RISK OF URINARY TRACT CANCER FROM EXPOSURE TO ARSENIC IN DRINKING WATER

by

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“If you aren't in over your head, how do you know how tall you are?”

— T.S. Eliot

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ABSTRACT

Background: Nova Scotia (NS), a province of Atlantic Canada, has high rates of urinary bladder and kidney cancers. The causes driving this excess burden are unknown. Exposure to high-levels of arsenic—a naturally occurring carcinogen in drinking water—is associated with a range of health effects, including bladder and potentially, kidney cancer. The threshold at which cancer develops is uncertain at lower-levels of exposure, but recent studies suggest health risks at levels previously considered safe (i.e. current regulatory guidelines of 10 μg/L). NS arsenic-rich geology contributes to elevated levels of arsenic in some private water wells—the source upon which 45% of the population is reliant. This thesis quantifies the risk of developing urinary cancers from exposure to arsenic-contaminated drinking water; contributes knowledge about cancer risk at lower levels of exposure and sheds light on the excess of urinary cancers in NS.

Methods: First, using a meta-analytical literature review framework, this study quantifies the risk of bladder/kidney cancer at varying levels of arsenic exposure. Second, using socio-demographic data, the study develops and validates proxies to smoking to adjust for variations in cancer risk due to this important co-factor. Third, geospatial methods—Besag York and Mollié model and Local Expectation maximization algorithm—are applied to examine spatial and spatio-temporal patterns of urinary cancers in NS. Fourth, using a Bayesian approach, urinary cancer risk is modeled at levels around 10 μg/L.

Results: Based on meta-analytical findings, exposure to 10 μg/L of arsenic in drinking water may increase the risk of bladder cancer by at least 40%. Based on findings from NS, exposure to 2–5 μg/L and >5 μg/L of arsenic may increase the risk of bladder cancer by 16% and 18%, respectively and; similarly, the risk of kidney cancer by 5% and 14%, respectively

Conclusions: The study suggests an increased urinary cancer risk from exposure to arsenic-levels around regulatory limits. It also suggests that 115,000 Nova Scotians may be at an increased risk of urinary cancer due to arsenic-contaminated well water. The findings contribute to the international body of evidence suggesting the need for a reassessment of regulatory limits for arsenic in drinking water.

LIST OF ABBREVIATIONS USED

AS	Arsenic
[AS]	Arsenic concentration
BW	Bandwidth
BYM	Besag York and Mollié
BMI	Body mass index
CB	Cape Breton
CSD	Census sub-divisions
DA	Dessimination areas
EA	Enumeration areas
FIG	Figure
ICDO	International classification of disease for oncology
INLA	Integrated Nested Laplace Approximations
MAC	Maximum acceptable concentration
MAUP	Modifiable areas unit problem
MWSZ	Municipal drinking water supply zone
NS	Nova Scotia
NSE	Nova Scotia Department of Environment
PCA	Principal component analysis
PCCF+	Postal code conversion file
PM	Premature mortality
PUBMED	Public/Publisher MEDLINE
RR	Relative rate
SIR	Standardised incidence rate
SMR	Standardised mortality rate
SW	Southwestern Nova Scotia
US	United States of America
UTC	Urinary tract cancer
WHO	World Health Organization

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CHAPTER 1— Introduction

This is a doctoral dissertation composed of a collection of research papers published as journal articles or to be submitted for publications. A general introduction describes the scope of the research presented, placing the content of each published article in a broader international context. A general conclusion closes the work by integrating findings from each published article and by explaining their contribution to the broader international body of research. Each article is presented as a thesis chapter that comprises the following sections: Abstract, Introduction, Methodology, Results, Discussion and Conclusions.

1.1 Background

Cancer is a chronic disease that affects over 14 million people worldwide annually (Ferlay et al. 2013). Across the globe, it is responsible for an approximate 8 million deaths each year. Prostate, breast, colorectal and lung cancer are the most common type of cancer, accounting for about 42% of all reported cases (Ferlay et al. 2013). Urinary tract cancers such as that of the urinary bladder and kidney are comparatively less common; bladder being the ninth most common type of cancer worldwide (~430,000 cases per year) and 13th most common cause of death from cancer (~ 165,000 death per year); kidney ranking 13th in terms of incidence (~338,000 cases per year) and 16th in

terms of cancer related mortality (~144,000 death per year; (Ferlay et al. 2013; Parkin 2008).

1.2 Urinary Tract Cancer Risk

Internationally, the incidence rates of urinary tract cancers have been reported to vary as much as ten-fold between countries (Ferlay et al. 2013; Parkin 2008). For bladder cancer, age-standardized rates tends to be higher in North America (11.6 per 100,000), Europe (9.6 per 100,000), North Africa (Egypt: 13.1 per 100,000) and Western Asia (10.6 per 100,000) and; lower in South-Eastern and South-Central Asia (2.5 and 2.2 per 100,000, respectively). For kidney cancer, age-standardized rates tend to also be higher in North America (11.7 per 100,000) and Europe (8.8 per 100,000) along with Australia/New Zealand (9.3 per 100,000) and; lower in Africa (1.2 per 100,000) and South-central Asia (1 per 100,000). Over time, several countries show increasing incidence for both bladder and kidney cancers, although with evidence of some stabilization or even decreases during the 1990s (Mathew et al. 2002; Parkin 2008). Regardless of the region or time period, rates of bladder cancer are consistently higher for males (Burger et al. 2012; Janković and Radosavljević 2007; Leppert et al. 2006; Mathew et al. 2002; Shariat et al. 2010). In fact, in most developed countries, males have at least a three to five time greater risk than females. Rates of kidney cancer in males are generally twice of those in females (Burger et al. 2012; Mathew et al. 2002).

In Canada, bladder cancer is the fourth leading cancer cause amongst males; kidney cancer is the sixth (Canadian Cancer Society and National Cancer Institute of Canada 2015). Over time, incidence rates for bladder cancer increased from 1970 to 1981 and

have since gradually declined or stabilized (De et al. 2014; Kachuri et al. 2013). Kidney cancer rates have also stabilized in recent years among females, but continue to increase at a rate of about 1.3 % among males (Canadian Cancer Society and National Cancer Institute of Canada 2015; Government of Canada 2015; Kachuri et al. 2013; Liu et al. 1997). In 2012, these rates positioned Canada in the top decile of urinary tract cancer worlwide (Ferlay et al. 2013). The rates are particularly high in Nova Scotia, a province of 940,000 people, in Atlantic Canada. For bladder cancer, age adjusted incidence rates estimated for 2015 exceeded those of the national average by about 25 and 30 % among males and females, respectively (Canadian Cancer Society and National Cancer Institute of Canada 2015). Similarly, for kidney cancer, excesses of 30 and 45 % have been reported among males and females, respectively. In 2015, the rate of kidney cancer in Nova Scotia was twice of that reported in British Columbia. The causes associated with this excess burden are unknown.

1.2.1 Urinary Tract Cancer Risk Factors

Several factors affect the incidence of urinary tract cancers worldwide. Exposure to tobacco smoke, occupational toxins (e.g. aromatic amines) and in some areas of the world, infectious agents (e.g. *Schistosoma haematobium*) are amongst well established risk factors for bladder cancer (Janković and Radosavljević 2007). Other potential risk factors include other urinary tract infections, and drinking water with disinfection by-products or arsenic (Janković and Radosavljević 2007; Leppert et al. 2006). Tobacco smoking (Burger et al. 2012; Chow et al. 2010; Ferrís et al. 2013; Freedman et al. 2011; Gandini et al. 2008; Janković and Radosavljević 2007; Pou et al. 2011; Sasco et al. 2004), obesity

(Chow et al. 2010; Lipworth et al. 2006; Wang et al. 2007), hypertension (Chow et al. 2010), the use of phenacitincontaining analgesics and exposure to trichloroethylene (an industrial solvent) and polycyclic aromatic hydrocarbons (a product of incomplete combustion of carbonaceous material; Chow et al. 2010; Haalboom et al. 2006; Kiriluk et al. 2012; Lambert et al. 2006) increase kidney cancer risk. Long-term exposure to high levels of arsenic in drinking water has also been identified as a potential risk factor in the development of kidney cancer (IARC 2012; Saint-Jacques et al. 2014). Whether measured independently or synergistically, the magnitude of influence of these risk factors for the development of urinary tract cancer varies. A meta-analysis combining data from 1961 to 2003 suggested, for instance, that tobacco smoking could increase the risk of bladder and kidney cancer by at least 270 and 50 %, respectively, in current smokers compared to non-smokers (Gandini et al. 2008; see also Zeegers et al. 2000). Exposure to very high levels of arsenic in drinking water pointed effects of similar magnitude (IARC 2012). Finally, obesity has been reported to account for 30–40 % of kidney cancer cases in Europe and the United States; and is known to increase the risk of renal cell carcinoma in a dose–response relationship (Calle and Kaaks 2004; De et al. 2014).

1.3 Arsenic in Drinking Water

1.3.1 Arsenic

Arsenic, a risk factor in the development of large number of illness, including bladder and potentially kidney cancer, is a class 1 human carcinogen (IARC 2012) that ranks as the second most important global health hazard related to drinking water, next to

contamination by pathogenic microorganisms (van Halem et al. 2009). It is a naturally occurring toxic metalloid and the 20th most common element in the earth's crust with an average abundance of about 5 mg/kg. Arsenic is widely distributed around the world and occurs in more than 200 mineral forms, including arsenides, sulphides, oxides, arsenates and arsenites (Mandal and Suzuki 2002). The main mineral hosts are three arsenic sulfide ores: arsenopyrite, orpiment, and realgar (Garelick et al. 2008; IARC 2004; Smedley and Kinniburgh 2002; Wang and Mulligan 2006a). Some of the highest arsenic concentrations have been observed in black shale, coal, ironstone and Fe-rich rocks (Smedley and Kinniburgh 2002). Weathering of rocks converts the various forms of arsenic sulfides to arsenic trioxide, which enters the arsenic cycle as dust or by dissolution in rain, surface or groundwater. In water, arsenic is present predominantly as inorganic arsenic, the most toxic form. Approximately 85% of arsenic occurs in a dissolved (< 0.45 μm), mobile and more biologically active state (Parsons 2009).

Arsenic exists as both inorganic and organic compounds and in four oxidation states (-III, 0, +III, and +V). The specific forms (species) of arsenic found are dependent upon a number of factors including, geology, type and amount of sorbents, pH, redox potential, and microbial activity (Smedley and Kinniburgh 2002; Wang and Mulligan 2006a). Under both aerobic and anaerobic conditions, organisms (i.e. bacteria, algae, fungi, invertebrate, humans) can transform inorganic arsenic into (bio)methylated organic forms such as MMA (monomethyl arsenic acids), DMA (dimethyl arsenic acids) and volatile TMA (trimethyl arsenic acids) (Chen et al. 2003; Singh et al. 2007; Thomas et al. 2001). TMA in the air is rapidly converted into water-soluble species. Inorganic arsenate (AsV)

and arsenite (AsIII) are the major species in natural water (IARC 2007). AsV dominates under oxidizing conditions whereas AsIII is more common under reduced conditions.

1.3.2 Arsenic Toxicity and Bioaccessibility

The toxicity and mobility of arsenic species differ with their chemical forms and oxidation states (Hughes et al. 2011; Thomas et al. 2001). The methylation of inorganic arsenic into organic forms was once considered a detoxification process which reduced the affinity of the compound for tissue (Schuhmacher-Wolz et al. 2009). However, more recently, MMAIII and DMAIII have been reported to be more toxic than inorganic arsenic because of their efficiency at causing DNA breakdown (Dopp et al. 2004; Singh et al. 2007). Dopp and colleagues (Dopp et al. 2004) suggest that the likelihood of DNA damage decreases in the following order: DMAIII > MMAIII > AsIII > AsV > MMAV > DMAV > TMAOV. Inorganic AsIII is reported to be about 10 times more toxic than AsV and 70 times more toxic than organic MMAV and DMAV (Wang and Mulligan 2006a). Typically, the trivalent state is more toxic than the oxidized pentavalent state (Hughes 2002; Jain and Ali 2000).

The physical characteristics of arsenic-bearing particles (crystallinity, mineralogy, density, size, shape or morphology, surface charge) combined with their mode of occurrence (surface-sorbed or encapsulated within a crystal structure, oxidation state) determines the solubility of arsenic in human body fluids and thus, its bioavailability for absorption (Plumlee et al. 2006; Reeder et al. 2006; Ruby et al. 1999; Walker et al. 2009). Ultimately, the quantity of arsenic actually absorbed across a cell membrane

(bioaccesssibility) will determine the potential of the compound to produce cellular damage and affect human health (Nagar et al. 2009).

1.3.3 Exposure Pathways

Exposure of individuals to inorganic arsenic and their organic derivatives involve multiple environmental and occupational pathways including: direct consumption through arsenic contaminated food and water (Ahmed et al. 2016; Chung et al. 2014; Gundert-Remy et al. 2015; Kar et al. 2011; Mondal et al. 2010); inhalation and ingestion of contaminated mine tailings, dusts and soils (IARC 2004, 2012; Jones 2007); exposure to cigarette smoke and fossil fuels; exposure to smelting by-products, arsenic-based pesticides and treated wood products; and absorption of arsenic through the skin from showering, washing, swimming (Enterline et al. 1995; Liu et al. 2002; Silverman et al. 2006; Singh et al. 2007). In addition, arsenic has been and continues to be used extensively for the treatment of diseases such as syphilis, asthma, rheumatism, cough, pruritus and itching (Singh et al. 2007); pentavalent arsenic is used to treat advanced trypanosomiasis while arsenic trioxide is used to treat acute promyelocytic leukemia. Drinking water is, however, the primary route of human exposure to arsenic (Chung et al. 2014; Health Canada 2006; Meacher et al. 2002; Singh et al. 2011; World Health Organization 2012).

Many parts of the world draw their drinking water from arsenic contaminated groundwater sources. Worldwide, arsenic affects the health of hundreds of millions people and is responsible for hundreds of thousands of deaths (Ng et al. 2003; World

Health Organization 2001). Combined evidences from a succession of epidemiological studies in support of a wide range of acute and chronic health effects, including cancer, has led the WHO to lower the maximum acceptable concentration (MAC) of arsenic in public drinking water supplies from 200 μg/L (1958); 50 μg/L (1963) and; 10 μg/L (1993; (Smith 2002).). Based on their health criteria, the value should actually be lower than 10 μg/L; however, due to practical limits of arsenic detection, this value was instead adopted as a provisional guideline. In the US, the so-called Maximum Contamination Level (MCL) for arsenic in drinking water was reduced from 50 μg/L to 10 μg/L only recently, in 2006, by the US Environmental Protection Agency. In the same year Canada also lowered the effective limit for arsenic in drinking water from 25 μg/L to 10 μg/L.The later standard adopted by the US and Canada for public water supplies serves as a recommended guideline for safe drinking water for private water sources for which no enforceable standard have yet, been established (Chappells et al. 2014).

While the debate to further lowering standards is ongoing hundreds of millions of people continue to rely upon drinking water with arsenic levels exceeding these guidelines. In fact, most developing countries currently endorse a MAC 50 μg/L (IARC 2004; Shankar et al. 2014, 2014; Uddin and Huda 2011). A study reports (McClintock et al. 2012) that an estimated 4.5 million people being chronically exposed to arsenic levels > 50 μg/L, some to as high as 2000 μg/L, in Latin America. West Bengal, Bangladesh and Taiwan are amongst the most affected populations worldwide (Alam et al. 2002; Lan et al. 2011; Rahman et al. 2001; Singh et al. 2007; Smith et al. 2000). In West Bengal, the arsenic concentration in drinking water ranges from about 60 to 3,700 μg/L, affecting over 40

million people (Acharyya 2002). In the middle Ganga plain, Bihar, 56.8% of tube wells have arsenic concentration in excess of 50 μg/L and 19.9% have levels above 300 μg/L (Acharyya et al. 1999; Chakraborti et al. 2003). In Bangladesh, more than 70-80 million people are at risk of drinking contaminated water with arsenic levels as high as 4,700 μg/L (Kinniburg and Smedley 2001).

High levels of inorganic arsenic in drinking water have also been measured elsewhere including: Taiwan (10 to > 3,000 μg/L (Chen et al. 2010; IARC 2004); Inner Mongolia and Xinjiang (> 600 μg/L (Yang et al. 2002); Argentina (100 to 2,000 μg/L (Aballay et al. 2011; Singh et al. 2007); Chile (750 to 800 μg/L(Smith et al. 2000); Australia (13 to 1,077 μg/L) and Northern Mexico (160 to 740 μg/L (Rosas et al. 1999). Drinking water arsenic levels in excess of 150 μg/L have been reported in Romania and Hungary (Pavittranon et al. 2003; WHO 2003), Nepal (Shrestha et al. 2003), Thailand (Pavittranon et al. 2003), Vietnam (Berg et al. 2001) and Canada (McGuigan et al. 2010; Meranger 1984; Wang and Mulligan 2006b). Finland as well as several US states including Alaska, Nevada, New England, New Hampshire, New Mexico, Michigan, and Utah report arsenic levels in drinking water above 50 μg/L (Kumar et al. 2009; Kurttio et al. 1999; Lubin et al. 2007; Singh et al. 2007; Smedley and Kinniburgh 2002). In North America, an estimated 30 million people may be exposed to arsenic in drinking water (Natural Resources Defense Council 2000).

1.3.4 Arsenic Carcinogenesis

Induction of cancer by inorganic arsenic occurs inconsistently between species, between routes of exposure, and show different dose-response relationships between different target organs (Byrd et al. 1996; Martinez et al. 2011). Large inter-individual variations have also been observed in laboratories studies of arsenic-induced genotoxicity and cell proliferation (Hernández and Marcos 2008; Rossman 2003). In humans, arsenic compounds are metabolized by methylation which occurs primarily in the liver and then excreted in urine (Schuhmacher-Wolz et al. 2009; Tchounwou et al. 2003, 2004; Tseng 2007). Methylated arsenic species tend to be excreted at a faster rate and in greater proportion than inorganic species. It is estimated that 60-70% of daily-ingested inorganic arsenic is excreted in urine and that most humans exposed to arsenic excrete 10-30% as inorganic arsenic, 10-20% as MMA(V+III) and 60-80% as DMA(V+III) (Mandal and Suzuki 2002; Vahter and Concha 2001). Excretion rates vary between individuals but studies using radioactively labeled As74 arsenate in humans have demonstrated that 38% of the ingested dose is excreted within 48 hours and 58% within 5 days (Mandal and Suzuki 2002). Women generally tend to have higher methylation capacity than men which may result in lower MMA concentrations in urine relative to men (Lindberg et al. 2007; Schuhmacher-Wolz et al. 2009; Steinmaus et al. 2007).

Scientific consensus on the possible modes of action of arsenic carcinogenesis has yet to be reached. The mechanisms that have been suggested include: induced chromosomal abnormalities; oxidative stress; altered DNA repair; altered DNA methylation; altered growth factors; cell proliferation; tumor promotion/progression; gene amplification; and

suppression of p53 (Andrew et al. 2009; Byrd et al. 1996; Cohen et al. 2007; Hughes 2002; Kitchin 2001; Luster and Simeonova 2004; Mandal and Suzuki 2002; Rossman 2003; Schoen et al. 2004; Snow et al. 2005). Arsenic is not mutagenic in the traditional sense of either generating DNA adducts or inducing revertants at specific loci. Rather, it acts primarily as a tumor promoter, inducing both cell proliferation and clastogenic events (see review by Kitchin 2001)). Two common causes of cell proliferation are mitogenic stimulation and cell toxicity and death followed by compensatory regeneration. Errors of replication ensuing unrepaired DNA damage present at the time of replication can cause mutation of genetic material (Kitchin 2001). Thus, aberrant cell proliferation can lead to abnormal mitosis, resulting in chromosomal abnormalities. In addition, arsenic could cause oxidative stress by depleting the cell's antioxidants and by generating a series of free radical molecules from DMA within the pathway of arsenic metabolism. Human bladder may particularly be responsive to arsenic carcinogenesis from oxydative stress because of the high concentration of DMA and MMA that is stored in the lumen of the bladder and the amount of DMAIII and MMAIII that might be generated by reductive processes (Gonzalgo et al. 2000; Kitchin 2001). Similarly, kidneys are exposed to high concentrations of DMA as they filter DMA into the urine.

Trivalent methylated arsenic metabolites, particularly MMAIII and DMAIII are highly biologically active and unusually capable of interacting with proteins and DNA (Kitchin 2001). DMA causes several genotoxic or clastogenic effects, including single strand breaks, formation of apurinic/apyrimidic sites, DNA base damage and oxidative base damage, DNA-protein crosslinks, chromosomal aberrations and aneuploidy. Several

studies of long-term exposure to drinking water containing 400 µg/L of arsenic provided consistent evidence of increased chromosome aberrations in peripheral blood lymphocytes, increased micronuclei formation in lymphocytes, exfoliated oral mucosa cells, and exfoliated urinary bladder epithelial cells. More recently, reduced expression of DNA repair genes was also observed in subjects exposed to arsenic concentrations in drinking water > 5 µg/L; tumour-supressor genes were also suppressed in bladder-cancer cases exposed to moderate levels of arsenic in drinking water (Andrew et al. 2006; Marsit et al. 2006).

The mode of carcinogenic action of arsenic remains an area of active scientific research and disagreement. Currently, positive evidence exists for three of the nine suggested modes of actions, both in experimental systems (animal and human cells) and in human tissues that warrant preeminence: induced chromosomal abnormalities, oxidative stress, and a continuum of altered growth factors involving cell proliferation and promotion of carcinogenesis. However, regardless of the specific mode of action, the dose-response relationship at low arsenic concentration is not known (Rossman 2003; Schuhmacher-Wolz et al. 2009). Rossman (Rossman 2003) suggests that high concentrations of arsenite may result in its sudden accumulation in cells and so may have effects that differ from a slower accumulation where tolerance mechanisms may exist.

1.3.5 Arsenic in Drinking Water and Human Health

High levels (> 150µg/L) of arsenic in drinking water have been associated with increased risk of: cardiovascular diseases; diabetes mellitus; gastrointestinal,

vascular, respiratory and neurological effects; adverse obstetric and pregnancy outcomes; and cancer, including lung, bladder, non-melanoma skin, liver, and kidney cancers (Aballay et al. 2011; Bardach et al. 2015; Celik et al. 2008; Chen et al. 1985, 2009, 2011; Chiu et al. 2004; Huang et al. 2015; Hsu et al. 2013; IARC 2012; Kapaj et al. 2006; Navas-Acien et al. 2005; Saint-Jacques et al. 2014; Vahidnia et al. 2007; Wang et al. 2014; Yoshida et al. 2004; Vahter 2008; Rahman et al. 2009; Lubin et al. 2007). Much emphasis has been placed on cancer since cancer mortality predominates over all other causes of death involving arsenic. A recent review of the global geographical distribution of health effects from exposure to arsenic contaminated drinking water further suggest that bladder cancer rank as the top malignancy, with the highest standardized mortality ratio (SMR), especially among populations with high exposure levels; and globally, SMRs tend to be higher in women than in men for all populations (Huang et al. 2015).

To date, most of the evidence for strong associations and dose-response relationships between arsenic in drinking water and cancer are derived from highly exposed populations. The threshold at which cancer develops is uncertain at lower levels of arsenic exposure. Several studies fail to demonstrate the risk that might be expected by extrapolation of findings related to higher levels, some suggesting that arsenic may have a dose threshold below which exposure is not harmful (Cantor and Lubin 2007; Chu and Crawford-Brown 2006; Lamm et al. 2014, 2015; Meliker et al. 2010; Mink et al. 2008; Tsuji et al. 2014). However, recent evidence indicates that arsenic in drinking water may increase the risk of a number of health outcomes, including bladder and kidney cancers,

at levels previously considered safe (see: Baris et al. 2016; Bräuner et al. 2014; D'Ippoliti et al. 2015; Dutta et al. 2015; García-Esquinas et al. 2013, 2013; Gilbert-Diamond et al. 2013; Karagas et al. 2015; Moon et al. 2013; Mukherjee et al. 2014; Pan et al. 2013; Saint-Jacques et al. 2014; Steinmaus et al. 2014; Wade et al. 2015). Considering the mixed findings, studies reporting on low-levels of arsenic exposure in drinking water, especially at concentrations around current WHO guidelines (10 μg/L), are needed to continue to inform the global debate on what is an acceptable threshold for safe drinking water.

1.4 Arsenic in Drinking Water in Nova Scotia, Canada

Nova Scotia is an ideal location to address this need. Typical arsenic concentrations in well drinking water fall within the lower-level range although, with some levels being comparable to those reported in arsenic-endemic regions. Also, arsenic contaminated well water was recently observed to be a major contributor to arsenic body burden (i.e. as measured in toenail clippings) in a small cohort of Nova Scotians, confirming the accumulation of the carcinogen in the body of those exposed (Dummer et al. 2015; Yu et al. 2014). As about 45% of the Nova Scotia population sources its water from unregulated private wells, exposure to arsenic from contaminated water is a real public health concern. However, the health consequences possibly resulting from chronic exposure to low-levels of arsenic in well water are currently unknown.

Nova Scotia geological formations contain large amounts of the mineral arsenopyrite, one of the main mineral hosts for arsenic (Dummer et al. 2015; Smedley and Kinniburgh 2002). Under certain pH and Redox conditions, arsenopyrite breaks down into soluble

arsenic species that contaminates water supplies (for details, see Dummer et al. 2015). In Nova Scotia, the contamination of groundwater with arsenic was first identified in 1976 when the well of a resident victim of arsenic intoxication was tested, revealing levels of 5,000 μg/L. Following the event, Meranger and colleagues analyzed arsenic concentrations from 94 wells in 7 communities within Halifax County (Meranger 1984). The results revealed that 93% of the wells had levels exceeding 10 μg/L, current MAC for arsenic in drinking water supplies adopted by Health Canada and the World Health Organization guidelines (WHO; World Health Organization 2001); 70% of the wells had levels exceeding the previous guideline limit of 50 μg/L and; 10% of the wells had levels above 500 μg/L. Between 1991 and 1997 the Environmental Chemistry Laboratory in Halifax tested over 21,000 private well water samples province-wide and found that 9% had arsenic levels > 25 μg/L. That same proportion was estimated to be about 20% in areas where the local geology suggested a high probability of arsenic contamination. Recently, Dummer et al. (2015) reported that based on regional hydrogeology, mainland southwestern Nova Scotia and the northeast shore of Cape Breton could be the most affected regions with a well water mean arsenic concentration around 3.0 μg/L and a 95th percentile up to 65 μg/L. The maximum arsenic level recorded in that study was 3,900 μg/L and 17% of the 10,498 private well sampled, had levels exceeding the Health Canada MAC of 10 μg/L.

In Nova Scotia, similar to all Canadian provinces and most states in the US, well monitoring is placed in the hands of well owners. Government agencies advise regulary testing for arsenic and other contaminants, but legal requirements to comply with these

recommendations do not exist (Chappells et al 2014). A complex interplay of risk perception, social and economic factors largely accounts for a general lack of compliance with testing and remediation recommendations (Chappells et al, 2015). Arsenic invisibility in well water makes risk identification difficult. With no aesthetic or sensory change in water quality, public awareness can be low and confidence in water quality high, despite the presence of a documented environmental risk such as arsenic in water (Chappells et al 2015).

1.5 Study Aims and Hypothesis

This thesis hypothesizes that arsenic exposure from drinking water may be responsible for some of the excess risk of bladder and kidney cancer observed in Nova Scotia. The aim of the thesis is thus, two-fold: first, to quantify the risk of developing bladder or kidney cancer as a result of being potentially exposed to drinking well water containing arsenic, and; second, to contribute to the body of knowledge where studies reporting on level of arsenic exposure around current guidelines are still largely lacking. To our knowledge this is the first attempt to model the risk of bladder and kidney cancer in Nova Scotia in relation to environmental exposure of arsenic in drinking water from private well supplies. The work is presented through a succession of five thesis chapters described as following:

1.6 Thesis Overview

Chapter 2 presents a systematic review of 30 years of epidemiological studies that compiles findings from 40 studies reporting on the association between arsenic in drinking water and urinary tract cancers. It also quantifies the risk of urinary tract cancers

due to exposure to arsenic contaminated drinking water by combining risk estimates from seventeen of the forty reviewed studies within a meta-analytical framework. Most studies report on specific levels of arsenic exposure in drinking water. For examples, studies of highly exposed populations can report on exposure levels greater than 1,000 µg/L; other studies report on much lower levels, in the mid- (~ > 100, < 300 µg/L) or low-ranges (< 100 µg/L) and; a few focus on levels around the current WHO MAC limit, where most information is lacking. By combining studies reporting varying exposure-levels, the review profiles a more complete and continuous range of exposure from which to better assess and predict cancer risks associated with varying concentrations of arsenic in drinking water. This approach is particularly important to shed light on dose-response relationship, especially at the lower range, around current WHO guidelines (i.e. 10 µg/L), where studies are needed as to inform the global debate on what is an acceptable threshold for safe drinking water.

Chapter 3 explores the uses of small-areas based social and material deprivations indices as proxy for unavailable individual-level measures of lifestyle factors (e.g. smoking, obesity etc.). Accounting for smoking when quantifying the risk of bladder or kidney cancer from exposure to arsenic in drinking water, is particularly important. This is because smoking is an established risk factor in the development of both bladder and kidney cancer and a possible effect modifier in the urinary tract cancer and arsenic relationship. As such, any variations in cancer risk due to this factor must be adjusted for. Studies of populations from England, Wales, Poland, the United States and Canada have demonstrated that residential deprivation can independently predict smoking habit in both

men and women and that lower neighborhood socioeconomic status is largely associated with higher prevalence of cigarette smoking and other health outcomes, including premature mortality (PM). Thus, in Chapter 3 indices of deprivation to be used as proxy indicators of lifestyle (e.g.smoking, obesity etc.) in the analyses presented in Chapter 4 and 5, were developed and described in details. As well, in this Chapter, each index is validated by examining the relationship between social and material deprivation in Nova Scotia and PM; outcome linked to both increased socioeconomic deprivation and smoking.

Chapter 4 describes spatial and spatio-temporal variations in the risk of bladder and kidney cancer for Nova Scotia. The work aimed to identify areas where rates are higher than what would be expected given the prevalence of known risk factors and; to determine whether high risk estimates at a given location are sustained over time or changes over time. Detangling these scenarios can provide clues on the occurrence and influence of extrinsic factors involved in the rise or fall of a disease. For example, in the first scenario, spatial variations that are consistent over time could be induced by environmental or socio-demographic risk factors that act in a sustained manner. In the second scenario, the rate of case accumulation may be more temporally clustered with distinct variability, possibly reflecting emerging short latency risk factors that would generate high excess cases in shorter time intervals or, alternatively, due to artificial or sudden variations associated with changes in disease coding or screening practices. Spatio-temporal variations independent of individual-risk factors can thus point to a risk that may be environmental. As such, this spatio-temporal exploration of the variations in

bladder and kidney cancer rates was an important step; the aim of the thesis being to assess excess risk in relation to environmental exposure to arsenic in drinking water. In Chapter 4, two geospatial methods for modeling disease risk, both of which are appropriate for low-density population such as that of Nova Scotia, are described and applied. The first approach is a Community-level analysis using a Besag, York and Mollié (BYM) model, a widely used and convenient spatially structured model for count data referenced to discrete spatial regions. The second approach estimates spatially continuous variation in risk using a Local Expectation Maximization (local-EM) smoothing algorithm, an emerging geostatistical method which models spatial and temporal variation in risk when cases are aggregated to time-varying spatial boundaries.

Chapter 5 addresses the primary aim of the study, building upon the knowledge acquired from all previous chapters. In this Chapter, we quantify the risk of developing bladder or kidney cancer as a result of potential exposure to arsenic in drinking well water in Nova Scotia, Canada. Using the BYM model described in Chapter 4, cancer risk is modeled at three levels of arsenic exposure— 0–2 μg/L; 2–5 μg/L and; >5 μg/L (based on 10,498 private well samples), in 864 bladder and 525 kidney cancer cases diagnosed in Nova Scotia between 1998-2010. Model fitting is performed separately for bladder male, bladder female, bladder sex combined, kidney male, kidney female, kidney sex combined; all models account for spatial dependencies and include covariates (i.e. smoking proxies developed in Chapter 3). The work presented in this chapter contributes to the body of knowledge reporting on the association between urinary tract cancer risk and arsenic in drinking well water at exposure levels around current WHO guidelines.

Chapter 6 integrates the findings presented in each chapter of the thesis, explains how these relate to earlier work and ultimately contribute to the international body of research reporting on the health effect in populations exposed to low to moderate levels of arsenic in drinking water. While acknowledging some of the limitations inherent to the research, we also highlight the potential impact of the findings on public health in Nova Scotia and elsewhere, where a large number of people may be exposed to similar levels of the carcinogen. Finally, the chapter discusses how the work developed though the thesis could be extended and applied to benefit future research.

CHAPTER 2— Arsenic in Drinking Water and Urinary Tract Cancers: A Systematic Review of 30 Years of Epidemiological Evidence

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Authors' Contributions

NSJ conducted the literature search for this review, specified the inclusion and exclusion criteria, abstracted published data, modeled combined risk estimates, constructed tables and figures, drafted and revised the manuscript; LP and TJBD supervised the review, reviewed the article critically for important intellectual content and provided important assistance in the interpretation. PB provided intellectual content and statistical advice to carry the meta-analyses. All of the authors gave final approval for this journal article to appear in this thesis.

Please note that this journal article has been modified further for inclusion in this thesis.

ABSTRACT

Background: Arsenic in drinking water is a public health issue affecting hundreds of millions of people worldwide. This review summarizes 30 years of epidemiological studies on arsenic exposure in drinking water and the risk of bladder or kidney cancer, quantifying these risks using a meta-analytical framework.

Methods: Forty studies met the selection criteria. Seventeen provided point estimates of arsenic concentrations in drinking water and were used in a meta-analysis of bladder cancer incidence (7 studies) and mortality (10 studies) and kidney cancer mortality (2 studies). Risk estimates for incidence and mortality were analyzed separately using Generalized Linear Models. Predicted risks for bladder cancer incidence were estimated at 10, 50 and 150 μg/L arsenic in drinking water. Bootstrap randomizations were used to assess robustness of effect size.

Results: Twenty-eight studies observed an association between arsenic in drinking water and bladder cancer. Ten studies showed an association with kidney cancer, although of lower magnitude than that for bladder cancer. The meta-analyses showed the predicted risks for bladder cancer incidence were 2.7 [1.2–4.1]; 4.2 [2.1–6.3] and; 5.8 [2.9–8.7] for drinking water arsenic levels of 10, 50, and 150 μg/L, respectively. Bootstrapped randomizations confirmed this increased risk, but, lowering the effect size to 1.4 [0.35–4.0], 2.3 [0.59–6.4], and 3.1 [0.80–8.9]. The latter suggests that with exposures to 50 μg/L, there was an 83% probability for elevated incidence of bladder cancer; and a 74% probability for elevated mortality. For both bladder and kidney cancers, mortality rates at 150 ug/L were about 30% greater than those at 10 μg/L.

Conclusions: Arsenic in drinking water is associated with an increased risk of bladder and kidney cancers, although at lower levels (<150 μg/L), there is uncertainty due to the increased likelihood of exposure misclassification at the lower end of the exposure curve. Meta-analyses suggest exposure to 10 μg/L of arsenic in drinking water may double the risk of bladder cancer, or at the very least, increase it by about 40%. With the large number of people exposed to these arsenic concentrations worldwide the public health consequences of arsenic in drinking water are substantial.

Keywords: Arsenic, Drinking water, Bladder, Kidney, Urinary tract, Cancer risk, Systematic review, Meta-analysis

2.1 Introduction[1]

Arsenic (As) is a naturally occurring toxic metalloid prevalent in the earth's crust [1]. It enters drinking-water sources in a dissolved state primarily resulting from the weathering of rocks [2]. Human exposure to As involve multiple pathways [3-9], with drinking water being the primary route of exposure for the majority of highly exposed populations [4,9,10]. West Bengal, Bangladesh and Taiwan are the most affected regions worldwide [4,11-14]. In these areas, As concentration as high as 4,700 μg/L have been reported in drinking water, and levels in excess of 300 μg/L are common. High levels of As in drinking water have also been reported elsewhere, such as North and South America, Central and Eastern Europe as well as Australia [4,11,15-22].

The contamination of drinking water by As has become an ongoing public health issue affecting hundreds of millions of people worldwide. A growing body of evidence supporting a wide range of acute and chronic effects on health, including cancer [5,20-72], has led the World Health Organization (WHO) to lower the advisory limit for concentration of As in drinking water from 25 μg/L to a provisional guideline limit of 10 μg/L [10]. However, many developing countries continue to endorse an effective upper limit of 50 μg/L [4].

The International Agency for Research on Cancer (IARC) has classified inorganic As in drinking water as a Group 1 carcinogen [73]. Suggested mechanisms of action for As carcinogenesis include oxidative damage, epigenetic effects and interference with DNA repair, mechanisms which have been specifically implicated in the development of As-

[1] Numerical format was used for referencing citations in this chapter as per the original publication.

related urinary tract cancers which are the focus of this review [74-81]. Urinary tract cancers comprise primarily cancers of the urinary bladder and kidney, the former being the ninth most common cause of cancer worldwide [82]. Most studies generally report on bladder or kidney cancer, although some of the studies included in this review and meta-analysis reported histologies, mostly urothelial/transitional cell and renal cell carcinomas. Tobacco smoking and most notably, the ingestion of high levels of inorganic As are two important risk factors for bladder and kidney cancers [83-86].

To date, epidemiological studies of populations exposed to high levels of total inorganic As have shown strong associations and dose–response relationships between As in drinking water and bladder cancer and; potential associations with kidney cancer [23]. Typically, these studies report on areas of extreme exposure where levels of As in drinking water range from 150 to over 1000 ug/L. The extent to which health effects may develop remain uncertain at lower levels of exposure (< 150 μg/L), with many studies failing to demonstrate the risk that might be expected by extrapolation from findings related to high levels of exposure [5].

