Occupational exposure to arsenic and risk of nonmelanoma skin cancer in a multinational European study

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Occupational studies show a high risk of lung cancer related to arsenic exposure by inhalation; however, only a few studies, and with conflicting results, previously examined a potential link between arsenic exposure at work and skin cancer. The aim of this study is to assess airborne arsenic exposures at the workplace and to quantify associations with nonmelanoma skin cancer (NMSC). The study sample consists of 618 incident cases of NMSC and 527 hospital-based controls aged 30–79 years from Hungary, Romania and Slovakia. Exposures were evaluated by local experts using occupational histories. Information on host factors and other exposures was collected and used to adjust the associations of interest using multivariable logistic regression. The lifetime prevalence of exposure to work-related arsenic is 23.9% for cases and 15.5% for controls. No significant association between arsenic exposure in the workplace and NMSC was detected, although an increased adjusted odds ratio was observed for participants with higher cumulative lifetime workplace exposure to arsenic in dust and fumes compared to referents [odds ratios (OR) = 1.94, 95% confidence interval (CI) = 0.76–4.95]. There is evidence for modification of the workplace arsenic–NMSC association by work-related sunlight exposure in women, with a markedly increased adjusted OR in the presence of workplace sunlight exposure (OR = 10.22, 95% CI = 2.48–42.07). Workplace coexposure to arsenic and sunlight may thus pose an increased risk of NMSC.

Key words: nonmelanoma skin cancer, basal cell carcinoma, squamous cell carcinoma, occupational exposure, arsenic exposure

Abbreviations: BCC: basal cell carcinoma; DMA: dimethylarsinic acid; MA: methylarsonic acid; NMSC: nonmelanoma skin cancer; SCC: squamous cell carcinoma; UV: ultraviolet

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Nonmelanoma skin cancer (NMSC) is the most common type of cancer worldwide and its incidence is rising. Although exact statistics are not known as these tumors are not generally reported to cancer registries, the trend is confirmed by a report published by the International Agency for Research on Cancer in 2008.1 The two main histological types of NMSC linked to arsenic exposure are squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs), occurring not only on sun-exposed areas of the body but also develop on sun-unexposed skin.2,5 If NMSC is not diagnosed and treated in early stages, high morbidity and substantial disfigurement due to local invasion is of great concern for public health and is an important source of healthcare expenditure.3

NMSC has also been associated with other environmental and occupational risk factors, including ultraviolet (UV)
What’s new?
While it is established that inhalation of arsenic can cause lung cancer, associations with other cancer types is less clear. Here, the authors examined a possible link of workplace exposure to the chemical element in dust and fumes with non-melanoma skin cancer (NMSC). They find that women are at higher risk of NMSC from arsenic workplace exposure than men with a markedly increased odds ratio in the presence of additional sunlight exposure. Thus, the combined exposure to arsenic and sunlight poses a considerable risk for the development of skin cancer.

radiation, ionizing radiation and polycyclic hydrocarbons.\textsuperscript{5–7} Moreover, there is growing evidence that arsenic can act synergistically with sunlight and individual genetic susceptibility in the development of NMSC.\textsuperscript{8,9}

Arsenic exposure has been widely implicated in NMSC, with the strongest evidence coming from studies of populations consuming highly contaminated drinking water.\textsuperscript{2,3,10} Findings from occupational studies, where the primary exposure mechanism is inhalation, have been inconsistent.\textsuperscript{11,12} Work-related exposure to arsenic has been reported in diverse occupations, including mining and metallic ore smelting, manufacture and use of agricultural products and wood preservatives, use of animal feed additives, production of electronic semiconductors and in glass and pigment factories.\textsuperscript{11,13,14}

Previous studies of occupational arsenic exposure and NMSC have generally been limited by nonspecific exposure assessments, inadequate adjustment for socioeconomic status, host factors or lifestyle and no consideration for potential heterogeneity of effect (i.e., effect modification) by these and other factors.\textsuperscript{13,15,16} In our study, expert assessment was used to estimate individual airborne arsenic exposure at the workplace to quantify associations with NMSC in a large case-control investigation. Information on host factors as well as other known occupational and environmental carcinogenic exposures was collected and used to adjust the associations of interest and to assess heterogeneity of effects.

Material and Methods
Study population
Our research findings are based on data collected from the Arsenic Health Risk Assessment and Molecular Epidemiology (ASHRAM) study, a multinational European project that was conducted in eight counties in Hungary, Romania and Slovakia in 2003–2004. Incident cancer cases of skin carcinoma, bladder and kidney cancers were recruited as well as hospital cases. The overall response rate was 85%; 81.6% among cases and 90% among controls.

