Susceptibility to arsenic-induced skin lesions from polymorphisms in base excision repair genes

Carrie V BRETON1, Wei ZHOU2, Molly L KILE3, E. A. HOUSEMAN4, Quazi QUAMRUZZAMAN2, Mahmuder RAHMAN5, Golam MAHIUDDIN4 and David C CHRISTIANI1,2

1Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA. 2Department of Environmental Health, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA. 3Department of Work Environment, University of Massachusetts Lowell, Kitson Hall, 202E, One University Avenue Lowell, MA 01854, USA and 4Dhaka Community Hospital, 190/1 Baro Moghbazar, Wireless Railgate, 1217, Dhaka, Bangladesh

E-mail: cbreton@hsph.harvard.edu

Abbreviations: APE1, apurinic/apyrimidinic endonuclease; BER, base excision repair; BML, body mass index; CIs, confidence intervals; hOGG1, human 8-oxoguanine DNA glycosylase; HWE, Hardy–Weinberg equilibrium; POLb, polymerase hOGG1, APE1, and XRCC1

Introduction

Chronic arsenic exposure has been linked to a wide variety of diseases including cancers, peripheral vascular disease, chronic cough, bronchitis, cardiac disease and peripheral neuropathy (1, 2). In Bangladesh, where arsenic-contaminated drinking water is endemic in many regions, the earliest observed physical manifestations of arsenic toxicity are skin lesions including hyperkeratosis and keratosis, which can later lead to skin cancer such as Bowen’s disease, basal cell and squamous cell carcinomas (3, 4, 5, 6). However, not everyone exposed to arsenic develops skin lesions, suggesting other factors play a role in individual susceptibility to arsenic toxicity.

Arsenic can generate DNA damage that needs to be repaired (7) and change cellular capacity for DNA repair (8, 9, 10, 11). If the development of skin lesions is dependent in part on the accumulation of unrepaired DNA damage resulting in proliferation of aberrant skin cells that subsequently progress into visible skin lesions, polymorphisms in DNA repair pathways could influence susceptibility to arsenic. Not only could polymorphisms in DNA repair pathway genes alter DNA repair function in general but also they may do so in a manner conditional on arsenic exposure.

Base excision repair (BER) and nucleotide excision repair are two main DNA repair pathways through which the body repairs spontaneous and endogenously produced DNA damage (12, 13, 14). Nucleotide excision repair plays a role in repairing non-bulky lesions and a polymorphism in ERCC2 was recently shown to confer increased risk for development of hyperkeratosis among an arsenic-exposed population in West Bengal (15). However, BER is the most important pathway for the removal of oxidative lesions (14), which are hypothesized to play a key role in arsenic toxicity (7, 16, 17), and thus was the focus for this investigation.

Many proteins are involved in BER, but three of the most well-studied are X-ray repair-complementing group 1 (XRCC1), apurinic/apyrimidinic endonuclease (APE1) and human 8-oxoguanine DNA glycosylase (hOGG1). XRCC1, a scaffolding protein, can interact with multiple enzymatic components at each stage of the repair process, including DNA polymerase β (POLβ), hOGG1 and APE1 (18). Additionally, XRC11 repairs single strand breaks resulting either from the BER process itself or damage to deoxyribose. APE1 is the essential protein that excises apurinic/apyrimidinic sites generated when glycosylases initiate repair of a damaged base (18). APE1 also helps recruit POLβ and facilitate further steps in the repair process. hOGG1 is a protein specific for the repair of oxidative damage, primarily the DNA adduct 8-Hydroxy-2′-deoxyguanosine (19).

Polymorphisms in XRCC1, APE1 and hOGG1 have been shown to reduce the capacity to repair oxidative damage (20), which could result in an increased risk for accumulating DNA damage and developing diseases such as skin lesions or skin cancer. Recent human studies indicate possible associations between XRCC1 and hOGG1 polymorphisms and various cancers (13, 21, 22, 23), although only XRCC1 has been associated specifically with basal cell and squamous cell carcinomas of the skin (24, 25). APE1 has not yet been studied extensively in relation to human disease risk (26).

