90-day studies. The No-Observed-Adverse-Effect-Level (NOAEL) for liver cell proliferation, the most sensitive end point in female mice, was 10 ppm.[9] They concluded that no increase in liver cancer would occur in female mice at that inhaled dose.

Maximum Contaminant Level Goals (MCLGs) are nonregulatory benchmarks in the United States set at the level at which no known or anticipated adverse effect on health would occur with a margin of safety. The current individual US MCLGs are TCM, 0.07 mg/L; BDCM, zero; DBCM, 0.06 mg/L; and TBM, zero. The WHO's current health-based guideline values are TCM, 0.3 mg/L, BDCM, 0.06 mg/L, DBCM, 0.1 mg/L, TBM, and 0.1 mg/L (WHO/GDWQ, 2017).[56]

Epidemiology of THMs

Some epidemiology studies have suggested, but not consistently, that colon and rectal, and especially bladder cancers could be associated with TTHM exposures.[10,49] However, existing data suggest that TTHMs are not good surrogates for some other chlorination by-products that may increase bladder cancer risk.[11] Some of the observed associations between TTHMs and bladder cancer have been interpreted by some as causal.[12] Hrudey (2008) concluded that "none of the THMs, nor any other concurrently identified DBPs, have both the capability of acting to cause bladder tumors and sufficient potency and exposure concentration to yield bladder cancer predictions that would accord with epidemiological predictions".[46] The USEPA[13] estimated in its Stage 2 Disinfection By-Products Rule analysis that lower and upper confidence limits of risks of bladder cancer for chlorination of drinking water ranged from 2% to 17%. Bull[12] reported that results from meta-analyses suggested estimates of approximately 1/1000 lifetime risk of developing bladder cancer from consumption of chlorinated drinking water. Regli et al[14] examined several epidemiology studies involving organobromine exposures and estimated an increased lifetime bladder cancer risk of 1/10 000 per incremental microgram per liter of TTHM. The USEPA[15] cautioned that the level of confidence in its estimates did not preclude the actual number of cases with bladder cancer related to drinking water could be zero because causation had not been

proven, and a similar statement regarding lack of causation was in EPA's 6-year review of the toxicology and epidemiology of DBP.[55]

Cancer epidemiology and toxicology studies on chemicals in drinking water. Hrudey[10] updated and assessed evidence from 56 studies of various designs attempting to link TTHM and other chemicals with potential human cancer risks. Six individual data sets from 13 studies provided indications for a correlation between TTHMs and incidence of bladder cancer, with odds ratios typically in the range of 1.2 to 2.0.[10] Bull[12] concluded that potential effects of THMs on bladder cancer would be about 2 orders of magnitude lower than the observed cancer rates reported by some epidemiological studies.

Brominated THMs and many non-DBP chemicals are metabolized by glutathione transferase theta 1-1, and some produce a mutagenic product, so the possibility of a genotoxic mechanism may exist for them.[54] Some studies in Spain have reported a higher risk of bladder cancer among a population subset with genetic polymorphisms coding for activation of brominated THMs, oxygenation of some haloacetic acids, as well as metabolism of many industrial chemicals and oxidation of THMs[45]. Bull[12] states that these findings provide substantive evidence that chlorinated drinking water contributes to bladder cancer, but, for a number of mechanistic reasons, it does not provide strong evidence that THMs are causally involved.

Cellular-level in vitro studies employing cytotoxicity and genotoxicity have evaluated numerous DBPs for their biological activities. Such studies often suffer from the lack of consideration of whole animal post ingestion metabolism and *in vivo* organ dosages at target organs and cells in addition to existence of repair processes. Nevertheless, they indicate very low in vitro activity for THMs.[16,17]

Woo et al[18] provided a structure–activity assessment of 209 DBPs for carcinogenic potential. None received high ratings; high–moderate ratings were attributed to 3 MX (halofuranone) chemicals; 1 MX 5 haloalkanes/haloalkenes, 6 halonitriles, 2 haloketones, 1 haloaldehyde, 1 halonitroalkane, and 1 non-halogenated aldehyde were moderate. The MX compounds are mutagenic in *Salmonella* assays but not considered very carcinogenic because they are likely readily detoxified after ingestion. The remaining 189 DBPs were assigned low–moderate (58), low (98), or marginal (33) cancer concern.

Hrudey et al[19] reviewed 10 higher quality case–control studies with some study overlaps, 8 of which suggested an association with bladder cancer with odds ratios for men between 1.4 and 2.5, and 2 meta analyses. They concluded that:

> Quantitative risk estimates derived from toxicological risk assessment for CxDBPs (chlorination DBPs) currently cannot be reconciled with those from epidemiologic studies, notwithstanding the complexities involved, making regulatory interpretation difficult . . . Replication of epidemiologic findings in independent populations with further elaboration of exposure assessment is needed to strengthen the knowledge base needed to better inform effective regulatory approaches (p. 214).

They also concluded that "no causal agent with sufficient carcinogenic potency has been identified, nor has a mechanistic model been validated." It is possible that imprecise DBP exposure variables and other assumptions and consequences of multiple contributing risk factors may be larger than the magnitude of potential water treatment-related risks being studied.

Risk Factors of Bladder Cancer

Rates of bladder cancer vary substantially by region and country. Europe and North America have the highest rates. Age-standardized rates in the European Union in 2008 were 27.4 and 5.6 per 100 000 among males and females, respectively. The highest rates were in Spain, followed by Denmark, Czech Republic, and Germany; the lowest were in Slovenia, Finland, and the United Kingdom.[20] Comparable US incidence was 19.8/ 100 000 for 2014.[21] Race and ethnicity appear to be significant factors in the United States: The rate per 100 000 was 21.1 for whites, 11.4 for blacks, 10.7 for Hispanics, 8.1 for Asian/Pacific Islanders, and 8.4 for American Indian/Alaska Native.[21]

Incidence of bladder cancer is correlated with age; about 90% of bladder cancers occur over 55 years of age, 70% are older than 65, and median age at diagnosis is 73.[22] Five-year survival is 77.3%.[23] Numerous risk factors contribute to age-related incidences of bladder cancer including predominantly smoking, exposure to aromatic amines, and several occupations.[24,43,47] Some reports suggest that bladder cancer risk may be about 40% in patients with type 2 diabetes and more so in men than in women.[25-27]

Diabetes, smoking, age, gender, ethnicity, and chemical contributors may interact to impact risks. Other small risk factors such as arsenic and PAH exposures add to contributions from certain medical treatments.[28] Men are about 2 to 4 times more likely to contract bladder cancer than women in their lifetimes; smokers are at least 3 times as likely as nonsmokers, and smoking causes about half of all bladder cancers in both men and women.[28] Some occupational risks are aromatic amines and mineral oils and other chemical exposures in the rubber industry and among hairdressers, painters, and leather workers. Several medical treatments including some drugs and diagnostic ionizing radiation accounted for about 3% of bladder cancers.[42] Renal transplant recipients are at 3 times higher risk. Overweight, obesity, human papilloma virus, HIV[29] infections, and prior cancers were also risk factors.[48] Some studies suggest that increased drinking water consumption tended to lower risks.[28] Most dietary components were not associated with bladder cancers (Cancer Research UK, 2017).[48]

Arsenic is a risk factor at high exposure.[32] Saint-Jacques et al (2017) associated bladder cancer and arsenic in drinking water at >150 µg/L but at <150 µg/L with lower confidence.[50] Other studies have not found increased cancer risk when arsenic occurs at lower levels of 3 to 60 µg/L[30] or <100-200 µg/L, especially for nonsmokers.[31] Median US drinking water levels in 2006 to 2010 were 1.5 µg/L (95th percentile was 15.4 µg/L).[32]

Bladder cancer latency. There is no consensus on post initial exposure latency for bladder cancers. One study[33] indicated occupational latencies of 20 to 30 years or beyond. Scarselli et al[34] suggested an average latency of 20 years. Other studies have estimated latencies from <10 years to more than 30 years.[25,33]

Methods for this National-Level Ecological Assessment of Bladder Cancer Risks

Background

The overall question is whether reduced exposure to TTHMs have resulted in demonstrably lower risks of bladder cancer. Given that THMs are not carcinogenic in whole animal bioassays, are there other DBPs that are quantitatively related to TTHM concentration, such that TTHM reductions might reflect concurrent reductions in those DBPs? We hypothesized that reduced drinking water concentrations of TTHMs should concurrently result in reduced exposure to many other DBPs and therefore possibly reduce any attributable risk of bladder cancer.

We undertook a broad, multicountry ecological assessment of national trends in TTHM occurrence and bladder cancer incidence rates since TTHM detection and regulation began. Given the challenges of epidemiological and exposure assessment studies, an aggregated approach may provide a better understanding of any observed trends.

Methodology Specifics

This study compared trends of bladder cancer and TTHMs in drinking water systems from about 1974, when chlorine-related DBPs in drinking water were first reported, to approximately 2015. National statistical data were assembled from 8 countries (United States, Canada, United Kingdom, Netherlands, Sweden, Germany, Australia, and Japan) on cancers, smoking, and TTHMs from national health statistical registries, national regulatory agencies, and published reports. Historical water chlorination practices from published literature and national regulatory agencies were also examined. The compiled TTHM data were supplemented with qualitative information on chlorination practices obtained from national regulators. Annual national average smoking prevalence and lung cancer incidence were also included for a more complete picture of important contributing factors and possible concurrent health outcomes.

Total trihalomethanes in drinking water systems. Annual average TTHM concentrations in drinking water systems were compiled during the study period. Sufficient quantitative data on TTHM concentrations in drinking water systems were only available for the United States. The TTHM data were extracted from various national or multicity reports and summaries, primarily from US EPA national surveys. National annual average TTHM concentrations were either extracted from published reports or calculated by averaging concentrations across all water systems and all time points with available data in a given year (Table A1). For other countries, published reports and information provided by national regulators were used. Absent TTHM data,

chlorination, and historical water treatment technology trends were used for qualitative judgments regarding TTHM trends.

Incidence of bladder cancer. Age-adjusted incidence estimates for bladder cancer were retrieved from national or regional online cancer registry databases (Table A2). Annual national bladder cancer incidence rates for the United States, Canada, and Australia are age-standardized to each country's national population. Incidence rates for the Netherlands, Sweden, and the United Kingdom are age-standardized to the European population, and rates for Germany and Japan are age-standardized to the world population.

Smoking prevalence. Smoking prevalence statistics were included because smoking is considered to be a risk factor for bladder cancers and especially lung cancers. Historical smoking prevalence is pertinent with emphasis on the smoking rates in the earlier periods due to the latency periods for postexposure cancer occurrence.

Annual national age-adjusted smoking prevalence data were obtained primarily via International Smoking Statistics reports (Table A3). Other data sources for the United States included online data tables and published reports from the National Health Interview Survey (NHIS). Smoking statistics for Japan were received directly from the National Institute of Public Health, Japan.

Incidence of lung cancer. Annual national lung cancer incidence was included to compare smoking and lung cancer and smoking and bladder cancer incidences. Lung cancer incidence may be concurrent with smoking-related bladder cancer.[52] Lung cancer was defined as invasive lung and bronchus cancers for all countries except Japan, where lung and trachea cancers were combined for a single incidence rate. Lung cancer age-standardized incidence rates (ASIR) were available from national or regional online cancer registry databases or published reports (Table A2).

Supplemental information on drinking water treatment and water quality data. National information and trend reports of prevalence and changes in drinking water treatment processes during the study period, including chlorination and other disinfection technologies, were requested from participating countries. Such information is not necessarily documented at a national level, so it was likely that the regulators would have the best knowledge of past and current treatment applications. Data on TTHM concentrations in drinking water for non-US countries were requested, given the limited data from online databases or publications.