For the purpose of this research, skin cancer represents the outcome of interest and consists of new cases of NMSC aged 30–79 years, who resided for at least 1 year in the study region and were identified at the county hospitals in the study area, as previously reported.\textsuperscript{17} In brief, only cases confirmed by histology report (International Classification of Diseases, 10th Revision codes C44) or dermatology specialist opinion were included in the final study sample. County hospital pathologists examined tissue specimens collected from potential skin cancer cases, both outpatients and inpatients, identified at any healthcare facility (e.g., private office, hospital and clinic) in the study area. Furthermore, case recruitment was not likely to be influenced by employment or other socioeconomic factors, which may be associated with arsenic exposure, as the source population is provided universal access to medical services. The anatomical location of tumors and histological types (i.e., BCC or SCC) were extracted from hospital pathology reports for 94% of cases. Controls were defined as hospital patients residing in the study area for at least 1 year, who were diagnosed and treated during the study period for general surgery conditions such as appendicitis, abdominal hernias, duodenal ulcer and cholecystitis or for orthopedics and traumatology conditions such as fractures. Controls were frequency matched to cases by county of residence, sex and 5-year-age group. To ensure that our controls represented the source population for cases, participants were recruited from all healthcare facilities in the study area that treated control diagnoses, including county hospitals. The only control diagnosis that may be plausibly associated with occupational exposure to arsenic is injury such as fracture. However, as fractures accounted for only 29% of all controls, any bias would be diluted by the other control diagnoses.

Informed consent was obtained from all the subjects included in the study. The privacy of the study participants and the confidentiality of the information collected were assured according to the principles of the Helsinki Declaration. Ethical approvals were obtained from all the countries involved in data collection and data analysis (Hungary, Romania, Slovakia, Austria, Sweden, Germany, the United Kingdom and the United States).

Occupational exposure assessment
A study questionnaire was developed and pilot tested in the study area. Questions covered participants’ age, sex, education, skin pigmentation, skin propensity to sunburns or ability to tan, family history of cancer, smoking and leisure sunlight exposure, and a detailed residential history was recorded. The questionnaire also captured a complete occupational history, and potential occupational risk factors with evidence for carcinogenicity were identified prior to diagnosis. The information was collected by investigators during an interview conducted within 3 months of participant enrollment.

Occupational exposure assessment was based on experts’ judgment of self-reported lifetime occupational history.
regarding participants’ job titles held for at least 1 year, job tasks, period working in the specified job and industry. Job titles and industries were coded according to the International Standard Classification of Occupations and the Classification of Economic Activities in the European Community. For each job title, occupational exposure was evaluated in terms of intensity, frequency and probability using a semiquantitative three-level scale (i.e., low, medium and high). The occupational coding guideline developed for our study is an adaptation of the method used by Siemiatycki. Standardization of the exposure assessment was assured by following the same coding guideline in all countries and by training local exposure-coding experts.

The intensity of occupational exposure was coded as “low” for participants suspected to be exposed to arsenic above the background environmental level, but less than 50% of the threshold limit value (i.e., TLV = 0.01 mg/m³ and is defined as a safe exposure for all workers, including sensitive subgroups), “medium” for arsenic exposure from 50 to 150% TLV and “high” for arsenic exposure higher than 150% TLV. More specifically, the intensity of arsenic exposure was coded as “low” for the use of insecticides (i.e., calcium, sodium and lead arsenate) before 1960; “low” or “medium” for jobs in foundries from 1960 to 1975, wood treatment and glass or electronics industries and “medium” or “high” for occupations in tanneries before 1950, foundries before 1960 and manufacture of arsenical pesticides or wood preservatives. Frequency was coded as “low” for arsenic exposure during 1–5% of the workday, “medium” for arsenic exposure during 5–30% of the workday and “high” for arsenic exposure for more than 30% of the workday. The exposure probability was coded as “low” for possible but not probable exposure, “medium” for probable exposure and “high” for certain exposure.

Individual residential exposure to arsenic via drinking water was estimated using self-reported consumption data weighted by arsenic concentrations measured in sources with hydride generation atomic absorption spectrometry. Several time-weighted exposure indicators were constructed, including lifetime average concentration of arsenic in residential drinking water sources. Detailed information on the drinking water exposure assessment was reported elsewhere.

