Skin Cancer Risk in Relation to Toenail Arsenic Concentrations in a US Population-based Case-Control Study

Margaret R. Karagas,1,2 Therese A. Stukel,1,2 J. Steven Morris,3 Tor D. Tosteson,1,2 Julia E. Weiss,1,2 Steven K. Spencer,2,4 and E. Robert Greenberg1,2,4

Arsenic is a known carcinogen specifically linked to skin cancer occurrence in regions with highly contaminated drinking water or in individuals who took arsenic-containing medicines. Presently, it is unknown whether such effects occur at environmental levels found in the United States. To address this question, the authors used data collected on 587 basal cell and 284 squamous cell skin cancer cases and 524 controls interviewed as part of a case-control study conducted in New Hampshire between 1993 and 1996. Arsenic was determined in toenail clippings using instrumental neutron activation analysis. The odds ratios for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) were close to unity in all but the highest category. Among individuals with toenail arsenic concentrations above the 97th percentile, the adjusted odds ratios were 2.07 (95% confidence interval (CI): 0.92, 4.66) for SCC and 1.44 (95% CI: 0.74, 2.81) for BCC, compared with those with concentrations at or below the median. While the risks of SCC and BCC did not appear elevated at the toenail arsenic concentrations detected in most study subjects, the authors cannot exclude the possibility of a dose-related increase at the highest levels of exposure experienced in the New Hampshire population. Am J Epidemiol 2001;153:559–65.

Arsenic, a ubiquitous metalloid element, is a known human carcinogen and is specifically linked to skin cancer occurrence at high levels of exposure (1, 2). Epidemiologic data regarding drinking water arsenic and skin cancer have come largely from a region in the southwest of Taiwan that had well water arsenic concentrations as high as 1,220 µg/liter (3). In a household survey, skin cancer prevalence was about eight times higher in villages with a median drinking water concentration of 800 µg/liter compared with those with a median concentration of 170 µg/liter (3). In the United States, the maximum contaminant level for arsenic in public drinking water permitted by the Environmental Protection Agency was 50 µg/liter. This level is several times lower than the reference category in the Taiwanese study. Risk assessment models have relied on low-dose extrapolation of the Taiwanese data, and later analyses indicate an excess cancer risk below the current maximal contaminant level (4). In the absence of direct data, the shape of the dose-response curve at the lower end of the exposure range remains speculative. Yet, because of accumulating data on the health effects of arsenic, the US Environmental Protection Agency recently reduced the maximal contaminant level to 10 µg/liter, half a magnitude lower than the previous standard (5).

Prior epidemiologic studies in the United States have found no relation between skin cancer and drinking water arsenic concentrations (6–9); however, these studies involved ecologic analyses using geographic areas with widely varying arsenic levels or included too few subjects to detect small elevations in risk. Studies based on skin cancer mortality (10) were possibly inconclusive because non-melanoma skin cancer is rarely fatal. Arsenic concentrations in toenails, which presumably reflect body burden from all sources of exposure, correlate with arsenic concentrations found in drinking water in areas with high arsenic levels (11, 12). In areas with low water levels of arsenic, however, other sources of exposure (i.e., food or occupation) may be more important (12); thus, in such areas, substantial misclassification could result from an exposure measure based on water concentrations alone. As part of a US population-based case-control study of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, an assessment was made of the risks of these malignancies in relation to arsenic concentrations measured in individual toenail clipping samples.
MATERIALS AND METHODS

