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Drinking Water Arsenic Contamination, Skin Lesions, and Malignancies: A Systematic Review of the Global Evidence

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Abstract

Skin lesions and cancer are known manifestations of chronic exposure to arsenic contaminated drinking water. Epidemiologic data primarily comes from regions with exposures 1–2 orders of magnitude above the current World Health Organization (WHO)'s guidelines of 10 μg/L. Emerging evidence indicates that more common exposures may also be related to both non-cancerous and cancerous changes to the skin. In this review, we focus on the body of epidemiologic literature that encompasses exposures within the WHO guidelines, excluding studies that lacked individual exposure estimates and case reports. For skin lesions and skin cancers, 15 and 10 studies were identified that met our criteria, respectively. For skin lesions, a consistent dose-response relationship with water arsenic has been observed, with increased risk evident at low- to moderate-dose exposure. Of the larger studies of specific histologic types of skin cancers, although with differing exposure definitions, there was evidence of dose-related relationships with both basal cell carcinomas and squamous cell carcinomas. The effect of arsenic exposure on skin lesion risk is likely modified by genetic variants that influence arsenic metabolism. Accumulating evidence suggests that arsenic may increase risk of skin lesions and skin cancers at levels not previously considered harmful, and that genetic factors may influence risk.

Keywords

arsenic; total arsenic; inorganic arsenic; organic arsenic; arsenic metabolism; skin cancer; basal cell carcinoma; squamous cell carcinoma; skin lesions; low dose exposure; drinking water exposure

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Conflict of Interest

Margaret R. Karagas, Anala Gossai, Brandon Pierce, and Habibul Ahsan declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Introduction

The skin is a sentinel organ for the effects of chronic arsenic exposure, including exposure through drinking water. In particular, arsenical skin lesions are the hallmark of chronic arsenic poisoning and typically begin to appear within a few years of exposure [1, 2]. Individuals with these lesions are considered to be at higher risk for skin and other cancers [3]. Skin lesions typically begin with a diffuse hyper-pigmentation (often with hypopigmented spots) of chest, neck and trunk, with concomitant or later appearance of hyperkeratosis of palms and soles [4, 5].

According to the International Agency for Research on Cancer (IARC), there is sufficient human evidence of arsenic's skin carcinogenicity [6–8]. The earliest links came from patients treated for psoriasis and other ailments with arsenic-containing compounds (e.g. Fowler's Solution containing 1% potassium arsenite), and later in German vintners exposed to inorganic arsenic (iAs)-pesticides [8]. Furthermore, several regions with highly arsenic-contaminated drinking water have reported cases of skin cancers (reviewed in IARC, 2004 [7]). In 1968, Tseng and colleagues published an ecologic analysis of village drinking water and skin cancer prevalence based on a household survey in the southwest of Taiwan's Blackfoot endemic region, where residents consumed arsenic-contaminated artesian well water for many decades [9]. A clear increasing trend in skin cancer prevalence was observed from low (<300 μg/L), medium (300 – 600 μg/L) and high (>600 μg/L) arsenic areas of 2.6, 10.1 and 21.4 cases per 1000 persons – demonstrating an 8-fold difference from the highest to lowest category of arsenic exposure. Elevated standardized mortality ratios of skin cancer both in the southwest of Taiwan and in a northern region of Chile served by an arsenic contaminated water supply (of up to 870 μg/L) further pointed to excess skin cancers among populations exposed to high drinking water concentrations of arsenic [7, 8]. The characteristics of arsenic-associated skin tumors include squamous cell carcinomas (SCC) (including Bowen's disease) arising in keratoses and multiple basal cell carcinomas (BCC) [10–12]. While there is an intriguing report of an association between arsenic exposure and melanoma skin cancer in a US population [13], this association has not been evaluated in other populations and it has not yet been deemed causal.

Further, it has been hypothesized that individuals vary in their susceptibility to arsenic toxicity due in part to inter-individual differences in inherited genetic factors (with other environmental, nutritional, and/or lifestyle susceptibility factors likely to play a role). For instance, genetic variants that influence an individual's capacity to metabolize and excrete arsenic could impact an individual's body burden of arsenic and also affect an individual's susceptibility to exposure. One example of this phenomenon is the 10q24.32 region, which contains the AS3MT gene (arsenite methyltransferase). There are multiple variants in this region that show independent association with relative concentrations of arsenic metabolites in urine, suggesting they impact arsenic metabolism efficiency and toxicity risk [14–18].

An outstanding question is whether skin lesions and cancers occur globally in populations with lower, more common levels of exposure to arsenic in drinking water, including those around the current WHO drinking water guideline of 10 μg/L [19]. The majority of the skin

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lesions are potentially reversible, except for very advanced keratotic nodules which persist for decades in some individuals. Moreover, it is as yet uncertain how risks may be altered by individual differences in arsenic metabolism that may be particularly relevant to populations with lower exposure levels. As this emerging literature has not been extensively reviewed, we focus here on epidemiologic case-control and cohort studies of skin lesions and malignancies characterized by individual estimates of exposure to arsenic through drinking water or biomarkers of arsenic exposure that correlate with drinking water exposure at exposures levels encompassing the WHO guideline value. Our review does not encompass laboratory experiments or mechanistic-based studies.

Methods

To systematically review the epidemiologic literature on skin lesions and skin cancer, we searched for articles published and catalogued in PubMed prior to July 2014. Study designs other than case-control or cohort studies (e.g., studies lacking individual exposure estimates and case reports) were excluded from this review. We did not consider studies based on skin cancer mortality as an endpoint [20–22] as these conditions are not typically fatal and do not accurately reflect the incidence of these outcomes. Further, we removed studies that only included exposure above 100 μg/L. Thus, studies exclusively reporting on high levels of arsenic exposure (e.g., in regions in Taiwan or South America) were omitted [9, 23–26]. Studies that used individual estimates from drinking water arsenic measurements or a biomarker known to correlate with drinking water arsenic (e.g., urine or toenails [27, 28]) were included in the review, but those which considered arsenic-containing medicines were excluded [29]. However, occupational arsenic exposure, disease-surrogates (e.g., when Blackfoot disease was used to define exposure), or exposures classified solely by self-report were excluded. Studies that did not report original research; only presented effect estimates modified by some other factor; were carried out *in vitro*, in animal models, or in human tissues to primarily study biological mechanisms were not considered in this review. In addition to articles identified through PubMed, we searched reviews of arsenic and skin lesions or cancer (including IARC 2004 and 2009 [7, 8], EFSA 2009 [30], and NAS 2014 [31]) as well as the reference lists of the articles we reviewed to identify any additional articles. Two authors reviewed the papers for inclusion/exclusion criteria and questions were resolved by consensus.