To investigate the potential impact of interindividual variation in arsenic metabolism on skin cancer in relation to arsenic exposure, urine samples were collected from the study subjects and analyzed for metabolites of arsenic including methylarsonic acid (MA) and dimethylarsinic acid (DMA) using an inductively coupled plasma mass spectrometer. The relative amount of DMA and MA in urine was expressed as the percent of total urinary arsenic. Details regarding arsenic species measurements and levels have been published previously. High arsenic methylation efficiency results in fast excretion of arsenic as DMA (60–80%) with a small percentage of urinary arsenic as MA (10–20%). A high proportion of DMA is indicative of lower arsenic retention and consequently a lower risk for arsenic-related toxicity.

### Statistical analysis

Occupational exposure to arsenic was defined as ever versus never exposure and cumulative lifetime exposure (CLE). A participant was defined as ever exposed if at least one job involved potential arsenic exposure. The CLE was calculated by multiplying the exposure intensity, frequency, probability (low, medium and high scores received weights) and duration for each job classified as exposed, and then summed over all jobs, as presented in the equation below:

\[
CLE_{(hr)} = \sum_{j} I_j F_j P_j D_j,
\]

where \( j \) is the job in which the exposure occurred; \( I \) is the intensity of exposure (\( I = 0.25, 0.50, 1.00 \)); \( F \) is the frequency of exposure (\( F = 0.03, 0.18, 0.65 \), corresponding to the midpoint of the frequency ranges); \( P \) is the probability of exposure (\( P = 0.25, 0.50, 1.00 \)) and \( D \) is the duration of exposure in hours (\( D = 2,000 \text{ hr per working year} \)).

The cumulative exposure was further categorized in tertiles of the exposure distribution among controls, defined as low, medium, and high exposure. Participants who had “never” been exposed to arsenic at work were defined as the referent group.

Descriptive statistics were used to describe the distribution of study participants’ exposures and demographic characteristics by case status. Based on prior scientific evidence, potential confounders were investigated using bivariate analysis (i.e., association with both NMSC among unexposed group and occupational arsenic exposure among controls). Odds ratios (OR) and 95% confidence intervals (95% CI) for NMSC were calculated to estimate the associations with occupational exposure to arsenic using unconditional logistic regression. ORs were adjusted for the matching variables sex, age and county of residence to avoid selection bias. The results were also adjusted for skin propensity to sunburns, family history of cancer and exposure to arsenic in drinking water that were identified as confounders and continued to be significant predictors for NMSC in multivariable regression models. A number of other risk factors possibly associated with NMSC and occupational exposure to arsenic were also considered (i.e., education level, skin pigmentation, tobacco smoking, self-reported sunlight exposure during the weekends and occupational sunlight exposure).

Modifying factors for the effect of occupational arsenic exposure on skin cancer were also assessed. Occupational sunlight exposure, exposure to arsenic through consumption of contaminated drinking water and individual susceptibility as indicated by %DMA and %MA were evaluated in multivariable regression models as two-way interaction terms with occupational exposure indicators and tested for significance according to the Wald test. The potential modifying effect of sex was evaluated by stratified analysis.

The potential latency effect of arsenic exposure for the development of NMSC is still uncertain and was explored by including in the regression models 15-, 20-, and 25-year lag
periods. Lag periods before the interview were considered not exposed. Separate regression models were conducted to investigate the relationship between arsenic exposure at work and skin cancer histology and anatomical topography. All analyses were conducted using SAS 9.2 statistical software (SAS Institute, Cary, NC). Statistical significance was defined as $p < 0.05$ for a two-tailed test.

**Results**

Our study consists of 527 controls and 618 incident cases of NMSC, 515 BCC and 70 SCC. Characteristics of the study subjects are presented in Table 1. Cases are more likely to be older, particularly for SCC, and to have higher skin propensity to sunburns with or without blisters than controls. Cases are also more likely to have reported a family history of cancer and had a slightly higher prevalence of occupational sunlight exposure. The median value of arsenic concentration in drinking water and the %DMA in urine is higher in control subjects, whereas the %DMA median value is higher in cases.

Coding experts examined 5,589 job periods (4.9 job periods per subject on average) and classified occupational exposure to arsenic based on self-reported work histories. Exposure to arsenic in dust was established for 249 job periods and in fumes for 109 job periods. Of 229 participants ever exposed to work-related arsenic, 141 are exposed through dust, 74 through dust and fumes and the remaining 14 participants are exposed only through fumes. Because of the small number of subjects exposed to arsenic in fumes only, the results for this group are not presented separately. The vast majority of subjects ever exposed to occupational arsenic worked in agricultural related activities (84.4%).