Study group

A detailed account of the study design appears elsewhere (13). Briefly, we enlisted the collaboration of dermatologists and pathology laboratories throughout New Hampshire and bordering regions to identify cases of BCC and SCC (14). We selected for interview a sample of BCC and all cases of invasive SCCs diagnosed among New Hampshire residents, aged 25–74 years, from July 1, 1993, to June 30, 1995, identified through our survey by March 1996. In this age group and diagnostic period, there was an almost 4/1 BCC/SCC ratio. For efficiency, we chose a 2/1 BCC/SCC ratio of cases and randomly sampled according to the age and sex distribution of the total identified cases of BCCs to ensure that the subset would be representative of the population of BCC cases at large. To be eligible for the study, subjects were required to have a listed telephone number and to speak English. We sought physician consent before contacting eligible BCC and SCC patients. Of the 882 BCC and 471 SCC cases initially selected, 16 percent lacked a listed telephone number. We sought physician consent before contacting eligible BCC and SCC patients. Of the 882 BCC and 471 SCC cases initially selected, 16 percent lacked a listed telephone number. We attempted to obtain an equal number of controls to BCC cases (or a 2/1 ratio to SCC cases). For interviewing purposes, controls were randomly assigned a comparable telephone number, and sex to the combined distribution of the SCC and BCC cases. To select controls for cases aged less than 65 years, we used population lists obtained annually from the New Hampshire Department of Transportation. The file contains the names and addresses of those holding a valid driver’s license for the state of New Hampshire. We selected controls for cases aged 65 years and older from data files provided annually by the Health Care Financing Administration’s Medicare Program. The method of control selection in our study has been successfully used in other case-control studies conducted in the region (15).

We attempted to obtain an equal number of controls to BCC cases (or a 2/1 ratio to SCC cases). For interviewing purposes, controls were randomly assigned a comparable reference number that did not disclose to the interviewers. To ensure consistent quality of the study interviewer, interviews were tape recorded with the consent of the participants and routinely monitored by the interviewer supervisor (<1 percent of participants refused to be taped). To assess comparability of cases and controls, we asked subjects if they currently held a driver’s license or a Medicare enrollment card.

Personal interview

Beginning in January 1994, we sent an introductory letter to potential cases and controls explaining the general purpose of the study and that an interviewer would soon telephone. Those who agreed to take part underwent a detailed in-person interview, usually at their home. Questions covered sociodemographic information (including level of education), use of tobacco, and medical history (including previous radiotherapy) prior to the reference date. Participants were queried about their skin sensitivity to the sun after first exposure in the summer and after prolonged exposure (i.e., tendency to sunburn).

Questions relating to household water supply included type of water source used in their current residence (e.g., private well vs. public water), years of use of their current water system, and use of water filters. For private, domestic systems, we asked whether the water source was a dug/surficial well, spring, or deep/artesian well. We further asked the average number of glasses of water they consumed each day from the household water system. In 1995, we began collecting a tap water sample from participants’ homes to permit comparison of arsenic concentrations in water with those in toenails (12).

The case-control status and main objectives of the study were not disclosed to the interviewers. To ensure consistent quality of the study interviewer, interviews were tape recorded with the consent of the participants and routinely monitored by the interviewer supervisor (<1 percent of participants refused to be taped). To assess comparability of cases and controls, we asked subjects if they currently held a driver’s license or a Medicare enrollment card.

Arsenic determinations

In addition to the study interview, we requested a toenail clipping sample for analysis of arsenic. Subjects were mailed the instructions and materials to save a toenail clipping specimen prior to the interview; a self-addressed envelope was left for those who needed to send their sample in after the interview. Samples were analyzed for arsenic using instrumental neutron activation analysis at the University of Missouri’s research reactor center (Columbia, Missouri) (16). Prior to analysis, nail samples were carefully washed to remove external contamination. Each batch of analyses included quality control samples composed of matrix-matched samples with known content and analytical blanks along with study samples and standards. The between-assay coefficient of variability for matrix-matched samples is about 8 percent. All samples were labeled with an identification number that did not reveal the case-control status of the study participants.