Results

The following figures and summaries present national trends of bladder and lung cancer incidences, smoking prevalence, and drinking water TTHM concentrations as reported based on available data.
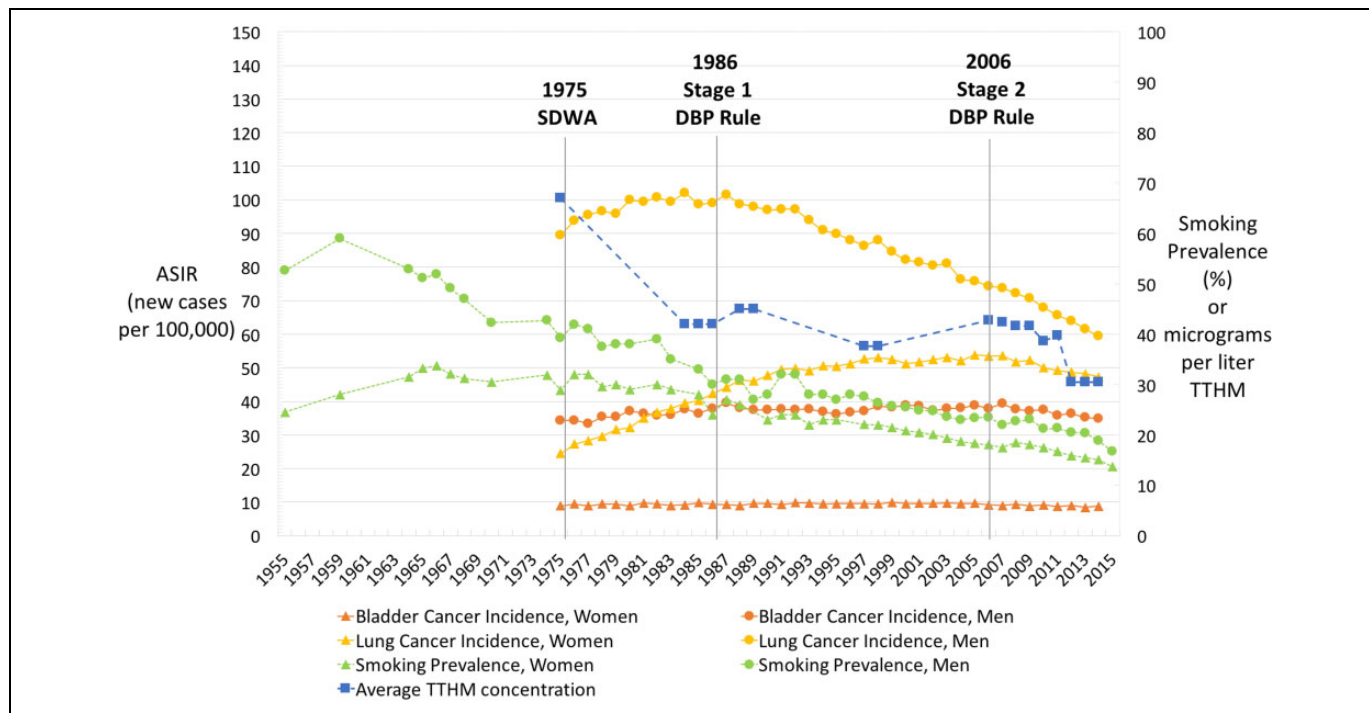
Figure 1. United States of America: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, and total trihalomethane (TTHM) concentrations in drinking water systems, 1955 to 2015.

United States of America

Statistics for 1955 and 1959 reported that 52.6% and 59% of men were smokers during those years (Figure 1). By 1975, male smoking prevalence had decreased to 39.3%, and the average TTHM concentration was 67 μg/L. By 1986, male smoking prevalence had declined to 30% and TTHM concentrations to 42 μg/L. Smoking declined to 16.7% by 2015 and TTHMs to 30 μg/L. While both smoking and TTHMs had steadily decreased, bladder cancer incidence among men *increased* to about 39.5/100 000 (1987) from 34.4/100 000 (1975) and then returned to 34.9/100 000 in 2014. Smoking had been in decline for about 60 years and TTHMs for about 35 to 40 years, and male bladder cancers were relatively stable. Women's smoking prevalence increased from 24.5% (1955) to 28% (1959), then to 33.7% (1966), and then decreased to 13.7% (2015). Incidence of female bladder cancer has remained essentially level during the entire period, ranging between 8.5 and 9.9/100 000 despite a significant increase then a decrease in smoking prevalence. Male to female bladder cancer incidence ratio was about 3.5 between 1975 and 2014. Lung cancer incidence was 89.3/100 000 for males and 24.5/100 000 for females in 1975. Male incidence rose to 97.2/100 000 in 1992 and then declined to 59.3/100 000 by 2014. Female incidence in 1975 doubled to 53/100 000 (1998) then declined to 47.3/100 000 (2014).

Total Trihalomethanes and Treatment Technology Trends

Chlorine has been widely used since its introduction in 1907. The United States has multiple large comprehensive databases

from the regulatory monitoring requirements and national surveys. The National Organics Reconnaissance Survey (NORS) and the National Organics Monitoring Survey (NOMS) in the 1970s related TTHMs to chlorination and water conditions (Table A1). The TTHM averages reflect regulatory and treatment technology changes. Average TTHMs in US drinking water supplies were 67 μg/L in 1976, 42 to 45 μg/L in 1986, and 30 μg/L in 2013 to 2015. The TTHM levels were probably at least 67 μg/L prior to the 1970s when there were no constraints. The highest NORS survey level exceeded 300 μg/L in a water supply in a warm climate with high TOC water; chlorine was used as disinfectant and to bleach colored humic substances. Numerous water suppliers have shifted from free chlorine to chloramine residuals to meet regulations. Increased ozone and some chlorine dioxide applications have occurred.

Supplemental Sources

USEPA. Safe Drinking Water Act Information System (SDWIS). 2015. http://www.epa.gov/enviro/facts/sdwis/search.html.

Canada

Male smoking prevalence declined from 58% (1965) to 22% (2004; Figure 2). Small peaks occurred in 1978, 1986, and 1988. Incidence of male bladder cancer in 1988 was 44.2/100 000, declining to 40/100 000 and remaining steady until 1999, and then declining to 35.7/100 000 (2013). Bladder cancer incidence marginally increased among men in 1997 and
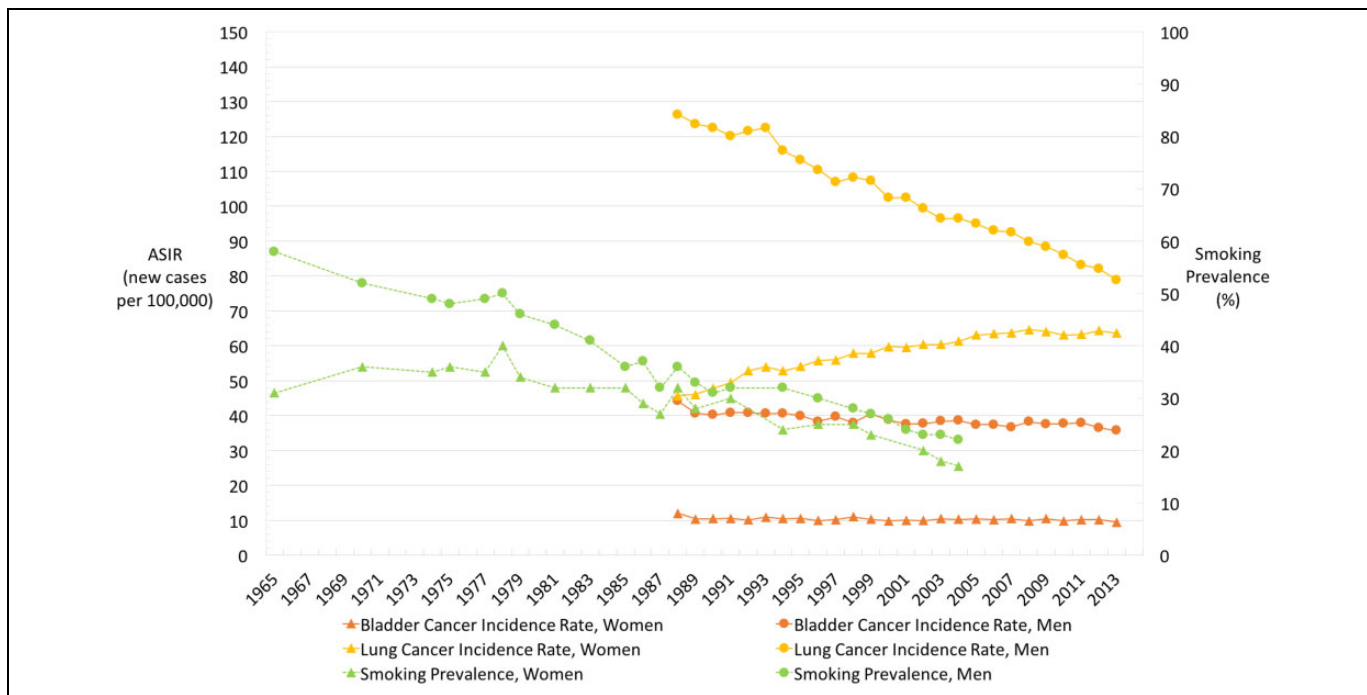
Figure 2. Canada: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, 1965 to 2013.

1999—about 20 years after the first peak in smoking prevalence—and in 2008—about 20 years after the second peak. For women, smoking prevalence was 31% (1965), 40% (1978), and then 17% (2004). Bladder cancer incidence among women was 12% (1988) and then remained stable around 10% between 1988 and 2013 (Figure 2). The ratio of male to female bladder cancers was 4 (1989) and 3.6 (2013). Incidence of male lung cancer decreased from 126.3/100 000 (1988) to 78.9/100 000 (2013). Female lung cancer incidence was 45.7/100 000 (1988); it increased steadily and plateaued at 63.1 to 64.6/100 000 from 2005 to 2013, in contrast to flat female bladder cancer incidence, declining female smoking prevalence and lung cancer incidence in males.

Total Trihalomethanes and Treatment Technology Trends

The Canadian national guideline for chloroform is 100 μg/L (0.1 mg/L) using tolerable daily intake calculations.[44] A summer/winter survey of treated and distributed water from 53 selected water plants in 1993 found that TCM, dichloroacetic acid, and trichloroacetic acid were the major DBPs detected, and HAAs often equaled or exceeded TTHM concentrations.[51] The population-weighted TTHM average was 30.8 μg/L, surface water 31.1 μg/L, and groundwater 15.6 μg/L. Thirty-seven plants used conventional disinfection and alum coagulation and 15 only disinfected. Most (35) used pre- and postchlorine dosage; total chlorine doses ranged from 0.1 to 5.75 mg/L (winter) and from 1 to 13.6 mg/L (summer). Ammonia followed prechlorination in 10 facilities. Chlorine doses ranged from 1.2 to 8.5 mg/L (winter) and 1.2 to 7.6 mg/L (summer). Facilities (7) using ozone followed by chlorine or chloramine

had total chlorine dosages from 0.5 to 3.3 mg/L (winter) and 0.5 to 4 mg/L (summer).

The TCM was the major THM except in 3 groundwater treatment systems where BDCM or TBM predominated. Distribution system data from chlorinating plants ranged from 2.8 to 221.1 μg/L (mean 34.4, winter) and from 0.3 to 342.4 μg/L (mean 62.5, summer). Chloramine/chloramine and ozone/chloramine TTHM values ranged from 0.6 to 42.1 μg/L (means 9.9-13.7, winter) and 2.5 to 107.8 μg/L (means 32.8-66.7, summer).

A 2009 to 2010 survey in 65 selected facilities indicated a decline in concentrations and reported a population TTHM average of 20.7 μg/L and included some small systems. Systems employed chlorination (51), chloramination (12), ozonation (8), and ultraviolet (UV) light (11). The average of surface water facilities was 20.9 μg/L; the groundwater average was 11.6 μg/L.[35]

Distribution of technologies was similar except for several UV systems in the later survey. UV has sometimes replaced free chlorine for primary disinfection for cryptosporidium in surface water. Chlorine or chloramines are used for maintaining residual disinfection in the distribution systems.

Supplemental Sources

Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Trihalomethanes. 2013. https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-trihalomethanes/page-13-guidelines-canadian-drinking-water-quality-trihalomethanes.html#a11. Accessed September 4, 2017.