For skin lesions, we searched PubMed for the words ‘arsenic’ and ‘skin lesions’ or ‘skin lesion’ or ‘dermal lesion’. In total, 273 publications were returned by the search, of which 22 publications met our inclusion criteria. For multiple studies from the same cohort, we presented the publication with the longest follow-up provided it included results with detailed exposure information. Of the 22 publications, 8 reported on the same study, so only 1 [32] of the 8 publications was presented (the other 7 were identified in the comments section of Table 1). In the end, 15 publications were reviewed (Figure 1a).

For skin cancers, we reviewed original research relevant to non-melanoma skin (NMSC) or keratinocyte cancers (i.e., squamous cell and basal cell carcinomas of the skin – including Bowen’s disease), as arsenic is known to cause these malignancies. Melanoma was excluded from this review, as so far very few studies have evaluated the association between arsenic

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and melanoma. In PubMed, we searched for the words 'arsenic' and 'non-melanoma skin cancer' or 'SCC' or 'BCC' or 'squamous cell carcinoma' or 'basal cell carcinoma' or 'keratinocyte cancer'. In total, 156 publications were returned by the search and 10 publications were identified that met our criteria (Figure 1b).

Results

Skin lesions and arsenic

Of the 22 published studies (15 individual studies representing unique research) that evaluated the association between arsenic exposure and skin lesions, the majority were conducted within South Asian populations and the others were from China (Table 1). All publications were identified in PubMed, except for one study identified by a hand search (Figure 1a). There were thirteen case-control or cross-sectional studies and two cohort studies that met our criteria.

South Asia—A total of 9 studies were conducted in Bangladesh [32–40]. In general, a well-established dose-response relationship was evident for the association between the concentration of arsenic in drinking water and skin lesions. For the Bangladeshi population, the risk of skin lesions was reported to begin at drinking water concentrations as low as 10 μg/L [32, 41]. In the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh, there was a 70% increased risk of skin lesions for those exposed to 50–100 μg/L water arsenic as compared to those with <10 μg/L, and this risk increased monotonically with higher concentration, with more than three-fold increased risk for the highest exposed group (200+ μg/L) [32].

Several other studies in South Asian populations reported increased risk for water arsenic [33, 36, 38, 42, 43]. In West Bengal, India, the risk for skin lesions also began to increase with water arsenic concentrations >50 μg/L [42] as had been observed in many Bangladesh studies, and prevalence estimates showed an increase in skin lesion cases also beginning around 50 μg/L with a significant trend of increasing prevalence as water arsenic levels increased [43]. The Sindh region of Pakistan's elevated water arsenic levels resulted in significantly increasing prevalence of skin lesions with increasing water arsenic and cumulative ingested dose or urinary excretion [44, 45].

In addition to well water concentrations of arsenic, measures of urinary arsenic, urinary arsenic metabolites, and arsenical toenail concentration can inform to what extent the internal dose of arsenic drives skin lesion status [46]. In Bangladesh, numerous studies have reported increased risk of skin lesions with higher levels of urinary arsenic [32–34, 39]. In HEALS, creatinine-adjusted total urinary arsenic was associated with increasing risk of skin lesions in a significant trend, with those excreting the highest levels of arsenic in urine (>393 μg/g) having 2.4-fold increased odds of skin lesions compared to those with the lowest levels of urinary arsenic [32].

Some of these studies also evaluated modifiers of skin lesion risks. In HEALS and other study populations, skin lesion risk related to arsenic was modified by host factors including gender [47], genetic variations as described below [37], and diet [48, 49].

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China—A case-control study conducted in the Inner Mongolia region of China reported significantly increased risk of skin lesions beginning from 5.1 μg/L of arsenic in well water, with increasing risk as water concentrations increased [50]. Similarly, a cross-sectional analysis of a study conducted in Inner Mongolia calculated greatly increased risk of skin lesions when exposed to >50 μg/L of arsenic in water – even after adjusting for duration of exposure [51]. The dose-response trends between arsenic concentration in water and skin lesion risks are very similar to those reported for water arsenic in the HEALS cohort in Bangladesh.

Skin cancers and arsenic

The 10 publications identified as meeting our criteria were from eight distinct study populations reported from seven countries (Table 2). Two publications were derived from the same study [52, 53], but presented different analyses (one categorical and one continuous) so are represented in Table 2 as one study. Two publications were conducted on different samples drawn from the same study population, and therefore are presented separately in Table 2 [54, 55]. Six publications were identified from PubMed and four publications from a hand search (Figure 1b). There were two cohort studies and eight case-control studies that met our criteria.

Northern Europe—An analysis based on the prospective Diet, Cancer and Health (EPIC) study from Denmark (n=56,378 persons) determined drinking water concentrations for individual cohort members by linking their addresses to average water concentrations of the water utilities serving the area [56]. For individuals who lived in residential areas served by multiple utilities, drinking water concentrations were averaged over these utilities. Data on potential confounders were collected from questionnaires at enrollment and included skin reaction to the sun, but not information on sun exposure history itself. First non-melanoma skin cancers were identified in the cohort by linking to the Danish Cancer Registry that ascertains these malignancies; however analyses were not performed separately for basal cell carcinomas and squamous cell carcinomas (i.e., they were grouped in the analysis). Estimated water concentrations ranged from 0.05 μg/L to 25.3 μg/L with 95% of the population being at or below 2.1 μg/L – and thus had very low exposure. No overall association with skin cancer was observed (IRR 0.99, 95% CI = 0.94, 1.06, per μg/L increase in time-weighted average exposure since age 41).