Statistical analysis

We classified cases (i.e., BCC, SCC) based on their first primary skin cancer diagnosed during our survey. Controls were mentally incompetent or too ill to take part. A total of 540 controls were interviewed, of which 524 (97.0 percent) had a toenail sample analyzable for arsenic.
selected for interview who had skin cancer before the study
period (or who subsequently developed skin cancer) remained as controls in the primary analysis. Likewise, a case of SCC was analyzed as such, even if he or she later
developed BCC or had a BCC before our survey period. Nonmelanoma skin cancer is highly curable. Therefore, it is
usually possible to distinguish new primaries from recurrences. Classification of subjects according to this plan
should result in relative risk estimates that are accurate esti-
mates of incidence density ratios (17).

To assess the relation between toenail arsenic and the risk
of BCC and SCC, we first conducted a logistic regression
analysis using categories of toenail arsenic, classifying sub-
jects by percentiles of the control distribution. To evaluate
the form of the dose-response function, we plotted the
smoothed observed proportions of cases as a function of log
toenail arsenic values (18). Since the distribution of toenail
arsenic values was right skewed, a natural log transforma-
tion was used to provide more normally distributed data. We
used logistic regression to model the continuous arsenic val-
ues using both linear and quadratic models (19). Separate
logistic regression models were run for each histologic type
of skin cancer, BCC and SCC. All models controlled for age
and sex. We conducted the analyses controlling for the origi-
nal age categories applied for control selection and com-
pared the results using age as a continuous variable. Because
results were essentially the same, we used continuous age in
the final models. We further evaluated the potentially con-
foundling effects of educational attainment (high school or
less, college, or graduate school), smoking status (never,
former, or current), skin reaction to first exposure to the sun
in the summer (blister, peel, mildly burn, or tan) or after pro-
longed exposure (very tan, moderately tan, mildly tan, or
freckle/no tan), and history of radiotherapy (no or yes).

RESULTS

Selected characteristics of cases and controls are shown
in table 1. BCC cases tended to be younger than SCC cases
(table 1). Controls were comparable with the combined age
and sex distribution of the BCC and SCC cases because of
matching (table 1). Nearly all subjects reported being of the
White race, especially the BCC and SCC cases (table 1).
The level of educational attainment was somewhat lower
among controls than cases, whereas the history of cigarette
smoking was slightly higher (table 1). Compared with con-
trols, a smaller percentage of both BCC and SCC cases
tended to tan with first summer or prolonged sun exposure,
and a higher percentage had a history of radiotherapy (table
1). Overall, 38 percent of the study participants reported
exposure to water arsenic at their home (table 1). About 30 percent currently had a drilled or bedrock well, and
about 8 percent had a shallow or dug well or spring. On
average, participants used their current water system for
over 15 years.

The toenail arsenic concentration ranged from 0.01 to
0.81 µg/g from controls, from 0.01 to 2.03 µg/g among
BCC cases, and from 0.01 to 2.57 µg/g among SCC cases.
The geometric mean values of toenail arsenic were 0.098
µg/g (standard error (SE) of the geometric mean = 0.003),
0.090 µg/g (SE = 0.004), and 0.094 µg/g (SE = 0.003)
among BCC and SCC cases and controls, respectively. In
the categorical data analysis, the odds ratios for SCC and
BCC were close to unity in all but the highest category
(table 2). Among those with toenail arsenic concentrations
above the 97th percentile, the odds ratio for SCC was 2.07
(95 percent confidence interval (CI): 0.92, 4.66), and for
BCC it was 1.44 (95 percent CI: 0.74, 2.81) (table 2). With
the linear model, the odds ratio per µg/g increase was 1.08
(95 percent CI: 0.85, 1.36) for SCC and 1.03 (95 percent CI:
0.85, 1.25) for BCC. By inspection, the quadratic model
appeared to fit the observed data. However, the addition of
the quadratic term to the linear model was not statistically
significant for BCC (p = 0.34) or SCC after excluding the
case with the highest arsenic concentration (p = 0.043 over-
all; p = 0.13 for the model excluding a value above 2 µg/g). Adjustments for other covariates had no appreciable effect on
the relative risk estimates.