This paper reviews findings from epidemiological studies published over the past 30 years, including a number of recent publications focusing on low-levels exposure and bladder and kidney cancer outcomes [60,63,67,87]. It also quantifies the risk of urinary tract cancers due to exposure to As in drinking water, combining risk estimates from published epidemiological data. As such, this work complements the recent systematic review of IARC which reports on carcinogenicity following exposure to As [23]. Most studies reporting on urinary cancers risk and As exposure tend to focus on specific levels of exposure. By combining exposure levels from multiple studies, the review profiles a

more complete and continuous range of As exposure from which to better assess and predict cancer risks associated with varying levels of exposure. This meta-analytical approach is especially relevant to shed light on dose–response relationship, especially at the lower end of the curve where there has been the most uncertainty and where a large number of people may be at risk.

2.2 Methodology

2.2.1 Review Process

Searches of the Medline (PubMed) and Embase databases were conducted to identify studies reporting on exposure to As in drinking water and urinary tract cancer outcomes and published prior to January 2013. The search conditions are presented in Table 2.1. Searches were also undertaken using Google Scholar and the WHO and the IARC publications [3,23]. Studies were selected based on the selection criteria listed in Table 1. Information abstracted from reviewed articles is shown in Tables 2.2, 2.3, 2.4, 2.5, 2.6. When the distribution of As in drinking water was detailed in another publication, that information was also retrieved. Where available, the adjusted relative risks estimates and associated 95% confidence intervals were selected.

2.2.2 Data Analysis

Epidemiologic data from studies which explicitly provided point estimates of As levels in drinking water were used in a meta-analysis to examine the association between cancer outcomes and As exposure over a broader and more continuous range of As than previously available (Tables 2.2, 2.3, 2.4, 2.5, 2.6, studies with an asterisk). Studies using

cumulative exposure to As in drinking water, years of artesian well water consumption or As toenail/urine concentrations were not included in the meta-analyses. Risk estimates from studies reporting on bladder cancer mortality (10 studies) were analysed separately from those reporting on incidence (7 studies). With regards to kidney cancer, only risk estimates for mortality could be analysed (2 studies) as there were insufficient studies reporting on kidney cancer incidence.

Table 2.1 Search conditions and criteria for study selection

Search conditions	Study selection
((arsenic) AND ("bladder cancer*" OR "kidney cancer*" OR "urinary tract cancer*" OR "upper urinary tract cancer*" OR "urinary tract cancer*" OR "urologic neoplasm*" OR "cancer*, urinary tract" OR "kidney neoplasm*" OR "carcinoma, renal cell*" OR "urinary bladder neoplasm*" OR "urinary tract disease*" OR "kidney tumour*" OR "bladder tumour*" OR "bladder tumor*"OR "kidney tumor*" OR renal cell* carcinoma" OR "bladder neoplasms") AND ("water" OR "drinking water" OR "water supply" OR "toenail" OR "urine" OR "well water") †	1. Arsenic in drinking water, toenail or urine, as exposure of primary interest. 2. Urinary tract cancers incidence and mortality as primary outcome. 3. Original study that published the data. 4. Relative risk estimates, measures of variability (i.e., confidence intervals) documented. 5. Epidemiological study designs, including ecological, case-control or cohort study 6. English language publications.

† The wildcard (*) was used to identify any other characters.

Combined risk estimates from studies reporting on standardized mortality ratios (SMR) were modeled using a least squares linear regression model for the logged SMRs; studies reporting mortality rates or relative risk (RR – incidence data only) were analyzed with a Generalized Linear Model having a Gamma-distributed response and a log link function, a combination well suited to analyses with highly variable risk estimates [97]. Risk estimates were modeled as a function of logged As and a categorical variable with a level

for each study. The latter accounted for possible variations in baseline risk between studies due to differing methodological designs, study quality, populations, etc., and was assumed to be a fixed effect (herein, referred to as Model I, see Boreinsteign et al. [98]). The robustness/sensitivity of the predicted risk estimates obtained with the fixed effects As-risk models was assessed with bootstrap randomizations (10,000 permutations) which estimated the effect size at 10, 50 and 150 μg/L of As in drinking water (herein, referred to as Model II, see Efron and Tibshirani [99]). A random effects assumption was also examined; however, the small number of studies entering each model precluded a stable estimation of the variance components. Meta-analyses (Model I and II) modeling SMR and RR were only performed for bladder cancer due to the limited number of studies reporting on kidney cancer. Inference of risk at 10, 50 and 150 μg/L of As in drinking water and based on Model I, was only possible for bladder cancer incidence for which a reliable referent population and sufficient number of studies were available. Finally, the effect of sex and smoking on cancer risk was examined; however, analyses could not be completed due to insufficient degrees of freedom. Six of the 7 studies included in the meta-analysis of the RR had been adjusted for tobacco smoking in the original publication – an important risk factor in the development of urinary tract cancers and a possible effect modifier in the cancer-As relationship [51,86,100]. Only one of the 8 studies included in the analyses of the SMR adjusted for smoking [34], as these were generally ecological studies with no individual-level information on smoking. A list of covariates assesses in the original publication appear on Tables 2.3, 2.4, 2.6. Analyses were performed using R 2.13.0 [101].

2.3 Results

2.3.1 Study Characteristics

The search resulted in the review of 249 abstracts, with 50 studies being retained for full text review (Figure 2.1). In total, forty studies met the inclusion criteria (principally, As in drinking water, toenail or urine as exposure measure and urinary tract cancer as outcome of interest) as listed in Table 2.1. Of these, 20 were ecological, 11 were case–control and 9 were cohort epidemiological studies. Thirty-seven of the 40 studies reported on bladder cancer outcomes and of these, 13 also reported on kidney cancer outcomes. One study focused exclusively on kidney cancer mortality [61]. Seventeen studies qualified for inclusion in the meta-analysis, 7 reporting on bladder cancer incidence and 10 on bladder cancer mortality. Two studies also reported on kidney cancer mortality, which was analysed independently from bladder cancer outcomes. Metrics of exposure included: As in well drinking water (median, average or range), cumulative As exposure, years of artesian well water consumption and As in toenails or urine. When measured in drinking water, exposure covered a broad spectrum of As concentrations, ranging from the study-specific detection limit to over 3,500 μg/L and with most study areas showing levels exceeding the WHO advisory limit (Figure 2.2). Adverse cancer outcomes were reported over the entire range of concentrations, although more consistently in regions where exposure levels were high, typically above 150 ug/L (Figure 2.2).

2.3.2 Quality Assessment

The quality of the studies was variable. For example, all ecological studies assessed As exposure using group level (median or average) or ecologic measurements of drinking water (well or tap water), whereas all case–control and most cohort studies (7 of 9 studies) assessed As exposure using either a direct measure of As in tap/well water or body burden (e.g. urine or toenail As concentrations) or an individual level measure estimated from a range of metrics, including the reconstruction of past exposures based on residential history, knowledge of water source and duration of exposure to As contaminated well drinking water (see Table 2.2, 2.3, 2.4, 2.5, 2.6, As exposure assessment). Fifteen ecological studies and one cohort study stratified the analysis by gender (Tables 2.2, 2.4, 2.5, 2.6). With the exception of one study [70], all case–control and cohort studies included in this review accounted for tobacco smoking and one ecological study used lung cancer mortality rates as surrogate to smoking [63].

2.3.3 Arsenic Exposure and Bladder Cancer

Ecological Studies

Fifteen of the 20 ecological studies reviewed reported on bladder cancer mortality (Table 2.2). These studies provided consistent evidence for an increased risk of death from bladder cancer with exposure to As in drinking water. There were two exceptions, however, they focused only upon low exposures (< 60 μg/L As in water; [89,90]). Risk estimates amongst males and females were comparable, with the exception of those reported by Chen et al. [24] which showed a near doubling of risk in females on the southwest coast of Taiwan (Table 2.2). Chen [26] was also first to describe a dose–

response relationship between well water As and rates of mortality from bladder cancer. In accordance with the three levels of As exposure examined (< 300; 300 – 590; > 600 μg/L As), age-adjusted cancer mortality rates per 100,000 were as follows: 15.7, 37.8, 89.1 per 100,000 males and 16.7, 35.1, 91.5 per 100,000 females. While these findings profiled the highly exposed populations of Taiwan, increased mortality from bladder cancer due to As exposure in drinking water was also observed in Argentina [35,36,62,63] and Chile [38,39,55]. For example, compared to uncontaminated areas, males and females from the highly contaminated Region II of Chile, experienced mortality rates due to bladder cancer, 6.0 and 8.2 times greater, respectively [39]. Within the same region, Rivara et al. [38] reported on mortality rates of an order of magnitude higher (sex combined) relative to those observed in the rest of Chile. Findings from the 4 ecological studies reporting on bladder cancer incidence were generally consistent with those of studies based on mortality, providing evidence for an association between bladder cancer and exposure to As in drinking water. The exception was a study by Hinwood et al. [88] which was limited by low power and exposure misclassification.

Case–Control Studies

Ten of the 11 case–control studies reviewed reported on bladder cancer incidence [20,31,51,67,87,91-95]; one reported on mortality ([25]; Table 2.3). Four studies observed a significant As-related increase in bladder cancer incidence; one study observed an increased risk of death with increasing years of artesian well water consumption in Blackfoot disease endemic areas of Taiwan ([25]; Table 2.3).

Table2.2 Summary from ecological studies reporting on arsenic exposure and the risk of bladder cancer

Study [reference] (Table from original publication)	Study locale	Outcome	Exposure[1] [comments]	ICD[2]	Outcome measure	Cases	Risk estimate (95% CI)
Chen et al. 1985[3] [24]	84 villages from 4 neighbouring townships on SW coast, Taiwan	Mortality 1968-82	Median arsenic content of artesian well and (range): 780 $\mu g \cdot L^{-1}$ (350–1,140); in shallow well: 40 (0.0–300). Period of samples collection not reported.	ICD 188	SMR_{male}	167	11.0 (9.33–12.7)
					SMR_{female}	165	20.1 (17.0–23.2)
			[Comparison of mortality rate in Blackfoot disease-endemic areas (BFD) with those of the general population.]				
*Chen et al. 1988[4] [26] (Table One)	BFD endemic area, Taiwan	Mortality 1973-86	Arsenic well water concentration ($\mu g \cdot L^{-1}$). Period of samples collection not reported.	ICD9 188			
			General population		$ASMR_{male}$		
			< 300			–	3.1
			300-590			–	15.7
			≥ 600			–	37.8
						–	89.1
			General population		$ASMR_{female}$		
			< 300			–	1.4
			300-590			–	16.7
			≥ 600			–	35.1
			[Comparison of mortality rate in BFD with those of the general population.]			–	91.5
*Wu et al. 1989[5] [27] (Table Three)	BFD endemic area, Taiwan (42 villages)	Mortality 1973-86	Arsenic well water concentration ($\mu g \cdot L^{-1}$) based on well water samples collected between 1964–66.	ICD8 188			
			< 300		$ASMR_{male}$	23	22.6
			300–590			36	61.0
			≥ 600			26	92.7
			< 300		$ASMR_{female}$	30	25.6
			300–590			36	57.0
			≥ 600			30	111.3
Chen and Wang 1990[6] [28] (Table Four)	314 precincts & townships in Taiwan, including 4 from BFD endemic area	Mortality 1972-83	Average arsenic levels in water samples of all 314 geographical units. 73.9% had < 5% of wells with > 50 $\mu g \cdot L^{-1}$; 14.7% had 5-14%; 11.5% had ≥ 15%. Well water samples collected between 1974–76.	ICD 188			
			All precincts & townships		$ASMR_{male}$	–	3.9 (0.5)
					$ASMR_{female}$	–	4.2 (0.5)
			Southwestern townships		$ASMR_{male}$	–	3.7 (0.7)
					$ASMR_{female}$	–	4.5 (0.7)

Table2. 2 Summary from ecological studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

Chiang et al. 1993[7] [29] (Table Two)	BFD endemic area in Taiwan and 2 neighbouring areas	Incidence 1981-85	Exposure not evaluated, but based on Chen et al. 1985, the median arsenic content of artesian well in this area was 780 μg·L^{-1} (350 – 1,140); that of shallow well was 40 μg·L^{-1} (0.0 – 300). Period of samples collection not reported. [Comparison of incidence rate in BFD with those of neighbouring areas and Taiwan as a whole.]	N/A	Endemic area		
					$IR_{\_both\_sex}$	140	23.5
					IR_{male}	81	26.1
					IR_{female}	59	21.1
					Neighbouring Endemic area		
					$IR_{\_both\_sex}$	13	4.45
					IR_{male}	7	4.65
					IR_{female}	6	4.28
					All Taiwan		
					$IR_{\_both\_sex}$	2,135	2.29
					IR_{male}	1,608	3.31
					IR_{female}	527	1.17
Hopenhayn-Rich et al. 1996[8] [35] (Table Three) *Hopenhayn-Rich et al. 1998 [36] (Tables Three, Four)	26 counties in Cordoba, Argentina	Mortality 1986-91	Arsenic drinking water concentration ranging from 100 to 2,000 μg·L^{-1}. Low Medium High (178 μg·L^{-1} on average) Low Medium High (178 μg·L^{-1} on average) [Arsenic measurements from a variety of sources, including official reports of water analyses from the 1930, 2 scientific sampling studies and a water survey.]	ICD9 188	SMR_{male} SMR_{female}	113 116 131 39 29 27	0.80 (0.66–0.96) 1.28 (1.05–1.53) 2.14 (1.78–2.53) 1.21 (0.85–1.64) 1.39 (0.93–1.99) 1.82 (1.19–2.64)
Guo et al. 1997[9] [37] (Table Two)	243 townships in Taiwan	Incidence 1980-87	Arsenic well water concentration ranging from < 50 to > 640 μg·L-^{1}. Estimate presented measured at > 640 μg·L^{-1}. [Arsenic measurements from a National survey of 83,656 wells in 243 townships, collected mostly between 1974–76.]	ICD 188	RD_{male} RD_{female}	– –	0.57 (0.07) 0.33 (0.04)
Rivara et al.1997 [38] (Table Four)	Chile	Mortality 1950-92	Annual average arsenic concentration in drinking water for Antofagasta (Region II of Chile) ranging between 40 to 860 μg·L^{-1}. Data from historical records from 1950–1992. [Comparison of mortality rate in Region II (exposed populations) vs Region VIII (control populations.]	ICD 188	RR	–	10.2 (8.6–12.2)

Table2. 2 Summary from ecological studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

Smith et al. 1998 [39]	Chile	Mortality 1989-93	Region II of Northern Chile with population weighted average arsenic concentration in drinking water up to 569 μg·L^{-1} compared with the rest of Chile; exposure generally < 10 μg·L^{-1}. [Arsenic measurements from 1950–94.]	N/A	SMR_{male} SMR_{female}	93 64	6.0 (4.8–7.4) 8.2 (6.3–10.5)
Hinwood et al. 1999 [88] (Table Two)	22 areas in Victoria, Australia	Incidence 1982-91	Median water arsenic concentration ranging 13 μg·L^{-1} to 1,077 μg·L^{-1}. [Selected areas were those where samples with soil and/or water arsenic concentration were generally in excess of 10 μg·L^{-1}. Period for samples collection is not available.]	ICD 188, 189.1-189.3	SIR	303	0.94 (0.84–1.06)
*Tsai et al. 1999 [41] (Tables Two, Three)	4 townships from BFD endemic area in SW coast, Taiwan	Mortality 1971-94	Median arsenic content of artesian well: 780 μg·L^{-1} (range: 350–1,140). Period of samples collection not reported. Authors state that artesian wells were no longer used by the mid-1970s. [Comparison of mortality in BFD endemic area with that of a local reference population (Chiayi-Tainan county) and that of Taiwan as a whole.]	ICD9 188	$SMR_{local\ male}$ $SMR_{national\ male}$ $SMR_{local\ female}$ $SMR_{national\ female}$	312 312 295 295	8.92 (7.96–9.96) 10.5 (9.37–11.7) 14.1 (12.51–15.8) 17.8 (5.70–19.8)
*Lamm et al. 2004[10] [89] (Table One)	133 counties in 26 states, USA	Mortality 1950-79	Arsenic groundwater water concentration (μg·L^{-1}). Period of samples collection not reported. 3.0–3.9 4.0–4.9 5.0–7.4 7.5–9.9 10.0–19.9 20.0–49.9 50.0–59.9 [Median arsenic concentration ranged between 3–60 (μg·L^{-1}), with 65% of the counties and 82% of the population in the range of 3–5 (μg·L^{-1}).]	N/A	 SMR_{white_male} SMR_{white_male} SMR_{white_male} SMR_{white_male} SMR_{white_male} SMR_{white_male} SMR_{white_male}	Counties 53 22 28 14 11 3 2	 0.95 (0.89–1.01) 0.95 (0.88–1.02) 0.97 (0.85–1.12) 0.89 (0.75–1.06) 0.90 (0.78–1.04) 0.80 (0.54–1.17) 0.73 (0.41–1.27)
Marshall et al. 2007 [50] (Table Three)	Chile	Mortality 1950-2000	Northern Chile (Region II) with population weighted average arsenic concentration in drinking water up to 569 μg·L^{-1} vs Region V which is otherwise similar to Region II but not exposed to arsenic. Between 1958–1970, arsenic concentration in water supply of Antofagasta and nearby Mejillones (Region II) averaged 870 μg·L^{-1} and declined in the 1970s when water treatment plants were installed.	ICD 188	$RR_{male\ 1971–73}$ $RR_{male\ 1974–75}$ $RR_{male\ 1977–79}$ $RR_{male\ 1980–82}$ $RR_{male\ 1983–85}$ $RR_{male\ 1986–88}$ $RR_{male\ 1989–91}$	9 9 17 35 41 47 52	1.71 (0.80–3.69) 5.95 (2.22–16.0) 2.10 (1.19–3.72) 5.04 (3.13–8.10) 5.77 (3.66–9.09) 6.10 (3.97–9.39) 4.73 (3.23–6.94)

Table 2.2 Summary from ecological studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

					$RR_{male\ 1992–94}$	62	4.95 (3.47–7.06)
					$RR_{male\ 1995–97}$	56	4.43 (3.07–6.38)
					$RR_{male\ 1998–2000}$	58	4.27 (2.98–6.11)
					$RR_{female\ 1971–73}$	7	3.45 (1.34–8.91)
					$RR_{female\ 1974–75}$	4	3.09 (0.90–10.6)
					$RR_{female\ 1977–79}$	10	5.39 (2.24–13.0)
					$RR_{female\ 1980–82}$	22	9.10 (4.59–18.1)
					$RR_{female\ 1983–85}$	22	8.41 (4.30–16.4)
					$RR_{female\ 1986–88}$	37	7.28 (4.44–12.0)
					$RR_{female\ 1989–91}$	35	6.61 (4.02–10.9)
					$RR_{female\ 1992–94}$	42	13.8 (7.74–24.5)
					$RR_{female\ 1995–97}$	44	7.60 (4.78–12.1)
					$RR_{female\ 1998–2000}$	50	9.16 (5.76–14.5)
*†Meliker et al. 2007 [90] (Table Two)	6 counties, Southeastern Michigan, USA	Mortality 1979-97	Population weighted median arsenic concentration in water of 7.58 $\mu g \cdot L^{-1}$. Data from 9,251 well water samples collected between 1983–2002.	ICD9 188	SMR_{male}	348	0.94 (0.82–1.08)
					SMR_{female}	171	0.98 (0.80–1.19)
*†Pou et al. 2011[12] [63] (Table Two)	26 counties in province of Cordoba, Argentina	Mortality 1986-2006	Arsenic drinking water concentration ($\mu g \cdot L^{-1}$). Period of samples collection not reported.	ICD10 C67			
			Low (0–40)		SMR_{male}	–	3.14 (2.9–3.4)
			Medium (40–320)			–	4.0 (3.6–4.5)
			High (320–1,800)			–	4.7 (4.1–5.4)
			Low (0–40)		SMR_{female}	–	1.0 (reference)
			Medium (40–320)			–	0.94 (0.84–1.1)
			High (320–1,800) [Arsenic measurements from many surveys, one dating 50 years prior to study publication but with arsenic levels showing high degree of consistency with a more recent survey with no exact date detailed.]			–	1.2 (1.04–1.4)
*†Su et al. 2011 [64] (Table Two)	BFD endemic area, Taiwan	Mortality 1979-2003	Median arsenic content of artesian well: 780 $\mu g \cdot L^{-1}$ (range: 350–1,140). [Period of samples collection not reported. Artesian wells in the region were dug in the 1920s but no longer used by mid-1970s. Results show a comparison of mortality in BFD endemic area with that of Taiwan.]	ICD9 188	SMR	785	5.3 (4.9–5.6)
†Aballay et al. 2012[11] [62] (Table Two)	123 districts in province of Cordoba, Argentina	Incidence 2004	Arsenic water samples from 3 aquifers: (1) Rjojan plain (concentration ranged 0–40 $\mu g \cdot L^{-1}$ - 23 wells), (2) Pampean mountains (0–320 $\mu g \cdot L^{-1}$ - 114 wells) and (3) Chaco-Pampean plain (0–1,800 $\mu g \cdot L^{-1}$ - 301 wells). In 80 wells, arsenic was undetected.	N/A	RR_{male}	–	13.8 (6.80–28.0)
					RR_{female}	–	12.7 (2.51–63.9)

Table 2.2 Summary from ecological studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

†Fernández et al. 2012 [55]	Antofagasta, Chile	Mortality 1983-2009	Arsenic drinking water concentration ranging 800–900 μg·L [1]. [Arsenic levels based on the last 60 years and obtained from the local tap water company in Antofagasta. Results compares mortality rate in Antofagasta with the rest of Chile.]	ICD10 C67	RR_{male}	–	5.3 (4.8–5.8)
					RR_{female}	–	7.8 (7.0–8.7)
					RR_{both_sex}	–	6.1 (5.7–6.6)

*Study included in meta-analyses.
†Recent study not included in the International Agency for Research on Cancer 2012 review (Monograph 100C [23]).
[1] All ecological studies assessed arsenic exposure at the group-level.
[2]ICD = International Classification for Disease for cancer site abstracted which included, bladder and urothelial/transitional cell carcinoma of the bladder or kidney. Transitional cell carcinoma of the renal pelvis often share the same etiology as bladder cancer, and as such, have been treated as bladder within the meta-analyses as recommended by IARC [23]. N/A = not available.
[3]SMR, standardized mortality ratio.
[4]Age-standardized mortality rates per 100,000 using the 1976 world population as standard population and based on 899,811 person-years.
[5]All age-standardized mortality rates shown are significant at $p < 0.001$ based on trend test.
[6] Regression coefficient showing an increase in age-adjusted mortality per 100,000 persons-years for every 0.1 ppm increase in arsenic level, adjusting for indices of industrialization and urbanization. Standard errors are in brackets. Bladder cancer was significantly correlated with average arsenic level in water.
[7]Incidence rate per 100,000, adjusted for age.
[8]County is the unit of analysis.
[9]RD, rate difference (per 100,000 person-years) for one unit increase in the predictor and associated standard error for exposure > 640 $\mu g \cdot L^{-1}$(SE). Results shown for transitional-cell carcinoma.
[10]Average annual age-adjusted (to U.S. 1970 standard population) death rates per 100,000 abstracted at the state level for each decade were used as standard rates to calculate county-specific SMRs.
[11]Incidence rate ratio estimates with arsenic as continuous.
[12]Used lung cancer mortality rates as surrogate to smoking - may result in an overestimation of risk where smoking has declined; an underestimation of risk where smoking has increased; and an over-adjusted model as lung cancer is also associated with arsenic exposure.

Table 2.3 Summary from case-control studies reporting on arsenic exposure and the risk of bladder cancer

Study [reference] (Table from original publication)	Study locale	Outcome	ICD[1]	Arsenic exposure assessment	Exposure [comments]	Cases: Controls	All participants		Never smokers		Ever smokers		Covariates assessed
							n	OR[2], (95% CI)	n	OR, (95% CI)	n	OR, (95% CI)	
Chen et al. 1986[3] [25] (Table Four)	4 neighbouring Blackfoot disease (BFD)-endemic areas, Taiwan	Mortality 1996-2000	N/A	Individual level 'estimated'	Year of artesian water consumption:	69:368							age, sex, cigarette smoking, tea drinking habit, vegetarian habit, vegetable consumption frequency, fermented bean consumption frequency
					0 (referent)		17	1.0	–	–	–	–	
					1 – 20		19	1.27	–	–	–	–	
					20 – 40		10	1.68	–	–	–	–	
					≥ 40		23	4.10	–	–	–	–	
					[Median arsenic content of artesian wells and (range): 780 $\mu g \cdot L^{-1}$ (350 – 1,140). History of artesian well water noted.]								
Bates et al. 1995 [31] (Table Three)	Utah, USA	Incidence	N/A	Individual level 'measured'	Cumulative dose index of arsenic (mg):	117:266							age, sex, smoking, exposure to chlorinated surface water, history of bladder infection, education, urbanization of the place of longest lifetime residence, and ever employed in high-risk occupation
		Diagnosis in a 1-year period around 1978			< 19 (referent)		14	1.0	10	1.0	4	1.0	
					19 to < 33		21	1.56 (0.8–3.2)	10	1.09 (0.4–3.1)	11	3.33 (1.0–10.8)	
					33 to < 53		17	0.95 (0.4–2.0)	7	0.68 (0.2–2.3)	10	1.93 (0.6–6.2)	
					≥ 53		19	1.41 (0.7–2.9)	4	0.53 (0.1–1.9)	15	3.32 (1.1–10.3)	
					[Arsenic water concentration ranged 0.5 - 160 $\mu g \cdot L$ and averaged 5 $\mu g \cdot L$. Data on arsenic levels in public drinking water supplies were collected in 1978–79. Results are based on the 71 cases who had lived in study towns for at least half of their lives. Residential history and water source used in exposure assessment.]								
*Kurttio et al. 1999 [20] (Tables Six, Seven)	Areas in Finland with < 10% population with municipal drinking-water system	Incidence 1981-95	N/A	Individual level 'measured'	Arsenic water concentration ($\mu g \cdot L^{-1}$):	61:275							age, sex, smoking
					< 0.1		23	1.0	8	1.0	8	1.0	
					1.1 -0.5		19	1.53 (0.75–3.09)	4	0.95 (0.25–3.64)	3	1.10 (0.19–6.24)	
					≥ 0.5		19	2.44 (1.11–5.37)	5	0.87 (0.25–3.02)	7	10.3 (1.16–92.6)	
					(log) continuous		61	1.37 (0.95–1.96)		–		–	

Table 2.3 Summary from case-control studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

					[Only subjects with drilled wells; median total arsenic concentration of 0.1 μg·L ; max.concentration of 64 μg·L and 1% exceeding 10 μg·L. Water sampled from wells used by the study population at least for 1967–80. Exposure in the 3rd-9th calendar year prior to cancer diagnosis. Residential history and drinking water consumption used in exposure assessment.]								
Chen et al. 2003 [91] (Table Two)	Southwestern Taiwan	Incidence 1996-99	ICD9 188	Individual level 'estimated'	Cumulative arsenic exposure (mg·L ^{1}·year):	49:224							age, sex, BMI, cumulative arsenic exposure, cigarette smoking, hair dye usage, education
					0 – 2		30	1.0	–	–	–	–	
					> 2 – 12		4	0.6 (−1.1–3.0)	–	–	–	–	
					> 12		10	1.86 (0.2–5.10)	–	–	–	–	
					[Arsenic concentration in artesian well water from survey of 83,656 wells between 1974–76. Questionnaires used to determine village in which subjects lived 30 years ago. Residential history and duration and; source of drinking water used in exposure assessment.]								
Steinmaus et al. 2003 [92] (Tables Three, Four)	6 counties in Nevada; 1 county in California, USA	Incidence 1994-2000	N/A	Individual level 'estimated'	Cumulative exposure to arsenic in water (mg·L ^{1}·year):	181:328							OR for all participants adjusted for age, gender, occupation, smoking history (<1 pack per day (ppd), ≥1 ppd, former smoker, never smoker), income, education and race
					< 6.4		153	1.0	23	1.0	130	1.0	
					6.4 – 82.8		9	1.63 (0.64–4.13)	3	2.65 (0.49–14.2)	6	1.06 (0.34–3.33)	
					> 82.8		19	1.40 (0.73–2.70)	3	0.50 (0.12–2.05)	13	2.25 (0.97–5.20)	
					[Arsenic concentration from 7,000 samples from community and domestic wells. Results for a 40 years lagged exposure; 88.4% of cases and 91.8% of controls being exposed to arsenic levels ranging from 0 to 19 μg·L, respectively. Residential history, source of drinking water and intake used in exposure assessment.]								

Table 2.3 Summary from case-control studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

*Bates et al. 2004 [93] (Tables Two, Three)	Cordoba, Argentina	Incidence 1996-2000	N/A	Individual level 'measured'	Arsenic water concentration ($\mu g \cdot L^{-1}$):	114:114							*mate con bombilla* consumption, education, and home tap-water consumption in all groups; and adjusted for the highest daily number of cigarettes subjects reported ever having smoked in the smoker group
					0–50		70	1.0	22	1.0	65	1.0	
					51–100		13	0.88 (0.3–2.3)	2	1.05 (0.2–6.9)	7	1.29 (0.3–5.0)	
					101–200		22	1.02 (0.5–2.3)	3	1.10 (0.2–6.3)	10	0.96 (0.3–3.0)	
					> 200		9	0.60 (0.2–1.7)	1	0.58 (0.1–6.2)	2	0.17 (0.0–1.0)	
					[Average arsenic concentration of 5 years of highest exposure during the period 6–40 years before interview. On average, cases and controls had 25.7 and 25.6 years of well-water consumption, respectively; also approximately 50% of all well years were derived from proxy-well data. Results shown for transitional cell bladder cancer.]								
Karagas et al. 2004 [94] (Table Two)	New Hampshire, USA	Incidence 1994-98	N/A	Individual level 'measured'	Arsenic toenail concentration ($\mu g \cdot g^{-1}$):	383:641							age, sex, smoking status (ever/never)
					0.009–0.059		90	1.0	15	1.0	75	1.0	
					0.060–0.086		119	1.37 (0.96–1.96)	20	0.85 (0.38–1.91)	99	1.53 (1.02–2.29)	
					0.087–0.126		88	1.08 (0.74–1.58)	22	1.18 (0.53–2.66)	66	1.02 (0.66–1.56)	
					0.127–0.193		48	1.04 (0.66–1.63)	11	1.10 (0.42–2.90)	37	1.00 (0.60–1.67)	
					0.194–0.277		2	1.33 (0.71–2.49)	3	0.49 (0.12–2.05)	18	1.78 (0.86–3.67)	
					0.278–0.330		3	0.41 (0.11–1.50)	0	–	3	0.50 (0.13–1.88)	
					0.331–2.484		14	1.36 (0.63–2.90)	0	–	14	2.17 (0.92–5.11)	
					[Levels of arsenic in toenails reflect exposures occurring between 9–15 months prior to sample collection. On average cases and controls had 16.5 and 17.2 years exposure to their water system. Results shown for transitional cell bladder cancer.]								

Table 2.3 Summary from case-control studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

Michaud et al. 2004 [95] (Table Two)	Southwestern Finland	Incidence 1985-99	ICD9 188, 233.7	Individual level 'measured'	Arsenic toenail concentration ($\mu g \cdot g^{-1}$):	280:293							age, toenail collection date, intervention group, number of cigarettes per day, and number of years smoking
					< 0.105		–	–	–	–	136	1.0	
					0.105–0.160		–	–	–	–	73	1.10 (0.73–1.64)	
					0.161–0.259		–	–	–	–	37	0.93 (0.56–1.54)	
					0.260–0.399		–	–	–	–	20	1.38 (0.68–2.80)	
					> 0.399		–	–	–	–	14	1.14 (0.52–2.51)	
† Pu et al. 2007 [51] (Tables Four, Five)	Taiwan	Incidence 2002-04	N/A	Individual level 'measured'	Arsenic urine concentration ($\mu g \cdot g^{-1}$ creatine):	177:313							OR (all participants): age, sex, education, parents' ethnicity, alcohol drinking, pesticides use
					≤ 15.4		24	1.0	–	–	–	–	
					15.5–26.4		44	1.9 (1.1–3.4)	–	–	–	–	
					>26.4		109	5.3 (3.1–9.0)	–	–	–	–	
					≤ 20.3		–	–	17	1.0	21	1.0	OR (never/ever smokers): age, sex
					≥ 20.3		–	–	68	4.4 (2.3–8.5)	61	8.2 (3.8–17.8)	
					[Smokers include current and former smokers. Non-smokers with ≤ 20.3 ($\mu g \cdot g^{-1}$ creatine) was used as referent category.]								
*†Meliker et al. 2010 [87] (Table Three)	11 counties of Southeastern Michigan, USA	Incidence 2000-04	N/A	Individual level 'measured'	Arsenic water concentration ($\mu g \cdot L^{-1}$):	411:566							age, sex, race, smoking history, education, history of employment in high risk occupation, family history of bladder cancer
					< 1		187	1.0	–	–	–	–	
					1–10		182	0.84 (0.63–1.12)	–	–	–	–	
					> 10		38	1.10 (0.65–1.86)	–	–	–	–	
					[Arsenic water concentrations obtained from: 6,050 private untreated wells sampled between 1993–2002; 371 well water measurements from participants' current residence and; 1,675 measurements from public well water supplies collected between 1983–2004, which were used to estimate arsenic concentrations at past residences.]								

Table 2.3 Summary from case-control studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

*†Steinmaus et al. 2013 [67] (Table Two)	Region I and II, northern Chile	Incidence 2007-10	N/A	Individual level 'estimated'	Arsenic water concentration ($\mu g \cdot L^{-1}$):	306:640							no covariates assessed, although subjects were frequency matched on age, sex
					0–59		23	1.0	–	–	–	–	
					60–199		27	0.84 (0.46–1.52)	–	–	–	–	
					200–799		60	2.50 (1.48–4.22)	–	–	–	–	
					> 800		122	4.44 (2.75–7.15)	–	–	–	–	
					[Each city/town of residence in which each subject lived was linked to a water arsenic measurement for that city/ town so that an arsenic concentration could be assigned to each year of each subject's life. Study also present OR in relation to various metrics of arsenic exposure such as lifetime and cumulative average exposure and; lifetime and cumulative intake. Residential history used in exposure assessment.]								

*Study included in meta-analyses.
†Recent study not included in the International Agency for Research on Cancer 2012 review (Monograph 100C [23]).
[1]ICD = International Classification of Disease. N/A = not available.
[2]OR = Odds ratios.
[3]OR crude = 1.0, 1.17, 1.60, 3.90 for corresponding years of exposure shown in table.

Table 2.4 Summary from cohort studies reporting on arsenic exposure and the risk of bladder cancer

Study [reference] (Table from original publication)	Study locale	Outcome	ICD1	Arsenic exposure assessment	Exposure [comments]	Outcome measure	Cohort size	Cases	Risk estimate (95% CI)	Covariates assessed
Chen et al. 1988 [70] (Table Six)	4 neighbouring townships from Blackfoot disease (BFD) endemic area, Taiwan	Morality 1968-83	N/A	Group level	Median arsenic content of artesian well and (range): 0.78 ppm (0.35–1.14); in shallow well: 0.04 (0.00-0.30). General population used as reference. 95% CI obtained from IARC 2012 review [23].	SMR	871	15	38.8 (21.7–64.0)	
Chiou et al. 1995 [32] (Table Four)	4 neighbouring townships from BFD endemic area, Taiwan	Incidence 1988 (Follow-up period ranged 0.05 to 7.7 years)	N/A	Individual level 'estimated'	Cumulative arsenic exposure ($mg \cdot L^{-1} \cdot year$):	RR	2,556	29		age, sex, cigarette smoking
					0				1.0	
					0.1–19.9				1.57 (0.44–5.55)	
					> 20				3.58 (1.05–12.19)	
					unknown				1.25 (0.38–4.12)	
					[Median arsenic content of artesian well and (range): 0.78 ppm (0.35–1.14); in shallow well: 0.04 (0.00-0.30). Histories of residential address and duration of drinking well water used to derive cumulative exposure.]					
*Tsuda et al.[2] 1995 [34] (Table Three)	Niigata, Japan	Mortality 1959-92 (Recruitment in 1959, followed until 1992)	Transitional cell carcinoma	Individual level 'measured'	Arsenic water concentration ($\mu g \cdot L^{-1}$):	SMR	443			age, smoking habits
					< 50			254	0.00 (0–12.50)	
					50 – 990			76	0.00 (0–47.05)	
			ICD9 188, 189 ICDO histology N/A		≥ 1,000			113	31.18 (8.62–91.75)	
					[Arsenic-polluted area. Exposure to be between 1955-59. All 34 wells in the area were sampled and arsenic concentration ranged from non detectable to 3,000 $\mu g \cdot L^{-1}$).]					

Table 2.4 Summary from cohort studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

Lewis et al. 1999[3] [40] (Table Four)	Millard County in Utah, USA	Mortality (Recruitment 1900–1945)	N/A	Group level	Cumulative arsenic exposure derived from: low exposure (< 1000 ppb-year); medium (1,000-4,999 ppb-year); high (≥ 5,000 ppb-year):		4,058			Individual data on cofactors not available. However, the cohort was assembled from historical membership records of the Church of Jesus Christ of Latter-day Saints (Mormons) which prohibits tobacco use and the consumption of alcohol and caffeine.
						SMR_{male}		–	0.42 (0.08–1.22)	
						SMR_{female}		–	0.81 (0.10–2.93)	
					< 1,000 ppb•year	SMR_{male}		–	0.4	
						SMR_{female}		–	1.18	
					≥ 5,000 ppb•year	SMR_{male}		–	0.95	
						SMR_{female}		–	1.10	
					[Residential history combined with local water records used to assess exposure. High variability in exposure estimates in each community with median arsenic concentrations ranging from 14 to 166 ppb. Records of arsenic measurements dating back to 1964.]					
*Chiou et al. 2001[3] [33] (Table Five)	18 villages in four townships in Lanyang Basin, North-eastern Taiwan	Incidence 1991-1994 (Follow-up period from time of enrollment to Dec.1996)	Urinary organs	Individual level 'estimated'	Arsenic water concentration ($\mu g \cdot L^{-1}$):	RR	8,102			age, sex, cigarette smoking, duration of well water drinking
			ICD9 188, 189		0–10.0	Urinary organs		3	1.0	
					10.1–50.0			3	1.5 (0.3–8.0)	
					50.1–100.0			2	2.2 (0.4–13.7)	
			Transitional cell carcinoma		> 100.0			7	4.8 (1.2–19.4)	
					Arsenic water concentration ($\mu g \cdot L^{-1}$);	RR Transitional cell carcinoma				
					0–10.0			1	1.0	
			ICDO1 8120.2, 8120.3, 8130.3		10.1–50.0			1	1.9 (0.1–32.5)	
					50.1–100.0			2	8.2 (0.7–99.1)	
					> 100.0			6	15.3 (1.7–139.9)	
					[Arsenic levels in shallow well ranging from < 0.15 to 3,590 $\mu g \cdot L^{-1}$ and collected from 3,901 well water samples between 1991–94.]					