Eastern Europe—A population-based case-control study in Slovakia included 264 histologically confirmed first primary NMSC registered in the region (of which 91% were basal cell carcinoma) and 286 randomly selected age and sex matched controls [57]. In a

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stepwise regression analysis, adjusted for urinary creatinine, sex, renal disorder, current smoking status, place of residence, self-supply with homegrown food, arsenic in house dust samples, arsenic in soil samples, and age, total urinary arsenic was higher in NMSC cases than controls (P=0.03) as was inorganic urinary arsenic (P<0.001) and DMA (P = 0.045). Exposure to arsenic in this population was largely due to emissions from a coal burning power plant, and arsenic in drinking water was estimated to be relatively low [58].

The Arsenic Health Risk Assessment and Molecular Epidemiology (ASHRAM) study was a larger case-control study of 529 newly diagnosed, histologically confirmed basal cell skin cancer cases identified from hospital pathologists and 540 hospital (mostly general surgery, orthopedic, and trauma, e.g., appendicitis, abdominal hernia, duodenal ulcer, cholelithiasis, or fracture in-patients) controls from Hungary, Romania, and Slovakia [59]. An odds ratio of 1.18 (95% CI = 1.08, 1.28) was associated with each 10 μg/L increase in average lifetime drinking water concentration of inorganic arsenic.

Taiwan—In a cross-sectional study of 1,081 individuals from the southwest of Taiwan, skin cancer prevalence was associated with average drinking water concentrations in their village of residence and cumulative drinking water arsenic exposure, with evidence of a dose-response relationship [54]. Similar trends were observed with incident skin cancer occurrences (n=33) during the follow-up period [55]. Also in southwest Taiwan, a hospital-based case-control study included 76 newly diagnosed NMSC cases with histologically confirmed Bowen's disease (29.2%), basal cell carcinoma (33.3%) or squamous cell carcinoma (47.2%) from National Cheng-Kung University Hospital compared to 224 hospital controls (with diagnoses of fractures or cataracts) [60]. Urinary arsenic measurements were taken along with estimates of cumulative arsenic exposure derived from the average artesian well water concentration in their village of residence 30 years ago and duration of consuming that water. While no association was observed with NMSC and total urinary arsenic, an increasing trend was found with cumulative arsenic exposure (P for trend=0.007).

USA—In a population-based case-control study of incident basal cell (n=587) and invasive squamous cell skin cancers (n=284) and 524 age- and sex-matched controls from New Hampshire, USA, there was evidence of an increased risk of invasive squamous cell carcinoma (OR = 2.07, 95% CI = 0.92, 4.66) and to a lesser extent basal cell carcinoma of the skin (OR = 1.44, 95% CI = 0.74, 2.81) among those with the highest levels of toenail arsenic concentration compared to those with the lowest levels of toenail arsenic concentration [52]. Fitting a two-segment linear model with continuous toenail arsenic concentrations, a dose-response relationship was observed above the change-point of 0.105 μg/g that translated to 1–2 μg/L in drinking water [53]. A large proportion of the study population (30–40%) had a private, unregulated water system at their place of residence, with over 10% of the private systems containing arsenic above 10 μg/L. A subsequent population-based case-control study from New Hampshire specifically investigated squamous cell carcinomas of the skin using urinary arsenic detection. In this study, a linear dose-related increase was observed with total urinary arsenic (excluding arsenobetaine) (OR=1.37, 95% CI = 1.04, 1.80 per unit increase of ln-transformed concentrations of

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arsenic). There was an increasing trend in the odds ratios for SCC with each urinary fraction (absolute concentrations of iAs; monomethylated arsenic species, MMA; dimethylated arsenic species, DMA), with the strongest association for MMA [61].

Mexico—A small dermatology clinic-based case-control study from Lagunera, Mexico involved 42 prevalent clinically diagnosed NMSC cases and 48 controls [62]. Individual arsenic exposure was determined by urinary arsenic and historic exposures using drinking water arsenic concentrations for their place of residence multiplied by the number of years they lived there. The investigators hypothesized that human papillomavirus (HPV) infection might contribute to NMSC risk among those chronically exposed to arsenic as a result of enhanced viral susceptibility to infection consequent to arsenic-induced immunosuppression. While they found no association with urinary arsenic or historic exposure among those seronegative for HPV 16, a higher odds ratio was found among those with high historic arsenic exposure who were HPV 16 positive (OR=16.5, P=0.001, 95% CI = 2.97, 91.75) when compared to those who were HPV 16 negative and had low arsenic exposure. This subgroup finding however was based on very small stratum sizes, and may have been due to chance, particularly since HPV16 is not among the cutaneous HPVs (e.g., reviewed in Farzan et al. 2013 [63]).

Interactions with Arsenic Metabolites or Genetic Polymorphisms in ASMT (arsenite methyltransferase)

Several epidemiological studies have reported associations between arsenic metabolite percentages measured in urine and risk for arsenical skin lesions [33, 35, 37, 64, 65]. More specifically, higher MMA% (and/or lower DMA%) in urine have been related to reduced methylation capacity and an increased risk of skin lesions [37]. This suggests that low arsenic metabolism capacity is a risk factor for arsenic toxicity because individuals with low-capacity genotypes will retain more arsenic in the body. These findings further imply that metabolism capacity (and genetic variants that influence this capacity) may interact with arsenic exposure to influence skin lesion risk. These results also are consistent with *in vitro* and animal studies that provide evidence that MMA is a potential driver of arsenical skin lesions risk. [37]

In Bangladesh, a case-control study found participants excreting higher proportions of MMA (>12%) but lower DMA proportions (<76%) to be at significantly higher risk of skin lesions [35], and the increased risk associated with higher MMA% (starting around 13%) was also seen in another study conducted in Bangladesh [37]. A case-control study from Bangladesh used path analysis to determine that the odds of skin lesions were significantly associated with $\log_{10}$ MMA%, but found no association with DMA [33]. A small Taiwanese case-control study of 26 skin lesion patients with gender- and age-matched controls indicated that participants with high MMA% (more than 15.5%) had an odds ratio of skin lesions of 5.5, compared to those with low MMA%, and those with low DMA% (less than 72.2%) had an odds ratio of 3.25, compared to those with high DMA% [66]. A Mexican cross-sectional study of 104 residents of neighborhoods in close proximity to mining operations and contaminated groundwater found a difference in the mean percentage of MMA in the urine among As-exposed subjects, with residents displaying skin lesions having

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7.7% MMA, and residents without lesions having 5.9% (P=0.072) [64]. Yet another study conducted in the Huhhot Basin of China found the proportion of arsenic metabolites within urine samples to influence risk of skin lesions, with lowered arsenic methylation capacity (i.e., lower DMA% and higher MMA%) suggested to increase the risk of arsenic-induced skin lesions [67].