Limited research suggests that certain BER genetic polymorphisms influence skin cancer (24, 27, 28). Because DNA damage, particularly that caused by reactive oxygen species, has been shown to play a role in skin carcinogenesis (29), we investigated the association of four common polymorphisms in BER genes on the presence of arsenic-induced skin lesions in a large case–control study conducted in an arsenic-endemic region of Bangladesh. Specifically, we evaluated the combination of XRCC1 Arg399Gln (rs25487), XRCC1 Arg194Trp (rs1799782), hOGG1 Ser326Cys (rs1052133) and APE1 Asp148Glu (rs3136820) polymorphisms, including gene–environment interactions with arsenic exposure.

Materials and methods

Participant selection

Nine hundred case–control pairs were recruited from 23 villages within the Pabna district of Bangladesh that are serviced by the Pabna Community Clinic, a primary care satellite clinic of Dhaka Community Hospital. District residents were made aware of the study and asked to participate through a series of community meetings from 2001 to 2003. Two physicians, trained by a dermatologist in characterizing arsenic related skin lesions, screened volunteers in their homes to identify eligible cases and controls. Individuals were considered eligible cases if they resided within the Pabna Community Clinic catchment area of Pabna and had 70% or more of their toenails covered by skin lesions, and as controls if they did not have any skin lesions.

Susceptibility to arsenic-induced skin lesions from polymorphisms in base excision repair genes Carcinogenesis vol. 28 no. 7 pp. 1520–1525, 2007 doi:10.1093/carcin/bgm063 Advance Access publication March 20, 2007 © The Author 2007. Published by Oxford University Press. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org 1520

Downloaded from https://academic.oup.com/carcin/article-abstract/28/7/1520/2526709 by guest on 23 April 2019
zone, were at least 16 years of age and were diagnosed with one or more types of skin lesions: diffuse/spotted keratosis, diffuse/spotted melanosis, hyperkeratosis, leukomelanosis or squamous cell carcinoma. A subset of lesions, including all suspected squamous cell carcinomas, were histologically confirmed. Controls were individuals selected from the same communities and did not have any skin lesions. One control was matched per case and was selected due to an implausible computed BMI of 60. This resulted in 99 cases and 99 controls available for 1684 of these participants, one of whom was excluded due to an implausible computed BMI of 60. This resulted in 99 cases and 99 controls available for analysis.

Toenail clippings were collected and prepared as described by Chen et al. (35). Total arsenic was measured using inductively coupled plasma mass spectrometry (ICP-MS Model 6100 DRC, PerkinElmer, Norwalk, CT) and each sample was subjected to five replicate analyses. Instrument performance and the digestion process were validated using standard reference material water (NIST 1643d and NIST 1643e Trace Elements in Water; National Institute of Standards and Technology, Gaithersburg, MD) and certified human hair reference material (CRM Hair; Shanghai Institute of Nuclear Research, Academia Sinica, China) as described previously (36).

Toenails provide an easily measurable and valid biomarker of arsenic exposure. Several studies have demonstrated a strong association between drinking water arsenic exposure and arsenic concentration in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a non-linear association between arsenic exposure and skin lesions in toenails. In a previous study in this population in Bangladesh, we found a n...
Crude (models 1a–e) and adjusted (model 2) odds ratios showing the effect of toenail arsenic and each genotype on skin lesions are displayed in Table II. After adjusting for covariates and other genes, a 10-fold increase in toenail arsenic concentration was associated with a 7.35-fold increase in odds of skin lesions (95% CI 5.17, 10.45). Individuals with the APE1 148Glu homozygous variant had a nearly 2-fold increased odds of skin lesions compared with those homozygous for the 148Asp allele (odds ratio 1.93; 95% CI 1.15, 3.19). No associations were observed for the XRCC1 and hOGG1 polymorphisms. When the XRCC1 194Trp/Trp and Trp/Arg genotypes were

