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Baseline Comorbidities in a Skin Cancer Prevention Trial in Bangladesh

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Abstract

Background—Epidemiologic research suggests that increased cancer risk due to chronic arsenic exposure persists for several decades even after the exposure has terminated. Observational studies suggest antioxidants exert a protective effect on arsenical skin lesions and cancers among those chronically exposed to arsenic through drinking water. This study reports on the design, methods, and baseline analyses from the Bangladesh Vitamin E and Selenium Trial (BEST), a population based chemoprevention study conducted among adults in Bangladesh with visible arsenic toxicity.

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CONTRIBUTIONS

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Materials and methods—BEST is a 2×2 full factorial double-blind randomized controlled trial of 7,000 adults having manifest arsenical skin lesions evaluating the efficacy of 6-year supplementation with alpha-tocopherol (100 mg daily) and *L*-selenomethionine (200 µg daily) for the prevention of non-melanoma skin cancer.

Results—In cross-sectional analyses, we observed significant associations of skin lesion severity with male sex (female prevalence odds ratio (POR)=0.87; 95% CI=0.79–0.96), older age (aged 36–45 POR=1.27; 95% CI=1.13–1.42; aged 46–55 POR=1.44; 95% CI=1.27–1.64; and aged 56–65 POR=1.50; 95% CI=1.26–1.78 compared to aged 25–35), hypertension (POR=1.29; 95% CI=1.08–1.55), diabetes (POR=2.13; 95% CI=1.32–3.46), asthma (POR=1.55; 95% CI=1.03–2.32), and peptic ulcer disease (POR=1.20; 95% CI=1.07–1.35).

Conclusions—We report novel associations between arsenical skin lesions with several common chronic diseases. With the rapidly increasing burden of preventable cancers in developing countries, efficient and feasible chemoprevention study designs and approaches, such as employed in BEST, may prove both timely and potentially beneficial in conceiving cancer chemoprevention trials in Bangladesh and beyond.

Keywords

dietary supplements; selenium; vitamin E; skin neoplasms; Bangladesh

INTRODUCTION

An increase in worldwide cancer incidence and deaths has been projected for the next decade, one that is largely attributed to increased cancers in developing countries [1]. Several factors have contributed to the increasing cancer burden, including increased longevity, adoption of a Western lifestyle, and exposure to environmental carcinogens [2]. Notably, many of these cancers are due to largely preventable risk factors [1]. Prevention trials in economically developing nations are needed to address the impending epidemic of cancer in these populations as well as to gain knowledge that may be useful in developed nations as well.

Arsenic exposure is a major public health problem in Bangladesh, where an estimated 28–57 million people have been chronically exposed to arsenic through the consumption of naturally contaminated groundwater, which is the country's main source of drinking water [3]. Many of the human health effects of arsenic have been described in epidemiologic studies, which have demonstrated significant associations between the consumption of arsenic through drinking water and cancers of the skin, lung, bladder, liver, and kidney [4, 5], as well as other non-malignant diseases [6–9].

No unified hypothesis on the mechanism of arsenic toxicity has yet been reached; however, oxidative stress is a key pathway considered to underlie arsenic carcinogenesis [10]. There has been increasing *in vitro* evidence demonstrating the generation of reactive oxygen species (ROS) resulting from arsenic [11–13]. Epidemiologic evidence has shown arsenic exposure to be associated with oxidative stress, measured by serum lipid peroxides [14], urinary 8-hydroxy-2'-deoxyguanosine levels [15], and negatively correlated with antioxidant capacity in blood [16]. Additionally, arsenic-related skin tumors were observed to have more oxyradical-induced base modifications than arsenic-unrelated skin tumors [17].