Table 2 shows the adjusted ORs of NMSC associated with ever exposure and lifetime cumulative exposure to arsenic at work. Lifetime prevalence of exposure to work-related arsenic is 23.9% for cases ($n = 144$) and 15.5% for controls ($n = 80$). No association is found between occupational exposure to arsenic and NMSC. However, higher adjusted odds ratios of NMSC are observed particularly in relation to arsenic in dust and fumes for the ever exposure ($OR = 1.61$, 95% CI $= 0.89$–2.92) and for the higher lifetime cumulative exposure ($OR = 1.94$, 95% CI $= 0.76$–4.95). The results are comparable when limited to cases of BCC. Point estimates are slightly higher for SCC, yet imprecise given the small the number of exposed cases. A latency analysis found similar results. Therefore, lag periods are not reported for subsequent analyses.

Table 3 reports associations between arsenic exposure at work and skin cancer stratified by anatomical site. The adjusted ORs of total NMSC and BCC are increased in subjects exposed to arsenic at work for tumors located on sunlight-exposed anatomical sites such as the face, head and neck compared to other sites less likely to be exposed, suggesting that UV radiation may enhance the carcinogenic effect of arsenic. However, none of the associations are statistically significant. ORs of SCC are not reported because the number of exposed cases with SCC on anatomical sites other than face, head and neck is too small to permit a separate analysis for this histologic type.

As shown in Table 4, there is evidence for modification of the association between workplace arsenic and NMSC in women by work-related exposure to sunlight ($p < 0.05$). The results indicate that work-related arsenic exposure is associated with a significantly increased adjusted ORs for NMSC (OR $= 8.73$, 95% CI $= 2.18$–34.99), mainly due to BCC (OR $= 10.22$, 95% CI $= 2.48$–42.07), among women also exposed to sunlight at work, yet there is no increase in risk in the absence of occupational sunlight coexposure. Exposure to arsenic in drinking water has no significant impact on the relationship between arsenic exposure at work and NMSC, although higher adjusted ORs are suggested for women exposed to elevated concentrations of arsenic in drinking water than for those exposed to low concentrations. The NMSC ORs associated with arsenic exposure at work are not significantly different between women with lower and higher percentages of arsenic metabolites. No heterogeneity is detected for the effect of workplace arsenic on total NMSC or BCC among men. The number of SCC cases with combined exposures is insufficient in our study to support a heterogeneity analysis restricted to this histologic type.

**Discussion**

Our case–control study does not support a link between NMSC and overall arsenic exposure at work. However, the exposure to arsenic in dust and fumes in particular has increased risks for both BCC and SCC. Associations between workplace arsenic exposure and NMSC, largely due to BCC, vary by sex and occupational exposure to sunlight. Among women, there was evidence of an interaction between occupational exposures to arsenic and sunlight, with an OR of 10.2 for BCC. However, this finding was based on only four exposed controls, and thus, it cannot be considered robust. Based on human evidence alone, the International Agency for Research on Cancer and the U.S. Environmental Protection Agency concluded that there is sufficient evidence to implicate arsenic as a skin carcinogen. A small number of epidemiological studies conducted in the 1990s and earlier attempted to evaluate the link between work settings with potential exposure to airborne arsenic and skin cancer. Our results are in line with most previous studies that did not find an association between arsenic exposure from occupations involving application of arsenical pesticides or farming. We do not find a relationship between NMSC and workplace exposure to arsenic in spite of a well-documented skin cancer risk from exposure to arsenic in drinking water. The workplace arsenic exposure investigated in our study is relatively low compared to arsenic exposure from consumption of highly contaminated drinking water in certain parts of the world and may explain this discrepancy. Workplace arsenic exposures have decreased in our study.
area over recent decades through elimination of inorganic arsenic-based pesticides, improvement of control measures of the work environment and the use of personal protection equipment. In our study, about 85% of participants exposed to occupational arsenic worked in agriculture for much of their lives; however, only the use of insecticides before 1960 was coded for exposure to airborne arsenic and with low exposure intensity.

The exact molecular mechanisms of action for arsenic toxicity are still unknown; however, the available scientific evidence suggests that oxidative stress and altered growth factors play major roles. Byrd et al. reviewed potential hypotheses that may explain in part the variation of arsenic carcinogenesis by route of exposure (e.g., arsenic inhalation causes primarily lung cancer, whereas arsenic ingestion causes primarily skin cancer and is also associated with bladder, kidney and lung cancer) and exposure level (i.e., arsenic-induced carcinogenesis appears to increase at relatively high arsenic concentrations in environmental media). For example, differences in distribution of arsenic absorbed after inhalation versus ingestion may determine the target organ carcinogenesis. Saturation or alteration of arsenic methylation and excretion at higher doses may magnify the arsenic concentration at target tissues and increase the risk of cancer development.

