Environmental Toxicology and Pharmacology 56 (2017) 106–113

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Genetic susceptibility to breast cancer risk associated with inorganic arsenic exposure

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ARTICLE INFO

Keywords:
Inorganic arsenic
Arsenic metabolism
Polymorphisms
Breast cancer
Genetic susceptibility

ABSTRACT

Objective: To evaluate whether the association between breast cancer (BC) and inorganic arsenic (iAs) exposure is modulated by selected polymorphisms in iAs metabolism.
Methods: A population based case-control (1016/1028) study was conducted in Northern Mexico. Urinary arsenic metabolites were measured by High Performance Liquid Chromatography. Metabolites percentages and methylation ratios, were estimated. Genotypes of selected polymorphisms were determined by allelic discrimination. The interaction between polymorphisms and iAs metabolites percentages and methylation ratios on BC was assessed with unconditional logistic regression models.
Results: A significant interaction ($p = 0.002$) between *MTR* c.2756A > G polymorphism and percentage dimethylarsinic acid (DMA) on BC was found; BC risk related with %DMA was lower in AG + GG carriers than in AA carriers. No other significant interactions were found.
Conclusion: *MTR* c.2756A > G polymorphism may confer protection for BC associated with iAs exposure. Further research is warranted to elucidate the potential involvement of other polymorphisms in iAs-related BC.

1. Introduction

A higher percentage of urinary monomethylarsonic acid (%MMA) has been recently related to an increased breast cancer (BC) risk (López-Carrillo et al., 2014). MMA is an intermediate metabolite of inorganic arsenic (iAs) metabolism (Sattar et al., 2016). MMA percentage in urine has also been positively related to bladder and lung cancer (Gamboa-Loira et al., 2017).

Ingested iAs is eliminated in urine as dimethylated metabolites (DMA^{+3} and DMA^{+5}) in a greater percentage than the monomethylated forms (MMA^{+3} and MMA^{+5}), and a small quantity that remains as iAs (Shen et al., 2016). Individuals with a greater capacity to methylate iAs to MMA and less capacity to further methylate it to dimethylarsinic acid (DMA), may be at higher cancer risk (Gamboa-Loira et al., 2017). Individual capacity to methylate iAs is determined by genetic, dietary, and environmental factors (Hernández and Marcos, 2008; Tseng, 2009).

Variations in genetic susceptibility to iAs exposure may be determined by polymorphisms in key genes that encode enzymes involved in one-carbon metabolism and iAs methylation pathways. In the former, the dietary ingestion of folate, methionine, choline, etc., is the input of methyl groups that are cycled to synthetize S-Adenosylmethionine (SAM), the universal methyl donor for many reactions in the cell, including iAs methylation. In the later, reduced iAs and MMA forms are methylated by arsenite methyltransferase (AS3MT) to form the most soluble metabolite DMA (Hall and Gamble, 2012).

Information has consistently shown that heterozygous and variant allele homozygous of one-carbon metabolism genetic variant *MTHFR* c.665C > T have a reduced iAs methylation capacity compared to wild genotype carriers (Deng et al., 2007; Engström et al., 2007; Lindberg et al., 2007; Porter et al., 2010; Steinmaus et al., 2007), however, it does not show an increased bladder cancer risk (Beebe-Dimmer et al., 2012; Chung et al., 2010; Karagas et al., 2005; Moore et al., 2004). In addition, *MTHFR* c.1286A > C variant allele carriers might have a higher methylation capacity than wild allele carriers (Porter et al., 2010; Steinmaus et al., 2007), likewise with no association with bladder cancer risk (Beebe-Dimmer et al., 2012). No significant associations between variant allele carriers of *MTR* c.2756A > G and iAs methylation capacity have been reported (Engström et al., 2007; Porter et al., 2010). Scarce information suggests a lower %iAs among mutated carriers of *MTRR* c.66A > G (Engström et al., 2009).

A decreased capacity to methylate iAs has been also related to

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http://dx.doi.org/10.1016/j.etap.2017.08.032
Received 27 July 2017; Accepted 29 August 2017
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variant *AS3MT* c.860T > C genotypes (Engström et al., 2011; Lindberg et al., 2007; Rodrigues et al., 2012; Valenzuela et al., 2009), with no increase in premalignant skin lesions (De Chaudhuri et al., 2008; Valenzuela et al., 2009) and bladder cancer (Beebe-Dimmer et al., 2012; Lesseur et al., 2012). Other two polymorphic sites in this gene (c.529-56G > C and c.1021-498T > C), may confer an increased iAs methylation capacity (Chung et al., 2009; Engström et al., 2011; Meza et al., 2005; Valenzuela et al., 2009).

Certain genetic variations have been shown to alter the capacity to methylate iAs, but up until now, no association has been established between such variations and premalignant or malignant conditions related with iAs exposure. The aim of this study was to evaluate whether the association between BC and iAs exposure is modulated by selected polymorphisms involved in iAs metabolism.

2. Methods

This is the second report of a case-control study conducted in five Northern Mexico states (Chihuahua, Coahuila, Durango, Nuevo León, and Sonora), between 2007 and 2011, to identify genetic and environmental factors associated with BC in that region (López-Carrillo et al., 2014).

Cases were women with histopathologically confirmed BC, 18 years or older, without a previous cancer diagnosis, with more than one year of residency in the study area. Patients were identified in 17 public tertiary care hospitals. The response rate among cases was 93.7% (1016/1084).