There is known inter-individual variability in the capacity to metabolize arsenic (as reviewed in [18]), which has been hypothesized to partly explain the variability in susceptibility to arsenic toxicity. Arsenic is primarily present in the inorganic form (arsenate and arsenite) in drinking water [19]. Once internalized, it goes through a series of reduction

and oxidative methylation steps to form pentavalent and trivalent monomethylated arsenic (MMA) and dimethylated arsenic (DMA) metabolites [20]. There is mounting evidence that the methylation of arsenic increases its toxicity *in vivo* particularly with the trivalent monomethylated arsenic (MMA^{III}) species that is more toxic than the inorganic and pentavalent methylated arsenic species [21–24]. Recent epidemiologic studies have observed associations between antioxidants and urinary arsenic metabolites, with increased serum and urinary selenium [25–27] as well as plasma vitamin E [26, 28] associated with enhanced arsenic methylation and excretion.

While there has been considerable research evaluating the role of antioxidants in arsenic-exposed populations [26, 29, 30], little research had been conducted within Bangladesh. Between 2000 and 2002, we established the Health Effects of Arsenic Longitudinal Study (HEALS) in Araihaaz, Bangladesh, to evaluate arsenic toxicity [31]. Within the HEALS cohort, we observed a significant inverse association between blood selenium and arsenical skin lesion incidence [32]; an inverse association between dietary intake of vitamin E and risk of arsenical skin lesions [33]; a positive association of arsenic exposure with peripheral blood leukocyte DNA methylation [34] and an inverse association with plasma selenium concentrations [35]. Among arsenical skin lesion patients in HEALS, we conducted a 6-month randomized placebo-controlled trial and showed that supplementation with alpha-tocopherol and selenium, either alone or in combination, slightly improved skin lesion status [36]. Subsequently, gene expression was evaluated for individuals who were supplemented with selenium, and we showed up-regulation of antioxidant-related genes with selenium supplementation [37]. Many of the significantly up-regulated genes following selenium-supplementation were previously found by us to be down-regulated in a different set of individuals with arsenical skin lesions compared to those without [37, 38].

Skin lesions are a classical sign of chronic arsenic toxicity, and non-melanoma skin cancer (NMSC) is the most established arsenic-related cancer in humans, with epidemiologic evidence consistently reporting a dose-response relationship between arsenic levels in drinking water and risk of skin lesions and skin cancers from populations in Asia [39, 40], South America [41], North America [42], and Europe [43, 44]. Furthermore, studies from Taiwan and Chile indicate that elevated cancer risk among arsenic exposed populations persists for several decades after cessation of exposure [45–47]. Having identified a large at-risk population through our ongoing work in Bangladesh, as well as two potential chemoprevention agents, we implemented the Bangladesh Vitamin E and Selenium Trial (BEST), to investigate the efficacy of vitamin E and selenium in preventing NMSC.

MATERIALS AND METHODS

Study design

BEST is a 2×2 full factorial double-blind RCT with 7,000 adults having manifest arsenical skin lesions, and is designed to evaluate the efficacy of 6-year supplementation with vitamin E (100 mg daily) and *L*-selenomethionine (200 µg daily) for the prevention of NMSC. Secondary endpoints include all-cause and cancer-related mortality, diabetes mellitus, and oxidative stress biomarkers.

Study population

Individuals were recruited from the Narayanganj, Comilla, Noakhali, and Chandpur districts of Bangladesh. For study administrative purposes, we stratified randomization by study site and gender, utilizing Araihaaz and Matlab as the two main study strata since we have centralized field offices located in those sites. Narayanganj, Comilla, and Noakhali districts

were randomized under the “Araihazar” study site and Chandpur district was randomized under the “Matlab” study site.

Enrollment visits were conducted at the home of potential participants by three-person interview teams consisting of a physician, a research assistant, and a local village health worker. If the person was eligible (criteria listed in Supplemental Material Table S1) and agreed to be enrolled by participating in the interview, clinical assessment, and biological specimen collection, then written informed consent was obtained and the individual was randomized. Participant randomization was initiated in April 2006 and completed in August 2009. The 6-year intervention is expected to be completed by summer 2015.