Table 2.4 Summary from cohort studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

† Baastrup et al. 2008 [96] (Table Three)	23 municipalities in Copenhagen & Asrhus areas, Dannemark	Incidence 1993-1997 (Follow-up from enrollment until date of first cancer diagnosis, emigration, death, or Aug. 2003)	N/A	Individual level 'estimated'	Cumulated arsenic exposure (5 mg·):	IRR	56,378	214	1.0 (0.98–1.04)	smoking status, smoking duration, smoking intensity, education, occupation
					Time-weighted average exposure (µg·L ^{1}):	IRR		214	1.01 (0.93–1.11)	
					[Average arsenic exposure from 0.05 to 25.3 µg·L ^{1}, with mean of 1.2 µg·L ^{1}. Average arsenic concentrations obtained from 4,954 samples from 2,487 water utilities collected, 1987–2004, with most samples dating 2002–04. Residential history 1970–2003.]					
*†Huang et al. 2008 [53] (Table Two)	3 villages in Putai Township, in BFD endemic area of southern Taiwan	Incidence 1989 (Average follow-up period of 12 years)	Urothelial carcinoma	Individual level 'estimated'	Arsenic water concentration (µg·L ^{1}):	RR	1,078			age, sex, cigarette smoking, education
					0–400			1	1.0	
			ICDO3 M-codes 8120/3, 8230/3		401–700			14	5.2 (0.7–39.8)	
					710–900			9	6.7 (0.8–53.4)	
					≥ 900			7	6.5 (0.8–53.1)	
					Cumulative arsenic exposure (mg·L ^{1}·year):	RR				
					0			0	–	
					0.1–11.9			2	1.0	
					12.0–19.9			9	4.6 (1.0–21.8)	
					≥ 20.0			20	7.9 (1.7–37.9)	
					[Period of arsenic water samples collection not reported. Participants used artesian well water more > 30 years when recruited. Information from interview included history of well-water consumption, residential history, lifestyle factors].					
*†Chen et al. 2010[5] [60] (Tables One, Two)	Taiwan	Incidence 1991-1994 (Average follow-up period of 11.6 years)	Urothelial carcinoma	Individual level 'measured'	Arsenic water concentration (µg·L ^{1}):	RR	8,086			age, sex, cigarette smoking status, education, alcohol

Table 2.4 Summary from cohort studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

			ICDO histology		< 10	Urothelial carcinoma		3	1.0	consumption at enrolment, and whether subject started drinking well water from birth
			N/A		10–49.9			6	1.85 (0.45–7.61)	
			Urinary organs		50–99.9			3	2.19 (0.43–11.1)	
			ICD9 188, 189, 189.1-189.9		100–299.9			7	5.50 (1.39–21.8)	
					≥ 300			10	10.8 (2.90–40.3)	
					unknown			7	4.34 (1.06–17.7)	
					Cumulative arsenic exposure (μg·L^{-1}•year):					
					< 400	RR		6	1.0	
					400– < 1,000	Urinary organs		3	1.16 (0.29–4.64)	
					1,000– < 5,000			12	2.44 (0.91–6.50)	
					5,000– < 10,000			5	3.88 (1.18–12.7)	
					≥ 10,000			11	7.55 (2.79–20.4)	
					Unknown			8	2.90 (1.01–8.37)	
					[Arsenic concentration ranged < 0.15 to > 3,000 μg·L^{-1} and was estimated using 3,901 water samples from residence of participants at time of interview. Other measures of arsenic exposure included, duration of exposure, age starting/ending drinking well water, and cumulative exposure.]					
*†Chung et al. 2013[6] [6:5] (Table One)	3 villages in Putai Township, in BFD endemic area of southern Taiwan	Mortality 1996-2010 (Average follow-up period of 17.8 years)	ICD9 188	SMR based analyses: Group level	Median arsenic content of artesian well (range: 700–930 μg·L^{-1}) measured in the early 1960s.	SMR_{male}	1,563	24	2.9 (27.5–63.8)	SMR adjusted for age
						SMR_{female}		19	59.4 (35.7–92.7)	

Table 2.4 Summary from cohort studies reporting on arsenic exposure and the risk of bladder cancer *(Continued)*

		[Used age-adjusted mortality rate in Taiwan as standard rates.]				
	HR based analyses: Individual level 'estimated'	Average arsenic concentration in artesian well ($\mu g \cdot L^{-1}$):	HR			HR adjusted for age, gender, education, smoking habits
		< 50		1	1.0	
		50–710		15	4.35 (0.56–33.52)	
		> 710		22	7.22 (0.95–55.04)	
		[Duration of drinking artesian well water and history of residential address obtained from questionnaires. Authors found a significant association with duration of well water drinking.]				

*Study included in meta-analyses.
†Recent study not included in the International Agency for Research on Cancer 2012 review (Monograph 100C [23]).
[1]ICD = International Classification of Disease. ICD for cancer site abstracted which included bladder and urothelial/transitional cell carcinoma of the bladder or kidney. Transitional cell carcinoma of the renal pelvis often share the same etiology as bladder cancer, and as such, have been treated as bladder within the meta-analyses as recommended by IARC [23]. N/A = Not available.
[2]Cases = number of persons exposed between 1955-1959.
[3]95% Confidence intervals not available for data at low and high exposure.
[4]Results for transitional cell carcinoma were included in the meta-analysis.
[5]Results for urothelial carcinoma were included in the meta-analysis.
[6]Results from SMR were included in the meta-analyses.

Table 2.5 Summary from ecological studies reporting on arsenic exposure and the risk of kidney cancer

Study [reference] (Table from original publication)	Study locale	Outcome	Exposure[1] [comments]	ICD[2]	Outcome measure	Cases	Risk estimate (95% CI)
Chen et al. 1985[3] [24] (Table One)	84 villages from 4 neighbouring townships on SW coast, Taiwan	Mortality 1968-82	Median arsenic content of artesian well and (range): 780 μg·L^{-1} (350–1,140); in shallow well: 40 (0.0–300). Period of samples collection not reported.	ICD 189	SMR_{male}	42	7.72 (5.37–10.1)
			[Comparison of mortality rate in Blackfoot disease (BFD) with those of the general population.]		SMR_{female}	62	11.2 (8.38–14.0)
*Chen et al. 1988[4] [26] (Table One)	BFD endemic area, Taiwan	Mortality 1973-86	Arsenic well water concentration (μg·L^{-1}). Period of samples collection not reported.	ICD 189			
			General population		$ASMR_{male}$	–	1.1
			< 300			–	5.4
			300-590			–	13.1
			≥ 600			–	21.6
			General population		$ASMR_{female}$	–	0.9
			< 300			–	3.6
			300-590			–	12.5
			≥ 600			–	33.3
			[Comparison of mortality rate in BFD with those of the general population.]				
*Wu et al. 1989[5] [27] (Table Three)	BFD endemic area, Taiwan (42 villages)	Mortality 1973-86	Arsenic well water concentration (μg·L^{-1}) based on well water samples collected between 1964–66.	ICD8 189			
			< 300		$ASMR_{male}$	9	8.42
			300–590			11	18.9
			≥ 600			6	25.3
			< 300		$ASMR_{female}$	4	3.42
			300–590			13	19.4
			≥ 600			16	58.0
Chen and Wang 1990[6] [28] (Table Four)	314 precincts & townships in Taiwan,	Mortality 1972-83	Average arsenic levels in water samples of all 314 geographical	ICD 189			

Table 2.5 Summary from ecological studies reporting on arsenic exposure and the risk of kidney cancer *(Continued)*

	including 4 from BFD endemic area		units. 73.9% had < 5% of wells with > 50 μg·L^{-1}; 14.7% had 5-14%; 11.5% had ≥ 15%. Well water samples collected between 1974–76.				
			All precincts & townships		$ASMR_{male}$	–	1.1 (0.2)
					$ASMR_{female}$	–	1.7 (0.2)
			Southwestern townships		$ASMR_{male}$	–	1.2 (0.2)
					$ASMR_{female}$	–	1.7 (0.3)
Guo et al. 1997[7] [37] (Table Two)	243 townships in Taiwan	Incidence 1980-87	Arsenic well water concentration ranging from < 50 to > 640 μg·L^{-1}.	ICD 189.0, 189.1	RDmale	–	0.03 (0.02)
			Estimate presented measured at > 640 μg·L^{-1}. [Arsenic measurements from a National survey of 83,656 wells in 243 townships, collected mostly between 1974–76.]		RDfemale	–	0.14 (0.013)
Rivara et al.1997 [38] (Table Four)	Chile	Mortality 1950-92	Annual average arsenic concentration in drinking water for Antofagasta (Region II of Chile) ranging between 40 to 860 μg·L^{-1}. Data from historical records from 1950–1992.	ICD 189	RR	–	3.8 (3.1–4.7)
			[Comparison of mortality rate in Region II (exposed) populations vs Region VIII (control population.]				
Smith et al. 1998 [39]	Chile	Mortality 1989-93	Region II of Northern Chile with population weighted average arsenic concentration in drinking water up to 569 μg·L^{-1} compared with the rest of Chile; exposure generally < 10 μg·L^{-1}.	N/A	SMR_{male}	39	1.6 (1.1–2.1)
					SMR_{female}	34	2.7 (1.9–3.8)
			[Arsenic measurements from 1950–94.]				
Hinwood et al. 1999 [88] (Table Two)	22 areas in Victoria, Australia	Incidence 1982-91	Median water arsenic concentration ranging 13 μg·L^{-1} to 1,077 μg·L^{-1}. [Selected areas were those where samples with soil and/or water arsenic concentration were generally in excess of 10 μg·L^{-1}. Period for samples collection is not available.]	ICD 189.0, 189.9	SIR	134	1.16 (0.98–1.37)
*Tsai et al. 1999 [41] (Tables Two, Three)	4 townships from BFD endemic area in SW coast, Taiwan	Mortality 1971-94	Median arsenic content of artesian well: 780 μg·L^{-1} (range: 350–1,140).	ICD 189	$SMR_{local\ male}$	94	6.76 (5.46–8.27)
					$SMR_{national\ male}$	94	6.80 (5.49–8.32)
			Period of samples collection not reported. Authors state that artesian		$SMR_{local\ female}$	128	8.89 (7.42–10.6)

Table 2.5 Summary from ecological studies reporting on arsenic exposure and the risk of kidney cancer *(Continued)*

			wells were no longer used by the mid-1970s.				
			[Comparison of mortality in BFD endemic area with that of a local reference population (Chiayi-Tainan county) and that of Taiwan as a whole.]		$SMR_{national\ female}$	128	10.5 (8.75–12.5)
*†Meliker et al. 2007 [90] (Table Two)	6 counties, Southeastern Michigan, USA	Mortality 1979-97	Population weighted median arsenic concentration in water of 7.58 $\mu g \cdot L^{-1}$, with a range between 10–100 $\mu g \cdot L^{-1}$. Data from 9,251 well water samples collected between 1983–2002.	ICD9 189	SMR_{male}	325	1.06 (0.91–1.22)
					SMR_{female}	194	1.00 (0.82–1.20)
†Yuan et al. 2010 [61] (Tables Two, Three)	Region II and V, Chile	Mortality 1950-2000	Northern Chile (Region II) with population weighted average arsenic concentration in drinking water up to 569 $\mu g \cdot L^{-1}$ vs Region V with exposure close to 1 $\mu g \cdot L^{-1}$. Between 1958-70, arsenic concentration in water supply of Antofagasta and nearby Mejillones (Region II) averaged 870 $\mu g \cdot L^{-1}$ and declined in 1970s when treatment plants were installed.	ICD9 189; ICD10 C64-C66, C68	Men and women aged 30+ years		
					$RR_{male\ 1950–54}$	4	0.69 (0.23–2.02)
					$RR_{male\ 1955–59}$	9	1.43 (0.66–3.10)
					$RR_{male\ 1960–64}$	7	0.91 (0.40–2.08)
					$RR_{male\ 1965–69}$	12	2.51 (1.22–5.17)
					$RR_{male1970–74}$	15	1.45 (0.81–2.60)
					$RR_{male1975–80}$	19	2.13 (1.24–3.68)
					$RR_{male1981–85}$	39	3.37 (2.21–5.11)
					$RR_{male1986–90}$	63	2.81 (2.05–3.85)
					$RR_{male1991–95}$	50	1.78 (1.28–2.47)
					$RR_{male1996–00}$	66	1.61 (1.21–2.14)
					$RR_{female\ 1950–54}$	2	1.27 (0.27–6.00)
					$RR_{female\ 1955–59}$	2	0.30 (0.07–1.25)
					$RR_{female\ 1960–64}$	7	1.66 (0.71–3.91)
					$RR_{female\ 1965–69}$	3	0.76 (0.23–2.57)
					$RR_{female1970–74}$	13	3.70 (1.81–7.56)
					$RR_{female1975–80}$	9	1.71 (0.80–3.65)
					$RR_{female1981–85}$	25	2.89 (1.77–4.72)
					$RR_{female1986–90}$	41	3.23 (2.18–4.78)
					$RR_{female1991–95}$	49	4.37 (2.98–6.41)
					$RR_{female1996–00}$	47	2.32 (1.64–3.28)
					Young adults aged 30-39 years, born during and just before high-exposure period; and for ages 40+, born before 1950 with no early life exposure.		

Table 2.5 Summary from ecological studies reporting on arsenic exposure and the risk of kidney cancer *(Continued)*

	$SMR_{male\_30\ 49\ years}$	4	5.63 (1.52–14.4)
	$SMR_{male\_40\ years+}$	103	2.68 (2.19–3.26)
	$SMR^{female\_30\ 49\ years}$	4	9.52 (2.56–24.4)
	$SMR_{female\_40\ years+}$	84	3.91 (3.12–4.84)
	$SMR_{total\_30\ 49\ years}$	8	7.08 (3.05–14.0)
	$SMR_{total\_40\ years+}$	187	3.12 (2.69–3.61)

*Study included in meta-analyses.
†Recent study not included in the International Agency for Research on Cancer 2012 review (Monograph 100C [23]).
[1]All ecological studies assessed arsenic exposure at the group-level.
[2]ICD = International Classification of Disease. N/A = not available.
[3]SMR, standardized mortality ratio.
[4]Age-standardized mortality rates per 100,000 using the 1976 world population as standard population and based on 899,811 person-years.
[5]All age-standardardized mortality rates shown are significant at $p < 0.001$ based on trend test.
[6]Regression coefficient showing an increase in age-adjusted mortality per 100,000 persons-years for every 0.1 ppm increase in arsenic level, adjusting for indices of industrialization and urbanization. Standard errors are in brackets. Kidney cancer was significantly correlated with average arsenic level in water.
[7]RD, rate difference (per 100,000 person-years) for one unit increase in the predictor and associated standard error for exposure > 640 $\mu g \cdot L^{-1}$(SE).

Table 2.6 Summary from cohort studies reporting on arsenic exposure and the risk of kidney cancer

Study [reference] (Table from original publication)	Study locale	Outcome	ICD[1]	Arsenic exposure assessment	Exposure [comments]	Outcome measure	Cohort size	Cases	Risk estimate (95% CI)	Covariates assessed
Chen et al. 1988 [70] (Table Six)	4 neighbouring townships from Blackfoot disease (BFD) endemic area, Taiwan	Morality 1968-83	N/A	Group level	Median arsenic content of artesian well and (range): 0.78 ppm (0.35–1.14); in shallow well: 0.04 (0.00-0.30). General population used as reference. 95% CI obtained from IARC 2012 review [23].	SMR	871	3	19.5 (4.0–57.0)	
Lewis et al. 1999[2] [40] (Table Four)	Millard County in Utah, USA	Mortality (Recruitment 1900–1945)	N/A	Group level	Cumulative arsenic exposure derived from: low exposure (< 1000 ppb-year); medium (1,000-4,999 ppb-year); high (≥ 5,000 ppb-year):	SMR_{male}	4,058	–	1.75 (0.80–3.32)	Individual data on cofactors not available. However, the cohort was assembled from historical membership records of the Church of Jesus Christ of Latter-day Saints (Mormons) which prohibits tobacco use and the consumption of alcohol and caffeine.
						SMR_{female}		–	1.60 (0.44–4.11)	
					< 1,000 ppb•year	SMR_{male}		–	2.5	
						SMR_{female}		–	2.4	
					1,000 - 4,999 ppb•year	SMR_{male}		–	1.1	
						SMR_{female}		–	1.3	
					≥ 5,000 ppb•year	SMR_{male}		–	1.4	
						SMR_{female}		–	1.1	
					[Residential history combined with local water records used to assess exposure. High variability in exposure estimates in each community with median arsenic concentrations ranging from 14 to 166 ppb. Records of arsenic measurements dating back to 1964.]					
†Baastrup et al. 2008 [96] (Table Three)	23 municipalities in Copenhagen & Asrhus areas, Dannemark	Incidence 1993-1997 (Follow-up from enrollment until date of first cancer diagnosis, emigration, death, or Aug. 2003)	N/A	Individual level 'estimated'	Cumulated arsenic exposure (5 mg·):	IRR	56,378	53	0.94 (0.84–1.06)	smoking status, smoking duration, smoking intensity, education, occupation
					Time-weighted average exposure ($\mu g \cdot L^{-1}$):	IRR		53	0.89 (0.65–1.21)	
					[Average arsenic exposure from 0.05 to 25.3 $\mu g \cdot L^{-1}$, with mean of 1.2 $\mu g \cdot L^{-1}$. Average arsenic concentrations obtained from 4,954 samples from 2,487 water utilities collected, 1987–2004, with most samples dating 2002–04. Residential history 1970–2003.]					

†Recent study not included in the International Agency for Research on Cancer 2012 review (Monograph 100C [23]).
[1]ICD = International Classification of Disease. N/A = not available.
[2]95% Confidence intervals not available for data at low, medium and high exposure.

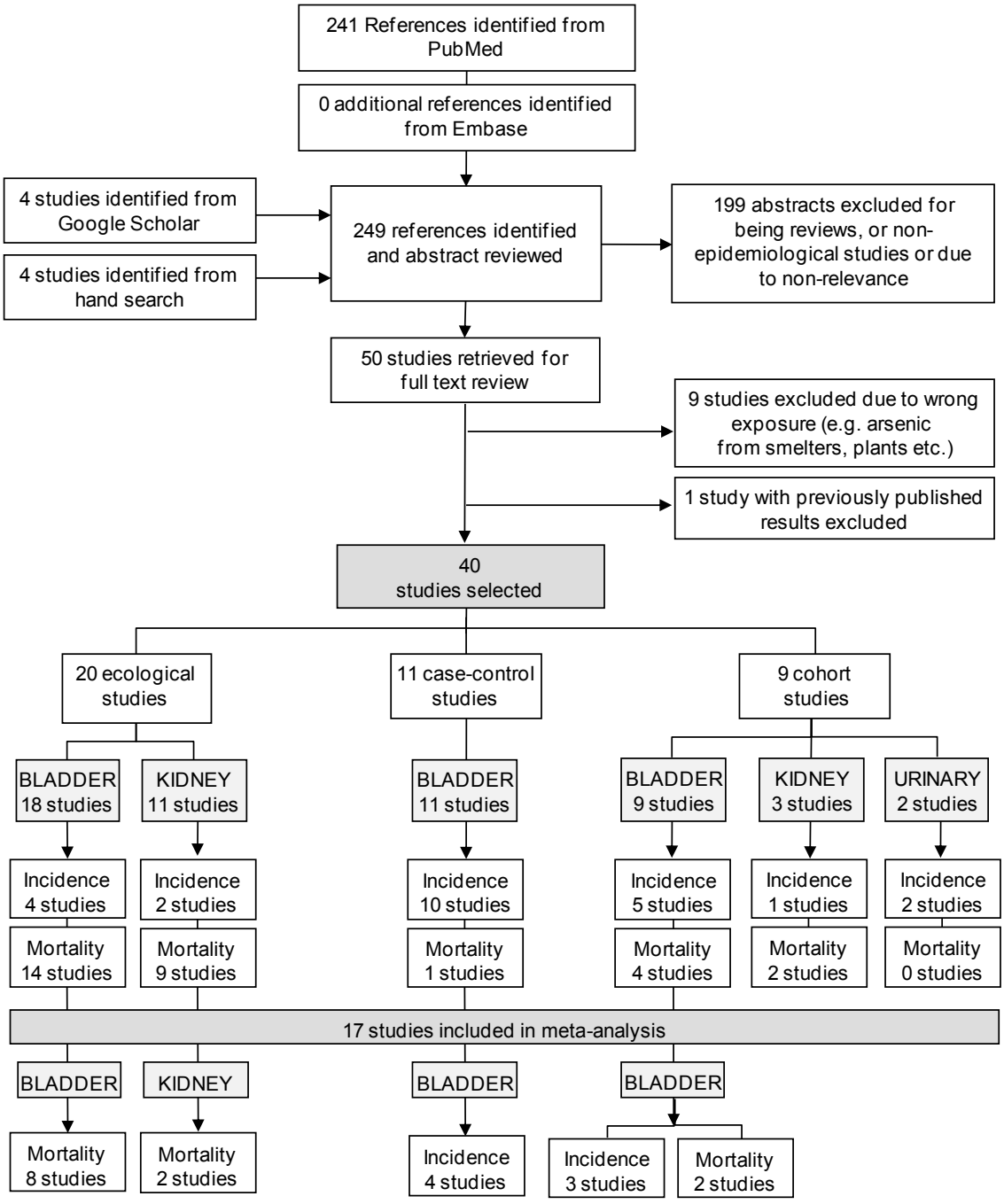

Figure 2.1 Study selection process. Note that several studies report on more than one cancer site.

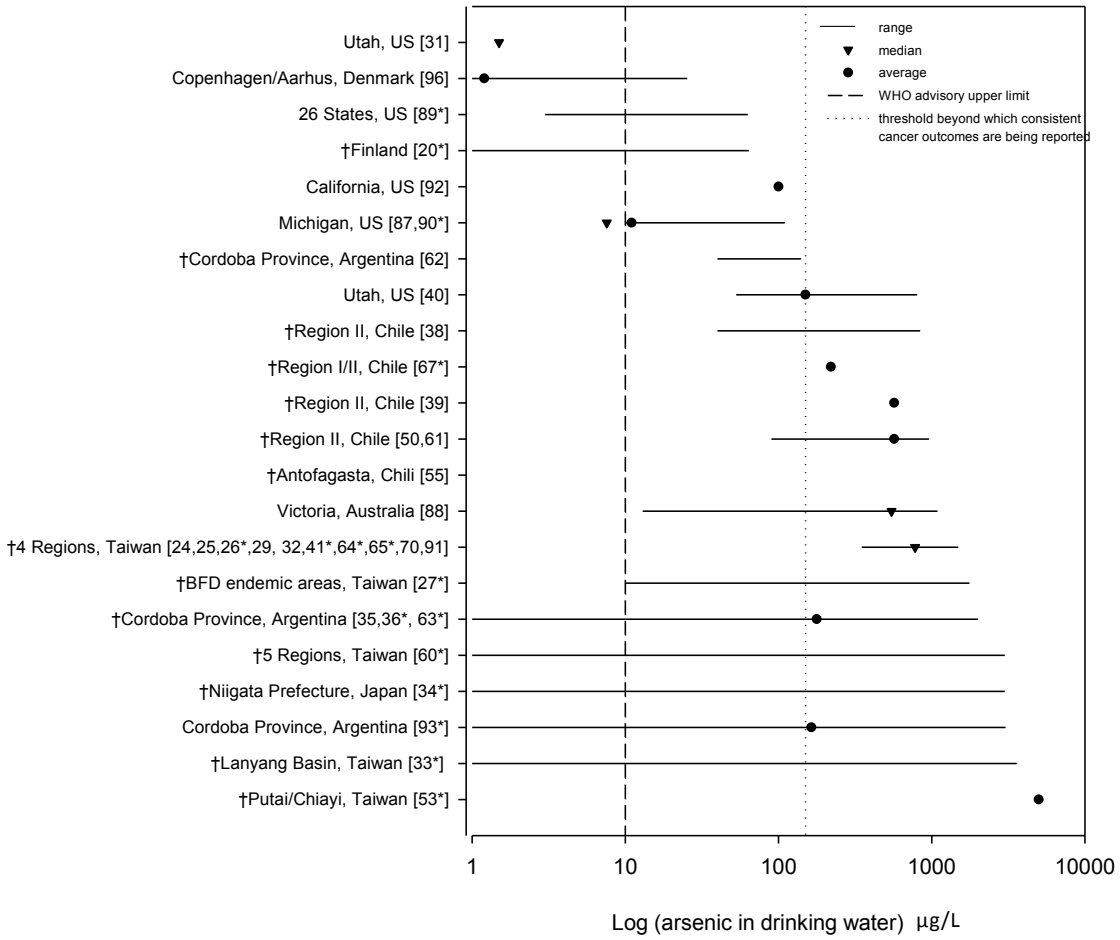

Figure 2.2 Arsenic concentrations from studies reporting on urinary tract cancers outcomes and arsenic exposure in drinking water. † indicates studies reporting significant associations and square brackets indicates citation number. Studies included in the meta-analysis are shown with an asterisk (*). Of the 40 studies reviewed, 3 used biomarkers to measure As exposure [51,94,95] and 2 failed to provide a specific measure of As-concentration [28,37].

Four studies observed a significant As-related increase in bladder cancer incidence; one study observed an increased risk of death with increasing years of artesian well water consumption in Blackfoot disease endemic areas of Taiwan ([25]; Table 2.3). Two of these studies assessed As exposure from As in tap/well water, one from urine, one from cumulated exposure and one from years of artesian well water consumption. Three of the

five studies reporting a significant association, also provided risk estimates by smoking status [20,31,51]. Two studies failed to find an effect among non-smokers [20,31]; one study reported a risk of about half the magnitude of that observed among smokers (never smokers: 4.4 [2.3 – 8.5] vs smokers: 8.2 [3.8 – 17.8]; Table 3) [51]. Regardless of the type of metric used to measure exposure (i.e. cumulative dose index, As in drinking water, body burden etc.), the risk of developing bladder cancer as a result of exposure to As, was consistently higher among smokers.

Cohort Studies

Five of the 9 cohort studies reviewed reported on bladder cancer incidence [32,33,53,60,96]; four reported on mortality (34,40,65,70]; Table 2.4). Seven of the 9 cohort studies showed an association between exposure to As contaminated drinking water and either bladder cancer incidence (4 studies, [32,33,53,60]) or mortality (3 studies, [34,65,70]). The work of both Chiou et al. [33] and Chen et al. [60] provided significant evidence for a dose–response relationship over a broad range of As exposure, from < 10 μg/L to ≥ 300 μg/L. Chen et al. [60] report relative risk estimates for bladder cancer increasing from 1.9, 2.2, 5.5 and 10.8 for exposure to As ranging from < 10, 10 – 49.9, 50 – 99.9, 100 – 299.9 and ≥ 300 μg/L, respectively. Consistent with these findings, Chiou et al. [33] report risks of similar magnitude, increasing from 1.9, 8.2, and 15.3 for exposure to As ranging from 10 – 50 μg/L, 50.1 – 100 μg/L and > 100 μg/L, respectively. The largest cohort study involving 56,378 cases failed to provide evidence of an association [96]. However, average exposure ranged of 0.05 and 25.3 μg/L and mean

exposure level was 1.2 μg/L, with the authors indicating that only a small proportion of subjects were exposed to drinking-water containing As at > 2 μg/L. Eight of the 9 cohort studies retained in this review adjusted for the effect of tobacco smoking [32-34,40,53,60,65,96].

2.3.4 Arsenic Exposure and Kidney Cancer

Ecological Studies

Nine of the 20 ecological studies reviewed reported on kidney cancer mortality (Table 2.5). Eight of these studies provided evidence for an increased risk of death from kidney cancer with exposure to As in drinking water [24,26-28,38,39,41,61]; one study found no association [90]. At high levels of As exposure risk estimates were generally higher amongst females. Chen [26] was again, first to describe a dose–response relationship between well water As and rates of mortality from kidney cancer, reporting age-standardized rates increasing from: 5.4, 13.1, 21.6 per 100, 000 males and 3.6, 12.5, 33.3 per 100,000 females, with exposure to < 300, 300 – 590, and > 600 μg/L As, respectively (Table 5). Two ecological studies reported on kidney cancer incidence [37,88] and one of these provided evidence for an association between kidney cancer and exposure to As in drinking water [37].

Case–Control Ctudies

None of the 11 case–control studies identified in this review reported on kidney cancer.

Cohort Studies

One of the 9 cohort studies reported on kidney cancer incidence [96]; two reported on mortality [40,70] (Table 2.6). Of these 3 studies, one study showed a statistically significant increase in mortality with exposure to As contaminated drinking water [70]; the others reported a non significant increased risk in mortality [40] or incidence [96]. None of the cohort studies reviewed provided evidence for a dose–response relationship. Overall, as observed with ecological studies, the magnitude of the published risk estimates for kidney cancer was consistently lower than that observed for bladder or urinary organs cancer outcomes.

2.3.5 Meta-Analyses, Model I

Analyses based on combined epidemiologic data showed an increase in the risk of developing bladder cancer or dying from bladder or kidney cancers with exposure to increasing levels of As in drinking water (Figure 2.3A-C). Combined bladder cancer SMRs ranged from < 1.0 (As concentration mid-point < 10 μg/L) to 38.8 (As concentration mid-point of 780 μg/L; Figure 2.3A), showing a significant increase in risk at higher levels of exposure ($R^2 = 0.96$, $p < 0.0001$). Similarly, cancer mortality rates also significantly increased with increased well-water As (Figure 3B; $R^2 = 0.92$, $p < 0.001$). However, the magnitude of the association was three times greater in those dying from bladder cancer relative to those dying from kidney cancer ($p < 0.0001$). Bladder cancer mortality rates ranged from 15.7 (As mid-point of 150 μg/L) to 91.5 per 100,000 persons (As mid-point of 870 μg/L); kidney cancer mortality rates ranged from 5.4 (As mid-point of 150 μg/L) to 58.0 per 100,000 persons (As mid-point of 870 μg/L). Combined RRs for

bladder cancer incidence studies, ranged from 1.0 (As mid-point of 5 μg/L) to 15.3 (As mid-point of 1,845 μg/L) and also indicated a statistically significant increase in risk with increasing well-water As (Figure 2.3C; $R^2 = 0.87$, $p < 0.0001$). Predicted incidence risk of for bladder cancer increased 2.7 [1.2 – 4.1]; 4.2 [2.1 – 6.3] and; 5.8 [2.9 – 8.7], in those drinking water contaminated with 10 μg/L; 50 μg/L and; 150 μg/L of As, respectively.

2.3.6 Meta-Analyses, Model II

The robustness of the effect size at 10, 50 and 150 μg/L of As in drinking water for all three reported outcomes (mortality rates, SMR, RR) was assessed with Model II. The predicted risk derived from the bootstrapped randomizations (Figure 2.4A-D) confirms the non-linear increase in both bladder and kidney cancer mortality and in bladder cancer incidence with increasing levels of As in drinking water which was observed with Model I. However, the magnitude of the effect size for bladder cancer incidence (Figure 2.4D) was about 50% lower than those of Model I for exposure to 10, 50 and 150 μg/L of As in drinking water: 1.4, 2.3 and 3.1(Model II) versus 2.7, 4.2 and 5.8 (Model I; Figure 2.4D). For bladder cancer mortality, the median SMR increased from 1.0 to 1.7 and 2.2 at 10, 50 and 150 μg/L, respectively. For both bladder and kidney cancers, mortality rates at 150 μg/L was about 30% greater than those recorded at 10 μg/L (Figure 2.4A-C). Although, these effect sizes were not statistically significant, they did follow a dose–response relationship across all outcome measures. In addition, 51% and 65% of the probability density distribution in predicted SMRs and RRs, respectively, fell above 1.0 (no risk) at the lowest exposure benchmark of 10 μg/L, with these proportions increasing to 74% and

83% for SMR and RR at levels of 50 µg/L.

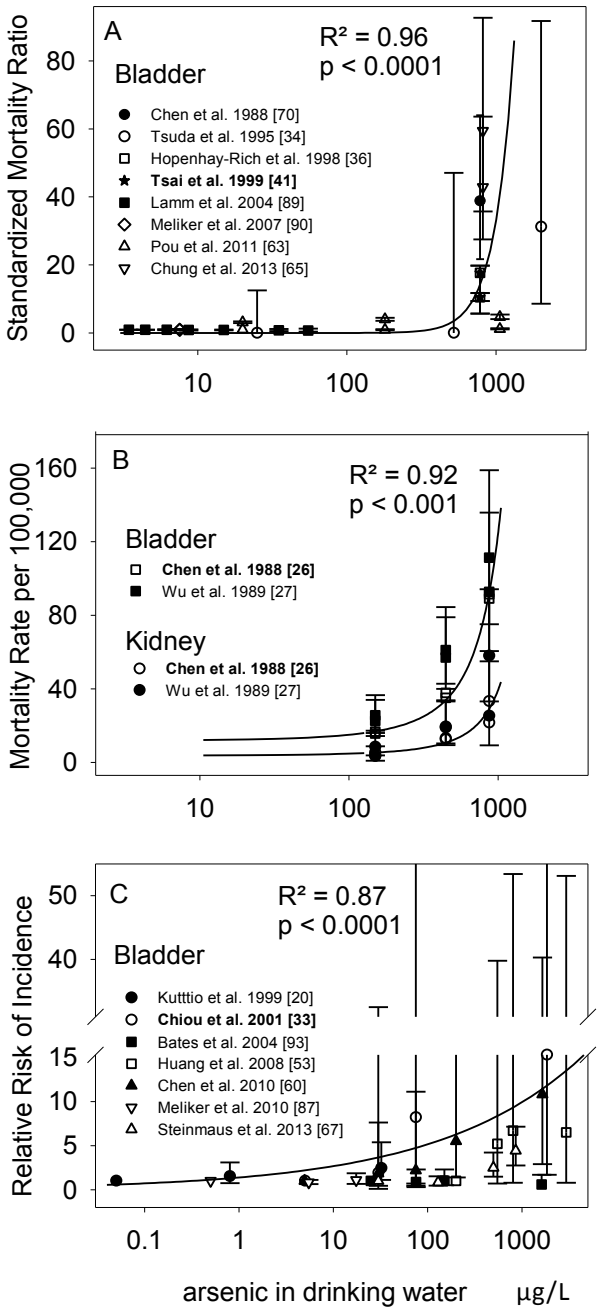

Figure 2.3 Published risk estimates for varying levels of arsenic in drinking water in relation to bladder and kidney cancer mortality (A-B) and bladder cancer incidence (C). Solid lines show the predicted risk from the model fitted values obtained from meta-analyses; referent study for analyses is in bold; R^2 is the coefficient of determination based upon best fit to distributional assumption. RRs were all adjusted for tobacco smoking. Citation for original publication is in square brackets.

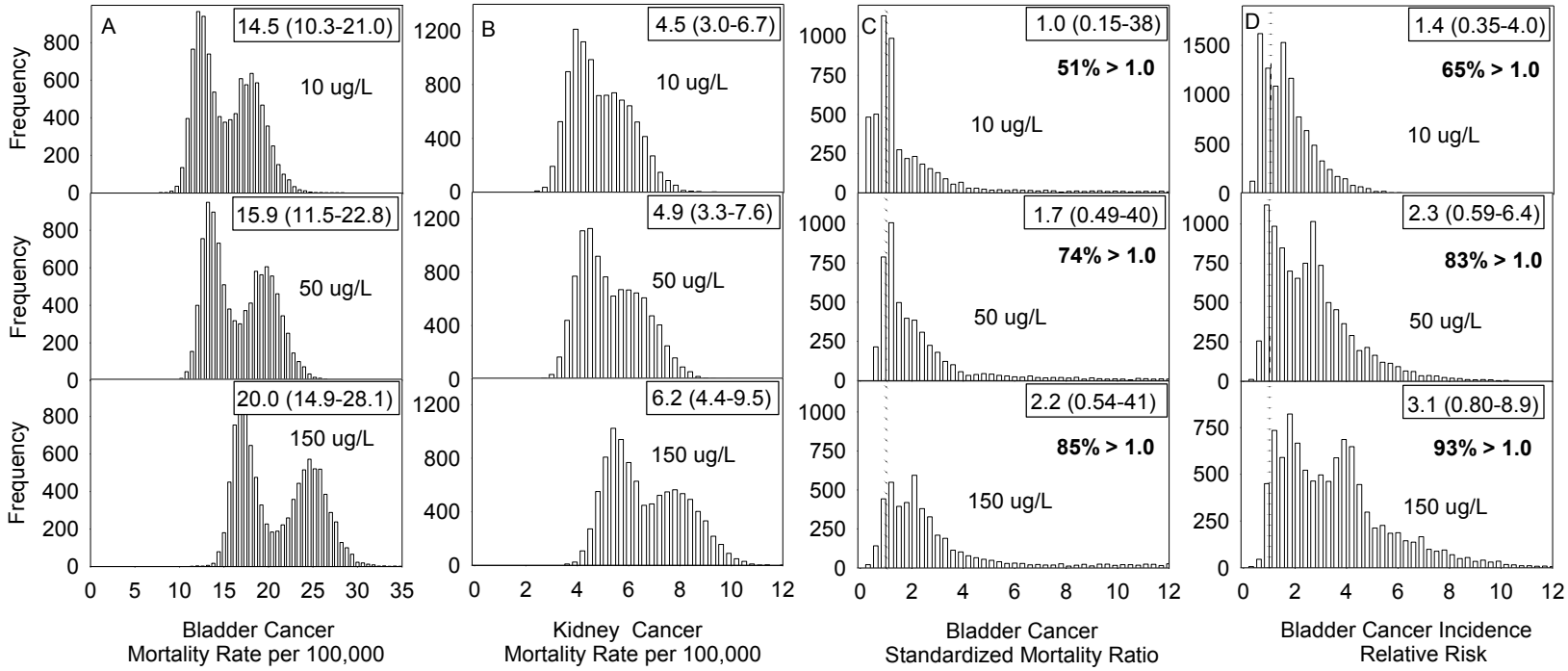

Figure 2.4 Published risk estimates for varying levels of arsenic in drinking water in relation to bladder and kidney cancer mortality (A-B) and bladder cancer incidence (C). Solid lines show the predicted risk from the model fitted values obtained from meta-analyses; referent study for analyses is in bold; R2 is the coefficient of determination based upon best fit to distributional assumption. RRs were all adjusted for tobacco smoking. Citation for original publication is in square brackets.

