Environmental Research 159 (2017) 338–343

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

# Low-level arsenic exposure from drinking water is associated with prostate cancer in Iowa

Taehyun Roh[a], Charles F. Lynch[b], Peter Weyer[c], Kai Wang[d], Kevin M. Kelly[e], Gabriele Ludewig[a,e,*]

[a] Interdisciplinary Graduate Program in Human Toxicology, University of Iowa, Iowa City, IA 52242, United States
[b] Department of Epidemiology, University of Iowa, Iowa City, IA 52242, United States
[c] Center for Health Effects of Environmental Contamination, University of Iowa, Iowa City, IA 52242, United States
[d] Department of Biostatistics, University of Iowa, Iowa City, IA 52242, United States
[e] Department of Occupational and Environmental Health, University of Iowa, Iowa City, IA 52242, United States

ARTICLE INFO

*Keywords:*
Arsenic
Prostate cancer
Drinking water
Iowa
Private well water

ABSTRACT

Inorganic arsenic is a toxic naturally occurring element in soil and water in many regions of the US including the Midwest. Prostate cancer is the second most common type of cancer in men in Iowa, surpassed only by non-melanotic skin cancer. Epidemiology studies have evaluated arsenic exposure from drinking water and prostate cancer, but most have focused on high-level exposures outside the US. As drinking water from groundwater sources is a major source of arsenic exposure, we conducted an ecologic study to evaluate prostate cancer and arsenic in drinking water from public water sources and private wells in Iowa, where exposure levels are low, but duration of exposure can be long.

Arsenic data from public water systems were obtained from the Iowa Safe Drinking Water Information System for the years 1994–2003 and for private wells from two Iowa Well Water Studies, the Iowa Community Private Well Study (ICPWS, 2002–2003) and Iowa Statewide Rural Well Water Survey Phase 2 (SWIRL2, 2006–2008) that provided data for 87 Iowa counties. Prostate cancer incidence data from 2009 to 2013 for Iowa were obtained from Surveillance, Epidemiology and End Results' SEER*Stat software. County averages of water arsenic levels varied from 1.08 to 18.6 ppb, with three counties above the current 10 ppb limit. Based on the tertiles of arsenic levels, counties were divided into three groups: low (1.08–2.06 ppb), medium (2.07–2.98 ppb), and high (2.99–18.6 ppb).

Spatial Poisson regression modeling was conducted to estimate the risk ratios (RR) of prostate cancer by tertiles of arsenic level at a county level, adjusted for demographic and risk factors. The RR of prostate cancer were 1.23 (95% CI, 1.16–1.30) and 1.28 (95% CI, 1.21–1.35) in the medium and high groups, respectively, compared to the low group after adjusting for risk factors. The RR increased to 1.36 (95% CI, 1.28–1.45) in the high group when analyses were restricted to aggressive prostate cancers (Gleason score ≥ 7). This study shows a significant dose-dependent association between low-level arsenic exposure and prostate cancer, and if this result is replicated in future individual-level studies, may suggest that 10 ppb is not protective for human health.

## 1. Introduction

Arsenic is a naturally occurring element in the earth's crust and has anthropogenic uses, including wood treatment, pigments, and semiconductor processing (IARC, 2009). The primary source of arsenic exposure is drinking water (Chung et al., 2014; Smith et al., 1992). In the Midwest of the United States including Northern Iowa, soils, composed of glacial sediments that migrated 16,000–12,000 years ago during the late Wisconsin-aged glacial drift, contain higher concentrations of arsenic (Erickson and Barnes, 2005). Arsenic easily migrates from contaminated soil into ground water depending on geochemical conditions (Erickson and Barnes, 2005; Michael, 2013). Public water systems are regulated with a current drinking water standard for arsenic at 10 ppb under the Safe Drinking Water Act (EPA, 2009), but private wells are not regulated or monitored.