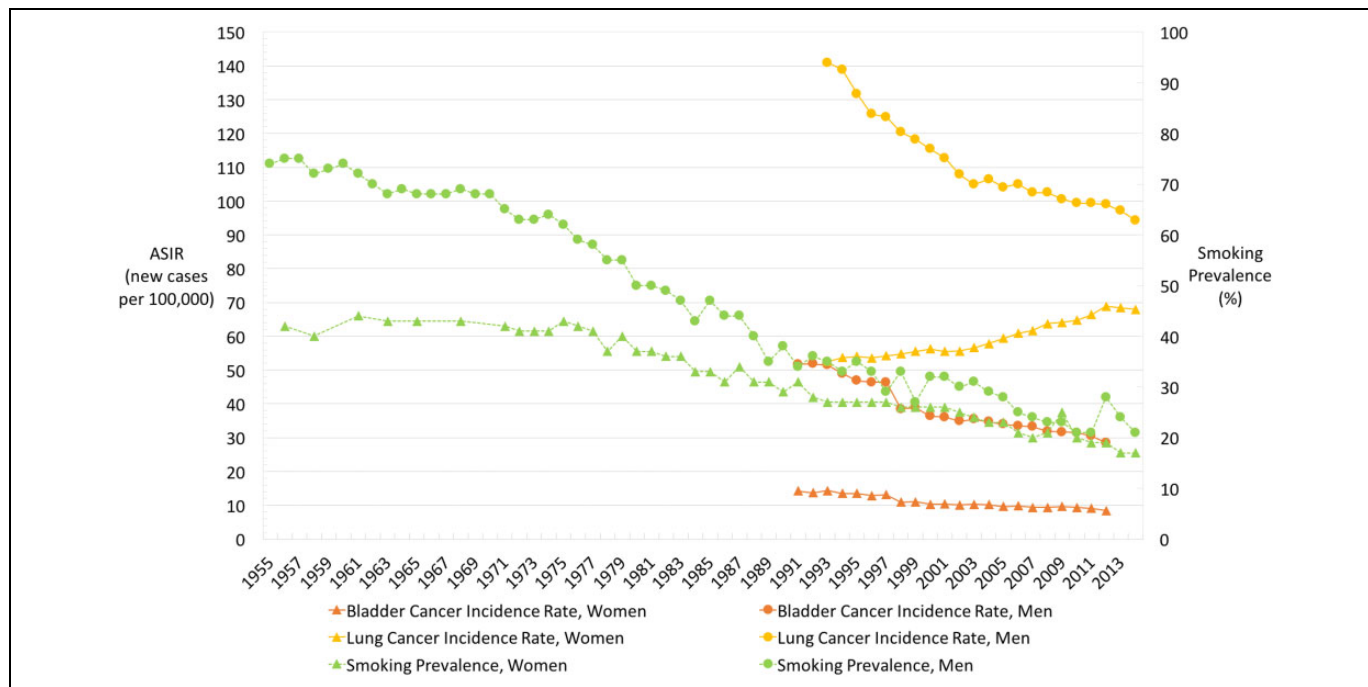Giddings, M. *Manager, Water Quality and Science Division, Health Canada*. 2017. Personal communications.

Figure 3. United Kingdom: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, 1955 to 2014.

Huck P. *Professor Peter Huck, University of Waterloo, Ontario, Canada*. 2017. Personal communication. Accessed September 15, 2017.

Hrudey SE. *Professor Steve E. Hrudey. University of Alberta, Edmonton, Alberta, Canada*. 2017. Personal communication. Accessed November 26, 2017.

Tugulea A-M. *National Survey of Disinfection by-products, 1993 and 2009-2010*. 2017. Personal communication. Accessed December 7, 2017.

United Kingdom

Male and female bladder cancer rates declined in the study period as have smoking rates (Figure 3). Male smoking prevalence decreased from 75% (1956) to 21% (2014). Male bladder cancer incidences were 51.7/100 000 (1991) and 28.5/100 000 (2012). Female smoking prevalence was 42% (1974) and 17% (2014). Female bladder cancer rates were 14.2/100 000 (1991) and 8.4/100 000 (2012). The ratio of male to female bladder cancer incidence was 3.6 (1991) and 3.4 (2012). Male lung cancer incidence rates decreased from 140.9/100 000 (1993) to 94.3/100 000 (2014), while female incidence rates increased from 52.6/100 000 (1993) to 68/100 000 (2014). This might indicate that the latency periods for smoking-related lung cancer were more sensitive to smoking rates for males than for females, since smoking rates for both have declined. Concurrent bladder cancer reductions for males were also more consistent, whereas bladder cancers have been decreasing for females while lung cancers have been increasing.

Water Treatment Technology and TTHMs

The UK TTHM standard is 100 μg/L. The United Kingdom predominantly uses surface water and employs chlorination. Hyde and Zabel (1981) surveyed 358 water supplies serving 54% of supplied water; mean TTHMs in distributed water were 42 μg/L (52% were <25 μg/L and 5% >100 μg/L). The TCM was >60% of the TTHMs and brominated TTHMs were <10 μg/L. Higher values were typically in prechlorinated surface waters. An improvement program reduced chlorine doses, moved chlorination points, and enhanced coagulation. In 1990 to 1995, granular activated carbon (GAC) installations for pesticide removal likely increased THM precursor removals. Annual national data from 1995 to 2015 reported mean TTHM values between 32 and 41 μg/L (1995-2003), and 22 and 25 μg/L (2004-2015). Average values did not exceed 42 μg/L in earlier years and almost halved in the last 12 years.

Supplemental Sources

Hyde RA, Zabel TF. *Summary of the Department of the Environment Haloforms Survey*. 1981. http://webarchive.nationalarchives.gov.uk/20120905040320/http://dwi.defra.gov.uk/research/completed-research/reports/dwi0233.pdf

Marsden P. 2017. Peter.Marsden@defra.gsi.gov.uk. Personal communication.

Germany

Cancer and smoking data for Germany were available for a shorter time period. Smoking prevalence trends were varied (Figure 4). Male smoking prevalence decreased from 46%
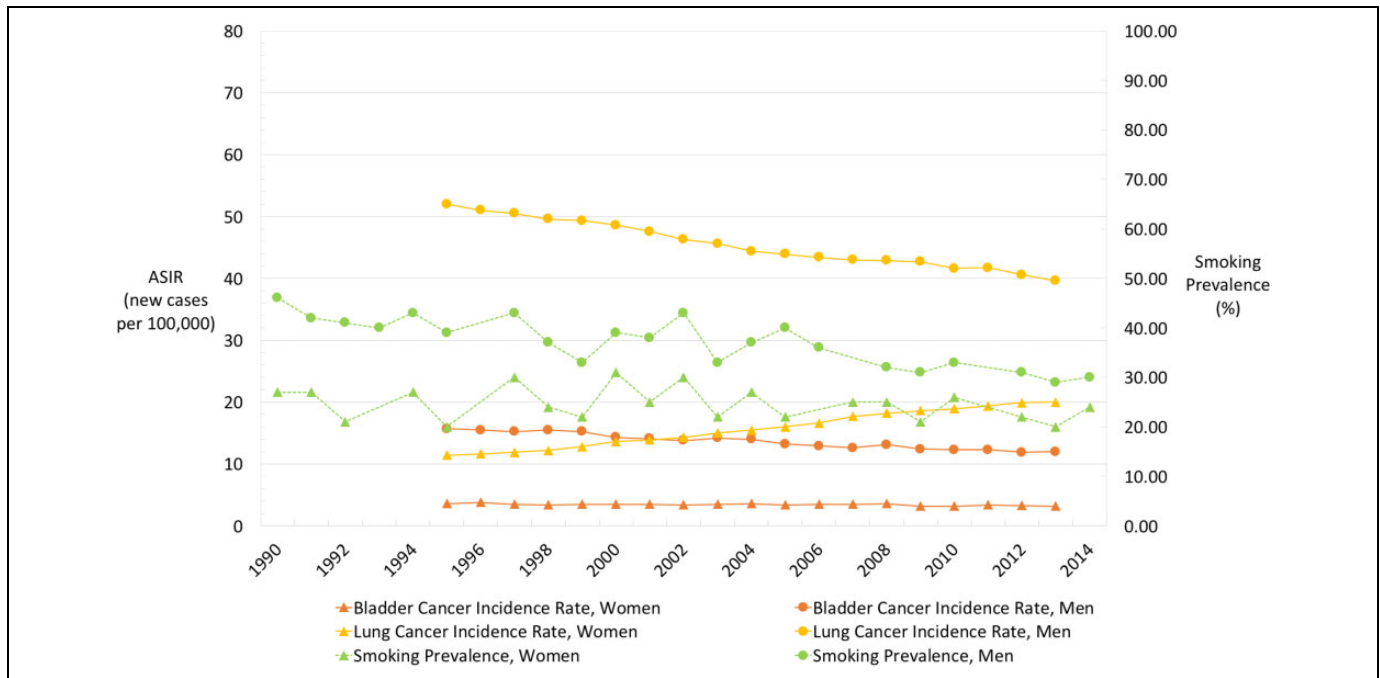
Figure 4. Germany: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, 1990 to 2014.

(1990) to 30% (2014). Male bladder cancer incidences decreased from 15.7/100 000 (1995) to 12/100 000 (2013). Limited availability of smoking prevalence and bladder cancer data in earlier years complicates analyses of longitudinal trends, given latency periods. Female smoking prevalence was 27% (1990), between 20% and 30% until 2002, and then 24% (2014). Female bladder cancer rates were low: 3.2 to 3.8/100 000 (1995-2013). The ratios of male to female bladder cancer incidence were 4.3 (1995) and 3.6 (2014). However, historical smoking statistics were only available from 1990 and bladder cancer trends only up to 2012. Overall, male bladder cancer incidence has slightly declined, and female bladder cancer incidence has been relatively constant. Male lung cancer rates decreased from 52/100 000 (1995) to 39.6/100 000 (2013), while female incidence rates increased from 11.4/100 000 (1995) to 20/100 000 (2013). These data may suggest that the latency period for smoking-related lung cancer may be shorter than that for bladder cancer.

Water Treatment Technology and TTHMs

Detailed TTHM data were not available. Chlorination has never been heavily used in Germany. About 70% of drinking water is from groundwater and not chlorinated. Water industry philosophy has been to minimize generation of organohalogenated chemicals; regulations limit chlorination applications to 0.3 mg/L, with 0.6 mg/L as an exception; residual chlorine maximum is 0.1 mg/L; occasional dosages >1.2 mg/L occur; 0.5 mg/L is the maximum dosing. Breakpoint chlorination is partially allowed; use of chlorine for oxidation was banned so it is used only as a disinfectant and at low doses. This led to

increased use of ozone and ozone/biologically activated carbon in surface waters.

Historic chlorine use has been limited and was further restricted after TTHM detections in the 1970s. The TTHM concentration limit has been 0.050 mg/L since 2003; all roughly 6000 water supplies report compliance with few exceptions. Male smoking prevalence has declined, and female smoking prevalence has slightly declined. There has been little change in chlorination practices or TTHM concentrations. Levels of TTHM were always low because of pretreatment technologies such as river bank filtration and limited chlorine applications. Groundwater supplies have historically not chlorinated.

Supplemental Sources

Chorus Ingrid. *Director Drinking Water and Swimming Pool Hygiene*. Federal Environment Agency; 2017. Personal communications.

Grunert Andreas. *Drinking Water Resources and Treatment. Federal Environment Agency*. 2017. Personal communications.

