Lung Cancer in a U.S. Population with Low to Moderate Arsenic Exposure

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Background: Little is known about the carcinogenic potential of arsenic in areas with low to moderate concentrations of arsenic (< 100 μg/L) in drinking water.

Objectives: We examined associations between arsenic and lung cancer.

Methods: A population-based case–control study of primary incident lung cancer was conducted in 10 counties in two U.S. states, New Hampshire and Vermont. The study included 223 lung cancer cases and 238 controls, each of whom provided toenail clippings for arsenic exposure measurement by inductively coupled–plasma mass spectrometry. We estimated odds ratios (ORs) of the association between arsenic exposure and lung cancer using unconditional logistic regression with adjustment for potential confounders (age, sex, race/ethnicity, smoking pack-years, education, body mass index, fish servings per week, and toenail selenium level).

Results: Arsenic exposure was associated with small-cell and squamous-cell carcinoma of the lung [OR = 2.75; 95% confidence interval (CI), 1.00–7.57] for toenail arsenic concentration ≥ 0.114 μg/g, versus < 0.05 μg/g. A history of lung disease (bronchitis, chronic obstructive pulmonary disease, or fibrosis) was positively associated with lung cancer (OR = 2.86; 95% CI, 1.39–5.91). We also observed an elevated risk of lung cancer among participants with a history of lung disease and toenail arsenic ≥ 0.05 μg/g (OR = 4.78; 95% CI, 1.87–12.2) than among individuals with low toenail arsenic and no history of lung disease.

Conclusion: Although this study supports the possibility of an increased risk of specific lung cancer histologic types at lower levels of arsenic exposure, we recommend large-scale population-based studies.

Key words: arsenic, bronchitis, chronic obstructive pulmonary disease, lung cancer, lung disease, New Hampshire, pulmonary fibrosis, small-cell carcinoma, smoking, Vermont. *Environ Health Perspect* 117:1718–1723 (2009). doi:10.1289/ehp.0900566 available via *http://dx.doi.org/* [Online 2 July 2009]

Arsenic in drinking water is a major environmental carcinogen. Worldwide, millions of people suffer debilitating health effects from inorganic arsenic exposure, including cancer and vascular, pulmonary, hematologic, neurologic, and developmental disorders [Heck et al. 2008a; International Agency for Research on Cancer (IARC) 2004]. In the United States, an estimated 13 million people are exposed to arsenic concentrations that exceed the U.S. Environmental Protection Agency's (EPA) maximum contaminant level of 10 ppb (U.S. EPA 2001).

An increase in the incidence of skin, bladder, and lung cancers at high arsenic concentrations is well established (IARC 2004). However, the cancer risk from exposure to lower levels (< 100 μg/L) of arsenic is largely unknown. The results from other studies have been inconsistent (Ahsan et al. 2000; Chen et al. 2004; Ferreccio et al. 1998; Karagas et al. 2001, 2002; Lamm et al. 2004; Lewis et al. 1999), perhaps due, in part, to exposure variation in settings where people have access to noncontaminated water sources. Inconsistencies in results may also be related to a lack of information on individual cofactors, such as smoking or relevant health conditions, or to regional differences in factors associated with arsenic susceptibility, such as nutrition (Heck et al. 2007, 2009).

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide. IARC (2004) has classified arsenic as a group 1 carcinogen for lung cancer (IARC 2004). This assessment was based on studies in which arsenic exposure was inferred by using area of residence or the arsenic concentration the in well water rather than using an individual biomarker of exposure (Chen et al.1985, 1986, 1988a, 1988b; Chen and Wang 1990; Chiou et al. 1995; Ferreccio et al. 2000; Hinwood et al. 1999; Hopenhayn-Rich et al. 1998; Lewis et al. 1999; Nakadaira et al. 2002; Rivara et al. 1997; Smith et al. 1998; Tsai et al. 1999; Tsuda et al. 1995; Wu et al. 1989). The studies not included in the IARC evaluation and those that have been published since also have been based on local or regional well-water concentrations (Baastrup et al. 2008; Chen et al. 2004; Ferreccio et al. 1998; Guo 2004; Han et al. 2008; Marshall et al. 2007; Mostafa et al. 2008; Smith et al. 2006).

The use of a biomarker of arsenic exposure may help to improve the assessment of low-dose health effects, including cancer incidence (Karagas et al. 2002). Trivalent inorganic arsenic binds to the sulfhydryl groups in nail keratin cells and thus makes toenail arsenic a reasonable measure of arsenic exposure. Depending on the toe and the speed of nail growth, toenail measurements represent exposures that occurred 3–12 months before sample collection. This finding has been found to be relatively stable over time (Garland et al. 1993). In this study, we used toenail arsenic concentration as a biomarker of exposure to examine the risk of lung cancer among persons in the U.S. population who had been exposed to low levels of arsenic in drinking water.

Materials and Methods

The New England Lung Cancer Study (NELCS), a population-based case–control study of lung cancer, was conducted in seven New Hampshire counties (Belknap, Carroll, Cheshire, Coos, Grafton, Merrimack, and Sullivan) and in three Vermont counties (Orange, Windham, and Windsor). We used the New Hampshire State Cancer Registry, the Dartmouth-Hitchcock Tumor Registry of the Norris Cotton Cancer Center, and the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire, to identify persons from 2005 to 2007 who had received a clinical diagnosis of lung cancer. We obtained the names of cases within 1 to 6 months of their initial diagnosis. Cases who had histologically confirmed primary incident lung cancer (World Health Organization 2000),

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We thank all participants in the New England Lung Cancer Study, the study staff (S. Akacem, O. Akinbobola, and A. Swoyer), the New Hampshire State Cancer Registry (J. Rees and B. Riddle), and the Dartmouth-Hitchcock Tumor Registry. We also thank J. Wakefield for his assistance.

This research was supported by P20RR018787 from the National Center for Research Resources, National Institutes of Health (NIH), and in part by P42ES007373 from the National Institute of Environmental Health Sciences, NIH.

The authors declare they have no competing financial interests.

Received 13 January 2009; accepted 2 July 2009.