Arsenic is classified as a group 1 carcinogen by IARC as there are sufficient experimental and epidemiologic studies supporting causation of skin, bladder, and lung cancers (IARC, 2009). As summarized in the

* Correspondence to: Dept. Occupational & Environmental Health, The University of Iowa, 100 UI Research Park, IREH, Iowa City, IA 52242-5000, United States.
*E-mail address:* gabriele-ludewig@uiowa.edu (G. Ludewig).

http://dx.doi.org/10.1016/j.envres.2017.08.026
Received 7 June 2017; Received in revised form 24 July 2017; Accepted 12 August 2017

IARC monograph, potential mechanisms of arsenic carcinogenesis may be through oxidative DNA damage, gene amplification, aneuploidization (by spindle disturbance), inhibition of DNA repair enzymes, and changes in DNA methylation and histone modifications, leading to altered gene expressions and changes in cell differentiation, proliferation, and response to signaling pathways (IARC, 2009). Prostate cancer has also been reported to be positively associated with arsenic exposure (IARC, 2009). Several epidemiologic studies of populations in Taiwan, Australia, Europe, Chile or the US reported increasing mortality or incidence of prostate cancer with arsenic exposure (Bardach et al., 2015; Brown et al., 2002; Bulka et al., 2016; Chen and Wang, 1990; Chen et al., 1988; Garcia-Esquinas et al., 2013; Gunduz et al., 2015; Hinwood et al., 1999; Lewis et al., 1999; Nunez et al., 2016; Rivara et al., 1997; Wu et al., 1989; Yang et al., 2008). Some measured arsenic levels in urine (Garcia-Esquinas et al., 2013) or levels in top soil (Nunez et al., 2016), but the majority focused on drinking water as source of arsenic exposure. Of these, most evaluated the association of high-level arsenic exposure and prostate cancer and all observed a positive association. For example, prostate cancer mortality was found to increase with exposure to arsenic up to 2500 ppb in Taiwan (Yang et al., 2008). Reports on the effects of low-level arsenic exposure on prostate cancer are sparse. One study from Denmark did not observe an association of low-level arsenic (0.05–25.5 ppb, mean 1.2 ppb) and prostate cancer (Baastrup et al., 2008). One recent ecologic study reported on the effect of low-level arsenic exposure and showed a 5–10% increased incidence of prostate cancer from arsenic exposure in a dose-response manner in Illinois counties with arsenic levels ranging from 0.33 to 16.23 ppb in public drinking water (Bulka et al., 2016). This finding and the fact that prostate cancer has the highest cancer incidence in men in the US (excluding non-melanotic skin cancer) (Brawley, 2012; IARC, 2009), justifies further analysis of the risks of low-level arsenic exposure from drinking water and prostate cancer. We therefore conducted an ecologic study to investigate the association between low-level arsenic exposure from drinking water and the incidence of prostate cancer in Iowa, accounting for both public water sources and private water wells as source of drinking water.