The Netherlands

Male smoking prevalence was 90% (1958), 66% (1975), and then 27% (2012; Figure 5). Male bladder cancer incidence was 24/100 000 (1989) and 20.9/100 000 (2012). Female smoking prevalence was 29% (1958), 40% (1975), and then 24% (2014). Female bladder cancer rates increased from 4.7/100 000 (1989) to 5.8/100 000 (2012). The ratio of male to female bladder cancer incidence was 5.1 (1989) and 3.6 (2012). Male lung cancer incidence rates decreased from 110.3/100 000 (1990)
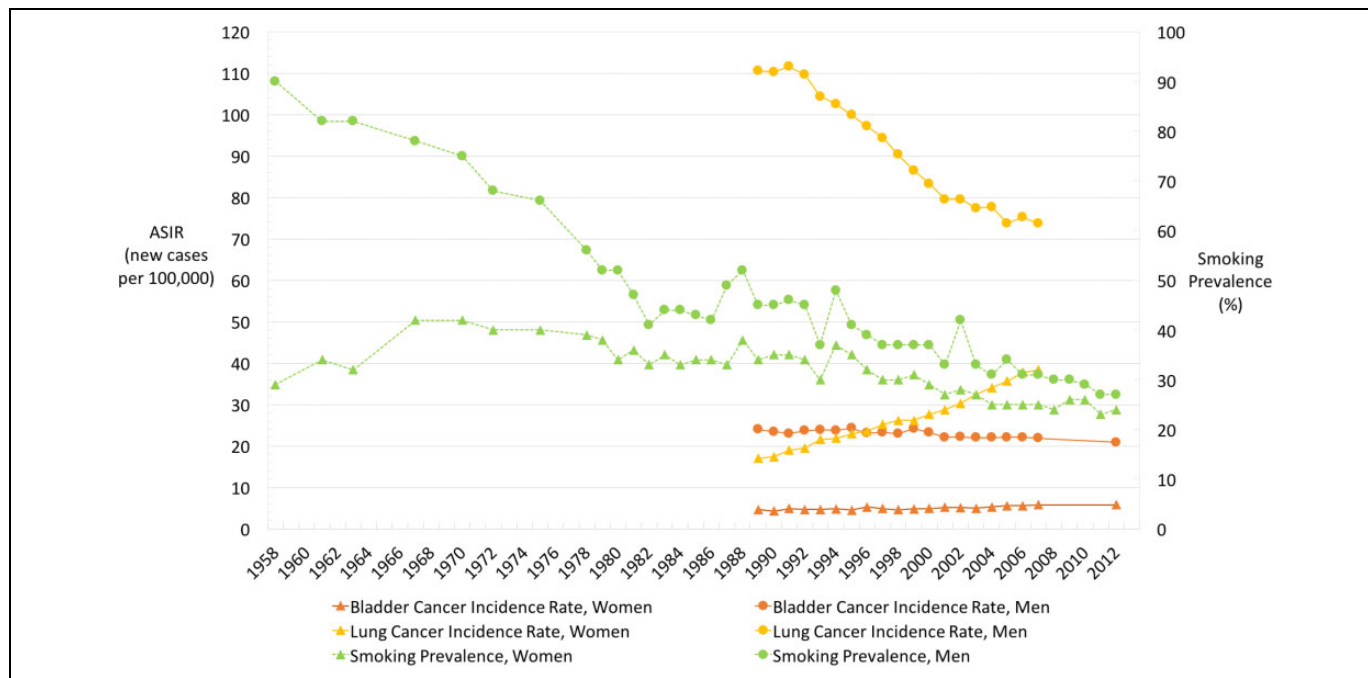
Figure 5. The Netherlands: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, 1958 to 2012.

to 73.7/100 000 (2007); female incidence rates increased from 17.4/100 000 (1990) to 38.4/100 000 (2007), likely reflecting increased female and decreased male smoking rates. Male bladder cancer incidence has declined slightly while rates increased slightly for women. Trends are consistent with the concurrent large declines in male smoking and large increases in female lung cancer, probable smoking consequences. These data may suggest that latency periods for smoking-related lung cancer are shorter than smoking-related bladder cancer, although increased female bladder cancer rates occurred to some degree.

Water Treatment Practices and TTHMs

The TTHMs in surface water supplies have declined since the late 1970s to early 1980s when regular chlorine use was reduced or eliminated by national requirements. Values approaching zero occur in many supplies, although short periods of chlorination are needed to control growths in transport piping. Drinking water for one-third of the population are surface waters that traditionally used chlorine in their water treatment; regular chlorination ended in 1993. Groundwater supplies are traditionally not chlorinated.

Chlorine was used in the Kralingen plant (eastern Rotterdam) after ozonation for post disinfection (1977-2005). Distributed water in 1979 to 1980 averaged 22.3 µg/L TTHMs; current levels are approximately 1 µg/L. Since 1966, drinking water for Rotterdam is also produced in the Berenplaat plant, which used chlorine for primary and post disinfection until November 2005 when UV-disinfection was implemented; breakpoint chlorination was used between 1966 and 1973. Since April 1973, pretreated water from the Biesbosch reservoirs had lower chlorine use; breakpoint chlorination was used

from 1973 to early 1980s; TTHM concentrations averaged 30 to 35 µg/L (50-54 µg/L maximum, data from 1979-1980 and 1997-2000). In 1979 to 1980, network THM concentrations at Berenplaat were 27.5 to 50.6 µg/L averaging 38.4 µg/L. Current TTHMs are 1 µg/L, except for short periods when chlorination is used to prevent mussel growth in pipelines from Biesbosch (April-November). The Hague and Groningen have always had low TTHM levels. Amsterdam's TTHM levels declined from about 20 µg/L (mid 1980 to 1981) to 12 µg/L (1982) and then to 1 µg/L in 1983. Since then, TTHM concentrations approach non-detect but slightly exceed 10 µg/L when chlorine is added for short periods.

In summary, values for TTHMs in surface water supplies in the Netherlands were lower than comparable US values in the early 1970s. They have declined substantially since the late 1970s to early 1980s when regular chlorine use was reduced or eliminated by national requirements. Values approaching zero have been occurring in many supplies, with some short periods of chlorine use as needed to control growths in transport piping or for other remedial causes.

Supplemental Sources

Ketelaars H. Manager Drinking Water Technology & Source Protection. Evides Water Company; 2017. Personal communications.

Rook JJ. Formation of haloforms during chlorination of natural waters. *Water Treat Exam*. 1974;23:234–243. RIVM. 2016.

Rook JJ. Het ontstaan van trihalomethanen bij de behandeling van drinkwater met chloor (Formation of trihalomethanes during drinking water treatment with chlorine). [PhD thesis]. Wageningen: Agricultural University Wageningen; 1978.
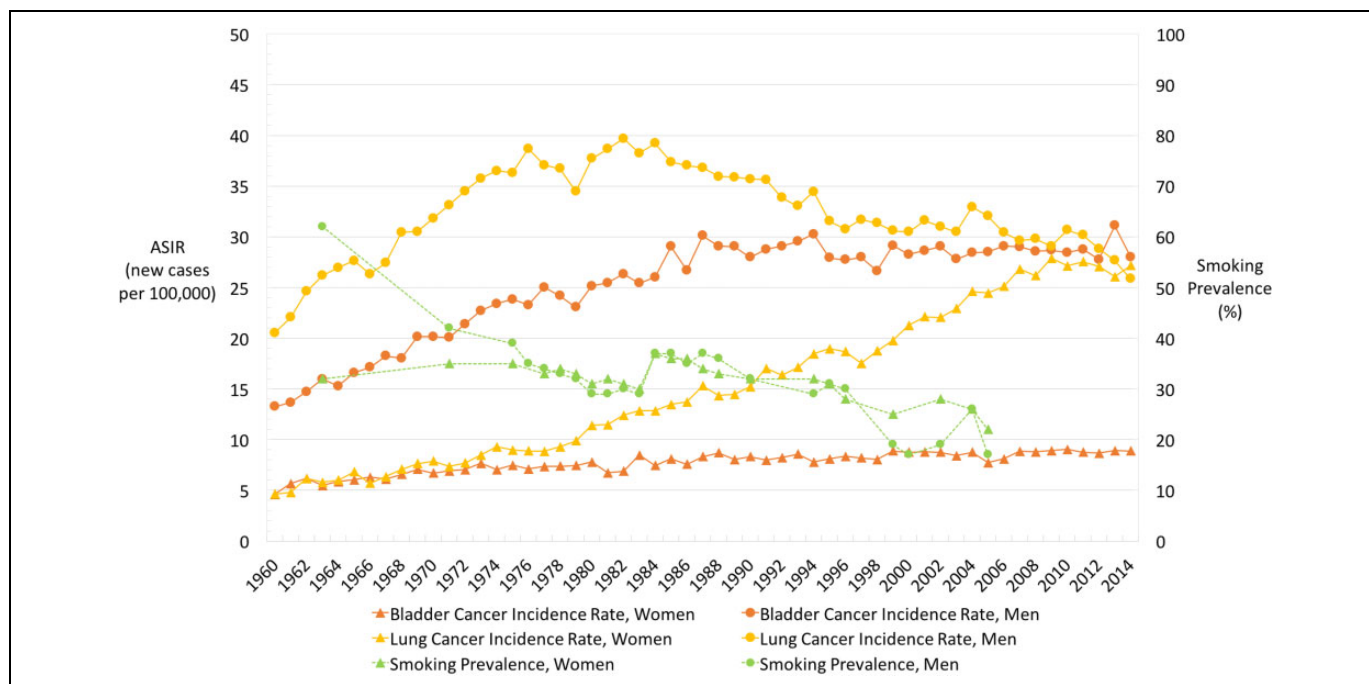
Figure 6. Sweden: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, 1960 to 2014.

Steen R. *Hoofd Markt & Advies*. Het Water Laboratorium; 2017. Personal communications.

van der Aa. National Institute for Public Health and the Environment (RIVM). 2017. Personal communications and assistance.

Sweden

Male smoking prevalence declined steadily from 62% (1963), 42% (1971), 30% (1996), 19% (2002), to 17% (2005) (Figure 6). Male bladder cancer incidence increased from 13.26/100 000 (1960) to 29/100 000 (1985) and approximately 28/100 000 (1988-2014). Female smoking prevalence generally declined from 32% (1963), 35% (1971), 28% (1996-2002), to 22% (2005). Female bladder cancer rates increased from 4.59/100 000 (1960) to 8.11/100 000 (1985) and then to 8.9/100 000 (2014). The ratio of male to female bladder cancer was 2.9 (1960), 3.6 (1985), and 3.2 (2014). Male lung cancer incidences were 20.5/100 000 (1960), 39.7/100 000 (1982), and 25.8/100 000 (2014); female lung cancer incidence increased from 4.6/100 000 (1960) to 27.1/100 000 (2014). Despite a decrease in male smoking prevalence from 62% to 17%, male bladder cancer increased by 4.3% between 1975 and 1985 and has since remained stable. This suggests that risk factors in addition to smoking may be important. Female smoking prevalence declined since 1986, but it is difficult to relate changes in smoking prevalence with increases in bladder cancer incidence, unless there are other factors or the latency period is long.

National census and cancer registry–linked data from 1971 to 1989 indicated 12% of male bladder cancers were attributable to shop and construction metal work, and 16% of female bladder cancers to clerk/secretary/stenographers and waitresses (Wilson et al, 2008). Patients with renal pelvis cancer also have bladder cancer (20%-50%). Tobacco smoking and ionizing radiation are associated with both cancers (Silverman et al, 2006). There has been increased usage of tobacco products such as snuff, possibly because of the 2005 ban on smoking in restaurants and pubs, while TTHMs have not significantly changed.

Water Treatment and TTHM Trend Estimates

The maximum permitted chlorine dosage in Sweden is 1 mg/L; limit values for chlorine residual leaving the water system are 0.4 mg/L (400 μg/L) and 0.050 mg/L (50 μg/L) for TTHMs at the tap. About 75% to 80% of the population receives primary or secondary chlorinated drinking water. Surface water provides 50% with 25% from infiltrated groundwater and 25% from groundwater. Sources and water treatment have not changed significantly in 40 years. Few samples exceed 50 μg/L, and most waterworks do not exceed 10 μg/L. Median free chlorine residuals in 2013 were 0.07 mg/L (90th percentile, 0.24 mg/L). The TTHM sampling began in the mid 198's; the 90th percentile was 15 μg/L with most below detection. Thus, TTHMs have likely been consistently at low concentrations since the 1970s (Säve-Soderberg, 2016).

Daily drinking water consumption average (2012-2013) is 1 L/day for cold tap water, 2.5 L for 99th percentile high consumers, and 1.85 for total water including coffee and tea. Women consume about 200 mL/day more water than men do. Bottled water consumption is low: 80% are nonconsumers; average consumption for consumers was 0.4 to 1.3 L/day (Westrell et al, 2006).