The observed results of increased arsenic-induced skin cancer risk in the presence of sunlight exposure suggest a possible interaction between the two workplace coexposures. These findings are consistent with the “cocarcinogen” arsenic hypothesis, suggesting that chronic exposure to arsenic enhances the mutagenicity of other carcinogens, including UV radiation. Recent literature showed that skin tumors developed only in mice exposed to both arsenic and sunlight. No tumors were observed in mice exposed to arsenic alone, and the risk from sunlight exposure alone was significantly lower than for coexposure.

Table 1. Selected characteristics of study subjects by case status

| Characteristic                        | Controls | NMSC | BCC | SCC |
|--------------------------------------|----------|------|-----|-----|
|                                      | n¹   | %   | n¹   | %   | n¹   | %   | n¹   | %   |
| Sex                                  |       |     |      |     |      |     |      |     |
| Female                               | 255  | 48.4| 333  | 53.9| 284  | 55.2| 32   | 45.7|
| Male                                 | 272  | 51.6| 285  | 46.1| 231  | 44.8| 38   | 54.3|
| Age at interview (years)             |       |     |      |     |      |     |      |     |
| Median (interquartile range)         | 527  | 61 (52–70)| 618 | 67.5 (59–73)| 515 | 67 (58–73)| 70 | 71.5 (66–74)|
| Country                              |       |     |      |     |      |     |      |     |
| Hungary                              | 240  | 45.5| 170  | 27.5| 155  | 30.1| 14   | 20.0|
| Romania                              | 156  | 29.6| 218  | 35.3| 158  | 30.7| 38   | 54.3|
| Slovakia                             | 131  | 24.9| 230  | 37.2| 202  | 39.2| 18   | 25.7|
| Family history of cancer             |       |     |      |     |      |     |      |     |
| No                                   | 412  | 78.2| 418  | 67.6| 342  | 66.4| 51   | 72.9|
| Yes                                  | 115  | 21.8| 200  | 32.4| 173  | 33.6| 19   | 27.1|
| Skin propensity to sunburns          |       |     |      |     |      |     |      |     |
| No change/tan without sunburn        | 226  | 43.6| 206  | 33.8| 162  | 32.0| 29   | 41.4|
| Mild sunburn that becomes a tan      | 156  | 30.1| 191  | 31.4| 168  | 33.2| 18   | 25.7|
| Sunburn without blisters             | 79   | 15.2| 126  | 20.7| 104  | 20.6| 12   | 17.1|
| Sunburn with blisters                | 58   | 11.2| 86   | 14.1| 72   | 14.2| 12   | 15.7|
| Occupational sunlight exposure        |       |     |      |     |      |     |      |     |
| Never                                | 426  | 88.2| 491  | 86.1| 412  | 86.6| 54   | 85.7|
| Ever                                 | 57   | 11.8| 79   | 13.9| 64   | 13.4| 9    | 14.3|
| Lifetime average concentration of arsenic in drinking water (µg/l) |       |     |      |     |      |     |      |     |
| Median (interquartile range)         | 523  | 1.8 (0.7–16.7)| 612 | 1.0 (0.7–13.3)| 509 | 1.0 (0.7–15.2)| 70 | 0.8 (0.7–7.0)|
| Dimethylarsinic acid (%DMA)²         |       |     |      |     |      |     |      |     |
| Median (interquartile range)         | 508  | 74.3 (67.1–83.1)| 611 | 77.3 (71.2–83.1)| 509 | 77.3 (70.9–83.0)| 70 | 76.6 (72.8–82.7)|
| Methylarsonic acid (%MA)²            |       |     |      |     |      |     |      |     |
| Median (interquartile range)         | 508  | 16.2 (10.9–21.1)| 611 | 15.3 (10.9–19.5)| 509 | 15.4 (11.0–19.6)| 70 | 14.5 (10.7–18.8)|

¹Total number of subjects may vary due to some missing data for covariates. ²Arsenic metabolites in urine. Abbreviations: NMSC: nonmelanoma skin cancer; BCC: basal cell carcinoma; SCC: squamous cell carcinoma.
To our knowledge, this is the first study to suggest heterogeneity for the effect of airborne arsenic exposure on human skin cancer by sunlight and to indicate that women may be at a higher risk than men. Two previous epidemiological studies investigated changes in the associations between drinking water arsenic and premalignant skin lesions (i.e., melanosis and keratosis) by sunlight exposure and reported elevated risks for men working outside with an uncovered upper body.\(^3\)\(^8\),\(^3\)\(^9\)