2.4 Discussion

2.4.1 Summary of Findings

This review evaluated 40 studies reporting on the association between As in drinking water and urinary tract cancers. Evidence supporting an increased risk of developing, or dying from, bladder cancer as a result of exposure to As in drinking water was obtained from 28 studies from Taiwan, Chile, Argentina, Japan and Finland. Furthermore, evidence supporting an increased risk of developing, or dying from, kidney cancer due to As in drinking water was obtained from 10 studies from Taiwan and Chile. The risk associated with kidney cancer was consistently of lower magnitude than that reported for bladder cancer outcomes.

Twenty of the 40 studies reviewed were ecological by design, not accounting for potential confounders and with As exposure assigned using well water concentration from geographic or other grouped measurements, which could have resulted in the misclassification of exposure. However, the majority of these studies focused on highly exposed populations where the magnitude of the effects reported was so high that potential confounding or misclassification bias could not fully explain the associations.

Tabulated risk estimates from studies assessing exposure from As in well/tap drinking water, were generally measured within a limited range of As concentrations and varied across, and within regions, even in areas where similar concentrations of As had been measured. Differences in exposure (e.g. As species, timing and duration of exposure)

[52] and population characteristics (e.g. genetic variations, lifestyle habits–smoking, diet etc.) have been suggested to contribute to differences in inter-individual susceptibility [52,102,103]. Thus, the methodological limitations of the studies reviewed, including study design, study quality (e.g. level of exposure assessment, lack of adjustment for potential confounders or effect modifiers such as age, sex, cigarette smoking, may have influenced the magnitude of the associations reported. For example, some case–control studies reporting on low exposure levels noted a significant association only among smokers [20,31] and of the cohort studies carried out in Taiwan, those adjusting for such covariates [33,53,60] reported risk estimates three to fourfold lower than ecological studies that did not [24,26].

2.4.2 Meta-Analysis of Arsenic in Drinking Water and The Risk of Developing Bladder or Kidney Cancers

The analyses of combined risk estimates presented in this review allowed for the examination of the association between cancer outcomes (i.e. mortality and incidence)– independently, and As exposure over a broader and more continuous range of As concentrations. After adjusting for differences in unaccounted bias associated with each study, the results showed that exposure to increasing levels of As in drinking water was significantly associated with an increased risk of bladder and kidney cancer mortality and bladder cancer incidence, regardless of the measure of association employed (i.e. mortality rate, SMR, RR; Model I). Risk estimates obtained from fitted values from Model I showed that people exposed to drinking water contaminated with 10 μg/L of As had more than a twofold increased risk of developing bladder cancer (2.7 [1.2 – 4.1]);

those exposed to 50 μg/L and 150 μg/L were expected of have a four- (4.2 [2.1 – 6.3]) and six fold (5.8 [2.9 – 8.7) increase in risk, respectively– relative to the meta-analyses referent group (the general population of Taiwan). Sub-analyses focusing on low-level exposure (≤ 150 μg/L) confirmed the trend, although the effect was slightly reduced at the 150 μg/L exposure level (10 μg/L, RR: 2.8 [1.3 – 4.3]; 50 μg/L, RR: 3.7 [1.7 – 5.7]; 150 μg/L, RR: 4.5 [1.8 – 7.2]). A near six fold increase in bladder cancer risk was also observed by Chen et al. [60] in northeastern Taiwanese residents exposed to levels of As in drinking water ranging between 100–299.9 μg/L (RR: 5.5 [1.4 – 22.0]). However, predicted risks for people exposed to 10 and 50 μg/L were about half of those obtained with Model I but comparable to those of Model II (Figure 4D; see also Chiou et al. [33] for a doubling of risk between 50-100 μg/L). Of note, a recent review reporting on low level As exposure in drinking water and bladder cancer did not support a significant association [56]. However, their findings were based on a meta-analytical approach that combined incidence and mortality outcomes, and studies using different metrics of exposure (e.g. As in toenails, well water, cumulated etc.), which possibly introduced statistical noise thereby attenuating the summary estimate (risk) towards the null. In this review, risk estimates derived from mortality were smaller than those of incidence data (Figure 2.4C-D). This possibly reflected patterns of prognosis [104], but perhaps more so, reduced statistical power due to misclassification as eight of the nine studies included in the meta-analyses of SMRs assessed exposure at the group-level, whereas all studies included in the analyses of the incidence data used individual-level measurements or estimations of As in drinking water.

The precise magnitude of excess cancer risk associated with drinking water containing As has been difficult to establish, especially in populations exposed to moderate to low As-levels. A major issue relates to the misclassification of As exposure arising from uncertainties in assessing exposures during the disease-relevant exposure period, which, for As, may extend many decades prior to diagnosis. These uncertainties relate to population mobility, characterization of drinking water sources, assignment of water As concentrations to subjects over time, assessment of fluid intake rates, assessment of dietary As intake, a likely major contributor to exposure in areas of low As-levels [103,105], and difficulties in measuring actual levels of As in drinking water as opposed to relying on estimated levels [56]. Such uncertainties lead to bias which typically results in an underestimation of the true risk— a risk that can be small but still biologically significant.

These uncertainties also act to increase the variability in the distribution of both the measured (e.g. Figure 2.3) and consequently, the predicted (e.g. Figure 2.4) risks, weakening the statistical significance of the risk estimate. Studies using biomarkers of exposure offer perhaps a way to reduce such uncertainties that create exposure misclassification. However, rather than limiting the dialogue around As-related health effects to a significance level, perhaps more informative is the high probability that a large proportion of people may be at elevated risk of dying from (Figure 2.4C, 51% probability) or being diagnosed with bladder cancer (Figure 2.4D, 65% probability), even at exposure levels as low as 10 μg/L. In this review, we estimate that with exposure to 50 μg/L of As in drinking water there is a 83% probability for an elevated risk of developing

bladder cancer and a 74% probability of elevated mortality. (Figures 2.4C, 2.4D). Yet, hundreds of millions of people worldwide rely upon drinking water containing As at these concentrations and consider them to be safe [3,69].

2.4.3 Limitations and Strengths

This review has some limitations. First, the search strategy was limited to computerized databases which could preferentially include studies with statistically significant findings [106,107]. While this is a concern, we are confident that publication bias was possibly minimal as a third of the studies included in this review presented non-significant results. Second, the analyses of combined risk estimates were limited to studies providing specific point estimates of As in drinking water, the most common metric of exposure reported. This selection reduced the number of studies eligible for meta-analyses but minimized heterogeneity associated with other exposure metrics such as cumulative As exposure or As concentrations in toenails or urine; two measures linked to population/individual-dependent factors (e.g. years of exposure, cumulated volume of contaminated water ingested, metabolic capacity etc.). Third, analyses were performed independently for studies reporting on different outcomes (i.e. cancer incidence vs. cancer mortality) and different measures of association (i.e. mortality rate, SMR, RR). This stratified approach reduced the statistical power required to analyze the combined data by sex and/or smoking status; the latter being an important effect modifier in the cancer-As relationship. Studies supporting a higher risk among ever smoker are growing in number and so predicted risks presented in this review may be conservative for populations with a high proportion of ever smokers.

Nonetheless, this review has important strengths. First, its broad scope allowed for the inclusion of 30 years of publications and a wide range of exposure from which combined analyses could be performed. Second, the use of a sensitive search strategy ensured a high level of search completeness. Third, while the independent analyses of incidence and mortality outcomes was presented as a limitation in terms of statistical power, it likely minimized possible ascertainment bias and exposure misclassification issues. This is because mortality data are generally less precise than incidence data and the survival rate for bladder cancer is relatively high. In addition, if survival for bladder cancer patients is related to As exposure, then mortality studies could be at greater risk of being confounded compared to incidence studies [104]. Furthermore, exposure in mortality studies is often derived from aggregate data which are more prone to misclassification and bias. Finally, this review updates and complements previously published work, but also provides data which quantifies the risk of developing bladder cancer at varying levels of As exposure, including that observed at lower levels exposure.

2.5 Conclusions

Epidemiological studies provide extensive evidence in support of a causal association between exposure to higher levels of As concentrations in drinking water and the risk of developing or dying from bladder cancer, although the thresholds at which health effects develop remain uncertain at lower levels of As exposure in drinking water. Evidence in support of an increased risk of dying from kidney cancer with exposure to As

is also accumulating, but studies reporting on incidence are lacking. The results of the meta-analysis were consistent with the generally observed findings from the full body of literature reporting on bladder and kidney cancer outcomes and As-exposure. They also confirmed patterns of dose-responses within exposed populations and quantified the evidence for potential health effects at the lower end of the exposure curve where most uncertainties remain. This meta-analysis suggests that populations exposed to 150 μg/L As in drinking water may be increasing their risk of dying from bladder or kidney cancer by 30% relative to those exposed to 10 μg/L. In addition, populations exposed to As concentrations as low as 10 μg/L in drinking water, (which corresponds to the WHO provisional guideline), may be doubling their risk of developing bladder cancer, or at the very least, increase it by approximately 40% compared to the unexposed populations included in the meta-analyses. Thus, with the large number of people likely exposed to As in drinking water at the lower range of concentrations throughout the world, we suggest that the public health consequences of As in drinking water may be substantial. Therefore, the current advisory limit for concentration of As in drinking water should be reviewed as well as policies on the promotion and support of household water arsenic remediation activities. Further studies focusing on populations exposed to low As concentrations with exposure measured at the individual level (e.g. biomarker studies), are required to confirm the observed health effect suggested in this review.

2.6 Abbreviations

WHO: World Health Organization; As: Arsenic; PubMed: Public/Publisher MEDLINE; BMI: Body mass index.

2.7 Competing Interests

The authors declare that they have no competing interests.

2.8 Acknowledgements

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CHAPTER 3— Premature Mortality Due to Social and Material Deprivation in Nova Scotia, Canada

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Authors' Contributions

NSJ contributed substantially to the conception and design of the project, participated in the acquisition of data and was responsible for data analysis/ interpretation and the design of the data programs as well as the drafting of the article; RD reviewed the article critically and provided programming support; YC extracted and tabulated the mortality data; LP and TJBD supervised the study; contributed substantially to the conception and design of the project; reviewed the article critically for important intellectual content and provided assistance in the interpretation. All authors read and approved the final manuscript for this journal article to appear in this thesis.

Please note that this journal article has been modified further for inclusion in this thesis.

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ABSTRACT

Introduction: Inequalities in health attributable to inequalities in society have long been recognized. Typically, those most privileged experience better health, regardless of universal access to health care. Associations between social and material deprivation and mortality from all causes of death— a measure of population health, have been described for some regions of Canada. This study further examines the link between deprivation and health, focusing on major causes of mortality for both rural and urban populations. In addition, it quantifies the burden of premature mortality attributable to social and material deprivation in a Canadian setting where health care is accessible to all.

Methods: The study included 35,266 premature deaths (1995–2005), grouped into five causes and aggregated over census dissemination areas. Two indices of deprivation (social and material) were derived from six socioeconomic census variables. Premature mortality was modeled as a function of these deprivation indices using Poisson regression.

Results: Premature mortality increased significantly with increasing levels of social and material deprivation. The impact of material deprivation on premature mortality was similar in urban and rural populations, whereas the impact of social deprivation was generally greater in rural populations. There were a doubling in premature mortality for those experiencing a combination of the most extreme levels of material and social deprivation.

Conclusions: Socioeconomic deprivation is an important determinant of health equity and affects every segment of the population. Deprivation accounted for 40% of premature deaths. The 4.3% of the study population living in extreme levels of socioeconomic deprivation experienced a twofold increased risk of dying prematurely. Nationally, this

inequitable risk could translate into a significant public health burden.

Keywords: Socioeconomic factors, Premature mortality, Small-area analysis, Deprivation index, Public health surveillance, Health equity

3.1 Introduction[1]

Inequities in health are entrenched in society, often reflecting disparities in the conditions in which people live, work, and play [1-3]. In 1980's, Townsend [4] articulated this concept as "deprivation": "an observable and demonstrable disadvantage relative to the local community or the wider society or nation to which the individual, family or group belong". Deprivation is, therefore, a measure made relative to some privileged group or social norm, a norm which can differ between places and change over time. Townsend distinguished two forms of deprivation: material deprivation which relates to the access of goods and conveniences and; social deprivation which refers to disadvantages related to social position. The influences of social and material deprivation on health are many and their magnitude and direction differ between health outcomes [5-10]. Mortality, a measure of population health, is often lower amongst privileged individuals or communities; a pattern observed across and within many countries, including those offering universal health coverage [11-18]. Recent trends for widening socioeconomic inequalities may further increase inequity in mortality rate—in particular, the rate of premature mortality [19-22]. From a societal view point, the cost of premature mortality (PM) can be measured directly through the increased burden of health care or, indirectly through the premature loss of individuals' contributions to society over their lifetime [23]. PM is thought to be avoidable and, therefore unacceptable [24]. In Canada, the impact of social and material deprivation on PM from all causes varies by geographic area, despite universal access to health care [14]. However, the relationship between social and material deprivation and major causes of premature death, as well as the overall

[1] Numerical format was used for referencing citations in this chapter as per the original publication.

magnitude of their effects, has yet to be reported, either at the national or provincial levels.

Compared to other provinces in Canada, Nova Scotia (NS) has high mortality rates and the second to lowest gross income per capita [25]. Further, NS has a high proportion of rural residents who in general have lower income and may experience a disproportionate burden of material and social deprivation. It is, therefore, an ideal location to examine the links between PM and socioeconomic deprivation. This study evaluates the relationship between social and material deprivation and PM in NS using a recently validated index [26]. It also quantifies the number and proportion of premature deaths directly attributable to socioeconomic deprivation, were the association considered to be causal. The results of this study will inform public health programs and policies aimed at addressing health inequities resulting from socioeconomic disparities.

3.2 Methods

3.2.1 Deprivation Indices

Area-based deprivation indices were developed in the UK [4,27,28] as a tool for investigating socio-economic variations in health and as a surrogate indicator of individual-level socioeconomic status. They have since been modified to reflect the local reality and data availability of various populations around the world [29-37]. For this study, two indices of deprivation were constructed following the methodology detailed by Pampalon and colleagues [38] developed to measure socioeconomic

deprivation within a Canadian context. The indices were composed of six variables from the 2001 Canadian census known to have utility as geographic proxies of socioeconomic conditions [21,33,39,40]. For people age 15 years and over, these variables were: the proportion of people with no high school diploma, the individual average income, the employment rate, the proportion of separated, divorced or widowed, the proportion of single-parent families (lone parent), and the proportion of persons living alone. The first three indicators reflect the material dimension of deprivation; the others reflect its social aspect. All variables, with the exception of the proportion of single-parent families, were adjusted to the age and sex structure of the 2001 NS population aged 15 years and older, using indirect standardization [41]. Transformations (log– for continuous variables, arcsin of square root– for proportional indicators) were applied to normalize the indicators. Variables were combined using Principal Component Analysis (PCA), a standard factorial approach that recognizes the interlinked nature of variables by accounting for their correlation and co-variation [42]. Following a varimax rotation, two independent components with eigenvalues exceeding 1.0 were retained for interpretation. These components were defined as ‘material index’ and ‘social index’ of deprivation, respectively.

The indices were constructed at the smallest unit of census geography, the dissemination area (DA), which comprises generally a population of 400–700 persons but which can be as low as 40 persons in rural NS and as high as 3,600 in urban NS. DAs were defined as urban when in proximity to a census metropolitan area with a population density of 400 or more people per square kilometer as outlined in Du Plessis et al. [43].

In the 2001 census, NS was covered by 515 urban and 771 rural DAs (excluding First Nations reserves, for which details of population and census variables were incomplete). PCA produced factor scores for all 1,286 DAs. The DAs were ranked according to their factor scores and grouped into weighted population quintiles, one distinct set of quintiles for each level of geography (i.e. urban, rural, NS as a whole). This was done to account for differences in the range of factor scores by level of geography. In all instances, quintile 1 (Q1) represented the most privileged segment of the population and quintile 5 (Q5), the least. This process was carried out separately for each of the deprivation indices.

3.2.2 Premature Mortality (PM)

Mortality data coded ICD-9 (1995 – 1999) or ICD-10 (2000–2005) for NS residents who died between 1995– 2005 were obtained from NS Vital Statistics. Deaths were grouped into five categories: cancer (ICD9—140- 208; ICD10—C00-C97), circulatory system (ICD9—390- 459; ICD10—I00-I99), external causes (ICD9—800-999; ICD10—V01-Y98), other causes and all causes. PM was defined as deaths occurring prior to the median age at death (75 for men, 81 for women) observed in this period. Age 75 is often used as a fixed upper threshold age for the calculation of PM, however, an older cut-off was used for females as to reflect their longer life expectancy. Residential postal code at death was used to assign each death to a DA using the Statistics Canada Postal Code Conversion program (PCCF+, version 5G). There were 87,484 deaths over the 11-year period. Of these, 74,610 deaths had postal code information and 73,088 (98%) were successfully geo-referenced to a DA. Two percent of deaths occurred before age 15 and

these were excluded. PM rates were based on a total of 35,266 premature deaths and calculated using the 2001 NS population aged 15 years plus, obtained from Statistics Canada. An aggregated dataset of premature death counts was used to estimate PM rates for each quintile of material and social deprivation, from the most (Q1) to the least privileged (Q5), and for groups experiencing extreme socioeconomic conditions, including those materially and socially most privileged (Q1material-Q1social; Q1 & Q1) which accounted for 7.0% of the NS population aged 15 years and older, and those materially and socially least privileged (Q5material-Q5social; Q5 & Q5) which accounted 4.3%.

3.2.3 Analytical Method

The influence of deprivation on PM was modeled with Poisson regression. In Model 1, quintiles of material and social deprivation were used as categorical variables and so accounted for the main effects of the two indices. In Model 2, for every combination of material and social deprivation quintiles, mean material and social deprivation scores were calculated and modeled with their interaction with population location (urban/rural). PM rate ratios and absolute excess mortality were also examined. Rate ratios (rate for the least privileged (Q5material-Q5social) divided by the rate for the most privileged (Q1material-Q1social), and corresponding 95% confidence intervals were derived from a Poisson regression model. The excess mortality measure estimated the absolute number of premature deaths for any subgroup that could be potentially avoided if the whole population had the same PM rate as that of the most privileged group. Data analyses were performed using SAS 9.1 and R 2.13.0. The study received ethics approval

from Capital Health and IWK Health Centre Research Ethics Boards (Appendix A).

3.3 Results

3.3.1 Socioeconomic Deprivation

The PCA identified two main components, together accounting for 67% of the variation associated with the six indicators. The first component reflected material deprivation, with high loadings for education (0.89), income (−0.84) and employment (−0.62); the second component reflected social aspects, with high loadings of the proportion of separated, divorced or widowed (0.89), the proportion of persons living alone (0.78) and of single parent families (0.64). The population profile by quintile of material and social deprivation is presented in Table 3.1. Of particular interest is the comparison between the least and most privileged groups (Q5material-Q5social vs. Q1material-Q1social, respectively) which shows that the former had 4.1 times higher proportion of people without a high school diploma (e.g. 47.6% vs. 11.5%); 1.7 times lower employment rates; 3.1 times higher number of people living alone; 2.4 times higher number of people identified as separated, divorced or widowed; and 6.1 times higher number of single-parent families. In addition, the least materially and socially privileged people earned less than half the income of the most privileged ($16.7 K vs. $40.5 K). These differences between the least and most materially and socially privileged groups were observed in both rural and urban NS, but were generally greater in urban populations (Table 3.1). The exception was for employment rate for which the gap between the most and least privileged group was greater in rural NS (Table 3.1).

Table 3.1 Characteristics of study population age 15 years and older, by quintile of material and social deprivation and those of the most and least materially and socially privileged population groups, Nova Scotia[a]

Deprivation quintile		No high school diploma %	Employment rate %	Individual average income $	Living alone %	Separated divorced widowed %	Lone parent %
Material							
privileged	Q1	15.5	63.0	34,224	14.1	19.7	12.4
	Q2	24.1	59.2	26,536	10.9	17.6	15.3
	Q3	31.9	54.8	23,785	9.8	17.7	16.3
	Q4	38.5	50.4	21,264	10.0	18.7	17.7
deprived	Q5	50.4	42.8	18,791	9.0	18.5	22.8
Social							
privileged	Q1	27.0	58.4	30,096	5.0	11.5	7.5
	Q2	34.1	54.7	25,113	7.1	14.8	12.4
	Q3	36.9	52.3	23,334	8.6	17.4	15.9
	Q4	32.2	51.5	24,406	12.2	20.2	20.0
deprived	Q5	31.2	52.8	22,274	19.9	27.5	27.7
ALL of Nova Scotia:							
Material and social							
Most privileged[b]	Q1 & Q 1	11.5	66.5	40,498	4.0	9.9	6.8
Most deprived[c]	Q5 & Q5	47.6	39.5	16,650	12.4	23.7	41.5
RURAL Nova Scotia:							
Material and social							
Most privileged	Q1 & Q 1	17.3	65.8	33,345	4.2	10.5	6.3
Most deprived	Q5 & Q5	47.3	39.6	17,410	9.8	20.8	34.2
URBAN Nova Scotia:							
Material and social							
Most privileged	Q1 & Q 1	7.8	66.1	47,091	4.9	9.9	7.8
Most deprived	Q5 & Q5	44.7	45.7	17,009	17.2	27.8	44.6

[a] Source: 2001 Census of Canada.
[b] Include those people who are most materially and socially privileged , Q1 & Q1.
[c] Include those people who are most materially and socially deprived , Q5 & Q5.

3.3.2 Socioeconomic Deprivation and Premature Mortality

Of the 35,266 premature deaths included in the study, 14,054 (40%) were attributed to cancer, 9,793 (28%) to disease of the circulatory system, 2,646 (8%) to external causes and 8,773 (25%) to other causes (Table 3.2). The total number of premature deaths was greater in rural than urban NS (20,506 vs 14,752) but crude PM rates did not differ significantly between urban and rural areas, with the exception of other causes mortality for which the rate was higher in urban populations (Table 3.2). Both crude (Table 3.2) and adjusted PM rates (Model 1, Figure 3.1) increased monotonically with increasing levels of material and social deprivation. For social deprivation, these rates showed higher mortality in Q4 for cancer and all causes mortality.

Crude rate ratios (RRs) in PM for those in the most and least privileged population groups are presented in Table 3.3. For all causes, the PM rate for NS was 2.5 times higher in people experiencing a combination of the most extreme conditions of material and social deprivation relative to the most privileged (Table 3.3). PM due to cancer, diseases of the circulatory system, external causes and other causes was 1.9, 2.9, 4.1 and 3.1 times higher in the least compared to the most privileged groups, respectively (Table 3.3). Non-significant differences in RR were observed between urban and rural populations, with RR in urban being slightly higher. Figure 3.2 shows the relationship between the mean material and social deprivation scores and PM, adjusting for interacting material, social and urban/rural effects (Model 2). Table 3.4 shows the predicted percentage change in PM corresponding to a change of one quintile level. Again, a significant increase in PM

for both major and all causes of death was observed with increasing material and social deprivation (Figure 3.2; Table 3.4). Material deprivation had a similar influence upon PM rates in urban and rural populations (Figure 3.2; Table 3.4). The exception was PM due to external causes for which an increase in material deprivation scores equivalent to one quintile was associated with a 17% increase in PM among those living in rural areas (Table 3.4) compared to a 7.7% increase in PM rate for those living in urban areas. The influence of social deprivation upon PM rates was also significant for major and all causes mortality and was generally of larger magnitude for rural populations (Figure 3.2; Table 3.4). An increase in social deprivation of one quintile was associated with an increase of 14%, 21%, 25% and 19% in PM, due respectively to cancer, circulatory system, other causes, and all causes of death, among rural populations. In contrast, an increase in social deprivation equivalent to one quintile was associated with significant, but lower comparative increases of 7.8%, 11%, 15% and 8.8% in PM among those living in urban areas. The exception to this pattern was external causes, for which an increase in social deprivation of one quintile resulted in a comparable increase in PM rate (20%; Table 3.4) in both rural and urban populations. However, irrespective of social deprivation, rural populations had a 16% higher risk of dying prematurely due to external causes than urban populations.

Considering the distribution of mean material and social deprivation scores for urban and rural populations, there is a greater distribution gap between the most and least privileged in urban NS.

Table 3.2 Population counts, premature death counts, crude premature death rates[a], and associated 95% confidence interval by geographic areas[b], quintiles of social and material deprivation, and major causes of mortality, Nova Scotia 1995-2005

		Cancer				Circulatory system				External causes				Other causes				All causes			
				95% CI				95% CI				95% CI				95% CI				95% CI	
Geographic area	Population[c] Count	Count	Rate	from	to	Count	Rate	from	to	Count	Rate	from	to	Count	Rate	from	to	Count	Rate	from	to
NS	742,580	14,054	172.1	169.2	174.9	9,793	119.9	117.5	122.3	2,646	32.4	31.2	33.7	8,773	107.4	105.2	109.7	35,266	431.7	427.2	436.3
Urban	309,660	5,880	172.6	168.2	177.1	3,991	117.2	113.6	120.9	1,060	31.1	29.3	33.1	3,821	112.2	108.6	115.8	14,752	433.1	426.1	440.1
Rural	432,920	8,174	171.6	167.9	175.4	5,797	121.7	118.6	124.9	1,585	33.3	31.7	35	4,950	103.9	101.1	106.9	20,506	430.6	424.7	436.5
Material																					
Q1	148,290	2,403	147.3	141.5	153.3	1,504	92.2	87.6	97.0	398	24.4	22.1	26.9	1,522	93.3	88.7	98.1	5,827	357.2	348.1	366.5
Q2	148,365	2,577	157.9	151.9	164.1	1,712	104.9	100.0	110.0	427	26.2	23.7	28.8	1,575	96.5	91.8	101.4	6,291	385.5	376.0	395.1
Q3	148,535	2,838	173.7	167.4	180.2	1,879	115.0	109.9	120.3	551	33.7	31.0	36.7	1,713	104.8	99.9	109.9	6,981	427.3	417.3	437.4
Q4	148,685	2,959	180.9	174.5	187.6	2,184	133.5	128.0	139.3	577	35.3	32.5	38.3	1,893	115.7	110.6	121.1	7,613	465.5	455.1	476.1
Q5	148,705	3,277	200.3	193.5	207.3	2,514	153.7	147.7	159.8	693	42.4	39.3	45.6	2,070	126.5	121.2	132.1	8,554	522.9	511.9	534.1
Social																					
Q1	147,870	2,221	136.5	130.9	142.3	1,343	82.6	78.2	87.1	351	21.6	19.4	24.0	1,154	70.9	66.9	75.2	5,069	311.6	303.1	320.3
Q2	148,755	2,684	164.0	157.9	170.4	1,727	105.5	100.6	110.6	509	31.1	28.5	33.9	1,489	91.0	86.4	95.7	6,409	391.7	382.1	401.4
Q3	148,250	2,893	177.4	171.0	184.0	2,017	123.7	118.3	129.2	486	29.8	27.2	32.6	1,643	100.8	95.9	105.7	7,039	431.6	421.6	441.8
Q4	148,805	3,283	200.6	193.8	207.5	2,344	143.2	137.5	149.1	601	36.7	33.8	39.8	2,153	131.5	126.0	137.2	8,381	512.0	501.1	523.1
Q5	148,900	2,973	181.5	175.0	188.2	2,362	144.2	138.5	150.1	699	42.7	39.6	46.0	2,334	142.5	136.8	148.4	8,368	510.9	500.0	522.0
Material and Social																					
Q1 & Q1	51,985	678	118.6	109.8	127.8	358	62.6	56.3	69.4	79	13.8	10.9	17.2	307	53.7	47.8	60	1,422	248.7	235.9	261.9
Q5 & Q5	31,830	777	221.9	206.6	238.1	645	184.2	170.3	199	198	56.6	48.9	65	574	163.9	150.8	177.9	3,194	626.6	600.7	653.4

[a] Rates per 100,000 people.
[b] A total of 8 deaths could not be assigned to a specific urban or rural area.
[c] 2001 Canadian census population, 15 years and older.

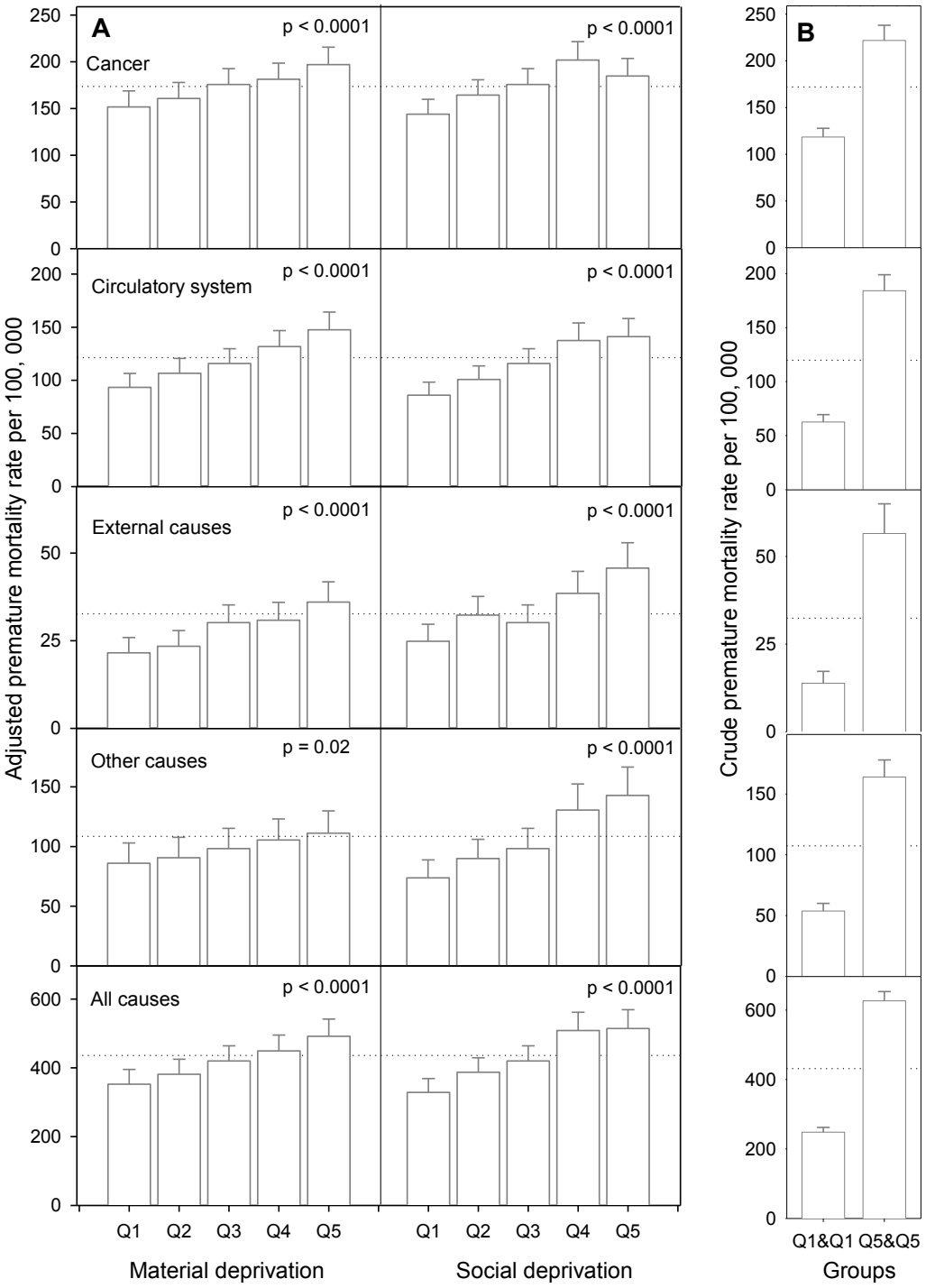

Figure 3.1 Adjusted (panel A) and crude (panel B) premature mortality rate for population age 15 years and older, by quintile of material and social deprivation and causes of death, Nova Scotia 1995–2005. Dotted line represents the adjusted (panel A) and crude (panel B) premature mortality death rates for Nova Scotia. P-values are from one-tailed test.

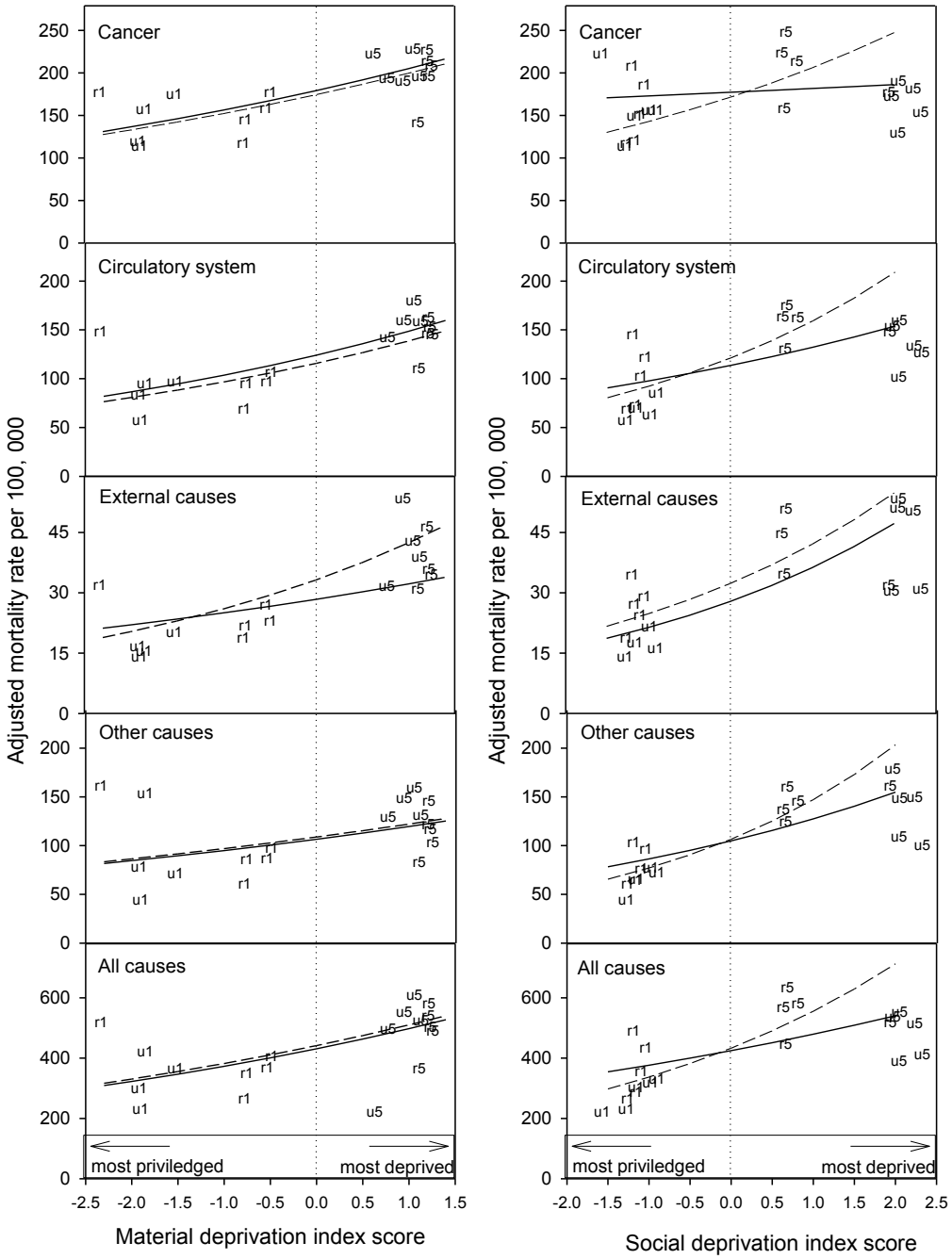

Figure 3.2 The relationship between material (left panel) and social (right panel) deprivation index scores and premature mortality rate adjusted for geographic area (urban, rural) and the other form of deprivation, Nova Scotia 1995–2005. The solid and dashed lines indicate Model 2 predictions for urban and rural populations aged 15 years and older, respectively. For illustrative purposes the mean material and social deprivation scores for the most (urban: u1; rural: r1) and least privileged (urban: u5; rural: r5) groups are shown. The dotted line represents the average population scores.