The most prominent example of genetic variation influencing arsenic metabolism capacity is the 10q24.32 locus, which harbors the *AS3MT* gene (encoding the arsenite methyltransferase enzyme). Genetic variants in this region have shown consistent association with arsenic metabolism capacity across several populations (reviewed in Agusa et al. [14]). A recent genome-wide association study (GWAS) of Bangladeshi individuals confirmed this finding and provided evidence of two independent association signals in this region, represented by rs9527 and rs11191527 [15].

Recent studies have reported associations between these 10q24.32 metabolism-related SNPs and skin lesion risk. A Bangladeshi study of 2,483 skin lesion cases and 2,857 controls demonstrated independent association for both metabolism-related 10q24.32 SNPs (rs9527 and rs11191527) and skin lesions status, with the high-methylation capacity alleles being associated with decreased risk [16]. These SNPs also showed evidence of interaction with arsenic exposure to influence skin lesions risk, with the effect of arsenic being stronger among individuals with low metabolism capacity alleles [16]. Similarly, in a study of arsenic-exposed Mexican individuals (71 skin lesions cases and 51 controls), the low-capacity allele of 10q234.32 SNP rs11191439 was associated with decreased DMA% and increased skin lesions risk. rs11191439 is a non-synonymous AS3MT SNP (Met287Thr) that is in moderate to strong linkage disequilibrium with rs9527 (r^2 of 0.29 to 0.95, depending on population). In contrast to these studies, data from 229 skin lesions cases and 199 controls sampled from an arsenic-exposed Indian population showed no association between AS3MT SNP rs11191439 (Met287Thr) and skin lesions status [17]. Aside from 10q24.32, no other genomic regions have shown consistent association with arsenic metabolism capacity or skin lesion risk across multiple studies (reviewed in [18]). Also, no additional regions were identified in the GWAS setting [15, 16].

To date, we know of no studies that have specifically evaluated associations or SNP-arsenic interactions for 10q24.32 variants in relation to skin cancer risk. However, there is some, albeit inconsistent evidence that arsenic metabolism may modify risk of skin cancer. For example, in a study from Slovakia, the ratio of inorganic to organic arsenic calculated as iAs/(MMA+DMA) was lower (P<0.05) amongst cases compared to controls [58]. Likewise, in the ASHRAM study, the association between urinary iAs and skin cancer was modified by participants' ability to metabolize iAs, with participants below the median of DMA% or above the median MMA% having greater risks [59]. One study from Taiwan found an association between skin cancer cases and a lower ratio of DMA/MMA but higher ratio of MMA/(AsIII+AsV) when compared to controls, suggesting cases differ from controls in their arsenic methylation capability [55]. In a case-control study from Taiwan conducted by Chen et al. 2003, a low DMA to MMA ratio was positively associated with skin cancer in participants with high cumulative arsenic exposure [60]. In contrast, in the US study reported by Gilbert-Diamond *et al.* 2011, while a strong association was observed for

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urinary MMA, the ratios or percentages of the metabolites did not appear to be related to risk of squamous cell carcinoma [61].

Aside from 10q24.32, no other genomic regions have shown consistent association with arsenic metabolism capacity or skin lesion risk across multiple studies (reviewed in [18]). Also, no additional regions were identified in the GWAS setting [15, 16].

Conclusions

Our review of the literature examined lower exposure levels of arsenic than reviewed previously. In aggregate, clear dose-related trends have been observed for arsenic-related skin lesions at levels below 100 μg/L in populations from South Asia and China. The evidence for arsenic exposure and skin cancer (specifically keratinocyte cancers) also suggests a similar dose-related trend, including evidence from South Asia, Taiwan, Mexico, Eastern Europe and the USA. As the impact on skin cancer may differ by histologic type, in future work it is critical to evaluate specific histologic types of lesions as well as measure exposure using sensitive markers, such as biomarkers. As emerging data indicates a role for genetic variation in arsenic metabolism, this also will be an important avenue of evaluation – particularly for skin cancers, for which attention has not yet focused on genetic variation in arsenic metabolism genes. Genetic variants that influence cellular defense against arsenic toxicity, as opposed to arsenic metabolism, could also interact with arsenic exposure to influence skin lesions or skin cancer risk. While no such variants have been identified to date, additional target SNP and large GWAS studies (and genome-wide GxE studies) of arsenic-related skin lesions and malignancies could facilitate the discovery of additional variants that modify the effect of arsenic disease. In summary, our review highlights the need to perform studies of arsenic exposure that estimate health risks at concentrations around the current WHO guideline of 10 μg/L, and that the investigation of skin lesions and skin cancers may be especially helpful in informing these risks.

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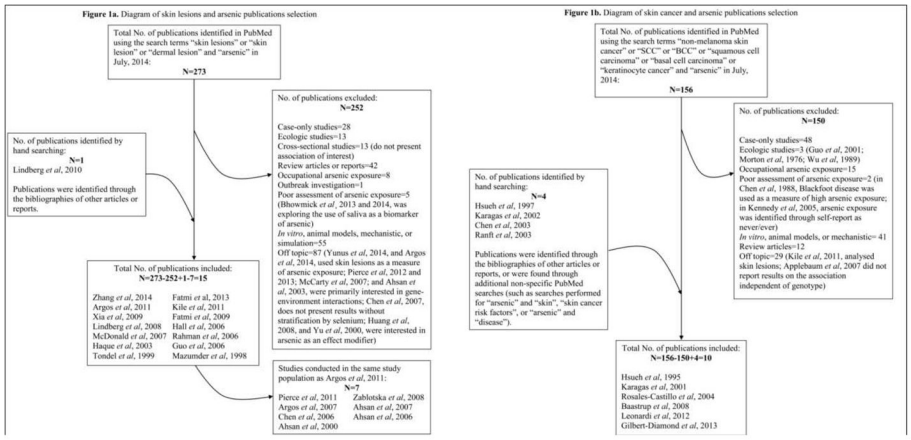

Figure 1.