DISCUSSION

In our case-control study of skin cancer conducted among
New Hampshire residents, toenail arsenic concentrations
were unrelated to risk at levels most commonly encountered
in the population we studied. However, for SCC, we found
some evidence of an increased risk at the highest levels of
exposure, but with wide confidence intervals. For BCC, the
relative risk estimates were closer to unity.

Despite concerns regarding the potential carcinogenic
effects of low levels of arsenic exposure, relatively few studies have examined this issue in the United States. Earlier
US studies of water arsenic and skin cancer were, for the
most part, ecologic studies using broad geographic areas
with varying arsenic concentrations. Thus, there was likely
significant misclassification of individuals who drank
arsenic-containing water. Additionally, one of the US stud-
ies (10) used mortality rates, a poor measure of non-
melanoma skin cancer occurrence. Studies conducted in
regions with unusually elevated well water concentrations
of arsenic in Alaska (n = 59 households) (8) and California
(n = 76 households) (9) were not designed to look at long-
term effects such as cancer and had too few subjects to
detect an excess skin cancer risk.

The skin cancer prevalence study reported by Tseng et al.
(3) involved over 40,000 households from the southwest coast
of Taiwan (primarily Chai-yi and Tainan counties). A striking
dose-response relation was observed between water arsenic
concentrations and skin cancer prevalence; rates were 26, 101,
and 214 per 1,000 for villages with median water concentra-
tions of 170 µg/liter, 470 µg/liter, and 800 µg/liter, respec-
tively. In a small case-control study that followed, the preva-
ance odds ratios of skin cancer increased with duration of
residence in endemic regions, duration of drinking well water,
and water arsenic concentrations (20). The occurrence of cuta-
neous conditions (inferred to be skin cancers) was associated
with drinking water arsenic in a comparison of two towns in
Mexico, one with a mean drinking water concentration of 411
µg/liter (“the highly exposed town”) and a similar town with
respect to “environmental and socioeconomic condition” with a mean concentration of 5 µg/liter (“the unexposed town”) (21). Similarly, drinking water arsenic contamination was linked to skin cancer mortality in a region of northern Argentina (22) with concentrations up to 960 µg/liter (23).

While these studies point to an etiologic link between drinking water arsenic and skin cancer, they do not provide data regarding the risk at lower levels of exposure. Consequently, the shape of the dose-response at these lower levels has not been determined. Several risk assessment