Table 3.3 Rate ratio in premature mortality for the most and least materially and socially deprived population groups (Q5 & Q5 vs Q1 & Q1), Nova Scotia 1995-2005

	Nova Scotia			Urban			Rural		
		95% CI[a]			95% CI		RR	95% CI	
	RR	from	to	RR	from	to		from	to
Cancer	1.9	1.7	2.1	1.7	1.4	2.0	1.8	1.6	2.1
Circulatory system	2.9	2.6	3.3	2.8	2.2	3.4	2.3	2.0	2.7
External causes	4.1	3.2	5.3	3.8	2.5	5.6	3.2	2.4	4.3
Other causes	3.1	2.7	3.5	3.3	2.6	4.2	2.4	2.0	2.9
All causes	2.5	2.4	2.7	2.4	2.1	2.7	2.2	2.0	2.4

[a] 95% confidence interval.

Table 3.4 Percent change in premature mortality (PM) associated with social and material deprivation by cause of death[a], Nova Scotia 1995-2005

Cause of death	Effect	% change in PM per quintile[b] URBAN	% change in PM per quintile RURAL	Chi-square	Pr >ChiSq[c]
Cancer	urban[d]			0.8	0.37
	material	9.9	9.9	48.2	< 0.001
	urban:material			.	> 0.05
	social	7.8	14	37.3	< 0.001
	urban:social			16.6	< 0.001
Circulatory system	urban			1.64	0.2
	material	14	14	52.7	< 0.001
	urban:material			.	> 0.05
	Social	11	21	51.8	< 0.001
	urban:social			6.03	0.01
External causes	urban			6.5	0.01
	material	7.7	17	30.9	< 0.001
	urban:material			3.9	0.05
	Social	20	20	81.8	< 0.001
	urban:social			.	> 0.05
Other causes	urban			0.07	0.8
	material	8.4	8.4	16.5	< 0.001
	urban:material			.	> 0.05
	Social	15	25	52.2	< 0.001
	urban:social			4.97	0.03
All causes	urban			0.21	0.65
	material	11	11	52.3	< 0.001
	urban:material			.	> 0.05
	social	8.8	19	65.2	< 0.001
	urban:social			10.3	0

[a] Based on Poisson regression Model 2 of material and social deprivation and potential interaction with urban and rural residence.

[b] Assuming that on a continuous scale, a 0.7 change in PCA score equates approximately to a change from one quintile level to the next.

[c] One-tailed test.

[d] Where 'urban' is defined as rural =0; urban =1 in Poisson regression model.

With regards to material wealth, those most privileged in urban areas (i.e. u1 [Q1 urban]; Figure 3.2) were comparatively better off than their rural counterpart (r1 [Q1 rural]; Figure 3.2). With regards to social wealth, those least privileged in urban areas (i.e. u5 [Q5 urban; Figure 3.2) were comparatively worse off than their rural counterparts (r5 [Q5 rural]; Figure 3.2). These differences observed between comparable quintiles in urban and rural populations, were not associated with a significant health advantage in those most materially privileged; nor with a significant health disadvantage in those most socially deprived.

3.3.3 Population Attributable Risk

Mortality attributable to variability in death rates across quintiles of material and social deprivation for urban and rural NS is presented in Table 5. Material deprivation alone may have accounted for 7,245 premature deaths over an 11 year-period in NS (3,825 in urban; 3,420 in rural). The independent effect of social deprivation was even more pronounced, accounting for 9,993 premature deaths (5,032 in urban; 4,961 in rural). Over an 11 year period, 14,693 premature deaths (6,878 in urban; 7,815 in rural) could have been avoided if material and social disparity did not exist (i.e. if all population quintiles had the same mortality rate as Q1, the most privileged). Overall, the combined effect of material and social deprivation accounted for nearly half of all premature deaths recorded in urban populations; and over a third of those recorded in rural populations (Tables 3.2 and 3.5). These proportions varied by cause of death, ranging from 31% (cancer), 43% (circulatory system), 44% (external causes) and 42% (other causes) in rural areas; and from 34% (cancer), 51% (circulatory disease), 54% (external causes) and 60% (other

causes) in urban areas (Tables 3.2 and 3.5). For NS as a whole, the combined effect of material and social deprivation accounted for 42% of all premature deaths.

Table 3.5 Excess premature deaths[a] due to the independent and combined effect of material and social deprivation, by cause of death, urban and rural Nova Scotia 1995-2005

URBAN NOVA SCOTIA					
Quintile	**Cancer**	**Circulatory system**	**External causes**	**Other causes**	**All causes**
Independent effect of material deprivation					
Q1	REF[c]	REF	REF	REF	REF
Q2	284	208	34	272	798
Q3	218	158	23	114	513
Q4	335	282	88	226	932
Q5	484	549	130	420	1,583
Total:	**1,321**	**1,196**	**276**	**1,031**	**3,825**
Independent effect of social deprivation					
Q1	REF	REF	REF	REF	REF
Q2	217	231	66	232	745
Q3	390	508	93	486	1477
Q4	315	478	144	502	1440
Q5	187	462	192	529	1,371
Total:	**1,110**	**1,679**	**494**	**1,749**	**5,032**
Material and Social deprivation combined[b]					
Total:	**1,987**	**2,024**	**576**	**2,294**	**6,878**

RURAL NOVA SCOTIA					
Quintile	Cancer	Circulatory system	External causes	Other causes	All causes
Independent effect of material deprivation					
Q1	REF	REF	REF	REF	REF
Q2	28	56	73	−33	124
Q3	224	232	92	116	663
Q4	474	453	128	265	1,321
Q5	464	443	180	225	1,311
Total:	**1,190**	**1,185**	**472**	**573**	**3,420**
Independent effect of social deprivation					
Q1	REF	REF	REF	REF	REF
Q2	87	143	47	209	486
Q3	396	364	131	275	1,166
Q4	363	386	51	311	1,110
Q5	634	650	203	712	2,199
Total:	**1,480**	**1,543**	**431**	**1,507**	**4,961**
Material and Social deprivation combined[b]					
Total:	**2,569**	**2,493**	**692**	**2,062**	**7,815**

[a]Number of deaths that would be avoided if all Nova Scotians had the same premature mortality rate as those that are most privileged.

[b]These counts exclude deaths solely due to material or social deprivation.

[C] REF = Reference group.

3.4 Discussion

3.4.1 Summary of Findings

The study revealed substantial inequalities in socioeconomic conditions in NS, Canada. Similar disparities, although of varying magnitude, have been observed for other regions of the country [14]. For example, in British Columbia the ratios of the least to the most privileged persons were 2.5, 1.4, and 5.3 for the proportion of people without high school diploma, lower employment rate and number of single-parent families; compared to 4.1, 1.7, and 6.1 for Nova Scotia, respectively [14]. While these data indicate greater discrepancies between the 'rich and the poor' in NS, the gap in average income between the least and most privileged groups was greater in the larger metropolitan areas of both Toronto ($32.8K) and Vancouver ($28.9K) compared to Nova Scotia as a whole ($23.8K).

Inequalities in mortality were not confined to differences between the 'rich' and the 'poor' or between the most and least socially or materially deprived, but rather, were observed over the entire socioeconomic spectrum, thus affecting every segment of the population. PM rates decreased monotonically from the most to the least disadvantaged quintile for both major and all causes mortality, with the exception of cancer and all causes mortality for which social deprivation resulted in higher PM rates in Q4. Socioeconomic inequalities were associated with more than a doubling in PM rates (i.e. 2.5 time higher) for the approximate 32,000 Nova Scotians (i.e. 4.3% of the population) experiencing a combination of the most extreme levels of material and social deprivation. Inequalities of similar magnitude have also been reported for Canada as a whole [14])

and Scotland [17]. However, in Scotland, the ratio in PM rate between the most and least privileged, increased from 2.2 in 1981 to 4.3 in 2001 for all causes premature deaths. This widening gap was attributed to a sharp decline in PM in those most privileged at a time of increased PM in those most deprived.

The impact of material deprivation on PM was similar for urban and rural populations, whereas the impact of social deprivation on PM rates was significantly higher for those living in rural areas. The exception was PM due to external causes, which was higher in the most materially deprived rural populations and for which the impact of social deprivation on PM rate were similar in urban and rural populations. The mechanisms contributing to these overall differences are not well understood. With regards to external causes, some studies have reported increased mortality due to external causes with increasing material and social deprivation [44]; others have reported higher mortality due to external causes in rural populations [45,46]; but few have examined the impact of the interaction between urban and rural status, socioeconomic indices and external causes of PM.

This study showed that about 40% (14,696 deaths) of premature deaths over an 11 year-period were attributable to socioeconomic inequalities and thus, potentially avoidable. Of these, more than half were associated with social deprivation alone, a factor seldom accounted for in estimates of health risk in Canada. Due to varying study methodologies and limited research reporting on social disparities in premature mortality, it is difficult to compare these results to other studies. Nonetheless, a recent study indicates that up to

30% of excess deaths (all deaths) reported in sixteen European cities could be attributable to socioeconomic disparities [18]. This figure is somewhat lower than that reported here, but may reflect a greater impact of socioeconomic inequalities on premature mortality in comparison to its impact on all deaths. Thus, the magnitude of the burden of PM due to social and material inequalities has far-reaching implications worldwide. Inequalities are undesirable; they affect everyone in terms of loss of potentially productive members of society, and represent added costs for the health care system and public sector [13,47].

3.4.2 Strengths and Limitations

This study was based on 11 years of provincial vital statistics data of which 98% was successfully geo-referenced, enabling deaths to be linked to census-derived deprivation scores. Other strengths include the use of validated composite measures of deprivation [26], which provide a more complete representation of the variability in deprivation relevant to health than do single indicator variables such as income [42,48,49]. In addition, the weight assigned to each variable included in the construction of the material and social indices of deprivation is determined based on the correlation structure that exists among the variables at the geographic level of interest, rather than being etermined *a priori* [38].

A limitation of this study is the lower population densities of rural areas which can result in unstable modeled results [50-52]. Also, DAs can cover larger areas in rural NS, possibly resulting in more heterogeneous population profiles. In addition, as demonstrated earlier, the distribution in material and social wealth varied between urban

and rural populations. Each of these factors could have reduced the estimated inequalities in PM rates due to the social and material deprivation in rural populations. A second limitation is that area-based indices can be prone to ecological fallacy when inferences are generalized to the individual level [53]. They are also affected by the modifiable areas unit problem (MAUP), which affects the inference of the results from one scale of observation to another [53]. Third, this study did not account for spatial dependency between DAs. Spatially correlated random effect terms are often used to account for this dependency; however, data provided for the study was aggregated by quintile of social and material deprivation and urban/rural regions and so did not permit such an analysis. Failure to account for spatial dependency may have artificially narrowed the confidence intervals for the β coefficients and resulted in an underestimation of the type I error rate. Finally, when calculating a population attributable fraction one assumes a causal relationship between the risk factors and health outcome of interest and independence of the considered risk factors from other factors that influence risk [54]. However, it is unlikely that factors contributing to social and material deprivations are completely independent of other factors linked to PM, thus resulting in a possible overestimation in the overall attributable fraction.

3.4.3 Local and Global Perspective

Overall findings of a pervasive impact of socioeconomic deprivation on PM rates in NS are consistent with findings reported in other regions of Canada as well as in the United Kingdom, United States, Australia and elsewhere [1,15,20,37,38,47,55,56]. Poor health outcome was not confined to the most disadvantaged. Socioeconomic inequity affected

everyone; a pattern highlighted by the World Health Organization (WHO) not only for the most disadvantaged countries, but for countries of all income levels [24]. The estimated twofold difference in PM rate between the least and most privileged population segments of NS is comparable to the 2.3 fold difference in PM rates seen between lower and higher income countries [57]. Canada acknowledges that raising the health status of people with the greatest need would have a major impact on overall health and could also improve the nation's productivity, as suggested by the WHO Commission's report on health equity. Using a recently validated index of deprivation, our study demonstrates the feasibility of identifying and quantifying, at a small area-level, social and material factors that contribute to PM and health inequity. It is likely that the overall impact of social and material inequalities on health will continue to increase as the difference in wealth between the rich and the poor continues to grow [58]. Provincial and Federal governments in Canada and elsewhere have a responsibility to acknowledge and address these serious and growing issues that impact health equity. Part of the effective delivery and evaluation of such policy changes must be the compilation of small area-level measures of health inequity and their determinants.

3.5 Conclusions

In NS, approximately 32,000 people aged 15 years and older live in areas with extreme levels of deprivation, resulting in a doubling of their likelihood of dying prematurely. In this study, deprivation accounted for approximately 40% of premature deaths between 1995 and 2005, despite universal health care in Canada. The significant increases in PM with decreasing levels of social and material wealth observed in NS may reflect a small

picture of what is happening at the national level and could translate into a serious public health burden. Also, while PM rates in those most privileged have been reported to be declining in recent years, those in the lower socioeconomic groups have either experienced slower proportional mortality decline or exhibited continued increase in PM. Part of this widening in health inequity may be due to a combination of individual characteristics and the environmental demands and constraints that affects the likelihood of adopting health promoting behaviours. However, it could be argued that this growing inequity in health is rooted in greater societal inequities. Addressing the key factors that contribute to deprivation (e.g. employment, education, living arrangement), may suggest a form of intervention that would enable the individual to act on decisions that improve their health, which in turns would not only improve the health outcomes of Nova Scotians, but simultaneously reduce the health costs and burdens associated with an unnecessary and premature loss of life. Future studies should be designed to explore sex and age-specific patterns of socioeconomic deprivation on health. Analyses of age at death would allow the quantification of the number of potential years of life lost due to material and social deprivation. Based on a median age at death of 75 years, a person dying at 15 years of age results in the loss of 60 potential years of life, while that of a person aged 74 years results in the loss of only 1 potential years of life. Such quantification would allow the assessment of the absolute impact of socioeconomic disparity on health and provide a more focused profile of the global burden of health inequity.

3.6 Competing Interests

The authors declare that they have no competing interests.

3.7 Acknowledgments

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CHAPTER 4— Small-Area Spatio-Temporal Analyses of Bladder and Kidney Cancer Risk in Nova Scotia, Canada

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Authors' Contributions

NSJ extracted the cases files; georeferenced cases; conducted all analyses relating to BYM application, constructed tables and figures, drafted and revised the manuscript; JL modified existing Local-EM methods to incorporate temporality, carried-on all work relating to local-EM based analysis; PB devised the study, drafted section describing Local-EM methods, reviewed the article critically for important statistical content, provided assistance in the interpretation of the results, supervised NSJ and JL for statistical work; JS assisted JL in developing the local-EM methodology, supervised JL, reviewed the article critically for important statistical content; LP devised the study, reviewed the article critically for important intellectual content and provided assistance in the interpretation. TJBD devised the study, supervised the overall work, reviewed the article critically for important intellectual content and provided assistance in the interpretation. All authors read and approved the final manuscript for this journal article to appear in this thesis.

Please note that this journal article has been modified further for inclusion in this thesis..

ABSTRACT

Background: Bladder and kidney cancers are the ninth and twelfth most common type of cancer worldwide, respectively. Internationally, rates vary ten-fold, with several countries showing rising incidence. This study describes the spatial and spatio-temporal variations in the incidence risk of these diseases for Nova Scotia, a province located in Atlantic Canada, where rates for bladder and kidney cancer exceed those of the national average by about 25 % and 35 %, respectively.

Methods: Cancer incidence in the 311 Communities of Nova-Scotia was analyzed with a spatial autoregressive model for the case counts of bladder and kidney cancers (3,232 and 2,143 total cases, respectively), accounting for each Community's population and including variables known to influence risk. A spatially-continuous analysis, using a geostatistical Local Expectation-Maximization smoothing algorithm, modeled finer-scale spatial variation in risk for south-western Nova Scotia (1,810 bladder and 957 kidney cases) and Cape Breton (1,101 bladder, 703 kidney).

Results: Evidence of spatial variations in the risk of bladder and kidney cancer was demonstrated using both aggregated Community-level mapping and continuous-grid based localized mapping; and these were generally stable over time. The Community-level analysis suggested that much of this heterogeneity was not accounted for by known explanatory variables. There appears to be a north-east to south-west increasing gradient with a number of south-western Communities having risk of bladder or kidney cancer more than 10 % above the provincial average. Kidney cancer risk was also elevated in various northeastern communities. Over a 12 year period this exceedance translated in an excess of 200 cases. Patterns of variations in risk obtained from the spatially continuous

smoothing analysis generally mirrored those from the Community-level autoregressive model, although these more localized risk estimates resulted in a larger spatial extent for which risk is likely to be elevated.

Conclusions: Modelling the spatio-temporal distribution of disease risk enabled the quantification of risk relative to expected background levels and the identification of high risk areas. It also permitted the determination of the relative stability of the observed patterns over time and in this study, pointed to excess risk potentially driven by exposure to risk factors that act in a sustained manner over time.

Keywords: Small-area disease mapping, BYM model, Local-EM algorithm, Bladder and kidney cancer risk, Geostatistical analysis, Spatial autoregressive analyses

4.1 Introduction[1]

Urinary tract cancers comprise primarily cancers of the urinary bladder and kidney, the former accounting for approximately two-thirds of all cases diagnosed. Bladder cancer is the ninth most common type of cancer worldwide (~360,000 cases per year) and the 13th most common cause of death from cancer (~145,000 deaths per year worldwide) [1, 2]. Kidney cancer is comparatively less common, ranking twelfth and accounting for an approximate 150,000 new cases and 78,000 deaths annually [3, 4].

Internationally, the incidence rates for bladder and kidney cancer have been reported to vary by as much as ten-fold between countries. Incidence tends to be higher in Southwestern Europe, North Africa (Egypt) and North America; and lower in South America and Asia [1, 4, 5]. Parkin [2] reports the highest estimated mortality rates to be in Egypt, where the world-standardized rate of 34 per 100,000 (in men) is more than three times higher than the highest rates in Europe (Denmark 10.4, Spain 9.7) and eight times that in the United States (US) (3.4).

Several countries show increasing incidence for both bladder and kidney cancers, although with evidence of some stabilization or even decreases during the 1990s [2, 4]. Recent trends in stage-specific incidence rates for bladder cancer in some US populations, suggest however, that rates may be stabilizing in late stage disease but continue to increase in noninvasive predominantly low grade disease [6]. Regardless of space, time or stage at diagnosis, rates are consistently higher for males than females [4, 5, 7–9]. In

[1] Numerical format was used for referencing citations in this chapter as per the original publication.

fact, in most developed countries, men are at least, a three to five time greater risk than women.

Past variations in the prevalence of known etiological factors, whether genetic, environmental, occupational or behavioural, may to some extent, contribute to the reported temporal and geographical variations of urinary tract cancers among populations worldwide. In addition, differences in the scope of case ascertainment between national cancer registries may result in some countries reporting solely invasive diagnoses while others may include non-invasive or in situ diseases. Some countries count only one primary cancer in subjects with multiple cancers in the urinary tract. In the Netherlands, such practice is thought to reduce the reported incidence of bladder cancer by up to 10 % [2]. Finally, variations in rates within and/or between countries can be partly driven by the introduction of new imaging techniques enabling the detection of pre-symptomatic tumours.

In Canada, bladder cancer incidence rates increased from 1970 to 1981 and have since gradually declined or stabilized [10–12]. Kidney cancer incidence rates have also stabilised in recent years among females, but continue to increase at a rate of about 1.3 % among males [10, 11, 13, 14]. Rates of both bladder and kidney cancer are particularly high in Nova Scotia (NS), a province of 940,000 people, in Atlantic Canada. NS consistently has some of the highest rates of cancer in Canada for both males and females and continues to show increases in the age-standardized incidence rates of both bladder and kidney cancers. For bladder cancer, age adjusted incidence rates estimated for 2015

exceed those of the national average by about 25 and 30 % among males and females, respectively [11]. Similarly, for kidney cancer, excesses of 30 and 45 % have been reported among males and females, respectively. This noted excess burden of urinary tract malignancies in NS is unlikely to result from health system related factors (e.g. scope of case registration, imaging technology) given the relative uniformity of health care delivery within the country.

This study thus, describes spatial and spatio-temporal variations in the risk of bladder and kidney cancer for NS in order to identify those areas where rates are higher than what would be expected given the prevalence of known risk factors. This is an important step to guide both etiological research and public health interventions in the province. We use two geospatial methods for modelling disease risk, both of which are appropriate for low-density populations such as NS. The first approach is a Community-level analysis using a spatial autogregression (or Besag, York and Mollie model), a Bayesian method that models diseases risk for spatially aggregated case counts [15, 16]. The second approach estimates spatially continuous variation in risk using a Local Expectation Maximization (local-EM) smoothing algorithm, an emerging geostatistical method developed by Fan, Stafford and Brown [17], which models spatial and temporal variation in risk when cases are aggregated to time-varying spatial boundaries. To our knowledge, this is the first attempt to model the risk of bladder and kidney cancer in NS and one of the first epidemiological applications of the Local-EM algorithm for cancer mapping in Canada.

4.2 Methods

4.2.1 Data Sources

Cancer incidence data were obtained from the NS Cancer Registry and were divided into two cohorts: Cohort 1 included all NS residents diagnosed with bladder or kidney cancer between 1998 and 2010 and aged 20 years and older; Cohort 2 included cases diagnosed between 1980 and 2010 and aged 20 years and older. Cases were coded according to the International Classification of Diseases (ICD-O) as following: bladder (ICDO: 188.0-188.9; ICD-O-2/3: C67.0-C67.9); kidney (ICDO: 189.0; ICD-O-2/3: C64.9). Because of a change in disease-coding over time, bladder cases included both, in situ (36 %, period 1998–2010; 21 %, period 1980–2010; Table 4.1) and invasive diagnoses; kidney cases included invasive diagnoses only.

The Community-level (BYM) analysis was restricted to Cohort 1. This is because the proportion of cases with incomplete residential addresses (i.e. civic street address) was fairly large prior to 1998. During those early years, most cases were assigned to a town or a six-digit postal code, which vary greatly in size, especially between urban and rural settings. Depending on the spatial scale of analysis, one postal code may belong to several geographic units or one unit of geography may contain several postal codes, resulting in the potential misclassification of the spatially aggregated data. The spatially continuous-grid based (local-EM) analysis was able to accommodate data from the entire 30 year period (Cohort 2) because the method allows for both changes in the spatial distribution of risk over time, and accounts for uncertainties in location of cases where civic street addresses are missing but postal codes or administrative regions are known.

Table 4.1 Cases characteristics for the two periods under study, Nova Scotia, Canada

Period 1998 - 2010	Bladder			Kidney		
Nova Scotia	Total	Females	Males	Total	Females	Males
Cases diagnosed	3,292	834	2,458	2,199	863	1,336
Cases analyzed*	3,232	820	2,412	2,143	848	1,295
In situ	1,164	298	866	0	0	0
Invasive	2,068	522	1,546	2,143	848	1,295
Mean age at diagnosis (years)	71	71.2	70.5	65	66	63.7
Spatial referencing (%)						
civic address	86.6	85.5	86.9	85.9	86.4	85.5
postal code	2.29	2.07	2.36	2.10	1.65	2.39
town name	11.1	12.4	10.7	12.0	11.9	12.1
Period 1980 - 2010	**Bladder**			**Kidney**		
Nova Scotia	Total	Females	Males	Total	Females	Males
Cases diagnosed†	6,473	1,642	4,831	3,762	1,493	2,269
Mean age at diagnosis (years)	70	70.5	69.9	65	65.9	63.8
South-western Nova Scotia						
Cases analyzed	1,810	423	1,387	957	358	599
In situ	386	86	300	0	0	0
Invasive	1,424	337	1,087	957	358	599
Spatial referencing (%)						
civic address	43.6	40.4	44.6	47.2	50.6	45.2
postal code	52.9	56.3	51.9	49.8	46.1	52.1
census division	3.4	3.3	3.5	2.9	3.3	2.7
Cape Breton Island						
Cases analyzed	1101	283	818	763	306	457
In situ	172	41	131	0	0	0
Invasive	929	242	687	763	306	457
Spatial referencing (%)						
civic address	43.7	45.9	42.9	53.7	54.2	53.4
postal code	47.0	41.3	48.9	39.2	36.6	40.9
census division	9.4	12.7	8.2	7.1	9.2	5.7

* Excludes 116 cases (2.1%) diagnosed in a Community for which population data was not available.
† Excludes 21 bladder cases (0.32%) and 10 kidney cases (0.27%) due to unavailable spatial information.

The Nova Scotia Civic Address File (NSCAF) was used to assign spatial locations (i.e. longitude-latitude coordinates) to all cases for which a civic street address was available. When civic address was unavailable, the Desktop Mapping Technologies Inc (DMTI) conversion file was used to geo-reference postal codes. For the Community-level model, where postal code was unavailable or located in rural areas, a gazetteer of place names was used to georeference the centroid of the town. For the spatially-continuous local-EM, where postal code was available, cases locations were treated as spatially censored somewhere within one of the census regions containing at least one address with the postal code in question. Where postal code was unavailable, the local-EM analysis used the Census Division boundaries as a second type of spatial censoring. Proportions of case by spatial data type, including the numbers of cases excluded from each analysis due to uncertainty in their spatial location, are shown in Table 4.1.

Population data from seven census years (1981, 1986, 1991, 1996, 2001, 2006, and 2011) were used for this study. Each census provided counts of people aged 20 years and older by age and sex group, and were used as the denominator for cases diagnosed within two years of a given census period.

For the modelling of risk using the spatial autoregressive model, population estimates were aggregated at the Community level, a set of geographic administrative units, which represent groupings of neighbourhoods with a degree of shared identity and social processes [18]. This level of spatial aggregation represents the finest unit of geography for which boundaries are stable over time. There were 311 Communities in NS over the

study period with population counts up to 30,900 persons. In total, 36 Communities (30 First Nations Communities and 6 wilderness and park Communities) were excluded due to unavailable population information.

The spatially-continuous (local EM) analysis used population counts by age and sex group at the finest level of geography for which digitized spatial boundary data were available. These were census subdivision level (CSD) for the 1981 and 1986 census years; enumeration areas (EA) for the 1991 and 1996 census years; and dissemination areas (DA) for census 2001 onward. There were 113 CSD in 1981 and 118 CSD in 1986. The number of EA/DA ranged from 1379 to 1645 between the 1991 and 2011 census periods; their size varied to target a population of 400 to 700 individuals.

It was assumed that populations were uniformly distributed within these finest levels of census regions, a not unreasonable assumption if one accepts that these census regions generally follow physical boundaries, such as major streets and waterways, and are designed to be fairly homogeneous. An exception is regions which are indicated by Statistics Canada to be partially uninhabited, or lying outside the population ecumene, in which case the population is assumed to be homogeneously distributed within the inhabited portion.

Covariates included in the Community-level spatial autoregressive model were indicators of socioeconomic deprivation and well water usage. The latter obtained

from NS Environment, aimed to account for spatial variations in risk which may relate to exposure to environmental sources of heavy metals such as arsenic in drinking water, a known risk factor for the development of bladder and kidney cancer [19]. Socioeconomic deprivation indicators were derived from socio-economic data obtained from Statistics Canada. They were constructed as Community-level area-based composite indices of social and material deprivation intended to be used as a proxy for unavailable individual-level measures such as smoking, a key factor in the development of urinary tract malignancies. Material and social deprivations indices were also used to capture the contextual setting of a place of residence, which has been shown to independently predict smoking habit in both men and women and other health outcomes [20-24]. Each index summarized information relating to six socioeconomic indicators from the 2006 Canadian Census; all of which having known links to health outcomes and known application as geographic proxies of socioeconomic conditions [21, 25-28]. For people age 15 years and over, these variables were: the proportion of people with no high school diploma, the individual average income, the employment rate, the proportion of separated, divorced or widowed, the proportion of single-parent families, and the proportion of persons living alone. The first three indicators reflect the material dimension of deprivation; the others reflect its social aspect. Variables were combined using a Principal Component Analysis (PCA), a standard factorial approach that recognizes the interlinked nature of variables by accounting for their correlation and co-variation [29]. Methodological details appear in Saint-Jacques et al. [30]. Covariates were not included in the spatially-continuous analysis as the local-EM method does not currently accommodate covariates.

4.2.2 Data Analyses

Community-Level Analysis

The Besag York and Mollié (BYM) model (see [15, 16]), a popular and convenient spatial autoregressive model for count data referenced to discrete spatial regions, was used to perform Community-level analysis. The approach treats the case counts by Community as response variables, rather than Standardized Incidence Ratios (SIR), because the latter is unstable when computed from low counts. This is particularly important in this study due to the low population density of NS and the rarity of the health outcomes measured. Possible spatial dependence in the data, with pairs of nearby Communities tending to be more similar than Communities situated far apart, is accounted for with the inclusion of a spatially autocorrelated random effect term. The BYM models the case counts as Poisson distributed and supports Baysesian inference for model fitting, which in this study, was performed separately for each data set (bladder male, bladder female; kidney male, kidney female) using Integrated Nested Laplace Approximations [31]. Further details pertaining to this analytical approach are described in Additional file 1.

Spatially-Continuous Analysis

The local-EM kernel smoothing was used to perform the spatially-continuous analysis. The method developed by Fan, Stafford and Brown [17] was extended by Lee et al. (Lee J, Nguyen P, Brown P, Stafford J, Saint-Jacques N: Local-EM Algorithm for Spatio-Temporal Analysis with application in Southwestern Nova Scotia. Submitted in *Ann Appl*

Stat; [32]) to accommodate the requirements of modelling the cancer incidence data presented here. Collected between 1980 and 2010, the data were subject to aggregation boundaries changing over time and were geocoded with varying degrees of precision. Exact spatial locations were derived from full residential civic street addresses for most of the recent cancer cases, though the proportion of cases spatially referenced with partial street address (i.e. postal codes) or with census regions, increased with the age of the data. Where exact location is unavailable, the local-EM kernel smoothing algorithm produces an optimal risk surface which averages out all the possible locations at which each case could be located. The bandwidth of the smoothing kernel is chosen by cross-validation (see Additional files 2 and 3) and determines the degree of smoothing in the risk surfaces. A detailed description of the methodology is contained in Lee et al. (Lee J, Nguyen P, Brown P, Stafford J, Saint-Jacques N: Local-EM Algorithm for Spatio-Temporal Analysis with application in Southwestern Nova Scotia. Submitted in *Ann Appl Stat*) and in Nguyen et al. [32], and summarized in Additional file 1.

In this study, local-EM analyses focused on two regions of the province which the BYM models suggested risk was particularly high, as to describe localized patterns in risk. Two models were applied: (1) a spatial model testing for significant variation in risk over space, and where a spatial effect was detected; (2) a spatiotemporal model was applied to determine whether risk also varied significantly over time. Maps were produced where statistically significant spatial or spatio-temporal effects were detected. Estimated risk surfaces based on local-EM are not presented to minimize risk of disclosure of personal health information. Rather, a p-value for testing for relative risk being lower than 1.1

(risk less than 10 % above the population average) at each location and time is presented. These p-values were computed with a parametric bootstrap, with 100 synthetic datasets simulated with a constant relative risk of $\lambda(s,t) = 1.1$ and for each s and t the p-value is the proportion of these datasets where the local-EM algorithm yields risk estimates exceeding the estimate produced by the data. Shown are exceedance probabilities, or one minus the p-values, which are large when risk is believed to exceed 1.1.

The software used was R version 3.1.1 (http:// www.r-project.org) in combination with the disease mapping package [33] and the INLA software [34]. This study received ethics approval from Capital Health Research Ethics Board (Appendix A). The study was a secondary analysis of anonymised cancer registry data obtained from the NS Provincial Cancer Registry and a waiver of consent was approved.

4.3 Results

4.3.1 Cohort Characteristics Summary

A total of 6,473 bladder cancers and 3,762 kidney cancers were diagnosed in NS between 1980 and 2010 (Table 4.1), 95 % of which included spatial information on residence at time of diagnosis and were successfully geo-referenced. In total, 3,232 bladder and 2,143 kidney cancers were included in the analyses focusing on the 1998–2010 time period, and; 2,911 bladder and 1,720 kidney cancers were included in the analyses covering the 1980–2010 time period, which focused specifically on cases diagnosed in south-western (SW) NS (2,767 cases) and Cape Breton (CB; 1,864 cases) — two regions where risk

was mapped at a finer spatial resolution. Georeferencing based on exact residential location at diagnosis was more common for cases diagnosed in the most recent time period, between 1998 and 2010 (bladder 86.6 %; kidney 85.9 %) than for cases diagnosed between 1980 and 2010 (SW: bladder 43.6 %; kidney 47.2 %; CB: bladder 43.7 %; kidney 53.7 %). On average, kidney malignancies were diagnosed at a slightly younger age than bladder cancers (65 vs 70 years). Overall, the male to female ratio was about 2.9 and 1.5 for bladder and kidney cancer diagnoses, respectively.

4.3.2 Spatial Patterns of Bladder Cancer

Community-Level Analysis

Estimates and credible intervals for regression and variance parameters obtained from the BYM models are shown in Table 4.2. These coefficients represent the log relative risk in bladder cancer incidence over the entire province and study period. None of the covariates – well water usage or material and social deprivation – significantly affected the estimated risk for bladder cancer among males and females (Table 4.2). Thus, much of the observed spatial heterogeneity in risk relates to unmeasured risk factors which appeared to have a similar effect on the distribution of disease in both males and females. Both the spatially correlated and the independent random errors have standard deviations in the range of 0.1 to 0.4, reasonably large values considering that they apply to risk on the log scale (Table 4.2).

Table 4.2 Posterior summaries for regression and variance parameters – Bladder cancer, Nova Scotia 1998-2010

BLADDER CANCER	MALES			FEMALES		
Parameter	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**
Intercept	-0.105	-0.297	0.086	0.007	-0.301	0.309
% using well water	0.001	-0.002	0.003	-0.001	-0.005	0.003
Material deprivation	-0.297	-0.109	0.048	0.055	-0.067	0.178
Social Deprivation	0.046	-0.023	0.116	-0.018	-0.130	0.094
Spatial standard deviation	0.228	0.157	0.352	0.199	0.086	0.439
Unstructured standard deviation	0.124	0.072	0.193	0.240	0.126	0.421

Figure 4.1 maps the residual spatial variation in bladder cancer risk, more specifically the posterior means E[exp(U_i)|data] of the exponentiated random effects, among males (Fig. 4.1A) and females (Fig. 4.1B). These values are equivalently the ratio between the predicted risk λ_i for each community and the risk exp($\mu + X_i\beta$) which is typical given the region's covariates X_i. Regions of elevated risk are common in the south-western section of the province where several communities exhibit risk well above what is typical (i.e. > 1.2). Looking at these Community-level variations for the province, one identifies a clear southwest to northeast gradient among females, additional pockets of high risk being observed in Cumberland County (north central region).

Uncertainties associated with these maps can be visualized with exceedance probabilities, which are the probabilities that the risk in a Community or location exceeds a given threshold, defined here as 10 % above the risk that would be typical given the region's deprivation and well water usage.

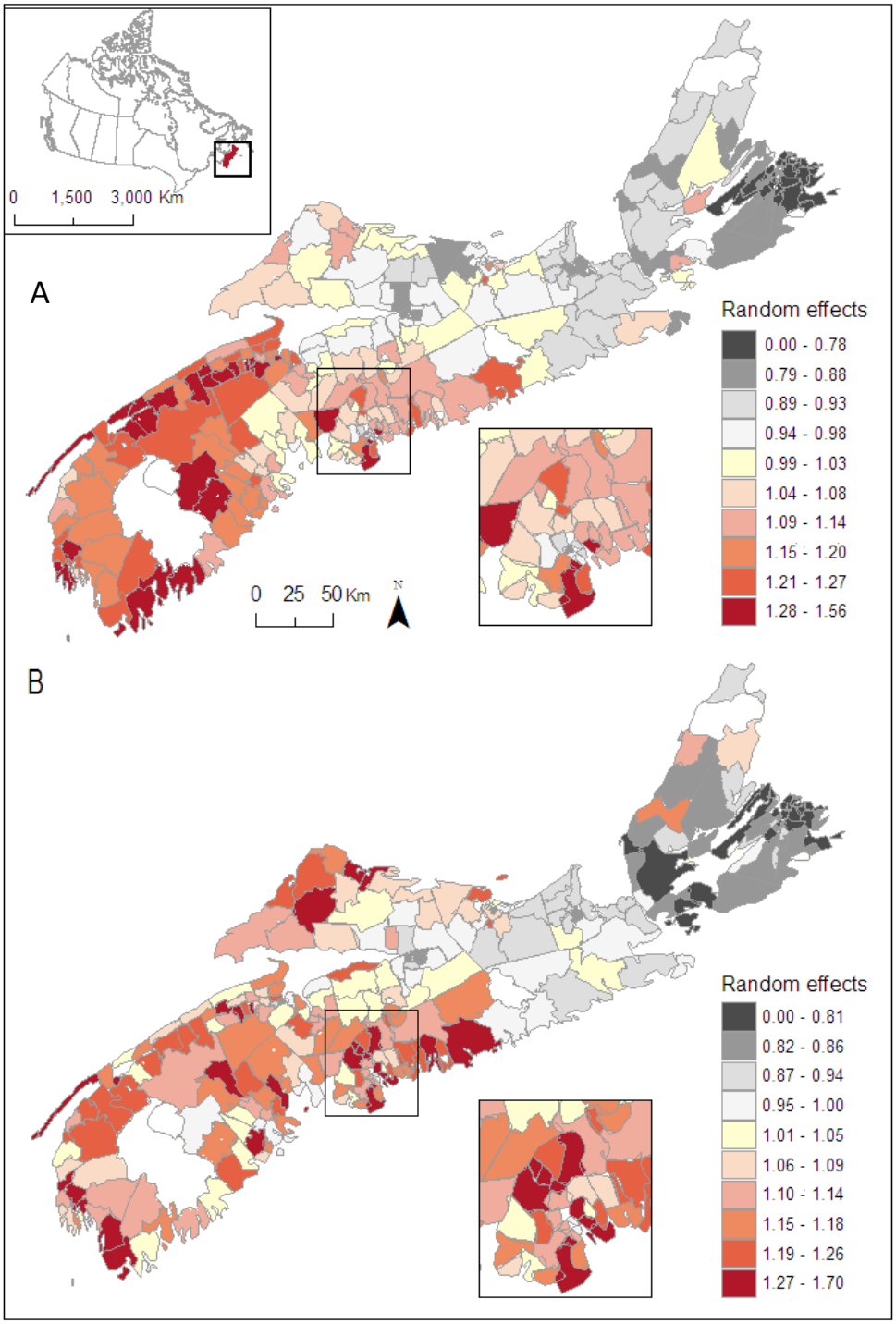

Figure 4.1 Posterior means relative risks for male (A) and female (B) bladder cancer, Nova Scotia 1998-2010

We denote these probabilities as $P_i(10\ \%) = Pr\{\lambda_i > [1.1\ \exp(\mu + X_i\beta)] \mid \text{data}\}$, or equivalently $Pr[\exp(U_i) > 1.1|\text{data}]$. Figure 4.2A shows exceedance probabilities for bladder cancer amongst males, with 28 communities in SW NS having a probability $P_i(10\ \%)$ in excess of 80 % and four communities having $P_i(10\ \%) > 95\ \%$, again supporting a southwest to northeast gradient. Estimated risk in these communities ranged between 1.24 –1.56, and between 1.39 – 1.56, respectively. The exceedance probabilities for females in SW NS are for the most part in the range of 0.2 – 0.8 (Fig. 2B), as the smaller number of cases for female cancers makes it more difficult to assess with any certainty whether a region has risk above or below a given threshold. In total of 9 Communities show exceedance probabilities for female risk above 80 % and 2 have probabilities above 95 %, the latter located in south central NS (Fig. 4.2B). Risk in those areas was higher than that estimated for males, with risk ranging between 1.38 – 1.69 and between 1.58 –1.69, respectively. Over the 12 year period, high risk areas ($Pr[\exp(U_i) > 1.1|\text{data}] > 80\ \%$) had 33 and 52 % more cases of male and female bladder cancer being diagnosed, respectively.