Supplemental Sources

Bo Thunholm & Helena Whitlock. [Egenskaper hos vattenanalysdata i Vattentäktsarkivet] Properties of water analysis data in the Vattentäktsarkivet (in Swedish). SGU-rapport 2014:17, Sweden: Uppsala; 2014.

Cedergren MI, Selbing AJ, Löfman O, Källen BA. Chlorination byproducts and nitrate in drinking water and risk for congenital cardiac defects. *Environ Res*. 2002;89(2):124-130.

Drinking water summaries. http://resources.sgu.se/producte r/sgurapp/s1417-rapport.pdf in Swedish.

Melle Säve-Söderbergh, National Food Agency, Upsala, Sweden. Personal communication 2016.

Säve-Söderbergh M, Toljander J, Mattisson I, Åkesson A, Simonsson M. Drinking water consumption patterns among adults – SMS as a novel tool for collecting repeated consumption estimates. *J Expo Sci Environ Epidemiol*. 2017;00:1–9. http://www.nature.com/jes/journal/vaop/ncurrent/pdf/jes20178a.pdf

Silverman DT, Devesa SS, Moore LE, Rothman N. Bladder cancer. In: Schottenfeld D, Fraumini JF Jr, eds. *Cancer Epidemiology and Prevention*. 3rd ed. New York: Oxford University Press; 2006.

Swedish Water & Wastewater Association (SWWA). [Analysdata 1994-Uppgifter över bakteriologisk och kemisk beskaffenhet hos råvatten och dricksvatten vid kommunala vattenverk] Analysis data 1994- Information on the bacteriological and chemical nature of raw water and drinking water at municipal waterworks (in Swedish). VAV AD94. 1996.

Westrell T, Andersson Y, Stenstrom TA. Drinking water consumption patterns in Sweden. *J Water Health*. 2006;4(4):511-522.

Wilson RT, Donohue M, Gridley G, Adami J, El ghormli L, Dosemeci M. Shared occupational risks for transitional cell cancer of the bladder and renal pelvis among men and women in Sweden. *Am J Ind Med*. 2008;51(2):83-99.

Australia

Male smoking prevalence was 45% (1974), 33% (1993), and 23% (2003; Figure 7). Male bladder cancer incidence was 30.8/100 000 (1982) and declined to 16.5/100 000 (2013). Female smoking prevalence was 30% (1974), 26% (1993), and declined to 19% (2003). Female bladder cancer rates halved from 8.6/100 000 (1982) to 4.1/100 000 (2013). The ratio of male to female bladder cancer incidence was 1.8 (1982) and 2.1 (2013). These ratios are low compared to other countries. Smoking statistics were available from 1990 and bladder cancer to 2013. Lung cancer incidence rates for males decreased from 61/100 000 (1982) to 36.9/100 000 (2014). Female incidence rates were 13.9/100 000 (1982) and increased to 23.3/100 000 (2013). Concurrent probable male smoking-related bladder cancer reductions were consistent, whereas bladder cancers have been decreasing for females while lung cancers have been increasing. Male and female bladder cancer incidences are low and declining, although TTHM levels are higher than other countries that were studied. Australian male and female bladder cancer data are comparable to the UK's, whereas United States, Canada, and Germany have been more stable during the study period. This points to the difficulty in attempting to detect a potential bladder cancer risk relationship considering just those 2 factors.

Water Treatment Technology and TTHMs

The Australian TTHM guideline value has been 0.250 mg/L since 1996, so TTHM levels in Australia would tend to be higher than the other countries. Chlorination has consistently been the disinfectant of choice. Brisbane and parts of Sydney use chloramination, while other large cities use chlorination. The primary source of drinking water for all large cities is surface water with the exception of Perth (41% desalinated water, 42% groundwater, and 17% surface water). Prior to desalination beginning in the early 2000s, 75% of Perth's water supply was groundwater and 25% was surface water (Cunliffe, 2017). Desalinated water has low TOC and low TTHM formation potential. Small rural community water supplies often use groundwater, but some receive treated water by pipeline, so TTHMs could increase during the transport. About 10% of households, especially in rural areas, have rainwater tanks as their main drinking water source. The Australian Bureau of Statistics reports bottled water purchases increased between 1994 and 2004 with lesser gains since then. In 1994, 3% of households reported purchasing bottled water, 12% (1998), 16% (2001), 21% (2004), and 19% (2007). Usage has stabilized or increased slightly in the recent years. Bottled water represents about 5% of water consumed (plain water beverages; Cunliffe, 2017).

Additional TTHM data were provided for the large capital city water supplies (2014-2015), providing drinking water to 67% of the population. Sources (2014-2015) were 84% surface water, 8% groundwater, and 8% desalination. Average TTHM concentration was 85 μg/L (population weighted), ranging from 34 to 125 μg/L (Cunliffe, 2017).

Supplemental Sources

Cunliffe D. *Principal Water Quality Adviser, Public Health Services, SA Health, Australia*. 2017. Personal communications.

Japan

Male smoking prevalence was very high at 82.3% (1965-1967) but decreased to 29.7% (2016) (Figure 8). Male bladder cancer rates increased from 5/100 000 (1975) to 9/100 000 (2002-2012). Female smoking was 15.7% (1965) and remained stable until 1981 and then decreased to 9.7% (2016). Female bladder cancer rates slightly increased from 1.5/100 000 (1975) to 2/100 000 (2012). The ratio of male to female bladder cancer incidence was 3.33 (1975) and 4.25 (2012). Male lung cancer incidence increased from 8.3/100 000 (1958) to the low 30s/100 000 (1989-2002), leveling off at 26.6 (2014). Female lung cancer incidence followed a similar pattern at much lower rates: 3.3/100 000 (1958), 8/100 000
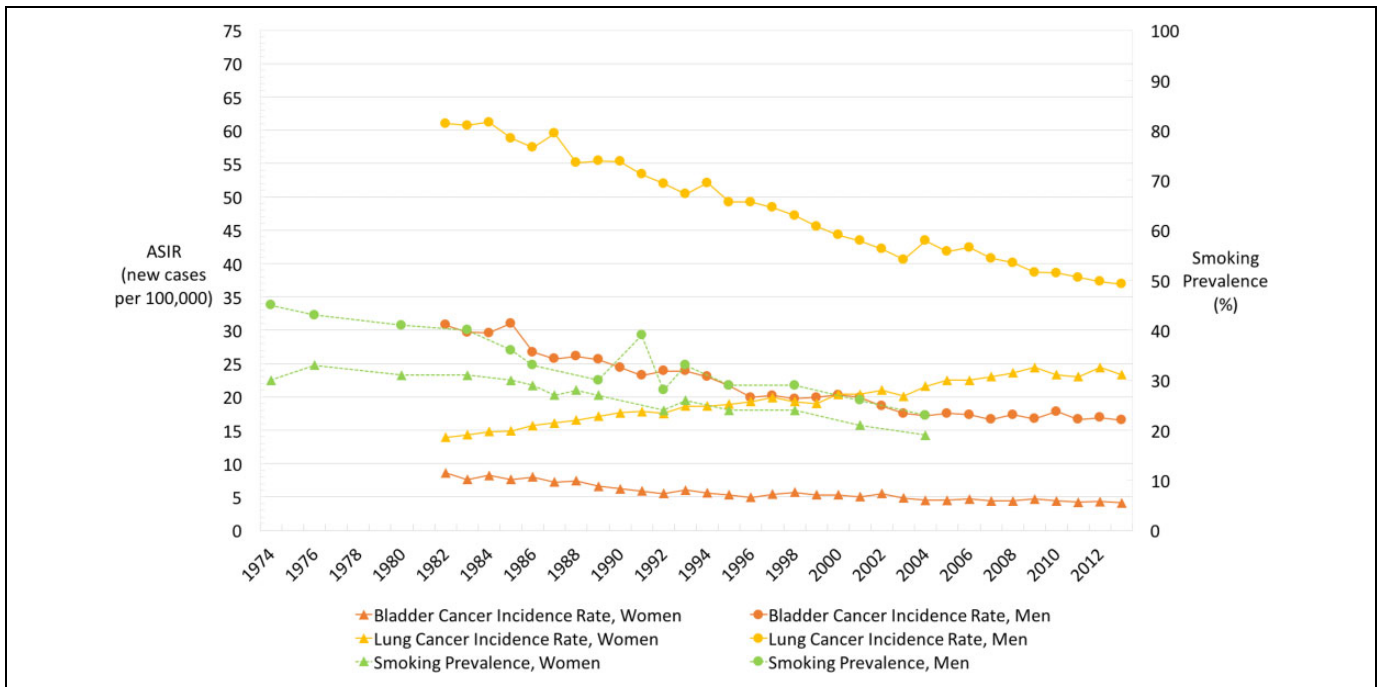
Figure 7. Australia: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, 1974 to 2013.
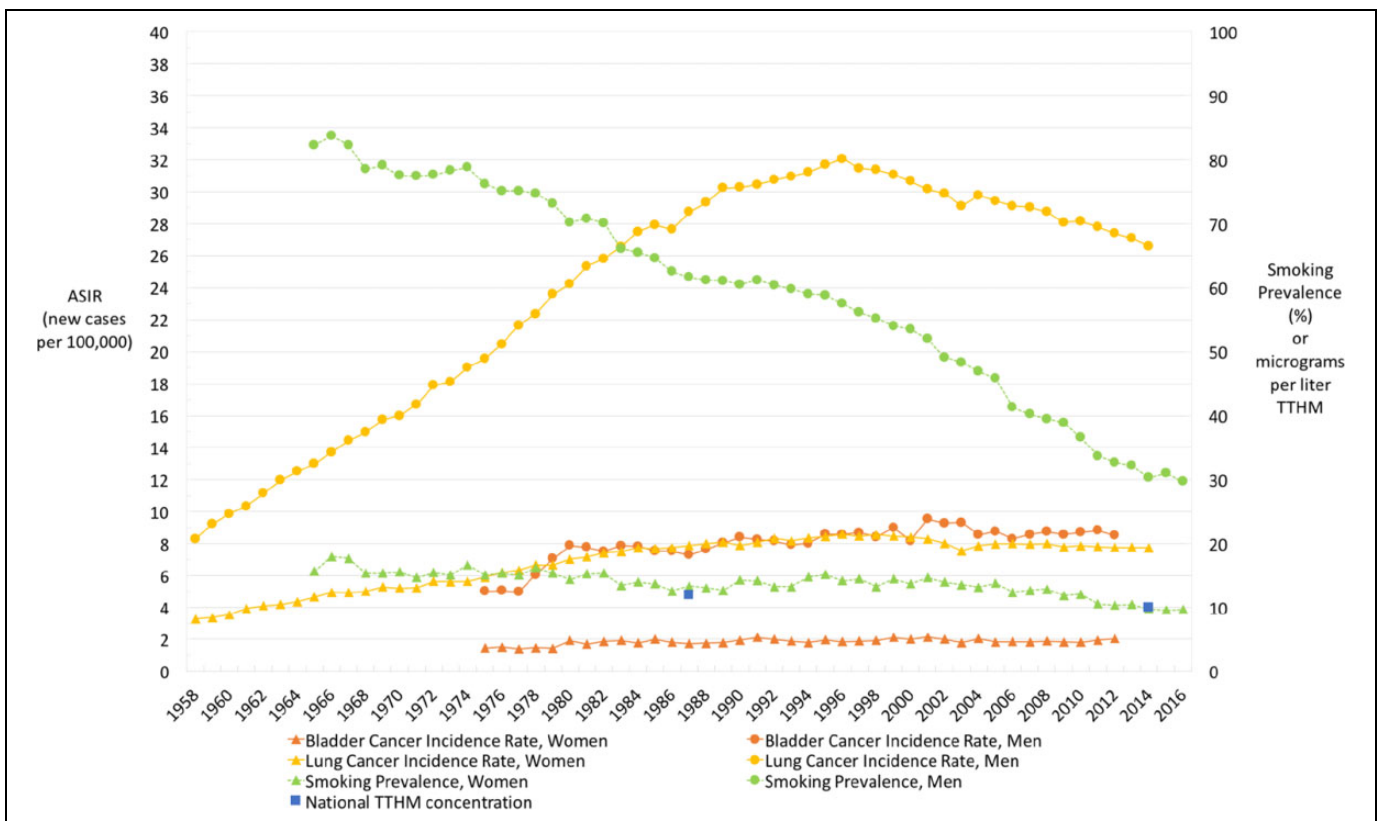
Figure 8. Japan: Annual age-adjusted smoking prevalence and bladder and lung cancer incidence, 1958 to 2016.