<table>
<thead>
<tr>
<th>Reference age (years)</th>
<th>Squamous cell carcinoma (n = 284)</th>
<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
</tr>
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<tbody>
<tr>
<td>&lt;40</td>
<td>3</td>
<td>42</td>
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<td>40–49</td>
<td>17</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>50–59</td>
<td>47</td>
<td>123</td>
<td>103</td>
</tr>
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<td>60–69</td>
<td>116</td>
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<tr>
<td>≥70</td>
<td>101</td>
<td>117</td>
<td>121</td>
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<th>Sex</th>
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<tr>
<td>Male</td>
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<td>338</td>
<td>315</td>
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<tr>
<td>Female</td>
<td>102</td>
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<td>209</td>
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<th>Basal cell carcinoma (n = 587)</th>
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<tbody>
<tr>
<td>White</td>
<td>280</td>
<td>577</td>
<td>505</td>
</tr>
<tr>
<td>Non-White</td>
<td>3</td>
<td>10</td>
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<th>Highest level of education</th>
<th>Squamous cell carcinoma (n = 284)</th>
<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
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<tbody>
<tr>
<td>High school or less</td>
<td>123</td>
<td>226</td>
<td>254</td>
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<td>College</td>
<td>88</td>
<td>215</td>
<td>164</td>
</tr>
<tr>
<td>Graduate school</td>
<td>72</td>
<td>146</td>
<td>105</td>
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<thead>
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<th>Smoking status</th>
<th>Squamous cell carcinoma (n = 284)</th>
<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
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</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>89</td>
<td>251</td>
<td>174</td>
</tr>
<tr>
<td>Former smoker</td>
<td>144</td>
<td>248</td>
<td>247</td>
</tr>
<tr>
<td>Current smoker</td>
<td>50</td>
<td>88</td>
<td>101</td>
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<table>
<thead>
<tr>
<th>Skin reaction to sun, first time in summer</th>
<th>Squamous cell carcinoma (n = 284)</th>
<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
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<tbody>
<tr>
<td>Blister</td>
<td>27</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>Peel</td>
<td>101</td>
<td>211</td>
<td>133</td>
</tr>
<tr>
<td>Mildly burn</td>
<td>128</td>
<td>303</td>
<td>263</td>
</tr>
<tr>
<td>Tan</td>
<td>26</td>
<td>45</td>
<td>79</td>
</tr>
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<table>
<thead>
<tr>
<th>Skin reaction to sun, after prolonged exposure</th>
<th>Squamous cell carcinoma (n = 284)</th>
<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very tan</td>
<td>40</td>
<td>107</td>
<td>171</td>
</tr>
<tr>
<td>Moderately tan</td>
<td>139</td>
<td>276</td>
<td>229</td>
</tr>
<tr>
<td>Mildly tan</td>
<td>70</td>
<td>161</td>
<td>89</td>
</tr>
<tr>
<td>Freckle/no tan</td>
<td>34</td>
<td>42</td>
<td>33</td>
</tr>
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<table>
<thead>
<tr>
<th>Prior radiation treatment</th>
<th>Squamous cell carcinoma (n = 284)</th>
<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>245</td>
<td>509</td>
<td>483</td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>78</td>
<td>40</td>
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<table>
<thead>
<tr>
<th>Household water supply</th>
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<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public</td>
<td>175</td>
<td>343</td>
<td>323</td>
</tr>
<tr>
<td>Private, drilled well</td>
<td>84</td>
<td>193</td>
<td>154</td>
</tr>
<tr>
<td>Private, shallow well or spring</td>
<td>23</td>
<td>39</td>
<td>42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years used current water supply</th>
<th>Squamous cell carcinoma (n = 284)</th>
<th>Basal cell carcinoma (n = 587)</th>
<th>Controls (n = 524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mean (SD))</td>
<td>18.1 (14.1)</td>
<td>15.7 (12.9)</td>
<td>16.7 (13.1)</td>
</tr>
</tbody>
</table>

* Data were missing on race (two controls and one squamous cell carcinoma case); education (one control and one squamous cell carcinoma case); smoking status (two controls and one squamous cell carcinoma case); skin reaction to the sun, first time in summer (four controls, one basal cell carcinoma case, and two squamous cell carcinoma cases); skin reaction to the sun, after prolonged exposure (two controls, one basal cell carcinoma case, and one squamous cell carcinoma case); prior radiation treatment (one control and two squamous cell carcinoma cases); household water supply (five controls, 12 basal cell carcinoma cases, and two squamous cell carcinoma cases); and mean years used current water supply (36 controls, eight basal cell carcinoma cases, and 10 squamous cell carcinoma cases).

† SD, standard deviation.
models are based on linear extrapolations of the Taiwanese and Mexican data. These models suggest an excess cancer risk at concentrations below the current US maximal contaminant level of 50 µg/liter (4). In a later reanalysis of the Taiwanese skin cancer survey, a quadratic model appeared to fit the data slightly better than did the linear model, although no definitive conclusions were drawn about the shape of the dose-response curve (4). In our study, the quadratic model also appeared to fit the data. However, because of the small number of subjects at the highest and lowest levels of exposure, we had limited power to determine the exact form of the dose-response model.