The current findings show higher skin cancer risks associated with workplace arsenic exposure in women but not men, with particularly elevated risks among those with coexposure to sunlight at work. Previous reports in populations exposed to arsenic in drinking water showed mixed results, with a higher risk of skin cancer in women compared to men\(^4\)\(^0\),\(^4\)\(^1\) and in men compared to women.\(^4\)\(^2\) Some studies also focusing on arsenic exposure via drinking water suggested that women methylate arsenic more efficiently than men,\(^4\)\(^3\),\(^4\)\(^4\) whereas others noted similar arsenic methylation by sex.\(^4\)\(^5\)

Despite increasing evidence for heterogeneity of arsenic carcinogenesis by sex, the underlying mechanisms are not clarified. In particular, more research is needed to investigate the contribution of sex-related differences (e.g., sex hormones and health-related behaviors) to NMSC associated with arsenic–sunlight coexposure. Vahter et al.\(^4\)\(^7\) reviewed some distinctions between males and females in terms of morphology and physiology or behavior and lifestyle that may lead to variations in exposure patterns, toxicokinetics (e.g., suggested higher methylation of arsenic during pregnancy) and toxicodynamics (e.g., altered gene expression).

We find no evidence for modification of occupational arsenic-related NMSC by exposure to arsenic in drinking water, and contrary to expectations, there is no evidence for heterogeneity of effects by individual variation in arsenic methylation. In contrast, inefficient methylation, as indicated by low urinary excretion of DMA and high urinary excretion of MA, was associated with an increased risk of NMSC in populations consuming drinking water highly contaminated by arsenic.\(^4\)\(^2\),\(^4\)\(^5\) Again, the difference in our results may be attributed to the comparatively low work-related arsenic exposures in our study population. In addition, occupational exposure is more likely to be via inhalation or dermal absorption than ingestion. It is unlikely that methylation

### Table 2. Adjusted odds ratios between occupational exposure to arsenic and NMSC, BCC and SCC

| Occupational exposure index | Controls | NMSC | BCC | SCC |
|----------------------------|----------|------|-----|-----|
|                            | OR\(^2\) 95% CI | OR\(^2\) 95% CI | OR\(^2\) 95% CI | OR\(^2\) 95% CI |
| Never exposed\(^1\)        | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Ever exposed               |           |      |     |     |
| Any arsenic\(^4\)          | 1.23 0.87–1.74 | 1.22 0.84–1.75 | 1.54 0.78–3.02 |     |
| Arsenic in dust            | 1.08 0.70–1.64 | 1.03 0.66–1.62 | 1.37 0.62–3.05 |     |
| Arsenic in dust and fumes  | 1.61 0.89–2.92 | 1.63 0.89–3.00 | 2.04 0.57–7.29 |     |
| Cumulative lifetime exposure|     |      |     |     |
| Any arsenic\(^4\)          | 1.51 0.90–2.54 | 1.51 0.87–2.59 | 1.79 0.66–4.82 |     |
| Arsenic in dust            | 0.82 0.47–1.43 | 0.73 0.40–1.33 | 1.36 0.53–3.48 |     |
| Arsenic in dust and fumes  | 1.40 0.81–2.42 | 1.47 0.83–2.58 | 1.54 0.49–4.85 |     |

1 Total number of subjects may vary due to some missing data for covariates.
2 Odds ratios (95% CI) adjusted for sex, age, county of residence, family history of cancer, skin propensity to sunburns and lifetime average arsenic concentration in drinking water.
3 Reference category for all odds ratios in this table.
4 Any occupational arsenic consists of arsenic in dust, arsenic in fumes (results omitted due to scarce data) and both; associations were estimated in two separate multivariable logistic regression models. Abbreviations: NMSC: nonmelanoma skin cancer; BCC: basal cell carcinoma; SCC: squamous cell carcinoma.
varies according to the route of exposure; however, this possibility cannot be ruled out as we are unable to delineate between different exposure routes or sources in our study.

A potential limitation of this case–control study is the use of hospital controls that may lead to a selection bias if selected controls do not represent the source population from which cases originate. We used a number of approaches to reduce the potential for selection bias in our study, including recruitment of controls from all healthcare facilities where control diagnoses were produced and selection of several control diagnoses from general surgery and trauma. These strategies were discussed in detail in a previous publication. As arsenic exposure and skin cancer already occurred at the time of investigation, another concern is the potential for differential recall of past exposures between cases and controls that may lead to a recall bias of study results. Recall bias was minimized by using a validated questionnaire administered via a face-to-face interview, with participants and interviewers unaware of our study hypothesis. Additional efforts were made to further minimize the potential for recall bias by training local interviewers and conducting interviews using a standardized protocol.