(1988), and 7.7/100 000 (2014). Cancer rates in Japan are about 60% of US rates, reflected in both bladder and lung cancer rates (GLOBOCAN, 2011). Bladder cancer incidence rates from 1965 to 2016 for women and men were lowest compared to other countries. Lung cancer rates were also low compared to Western countries.

Water Treatment and TTHMs

Approximately 75% of the population are on surface water supplies but much less for groundwater supplies. Since 1993, the TTHMs drinking water standard is 0.100 mg/L(100μg/L). Average concentrations of TTHMs in Japan were in the mid-50 μg/L range or less in surface water supplies in the 1970/1980s and reduced to around 10 μg/L by 1987 where they remain. Water treatment processes to reduce TTHMs were introduced in the 1970s. Increased GAC and ozone/granular carbon have achieved TTHMs reductions in cities located on rivers. Published TTHMs were 12 μg/L (1987) and 10 μg/L (2014) as water supply averages. Osaka using the Yodo River averaged 41 μg/L in 1981 and 60 μg/L until 1999. Ozone/granular carbon technology then reduced the average to 10 μg/L.

Given the high initial male smoking rates and the subsequent decline, and the very low incidence of bladder cancer in both sexes, a possible link between bladder cancer and smoking in that population is difficult to discern. TTHM concentration history does not indicate a relationship with bladder cancer.

Supplemental Sources

Cancer Registry and Statistics. *Cancer Information Service, National Cancer Center, Japan*. http://ganjoho.jp/reg_stat/statistics/dl/index.html. Accessed January 22, 2017.

GLOBOCAN. Global Cancer Observatory. http://healthhubs.net/cancer-cancer-rates-in-the-usa-compared-to-japan/. 2011. Accessed October 28, 2017.

Shinya E. *National Institute of Public Health, Japan*. Technology and TTHM data; 2017. Personal communications.

Discussion

The aim of this broad ecological study was to determine whether there were indications of linkages between TTHMs and bladder cancer trends. Bladder and lung cancer statistics, available TTHMs data, and water treatment trends were examined in 8 countries (U.S., Canada, Germany, UK, Netherlands, Sweden, Australia, and Japan) with diverse drinking water chlorination histories. Lung cancers were included because of their dominant association to smoking, a significant risk factor for bladder cancer.

National Trends Summary

National trends during the study period for TTHMs, smoking, bladder, and lung cancers by country and sex are summarized in Table 1 based upon the data presented in Figures 1 to 8.

National TTHM trends. The TTHM concentrations have declined or remained stable at low levels from the published reports and water treatment information from national regulatory authorities. The US averages halved between 1975 and 2015, and Canada's TTHM levels have also similarly declined between 1993 and 2010. The TTHM levels in the United Kingdom have approximately halved in the last 12 years.

Table 1. Summary of TTHM, Bladder and Lung Cancer Incidence, and Smoking Trends.[a]

Country	TTHM	Bladder Cancer ASIR		Lung Cancer ASIR		Smoking Prevalence	
		Male	Female	Male	Female	Male	Female
United States	↓	—	—	↓	↓-	↓	↓
Canada	↓	—	—	↓	↑	↓	↓
United Kingdom	↓	↓	↓	↓	↑	↓	↓
Germany	↓-	↓	–	↓	↑	↓	—
Netherlands	↓↓	↓-	↑-	↓	↑↑	↓	↓
Sweden	↓-	—	↑-	↓	↑↑	↓	↓-
Australia	—	↓	↓	↓	↑	↓	↓
Japan	↓	—	—	↓	—	↓↓	↓-

Abbreviations: ASIR, age-standardized incidence rate; TTHM, total trihalomethane.
[a] ↑, increasing trend; ↓, decreasing trend; -, modifier indicating a small effect; —, stable trend, little to no change.

Netherlands' TTHM levels have declined to <1 μg/L since virtual elimination of chlorination in 1993. Chlorination has been historically limited in Sweden and Germany, and they have not had significant chlorination usage changes, so their TTHM levels have likely remained low. Australia's standard has remained at 250 μg/L since 1996, so their TTHM levels have likely been consistently higher than the other countries. Japan's average TTHM concentrations have declined.

Detailed US TTHM data were available, but data were less comprehensive for other countries. The US downward TTHM trend and the Canadian trend were similar because of similar standards/guidelines and water treatment practices. The Canadian, and UK standards/guidelines are 100 μg/L. The UK information indicated that initial TTHM concentrations were generally somewhat lower than the United States and Canada's, with some exceptions. Germany's average TTHM levels have likely been lower than United States/Canada/United Kingdom because of their tradition of less chlorine usage, high proportion of groundwater usage, and standards limiting chlorine dosages and residual levels; the TTHM regulatory target level is also lower at 50 μg/L.

Average TTHM levels in German drinking waters had little change but perhaps slightly declined because of revised regulations. Netherlands reduced regular chlorine use in surface water supplies in the 1980s and essentially eliminated it by 1993; groundwater supplies generally have never been chlorinated. Earlier TTHM levels were similar to the United Kingdom's with averages from surface water sources likely in the 40 to 50 μg/L range but are currently <10 μg/L and often near zero. Sweden's TTHM concentrations in treated surface water supplies have historically likely been <50 μg/L, and water treatment practices have not changed significantly. Australia's TTHM guideline value is 250 μg/L, and chlorination practices have not changed significantly. The recent weighted average TTHM level was 85 μg/L for 67% of the population. Japan's national TTHM standard has been 100 μg/L since 1993.

Table 2. Smoking Prevalence Trends.[a]

	Male		Female	
Country	Peak %	Recent %	Peak %	Recent %
Netherlands	90	21	40	24
Japan	82	30	16	10
United Kingdom	75	21	42	17
Sweden	62	11	32	12
Canada	58	24	40	17
United States	55	17	34	14
Germany	46	12	27	24
Australia	45	23	30	19

[a]A "Peak" is defined as the highest prevalence across all years for which data are available. "Recent" is the current prevalence based on the most recent years of available data.

Chlorine is commonly used but treatment practices have been modifying since the 1970s/1980s. The TTHM concentrations have declined from the mid-50 μg/L levels for surface water supplies to about 10-12 μg/L in 1987 and beyond.

National smoking trends. National smoking trends for males and females have been in decline since the 1960s/1970s, but peak levels were different among the countries in this study (Table 2) based upon the data sources. Smoking prevalence was significantly lower among females than males in the early years but was more similar to males in several countries in intermediate years.

Tobacco smoke is a tumor-initiator carcinogen, and the induced inflammation is a promotor of carcinogenicity.[36] This is consistent with the findings that lung cancer risk decreases by 21% within 5 years of ceasing smoking,[53] and by half 10 years after smoking ceases, and risk of bladder cancer also decreases.[37]

National bladder cancer trends. Incidence of bladder cancer did not usually reflect declines in smoking rates; available data may not have exceeded the required latency period, and a greater effect might appear in later years. Incidence of male bladder cancer has been level or decreasing somewhat in recent years except for Sweden and Japan where it may have leveled. Female rates are lower than males but declining in the United Kingdom and Australia, increasing in Sweden and Japan, and level in United States, Canada, Germany, and the Netherlands. Smoking is an important risk factor for bladder cancer, and smoking rates have declined in all countries; male lung cancer generally decreased but increased for women. Japan has the lowest bladder cancer rates for both males and females. The ratios of male and female rates have ranged from 3.5 in the United States, 4 to 3.6 in Canada, 3.6 to 3.4 in the United Kingdom, 5.1 to 3.6 in the Netherlands, 4.3.to 3.6 in Germany, 2.9 to 3.2 in Sweden, 1.8 to 2.1 in Australia, and 3.3 to 4.25 in Japan.

Conclusions

Bladder cancer is a disease of older age with numerous major and minor risk factors that include gender, smoking, diabetes mellitus type 2, ethnicity, chemicals, occupations, arsenic, HIV, medical radiation, and certain drug treatments. There is not a consensus on latency period, but it may be well over 30 years based upon the median age at diagnosis (73 years in the United States). Incidence rates are country specific and have often been constant over many recent years. Male rates are 2 to 5 times greater than female rates. General smoking and lung cancer incidence data trends among the 8 nations were similar and country specific. Numerous factors contribute to bladder cancer risk, but there must be some different factors operating in the various countries; some may reflect differences of ethnic populations in the countries, as indicated in the US population data, where people identified as black, Hispanic, Asian/Pacific Islanders, and American Indian have significantly lower incidences than non-Hispanic whites.

Some increased bladder cancer risk has been the only partly consistent finding in some TTHM/drinking water epidemiology studies over the years. This study did not observe obvious linkages between TTHMs and bladder cancer trends in the 8 countries. Age-related bladder cancer accounts for about 5% of cancer incidence in the United States. Recent increases among women in Sweden and Japan reflect increases in smoking rates. Bladder cancer incidences were generally consistent with significant reductions in smoking prevalence. Occupational exposures to known agents such as aromatic amine dyes have likely been reduced, but other occupations indicated increased risks in Swedish studies.

The TTHMs have been regulated for almost 40 years as potential surrogates for other nondefined DBPs, but THMs themselves are not carcinogenic in water bioassays and are not very active in several cellular genotoxicity and cytotoxicity tests. It is doubtful that TTHMs are a suitable surrogate for other DBPs that may be carcinogens.[12] Woo et al[18] found no high-concern chemicals in the structure–activity assessments of 209 DBPs for potential carcinogenicity; most were in the low/marginal concern categories. Additional studies could aim to determine whether TTHM concentrations correlate with any of the medium or high–medium category chemicals.

Evidence for associations between DBP exposure and cancer risk remains inconsistent, and chemical toxicology does not correlate well with the positive epidemiology results, except possibly with certain genetic polymorphisms and organobromine chemicals that require further exploration. The USEPA has stated that the risks for bladder cancer derived from the several positive epidemiology results may actually be zero due to lack of established causality.

There are significant problems with attempting to correlate DBP chemicals in drinking water with potential low-risk chronic exposure health outcomes. The capability of traditional epidemiology studies to identify and quantify possible relationships between bladder cancer and TTHMs or other DBPs is limited because (1) latency periods for bladder cancer are not known, but lengthy; (2) the potential risks are likely small; and (3) long-term water composition and exposure contributors are so diverse and variable that exposure quantification requires major assumptions.

The latter is especially problematic. Distributed tap water DBP levels constantly change due to seasonal and system-specific variations and usage rates. Moreover, direct water consumption varies, and water composition changes occur during cooking and from uses in beverages and diet and are highly variable and difficult to quantify by recall surveys. Indirect sources also change the composition of at least some of the DBPs, that is, heating drives chemical reactions to completion and causes loss of volatiles. Exposures to some water components occur by inhalation during bathing, showering, and indoor air transmission. Dermal exposures to hydrophobic DBPs occur during bathing and showering. In addition, other significant exposures occur from chlorinated swimming pools, spas and therapy pools, immersion, inhalation at the water surface while swimming, dermal contact, incidental water ingestion, and from inhalation of volatiles from the air in indoor pool environments.[38]

Consumer choice variables adding to the complexity of DBP exposure assessments include changing rates of bottled water and bottled beverage consumption by age-group and over time. The default daily drinking water consumption value used in most risk assessments is 2 L/day, equal to about the 90th percentile of the population.[39] Mineral waters are not chlorinated. Processed bottled water from public drinking water sources is usually treated by ozonation and granular activated carbon (GAC) or Reverse Osmosis (RO), or both. The International Bottled Water Association Standard for TTHMs is 0.010 mg/L. Bottled water consumption in the United States in 2016 was 39.3 gallons/capita/year (almost a half-liter per person per day on average) up 9% from 2015, compared to 16.2 gallons/capita in 1999 and 1.6 gallons/capita in 1976. There are also significant regional differences, with Southwestern US consumption of 61.9 and Pacific 53.5 gal/capita/year versus West-central and East-central regions of 16.7 and 17.1 gal/capita/year, respectively. Bottled water consumption is in addition to bottled carbonated and still beverage consumption of 38.6 gallons in 2016.[40,41] Many refrigerators now come with carbon filters built into their water dispensers for drinking water and icemakers. Tap point-of-use or point-of-entry water treatment involving carbon cartridges or reverse osmosis units have also increased, adding to the population lifetime exposure quantitation problem. Pitchers have diverse treatments.