Study intervention

Participants were randomly assigned to receive identical-appearing tablets containing vitamin E (alpha-tocopherol, 100 mg daily), selenium (*L*-selenomethionine, 200 µg daily), vitamin E and selenium, or placebo (all supplied by Kabco Inc, Amityville, NY) for 6 years. Higher doses of alpha-tocopherol have been used in other cancer prevention trials (e.g., Selenium and Vitamin E Cancer Prevention Trial (SELECT) [48]). However, findings of increased risks of hemorrhagic stroke in subjects given these doses [49] raised safety concerns, and we chose to use 100 mg of alpha-tocopherol.

Post-randomization assessments

The schedule for data collection is shown in Supplemental Material Table S2. A health and lifestyle questionnaire is administered by the study physician in Bengali at baseline and each two-yearly follow-up examination which includes questions on socio-demographics, drinking water sources, drinking water intake (liters per day; estimated by average daily number of glasses consumed and volume of glass used), betel leaf use and cigarette smoking, sun and occupational exposures, medication use, and health history. A general clinical examination is conducted as well as a skin examination for clinical features of malignant skin lesions that are confirmed by skin biopsy. Biospecimens (blood, urine, and toenail samples) are collected as indicated in Supplemental Material Table S2. Toxicity outcomes are assessed at 6 and 12 months by the village health worker and at 24, 48, and 72 months by the study physician. Semiweekly household visits by village health workers serve to alert study physicians to a participant death, other adverse events (overnight hospitalization), or clinical event (physician or clinic visit), and a health outcome form is subsequently completed by the study physician accordingly.

Compliance assessments

Village health workers visit study participants on a semiweekly basis and document reported compliance to the study vitamin. Every 8 weeks the vitamin bottle is re-collected from participants and the new supply bottle of study vitamins is delivered. A pill count is conducted of tablets remaining in the bottle. Biological measures of compliance are evaluated based on blood selenium and plasma alpha-tocopherol levels in a sub-cohort of 2,000 consecutively enrolled participants.

Primary endpoint assessment

Skin lesion protocol—Through extensive piloting, training, and re-training of the study physicians, we established a structured protocol for the assessment and documentation of arsenical skin lesions and skin cancers to be used in the trial. Although skin lesions related to arsenic tend to occur in certain parts of the body (palms, soles, and upper chest), to ensure uniformity and completeness of the examination we use whole-body assessment adapted from methods used for quantifying the affected body surface area in burn patients [50]. The

body is divided into 37 specific segments (e.g., front of forearm, left) and the presence and absence of each type of arsenical skin lesion (melanosis, leucomelanosis, or keratosis) is recorded for each segment. The plantar and dorsal surfaces of the hands and feet are further subdivided into segments, and additional details for keratosis are recorded including the extent affected, number of nodules, and size of largest keratotic nodule. Both male and female physicians perform the examinations, ensuring full cooperation from both male and female respondents.

Skin cancer ascertainment—Due to the lack of well-developed healthcare infrastructure in rural Bangladesh, we needed to develop a surveillance mechanism to ensure that as few cases of skin cancer were missed as possible. Since we suspected that most cases of NMSC would remain undiagnosed in the study population unless very advanced, as part of the biennial clinical evaluation, a detailed skin cancer examination is conducted and participants are referred for skin biopsy if there is clinical evidence of Bowen's disease (squamous cell carcinoma *in situ*) or invasive skin cancer. We have developed and validated a 3-level evaluation for selecting individuals for skin biopsy. The first-level serves to broadly identify potential cases of invasive skin cancer or Bowen's disease by the study physician at the time of the scheduled follow-up visit. Participants identified as having a lesion with erythema or altered pigmentation and at least one of the following surface characteristics of the lesion, rough, elevated, or interrupted surface or border elevated, are referred for second-level evaluation. The study physicians have been trained to identify and exclude skin lesions known to be diffuse melanosis, typical benign nevi, or other common skin conditions clearly not consistent with characteristics of a skin carcinoma. The second-level evaluation is conducted by a senior and more extensively trained physician to evaluate the lesions for induration, scaly surface, ulceration, blood vessel prominence, and crusting/oozing. If any one of these characteristics is present then the participant progresses to the third-level of evaluation. The third-level evaluation is conducted by a specialist dermatologist (RK) who makes the final recommendation for skin biopsy based on overall clinical evidence of invasive skin cancer or Bowen's disease. Participants who pass the third-level evaluation are eligible for skin biopsy of the suspicious lesion. Lesions that are <5mm in diameter are punch-biopsied and those that are ≥5mm in diameter are excised. For an individual with multiple biopsy-eligible lesions, the lesion most likely to be malignant is biopsied. If the severity of all lesions is similar, a lesion on the trunk is preferentially selected over the extremities. Cryosurgery is provided for the lesions that are not selected for biopsy but are deemed clinically suspicious to be malignant. Prior to the biopsy, tetanus immune globulin (TIG) is administered to the participant in order to prevent tetanus infection. After the biopsy is conducted, study staff members follow-up with the participant to determine whether there is any unusual pain, infection, or slow healing of the biopsy site.