A, Diagram of skin lesions and arsenic publications selection. **B,** Diagram of skin cancer and arsenic publications selection.

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Table 1

Summary of epidemiological case-control and cohort studies on skin lesions in humans in relation to ingested arsenic exposure

Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls		Study Results		Comments
Case-control studies								
Kile *et al*, 2011	Bangladesh	Skin lesions (keratosis, melanosis, BD, SCC) (2001–2003)	Water, Urine (median water=23, range=≤1–1480 μg/L Median total urinary As=53.9, range=26.1–114.1 μg/L for controls)	859 cases (46.4% leukomelanosis, 44.0% melanosis, 15.6% keratosis, 4.6% hyperkeratosis, 0.9% skin cancer); 868 controls		Odds of skin lesions significantly associated with log10 percentage of MMA (adjusted OR=1.56, 95% CI=1.15–2.12), but not log10 percentage of iAs or DMA		Path analysis; Matched on sex, age, and village; Adjusted for water arsenic, sex, age, BMI, education, betel nut chewing, and log10 creatinine; Suggests excretion of higher proportion of MMA associated with greater risk of skin lesions;
Lindberg *et al*, 2010	Bangladesh	Skin lesions (hyperpigmentation, hypopigmentation, keratosis) (2002–2003, from Rahman *et al*, 2006))	Urine (Total urinary arsenic)	504 cases, 528 controls		OR (95% CI)		Case-referent study; Adjusted for sex, age, SES, and smoking;
				Females	Males	Females	Males	
			<51 μg/L	80 cases, 96 controls	87 cases, 78 controls	1.0 (reference)	1.0 (reference)	
			51–124 μg/L	56 cases, 89 controls	75 cases, 90 controls	0.76 (0.48–1.2)	0.75 (0.49–1.2)	
			>124 μg/L	96 cases, 94 controls	110 cases, 81 controls	1.2 (0.81–1.8)	1.2 (0.80–1.9)	
Xia *et al*, 2009	China (Inner Mongolia)	Skin lesions (hyperpigmentation, hyperkeratosis, depigmentation) (2004)	Water (median=21, range=0.05–637.7 μg/L)	622 cases, 10794 controls		OR (95% CI)		Adjusted for sex, age, education, household income, farm work, smoking, alcohol consumption, water source type; Only used participants with complete covariates;
			0–5 μg/L	58 cases, 3157 controls		1 (reference)		
			5.1–10 μg/L	32 cases, 813 controls		2.52 (1.47–4.30)		
			10.1–20 μg/L	53 cases, 1224 controls		2.83 (1.77–4.53)		
			20.1–50 μg/L	235 cases, 3194 controls		3.94 (2.78–5.59)		
			50.1–100 μg/L	128 cases, 1409 controls		6.03 (4.05–8.97)		
			100.1–300 μg/L	107 cases, 914 controls		8.83 (5.77–13.51)		

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results	Comments
			>300 μg/L	9 cases, 83 controls	7.94 (2.73–23.12)	
Lindberg *et al*, 2008	Bangladesh	Skin lesions (hyperpigmentation, hypopigmentation, keratosis) (2002–2003, from Rahman *et al*, 2006)	Urine (Total urinary arsenic)	504 cases, 528 controls	Adjusted OR (95% CI)*	Case-referent study; Adjusted for sex, age, SES, smoking; Subjects excreting elevated proportions of methylarsonate had higher risk of skin lesions;
			<51 μg/L	167 cases, 174 controls	1.0 (reference)	
			51–124 μg/L	131 cases, 179 controls	0.72 (0.51–1.0)	
			>124 μg/L	206 cases, 175 controls	1.5 (1.1–2.0)	
			% iAs (tertiles)		*P*-for-trend<0.001	
			<9.5	141 cases, 175 controls	1.0 (reference)	
			9.5–13	132 cases, 186 controls	0.93 (0.65–1.3)	
			>13	231 cases, 167 controls	1.8 (1.3–2.6)	
			% MMA (tertiles)		*P*-for-trend<0.001	
			<7.9	69 cases, 177 controls	1.0 (reference)	
			7.9–12	110 cases, 178 controls	1.1 (0.74–1.7)	
			>12	325 cases, 173 controls	2.8 (1.9–4.2)	
			% DMA (tertiles)		*P*-for-trend<0.001	
			<76	307 cases, 187 controls	1.0 (reference)	
			76–82	118 cases, 182 controls	0.39 (0.28–0.55)	
			>82	79 cases, 159 controls	0.41 (0.28–0.60)	
McDonald *et al*, 2007	Bangladesh	Skin lesions (2005–2006)	Drinking water	155 cases, 155 controls (women)	OR (95% CI)	Conditional logistic regression as cases and controls matched for village and age; Analysis of pairs >40 or <40 years suggested similar risks for older and younger women;
			0–10 μg/L	85 cases, 97 controls	1 (reference)	
			11–50 μg/L	53 cases, 49 controls	1.33 (0.77–2.28)	
			51+ μg/L	7 cases, 9 controls	2.96 (1.02–8.59)	
Guo *et al*, 2006	China (Inner Mongolia)	Skin lesions (keratosis, pigmentation, depigmentation) (2000)	Water	59 cases, 82 controls	Adjusted OR (95% CI)	Adjusted for duration of well use, sex, age, smoking;
			<50 μg/L	4 cases, 31 controls	1.0 (reference)	
			51–99 μg/L	2 cases, 4 controls	15.5 (1.53–248.7)	
			100–149 μg/L	14 cases, 16 controls	16.1 (3.73–69.63)	
			>150 μg/L	39 cases, 31 controls	25.7 (6.43–102.87)	