Spatially-Continuous Analysis

Table 3 shows optimal spatial and spatio-temporal bandwidths obtained from cross-validation scores (Additional files 2 and 3) and p-values of Scores-Test that assess the statistical significance for spatial and spatio-temporal effects in bladder cancer risk in SW NS and CB. Spatial and spatio-temporal bandwidths determine the extent of the smoothing kernel used in risk estimation, and in this study, they ranged between 3 km and 22 km in space and 5 to 13 years over time.

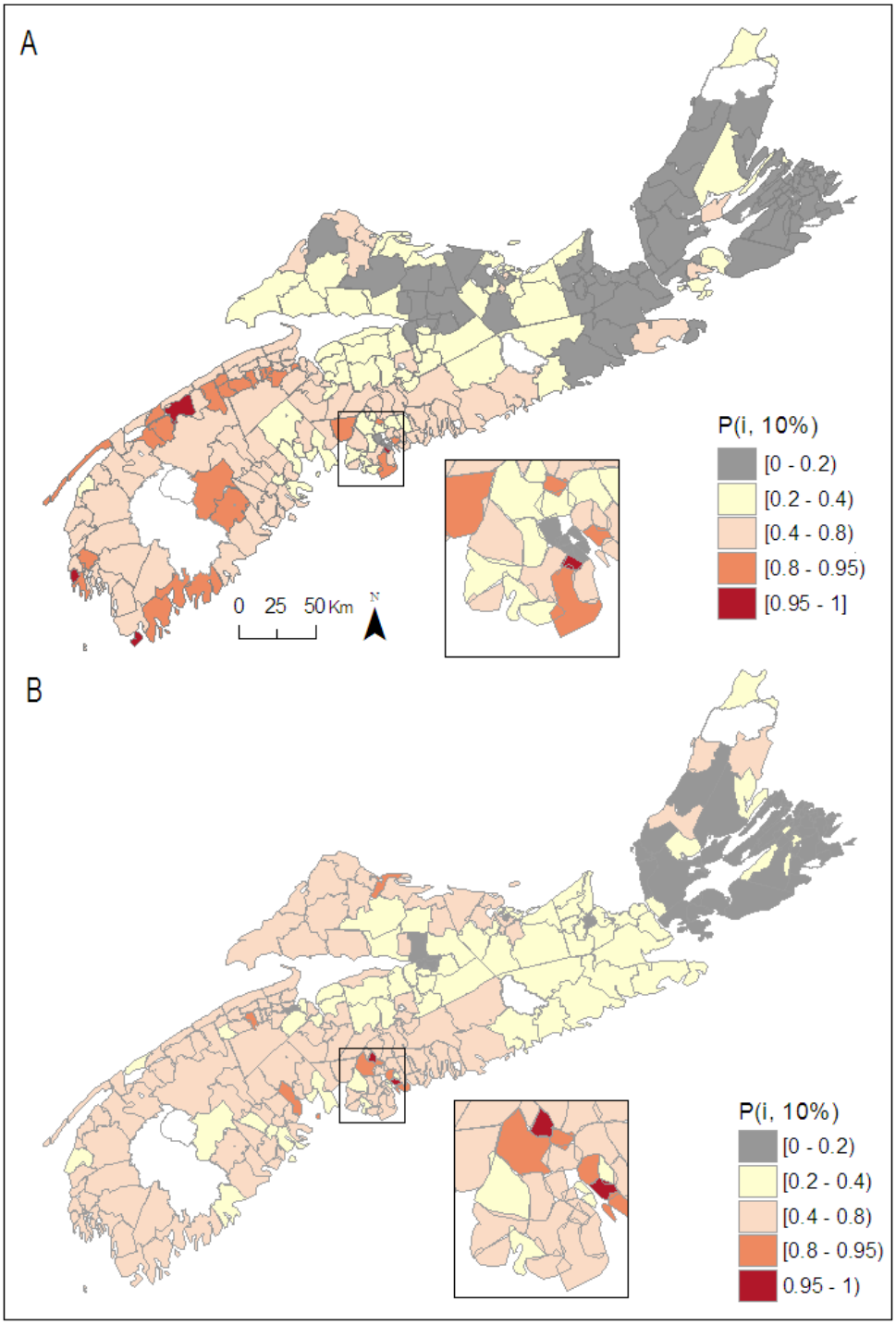

Figure 4.2 Exceedance probabilities (P_i(10%) for male (A) and female (B) bladder cancer, Nova Scotia 1998-2010

Table 4.3 Optimal spatial and temporal bandwidth from cross-validation scores, bladder and kidney cancer, Nova Scotia 1980-2010

		Spatial		Spatio-temporal		
Region	Sex	BW (Km)	P-value	BW (Km)	BW (years)	P-value
BLADDER						
SW	M	11	< 0.001	11	13	0.07
	F	3	0.41	-	-	-
CB	M	4	0.01	4	13	> 0.2
	F	22	0.79	-	-	-
KIDNEY						
SW	M	3	0.03	3	17	> 0.2
	F	7	0.05	7	13	> 0.2
CB	M	6	0.01	6	5	> 0.2
	F	10	0.38	-	-	-

Based on these bandwidths, we observed significant localized variations in the spatial distribution of bladder cancer risk for males from both SW NS and CB regions (Table 4.3). For SW NS, the results suggested that these spatial patterns also varied over time (Table 4.3; $p = 0.07$). Statistically significant spatial variations in bladder cancer risk were not observed in females from either SW NS or CB regions (Table 4.3). These results possibly reflect a combination of small case counts and location misclassification. For example, there were only 247 cases of female bladder diagnosed between 1980 and 2010 in Cape Breton, and 76 % of those were geocoded to a single location. During cross validation, half the cases would be excluded from model fitting and optimal spatial bandwidths would be determined based on too few events to produce stable and statistically significant results.

Exceedance probabilities obtained from fitting a spatially continuous risk surface with the local-EM algorithm are shown in Fig. 4.3 for male bladder cancer in SW NS and CB. These exceedance probabilities can be interpreted in a similar manner to the quantities from the BYM model shown in Fig. 4.2, with one difference being they refer to a threshold of 10 % above the average risk for NS without adjustment for deprivation and well water usage. Another difference is these probabilities vary over a continuous spatial surface as opposed to between Communities with set boundaries and, hence, provide insights on finer resolution patterns in risk. Thus, we write, $P(s;10\ \%)$ as one minus a p-value for testing $\lambda(s) < 1.1$ with probabilities being computed using parametric bootstrapping (see details in Nguyen et al. [32] and Lee et al. (Lee J, Nguyen P, Brown P, Stafford J, Saint-Jacques N: Local-EM Algorithm for Spatio- Temporal Analysis with application in Southwestern Nova Scotia. Submitted in *Ann Appl Stat*). As observed using Bayesian inference, results from these finer-scale analyses also show probabilities of above average risk in excess of 80 % along the Fundy shore and near Cape Sable Island and Shelburne, areas located on the south shore of NS (Fig. 4.3A). In Cape Breton, patterns of exceedance probabilities in excess of 80 % (Fig. 4.3B) pointed to areas of elevated risk where aggregated analysis based on BYM modeling had shown $P_i(10\ \%)$ to be less than 20 % (Fig. 4.2A).

Figure 4.4 shows the exceedance probabilities obtained from fitting a spatio-temporal risk surface to male bladder cancer for SW NS, a region where risk varied over time (Table 4.3).

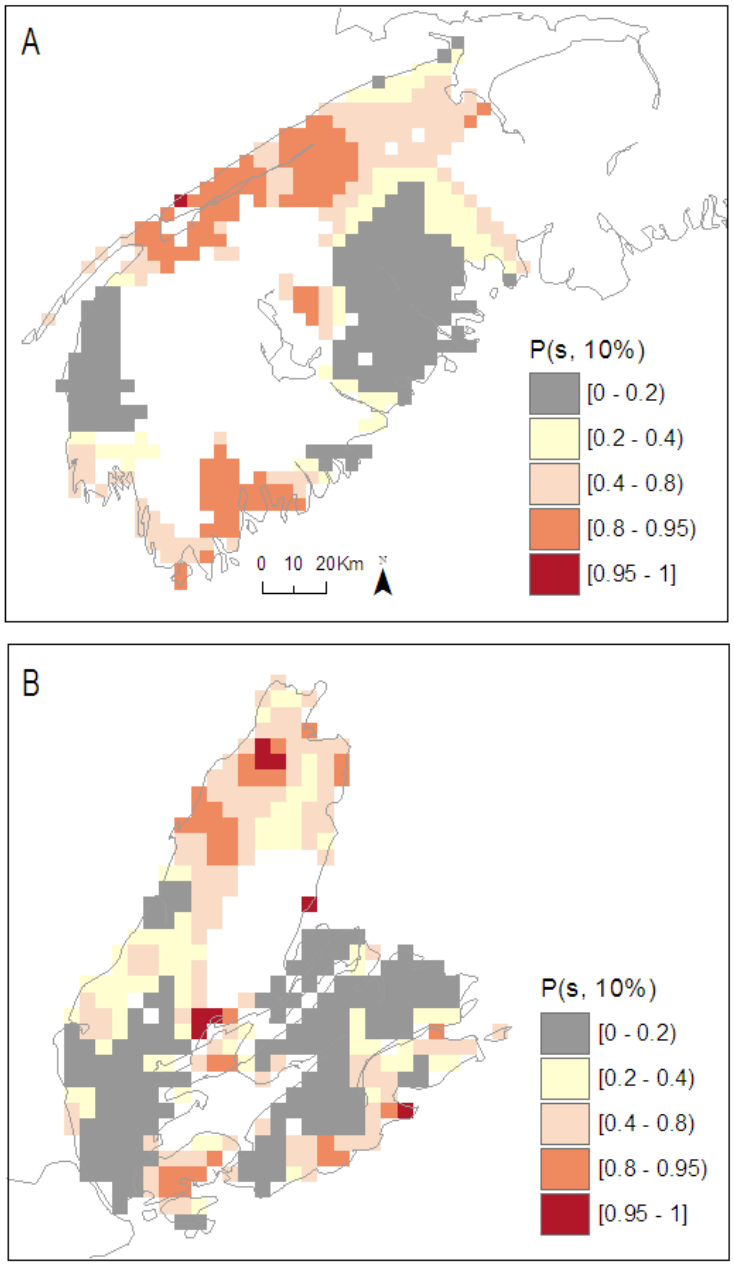

Figure 4.3 Bootstrapped exceedance probabilities (*P(s; 10%)*) for risk surface of male bladder cancer in south-western Nova Scotia (A) and Cape Breton (B) regions.

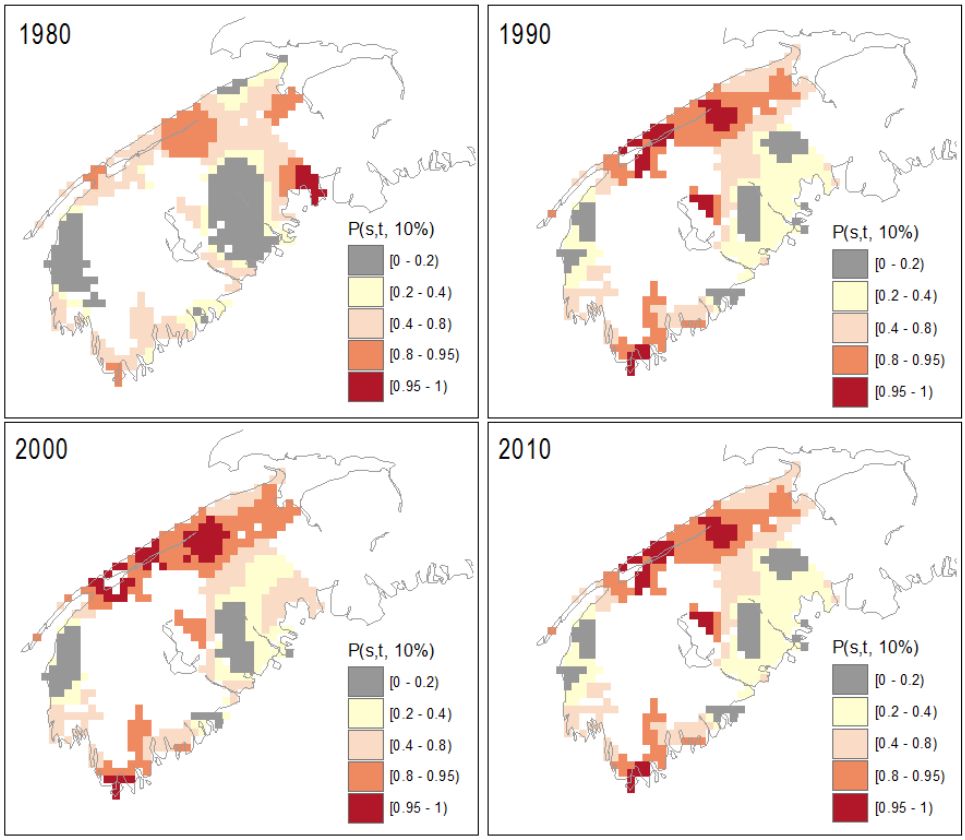

Figure 4.4 Bootstrapped exceedance probabilities (*P(s, t; 10%)*) for risk surface of male bladder cancer in south-western Nova Scotia.

In this latter model, where risk varies in time as well as in space, we write *P(s,t;10 %)* as one minus a p-value for testing $\lambda(s,t) < 1.1$. Here, *P(s,t;10 %)* is shown for four specific years, 1980, 1990, 2000 and 2010. Exceedance probabilities for the intervening years can be found in the supplementary materials and at http://pbrown.ca/jlee/spatio_temporal/. Note that while patterns of exceedance probabilities for year 2000 (i.e. Fig. 4.4, bottom left panel) includes data from 1980-2010, the 13 years closest to this index year will have the greatest influence upon parameters estimates. This is because the relative influence is determined by a weighting function that follows a Gaussian distribution with a standard deviation of 13 years (i.e. optimal temporal bandwidth for male bladder cancer). Simultaneously, the spatial weighting function associated with a point estimate also follows from a Gaussian distribution with a standard deviation of 11 km (i.e. optimal spatial bandwidth for male bladder cancer). Overall, the results are similar to those obtained with the spatial model, highlighting large areas with *P(s,t;10 %)* above 80 % along the Fundy Shore and south portion of the region. However, when adding a temporal component and thus further zooming into a finer scale of analyses, several locations show *P(s,t; 10 %)* surpassing 95 %, pointing to broad areas of significantly elevated risk where the estimated relative risk varied between 1.27 – 2.84 (not shown).

4.3.3 Spatial Patterns of Kidney Cancer

Community-Level Analysis

As observed for bladder cancer, posterior summaries for regression and variance parameters show that the measured covariates had no significant influence on the estimated risk of kidney cancer (Table 4.4). Random effects for both spatially and

unstructured random errors were significant, although showing greater unstructured heterogeneity for males than previously observed with male bladder cancer risk (i.e. ranging between 0.17 – 0.27 vs 0.07 – 0.19, respectively; Tables 4.2, 4.4). Maps of posterior means displayed strong spatial heterogeneity in male and female kidney cancer risk (Fig. 4.5A-B). Regions of elevated risk for male kidney cancer were common in the southwestern region of the province as well as in several communities of CB Island, correlating with the elevated risk observed amongst females which is uniformly high in that region (Fig. 4.5A-B). Female kidney cancer rates were elevated in some Communities along the southern shore of SW NS and around the south shore of central NS (Fig. 4.5B). Figure 4.6A-B shows $P_i(10\ \%)$ for kidney cancer and a risk threshold that would be typical given the region's deprivation and well water usage. In total, 11 Communities showed $P_i(10\ \%)$ in excess of 80 % amongst males (estimated risk: 1.36 – 2.52); 2 of these being statistically significant (i.e. $Pr[\exp(U_i) > 1.1|\text{data}) > 0.95$; estimated risk: 1.73 – 2.52).

Table 4.4 Estimates and credible intervals for regression and variance parameters – Kidney cancer, Nova Scotia 1998-2010

KIDNEY	MALES			FEMALES		
Parameter	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**
Intercept	0.032	-0.231	0.290	0.038	-0.259	0.326
% using well water	-0.001	-0.004	0.002	-0.001	-0.004	0.003
Material deprivation	-0.006	-0.112	0.097	0.052	-0.064	0.167
Social Deprivation	0.008	-0.087	0.103	0.0004	-0.107	0.109
Spatial standard deviation	0.138	0.048	0.298	0.156	0.052	0.366
Unstructured standard deviation	0.265	0.174	0.390	0.251	0.137	0.440

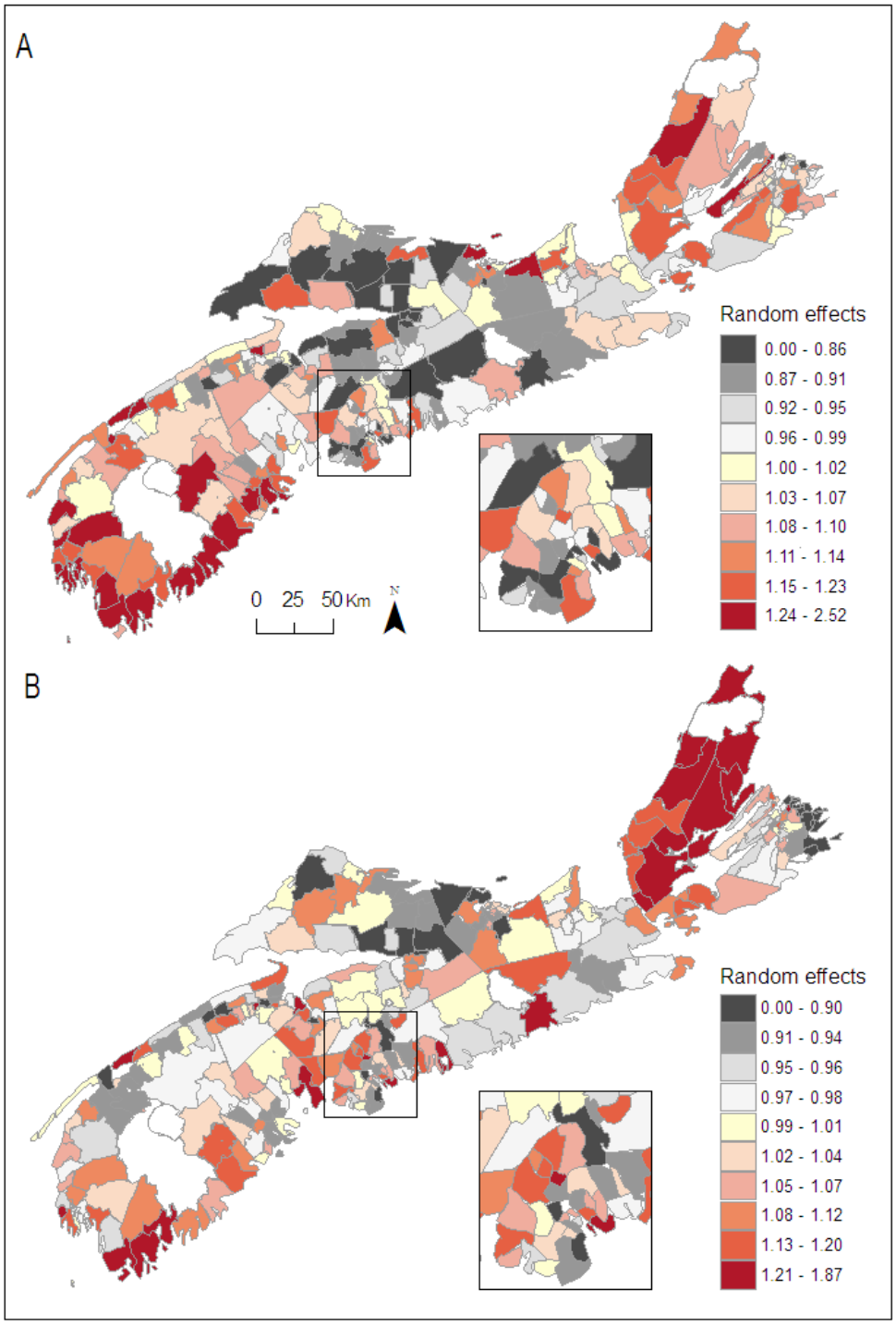

Figure 4.5 Posterior means relative risks for male (A) and females (B) kidney cancer, Nova Scotia 1998-2010

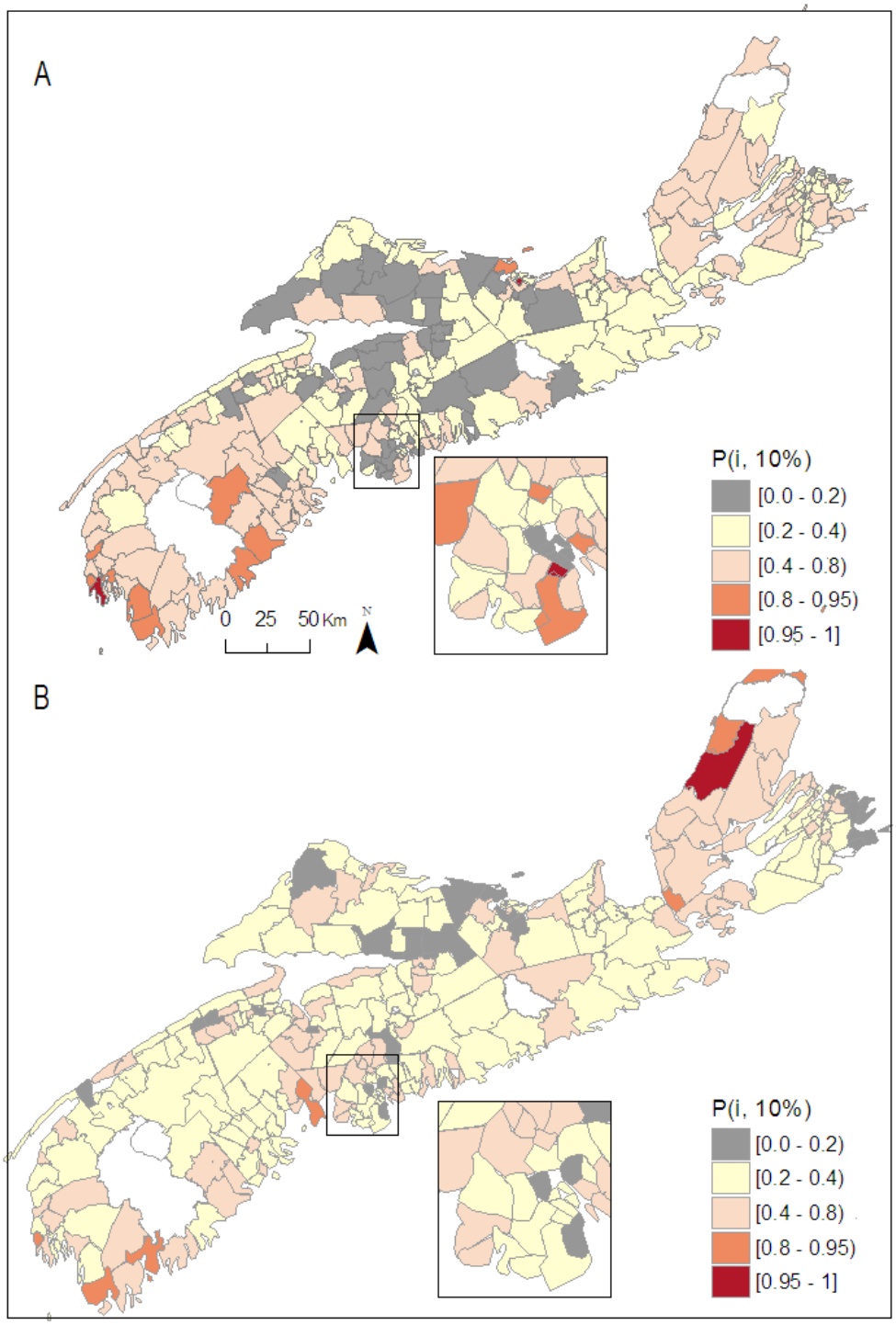

Figure 4.6 Exceedance probabilities ($P_i(10\%)$) for male (A) and female (B) kidney cancer, Nova Scotia 1998-2010

The majority of these Communities are located along the south shore of SW NS (Fig. 4.6A). Exceedance probabilities above 80 % for females risk were observed in 8 Communities (estimated risk: 1.35 – 1.86); 4 located along the south shore of SW NS and 4 along the north shore of CB (Fig. 4.6B). Of these, 1 had a statistically significant probability (estimated risk: 1.87). Over the 12 year-period, high risk areas (Pr[exp(U_i) >1.1|data]> 80 %) had 52 and 57 % more cases of male and female kidney cancer being diagnosed, respectively.

Spatially Continuous Analysis

Optimal spatial and spatio-temporal bandwidths from cross-validation scores (Additional files 2 and 3, see sections 4.10-11) and associated p-values testing for spatial and spatio-temporal effects in kidney cancer risk, are shown in Table 4.3. Based on these bandwidths, we observed significant variation in the spatial distribution of kidney cancer risk in males and females from SW NS and in males from CB. Statistically significant spatio-temporal effects were not observed (Table 4.3; $p > 0.2$) and therefore maps of exceedance probabilities were derived from the spatial models with 30 years of pooled data (1980–2010). In comparison to the results obtained with BYM modeling, probabilities in excess of 80 and 95 % had a larger spatial extent. This pattern was generally observed across regions and genders. In addition, the probabilities produced by local-EM were less spatially smooth, allowing the detection of more localized risk. Again, *P(s;10 %)* for males in SW NS showed a high probability of excess risk along the southern shore, but also toward the centre of the region. Significant probabilities of exceedance in risk of male kidney cancer were also

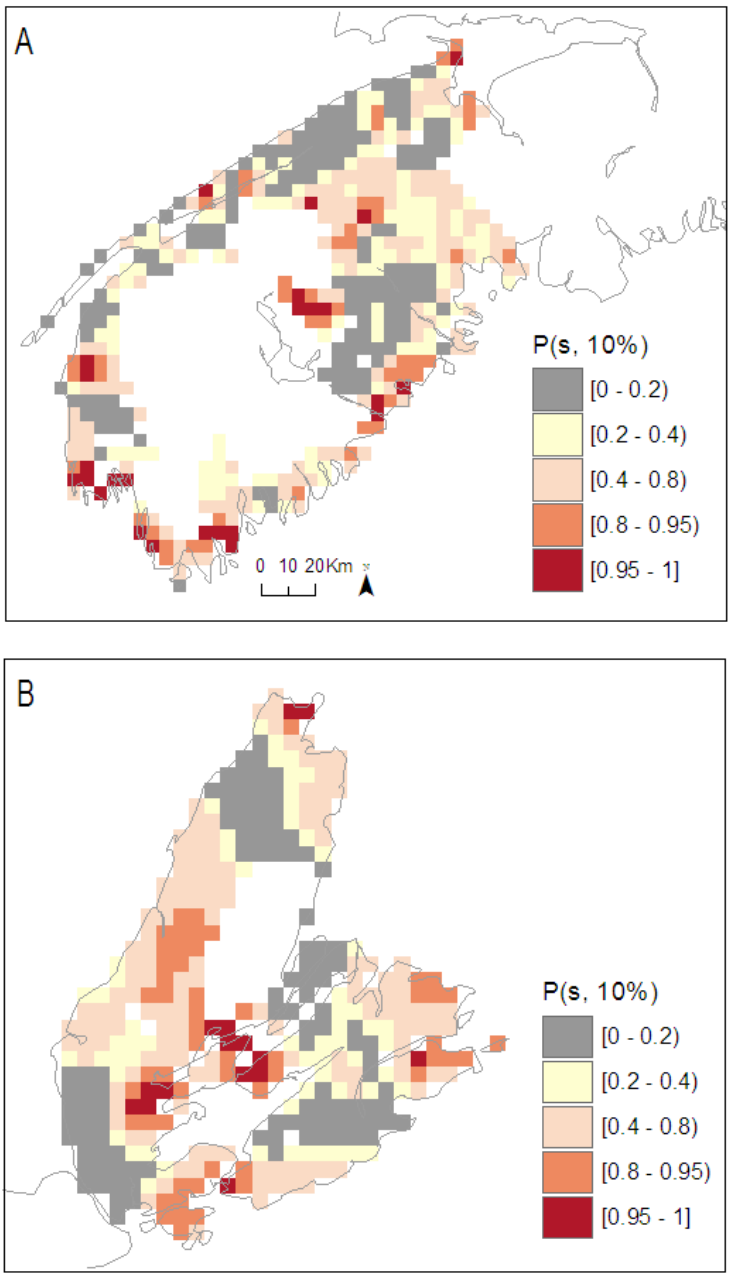

Figure 4.7 Bootstrapped exceedance probabilities (*P(s; 10%)*) for risk surface of male kidney cancer in south-western Nova Scotia (A) and Cape Breton (B) regions.

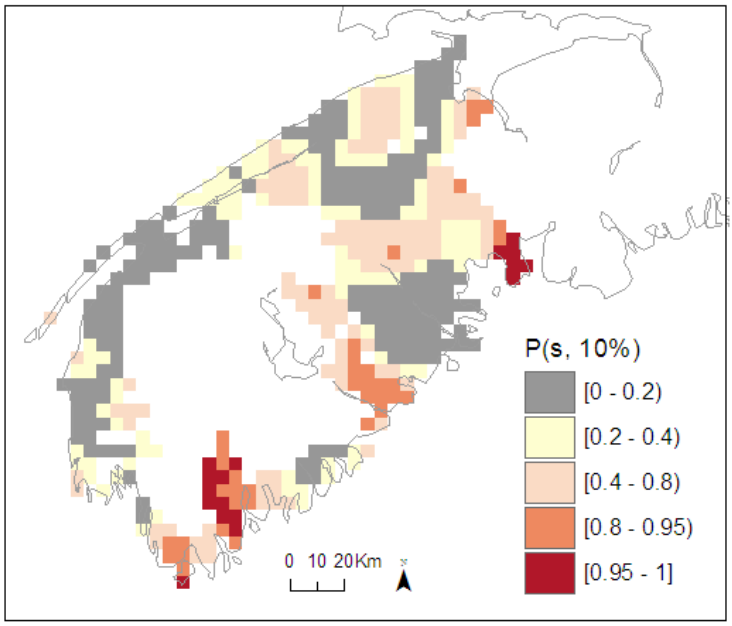

Figure 4.8 Bootstrapped exceedance probabilities (*P(s; 10%)*) for risk surface of female kidney cancer in south-western Nova Scotia.

4.4 Discussion

4.4.1 Summary of Findings

This study showed evidence of spatial variation in the risk of bladder and kidney cancer in Nova Scotia. Posterior summaries for regression and variance parameters suggested that much of the heterogeneity in risk is related to unmeasured risk factors. High risk areas for bladder cancer were predominantly distributed along a southwest to northeast gradient. Kidney cancer risk followed a similar distribution, although areas of elevated risk were also detected in various northeast Communities of Cape Breton, for both

genders. Focusing on aggregated spatial units (Communities), the study showed that areas identified to have high probability of exceedance (BYM: $Pr[\exp(U_i) > 1.1|\text{data}] > 80\ \%$) in the risk of male (28 Communities) or female (9 Communities) bladder cancers had

33 % (males) and 52 % (females) more cases diagnosed over the 12 year period, compared to the number of cases expected. Similarly, high risk areas for male (11 Communities) or female (8 Communities) kidney cancer had 52 % (males) and 57 % (females) more cases diagnosed than expected. From a public health perspective, this translates in an excess of nearly 200 urinary tract cancer (UTC) cases (150 bladder; 45 kidney) being diagnosed in those high risk areas where the estimated risk was observed to be at least 10 % above the NS average rate. Over a 12 year period, this corresponds to an additional 16 UTC cases annually, a conservative figure given that exceedance probabilities in excess of both 80 % and 95 % had much larger spatial extent when derived from the spatially-continuous analysis than with the Community-level model. This was true for risk measured in either sex or cancer site. Focusing on localized spatial patterns, this study also highlighted significant spatial and spatio-temporal variations in the risk of male bladder cancer within SW NS, with areas of elevated risk along the Fundy shore and south shore of the region. Elevated risk of both, male and female kidney cancer were also observed along the south shore of SW NS. In addition, risk for both male bladder and kidney cancer varied significantly in CB, although areas of elevated risk did not always overlap. Overall, spatial patterns were generally stable over time.

4.4.2 Interpretation of Spatial Patterns

Patterns of spatiotemporal heterogeneity in risk provide clues to the occurrence and influence of extrinsic factors involved in the rise or fall of a disease. In this study, patterns of spatial variations in bladder and kidney cancers risk were stable over time, suggesting persistent risk exposure. The exception being male bladder, for which the results pointed to a temporal effect. However, the pattern of spatial variations in risk remained stable over a 13 year period, possibly also reflecting persistent effects. Similarly, a study of space-time patterns of bladder cancer incidence in Utah, US, detected high risk areas that were persistent over time [35]. These high relative risk areas were subsequently found to be associated with the presence of Toxic Release Inventory sites, where the risk was observed to range between 1.14 and 1.82 for both genders combined and between 1.12 to 1.47 for males only. While the processes generating the elevated risk in NS are unknown, the magnitude of the estimated risk in high risk areas for NS was similar to that reported in Utah, ranging between 1.24 – 1.56 and 1.38 – 1.69 among males and females, respectively based on BYM and between 1.48 – 1.99 and 1.48 – 1.95 among male from SW NS and CB, respectively, when based on local-EM. The latter tighter lower bounds of the estimates are attributable to the more conservative rule of exceedance probability applied in NS (NS: Pi(10 %)>0.8 and P(s;10 %) > 0.8; Utah: P(exp(si) >1.0|data) > 0.8) for the determination of high risk areas. Both studies suggest an increased effect in females.

Several factors affect the incidence of urinary tract cancers worldwide. Exposure to tobacco smoke, occupational toxins and environmental source of heavy metals such as

arsenic in drinking water, are amongst well established risk factors for bladder cancer, in particular, transitional cell carcinoma which account for 90 % of the bladder cancer cases diagnosed in developed countries [5, 7, 19]. Tobacco smoking [5, 9, 36–41] and long term exposure to high levels of arsenic in drinking water also increase kidney cancer risk [19, 42] along with obesity [38, 43, 44], hypertension [38], the use of phenacitin containing analgesics and exposure to trichloroethylene and polycyclic aromatic hydrocarbons [38, 45–47]. Whether measured independently or synergistically, the magnitude of influence of these risk factors for the development of UTC varies. However, meta-analyses of over 30 years of epidemiological studies suggest, for instance, that tobacco smoking could increase the risk of bladder and kidney cancer by at least 270 and 50 %, respectively, in current smokers compared to non-smokers [37, 48]. Exposure to arsenic in drinking water shows effects of similar magnitude, increasing the risk of bladder cancer by about 40 %, 230 and 310 % at levels exposure of 10, 50 and 150 μg/L, respectively [19]. Obesity has been reported to account for 30–40 % of kidney cancer cases in Europe and the United States; and is known to increase the risk of renal cell carcinoma in a dose–response relationship [12, 49].

In this study, residual spatial variation and resulting probabilities of exceedance for bladder and kidney cancer risk suggest that smoking is not the only factor contributing to the observed spatial patterns. This is because the proxy measures of smoking included in the analyses (i.e. social and material deprivation indices) did not change the spatial variations in risk or its magnitude. As well, the heterogeneity in bladder and kidney cancer risk observed in high risk areas was greater than what could be accounted by

known spatial variations in smoking prevalence in Nova Scotia. Nonetheless, synergistic relationships between smoking and other un-measured risk factors cannot and should not be ruled out. This is especially important in Nova Scotia, a province known for its high prevalence of tobacco smoking [50], obesity [51] and where inorganic arsenic in drinking water was observed to be a major contributor to arsenic body burden in a study population [52]. Overall, the two spatial approaches used to model disease risk provided consistent and complementary results. Inclusion of a time varying component in the spatially-continuous models permitted the determination of whether high average risk in a given location was sustained over time or changed over time; two different situations that could be derived from the same number of accumulated cases in an area over a set time period. As described by Abellan et al. [53], the epidemiologic interpretations of these two situations are important. In one scenario, spatial patterns are more likely to occur in a constant manner over time and hence could be induced by environmental or socio-demographic risk factors that act in a sustained manner. In the second scenario, the rate of case accumulation may be more temporally clustered with distinct variability, possibly reflecting emerging short latency risk factors that would generate high excess cases in shorter time intervals or, alternatively, due to artificial or sudden variations associated with changes in disease coding or screening practices (see details in Abellan et al. [53]). Hence, it would not be unreasonable to suggest that the observed heterogeneity in the spatial distribution of high-risk areas for bladder and kidney cancer in both SW NS and CB, support a scenario in which risk factors act in a relatively sustained manner over time.