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>Main effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td>APE1 148Glu</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp/Asp</td>
<td>444 (56.1)</td>
<td>424 (53.5)</td>
<td>1</td>
</tr>
<tr>
<td>Asp/Glu</td>
<td>288 (36.4)</td>
<td>328 (41.1)</td>
<td>0.85 (0.69, 1.04)</td>
</tr>
<tr>
<td>Glu/Glu</td>
<td>60 (7.6)</td>
<td>40 (5.1)</td>
<td>1.46 (0.94, 2.25)</td>
</tr>
<tr>
<td>XRCC1 194Arg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>633 (79.9)</td>
<td>611 (77.2)</td>
<td>1</td>
</tr>
<tr>
<td>Trp/Arg</td>
<td>151 (19.1)</td>
<td>167 (21.1)</td>
<td>1.25 (0.94, 1.67)</td>
</tr>
<tr>
<td>Trp/Trp</td>
<td>8 (1.0)</td>
<td>14 (1.8)</td>
<td>2.07 (0.92, 4.67)</td>
</tr>
<tr>
<td>hOGG1 326Cys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser/Ser</td>
<td>364 (46.0)</td>
<td>373 (47.1)</td>
<td>1</td>
</tr>
<tr>
<td>Cys/Ser</td>
<td>345 (43.6)</td>
<td>340 (42.9)</td>
<td>1.04 (0.84, 1.30)</td>
</tr>
<tr>
<td>Cys/Cys</td>
<td>83 (10.5)</td>
<td>79 (10.0)</td>
<td>1.08 (0.77, 1.51)</td>
</tr>
</tbody>
</table>

Models 1a–e represent separate models for toenail arsenic and each gene in which the individuals were matched on age, gender and area of residence. Model 2 represents a single model in which the individuals were matched on age, gender and area of residence and the estimates were further adjusted for BMI, education, toenail arsenic (as a continuous variable), smoking biri, smoking cigarettes, betel nut chewing and other genotypes.
combined into a single categorical variable, similar results were observed. Furthermore, within model 2, subgroup analyses were performed to determine whether the effect of the APE1 148Glu homozygous variant was specific to a type of skin lesion (e.g. keratosis, melanosis, etc). Although statistical power was lacking, a comparison of point estimates suggested that the effect of the APE1 148Glu homozygous variant was greatest for individuals with melanosis (OR 1.75; 95% CI 0.75, 4.11), followed by those with leukomelanosis (OR 1.28; 95% CI 0.57, 2.85) and keratosis (OR 0.87; 95% CI 0.20, 3.79). There were too few individuals with hyperkeratosis and squamous cell carcinoma to analyze separately.

Several gene–environment interactions were also evaluated. Table III illustrates the interaction between the genotypes, XRCC1 Arg194Trp and APE1 Asp148Glu, with toenail arsenic. A 10-fold increase in toenail arsenic concentration translated to an odds ratio for skin lesions of 2.49 (95% CI 0.34, 17.89) for the XRCC1 Arg194Trp homozygous variant, 4.24 (95% CI 2.02, 8.93) for the heterozygote and 9.49 (95% CI 5.01, 17.99) for the wild-type genotype (Table III). A model in which the homozygous variant and heterozygote genotypes were combined yielded similar results (data not shown). When toenail arsenic was categorized into tertiles and evaluated jointly with genotype (Table IV), the odds ratio for skin lesions was highest among individuals with the XRCC1 wild-type genotype and the highest tertile of toenail arsenic concentration. Within the highest tertile, the variant genotypes conferred a much smaller odds ratio compared with the wild-type genotype. These results suggest that the presence of skin lesions was decreased in individuals possessing at least one variant allele as arsenic concentrations increased.

A marginal interaction was also observed between APE1 and toenail arsenic concentration. The odds ratio for skin lesions for a 10-fold change in toenail arsenic was 7.08 (95% CI 2.18, 23.01) for the APE1 148Glu homozygous variant, 5.62 (95% CI 2.95, 10.69) for the heterozygote and 9.49 (95% CI 5.01, 17.99) for the wild-type genotype. However, since there remained a highly significant negative main effect for the APE1 148Glu/Glu variant in the interaction model, the results are best interpreted by evaluating the overall effect of jointly having the variant APE1 genotype and various levels of toenail arsenic (Table IV). For APE1, the most notable differences in odds ratios were observed at low levels of arsenic, where individuals with the APE1 homozygous variant had a greater odds ratio compared with the heterozygote or wild-type genotypes. The largest odds ratios for skin lesions uniformly occurred in the highest tertile of toenail arsenic; however, these odds ratios did not differ much by genotype.