Another potential limitation to our study results is misclassification of arsenic exposure. Several approaches were used to minimize this source of bias. First, the exposure evaluation of work-related arsenic was based on expert assessments using detailed occupational histories, an approach offering improved validity and reliability over exposure classification by job title or industry, job-exposure matrices and self-reports. Second, local experts, blinded to disease status, coded job titles and industries based on standard classification codes. Any misclassification of exposure is expected to be similar among cases and controls. Exposure misclassification is unlikely to account for the observed effects among sun-exposed women. Analysis of associations restricted to participants with high probability and intensity of arsenic exposure at work would have the advantage of reducing potential exposure misclassification bias. However, the small number of participants in this subgroup (i.e., three participants) precluded a sensitivity analysis.

A major strength of our study is the high participant response rate and the large sample size that provided sufficient statistical power to detect relatively small associations (i.e., $\geq 85\%$ probability to detect a 1.6-fold increased odds). However, the number of subjects per cell became limited when evaluating heterogeneity by additional factors, restricting the precision of effect estimates. Another important strength is the diagnosis confirmation by pathological examination in almost all cases, permitting analysis by NMSC histological type. Additionally, detailed information was

| Occupational exposure index | Controls | Cases | 
|----------------------------|----------|-------|
|                            |          |       |
|                            | n1 | n1 | OR2 | 95% CI | n1 | OR2 | 95% CI |
| NMSC                      |       |     |     |       |     |     |       |
| Face, head and neck       |     |     |     |       |     |     |       |
| Never exposed             | 435 | 250 | 1.00 (Referent) | 95 | 1.00 (Referent) |
| Ever exposed              |     |     |     |       |     |     |       |
| Any arsenic3              | 80  | 82  | 1.21 | 0.81–1.82 | 15 | 0.93 | 0.47–1.86 |
| Arsenic in dust           | 52  | 45  | 1.02 | 0.62–1.70 | 5  | 0.53 | 0.19–1.50 |
| Arsenic in dust and fumes | 22  | 34  | 1.74 | 0.90–3.36 | 9  | 1.64 | 0.63–4.30 |
| BCC4                      |     |     |     |       |     |     |       |
| Face, head and neck       |     |     |     |       |     |     |       |
| Never exposed             | 435 | 216 | 1.00 (Referent) | 87 | 1.00 (Referent) |
| Ever exposed              |     |     |     |       |     |     |       |
| Any arsenic3              | 80  | 67  | 1.13 | 0.73–1.73 | 14 | 1.04 | 0.50–2.12 |
| Arsenic in dust           | 52  | 34  | 0.88 | 0.51–1.51 | 5  | 0.67 | 0.23–1.94 |
| Arsenic in dust and fumes | 22  | 30  | 1.73 | 0.88–3.40 | 8  | 1.56 | 0.57–4.24 |