## 2. Methods

### 2.1. Arsenic exposure data

Arsenic testing data from 1994 to 2003 from 723 public water systems in 97 of the 99 Iowa counties were obtained from the Iowa Safe Drinking Water Information System. Two counties were excluded because they did not have their own public water stations and therefore county-specific arsenic data were not available. Two different studies, the Iowa Community Private Well Study (ICPWS, 2002–2003) and the Iowa Statewide Rural Well Water Survey Phase 2 (SWRL2, 2006–2008), with water samples analyzed by the Iowa State Hygienic Laboratory, were combined and provided arsenic concentration data in water samples from 709 private wells in 89 counties (CHEEC, 2009; IDNR, 2004). In the ICPWS, 103 wells were randomly selected from 50 counties, and 133 wells were selected from 15 counties with assumed higher risk of contamination. In SWRL2, 116 wells, which were included in the original SWRL (1988–1989) study and still active currently, and additional 357 randomly selected wells were sampled (https://cheec.uiowa.edu/swrl2). Although the period of the Iowa Statewide Rural Well Water Survey was outside the 1994–2003 period, it was utilized in this study because a temporal stability of arsenic levels in ground water has been reported in studies from Argentina and Nevada (Concha et al., 2006; Steinmaus et al., 2005). All datasets were obtained from the Center for Health Effects of Environmental Contamination at the University of Iowa (https://cheec.uiowa.edu/cooperative-projects). There were no active private wells and therefore no well water data in 10 counties. Thus arsenic data for both public water systems and private wells were available for 87 of the 99 counties in Iowa. County arsenic levels in the drinking water were calculated from average arsenic levels in both municipal water and private well water with weighting by the percentages of county populations who use municipal water and private well water. If the concentration was lower than the limit of detection (LOD), half of LOD was assigned as the level (Lopez-Carrillo et al., 2010). LODs were 1 ppb for private wells, and varied from 0.01 to 10 ppb for public water systems. Iowa counties were categorized into three groups by tertiles of average arsenic level in the drinking water: low exposure (1.08–2.06 ppb), medium exposure (2.07–2.98 ppb), and high exposure groups (2.99–18.6 ppb).

**Table 1**
Prostate cancer cases and average annual population for 2009–2013 for white males by age group.

| Age group In years | Number of cases[a] (%) | Annual average population[b] (%) |
|---|---|---|
| 30–39 | 3 (0.003) | 171,826 (20.3) |
| 40–49 | 143 (1.43) | 186,727 (22.1) |
| 50–59 | 1966 (19.8) | 207,248 (24.5) |
| 60–69 | 4019 (40.4) | 146,164 (17.3) |
| 70–79 | 2624 (26.4) | 82,276 (9.7) |
| 80+ | 1192 (12.0) | 51,523 (6.1) |
| Total | 9947 (100.0) | 845,764 (100.0) |

[a] All newly diagnosed prostate cancer cases in Iowa for 2009–2013 were included.
[b] Population of white men in Iowa for 2009–2013 was obtained from SEER*Stat software and is based on U.S. Census estimates, and an average annual population was calculated.

### 2.2. Prostate cancer incidence data

Data of all new prostate cancer cases in the state of Iowa between 2009 and 2013 were obtained from the Surveillance, Epidemiology, and End Results (SEER) program via SEER*Stat version 8.3. This database provided the number of observed cases and the population distribution by age-specific categories for each county (Table 1). As people of other races accounted for 5.5% of population in Iowa, they were excluded and only white males were included in this study. Aggressive prostate cancer was identified as distant stage at diagnosis and/or poorly differentiated (Gleason score $\geq$ 7) or undifferentiated tumor grades using this software.

### 2.3. Covariates data

Percentages of the population that obtain their drinking water from a public water system or private well by county were obtained from Water Use Data for the Nation as part of National Water Information System (NWIS) for 1995 and 2000. Poverty rate for 2009–2013 was obtained from the Small Area Income and Poverty Estimates (SAIPE) of the Census Bureau and used as a proxy measure for socioeconomic status, which is related to cancer patterns (Singh et al., 2003). Poverty rate indicates the percentage of population below the federal poverty level based on household size and income (Proctor et al., 2016). Information on general cancer risk factors, including tobacco smoking rate (current smoker), binge drinking rate (5 or more drinks an occasion during the past 30 days), and obesity rate (BMI $\geq$ 30) in each county for 1997–2013 was acquired from the Iowa Behavioral Risk Factor Surveillance System (BRFSS) through a research agreement with the Iowa Department of Public Health (Park et al., 2006; Samanic et al., 2004; Thun et al., 1997; Yun et al., 2005). These data were also restricted to the white male population at the county level. In addition, county-level pesticide-use density was included as a proxy of pesticide exposure (Reynolds et al., 2005), calculated by annual pesticide use divided by land area. Pesticide use data and county land area were obtained from the U.S. Geologic Survey and U.S. Department of Agriculture (USDA, 2004; USGS, 2017).