Pathology review—Formalin-fixed biopsy tissue is processed at The Laboratory (a private surgical pathology laboratory in Dhaka, Bangladesh), and hematoxylin- and eosin-stained slides are reviewed by a single pathologist (MK) at Bangabandhu Sheikh Mujib Medical University. The slides are then shipped to The University of Chicago where they are reviewed by a single pathologist (CRS). A structured protocol was developed by the two study pathologists to develop an objective scoring system for evidence of basal cell carcinoma, squamous cell carcinoma, or Bowen's disease and methods for microscopic diagnosis. For specimens for which there is no consensus between the two pathologists, further sections for review are obtained. Finally, the pathologists discuss the discordant findings to reach a consensus diagnosis.

Reduction of continued arsenic exposure

Enrolled participants were informed by the study physicians on the sources and health effects of arsenic in drinking water. Efforts were undertaken to reduce continued arsenic exposure for all enrolled participants whose primary drinking water source had an arsenic concentration above the permissible level (50 µg/L) according to the Government of Bangladesh drinking water quality standards. Information about arsenic concentration in wells in our study areas was readily available from prior work [31, 51, 52]. For participants known to be drinking water with arsenic >50 µg/L at enrollment, we provided SONO filters (a three-bucket filtration system containing a composite iron matrix) [53]. These study-specific efforts are in addition to broader arsenic mitigation efforts in the study area, including installation of community wells, education campaigns, and new well testing.

Sample size and power calculations

One of the characteristic features of the factorial design is the efficiency to evaluate the effects of two or more treatments using a single study population. Based on our pilot trial [36], we do not anticipate *a priori* any interaction between vitamin E and selenium. With the assumption of no interaction between the agents (i.e., the effect of selenium does not vary in the presence or absence of vitamin E, and the effect of vitamin E does not vary in the presence or absence of selenium), we are able to exploit the full sample size to evaluate the treatment effects of vitamin E and selenium.

Statistical power for NMSC has been presented for a range of assumptions (Supplemental Material Table S3). While the majority of NMSC events are expected to be recorded at the scheduled screenings at the 24-, 48-, and 72-month time points, the power calculations shown are based on the formula for sample size calculations for time to failure, taking into account staggered enrollment over the first three years of the study, and withdrawals from observation due to death or loss of follow-up [54]. Calculations are based on comparison of incidence rates (total events/person-years at risk); however, the expected differences in proportions having events produce very similar results. For a potential follow-up period of 6 years for each subject, and factoring in attrition due to deaths and withdrawals, the projected statistical power based on a range of NMSC rates and treatment effect sizes is shown in Supplemental Material Table S3. For example, the study has over 86% power across a range of incidence rate values (93% at the observed event rate) for a 25% relative reduction or larger in NMSC. A 22.5% relative reduction can be detected with >84% power for annual incidence rates of 0.012 or greater (86% at the observed event rate).