1Total number of subjects may vary due to some missing data for covariates.
2Odds ratios (95% CI) adjusted for age, sex, county of residence, family history of cancer, skin propensity to sunburns and lifetime average arsenic concentration in drinking water.
3Any occupational arsenic consists of arsenic in dust, arsenic in fumes (results omitted due to scarce data) and both; associations were estimated in two separate multivariable logistic regression models.
4Insufficient number of exposed cases with squamous cell carcinoma (SCC) on anatomical sites other than face, head and neck to permit a stratified analysis. Abbreviations: NMSC: nonmelanoma skin cancer; BCC: basal cell carcinoma.
| Potential effect modifiers | Arsenic exposure at work |
|---------------------------|-------------------------|
|                           | Women                   | Men                      |
|                           | n^2 | OR^3 | 95% CI | n^2 | OR^3 | 95% CI | n^2 | OR^3 | 95% CI | n^2 | OR^3 | 95% CI |
| Controls                  |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 211 | 239  | 1.00 (Referent) | 207 | 1.00 (Referent) | 224 | 220  | 1.00 (Referent) | 180 | 1.00 (Referent) |
| Ever                      | 38  | 88   | 1.57 (0.96–2.56) | 71  | 1.58 (0.95–2.62) | 42  | 56   | 0.95 (0.56–1.59) | 42  | 0.90 (0.52–1.58) |
| Exposure to sunlight at work |
| Absent                    |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 184 | 220  | 1.00 (Referent) | 192 | 1.00 (Referent) | 170 | 161  | 1.00 (Referent) | 135 | 1.00 (Referent) |
| Ever                      | 33  | 67   | 1.46 (0.85–2.50) | 51  | 1.39 (0.79–2.43) | 28  | 30   | 0.82 (0.43–1.57) | 21  | 0.75 (0.37–1.51) |
| Present                   |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 20  | 13   | 1.00 (Referent) | 11  | 1.00 (Referent) | 22  | 27   | 1.00 (Referent) | 19  | 1.00 (Referent) |
| Ever                      | 4   | 21   | 8.73 (2.18–34.99) | 20  | 10.22 (2.48–42.07) | 10  | 17   | 0.99 (0.34–2.91) | 13  | 1.04 (0.33–3.25) |
| Exposure to arsenic in drinking water (μg/l)^5 |
| <16.7                     |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 154 | 180  | 1.00 (Referent) | 154 | 1.00 (Referent) | 170 | 176  | 1.00 (Referent) | 144 | 1.00 (Referent) |
| Ever                      | 33  | 71   | 1.44 (0.84–2.46) | 56  | 1.43 (0.82–2.49) | 31  | 41   | 0.85 (0.47–1.53) | 30  | 0.80 (0.42–1.51) |
| ≥16.7                     |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 57  | 59   | 1.00 (Referent) | 53  | 1.00 (Referent) | 54  | 44   | 1.00 (Referent) | 36  | 1.00 (Referent) |
| Ever                      | 5   | 17   | 2.30 (0.75–7.10) | 15  | 2.44 (0.78–7.63) | 11  | 15   | 1.22 (0.44–3.38) | 12  | 1.18 (0.40–3.42) |
| Dimethylarsinic acid (%DMA)^6 |
| <74.3                     |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 86  | 61   | 1.00 (Referent) | 54  | 1.00 (Referent) | 124 | 99   | 1.00 (Referent) | 83  | 1.00 (Referent) |
| Ever                      | 15  | 23   | 1.73 (0.79–3.82) | 17  | 1.51 (0.66–3.50) | 24  | 26   | 0.86 (0.43–1.74) | 21  | 0.85 (0.40–1.78) |
| ≥74.3                     |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 115 | 174  | 1.00 (Referent) | 149 | 1.00 (Referent) | 93  | 118  | 1.00 (Referent) | 95  | 1.00 (Referent) |
| Ever                      | 22  | 65   | 1.57 (0.86–2.87) | 54  | 1.68 (0.90–3.13) | 18  | 30   | 1.01 (0.48–2.09) | 21  | 0.92 (0.42–2.03) |
| Methylarsonic acid (%MA)^6 |
| <16.2                     |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 113 | 143  | 1.00 (Referent) | 123 | 1.00 (Referent) | 96  | 105  | 1.00 (Referent) | 82  | 1.00 (Referent) |
| Ever                      | 22  | 59   | 1.61 (0.87–2.98) | 49  | 1.69 (0.90–3.18) | 16  | 27   | 1.06 (0.49–2.28) | 19  | 1.02 (0.45–2.34) |
| ≥16.2                     |     |      |        |     |      |        |     |      |        |     |      |        |
| Never                     | 88  | 92   | 1.00 (Referent) | 80  | 1.00 (Referent) | 121 | 112  | 1.00 (Referent) | 96  | 1.00 (Referent) |
| Ever                      | 15  | 29   | 1.57 (0.74–3.33) | 22  | 1.48 (0.67–3.27) | 26  | 29   | 0.84 (0.43–1.64) | 23  | 0.79 (0.39–1.60) |

1Insufficient number of squamous cell carcinoma (SCC) cases with coexposures to permit a stratified analysis.
2Total number of subjects may vary due to some missing data for covariates.
3Odds ratios (95% CI) adjusted for age, sex, county of residence, family history of cancer, skin propensity to sunburns and lifetime average arsenic concentration in drinking water.
4p < 0.05 for interaction.
5Lifetime average concentration, below the three lower quartiles and above the highest quartile of the control group distribution.
6Arsenic metabolites in urine, below and above the median of the control group distribution. Abbreviations: NMSC: nonmelanoma skin cancer; BCC: basal cell carcinoma.
collected for important confounding factors that were used to adjust the associations of interest.

Conclusions
We do not find an association between workplace exposure to arsenic and NMSC. However, our findings suggest that women exposed to airborne arsenic with coexposure to sunlight at work may be more susceptible to NMSC than those without workplace sunlight exposure. To better explain the role of complex exposures and variation of individual susceptibility of skin cancer, future examinations on potential interactions with other risk factors and genetic polymorphisms are planned in our study population.

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