Quantifying exposures over the perhaps 30 or more years of bladder cancer latency is a major challenge, and simplifying assumptions are fraught with uncertainties perhaps not possible within limits smaller than the putative risks being investigated. Imprecise exposure variables and multiple contributing risk factors may be larger than the magnitude of potential water treatment-related risks being studied, thus making further studies of the same type not necessarily likely to resolve the issue.

Summation

This 8-country trend comparison did not find a strong or consistent linkage between TTHMs and bladder cancer. Latency periods may be longer for bladder cancers than for lung cancers, indicated by declines in lung cancer following declines in smoking prevalence (while bladder cancer did not always show declines following decreased smoking prevalence). Smoking is a dominant risk factor, among many others, making it difficult to attribute some portion of bladder cancer incidences or reductions to other factors such as TTHMs.

National trends in some countries showed increases in bladder cancer while TTHMs were either stable or decreasing; one country had higher TTHMs where bladder cancer was decreasing. Challenges in identifying a low-risk association could be that a longer exposure time period might be required if a risk exists and that combined sources of varying risk are difficult to isolate and quantify. This study sheds light on the limitations, where long-term variable exposures are occurring and limited data are available. While this ecological trend analysis of national-level data could not determine causal associations, it was robust in its breadth of observations across multiple countries and several decades.

Given the long latency period, the difficulty in precisely defining exposure to TTHM exposure, and the multitude of confounding factors, it may be very difficult to identify the contributing bladder cancer risks in epidemiologic studies. The results do not preclude drinking water being a contributing factor, but, if so, the contribution must be small. It may be that studies comparing populations consuming chlorinated versus nonchlorinated water would provide a better opportunity to resolve the issue. Also, perhaps studies of populations in communities never using chlorinated drinking water but regular users of chlorinated swimming pools could be useful. Multiple replications and consistent findings in very well-designed studies comparing carefully matched populations would be required. Since the latency period for bladder cancer is lengthy, it might be necessary for further studies to be conducted in 10 or 20 years when smoking rates have further stabilized.

Ecological studies such as this are intended to provide inferences and stimulate additional research to test them. Bladder cancer is a disease of older age, and its etiology is very complex with many contributing factors of varying degree. The potential for a measurable drinking water contribution to bladder cancer risk is not obvious from this review. This study points out the uncertainties caused by very imprecise drinking water TTHM exposure assessments, with assumptions that may have a greater range than the potential risks being assessed. This study shows the diversity of trends across several countries. It supports epidemiologic findings that bladder cancer risk from drinking water, if any, is small, and it is probably overwhelmed by many other larger risk factors such as smoking, diabetes, and other country-specific aspects.

Although potential drinking water bladder cancer risks remain uncertain and likely small compared to several other factors, DBP management using measurable surrogates remains an appropriate and practical strategy for maintaining drinking water quality and avoiding excessive unnecessary exposures. However, as reiterated by WHO, DBP management decisions should never compromise microbial disinfection efficacy and they should reflect costs and identifiable benefits.

Appendix A

Table A1. Summary of Data Sources for National Average TTHM Concentration in Drinking Water in the United States.

Time Period	Data Source	Sample Location	Statistical Summary	No. of Water Systems
1975	NORS	Finished water	Single samples	80
1975-1976	NOMS (phase 1)	Finished water	Single samples	111
1984-1986	AwwaRF	Distribution system	Single samples	727
1988-1989	35 City Survey	Finished water	Single samples averaged over 4 quarters	35
1997-1998	ICR	Distribution system	Average of 6 quarterly samples	479
2006-2010	6 Year Review	Distribution system	Single samples	167,000
2012-2015	Seidel (2017)	Distribution system	95th % quarterly samples	394

Abbreviations: NORS, National Organics Reconnaissance Survey; TTHM, total trihalomethanes.
Sources
McGuire MJ, Meadow RG. AWWARF Trihalomethane Survey. *J Am Water Works Assoc.* 1988;80(1):61-68.
McGuire MJ, McLain JL, Obolensky A. *Information Collection Rule (ICR) Data Analysis*. Denver, CO: AWWA Research Foundation and American Water Works Association; 2002.
McGuire MJ, Graziano N. *Trihalomethanes in US Drinking Water: NORS to ICR*. American Water Works Association; 2002.
Seidel CJ, Samson CC, Bartrand T, Ergul A, Summers RS. Disinfection byproduct occurrence at large water systems after stage 2 DBPR. *J Am Water Works Assoc.* 2017;109:17–30. doi:10.5942/jawwa.2017.109.0082
Symons JM, Bellar TA, Carswell JK, et al. National Organics Reconnaissance Survey (NORS) for Halogenated Organics. *Am Water Works Assoc J.* 1975;83(11):634-648.
U.S. Environmental Protection Agency. Six-year review 3 of drinking water standards; 2016. https://www.epa.gov/dwsixyearreview/six-year-review-3-drinking-water-standards.

Table A2. Summary of National Annual Bladder and Lung Cancer Incidence Data Sources.

Country	Time Period Lung Cancer	Time Period Bladder Cancer	Data Source
United States	1975-2014	1975-2014	National Cancer Institute, SEER Cancer Statistics Review
Canada	1988-2013	1988-2013	Government of Canada and the Canadian Cancer Society, 2017 Canadian Cancer Statistics Report
Australia	1982-2013	1982-2013	Australian Institute of Health and Welfare, Australian Cancer Incidence and Mortality Books
Germany	1995-2013	1995-2013	German Centre for Cancer Registry Data and the Robert Koch Institute
UK	1991-2012	1993-2014	Cancer Research United Kingdom
Sweden	1960-2014	1960-2014	NORDCAN
Netherlands	1989-2007	1989-2007	EUREG
	2012	-	EUCAN
Japan	1975-2014	1958-2014	Cancer Information Service, National Cancer Center, Japan

Abbreviations: NORDCAN, Cancer Statistics for the Nordic Countries; EUREG, European Network of Cancer Registries; EUCAN, Cancer Incidence Mortality and Prevalence in the European Union.
Sources
United States—National Cancer Institute, SEER Cancer Statistics Review.
Howlader N, Noone AM, Krapcho M, et al., eds. *SEER Cancer Statistics Review, 1975-2014, National Cancer Institute*. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
Canada—Government of Canada and the Canadian Cancer Society, 2017 Canadian Cancer Statistics Report.
Canadian Cancer Statistics. *Canadian Cancer Society's Advisory Committee on Cancer Statistics*. Toronto, ON: Canadian Cancer Society; 2017. cancer.ca/Canadian-CancerStatistics-2017-EN.pdf. Accessed June 28, 2017.
Australia—Australian Institute of Health and Welfare, Australian Cancer Incidence and Mortality Books.
Australian Institute of Health and Welfare (AIHW). *Australian Cancer Incidence and Mortality (ACIM) books: Bladder Cancer*. Canberra: AIHW; 2017. http://www.aihw.gov.au/acim-books.
Germany—German Centre for Cancer Registry Data and the Robert Koch Institute.
German Centre for Cancer Registry Data, Robert Koch Institute. www.krebsdaten.de/database. Accessed September 29, 2017.
Cancer in Germany, 1995-1996. Incidence and Trends. Second edition. Robert Koch Institute (ed.) and Association of Population-based Cancer Registries in Germany (ed.).
Cancer in Germany, 1997-1998. Incidence and Trends. Third edition. Robert Koch Institute (ed.) and Association of Population-based Cancer Registries in Germany (ed.).
UK—Cancer Research UK
Cancer Research UK, 2017. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer#heading-Three.
Netherlands—EUREG, EUCAN
Steliarova-Foucher E, O'Callaghan M, Ferlay J, et al. *European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe. Version 1.0*. European Network of Cancer Registries, International Agency for Research on Cancer; 2012. http://eco.iarc.fr. Accessed July 6, 2016.
Sweden—NORDCAN
Engholm G, Ferlay J, Christensen N, et al. *NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.3*. Association of the Nordic Cancer Registries; 2016. Danish Cancer Society. http://www.ancr.nu. Accessed September 29, 2017.
Japan—Cancer Information Service, National Cancer Center, Japan.
Cancer Information Service, National Cancer Center, Japan. http://ganjoho.jp/en/professional/statistics/table_download.html. Accessed October 6, 2017.

Table A3. Summary of National Smoking Prevalence Data Sources.

Country	Time Period	Data Source
United States	1955-1978	Smoking and Health: A Report of the Surgeon General, 1979
	1959, 1977, 1979-1996	ISS
	1997-2012	NHIS, Summary Health Statistics Reports
	2013-2015	NHIS, Summary Health Statistics Tables
Canada	1965-2004	ISS
Australia	1974-2004	ISS
Germany	1990-2014	ISS
United Kingdom	1955-2014	ISS
Sweden	1963-2005	ISS
Netherlands	1958-2012	ISS
Japan	1965-2016	National Institute of Public Health, Japan

Sources

US, Canada, Australia, Netherlands, Sweden, UK, Germany—ISS (International Smoking Statistics).

Forey B, Hamling J, Hamling J, Thornton A, Lee P. *International Smoking Statistics WEB Edition*. 2016. http://www.pnlee.co.uk/ISS.htm. Accessed July 11, 2016.

US—Smoking and Health: A Report of the Surgeon General, 1979.

Cigarette smoking in the United States, 1950-1978. *Smoking and Health: A Report of the Surgeon General, 1979*. United States Public Health Service. Office of the Assistant Secretary for Health. Office on Smoking and Health. A-1 to A-29. Available from https://profiles.nlm.nih.gov/ps/access/nnbcph.pdf.

US—NHIS Summary Health Statistics Tables.

CDC/National Center for Health Statistics, 2017. Tables of summary health statistics. National Health Interview Survey. https://www.cdc.gov/nchs/nhis/SHS/tables.htm.

US—NHIS Summary Health Statistics Reports.

Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: National Health Interview Survey, 2012. National Center for Health Statistics. *Vital Health Stat.* 2014;10(260).

Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. National Center for Health Statistics. *Vital Health Stat.* 2001;10(205).

Lethbridge-Çejku M, Rose D, Vickerie J. Summary health statistics for U.S. Adults: National Health Interview Survey, 2004. National Center for Health Statistics. *Vital Health Stat.* 2006;10(228).

Lethbridge-Çejku M, Vickerie J. Summary health statistics for U.S. adults: National Health Interview Survey, 2003. National Center for Health Statistics. *Vital Health Stat.* 2003;10(225).

Lethbridge-Çejku M, Schiller JS, Bernadel L. Summary health statistics for U.S. Adults: National Health Interview Survey, 2002. National Center for Health Statistics. *Vital Health Stat.* 2004;10(222).

Lucas JW, Schiller JS, Benson V. Summary health statistics for U.S. Adults: National Health Interview Survey. National Center for Health Statistics. *Vital Health Stat.* 2001;10(218).

Pleis JR, Ward BW, Lucas JW. Summary health statistics for U.S. adults: National Health Interview Survey, 2009. National Center for Health Statistics. *Vital Health Stat.* 2009;10(249).

Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. National Center for Health Statistics. *Vital Health Stat.* 2008;10(242).

Pleis JR, Lucas JW. Summary health statistics for U.S. adults: National Health Interview Survey. National Center for Health Statistics. *Vital Health Stat.* 2007;10(240). 2009.

Pleis JR, Lethbridge-Çejku M. Summary health statistics for U.S. adults: National Health Interview Survey, 2006. National Center for Health Statistics. *Vital Health Stat.* 2007;10(235).

Pleis JR, Lethbridge-Çejku M. Summary health statistics for U.S. adults: National health interview survey, 2005. National Center for Health Statistics. *Vital Health Stat.* 2005;10(232).