4.4.3 Strengths and Limitations

This study has important strengths. First, it is based on 30 years of cancer incidence data obtained from a population-based cancer registry adhering to registration standards of both the Canadian Cancer Registry and the North American Association of Central cancer Registries. Those standards allow for consistency in disease coding over time and; ensure case ascertainment and completeness through a network of activities including automated and manual edit processes, record linkages and data audits. In addition, the systematic collection of spatial information at time of diagnosis enabled 100 % of cases in Cohort 1 and 95 % of cases in Cohort 2 to be successfully geo-referenced with a high degree of certainty, thus minimizing location misclassification (Cohort 1, ~ 85 % exact location; Cohort 2, ~ 50 %). Second, the two statistical methods used in this study accounted for spatial dependence (random effects) in risk estimates which reduce the likelihood of Type I error – declaring an area as having elevated risk when in fact its underlying true rate equals the background level [54]. Third, the exceedance probability rules, $P_i(10\ \%) > 0.8$, $P(s;10\ \%) > 0.8$ and $P(s,t;10\ \%) > 0.8$, used here to classify spatial risk has high specificity even when data are sparse, further reducing the risk of false alarms, although perhaps increasing the likelihood of Type II error – declaring an area as having average risk when in fact its underlying true rate is elevated relative to background levels [54]. Fourth, the application of the local-EM algorithm treated risk as a continuously varying process in space and time and so was not constrained to be within arbitrary administrative boundaries which often change between census periods [52]. This allows for the integration and use of irregularly aggregated or point-location data within a single framework and minimizes loss of information. It presents a real advantage

for the estimation of disease risk in small-area analyses or for rare diseases that requires the monitoring and accumulation of cases collected over a long time period as it maximizes statistical power and results in more meaningful inference [55]. As such, it is reasonable to suggest that applying the Local-EM framework improved the sensitivity of the study, offering a balance to the Community level autoregressive model, a more conservative approach with generally lower sensitivity (see [54, 55]. Finally, modelling the spatio-temporal variation in risk with local-EM algorithm provided useful insights about the stability of the estimated spatial patterns of disease. It also produced predictions that were generally less spatially smooth, and as such, is a more sensitive tool for the detection of localized areas of elevated risk, which ultimately better informs health service planning, public health interventions and resource allocation.

Nonetheless, this study has limitations. First, location at time of diagnosis was used as a surrogate for the location where a person was thought to be exposed to factors which increased their risk of cancer. This is a common approach in the geographic analyses of many disease outcomes given the difficulty of obtaining a full history of residence and building estimates of lifetime exposure. The consequent exposure misclassification can result in less informative maps that impedes hypothesis generation or identification of environmentally or sociologically driven processes occurring over long time periods. Second, individual-level information on important risk factors such as smoking frequency and duration was not available as cancer registries do not routinely collect information unrelated to patient care. This study used neighbourhood social and material deprivation as a proxy for smoking prevalence. As a result, it is possible that maps of posterior means

relative risks include some residual confounding due to smoking. Third, current algorithms for local-EM estimation do not allow for the inclusion of covariates. Fourth, the method is computationally intensive. Finally, although the local-EM analyses benefited from the inclusion of cases diagnosed over a longer time period, when reporting for the Cape Breton region, the number of cases was still quite low, which resulted in unstable results. This was particularly evident when determining optimal spatial and temporal bandwidths in females risk for which incidence counts was about 1.5 to 3 times lower than for males.

4.5 Conclusions

Modeling the geographical distribution of disease within a population is essential to public health surveillance. It permits the quantification of the risk of disease relative to expected background levels, and the identification of unusually high and low risk areas which can guide health service planning, public health intervention resource allocation, environmental assessment and mitigation. The current approach further permits the estimation of residual spatial dependence resulting from exposure to unmeasured risk variables, and as such, helps identify areas where other etiological factors may be at play. In this study, spatial analyses demonstrated evidence of spatial heterogeneity in the risk of both bladder

and kidney cancers in Nova Scotia. The temporal component of the spatially-continuous approach permitted the determination of the relative time scales of high average risk in a given area and hence provided an understanding of the stability of the spatial patterns of the estimated risk; and the generation of hypotheses about the nature of possible exposure. Based on this information, we suggest that the excess bladder and kidney cancer risk for

both male and potentially, female in south-western NS may be driven by exposure to unknown risk factors that act in a sustained manner over time. Further research may uncover the nature of these factors and lead to future opportunities for disease prevention.

The findings from this study warrant further investigation in three main areas. First, further work is required in the area of exposure modeling in order to elucidate the potential factors driving the observed patterns of variations in the risk of UTC in NS. Second, they highlight the need for the development of local-EM methods that incorporate individual- and neighborhood-level covariates. Finally, they reaffirm the need for the establishment of a public health platform that would enable the collection of individual- and/or neighborhood level information relating to disease causing-risk factors, such as behavioural, occupational and environmental factors. Such information permits more accurate quantification and understanding of disease risk.

4.6 Competing Interests

The authors declare that they have no competing interests.

4.7 Acknowledgement

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4.10 Additional File 1

Analytical details

Community-level analysis – The BYM model [15, 16] applied in this study has the case count Y_i for each Community i modelled as Poisson distributed, with the expected count for Community i being the product of its relative risk λ_i and an expected count E_i derived from the age-specific incidence rates of NS applied to each Community's population composition. The model is log-linear, with the log of the relative risk λ_i being the sum of an intercept μ, the contribution of covariates $X_i\beta$ and the spatial random effect U_i. The model is written as

$$\begin{aligned} Y_i &\sim \text{Poisson}(E_i\,\lambda_i) \\ \log(\lambda_i) &= \mu + X_i\beta + U_i \\ (U_1, U_2 \ldots U_N)' &\sim \text{BYM}(\sigma^2, \tau^2) \end{aligned}$$

with the random effects U_1 to U_N having a spatially dependent joint distribution where adjoining regions having a direct influence upon one another. The sum of the two BYM variance parameters $\sigma^2 + \tau^2$ governs the 'importance' of the effect (how close to or far from zero each U_i is likely to be), with their ratio σ^2/τ^2, determining the smoothness or degree to which each U_i is influenced by its neighbours. More specifically, each U_i is the sum of an independent or unstructured random term and a spatially autoregressive (first order Gaussian Markov random field) component with variance parameters σ^2 and τ^2, respectively.

Bayesian inference were applied for model fitting using Integrated Nested Laplace Approximations to calculate the posterior marginals [31]. Uninformative prior distributions were specified for the μ and β parameters with the μ having improper flat priors and the β being assigned Normal priors with mean zero and variance 1000 (N(0,1000)). The variance parameters σ^2 and τ^2 were given identical priors with 95% intervals between 0.025 and 1.0 which resulted in a fairly unrestrictive upper limit considering that log-relative risks of U_i =-2 or U_i =2 (plus or minus two standard deviations) correspond to relative risks exp(U_i) of 0.135 or 7.4, respectively.

Spatially-continuous analysis– In applying the Local-EM kernel smoothing algorithm the algorithms for the locations of cancer cases are random Poisson process with an intensity surface at each location in space s and time t being the product of a `offset' surface $O(s,t)$ derived from the population at risk and a smoothly varying relative risk $\lambda(s,t)$. A local-likelihood algorithm is similar to a kernel smoother, with a kernel function $K(s\text{-}X_i,\ t\text{-}T_i)$ specifying the weight to assign to a case i located at (X_i,T_i) for the purpose of estimating risk $\lambda(s,t)$ at s and t. The local-EM algorithm deals with unobserved (or censored) locations (X_i,T_i) by having an estimate $\lambda(s,t)$ being the maximum of an expected likelihood subject to the constraint that (X_i,T_i) be located within the case's known census or postal region.

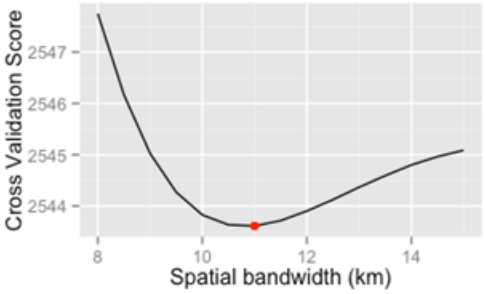
The local-EM algorithm does not impute a single location for each case. Rather, the estimated risk surface averages out all the possible locations at which each case could be located. The risk surface is sensitive to the bandwidth of the smoothing kernel used, with wider bandwidth giving smoother and flatter risk surfaces. Shorter bandwidths return

rougher surfaces and result from data inherently more heterogeneous where close neighbours— in space or time, have the greatest influence on risk estimation. The bandwidth of the kernel functions (one each in time and in space) were chosen by cross-validation (see Additional files 2-3), where data were systematically excluded from model fitting and the optimal bandwidths being those that are best able to predict the excluded data.

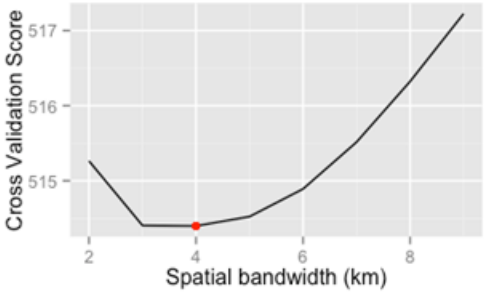
Finally, the $O(s,t)$ offset surface was calculated from: the population density for each age-sex group at the relevant location and during the most proximate census of population; an age and sex specific rate obtained from a reference population; and a yearly-varying relative risk term ensuring the observed count in each year and the total number of cases expected in that year are equal. A relative risk of $\lambda(s,t)=1$ everywhere would indicate $O(s,t)$ is an accurate quantification of the distribution of incident cases, whereas $\lambda(s,t)$ above or below 1 indicate a surplus or deficit of cancer cases respectively.

4.11 Additional File 2

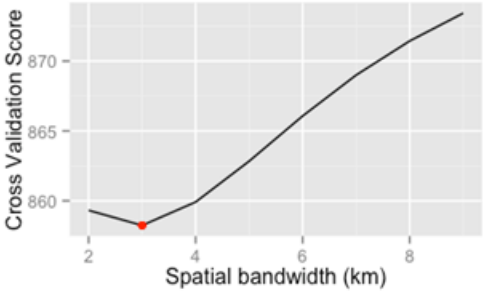
Spatial cross-validation scores for the selection of optimal bandwidths



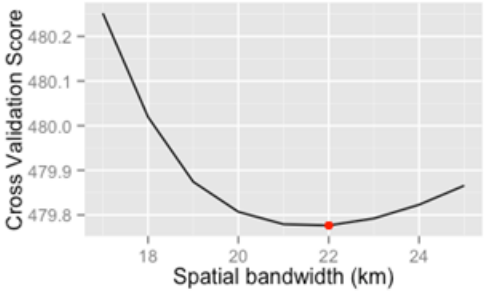
a) Male bladder, South-western NS



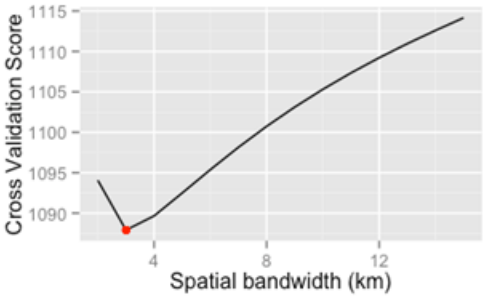
b) Male bladder, Cape Breton



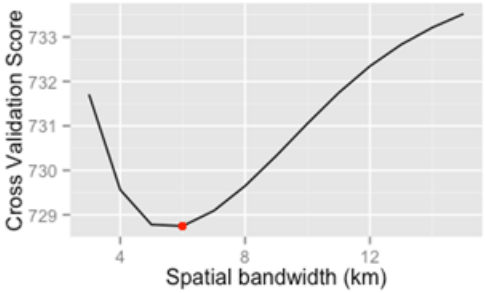
c) Female bladder, South-western NS



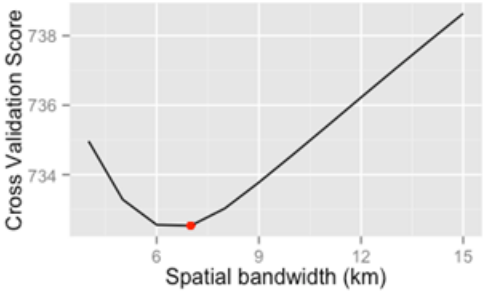
d) Female bladder, Cape Breton



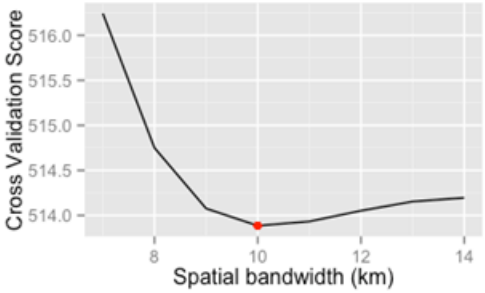
e) Male kidney, South-western NS



f) Male kidney, Cape Breton



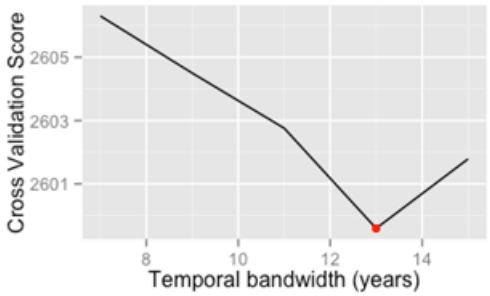
g) Female kidney, South-western NS



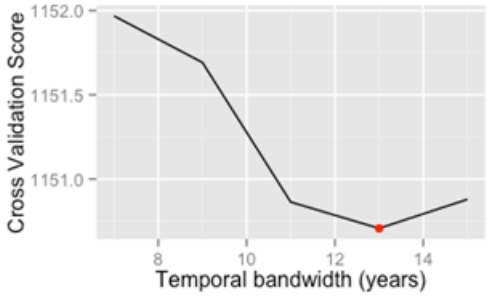
h) Female kidney, Cape Breton

4.12 Additional File 3

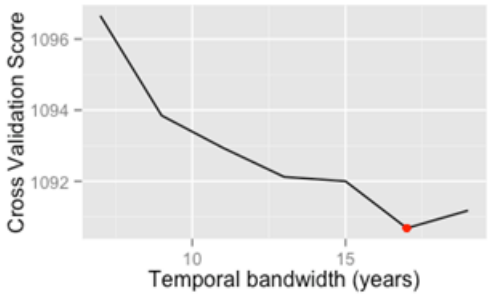
Temporal cross-validation scores for the selection of optimal bandwidths



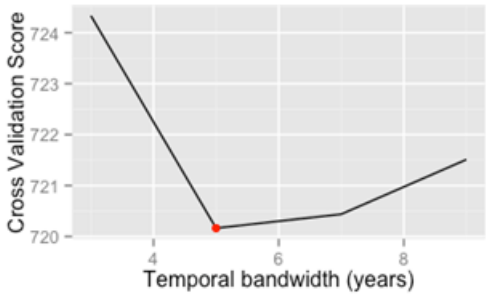
a) Male bladder, South-western NS



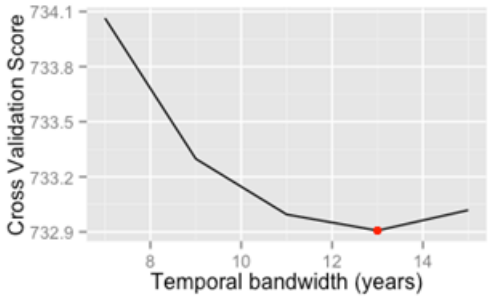
b) Male bladder, Cape Breton



c) Male kidney, South-western NS



d) Male kidney, Cape Breton



e) Female kidney, South-western NS

CHAPTER 5— Risk of Bladder and Kidney Cancer from Exposure to Low-Levels of Arsenic in Drinking Water, Nova Scotia, Canada

Nathalie Saint-Jacques[1,2], Patrick Brown[3], Laura Nauta[4], James Boxall[5], Louise Parker[6] and Trevor JB Dummer[7]

To be submitted for publication.

Authors' Contributions

NSJ extracted the cases files; georeferenced cases; conducted all analyses, constructed tables and figures, drafted and revised the manuscript; PB supervised NSJ for statistical work and R-programming, reviewed the article critically for important statistical content, provided assistance in the interpretation of the results; LN georeferenced well locations and calculated arsenic values at each unique location; ; JB reviewed the article critically for important intellectual content; LP devised the study, reviewed the article critically for important intellectual content and provided assistance in the interpretation. TJBD devised the study, supervised the overall work, reviewed the article critically for important intellectual content and provided assistance in the interpretation.

ABSTRACT

Background: Arsenic (As) in drinking water affects the health of millions of people. Although Bangladesh/Taiwan are among the most affected regions, with As-levels as high as 4,700 μg/L, high concentrations are also found in well water across the US and Canada. A strong association between As in drinking water and a range of diseases, including cancer, has been shown in populations where As exposure is high. However, these associations are inconsistent at low-levels of exposure, especially near 10 μg/L, which is the current World Health Organization regulatory limit. This study models the risk of bladder/kidney cancer in those exposed to well water As-levels around this limit.

Methods: A Bayesian approach models risk at 0–2 μg/L; 2–5 μg/L and; >5 μg/L of As in 864 bladder and 525 kidney cancers diagnosed in Nova Scotia Canada, 1998-2010. The model accounted for spatial dependencies and included proxy measures of lifestyle factors (e.g. smoking).

Results: Bladder cancer risk was 16% (2–5 μg/L) and 18% (>5 μg/L) greater than that of the referent group (<2 μg/L), with posterior probabilities of 88% and 93% for these risks being above 1. Effect sizes for kidney cancer were 5% (2–5 μg/L) and 14% (>5 μg/L) greater than that of the referent group (<2 μg/L), with probabilities of 61% and 84%. High-risk areas were predominantly in southwestern Nova Scotia, where higher As-levels are associated with local geology.

Conclusions: The study suggests an increased bladder/ kidney cancer risk from exposure to drinking water As around current regulatory limits.

Keywords: Arsenic, Drinking water, Bladder and kidney cancer risk, Small-area disease mapping, BYM model, Geostatistical analysis, Spatial autoregressive analyses

5.1 Introduction[1]

Arsenic (As) is a toxic metalloid occurring naturally in the environment [1]. Through the weathering of rocks As becomes available as dust, or by dissolution in rain, surface or groundwater. In water, As is present predominantly as inorganic arsenate (AsV) and arsenite (AsIII), the later being the most toxic form. Approximately 85% of As occurs in a dissolved, mobile and more biologically active state [2]. Human exposure to As involves multiple environmental and occupational pathways, with drinking water being the primary route of exposure for the majority of highly exposed populations [3–6]. West Bengal, Bangladesh and Taiwan are amongst the most affected populations worldwide. In these regions, As concentrations as high as 4,700 μg/L have been reported in drinking water and levels in excess of 300 μg/L are common. However, high levels of As have been observed across all continents, including North America where an estimated 30 million people may be exposed [7].

As is a class 1 human carcinogen [8] that ranks as the second most important global health hazard related to drinking water, next to contamination by pathogenic microorganisms [9]. Worldwide, it affects the health of hundreds of millions of people and is responsible for hundreds of thousands of deaths [10, 11]. Combined evidence supporting a wide range of acute and chronic As-related health effects, including cancer, led the World Health Organization (WHO) to lower the maximum allowable concentration (MAC) of As in public drinking water supplies from 200 μg/L (1958); 50 μg/L (1963); and, 10 μg/L (1993) [12]. The latter was adopted by the US in 2002 and

[1] Numerical format was used for referencing citations in this chapter as to be consistent with the format used in chapters 2-4.

Canada in 2006 as the regulatory MAC for public water supplies, and serves as the recommended guideline for safe drinking water from private well water sources, for which no enforceable standard has been established [13]. While the debate to further lowering standards is ongoing, many developing countries continue to use a MAC of 50 μg/L [14, 14, 15].

High levels (>150μg/L) of As in drinking water have been linked to: cardiovascular diseases; diabetes mellitus; gastrointestinal, vascular, respiratory and neurological effects; adverse obstetric and pregnancy outcomes; and cancer, including lung, bladder, non-melanoma skin, liver, and kidney cancers [16–24, 8, 25–30]. Much emphasis has been placed on cancer since cancer mortality predominates over all other causes of death involving As. To date, most of the evidence for strong associations and dose-response relationships between As in drinking water and cancer has been derived from highly exposed populations. The threshold at which cancer develops is uncertain at lower levels of As exposure, but recent evidence suggest that As may increase the risk of a number of health outcomes—including bladder and kidney cancers—at levels not previously considered harmful (see: [27, 31–35, 35–41]). Nonetheless, further studies reporting on low-level of As exposure, especially around current WHO guidelines, are still required to inform the global debate on what is an acceptable threshold for safe drinking water.

Nova Scotia (NS), a province of 940,000 people, is located in Atlantic Canada where rock formations contain significant amounts of the mineral arsenopyrite (AsFeS), one of the main mineral hosts for As [42, 43]. Under certain pH and Redox conditions

arsenopyrite breaks down into soluble As species (AsIII, predominantly) that contaminates water supplies [42]. Based on regional geology, mainland southwestern NS and the northeast shore of Cape Breton (CB) are the most affected regions, with average well water As concentrations around 3.0 μg/L, and a 95th percentile up to 65 μg/L [42]. Between 1991and 1997, the Environmental Chemistry Laboratory in Halifax, NS, tested over 21,000 private well water samples province-wide and found that 9% had As levels > 25 μg/L [13]. Around 45% the population of NS sources drinking water from unregulated private wells. Health effects due to As exposure from drinking water have not been evaluated in NS.

Rates of bladder and kidney cancers are consistently high in NS compared to other provinces, with age-standardized incidence rates exceeding those of the national average by about 25% and 35%, respectively [44]. The causes associated with this excess burden are unknown. However, small-area spatio-temporal analyses of bladder and kidney cancer risk in NS point to an excess risk potentially driven by exposure to risk factors that act in a sustained manner over time, with evidence for an increased cancer risk along a northeast to southwest gradient, possibly coinciding with the groundwater regions associated with high As levels [45]. The aim of the current paper is thus two-fold: first, to quantify the risk of developing bladder or kidney cancer as a result of potential exposure to drinking well water containing As; and second, contribute to the body of knowledge on the health effects of As exposure around current WHO guidelines. We modeled diseases risk using a Besag York and Mollié model, a Bayesian method that models risk for spatially aggregated case counts and that accounts for possible random spatial

dependencies. To our knowledge, this is the first attempt to model the risk of bladder and kidney cancer in NS in relation to environmental exposure of As in drinking water from private well supplies.

5.2 Methods

5.2.1 Data Sources

Cancer incidence data were obtained from the NS Cancer Registry and included all NS residents aged 20 years and older diagnosed with a first primary of bladder or kidney cancer between 1998 and 2010. Cases were coded according to the International Classification of Diseases (ICDO) as following: bladder (ICDO: 188.0-188.9; ICDO-2/3: C67.0-C67.9); kidney (ICDO: 189.0; ICDO-2/3: C64.9). Because of a change in disease coding over time, bladder cases included both, in situ (37%) and invasive diagnoses; kidney cases included invasive diagnoses only.

Residential address at time of diagnosis was used to assign spatial locations (i.e. longitude-latitude coordinates). Where civic address was available, cases were geo-referenced using the Nova Scotia Civic Address File (NSCAF), a file provided by the NS Government, which contains accurate spatial locations for every residential location in NS. Where civic address was unavailable, cases were geo-referenced using a Postal Code Conversion File (PCCF+), which linked postal codes to the finest level of geographic areas for which Statistics Canada provides coordinates.

Analyses included cases with a rural residential address outside a municipal drinking water supply zone (MWSZ). Rural areas were defined as regions outside census metropolitan areas with a population density of less than 400 people per square kilometer as outlined in [46]. Digitized spatial boundaries for MWSZ were provided by the Nova Scotia Department of Environment (NSE). Cases located outside the MWSZ were assumed to source their drinking water from private wells. The number of cases diagnosed, excluded and analyzed as well as the proportion of cases by spatial data type is shown in Table 5.1.

Population data were obtained from Statistics Canada for four census years (1996, 2001, 2006, and 2011). Each census provided counts of people aged 20 years and older by age and sex group, and were used as the denominator (i.e. population at risk) for cases diagnosed within two years of a given census period. Counts were obtained at the finest level of census geography for which digitized spatial boundary data were available. These were enumeration areas (EAs) for the 1996 census years, and dissemination areas (DAs) for census 2001 onward. The number of EAs/DAs ranged from 1,508 to 1,645 between the 1996 and 2011 census periods.

It was assumed that the population was uniformly distributed over the inhabited portion of these fine levels of census geography, having removed areas partially uninhabited or lying outside of the population ecumene. The approach is reasonable given that census boundaries are created and adjusted to make each area as homogeneous as possible with a population of 400 to 700 individuals.

Table 5.1 Cases characteristics for the two periods under study, Nova Scotia, Canada

Period 1998 - 2010		**Bladder**			**Kidney**	
Nova Scotia	Total	Females	Males	Total	Females	Males
Cases diagnosed[a]	3,201	809	2,392	2,129	840	1,289
In situ	1,182	302	880	0	0	0
Invasive	2,019	507	1,512	2,129	840	1,289
Mean age at diagnosis (years)	70.6	71.1	70.4	64.6	66.1	63.7
Spatial referencing (%)						
Civic address	86.5	85.7	86.8	86.0	86.8	85.5
Postal code	13.5	14.3	13.2	14.0	13.2	14.5
Cases excluded						
Residence outside	21	1	20	11	4	7
Residence in urban areas	1,208	325	883	802	325	477
Exposure unavailable	620	140	480	450	175	275
Residence in MWSZ[b]	485	141	344	340	133	207
Outlier	3	0	5	1	2	2
Cases analyzed	**864**	**202**	**660**	**525**	**201**	**321**

[a] Includes first primary disease only.

[b] Municipal water supply zones.

A high resolution lattice of grid cells (280 m^2) was overlaid over the study region to assign population counts from DA-level census geography to 5 km square cells, unit of geography for which exposure data was available. The proportion of a DA's population assigned to a given cell equaled that of the DA's surface area contained within the cell. Figure 5.1 shows smoothed population density estimates for NS, prior to rasterization.

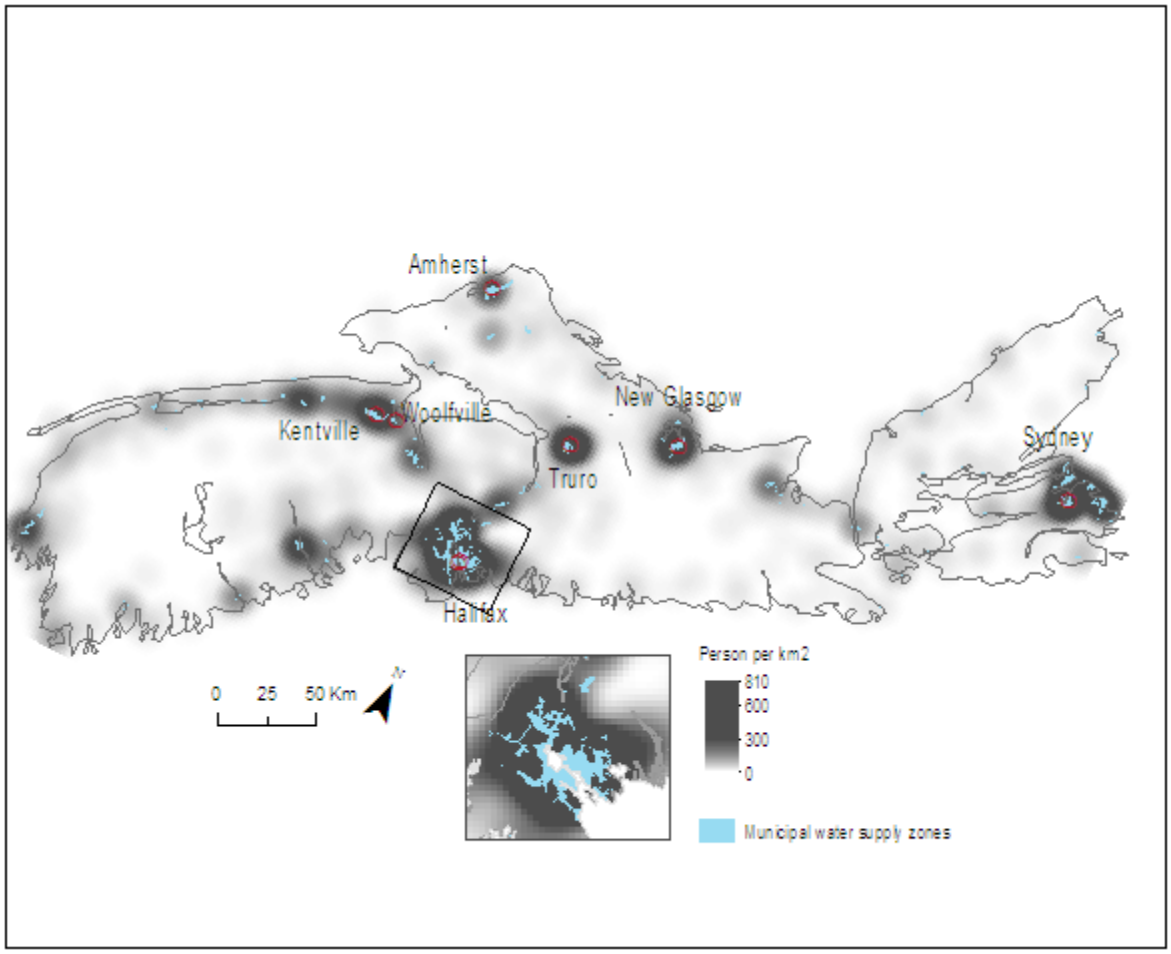


Figure 5.1 Population density, Nova Scotia 2006.

Exposure data were obtained from the NSE and included total As measurements collected from 10,498 private wells between 1991and 1999 in NS [42]. The maximum As level recorded in those wells was 3,900 µg/L and 17% of the wells had levels in excess of the Health Canada MAC of 10 µg/L. Spatial information was incomplete for the majority of the wells, creating issues for accurate georeferencing. As a result, 92% of wells were georeferenced using a gazetteer of community and place names; 7 % were georeferenced based on exact location using NSCAF and; 1 % were georeferenced at the six digits postal code level, using PCCF+. Based on this approach, many individual wells

were spatially coincident and led to pooling measurements from the 10,498 wells over 901

unique locations. Geographic coverage resulting from these unique locations was more limited in Cape Breton Island but extensive over mainland NS.

Mean As values were first obtained by averaging As concentrations from measurements pooled at each unique location and, subsequently, were further aggregated over a set of continuous 5 km square cells (see Figure 5.2). The size of the grid was determined based on sample density as per Fordyce et al.[47].

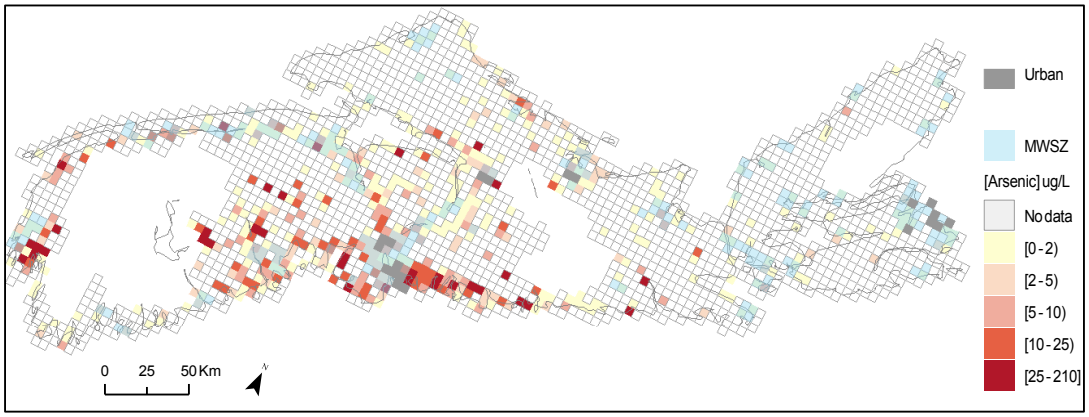


Figure 5.2 Mean arsenic concentrations in private drinking water wells, Nova Scotia. Study area includes grid cells outside municipal water service zones and urban areas.

Covariates included area-based composite indices of social and material deprivation. Methodological details relating to the calculation of these indices appear in Chapter 3 and in Saint-Jacques et al [48]. These indices were used as a proxy for unavailable individual-level measures of smoking, a key factor in the development of urinary tract malignancies

and; to capture the contextual setting of a place of residence, which has been shown to independently predict smoking habit in both men and women and other health outcomes [49–53]. Each index summarized information relating to six socioeconomic indicators compiled from the 2006 Canadian Census; all of which having known links to health outcomes and known application as geographic proxies of socioeconomic conditions. For people age 15 years and over, these variables were: the proportion of people with no high school diploma, the individual average income, the employment rate, the proportion of separated, divorced or widowed, the proportion of single-parent families, and the proportion of persons living alone. The first three indicators reflect the material dimension of deprivation; the others reflect its social aspect. Variables were combined using a Principal Component Analysis, a standard factorial approach that recognizes the interlinked nature of variables by accounting for their correlation and co-variation [54]. As with population data, socioeconomic variables were collected at the DA-level; rasterized using a high resolution lattice (280 m^2) and subsequently, aggregated to 5 km square cells as to match the spatial resolution of the exposure data.

5.2.2 Data Analyses

Modeling Cancer Risk

The Besag York and Mollié (BYM) model (see [55, 56]) was used to model the risk of developing bladder or kidney cancer as a result of varying levels of As concentrations in drinking water: 0–2 μg/L; 2–5 μg/L and; >5 μg/L. The BYM is a Bayesian spatially structured model for count data referenced to discrete spatial regions. In this study, the model treats the case counts for each 5 km square cells, as response variables, rather than

using a Standardized Incidence Ratios (SIR), the latter being unstable when computed from low counts. This is particularly important to this study, given the low population density of NS and the rarity of the health outcomes measured. Possible spatial dependence in the data, with pairs of nearby cells tending to be more similar than cells situated far apart, is accounted for with the inclusion of a spatially autocorrelated random effect term. The BYM models the case count Y_i for each 5 km square cells i as Poisson distributed, with the expected count for cell i being the product of its relative risk λ_i and an expected count E_i derived from the age-specific incidence rates of NS applied to each grid cell's population composition. The model is log-linear, with the log of the relative risk λ_i being the sum of an intercept μ, the contribution of covariates $X_i\beta$ and the spatial random effect U_i. The model is written as

$$\begin{aligned} Y_i &\sim \text{Poisson}(E_i\,\lambda_i) \\ \log(\lambda_i) &= \mu + X_i\beta + U_i \\ (U_1, U_2 \ldots U_N)' &\sim \text{BYM}(\sigma^2,\tau^2) \end{aligned}$$

with the random effects U_1 to U_N having a spatially dependent joint distribution where adjoining cells having a direct influence upon one another. The sum of the two BYM variance parameters $\sigma^2 + \tau^2$ governs the 'importance' of the effect (how close to or far from zero each U_i is likely to be), with their ratio σ^2 / τ^2, determining the smoothness or degree to which each U_i is influenced by its neighbours. More specifically, each U_i is the sum of an independent or unstructured random term and a spatially autoregressive (first order Gaussian Markov random field) component with variance parameters σ^2 and τ^2, respectively. Neighbours here followed the Queen's definition, where even cells meeting

at a single corner point were considered neighbours.

Bayesian inference was used for model fitting and performed separately for each data set (bladder male, bladder female, bladder sex combined; kidney male, kidney female, kidney sex combined) using Integrated Nested Laplace Approximations [57]. Uninformative prior distributions were specified for the μ and β parameters with the μ having improper flat priors and the β being assigned Normal priors with mean zero and variance 1000 (N(0,1000)). The variance parameters $\sigma 2$ and $\tau 2$ were given identical priors with 95% intervals between 0.02 and 2.0 which resulted in a fairly unrestrictive upper limit considering that log-relative risks of U_i =-2 or U_i =2 (plus or minus two standard deviations) correspond to relative risks exp(U_i) of 0.135 or 7.4, respectively.

The software used was R version 3.2.2 (http:// www.r-project.org) in combination with the disease mapping package [58] and the INLA software [59]. This study received ethics approval from Capital Health Research Ethics Board (Appendix A). The study was a secondary analysis of anonymised cancer registry data obtained from the NS Provincial Cancer Registry and a waiver of consent was approved.

5.3 Results

5.3.1 Cohort Characteristics Summary

A total of 3,201 first primary of bladder cancer and 2,129 first primary of kidney cancer were diagnosed amongst NS residents aged 20 years and older, between 1998 and 2010

(Table 5.1). Approximately a third of bladder cancer diagnoses were in situ diseases; all kidney cancer diagnoses were invasive. All cases were successfully georeferenced, 86 % based on the exact location of their civic residential address at time of diagnoses, and 14% using postal code. Nearly 75 % of the cases diagnosed were excluded from analyses due to their location falling outside the ecumene (21 bladder cases; 11 kidney cases) or within urban areas (1,208 bladder cases; 802 kidney cases); or within municipal water supply zones; or because they were located in areas where As measurements had not been collected (620 bladder cases; 450 kidney cases). Few cases were categorized as possible outliers. In total of 864 bladder and 525 kidney cancers were used for model fitting.