Lastly, the case-only analyses confirmed the presence of gene–arsenic interactions observed in the case–control analyses. The RORint estimates suggested strong gene–arsenic interactions for XRCC1 194Trp/Trp + Arg/Trp (RORint 0.61; 95% CI 0.44, 0.85) and APE1 148Glu/Glu + Asp/Glu (RORint 0.57; 95% CI 0.43, 0.74) genotypes compared with wild-type. These were similar to the case–control results for XRCC1 194Trp/Trp + Arg/Trp (RORint 0.42; 95% CI 0.23, 0.78) and APE1 148Glu/Glu + Asp/Glu (RORint 0.62; 95% CI 0.37, 1.03).

Discussion

This study provides epidemiological evidence that the BER genes APE1 and XRCC1 affected the odds of skin lesions for individuals living in an arsenic-endemic environment. While odds of skin lesions increased with toenail arsenic concentrations for all individuals regardless of genotype, the XRCC1 194Trp allele offered some protection. When arsenic concentrations were low, the odds of skin lesions were generally low, and few differences were observed between genotypes. However, as arsenic concentrations increased, individuals with at least one XRCC1 194Trp variant allele had lower odds of skin lesions compared with individuals with the wild-type genotype.

One possible explanation for this observation is that XRCC1 is known to interact with several enzymes in the BER pathway and, since the Arg194Trp polymorphism resides in the linker region separating the POL β domain from the poly (ADP-ribose) polymerase (PARP)-interacting domain, the polymorphism could affect XRCC1’s ability to bind to either POL β or poly (ADP-ribose) polymerase (12). If this resulted in decreased DNA repair ability, it could lead to increased accumulation of unrepair DNA damage that enhances apoptosis, thereby reducing the probability of the cell cycle replicating mutated DNA (24). Since arsenic exposure is genotoxic, individuals with the variant allele and high arsenic levels may have damaged skin cells that apoptosis more readily, making the variant protective. However, experimental evidence in support of functional changes of XRCC1 Arg194Trp is limited (45,46,47,48).

The association could also be explained if XRCC1 was differentially down-regulated as a result of arsenic exposure. While this mechanism is currently unknown, arsenic has been shown to down-regulate expression of several DNA repair genes in a time- and dose-dependent manner (28). If arsenic down-regulates transcription of the XRCC1 wild-type genotype more effectively than the XRCC1 heterozygote or homozygous variant, then the variant genotype would be protective because DNA repair would be inhibited to a greater extent in individuals with the wild-type genotype particularly at high arsenic levels.
Despite the lack of knowledge regarding XRCC1 Arg194Trp function, human evidence of a protective effect of the 194Trp allele is growing. Several reviews and a recent meta-analysis suggest that the 194Trp allele is protective against cancers (13,21,26), although the only study to evaluate an association between the Arg194Trp polymorphism and skin cancer found no effect (49). However, two other studies identified positive associations between the XRCCI Arg599Gln polymorphism and skin cancer (24,25). In the present study, neither did we observe any association between XRCCI Arg599Gln and skin lesions nor did we find evidence for a gene–environment interaction with arsenic exposure.

At low to moderate levels of toennail arsenic, an increased odds ratio for skin lesions was observed among individuals with the APEI 148Glu variant compared with wild-type. This could be a result of a general defect in BER capacity because individuals with the APEI variant allele may have a compromised ability to repair DNA, resulting in genetic instability and increased frequency of mutation even at very low levels of arsenic. As arsenic levels increase, arsenic-induced DNA damage is also likely to increase and may overwhelm the BER pathway such that it is less important which APEI genotype is present because neither is capable of repairing the accumulating damage. This would explain the observed APEI–arsenic interaction in which genotype seems to play a more important role at low arsenic levels than at high arsenic levels.

