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Arsenic methylation capacity is associated with breast cancer in northern Mexico

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ABSTRACT

Exposure to environmental contaminants, dietary factors and lifestyles may explain worldwide different breast cancer (BC) incidence. Inorganic arsenic (iAs) in the drinking water is a concern in many regions, such as northern Mexico. Studies in several countries have associated the proportion of urinary monomethylarsenic (%MMA) with increased risks for many As-related diseases, including cancer. To investigate the potential relationships between the risk of BC and the capacity to methylate iAs, a hospital-based case–control study (1016 cases/1028 controls) was performed in northern Mexico. Women were directly interviewed about their reproductive histories. The profile of As metabolites in urine was determined by HPLC-ICP-MS and methylation capacity was assessed by metabolite percentages and indexes. Total urinary As, excluding arsenobetaine (TAs-AsB), ranged from 0.26 to 303.29 μg/L. Most women (86%) had TAs-AsB levels below As biological exposure index (35 μg/L). Women with higher %MMA and/or primary methylation index (PMI) had an increased BC risk (%MMA $OR_{Q5vs.Q1} = 2.63$; 95%CI 1.89,3.66; p for trend <0.001; PMI $OR_{Q5vs.Q1} = 1.90$; 95%CI 1.39,2.59, p for trend <0.001). In contrast, women with higher proportion of urinary dimethylarsenic (%DMA) and/or secondary methylation index (SMI) had a reduced BC risk (%DMA $OR_{Q5vs.Q1} = 0.63$; 95%CI 0.45,0.87, p for trend 0.006; SMI $OR_{Q5vsQ1} = 0.42$, 95%CI 0.31,0.59, p for trend <0.001). Neither %iAs nor total methylation index was associated to BC risk. Inter-individual variations in iAs metabolism may play a role in BC carcinogenesis. Women with higher capacity to methylate iAs to MMA and/or a lower capacity to further methylate MMA to DMA were at higher BC risk.

Introduction

Breast cancer (BC) incidence is increasing worldwide with an estimated 1.38 million new cancer cases diagnosed in 2008 (Ferlay et al., 2010). Differences in environmental conditions throughout the world may be related to the wide BC incidence range among countries; however, information about specific environmental exposures and BC risk is limited, contradictory or absent (IOM, 2012). In the particular case of Mexico, BC incidence and mortality are concentrated in the states located along the US–Mexico border, where incidence rate is about 60% higher than in rest of the country (Palacio-Mejia et al., 2009). Fifty eight percent of BC cases occur in Mexican women under 54 years of age (Knaul et al., 2009), but only about a third of them have the high risk reproductive profile for BC (i.e. early age of menarche, nulliparity, late age at first birth, etc.) (Lopez-Carrillo et al., 1997). It is possible that contrasting exposures to environmental contaminants, dietary factors and lifestyles may contribute to explain the differences in BC incidence and mortality between northern and central-southern Mexico.

Arsenic (As) is a natural element of the earth's crust that occurs in the groundwater and surface water of many parts of the world. Arsenic is a recognized human carcinogen since epidemiological studies have shown that inorganic As (iAs) exposure is associated with cancer of the lung, skin, and bladder, and possibly with kidney, and liver tumors (ATSDR, 2007; IARC, 2012). The International Agency for Research on Cancer (IARC) has classified arsenic as a group 1 carcinogen (IARC, 2012). For many years, the presence of As in the drinking water of some areas of northern Mexico has been a major concern (Cebrián et al., 1994). Arsenic levels have ranged in Sonora from 71 to 305 μg/L

Abbreviations: BC, breast cancer; iAs, inorganic arsenic; TAs, total As; AsB, arsenobetaine; MMA(III), monomethylarsonous acid; MMA(V), monomethylarsonic acid; DMA(III), dimethylarsinous acid; DMA(V), dimethylarsinic acid; PMI, primary methylation index; SMI, secondary methylation index; TMI, total methylation index; GM, geometric means; OR, odds ratio; 95% CI, 95%: confidence interval; ODD, oxidative DNA damage.

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(Wyatt et al., 1998), Chihuahua from 15 to 300 μg/L (Camacho et al., 2011) and Región Lagunera from 7 to 600 μg/L (Del Razo et al., 1990).

Arsenic is metabolized in many organisms, including humans, by a series of reduction and methylation reactions. Arsenate is reduced to trivalent arsenite, then oxidatively methylated to monomethylarsonic acid (MMAV), reduced to monomethylarsonous acid MMA(III), methylated to dimethylarsinic acid (DMAV) and then reduced to dimethylarsinous acid DMA(III) (Thomas et al., 2001). In humans, some As remains in its inorganic form, which is readily excreted in urine along with its metabolites. In general terms, the biomethylation has long been thought to be a major detoxification process, as the pentavalent methylated metabolites are less reactive towards cellular macromolecules and are eliminated more rapidly. However, the intermediates MMA(III) and DMA(III) are highly toxic and may be partially responsible for As toxicity. Methylation capacity shows large inter-individual variations; typically ingested iAs is excreted as 10–30% iAs, 10–20% MMA, and 60–70% DMA (Vahter, 2002).