Baseline statistical analyses

In this paper, we present cross-sectional analyses of participant characteristics in relation to randomization allocation (indicated by coded treatment assignment) and skin lesion severity. Arsenical skin lesion assessment was conducted at the baseline skin examination, as described previously. Arsenical skin lesions were categorized as the presence of melanosis, leucomelanosis, or keratosis in body segments. For the purposes of this analysis, skin lesion segments were summarized and classified as skin lesions with no keratosis (melanosis and/or leucomelanosis only) if no segment had the appearance of keratosis (N=3,181) and skin lesions with keratosis if one of more segments had the appearance of keratosis (N=3,804).

All covariate data were derived from the baseline interview. Demographic factors included sex and reported age. Self-reported smoking history was categorized as current, former, and never smoker. The height and weight of each participant was measured by the study physician; body mass index was constructed as weight in kilograms divided by height in meters squared and categorized by the World Health Organization cutoff points for underweight, normal weight, and overweight/obese. Urinary total arsenic concentration was

measured in the collected spot urine sample by graphite furnace atomic absorption spectrometry, with a detection limit of 2 µg/L [55]. Urinary creatinine was measured by a colorimetric Sigma Diagnostics Kit (Sigma, St. Louis, MO), and urinary total arsenic was subsequently divided by creatinine to obtain a creatinine-adjusted urinary total arsenic concentration, expressed as µg/g creatinine.

Co-morbid conditions were ascertained by self-reported diagnosis for heart disease, diabetes, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, and peptic ulcer disease. Blood pressure was measured by the study physician at the baseline examination and, hypertension was defined as a systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg.

The association between each participant characteristic or co-morbid condition and skin lesion severity (0=skin lesions with no keratosis, 1=skin lesions with keratosis) was estimated by prevalence odds ratios (PORs) and their 95% confidence intervals (CIs) from logistic regression models employed by the LOGISTIC procedure in SAS. The PORs were adjusted for sex, age, study site, cigarette smoking, body mass index, and baseline creatinine-adjusted urinary total arsenic concentration.

RESULTS

There were 7,000 participants enrolled in the trial between April 2006 and August 2009. Selected baseline characteristics of study participants, stratified by treatment assignment, are shown in Table 1. Among randomized participants, approximately 60% are female, 65% are aged 25–45, 41% are considered underweight as measured by BMI, and 72% report no cigarette smoking history. All characteristics were balanced across treatment arms. The baseline characteristics of the randomized study participants stratified by skin lesion severity are shown in Table 2. We observed that more participants with severe skin lesions (individuals with keratosis) were enrolled in the Matlab study site. Over the accrual period, there was a decrease in the prevalence of skin lesion severity among enrolled participants. Male sex and older age were significantly associated with the prevalence of increased skin lesion severity.

The prevalence of co-morbid conditions at enrollment with respect to treatment assignment is summarized in Table 3. Peptic ulcer disease and hypertension were the most commonly reported co-morbidities among study participants. We observed that all co-morbidities were generally balanced across treatment arms. Co-morbid conditions at enrollment stratified by skin lesion severity are shown in Table 4. Hypertension, diabetes, asthma, and peptic ulcer disease were significantly associated with increased skin lesion severity prevalence.

DISCUSSION

The design and implementation of a population-based chemoprevention trial in a resource-limited setting presented several unique challenges, empirical experiences, and opportunities for innovative approaches, which we outlined in our description of the study design. In cross-sectional analyses using the baseline data from trial participants, we observed significant associations of skin lesion severity with male sex, older age, hypertension, diabetes, asthma, and peptic ulcer disease.

Previous epidemiologic studies have associated arsenic with hypertension [56] and inconsistently with diabetes [57]. Associations between ingested arsenic exposure and lung function and respiratory symptoms have been observed in prior epidemiologic research [58, 59]; however, no studies have evaluated the association between arsenic and an asthma endpoint. A prior epidemiologic study showed that skin lesion severity was associated with

increased serum immunoglobulin E (IgE) concentrations [60], and IgE is known to be related to allergic asthma [61]. No previous evidence on the association between arsenic and peptic ulcer disease is known.