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls		Study Results		Comments
Rahman *et al*, 2006	Bangladesh	Skin lesions (hyperpigmentation, hypopigmentation, keratosis) (2002–2003)	Water	504 cases, 1830 controls		Adjusted OR (95% CI)		Case-referent study; Adjusted for age and asset score;
				Females	Males	Females	Males	
			<10	12 cases, 127 controls	13 cases, 103 controls	1 (reference)	1 (reference)	
			10–49 μg/L	15 cases, 141 controls	38 cases, 120 controls	1.66 (0.65–4.24)	3.25 (1.43–7.38)	
			50–149 μg/L	65 cases, 287 controls	59 cases, 264 controls	3.06 (1.39–6.74)	2.28 (1.04–4.98)	
			150–299 μg/L	84 cases, 300 controls	110 cases, 251 controls	4.08 (1.86–8.93)	5.41 (2.52–16.2)	
			>300 μg/L	56 cases, 142 controls	52 cases 95 controls	6.88 (3.06–15.5)	9.56 (4.20–21.8)	
Haque et al, 2003	India (West Bengal)	Skin lesions (hyperpigmentation, keratosis) (1998–2000)	Water (peak categories) (mean=183 μg/L for controls)	192 cases, 213 controls		Unconditional adjusted OR (95% CI)		Conditional adjusted analysis showed similar results;
			<50 μg/L	6 cases, 57 controls		1 (reference)		
			50–99 μg/L	6 cases, 25 controls		2.5 (0.7–8.9)		
			100–199 μg/L	32 cases, 46 controls		7.4 (2.8–20.0)		
			200–299 μg/L	45 cases, 44 controls		11.4 (4.2–29.6)		
			>300 μg/L	103 cases, 41 controls		29.4 (11.1–77.5)		
Cohort Studies								
Argos et al, 2011	Bangladesh (Health Effects of Arsenic Longitudinal Study, HEALS)	Incident skin lesions (melanosis, leukomelanosis, keratosis) (2002–2004; 2004– 2006; 2007–2009)	Water	10182 (866 cases)		Hazard Ratio (95% CI)		Discrete-time hazard models; Adjusted for sex, age, BMI, education, education years, smoking; Similar association estimates also presented in Pierce et al, 2011, for same follow up time. Cross-Sectional HEALS studies:
				No. of Events		P-for-trend=0.0001		
			0.1–10 μg/L	137		1 (reference)		
			10.1–50 μg/L	134		1.17 (0.92–1.49)		
			50.1–100 μg/L	151		1.69 (1.33–2.14)		
			100.1–200 μg/L	201		1.97 (1.58–2.46)		
			>200.1	235		2.98 (2.40–3.71)		

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results	Comments
			Urine (creatinine-adjusted total As)		P-for-trend=0.0001	Zablotska et al, 2008: effect of vitamins and antioxidants
			7–88 μg/g	136	1 (reference)	Argos et al, 2007: association modified by land ownership
			89–155 μg/g	115	0.90 (0.71–1.15)	Chen et al, 2006: dependence upon smoking, sun, and occupational exposures Ahsan et al, 2006 and 2000
			156–240 μg/g	167	1.34 (1.07–1.68)	Case-Control HEALS study:
			241–392 μg/g	185	1.62 (1.29–2.02)	Ahsan et al, 2007: years 2000–2002 analyzed, genotype dependence
			>393 μg/g	233	2.39 (1.92–2.97)	
Hall et al, 2006	Bangladesh (HEALS)	Incident skin lesions (melanosis, leukomelanosis, keratosis) (2002–2004)	Water (mean=103.1 μg/L for subcohort)	303 cases, 849 subcohort		Case-cohort study; Adjusted for sex, age, BMI, smoking (complete-case analysis);
				No. of cases (Subcohort)	Rate Ratio (95% CI)	
			0.1–7 μg/L	48 (184)	1 (reference)	
			8–38 μg/L	31 (156)	0.92 (0.50–1.67)	
			39–94 μg/L	48 (173)	1.27 (0.73–2.20)	
			95–189 μg/L	81 (171)	1.92 (1.14–3.24)	
			190–564 μg/L	95 (165)	2.50 (1.52–4.14)	
			Urine (mean total urinary As=137.3 μg/L for subcohort)			
			3–35 μg/L	36 (175)	1 (reference)	
			36–64 μg/L	54 (166)	1.63 (0.92–2.89)	
			65–113 μg/L	54 (169)	1.73 (0.99–3.02)	
			114–201 μg/L	68 (172)	2.00 (1.13–3.56)	
			202–1230 μg/L	91 (167)	3.16 (1.73–5.76)	
Cross-sectional Studies						
Zhang et al, 2014	China (Huhhot Basin)	Skin lesions (skin pigmentation, depigmentation, hyperkeratosis; resulted in grade of arsenicosis)	Water (mean=250, range=20–368 μg/L), Urine	302 (79 cases, 223 non-cases)		Adjusted for sex, age, BMI, smoking, alcohol consumption;