Controls were selected randomly among women 18 years or older, residing for at least one year in the same area as cases, without a history of cancer, age-matched with cases (± 5 years). Detailed procedures of controls recruitment were published elsewhere (López-Carrillo et al., 2014). The response rate among controls was 99.7% (1028/1031). The main reason for not participating in the study, for cases and controls, was the lack of interest.

After signing the informed consent, cases were face to face interviewed in hospitals before receiving any treatment (hormonal, chemo, and/or radiotherapy), while controls were directly interviewed in their homes. Sociodemographic information, medical and reproductive history, as well as dietary habits, were obtained. Additionally, women were measured to obtain some anthropometric parameters, and they donated one blood and urine sample. This study was approved by the Ethics Committee of the Instituto Nacional de Salud Pública in Mexico.

2.1. Arsenic exposure

Arsenic exposure was measured through the concentration (μg/l) of urinary species arsenite (As^{+3}), arsenate (As^{+5}), monomethylarsonic acid (MMA^{+5}), dimethylarsinic acid (DMA^{+5}), arsenobetaine (AsB). Participants donated a first morning urine void, not necessarily on the same day of the interview. In all cases, urine samples were obtained before any cancer treatment was performed. Samples were collected in sterile polypropylene containers and stored at −70 °C until analysis.

Arsenic species concentrations were determined by high performance liquid chromatography inductively coupled plasma mass spectrometry (HPLC-ICP-MS), according to the described methodology (Gilbert-Diamond et al., 2011). The correspondg limit of detection of each As specie (AsB: 0.08; As^{+3}: 0.15; As^{+5}: 0.41; MMA^{+5}: 0.12 and DMA^{+5}: 0.12), divided by two (LOD/2) was imputed to samples that resulted below the LOD among cases: As^{+3} = 28.25%, As^{+5} = 56.20%, MMA^{+5} = 3.94%, DMA^{+5} = 0.49%, and AsB = 20.28% and among controls: As^{+3} = 19.26%, As^{+5} = 56.32%, MMA^{+5} = 1.95%, DMA^{+5} = 0.49%, and AsB = 24.32% (Barr et al., 2006). Creatinine concentrations (mg/dl) were determined by spectrophotometry with a commercially available kit (Randox, Antrim County, UK). Coefficients of variation were: MMA^{+5} = 8%, DMA^{+5} = 9%, As^{+3} = 8%, AsB = 18%, and creatinine = 2.76%. Measurements of As^{+5} in the same day were not available to calculate the coefficient of variation.

Table 1
Known breast cancer factors in the study population.

Factors	Cases (n = 1016)[a]	Controls (n = 1028)[a]	*OR (95% CI)*[b]
Age at menarche (years)			
> 12	585	639	1.00
≤12	430	389	1.12 (0.93–1.35)
Live births (number)			
≥4	495	658	1.00
1–3	442	341	1.83 (1.48–2.27)
Nulliparous	78	29	3.74 (2.41–5.81)
p for trend			*< 0.001*
Age at first full-term pregnancy (years)			
< 19	217	413	1.00
19–21	261	294	1.46 (1.15–1.86)
> 21	447	289	2.15 (1.69–2.72)
p for trend			*< 0.001*
Breastfed first child (months)			
0	269	135	1.00
1–6	332	279	0.57 (0.44–0.75)
7–12	196	362	0.20 (0.22–0.39)
> 12	134	220	0.35 (0.26–0.48)
p for trend			*< 0.001*
Menopause[c]			
No	387	346	1.00
Yes	629	682	0.68 (0.48–0.95)
First-degree relative with breast cancer[d]			
No	889	1019	1.00
Yes	127	9	13.90 (6.97–27.74)
Body Mass Index (kg/m^2)			
Premenopause			
< 25	108	70	1.00
25–29.9	142	105	0.84 (0.55–1.29)
30–34.9	90	92	0.63 (0.40–0.99)
≥35	39	79	0.35 (0.21–0.59)
p for trend			*< 0.001*
Postmenopause			
< 25	100	107	1.00
25–29.9	216	233	1.07 (0.76–1.50)
30–34.9	189	203	1.05 (0.74–1.50)
≥35	119	138	1.00 (0.68–1.47)
p for trend			*0.900*
Alcohol consumption[e]			
No	777	912	1.00
Yes	237	116	2.04 (1.58–2.64)
Tobacco smoke			
No	359	543	1.00
Yes	657	485	1.95 (1.62–2.34)

[a] Differences in the sample size across the cells are due to missing values.
[b] Adjusted for age (in five-year periods) and schooling (total years).
[c] Menopause ≥ 365 days without menstrual bleeding.
[d] Mother, sister and/or daughter.
[e] Mean ± SD, Min–Max in grams of ethanol per week, among consumers = 8.91 ± 27.24, 0.31–408.55.

2.2. DNA extraction and genotypification of: *AS3MT* c.860T > C, *AS3MT* c.529-56G > C, *FOLH1* c.223T > C, *MTHFD1* c.1958G > A, *MTHFR* c.665C > T, *MTR* c.2756A > G and *MTRR* c.66A > G

DNA was obtained from blood samples buffy coat with the Quick-gDNA MidiPrep kit (Zymo Research, Irvine, CA). DNA concentration was determined by spectrophotometry. DNA purity was evaluated at 280/260 nm and 260/230 nm wavelengths, samples with ratios of 1.7–1.9 and 2.0–2.2, respectively, were considered acceptable (Thermo Fisher Scientific, 2012). DNA integrity was evaluated visually in 2% agarose gels dyed with ethidium bromide, in 10% randomly selected

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