In these analyses, we highlight important co-morbid conditions, which are prevalent in individuals already known to be suffering from manifest arsenic toxicity. These analyses yielded some novel insights into resulting health effects of chronic arsenic exposure. The major strengths of this analysis were the large size of the study cohort, detailed data on skin lesions, multi-tiered evaluations in skin cancer ascertainment, and use of skin lesion severity as a proxy risk factor of interest. Inclusion of a large number of patients with arsenical skin lesions afforded us the opportunity to evaluate several novel associations. Skin lesion severity itself is a construct that represents a composite of the extent of arsenic exposure (including potentially cumulative exposure effects) and susceptibility (e.g., genetic, nutritional) to exposure. Skin lesion status as a predictor of disease risk was an approach recently taken by Hsu et al. in their analyses of skin lesion or cancer status in relation to future internal cancer risk [62]. One of the major distinctions of our analyses with that done by Hsu and colleagues, is that we evaluated co-morbid disease conditions in a study sample that all had arsenic-related skin lesions, using the least severe lesions as the reference category, as opposed to a skin lesion absent reference group. We deem that our approach minimizes the effect of any potentially unmeasured confounding factors relative to when a skin lesion absent group is used as the comparison.

There are limitations of this study that we also consider. We analyzed various co-morbid conditions that were based on self-report (i.e., heart disease, diabetes, COPD, asthma, tuberculosis, and peptic ulcer disease), which explains the lower prevalence of some of the health conditions than expected for the population due to limited access to medical care and undiagnosed health conditions. We presume that the under-reporting of co-morbid conditions was unlikely to be associated with skin lesion severity and would be expected on average to result in an underestimation of the true population effects. Finally, associations with co-morbid conditions should be examined in future prospective analyses since we are not able to evaluate whether arsenic is a risk factor for the development of these co-morbid conditions or contributes to their exacerbation or severity based on these cross-sectional analyses.

The implementation of BEST required the development of innovative but feasible strategies for the conduct of a clinical trial in a resource-limited setting. Protocols including ethical considerations such as arsenic exposure mitigation, strategies for randomization at the field location to maintain blinding, compliance assessment, clinical event documentation, and endpoint ascertainment all posed unique challenges which we anticipate could serve as models for the conduct of future clinical trials in other developing countries.

In conclusion, we report novel associations between arsenical skin lesion severity and several common chronic diseases. Prior epidemiologic research suggests that the health effects of arsenic in drinking water persist for several decades after the exposure has terminated [45–47]. While initiatives to reduce exposure to arsenic through drinking water are on-going, investigation into solutions to mitigate the resulting health effects of this catastrophe deserve urgent attention and resources. This highlights the importance of chemoprevention strategies in at-risk populations. Findings from BEST will have important implications for the prevention of NMSC in an arsenic-exposed population but also for the possible prevention of other arsenic-related cancers and non-cancer outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of randomized individuals stratified by treatment assignment