Previous studies have suggested that altered profiles of As species in urine reflect inter-individual differences in the efficiency of iAs metabolism and may determine individual cancer susceptibility. As compared to controls, subjects showing higher iAs, MMAV and its percentage (%MMA), and/or primary methylation index (PMI = MMA/iAs), as well as lower (DMAV) and its percentage (%DMA), and/or secondary methylation indexes (SMI = DMA/MMA) have higher risks of skin (Hsueh et al., 1997; Yu et al., 2000; Chen et al., 2003a), bladder (Chen et al., 2003b; Steinmaus et al., 2006; Pu et al., 2007; Huang et al., 2008) and lung (Steinmaus et al., 2010) cancer. Most of these studies were performed in populations exposed to As levels in drinking water above 200 μg/L (Steinmaus et al., 2006); however, limited information is available at lower exposure levels (Pu et al., 2007).

The available information regarding potential associations between As and BC incidence is scarce. In a prospective Danish cohort, a small but significantly increased risk for BC (incidence rate ratio = 1.05; 95% CI, 1.01–1.10) was reported in association with As exposure via drinking water (time-weighted average); however, no significant associations were found with cancers of the lung, bladder, liver, kidney, prostate, colorectal, or skin melanoma. The average As exposure for the cohort ranged between 0.05 and 25.3 μg/L (mean = 1.2 μg/L) (Baastrup et al., 2008). An ecological study in Argentina found no association between BC cases reported to a local cancer registry and As levels in ground water (ND-330 μg/L) (Aballay et al., 2012). More recently, García-Esquinas et al. (2013) reported that low to moderate exposure to inorganic As was prospectively associated with increased cancer mortality from lung, prostate, and pancreas, but not from BC in American Indians.

Experimental evidence has shown that sodium arsenite induced ROS generation, DNA oxidative damage, heme oxygenase, metallothionein and c-Myc proteins, NF- B activation along with decreased methylenetetrahydrofolate reductase (MTHFR) levels and cell proliferation in human BC MCF-7 cells (Ruiz-Ramos et al., 2009a,b). More recently, chronic As exposure was shown to drive human breast epithelial cells (MCF-10A) into a cancer cell phenotype through overexpression of aromatase, thereby activating oncogenic processes independent of ER (Xu et al., 2014). These findings suggest that As has the ability of inducing proliferation in normal and transformed breast epithelial cells.

To date no study has reported on the potential association between iAs metabolism and BC risk. Therefore, a hospital-based case–control study was conducted to investigate the potential relationships between the risk of BC and the capacity to methylate iAs, as assessed by the profile of urinary As metabolites.

Material and methods

Study population. A hospital-based case–control study was performed from 2007 to 2011 in northern Mexico (Coahuila, Chihuahua, Durango, Nuevo León, and Sonora). Incident cases were identified from main public tertiary hospital units in the study area population ($n = 17$), including Health Department (Secretaría de Salud), Social Security (Instituto Mexicano del Seguro Social), and State Workers' Social Security (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado) hospitals, as well as university health centers. A total of 1016 patients with histopathologically confirmed BC were identified, with the following inclusion criteria: minimal age of 18, without any other cancer history, and with a residency period of >1 year in the study area. Controls were 1028 healthy women, with no history of cancer, with a residency period >1 year in the same residence zone, matched by five years age with the index case. They were identified through the master sample framework used for the National Health Surveys from which a probabilistically selected list of housing addresses along with an access sketch to facilitate their location was obtained (Tapia-Conyer et al., 1992). In the houses where there was more than one eligible woman, only one participant was randomly chosen. Conversely, if no eligible woman was found in a household, or if she declined participation in the study, a new home was systematically located according to the standardized survey procedures. A grocery incentive was given to controls to increase the response rate. This study was approved by the Mexico National Institute of Public Health ethics committee.

Interviews. Information about sociodemographic characteristics; clinical, reproductive and family medical history, and dietary habits were obtained by face-to-face interviews to women who gave their informed consent. Their height and weight were also obtained. Patients were interviewed after their diagnosis, before any kind of treatment (average time from diagnosis to interview ~2 months). All participants were blinded to the study hypothesis. The response rates (participants/eligible) were 93.7% for cases and 99.7% for controls. The main reason given by the small proportion of women (71/2115; 3.36%) who refused participation in the study was lack of interest. There were no significant differences regarding age and years of education between participating and non participating women.

Urine samples. A first morning void urine sample was collected from each woman in a sterile disposable polypropylene urine collection cup. In all cases, urine samples were obtained before any cancer treatment was performed (including surgery and radiation therapy). An aliquot of 4 mL of urine was prepared in a Cryovial (Simport Scientific, Beloeil, QC, Canada) and stored frozen at or below −20 °C and then at −70 °C at CINVESTAV in Mexico City where creatinine was determined and samples were prepared for shipping to the University of Arizona to be analyzed for As.

Arsenic determination. Urinary concentrations (μg/L) of species As(III), As(V), MMA(V), DMA(V), and arsenobetaine (AsB) were determined by high-performance liquid chromatography ICP-MS system in The Analytical Section of the Hazard Identification Core at the University of Arizona according to Gilbert-Diamond et al. (2011). Measurements below the detection limit were imputed their corresponding value [As(III): 0.12; As(V): 0.20; MMA(V): 0.12; DMA(V): 0.08; AsB: 0.08] divided by two. Creatinine was determined by spectrophotometry using a commercial kit (Randox Creatinine Kit) with 1 mg/dL as DL, according to a previously described methodology (Blanco-Munoz et al., 2010).

Smoking and alcohol. Smoking was evaluated as the product of total years of smoking by the number of cigarette packs smoked per day (1 pack = 20 cigarettes). Duration was the number of years between the starting age and the age at which smoking stopped, or the age at interview for subjects still smoking.

Alcohol intake was estimated with a semi-quantitative food frequency questionnaire. Women were queried about the consumption