An important aspect of our study is that we used toenail concentrations of arsenic as an individual biomarker of past exposure. In our population, we found that toenail concentrations were correlated with well water concentrations, particularly among those with water concentrations of arsenic of 1 µg/liter or more ($r = 0.65$) (12, 24). However, among those with lower water concentrations, the correlation was not so good, raising the possibility of misclassification among persons with low levels of arsenic in drinking water. One of the difficulties in relying on water measurements alone is that the reproducibility of water arsenic is not well characterized, and concentrations could vary seasonally or over longer periods. Moreover, estimation of exposure based on water concentrations would require careful consideration of the amount consumed and the arsenic concentrations of water sources outside the home. We chose a biologic tissue to measure exposure since, in theory, it reflects all sources of exposure. Nonetheless, it is conceivable that exposure misclassification could have attenuated our risk estimates.

The precise latency period for arsenic’s effects on skin cancer remains uncertain. Therefore, our results based on toenail concentrations may not cover the relevant exposure period. Patients treated with potassium arsenite (Fowler’s solution) for psoriasis and other ailments developed skin cancers from 3 to 40 years after treatment (25). In the case-control study of bladder cancer conducted by Bates et al. (26), an elevated odds ratio of bladder cancer was observed among smokers beginning 10–19 years since exposure, with the highest risk after 30–39 years. Toenails reflect exposure in the past several months and perhaps even longer time periods. Based on data from the Nurses’ Health Study (27), toenail arsenic levels were correlated over a 6-year period ($r = 0.54$). Our study population was relatively stable and remediation efforts had not occurred; over 50 percent used the same water system for over 15 years. We did not find that the relative risk estimates varied significantly by how long subjects used their water system (data not shown).

Part of the current controversy regarding the maximum contaminant level for arsenic in the United States is whether the Taiwanese data apply to the US population. Not only are the levels of exposure far lower in the United States, but the underlying risk of skin cancer in the United States is vastly greater than it is in Taiwan. BCC and SCC, together, are the most common malignancies in the United States, and the incidence rates of these malignancies appear to be rapidly increasing (14). On the other hand, the validity of our findings could be questioned since we did not obtain full cooperation from all eligible subjects. The overall age and sex distributions of nonparticipants were not appreciably different from those of participants; the mean age was 61 years and the proportion of men was about 40 percent in both groups (data not shown). About 20 percent of the participants and nonparticipants lived in the three major urban regions of the state (data not shown). However, we cannot exclude the possibility that arsenic concentrations differed between participants and nonparticipants. Another possible source of bias is that controls with a driver’s license or Medicare enrollment may not represent the population at large. On the basis of a comparison of Medicare beneficiaries with US Census data, we expect over 90 percent coverage of residents aged 65 years and older (28). While we do not have comparable statistics for New Hampshire drivers’ license records, in a study done in Iowa, drivers’ license

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**TABLE 2. Odds ratios and 95% confidence intervals for squamous cell carcinoma and basal cell carcinoma according to percentiles of toenail arsenic concentrations in controls, New Hampshire, 1993–1996**