Characteristic	Randomized population (N=7,000)				Treatment A (N=1,753)				Treatment B (N=1,748)				Treatment C (N=1,752)				Treatment D (N=1,747)			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Study site																				
Araihazar	3,529	50.4	882	50.3	883	50.5	882	50.3	882	50.5	882	50.3	882	50.3	882	50.5	882	50.5	882	50.5
Matlab	3,471	49.6	871	49.7	865	49.5	870	49.7	865	49.5	870	49.7	865	49.7	865	49.5	865	49.5	865	49.5
Enrollment year																				
2006	945	13.5	237	13.5	237	13.6	234	13.4	237	13.6	234	13.4	237	13.4	237	13.6	237	13.6	237	13.6
2007	3,568	51.0	890	50.8	894	51.1	892	50.9	892	51.1	892	50.9	892	50.9	892	51.1	892	51.1	892	51.1
2008	1,487	21.2	377	21.5	369	21.1	375	21.4	366	20.9	375	21.4	366	20.9	366	20.9	366	20.9	366	20.9
2009	1,000	14.3	249	14.2	248	14.2	251	14.3	252	14.4	251	14.3	252	14.4	252	14.4	252	14.4	252	14.4
Sex																				
Male	2,840	40.6	714	40.7	712	40.7	710	40.5	704	40.3	710	40.5	704	40.3	704	40.3	704	40.3	704	40.3
Female	4,160	59.4	1,039	59.2	1,036	59.3	1,042	59.5	1,043	59.7	1,042	59.5	1,043	59.7	1,043	59.7	1,043	59.7	1,043	59.7
Age (yrs)																				
25-35	2,232	31.9	536	30.6	552	31.6	594	33.9	550	31.5	594	33.9	550	31.5	550	31.5	550	31.5	550	31.5
36-45	2,341	33.4	596	34.0	589	33.7	566	32.3	590	33.8	566	32.3	590	33.8	590	33.8	590	33.8	590	33.8
46-55	1,727	24.7	449	25.6	425	24.3	429	24.5	424	24.3	429	24.5	424	24.3	424	24.3	424	24.3	424	24.3
56-65	700	10.0	172	9.8	182	10.4	163	9.3	183	10.5	163	9.3	183	10.5	183	10.5	183	10.5	183	10.5
Body mass index (kg/m ²)																				
<18.5	2,894	41.3	717	40.9	737	42.2	729	41.6	711	40.7	729	41.6	711	40.7	711	40.7	711	40.7	711	40.7
18.5-22.9	3,118	44.5	780	44.5	756	43.2	793	45.3	789	45.2	793	45.3	789	45.2	789	45.2	789	45.2	789	45.2
>23.0	988	14.1	256	14.6	255	14.6	230	13.1	247	14.1	230	13.1	247	14.1	247	14.1	247	14.1	247	14.1
Cigarette smoking																				
Never	5,086	72.7	1,272	72.6	1,278	73.1	1,270	72.5	1,266	72.5	1,270	72.5	1,266	72.5	1,266	72.5	1,266	72.5	1,266	72.5
Former	495	7.1	127	7.2	120	6.9	121	6.9	127	7.3	121	6.9	127	7.3	127	7.3	127	7.3	127	7.3
Current	1,419	20.3	354	20.2	350	20.0	361	20.6	354	20.2	361	20.6	354	20.2	354	20.2	354	20.2	354	20.2

Table 2
Baseline characteristics of randomized individuals stratified by skin lesion severity

Characteristic	Skin lesions with no keratosis (N=3,181)		Skin lesions with keratosis (N=3,804)		POR* (95% CI) Keratotic vs. non-keratotic skin lesions
	N	%	N	%	
Study site					
Araihazar	1,704	53.6	1,809	47.6	1.0
Matlab	1,476	46.4	1,995	52.4	1.36 (1.23–1.50)
Enrollment year					
2006	317	10.0	612	16.1	1.0
2007	1,591	50.0	1,977	52.0	0.64 (0.55–0.75)
2008	696	21.9	791	20.8	0.60 (0.51–0.71)
2009	576	18.1	424	11.1	0.37 (0.31–0.45)
Sex					
Male	1,228	38.6	1,604	42.2	1.0
Female	1,952	61.4	2,200	57.8	0.87 (0.79–0.96)
Age (yrs)					
25–35	1,131	35.6	1,095	28.8	1.0
36–45	1,052	33.1	1,286	33.8	1.27 (1.13–1.42)
46–55	717	22.5	1,006	26.4	1.44 (1.27–1.64)
56–65	280	8.8	417	11.0	1.50 (1.26–1.78)
Body mass index (kg/m ²)					
<18.5	1,351	42.5	1,539	40.5	1.0
18.5–22.9	1,407	44.2	1,702	44.7	1.05 (0.94–1.16)
>23.0	422	13.3	563	14.8	1.15 (0.99–1.34)
Cigarette smoking					
Never	2,357	74.1	2,720	71.5	1.0
Former	183	5.7	309	8.1	1.12 (0.90–1.41)
Current	640	20.1	775	20.4	0.89 (0.75–1.05)

* PORs adjusted for sex, age, study site, cigarette smoking, body mass index, and enrollment creatinine-adjusted urinary total arsenic concentration.