5.3.2 Arsenic Exposure and Bladder Cancer

Estimates and credible intervals for regression and variance parameters obtained from the BYM models applied to bladder cancer data are shown in Table 5.2. These coefficients represent the smoothed relative risk in bladder cancer incidence over the entire province and study period. Risk was modeled at 3 levels of As exposure: 0 – 2 µg/L (median, 1 µg/L); 2 – 5 µg/L (median 3 µg/L) and; > 5 µg/L (median 12 µg/L). Based on these results, the risk of developing bladder cancer as a result of being exposed to 2 – 5 µg/L and > 5 µg/L of As in drinking water, was respectively 18 % (1.18 [0.91 – 1.51]) and 21 % (1.21 [0.96– 1.49]) higher amongst males; 13 % (1.13 [0.73 – 1.69]) and 9 % (1.09 [0.74– 1.55]) amongst females and; 16% (1.16 [0.91– 1.45]) and 18 % (1.18 [0.95 – 1.44]) for both sexes combined; relative to those exposed to < 2 µg/L. Material and social deprivation (proxy measures to lifestyle factors such as smoking and; socio-economic status) did not significantly affect these estimated risks. Both the spatially correlated and

the independent random errors have standard deviations in the range of 0.1 to 0.6, reasonably large values considering that they apply to risk on the log scale (Table 5.2).

Table 5.2 Posterior summaries for regression and variance parameters[a] – Bladder cancer, Nova Scotia 1998-2010

Bladder Cancer	**Males**			**Females**			**Combined sex**		
Parameter	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**
Intercept	0.85	0.72	0.99	0.84	0.62	1.09	0.86	0.73	0.98
[As] 2 – 5 µg/L	1.18	0.91	1.51	1.13	0.73	1.69	1.16	0.91	1.45
[As] > 5 µg/L	1.21	0.96	1.49	1.09	0.74	1.55	1.18	0.95	1.44
Material deprivation	1.04	0.93	1.15	1.03	0.87	1.22	1.04	0.93	1.15
Social deprivation	1.0	0.88	1.12	0.95	0.77	1.12	0.99	0.87	1.09
Log-scale									
Spatial standard deviation	0.11	0.012	0.35	0.09	0.03	0.35	0.12	0.02	0.33
Unstructured standard deviation	0.42	0.29	0.57	0.59	0.39	0.84	0.45	0.34	0.57

[a] The 95% credible intervals represent two-tailed distributional inferences upon whether a risk is different from 1. A more appropriate inference is one tailed, whether the estimated risk is greater than 1.0. The latter are presented in Figure 5.3.

The effect size presented in Table 5.2 are not statistically significant, but these are derived from credible intervals based on two-tailed distributional inferences which assess whether the risk of developing cancer at the varying levels of As exposure differs from 1.0 (no risk). A more appropriate inference is shown in Figure 5.3, and determines the probability of the risk being above 1.0, based on its posterior distribution. For males, the results showed that 89 % and 95 % of the probability density distribution in predicted risk was above 1.0 (no risk) in those exposed to 2 – 5 µg/L and > 5 µg/L, respectively. Corresponding figures for females were 70% and 65% and; for combined sex, these were

88 % and 93 %, respectively. The greater uncertainty associated with female outcome likely results from low case counts; in total, 88, 44 and 70 female cases contributed to the analyses at 0 – 2 µg/L ; 2 – 5 µg/L and; > 5 µg/L As in well water, respectively, relative to 267, 144 and 249 male cases.

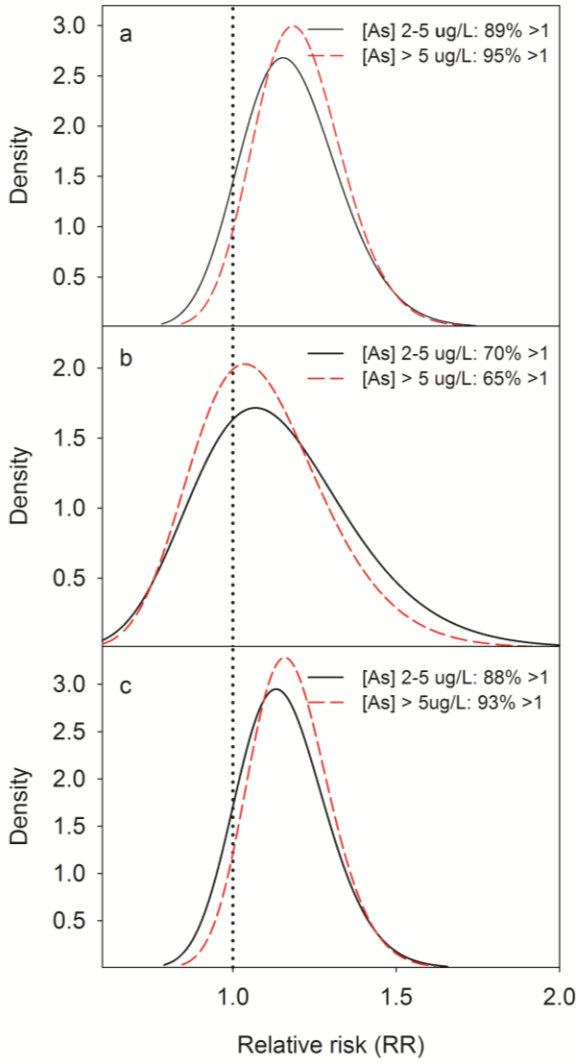


Figure 5.3 Distributions of the posterior means relative risk for bladder cancer in male (a), female (b) and combined sex (c) at different levels of arsenic exposure. The one-tailed inference of the RR > 1 is indicated.

Uncertainties associated with the predicted risk estimates can be visualized with exceedance probabilities, which are the probabilities that the risk in a location exceeds a given threshold, defined here at 10% above the risk that would be typical given the region's demographic structure. These probabilities are denoted as Pi(10%) = $Pr\{\lambda i >$ [1.1 exp($\mu + X_i\beta$)] | data}, or equivalently Pr[exp(U_i) >1.1|data]. Figure 5.4a shows exceedance probabilities for bladder cancer amongst males, with 24 locations having a probability P_i(10%) in excess of 80 %, and 3 locations having P_i(10 %) greater than 95 %. Estimated risk in these locations ranged between 1.44 – 2.16 and between 1.85 – 2.11, respectively. Exceedance probabilities for bladder cancer amongst females were mostly below 80% (Fig. 5.4b). Again, the fewer number of females diagnosed with bladder cancer compared to males, makes it more difficult to assess with certainty whether the risk at a given location is above threshold. In total, 6 locations showed exceedance probabilities for female risk above 80 % and in 1 location, that probability exceeded 95%. Estimated risk in those locations ranged between 1.58 – 3.05. Analyses based on males and females combined, showed 22 locations having a probability P_i(10%) in excess of 80 %, and 9 locations having P_i(10 %) greater than 95 % (Fig. 5.4c). Estimated risk in these locations, all of which located in southwestern NS, ranged between 1.58 – 2.59 and between 1.66 – 2.59, respectively. Over the 12 year-period, high risk areas (Pr[exp(U_i) >1.1|data > 80%) had about 173 % more cancer cases being diagnosed than what would be expected based on the age-sex distribution and social-material context of the population at these locations.

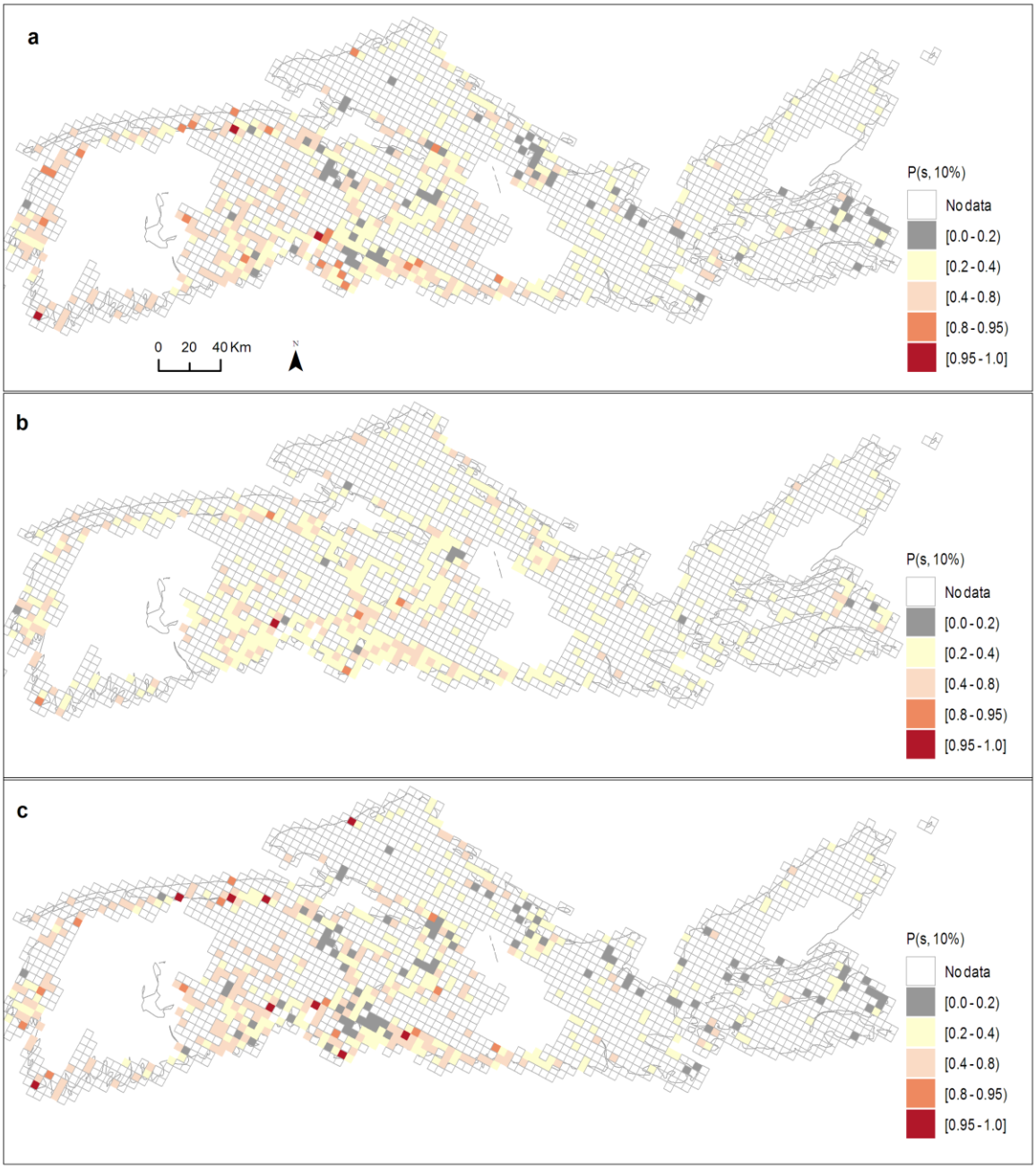


Figure 5.4 Exceedance probabilities ($P_i(10\%)$ for bladder cancer— male (a), female (b) and combined sex (c), Nova Scotia 1998-2010.

5.3.3 Arsenic Exposure and Kidney Cancer

Similar to bladder cancer, posterior summaries for regression and variance parameters confirmed that material and social deprivation did not significantly influence the estimated risk of kidney cancer (Table 5.3). The risk of developing kidney cancer as a result of being exposed to 2 – 5 µg/L and > 5 µg/L of As in drinking water, was respectively 10 % (1.10 [0.78 – 1.51]) and 15 % (1.15 [0.86– 1.51]) higher amongst males and; 5 % (1.05 [0.79 – 1.37]) and 14 % (1.14 [0.89 – 1.44]) for both sexes combined; relative to those exposed to < 2 µg/L. Females exposed to 2 – 5 µg/L of As in drinking water, showed no excess risk relative to the referent group (0.99 [0.66 – 1.43]; those exposed to > 5 µg/L, showed a statistically non-significant 10 % increase in risk (1.10 [0.79 – 1.51].

Table 5.3 Posterior summaries for regression and variance parameters[a] – Kidney cancer, Nova Scotia 1998-2010

Kidney Cancer	**Males**			**Females**			**Combined sex**		
Parameter	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**
Intercept	0.80	0.64	0.96	0.93	0.73	1.15	0.87	0.72	1.02
[As] 2 – 5 µg/L	1.10	0.78	1.51	0.99	0.66	1.43	1.05	0.79	1.37
[As] > 5 µg/L	1.15	0.86	1.51	1.10	0.79	1.51	1.14	0.89	1.44
Material deprivation	1.07	0.96	1.24	1.01	0.89	1.15	1.03	0.92	1.16
Social deprivation	1.02	0.86	1.16	1.08	0.92	1.22	1.05	0.92	1.16
Log-scale									
Spatial standard deviation	0.10	0.03	0.44	0.08	0.03	0.31	0.36	0.15	0.73
Unstructured standard deviation	0.38	0.20	0.60	0.16	0.03	1.04	0.33	0.17	0.59

[a] The 95% credible intervals represent two-tailed distributional inferences upon whether a risk is different from 1. A more appropriate inference is one tailed, whether the estimated risk is greater than 1.0. The latter are presented in Figure 5.

Using a one tailed inference based on the posterior distribution of the predicted risk, the results showed that 68 % of the probability density distribution in risk fell above 1.0 in males exposed to 2 – 5 µg/L and the value increased to 83 % at exposure > 5 µg/L (Fig.5.5a). Corresponding probability density distributions for females were lower, with a 45 % and 70 % probability of detecting a health effect in those exposed 2 – 5 µg/L and > 5 µg/L of arsenic in well drinking water, respectively (Fig. 5.5b). Again, as reported for bladder cancer, this greater uncertainty associated with female outcome may be due to low case counts. Pooling data from both sex, 61 % and 84 % of the probability density distribution in risk, fell above 1.0 in those exposed to 2 – 5 µg/L and > 5 µg/L, respectively (Fig.5.5c).

Maps of exceedance probabilities for predicted kidney cancer risk being at least 10% above the risk that would be typical given the region's demographic structure, were largely flat (Fig. 5.6a-c). For males, only one location showed a probability P_i(10%) in excess of 80 % for predicted risk being above the referent threshold (Fig.5. 6a). Uncertainties associated with the predicted risk estimates for females were even greater, with most locations showing a probability of exceedance below 40 % (Fig. 5.6b). Analyses based on combined sex showed 6 locations having a probability P_i(10%) in excess of 80 %, and 1 location having P_i(10 %) greater than 95 % (Fig. 6c). Estimated risk in these locations, 5 of which were located in southwestern NS, ranged between 1.64 – 1.97. Over the study period these high risk areas had, on average, about 259 % more cancer cases being diagnosed than what would be expected based on the age-sex distribution and social-material context of the population at these locations.

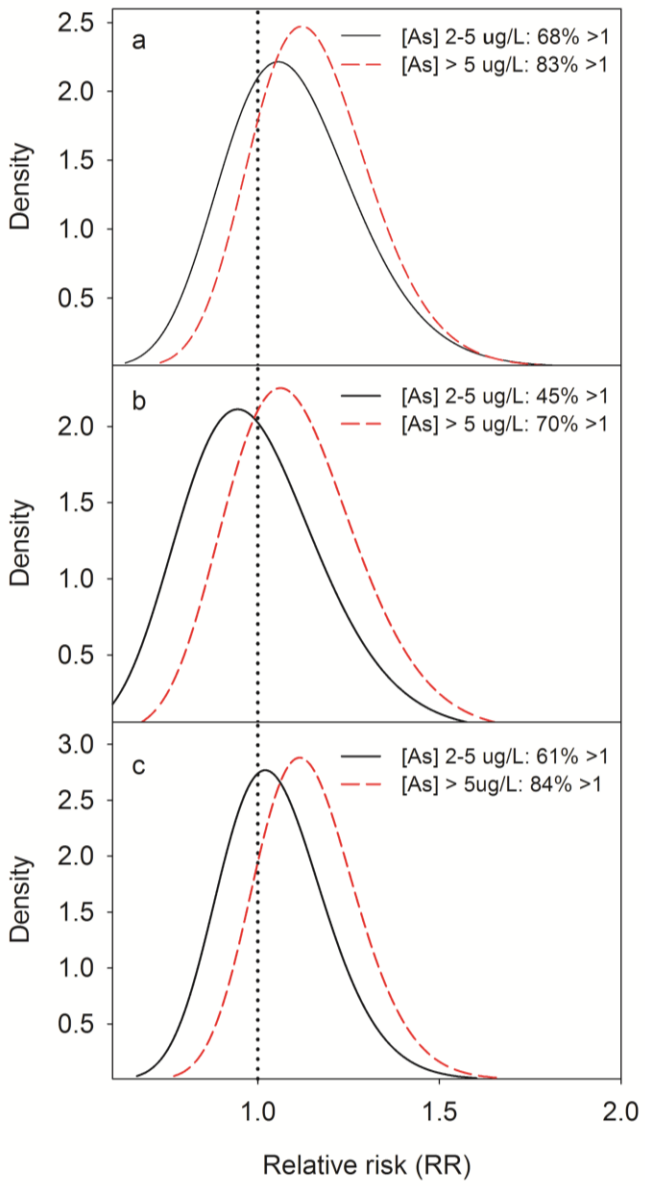


Figure 5.5 Distributions of the posterior means relative risk for kidney cancer in male (a), female (b) and combined sex (c) at different levels of arsenic exposure. The one-tailed inference of the RR > 1 is indicated.

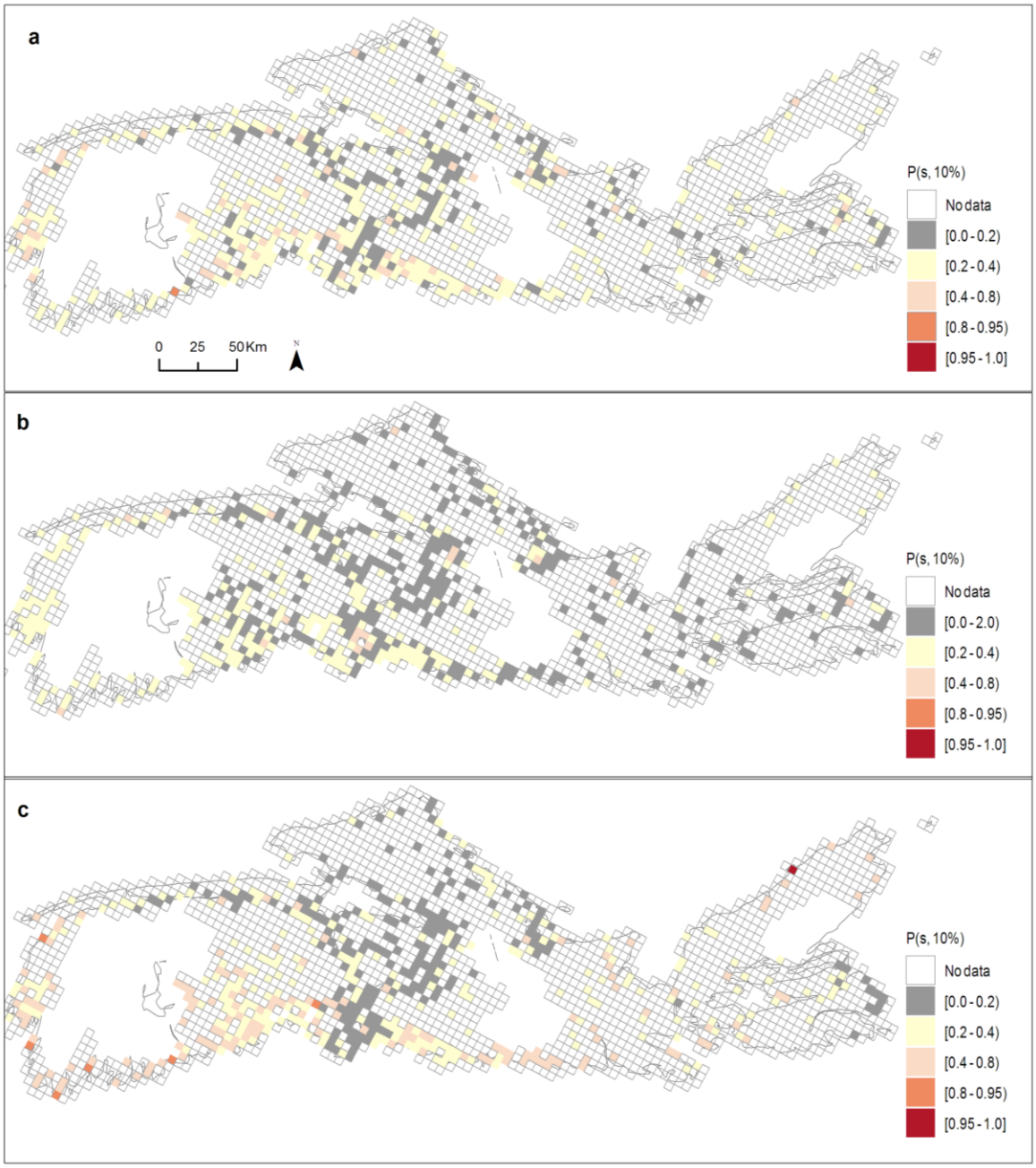


Figure 5.6 Exceedance probabilities ($P_i(10\%)$ for kidney cancer— male (a), female (b) and combined sex (c), Nova Scotia 1998-2010

5.4 Discussion

5.4.1 Summary of Findings

This study suggests that some of the excess incidence of bladder and kidney cancer in NS may be associated with living in rural areas where As levels in well water is around the current international guideline limit. People living in areas where As concentrations ranged between 2 – 5 µg/L were, on average, 16 % more likely to be diagnosed with bladder cancer; and 5% more likely to be diagnosed with kidney cancer than people living in areas where arsenic levels were below 2 µg/L. Those potentially exposed to As levels above 5 µg/L showed 18 % and 14 % excess risk for bladder and kidney cancer, respectively. For bladder cancer, there was an 88% and a 93% probability for the estimated risk to be greater than the risk of the referent population at levels between 2 – 5 µg/L and >5 µg/L. In males, these corresponding probabilities were slightly higher: 89 % and 95 %, respectively—suggesting evidence in support of an association between bladder cancer incidence and exposure to low-levels of As in drinking water. Probabilities for kidney cancer were lower, being 61 % and 87 % in those living in areas with well-As of 2 – 5 µg/L and 5 µg/L, respectively. Thus, the probability of an association between kidney cancer and As in drinking water was uncertain at levels < 5 µg/L, but findings did suggest a possible effect of similar magnitude than that observed for bladder cancer at levels above 5 µg/L. Considering that 27% of the well water samples had levels ≥5 µg/L approximately 115,000 Nova Scotians may draw water from a private well with As-levels exceeding 5 µg/L. For both cancer types stratified analyses by sex revealed slightly lower mean effect size and probabilities in females, a pattern likely attributable to low case counts which limits our ability to make inferences about

the presence or absence of effect. Finally, high risk areas detected in this study for bladder and kidney cancer were predominantly distributed in mainland southwestern NS, where the highest As levels were generally observed in well water and generally associated with the local geology (Dummer et al. 2015).

5.4.2 Global Context

Few studies report on the excess incidence of bladder or kidney cancer from exposure to As levels as low as those reported here. [60] and [61] are perhaps the only two studies with comparable exposure and measured outcome. At As levels > 0.5 µg/L, [60] report more than a doubling of bladder cancer risk (2.44 [1.11–5.37]) in a Finnish population. At As levels between 1–10 µg/L, [61], detect no excess risk (0.84 [0.63–1.12]) for an American population from Southeastern Michigan. Estimates obtained for NS are within these reported effect sizes (1.18 [0.95–1.44]). Assuming that the effect of As is additive to the background risk, risk of As-induced bladder cancer would be easier to detect in Finland than in the USA or Canada where the background risk is more than twice that of Finland (male standardized rates: 13, 33, 41 per 100,000 in Finland, Canada and USA, respectively; male:female: 4:1; [44, 62, 63].

Other studies, such as [27, 31] and, Ferreccio et al. [64], report effect sizes that also situate the NS estimates within a reasonable range. For smokers exposed to As-level of <11 µg/L, [64] report a risk of 4.1 [1.3–13]. For populations exposed to 10 µg/L of As in drinking water, Saint-Jacques et al. [27] report a risk of 1.4 [0.35–4.0] based on a meta-

analysis including 30 years of epidemiological studies. For an average long-term As exposure > 8.7 µg/L (for 40 years), Baris et al. [31] observed an increased risk of 1.49 [0.85–2.61]. Contextualizing our findings for kidney cancer is more difficult as, to our knowledge, there have been no studies reporting on the excess risk of kidney cancer incidence from exposure at lower As levels. The work of Mostafa and Cherry [65] report an effect size of 1.29 [0.86–1.91] at 10-50 µg/L, which is comparable to our finding (1.14 [0.89–1.44], As >5 µg/L).

5.4.3 Public Health Risk

As exposure is dependent on a specific population's lifestyle, location and dietary behaviors [66, 67]. From a public health perspective, the main concern for As is not so much its acute immediate toxicity; it is the carcinogenic properties and the long term health implications associated with prolonged exposure [67, 68]. Sauvé [68] suggests that the usual level of acceptable risk for carcinogens is 10^{-6}, a 1 in a million chance of getting a cancer in a lifetime. However, the excess cancer risk associated with lifetime As exposure above 10 µg/L is thought to be about 30 to 300 times higher than the cancer risks estimated for exposure to other known carcinogens in drinking water [12, 67–69]. While some studies fail to detect adverse health effects at levels of exposure around the 10 µg/L concentration level (e.g. [61, 70–74]), many recent studies suggest an increased risk of bladder [27, 31, 75], kidney [65], lung [40, 75], prostate [35] and skin cancers [37]; diabetes [32]; cardiovascular disease [38, 41]; inflammatory response and DNA damage [34], and neurobehavioral symptoms and depression [39] at the advisory limit level. Increase adult mortality due to a broad range of chronic diseases has also been

associated with long-term exposure to As levels in drinking water around the regulatory limit of 10 μg/L [33].

As is difficult to detect because it is tasteless, colorless, and odorless. Its short- and long-term impact on public health is also difficult measure, unless exposure levels are high. Early life exposure to As can lead to health effects that can be long lasting and latent for more than 50 years [67]. In addition, populations chronically exposed to As can experience As-induced health effects long after remediation [23, 76]. Elevated background risks associated with various health conditions in some populations, combined to exposure misclassification and inadequate sample sizes have been considerable stumbling blocks for the determination of a threshold for safe drinking water. However, as public health agencies pursue a safe, implementable and cost-effective regulatory limit for As in drinking water, people worldwide continue to be exposed to levels that are potentially harmful. Populations exposed to As through combined contaminant pathways, may further increase their health risk and in some populations. For example, Chou and colleagues [66] estimated that cooked rice contributed to 41% of iAs exposure risk in a Taiwanese population for which rice is a staple food source. Thus while the greatest threat to public health from As may originate from contaminated drinking water, exposure from other sources may be substantial, a concern that should be taken into account, when revisiting regulatory limits.

5.4.4 Strengths and Limitations

This study has some limitations. First, residential address at diagnosis was used as a surrogate for environmental exposure, a typical approach in spatial epidemiology due to the difficulty of obtaining complete residential history. However, when studying outcomes with long latencies, this can result in considerable non-differential exposure misclassification that may bias the estimated risks towards the null (see [77]). Also, digital boundaries of municipal drinking water supply zone (MWSZ) were used to determine water source, further contributing to possible misclassification. In fact, we estimated that 3 % of the cases in this study could have been incorrectly labeled as private well water user, based on information from a secondary dataset— the Atlantic Partnership for Tomorrow's Health project dataset (see [78]). In this dataset, 2.8 % of the participants reported drinking municipal water despite having a residential address outside the MWSZ. Second, this study used neighborhood social and material deprivation as a proxy for smoking prevalence and other lifestyle factors (e.g. obesity) because cancer registries do not routinely capture information unrelated to patient care. As a result, it is possible that relative risk estimates include residual confounding due to smoking. Third, the private well water data had georeferencing issues which resulted in a reduction in the spatial resolution of the exposure data and the use of mean As level at each unique well location, rather than the actual arsenic measurement of each individual well. In addition, these mean As values were further aggregated over a set of continuous 5 km square cells. Aggregating point data, such as well locations, over spatial units inevitably further reduced some of the variability inherent to the As measurements. However, this process allowed for increased spatial coverage and a more consistent representation of

environmental data. It also facilitated the combination of the various datasets utilized in this study. Alternatively, one could aggregate exposure data to match the census geography at which population and covariates information was available (i.e. DAs). However, DAs in rural NS vary in size, with some covering areas as large as 600 km^2. Aggregating mean As concentration over such large areas would likely over smooth the exposure dataset, and would not be representative of the distribution of As in the natural world. Fourth, given the ecological nature of the study, other correlates or combinations of factors with a similar distribution to that of As, could also in part explain the association reported. However, [42] showed that in NS, arsenic exposure from well water is a major contributor to arsenic body burden (measured in toenail clippings), suggesting that the spatial distribution of arsenic concentrations in well water is a reasonable approximate indicator of arsenic exposure in the population (see also [78]). Finally, some areas were sparsely populated, reducing statistical power; an important limitation of the study that impacted the analyses stratified by sex.

Nonetheless, this study has important strengths. First, it uses cancer incidence data from a population-based cancer registry adhering to registration standards of both the Canadian Cancer Registry and the North American Association of Central Cancer Registries. Those standards allow for consistency in disease coding over time and, ensure case ascertainment and completeness through a network of activities including automated and manual edit processes, record linkages and data audits. In addition, the systematic collection of spatial information at time of diagnosis enabled 100 % of cases to be successfully geo-referenced with a high degree of certainty, thus minimizing location

misclassification (~ 85 % exact location). Second, the inclusion of a spatial random effect in the model yields 95% intervals for the effect sizes which fully reflect the uncertainty induced by any spatial dependence in the data. Modelling case counts with a standard Poisson regression would have resulted in a high likelihood of declaring the effect of As was statistically significant even if As had no influence on cancer incidence (see [79]). Third, the exceedance probability rule, $P_i(10\ \%) > 0.8$ used here to classify spatial risk has high specificity even when data are sparse, further reducing the risk of false alarms, although perhaps increasing the likelihood of declaring an area as having an average risk when in fact its underlying true rate is elevated relative to background levels.

Finally, in the BYM, spatial dependence is a function of boundaries rather than distance. This is problematic in rural settings, where neighbours can be large geographic units that are far apart, and so exposed to diverse potential causative agents. The use of a relatively fine grid as the unit of geography helped to more accurately parameterize the influence of such factors, which ultimately improves our ability to discriminate localized risk estimates, relative to a traditional BYM.

5.5 Conclusions

As is a widely recognized carcinogen. Some studies suggest that As has a dose threshold below which exposures are not harmful; others suggest this threshold may not exist, such that any exposure, no matter how small, could induce a broad range of health effects [12, 68, 69]. This study supports the presence of cancer effects at levels of exposures below current regulatory limits. We estimate that even in a Canadian province with a population pool just under 1 million, about 115,000 people may be at increased risk of bladder and

possibly kidney cancer as a result of living in areas where As-levels in drinking water wells exceed 5 µg/L. Findings also suggest an increased risk of bladder cancer at levels below 5 µg/L, further raising the number of people at risk of cancer in the province. The work sheds light on some of the possible causes for the excess burden of urinary cancers reported in Nova Scotia. In a broader context, the findings also argue the need for future studies to investigate other health outcomes in relation to As exposure in NS and elsewhere, where comparable As-levels may be found.

Protecting against low-level exposure can, however, be challenging, costly, and in some cases unattainable and impractical. The results from this project contribute to the international body of evidence suggesting a reassessment of current advisory limits for maximum allowable concentrations of As in drinking water. Given the large number of people likely exposed to As at the lower range of concentrations in Canada and throughout the world, health risk reduction resulting from lowering these guidelines could be substantial. Findings from this research support health and environmental policies for safe drinking water and water security so as to protect the health of the individual. Findings also inform the public on the potential risks of well water supplies and help guide the development of risk reduction strategies to prevent cancer.

5.6 Abbreviations

As: arsenic; BYM: Besag York and Mollié; CB: Cape Breton; NS: Nova Scotia; UTC: urinary tract cancer.

5.7 Competing Interests

The authors declare that they have no competing interests.

5.8 Acknowledgement

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CHAPTER 6— Conclusions

Arsenic is a Class I carcinogen contaminating water supplies in many parts of the world via its natural occurrence in the earth's crust. It is a contaminant of key concern for public health agencies not only because of its widespread occurrence, but also due to its intrinsic characteristics that can accentuate exposure risk and make risk identification and remediation challenging; i.e.arsenic is colorless, tasteless and cannot be detected through smell. In acute doses, it has been known to be poisonous throughout history; in high doses, it has plagued the health of hundreds of millions of people worldwide via its occurrence in drinking water and, in some areas, food sources; in low doses, it has been at the centre of a global debate. Some studies suggest that arsenic in drinking water has a dose threshold below which exposures are not harmful; others suggest that regardless of the level, arsenic is a carcinogen that impacts health and thus, should be avoided.

The systematic review of 30 years of epidemiological studies and meta-analyses included in this thesis provided evidence in support of a causal association between exposure to high levels of arsenic in drinking-water and the risk of developing or dying from bladder cancer. Evidence in support of a causal association and dose-response relationship, while mostly derived from ecological, case-control and cohort studies of Taiwanese populations chronically exposed to high-levels of arsenic in well water sources, were also confirmed in other regions of the world. In fact, overall findings suggest a causal association between exposure to high levels of arsenic in drinking water and bladder cancer, as defined by the Bradford-Hill criteria and based on evidence of temporality between exposure and outcome; strength and consistency of associations reported; a dose-response

relationship and biological plausibility. The review also provided evidence of an increased risk of dying from kidney cancer as a result of being exposed to high-levels of As in drinking water; however, studies reporting on incidence were too few to take a definite stance. Associations at low-levels of exposure were inconsistent for both bladder and kidney cancer.

The work presented here combined a range of datasets and methodologies to estimate the risk of developing urinary tract cancer in a region where typical arsenic concentrations in well water fall within the lower-level range (i.e. around the current MAC) where health effects have yet to be quantified in a consistent manner. The findings provided evidence in support of carcinogenic effects at lower-levels of As exposure, levels below current regulatory limits. First, based on the predicted risks for bladder cancer incidence data of studies included in the meta-analyses presented in Chapter 2, it was estimated that exposure to 10 or 50 μg/L of arsenic in drinking water may increase the risk of bladder cancer by at least 40% and 130%, respectively. Second, the analyses revealed that high risk areas for bladder and kidney cancer in Nova Scotia— a province with historically high rates, are distributed in a region where high arsenic levels in well water have been observed and generally associated with the local geology. Third, the findings demonstrated that in Nova Scotia, exposure to 2–5 μg/L and >5 μg/L of As in drinking well water may on average, increase the risk of bladder cancer by 16% and 18%, respectively and; similarly, the risk of kidney cancer by 5% and 14%, respectively— effect sizes consistent with the predicted risk estimated from the randomization method presented in Chapter 2.

The work has some limitations, with exposure misclassification being central given the generally long latencies between exposure and disease onset and the ecological design of the study. Nonetheless, overall, the findings suggested the presence of health effects at levels of exposures below the current international guideline limit of 10 μg/L. It also suggested that in Nova Scotia alone, an approximate 115,000 people may be at an increased risk of developing cancer as a result of living in areas where arsenic levels in wells are near 10 μg/L, shedding light on some of the possible causes for the excess burden of urinary cancers reported in this province. In a broader context, findings from this thesis contribute to the international body of evidence suggesting the need for a reassessment of the advisory limits for maximum allowable concentrations of arsenic in drinking water. Given the large number of people likely exposed to arsenic at the lower range of concentrations in Canada and indeed, throughout the world, health risk reduction resulting from lowering the existing guidelines, could be substantial.

In Nova Scotia, deficits in public risk knowledge about well water safety have been reported despite elevated levels of arsenic in groundwater having been documentated for at least 40 years in the province. The onus on Canada's private well owners to ‘regulate’ their own drinking water supply has been shown to be largely ineffective to ensure safe drinking water and protect public health. The results presented here show a high probability for unregulated private well water in Nova Scotia to be associated with increased cancer risk. Regulatory interventions by government and environmental agencies need to be addressed and a shift from a traditional individual-based water

monitoring approaches to a collective community and institutional- based model should be developed and adopted.

The work presented here supports health and environmental policies for safe drinking water and water security so as to protect the individual health. Findings from this research can inform the public on the potential health risks associated with contaminated well water supplies. They can also guide the development of risk reduction strategies to prevent cancer and other arsenic-induced chronic illnesses. Finally, the portfolio of methodological approaches developed in this thesis and used to quantify arsenic-induced cancer from water source, provide a flexible framework that is transferable to other jurisdictions, health outcomes and environmental stressors—including those impacting water and air quality. Overall, it has the potential for further promoting collaborative and interdisciplinary research and supporting public health, locally and globally.

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APPENDIX A — Research Ethics Board Approval

Reply Reply All Forward

Annual Renewal - Letter of Approval - NSHA REB ROMEO FILE #: 1020416

Trenholm, Pamela

To: Dr. Louise Parker (Principal Investigator) [louise.parker@dal.ca]

Cc: Dummer, Trevor; Mr. David Thompson (Administrative Coordinator) [david.thompson@dal.ca]; Mr. Tyler Kinch (Administrative Coordinator) [tylerkinch@dal.ca]; Trenholm, Pamela

Nova Scotia Health Authority Research Ethics Board
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March 11, 2016

Dr. Louise Parker
IWK Health Centre
Population Cancer Research Program Dalhousie University 1494 Carlton Street PO Box 15000 Halifax NS B3H 4R2
Dear Dr. Parker:

RE: Arsenic and cancer risk in Nova Scotia

NSHA REB ROMEO FILE #: 1020416

Your request for Annual Approval has been reviewed by an assigned Co-Chair and on behalf of the Nova Scotia Health Authority Research Ethics Board (NSHA REB), I am pleased to confirm the Board's approval to continue this project up to the expiry date, March 11, 2017.

Sincerely,

Dr. Richard Hall, Executive Chair

This statement is in lieu of Health Canada's Research Ethics Board Attestation:
The Research Ethics Board for the Nova Scotia Health Authority operates in accordance with:
- Food and Drug Regulations, Division 5 "Drugs for Clinical Trials Involving Human Subjects"
- Natural Health Products Regulations, Part 4 "Clinical Trials Involving Human Subjects"
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)
- ICH Good Clinical Practice: Consolidated Guideline (ICH-E6)