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results	Comments
			(creatinine-adjusted median total=549.56, IQR=205.19–675.94			SMI=DMA/(MMA+DMA) negatively associated with skin lesions
			(creatinine-adjusted median total=549.56, IQR=205.19–675.94			
			(creatinine-adjusted median total=549.56, IQR=205.19–675.94			
			(creatinine-adjusted median total=549.56, IQR=205.19–675.94			
			(creatinine-adjusted median total=549.56, IQR=205.19–675.94			
			μg/g in controls)			
				Cases, Non-Cases	Adjusted OR (95% CI)	
			% iAs (tertiles)			
			<15.47	21, 79	1 (reference)	
			15.47–24.29	32, 69	1.90 (0.93–3.89)	
			>24.29	26, 75	1.65 (0.78–3.52)	
			% MMA (tertiles)			
			<12.88	13, 87	1 (reference)	
			12.88–17.85	34, 67	3.21 (1.46–7.04)	
			>17.85	32, 69	2.09 (0.94–4.65)	
			% MMA (tertiles)			
			<12.88	32, 68	1 (reference)	
			12.88–17.85	27, 74	0.58 (0.29–1.16)	
			>17.85	20, 81	0.50 (0.24–1.06)	
Fatmi et al, 2013	Pakistan (Sindh)	Skin lesions (melanosis, keratosis) (2008–2009)	Water	534 (72 cases, 462 non-cases)	Prevalence rate per 100 (95% CI)	Test kits for water As concentration measured as categories;
			>50–99 ppb	2 cases, 42 non-cases	4.5 (2.4–6.26)	
			100–299 ppb	47 cases, 268 non-cases	4.5 (2.4–6.26)	
			300–399 ppb	10 cases, 68 non-cases	11.7 (13.85–20.23)	
			≥400 ppb	13 cases, 84 non-cases	12.8 (9.24–14.76)	
Fatmi et al, 2009	Pakistan (Sindh)	Skin lesions (hypopigmentation, hyperpigmentation, hyperkeratosis) (2006)	Water (cumulative dose)	3874 (63 cases, 3811 non-cases)	Prevalence per 1000	Cumulative dose calculated using arsenic levels in water and average daily drinking of water over number of years, per body weight;
			<10 μg/L-yrs/kg		5.7	
			10–<50 μg/L-yrs/kg		11.8	
			50–<100 μg/L-yrs/kg		56.5	
			100+ μg/L-yrs/kg		38.5	
					P-for-trend<0.01	

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls		Study Results		Comments
			Urine					
			<10 μg/L			36.6		
			10–<50 μg/L			99.5		
			50–<100 μg/L			123.6		
			100+ μg/L			186		
						P-for-trend=0.06		
Tondel et al, 1999	Bangladesh	Skin lesions (keratosis, hyperpigmentation, hypopigmentation)	Water (range=10–2040 μg/L)	1481 (430 cases, 1051 non-cases)		Age-adjusted prevalence rate per 100 (95% CI)		As dose was calculated by dividing present As level by body weight; P-for-trend<0.001 for both sexes;
						Male	Female	
			≤5 μg/L-kg			19.6 (14.2–24.9)	19.7 (8.0–31.3)	
			>5–10 μg/L-kg			30.2 (23.9–36.5)	22.1 (12.4–31.7)	
			>10 μg/L-kg			34.8 (29.7–39.9)	30.8 (24.9–36.8)	
Mazumder et al, 1998	India (West Bengal)	Skin lesions (keratosis, hyperpigmentation) (1995–1996)	Water (range=nondetectable-3400 μg/L, ~80% of participants consumed <500 μg/L)	7683 (156 keratosis, 361 hyperpigmentation)		Age-adjusted prevalence per 100		Prevalences directly standardized to age distribution of all participants of same sex in study population; P-for-trend <0.0001 for both sexes and diagnoses;
				Female, Male cases:		Female, Male:		
				Keratosis	Hyperpigmentation	Keratosis	Hyperpigmentation	
			<50 μg/L	0, 4	5, 7	0.0, 0.2	0.3, 0.4	
			50–99 μg/L	2, 6	4, 13	0.4, 1.5	0.8, 3.2	
			100–149 μg/L	3, 4	16, 30	1.2, 1.6	5.7, 11.0	
			150–199 μg/L	6, 11	14, 19	2.3, 4.7	5.1, 7.8	
			200–349 μg/L	10, 22	32, 58	2.0, 4.9	6.5, 13.1	
			350–499 μg/L	7, 22	26, 38	2.7, 9.0	9.5, 15.7	
			500–799 μg/L	10, 26	17, 40	3.1, 8.9	5.3, 13.8	
			>800 μg/L	10, 13	13, 29	8.3, 10.7	11.5, 22.7	

OR, odds ratio; CI, confidence interval; IQR, interquartile range; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; As, arsenic; iAs, inorganic arsenic; MMA, monomethylarsonic acid; DMA, dimethylarsinic acid; ΣAs, total arsenic summed from iAs, MMA and DMA.

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Table 2

Summary of epidemiological case-control and cohort studies on skin cancer in humans in relation to ingested arsenic exposure, with emphasis on non-melanoma skin cancers

Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results		Comments
Case-control studies							
Gilbert-Diamond *et al*, 2013	United States (New Hampshire)	Histologically confirmed incident SCC (2003–2009)	Urine (iAs, MMA, DMA) Median ΣAs=4.76 (2.94–8.10) μg/L	470 invasive SCC, 447 control	OR (95% CI)		Logistic regression analyses; Matched on sex and age; Adjusted for urinary creatinine, sex, age, BMI, education, smoking, skin reaction to chronic sun exposure (excluded participants who consumed seafood 2 days prior to urine collection); Association strongest for MMA;
					ln(ΣAs)	1.37 (1.04, 1.80)	
					ln(iAs)	1.20 (0.97, 1.49)	
					ln(MMA)	1.34 (1.04, 1.71)	
					ln(DMA)	1.34 (1.03, 1.74)	
Leonardi *et al*, 2012	Hungary, Romania, and Slovakia (ASHRAM study)	Histologically confirmed, consecutively diagnosed BCC (2003–2004)	Water Median iAs=1.2 (0.7–13.8) μg/L	529 BCC, 540 controls		OR (95% CI)	Matched on sex, age, and area of residence; Adjusted for sex, age, education, area of residence, skin response to 1 hour of midday sun, skin complexion; For each 10 μg/L increase in iAs concentration;
					peak daily iAs dose rate	1.13 (1.07, 1.20)	
					cumulative iAs dose	1.10 (1.01, 1.19)	
					lifetime average water iAs concentration	1.18 (1.08, 1.28)	
Rosales-Castillo *et al*, 2004	Mexico (region Lagunera)	Prevalent, clinically diagnosed NMSC	Urine Mean As=34.7 (range=3.2–124.5) μg/L	42 NMSC,		OR (*P* value)	Adjusted for sex, age, sun exposure;
					Urinary As	1.01 (0.180)	

