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Arsenic metabolism and cancer risk: A meta-analysis

Brenda Gamboa-Loira[a], Mariano E. Cebrián[b], Francisco Franco-Marina[c], Lizbeth López-Carrillo[a,*]

[a] Instituto Nacional de Salud Pública, Av. Universidad 655, Col. Santa María Ahuacatitlán, C.P. 62100 Cuernavaca, Morelos, Mexico
[b] Departamento de Toxicología, Centro de Investigación y de Estudios Avanzados del IPN, Av. Instituto Politécnico Nacional 2508, Col. San Pedro Zacatenco, Del. Gustavo A. Madero, C.P. 07360 D.F., Mexico
[c] Instituto Nacional de Enfermedades Respiratorias, Calzada de Tlalpan 4502, Col. Sección XVI, C.P. 14080 Tlalpan, D.F., Mexico

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ABSTRACT

Objective: To describe the studies that have reported association measures between risk of cancer and the percentage distribution of urinary inorganic arsenic (iAs) metabolites by anatomical site, in non-ecological epidemiological studies.

Methods: Studies were identified in the PubMed database in the period from 1990 to 2015. Inclusion criteria were: non-ecological epidemiological study, with histologically confirmed cancer cases, reporting the percentage distribution of inorganic arsenic (iAs), monomethylated (MMA) and dimethylated (DMA) metabolites, as well as association measures with confidence intervals (CI) between cancer and %iAs and/or %MMA and/or %DMA. A descriptive meta-analysis was performed by the method of the inverse of the variance for the fixed effects model and the DerSimonian and Laird's method for the random effects model. Heterogeneity was tested using the Q statistic and stratifying for epidemiological design and total As in urine. The possibility of publication bias was assessed through Begg's test.

Results: A total of 13 eligible studies were found, most of them were performed in Taiwan and focused on skin and bladder cancer. The positive association between %MMA and various types of cancer was consistent, in contrast to the negative relationship between %DMA and cancer that was inconsistent. The summary risk of bladder (OR = 1.79; 95% CI: 1.42, 2.26, n = 4 studies) and lung (OR = 2.44; 95% CI: 1.57, 3.80, n = 2 studies) cancer increased significantly with increasing %MMA, without statistical heterogeneity. In contrast, lung cancer risk was inversely related to %DMA (OR = 0.58; 95% CI: 0.36, 0.93, n = 2 studies), also without significant heterogeneity. These results were similar after stratifying by epidemiological design and total As in urine. No evidence of publication bias was found.

Conclusion: These findings provide additional support that methylation needs to be taken into account when assessing the potential iAs carcinogenicity risk.

1. Introduction

In 1980 inorganic arsenic (iAs) was classified as a human carcinogen (International Agency for Research on Cancer, 1980), despite the limited evidence in animal models that contrasted with the available information from epidemiological studies, mainly ecological, showing that consumption of iAs contaminated water increases the risk of developing skin, lung and bladder cancer (International Agency for Research on Cancer, 2012, 2004). The ability to metabolize iAs entering the body is determined by genetic, dietary and environmental factors that might explain the inter-individual variations in cancer risk related to iAs exposure (Tseng, 2009).

Ingested iAs is eliminated in the urine as monomethylated metabolites (MMA^{+3} and MMA^{+5}), in a lower proportion than the dimethylated ones (DMA^{+3} and DMA^{+5}) (10–20%$_{MMA^{+3} + MMA^{+5}}$ vs. 60–70%$_{DMA^{+3} + DMA^{+5}}$), as well as iAs (10–30%) (Shen et al., 2016). Although the percentage distribution of these metabolites varies in relation to the presence of polymorphisms in genes involved in iAs metabolism (i.e. GSTM1 null, GSTT1 null, AS3MT Met287Thr, MTHFR A1298C and Ala222Val, etc.) (Hernández and Marcos, 2008), and it is also related, among other factors, to age, sex, pregnancy, magnitude of iAs exposure, smoking and nutritional status (Tseng, 2009), most variation remains unexplained.

More recently, some non-ecologic epidemiological studies have shown a positive relationship between skin, bladder, lung, kidney and breast cancer and urinary %MMA, as well as a negative association with

* Corresponding author.
E-mail addresses: brenda.gamboa@espm.insp.mx (B. Gamboa-Loira), mcebrian@cinvestav.mx (M.E. Cebrián), dequellegallega@gmail.com (F. Franco-Marina), lizbeth@insp.mx (L. López-Carrillo).