This observation is supported by in vitro and in vivo animal experiments. Functional studies on the APEI polymorphism show that the 148Glu allele may alter endonuclease and DNA-binding activity and reduce ability to communicate with other BER proteins (50). Bacteria deficient in APEI activity exhibit elevated sensitivity to oxidizing and alkylating agents and elevated spontaneous mutation frequencies (51). The loss of a single APEI allele in mice increased their predisposition to UV radiation-induced skin cancer (51). In addition, RNA-interference experiments of APEI function demonstrate that excess damage could lead to the accumulation of unrepaired oxidative lesions, abasic damage and POL β-mediated cross-link formation (52). Thus, cells may need to maintain high levels of APEI to handle the routine load of DNA damage generated by metabolic processes. With regard to individuals chronically exposed to arsenic, reduced expression or function of APEI could result in more DNA damage that goes unrepaired, leading to abberant skin cells and the development of skin lesions.

Despite evidence from animal models that suggests mutations in the hOGG1 gene increase susceptibility to skin carcinogenesis (27), no evidence supports an association with skin cancer in humans (23). Similarly, we observed no association between the hOGG1 326Cys allele and skin lesions or other BER genes may actually be responsible for the observed effects. Furthermore, BER is just one method for DNA repair and it is possible that genes in other DNA repair mechanisms such as nucleotide excision repair may also affect the occurrence of skin lesions. Nor can we rule out the possibility of confounding by sun exposure since UV exposure generates DNA damage and has been implicated as a co-carcinogen with arsenic on the development of skin lesions (6,54). We attempted to control for measures of sun exposure by evaluating three variables in our data set: childhood tan level, childhood skin reaction to two hours of sun exposure and number of hours exposed to the sun while working. While these variables provide only a crude measure of skin type and sun exposure, including them in our model did not appreciably change our results.

In the case–control analysis, APEI Asp148Glu departed from HWE among the controls. However, in the case-only analysis, which met HWE, the APEI interaction with arsenic was observed to be significant and supported the conclusions drawn from the case–control analysis. Although the case-only design relies on the assumption of independence between genotype and environmental exposure, we believe this assumption is robust since it is unlikely that individuals would know their BER genotypes or modify their exposure based upon this knowledge.

The outcomes evaluated in this study were a heterogeneous pool of skin lesions. Consequently, our results may be obscured or misleading if the true effect of arsenic and BER polymorphisms is only for one specific type of lesion. Subset analyses conducted to address this issue suggested that the main genetic effects were similar for individuals with melanosis or leukomelanosis but may differ for keratosis. However, these analyses lacked power in general and could not be conducted for individuals with hyperkeratosis nor gene–environment interactions be evaluated. Lastly, the odds ratios and CIs reported in the current study were not adjusted for multiple comparisons and should be validated in future research.

In conclusion, arsenic-induced skin lesions are an increasingly common health burden in Bangladesh and yet the etiology of their origin is not well understood. Individuals may have inherently different odds for developing skin lesions based in part on their genetic profile for BER and their arsenic exposure history. We observed that two genes in the BER pathway, APEI and XRCCI, were associated with arsenic-induced skin lesions. Whereas only 6% of the population was homozygous for the high-risk APEI variant allele, 78% of the population possessed the high-risk XRCCI wild-type 194Trp/Trp genotype. Therefore, future research on arsenic-induced skin lesions should consider the impact of genetically susceptible subpopulations.

Acknowledgements

The authors thank our colleagues, technicians, laboratory and administrative staff at Dhaka Community Hospital and the Pabna Community Clinic in Bangladesh. We also acknowledge the academic assistance of Tom Smith and Paul Catalano, and the technical expertise of Janna Frelich, Lia Shimada, Ian James, Li Su, Ema Rodrigues and Meredith Jones. This publication was made possible by National Institutes of Health grants T32 ES07069, ES011622, ES05947 and ES00002. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Conflict of Interest Statement: None declared.

References

BER genes and arsenic-induced skin lesions