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results		Comments
			Cumulative As geometric mean=769 (256–11,698) ppm-years	48 controls	Cumulative As (HPV-)	4.53 (0.11)	Association modified by HPV infection; Arsenic exposure measured as cumulative exposure determined by extrapolating a measurement of current arsenic in urine and participant's residential history;
Chen *et al*, 2003	Southwest Taiwan	Pathologically diagnosed, incident skin cancer (1996–1999)	Urine Mean total As=43.71 (standard deviation=29.34) μg/L Cumulative As mean=8.14 (standard deviation=15.48) mg/L-year	76 NMSC - 29.2% BD, 33.3% BCC, 47.2% SCC; 224 controls	mg/L-year 0–2 >2–15 >15 *P* for trend=0.007	OR (95% CI) 1.00 (reference) 1.87 (0.79–4.45) 2.99 (1.30–6.87)	Adjusted for sex, age, BMI, education, smoking, hair dye use; Association modified by primary and secondary arsenic methylation index; Cumulative arsenic exposure determined using artesian well water As concentration and duration of drinking artesian well water;
Ranft *et al*, 2003	Slovakia (Prievidza district)	Histologically confirmed, first NMSC diagnosis (1996–1999)	Urine (iAs, MMA, DMA) Median ΣAs=6.04 (range=1–4) μg/L	264 NMSC - 91% BCC, Pesch *et al*, 2002; 286 controls	ΣAs iAs DMA	Ratio of means (*P* value) 1.12 (0.03) 1.13 (0.001) 1.21 (0.045)	Step-wise regressions; Matched on sex and age; Adjusted for As in house dust samples, As in soil samples, urinary creatinine, sex, age, area of residence, self-supply with homegrown food,

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results			Comments
								smoking, renal disorder; smoking, renal disorder; Arsenic exposure primarily from residential proximity to a coal-burning power plant;
					ΣAs		1.12 (0.03)	
					iAs		1.13 (0.001)	
					DMA		1.21 (0.045)	
Karagas *et al*, 2001 Karagas *et al*, 2002	United States (New Hampshire)	Histologically confirmed incident BCC and SCC (1993–1995)	Toenails Geometric mean=0.094 (range=0.01–0.81) μg/g	587 BCC, 284 invasive SCC - BD excluded, 524 controls	OR (95% CI)			Matched on sex and age; Point at which dose-response increased for SCC as calculated with a two-segment linear model for BCC and SCC (maximum likelihood change point)=0.105 μg/g (95% CI=0.093, 0.219);
					μg/g	BCC	SCC	
					0.009–0.089	1.00 (reference)	1.00 (reference)	
					0.090–0.133	1.01 (0.76, 1.35)	0.93 (0.64, 1.34)	
					0.134–0.211	1.06 (0.74, 1.51)	0.98 (0.61, 1.58)	
					0.212–0.280	0.72 (0.40, 1.31)	1.10 (0.55, 2.21)	
					0.281–0.344	0.75 (0.31, 1.81)	1.00 (0.33, 3.01)	
					0.345–0.81	1.44 (0.74, 2.81)	2.07 (0.92, 4.66)	
Hsueh *et al*, 1995	Southwest Taiwan (Homei, Fuhsin, and Hsinming villages in Putai township)	Prevalent skin cancer (90% BD, and 91% BCC and SCC histologically confirmed) (1988–1989)	Water median range=0.70–0.93 ppm (Kuo, 1994)	1,081 persons (66 skin cancer cases, including BD)				Adjusted for sex and age; Some missing data regarding arsenic exposure;
			Average arsenic exposure (ppm):	Cases:	OR (95% CI):			
			0	2	1.00 (reference)			
			0.0–0.70	20	3.45 (0.70–17.0)			
			>0.71	30	5.04 (1.07–23.8)			
			P for trend		<0.05			
			Cumulative arsenic exposure (ppm-years)					

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results	Comments
			<4	1	1.00 (reference)	
			5–24	22	8.90 (1.07–73.75)	
			>25	28	13.74 (1.69–111.64)	
			P for trend		<0.05	
Cohort Studies						
Baastrup *et al*, 2008	Denmark (EPIC cohort)	First NMSC diagnosis (1993–2003)	Water mean=1.2 (0.05–25.3) μg/L	56,378 persons (1,010 NMSC cases)	Time weighted average arsenic levels IRR=0.99 (95% CI=0.94–1.06)	Adjusted for education, occupation, area of enrollment, skin reaction to sun, suntanned during summer; Exposure assigned based on place of residence, and included average concentrations across utilities for some individuals; Few subjects had exposure levels above 2 μg/L; No designation of histologic type (most could be BCC, but BCC and SCC grouped as single outcome), and complete coverage of NMSCs is questionable;
Hsueh *et al*, 1997	Southwest Taiwan (Homei, Fuhsin, and Hsinming villages in Putai township)	Incident skin cancer (1989–1992)	Water	654 persons (33 skin cancer cases, including BD)		Cox proportional hazards analysis; Matched on sex and age; Adjusted for educational;

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Reference	Study Population	Endpoint (Diagnosis Years)	Arsenical Exposure Assessment (Range)	Cohort size (No. of Cases) or No. of cases, No. of controls	Study Results	Comments
			Average arsenic concentration in drinking water (μg/L):	Cases:	Relative Risk (95% CI):	
			0	1	1.00 (reference)	
			10–700	12	3.30 (0.42, 35.76)	
			710–1100	13	8.69 (1.08, 65.50)	
			Unknown	7	4.75 (0.55, 40.35)	
			Cumulative arsenic exposure (μg/L-year):			
			0	1	1.00 (reference)	
			100–10,600	2	2.82 (0.25, 31.87)	
			10,700–17,700	5	2.61 (0.30, 22.90)	
			>17,700	18	7.58 (0.95, 60.33)	
			Unknown	7	5.14 (0.59, 44.41)	

OR, odds ratio; CI, confidence interval; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; BD, Bowen's disease; As, arsenic; iAs, inorganic arsenic; MMA, monomethylarsonic acid; DMA, dimethylarsinic acid; ΣAs, total arsenic summed from iAs, MMA and DMA.