Pleis JR, Benson V, Schiller JS. Summary health statistics for U.S. Adults: National Health Interview Survey, 2000. National Center for Health Statistics. *Vital Health Stat.* 2000;10(215).

Pleis JR, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey,. National Center for Health Statistics. *Vital Health Stat.* 1999;10(212). 2003.

Pleis JR, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey. National Center for Health Statistics. *Vital Health Stat.* 1998;10(209). 2002.

Schiller JS, Lucas JW, Peregoy JA. Summary health statistics for U.S. adults: National Health Interview Survey. National Center for Health Statistics. *Vital Health Stat.* 2011;10(256). 2012.

Schiller JS, Lucas JW, Ward BW, Peregoy JA. Summary health statistics for U.S. adults: National Health Interview Survey. National Center for Health Statistics. *Vital Health Stat.* 2010;10(252). 2012.

Japan—National Institute of Public Health, Japan.

Asami M. Chief Senior Researcher in the Department of Environmental Health, National Institute of Public Health, Japan. Cancer incidence and smoking trends data. 2017. Personal communications.

Authors' Note

This was presented in part at the Water Quality Technology Conference, Toronto, Ontario, Canada in November 2018. An extract of US and Canadian portions and introductory and supporting information has been submitted to the Journal of the American Water Works Association, as Cotruvo JA, Amato HK. Trihalomethanes:

Concentrations, cancer risks and regulations. *J Am Water Works Associat*. 2019;111(1):12-20.

Declaration of Conflicting Interests

Funding

References

1. Bellar TA, Lichtenburg JJ, Kromer RC. The occurrence of organohalides in finished drinking waters. *J Am Water Works Assoc*. 1974;66(12):703-706.

2. Rook. Formation of haloforms during chlorination of natural waters. *Water Treat Exam*. 1974;23:234-243.

3. NIPDWR. National interim primary drinking water regulations: Control of trihalomethanes in drinking water. *Federal Register*. 1979;44(231):68624-68707.

4. NPDWR. National primary drinking water regulations: Disinfectants and disinfectant byproducts. *Federal Register*. 1998; 63(241):69390-69476. December 16.

5. NPDWR. National primary drinking water regulations: Stage 2 disinfectants and disinfectant byproducts. *Federal Register* 2006; 71(2):388-493. January 4.

6. Jorgenson TA, Meierhenry EF, Rushbrook CJ, Bull RJ, Robinson M. Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3F1mice. *Fundam Appl Toxicol*. 1985;5(4):760-769.

7. NTP. NTP Toxicology and carcinogenesis studies of bromodichloromethane (CAS No. 75-27-4) in male F344/N rats and female B6C3F1 mice (Drinking Water Studies). *Natl Toxicol Program Tech Rep Ser*. 2006;(532):1-248.

8. WHO/GDWQ. *World Health Organization Guidelines for Drinking-Water Quality 4th Edition, and 1st Addendum*. 2017. http://www.who.int/water_sanitation_health/publications/drinking-water-quality-guidelines-4-including-1st-addendum/en/. Accessed October 10, 2018.

9. Larson JL, Templin MV, Wolf DC, et al. A 90–day chloroform inhalation study in female and male B6C3F1 mice: implications for cancer risk assessment. *Fundam Appl Toxicol*. 1996;30(1): 118-137.

10. Hrudey SE. Epidemiological inference and evidence on DBPs and human health. In: Hrudey SE, Charrois JWA, eds. *Disinfection Byproducts and Human Health*. London, UK: IWAPublishing; 2012:213-281.

11. Bull RJ, Rice G, Teuschler L, Feder P. Chemical measures of similarity among disinfection by-product mixtures. *J Toxicol Environ Health A*. 2009;72(7):482-493.

12. Bull RJ. Toxicological evaluation of experimental data that informs the magnitude of cancer risk from disinfection by-products. In: Hrudey SE, Charrois JWA, eds. *Disinfection Byproducts and Human Health*. London, UK: IWAPublishing; 2012:179-212.

13. USEPA. NPDR stage 2 disinfectants and disinfection byproducts rule. Proposed Rule Parts 141, 142, and 143. 68 FR, 49548-49681. 2003.

14. Regli S, Chen J, Messner M, et al. Estimating potential increased bladder cancer risk due to increased bromide concentrations in sources of disinfected drinking waters. *Env Sci & Technol*. 2015; 49(22):1394-1302.

15. USEPA. NPDR stage 2 disinfectants and disinfection byproducts rule. *40 CFR Parts 9, 141, 142. FR* 2006;71(2):388-494.

16. Huang Y, Zhang H, Zamyadi A, Andrews S, Hoffman R. Predicted impact of aeration on toxicity from trihalomethanes and other disinfection by-products. *Am Water Works Assoc J*. 2017; 100(10):13-21.

17. Plewa MJ, Wagner ED. *Mammalian Cell Cytotoxicity and Genotoxicity of Disinfection By-Products*. Denver: Water Research Foundation; 2009.

18. Woo YT, Lai D, McClain JL, Manibusan MK, Delarco V. Use of mechanism-based structure- activity relationships for drinking water disinfection by-products. *Env Health Perspectives*. 2002; 110(Supplement 1):75-87. February.

19. Hrudey SE, Backer LC, Humpage AR, et al. Evaluating evidence for association of human bladder cancer and drinking water chlorination disinfection by-products. *J Toxicol Environ Health B Critical Rev*. 2015;18(5):213-241. 4 July 2016.

20. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*. 2010; 46(4):765-781.

21. Centers for Disease Control and Prevention (CDC). *Special Topics. Cancer Types Grouped by Race and Ethnicity*. 2017. https://nccd.cdc.gov/uscs/cancersbyraceandethnicity.aspx. Accessed October 31, 2018.

22. Bladder Cancer. 2017. https://www.kenresearch.com/blog/2017/04/epicast-report-bladder-cancer-epidemiology-forecast-2025-ken-research/. Accessed October 30, 2018.

23. SEER. Cancer of the urinary bladder-cancer stat facts. 2017. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed December 2, 2017.

24. Action. The facts about bladder cancer. 2017. http://actionbladdercanceruk.org/the-facts-about-bladder-cancer/. Accessed December 2, 2017.

25. Diapedia. *Bladder Cancer and Diabetes*. 2014. http://www.diapedia.org/associated-disorders/661044761/bladder-cancer-and-diabetes. Accessed October 30, 2018.

26. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia*. 2006; 49(12):2819-2823.

27. Zhu Z, Wang X, Shen Z, Lu Y, Zhong S, Xu C. Risk of Bladder Cancer in patients with diabetes mellitus: an updated meta-analysis of 36 observational studies. *BMC Cancer*. 2013;13:310. June.

28. Michaud DS, Kogevinas M, Cantor KP, et al. Total fluid and water consumption and the joint effect of exposure to disinfection by-products on risk of bladder cancer. *Environ Health Perspect*. 2007;115(11):1569-1572. https://doi.org/10.1289/ehp.10281.

29. Chawki S, Ploussard G, Montlahuc C, et al. Bladder cancer in HIV-infected adults: an emerging issue? Case reports and

systematic review. *PLoS One*. 2015;10(12):e0144237. doi.1371/journal.pone.144237.

30. Lamm SH, Engel A, Kruse MB, et al. Arsenic in drinking water and bladder cancer mortality in the United States: an analysis based on 133 U.S. counties and 30 years of observation (1950-1979). *J Occup Environ Med*. 2004;46(3):298-306.

31. Tsuji J, Alexander DD, Perez V, Mink PJ. Arsenic exposure and bladder cancer. toxicology. 2014;317:17-30. 20 March.

32. Mendez WM, Eftim S, Cohen J, et al. Relationships between arsenic concentrations in drinking water and lung and bladder cancerincidence in U.S. counties. *J Expo Sci Environ Epidemiol*. 2016;27:235-243.

33. Miyakawa M, Tachibana M, Miyakawa A, et al. Re-evaluation of the latent period of bladder cancer in dyestuff-plant workers in Japan. *Int J Urol*. 2001;8(8):423-430.

34. Scarselli A, et al. Annali dell'instituto superiore di sanita. *Section II*. 2011;47(2):200-206. http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0021-25712011000200012. Accessed October 26, 2017.

35. Tugulea A-M.*Health Canada, Exposure and Biomonitoring Division, Environmental Health Science and Research Bureau, Environmental and Radiation Health Sciences Directorate*. Personal communication. 2017. January 9, 2017.

36. Takahashi H, Ogata H, Nishigaki R, Broide DH, Karin M. Tobacco smoke promotes lung tumorigenesis by triggering IKK-beta- and JNK1-dependent inflammation. *Cancer Cell*. 2010;17(1):89-97.

37. WHO World Health Organization. Tobacco Free Initiative Fact Sheet. 2017. http://who.int/tobacco/quitting/benefits/en/. Accessed December 3, 2017.

38. Villanueva CM, Gagniere B, Monfot C, Nieuwenhuijsen MJ, Cordier S. Sources of variability in levels and exposure to trihalomethanes. *Environ Res*. 2007;103(2):211-220.

39. USEPA. Estimated Per Capita Water Ingestion and Body Weight in the United States, An Update. Based on Data Collected by the United States Department of Agriculture's 1994–1996 and 1998. EPA 822-R-00-001. HERO ID 730449, 2004.

40. IBWA. Bottled Water Market. 2016. http://www.bottledwater.org/economics/bottled-water-market. Accessed October 30, 2018.

41. Statistica. U.S. Bottled Water Market Statistics & Facts. 2015. https://www.statista.com/statistics/183377/per-capita-consumption-of-bottled-water-in-the-us-since-1999/2015. Accessed October 30, 2018.

42. American Cancer Society. Bladder Cancer Risk Factors. 2017. https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html. Accessed October 30, 2018.

43. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urology*. 2013;63(2):234-241. http://www.europeanurology.com/article/S0302-2838(12)00878-0/fulltext.

44. Canada. 2017. https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table-health-canada-2012.html.

45. Cantor KP, Villanueva CM, Silverman DT, et al. Polymorphisms in GSTT1, GSTZ1, and CYP2E1, disinfection by-products, and risk of bladder cancer in Spain. *Environ Health Perspect*. 2010;118(11):1545.

46. Hrudey SE. Chlorination Disinfection by-Products (DBPs) in drinking water and public health in Canada. *Cancer Observatory*. 2008. http://healthhubs.net/cancer/cancer-rates-in-the-usa-compared-to-japan/.2011. Accessed October 28, 2017.

47. American Cancer Society. 2016/2017. https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html. Accessed October 23, 2017.

48. Cancer Research UK, 2017. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer#heading-Three. Accessed October 27, 2018.

49. Hrudey SE, Fawell J. 40 years on: what do we know about drinking water disinfection by-products and human health? *Water Sci Technol: Water Supply*. 2015;15(4):667-674. July.

50. Saint-Jacques N, Parker L, Brown P, et al. Arsenic in drinking water and urinary tract cancers: asystematic review of 30 years of epidemiological evidence. *Environ Health*. 2014;13:44.

51. Williams DT, LeBel GL, Benoit FM. Disinfection byproducts in Canadian drinking water. *Chemosphere*, 1997;34(2):299.

52. Lilienfeld AM. The relationship of bladder cancer to smoking. *AJPH* 1964;54(11):1864-1875.

53. Webmed. 2008. www.webmed.com/smoking-cessation/news/20080506/quit-smoking-death-rate-risk-drops-fast#1. Accessed October 27, 2018.

54. Ross MK, Pegram R. In vitro biotransformation and mutagenicity of the drinking water disinfection by-product: DNA binding mediated by glutathione transferase theta 1-1. *Toxicol Appl Pharmacol*. 2004;195:166-181.

55. USEPA. *Six-Year Review 3 of Drinking Water Standards, 2016. U.S. Environmental Protection Agency*. 2016. https://www.epa.gov/dwsixyearreview/six-year-review-3-drinking-water-standards.

56. WHO/GDWQ. *World Health Organization Guidelines for Drinking-water Quality 4th edition*. 2017. ISBN 978 92 4 154815 1. 2011. http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/.