Table 3

Baseline co-morbidities of randomized individuals stratified by treatment assignment

Characteristic	Randomized population (N=7,000)		Treatment A (N=1,753)		Treatment B (N=1,748)		Treatment C (N=1,752)		Treatment D (N=1,747)	
	N	%	N	%	N	%	N	%	N	%
Hypertension [†]										
No	6,431	91.9	1,606	91.6	1,621	92.7	1,607	91.7	1,597	91.4
Yes	569	8.1	147	8.4	127	7.3	145	8.3	150	8.6
Heart disease [†]										
No	6,928	99.0	1,737	99.1	1,730	99.0	1,730	98.7	1,731	99.1
Yes	72	1.0	16	0.9	18	1.0	22	1.3	16	0.9
Diabetes [†]										
No	6,912	98.7	1,729	98.6	1,719	98.3	1,734	99.0	1,730	99.0
Yes	88	1.3	24	1.4	29	1.7	18	1.0	17	1.0
COPD [†]										
No	6,973	99.6	1,744	99.5	1,741	99.6	1,747	99.7	1,741	99.7
Yes	27	0.4	9	0.5	7	0.4	5	0.3	6	0.3
Asthma [†]										
No	6,892	98.5	1,733	98.9	1,720	98.4	1,719	98.1	1,720	98.5
Yes	108	1.5	20	1.1	28	1.6	33	1.9	27	1.5
Tuberculosis [†]										
No	6,900	98.6	1,729	98.6	1,730	99.0	1,725	98.5	1,716	98.2
Yes	100	1.4	24	1.4	18	1.0	27	1.5	31	1.8
Peptic ulcer disease [†]										
No	5,483	78.3	1,384	78.9	1,356	77.6	1,380	78.8	1,363	78.0
Yes	1,517	21.7	369	21.1	392	22.4	372	21.2	384	22.0

Table 4

Baseline co-morbidities of randomized individuals stratified by skin lesion severity

Characteristic	Skin lesions with no keratosis (N=3,181)		Skin lesions with keratosis (N=3,804)		POR* (95% CI) Keratotic vs. non-keratotic skin lesions
	N	%	N	%	
Hypertension [†]					
No	2,966	93.3	3,451	90.7	1.00
Yes	214	6.7	353	9.3	1.29 (1.08–1.55)
Heart disease [‡]					
No	3,149	99.0	3,764	98.9	1.00
Yes	31	1.0	40	1.1	0.94 (0.58–1.52)
Diabetes [‡]					
No	3,157	99.3	3,740	98.3	1.00
Yes	23	0.7	64	1.7	2.13 (1.32–3.46)
COPD [‡]					
No	3,170	99.7	3,788	99.6	1.00
Yes	10	0.3	16	0.4	1.08 (0.49–2.40)
Asthma [‡]					
No	3,143	98.8	3,733	98.1	1.00
Yes	37	1.2	71	1.9	1.55 (1.03–2.32)
Tuberculosis [‡]					
No	3,133	98.5	3,751	98.6	1.00
Yes	47	1.5	53	1.4	0.91 (0.61–1.35)
Peptic ulcer disease [‡]					
No	2,560	80.5	2,913	76.6	1.00
Yes	620	19.5	891	23.4	1.20 (1.07–1.35)

* PORs adjusted for sex, age, study site, cigarette smoking, body mass index, and enrollment creatinine-adjusted urinary total arsenic concentration.

[†] Assessed by study physician at baseline clinical examination.

[‡] Self-reported physician diagnosis by participant.