<table>
<thead>
<tr>
<th>Toenail arsenic concentration (µg/g)</th>
<th>Percentile</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.009–0.089</td>
<td>≤50</td>
<td>155</td>
<td>54.6</td>
<td>263</td>
<td>50.2</td>
</tr>
<tr>
<td>0.090–0.133</td>
<td>50.1–75</td>
<td>64</td>
<td>22.5</td>
<td>136</td>
<td>25.9</td>
</tr>
<tr>
<td>0.134–0.211</td>
<td>75.1–90</td>
<td>33</td>
<td>11.6</td>
<td>73</td>
<td>13.9</td>
</tr>
<tr>
<td>0.212–0.280</td>
<td>90.1–95</td>
<td>14</td>
<td>4.9</td>
<td>26</td>
<td>5.0</td>
</tr>
<tr>
<td>0.281–0.344</td>
<td>95.1–97</td>
<td>5</td>
<td>1.8</td>
<td>11</td>
<td>2.1</td>
</tr>
<tr>
<td>0.345–0.81</td>
<td>97.1–100</td>
<td>13</td>
<td>4.6</td>
<td>15</td>
<td>2.9</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.009–0.089</td>
<td>≤50</td>
<td>281</td>
<td>47.9</td>
<td>263</td>
<td>50.2</td>
</tr>
<tr>
<td>0.090–0.133</td>
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<td>156</td>
<td>26.6</td>
<td>136</td>
<td>25.9</td>
</tr>
<tr>
<td>0.134–0.211</td>
<td>75.1–90</td>
<td>92</td>
<td>15.7</td>
<td>73</td>
<td>13.9</td>
</tr>
<tr>
<td>0.212–0.280</td>
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<td>22</td>
<td>3.7</td>
<td>26</td>
<td>5.0</td>
</tr>
<tr>
<td>0.281–0.344</td>
<td>95.1–97</td>
<td>10</td>
<td>1.7</td>
<td>11</td>
<td>2.1</td>
</tr>
<tr>
<td>0.345–0.81</td>
<td>97.1–100</td>
<td>26</td>
<td>4.4</td>
<td>15</td>
<td>2.9</td>
</tr>
</tbody>
</table>

* Odds ratios adjusted for age and sex as described in the text.
exposure found in the United States. [40x148]of the potential carcinogenic drinking water levels of arsenic [40x159]highlight both the feasibility and need for further investigation [40x170]maximal contaminant level (13). In summary, our findings [40x192]these wells have arsenic concentrations above the present [40x203]35–40 percent of the households and that over 10 percent of [40x225]ulated under the US Safe Drinking Water Act. In New [40x247]private wells (serving fewer than 15 households or 25 indi- [40x258]have levels below the maximal contaminant level. However, [40x302]about 350,000 residents drink water with arsenic concentra- [40x324]and Bangladesh (36), as well as the southwest coast of Taiwan (22), Mexico (21), Chile (34), and most recently India (35) [40x346]arsenic-contaminated drinking water has been detected in [40x357]several regions of the world including Silesia (33), Argentina (22), Mexico (21), Chile (34), and most recently India (35) [40x380]ascertainment of cases could be dependent on screening behav- [40x424]cally excluded in situ (intraepidermal) lesions because the [40x446]as multiple superficial lesions (25). In our study, we specifi- [40x468]dermal carcinomas, and 15 percent as basal cell carcinomas. [40x490]had multiple lesions. Among patients treated with Fowler’s solution, squamous cell lesions were commonly associated with keratoses and basal cell carcinomas frequently occurred as multiple superficial lesions (25). In our study, we specifically excluded in situ (intraepidermal) lesions because the ascertainment of cases could be dependent on screening behavior. We were unable to analyze the risk of multiple BCCs as a subgroup because of the scant number of these cases. Thus, it is possible that both major types of nonmelanoma skin cancer relate to arsenic ingestion, but that further data are needed.

Drinking water exposure to arsenic is a global concern. Arsenic-contaminated drinking water has been detected in several regions of the world including Silesia (33), Argentina (22), Mexico (21), Chile (34), and most recently India (35) and Bangladesh (36), as well as the southwest coast of Taiwan and other parts of Asia. In the United States, it is estimated that about 350,000 residents drink water with arsenic concentrations above the current maximal contaminant level and that over 2 million consume water with arsenic concentrations above 2 µg/liter (37). Public water systems are required to have levels below the maximal contaminant level. However, private wells (serving fewer than 15 households or 25 individuals) are common in rural areas. These sources are not regulated under the US Safe Drinking Water Act. In New Hampshire, we estimate that private wells serve roughly 35–40 percent of the households and that over 10 percent of these wells have arsenic concentrations above the present maximal contaminant level (13). In summary, our findings highlight both the feasibility and need for further investigation of the potential carcinogenic drinking water levels of arsenic exposure found in the United States.

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