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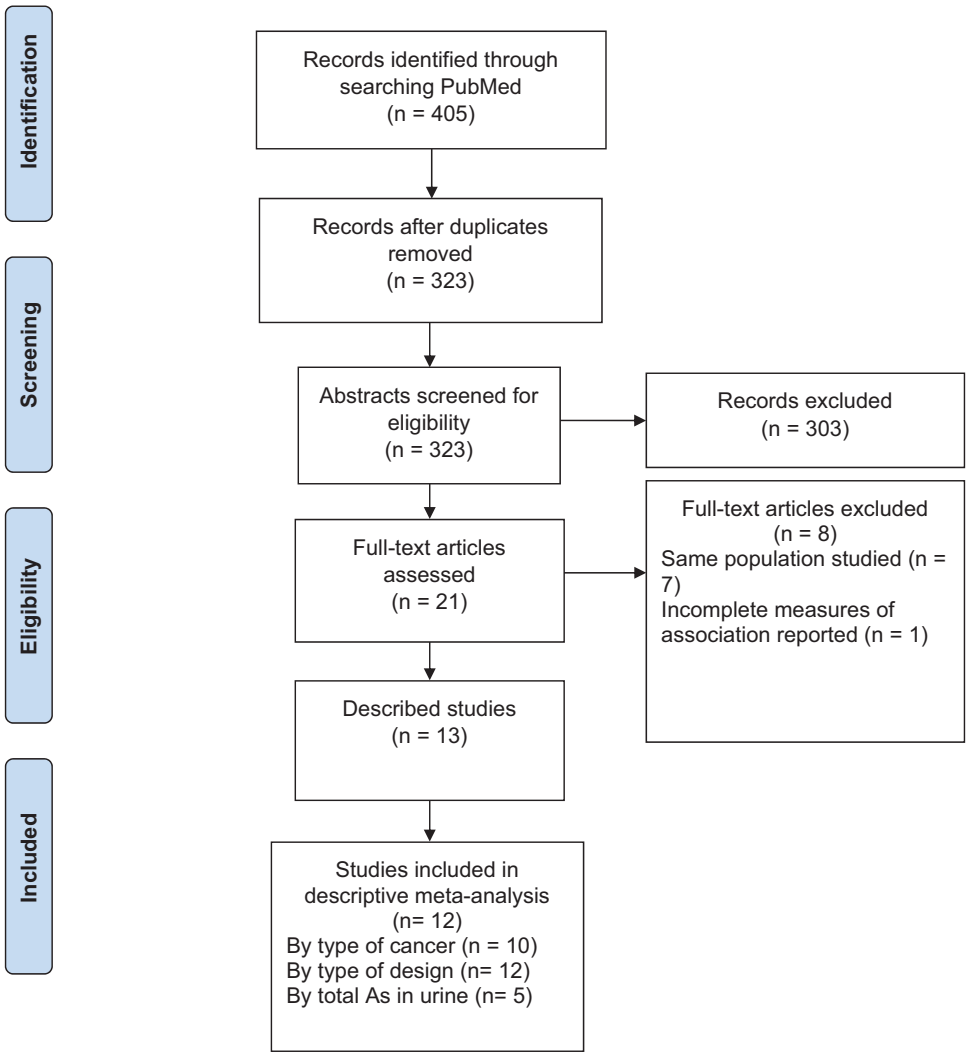

Fig. 1. Flow diagram of studies search.

%DMA (Chen et al., 2003; Chung et al., 2009; Hsueh et al., 1997; Huang et al., 2012, 2008a, 2008b; López-Carrillo et al., 2014; Melak et al., 2014; Pu et al., 2007; Steinmaus et al., 2006, 2010; Wu et al., 2013a; Yu et al., 2000). The aim of this paper was to describe the evidence regarding the association between the percentage distribution of urinary iAs metabolites and cancer risk by anatomical site, in non-ecological epidemiological studies.

2. Methods

We searched in the PubMed journal citation database (http://www.ncbi.nlm.nih.gov/pubmed/) for all the epidemiological references, published between 1990 and August 2015, including the following Medical Subject Headings (MeSH®): Arsenic, methylation, metabolism, cancer, carcinoma and epidemiological study. A total of 405 studies were identified, from which 82 were citation duplicates. Thus, the abstract of the 323 unique studies identified was reviewed to identify whether the study met the following eligibility criteria: non-ecological epidemiological study with histologically confirmed cancer cases, reporting estimates of an association measure (odds ratio, hazard ratio, or relative risk) and their respective confidence intervals (CI) between any analyzed cancer and %iAs and/or %MMA and/or %DMA.

A total of 21 articles (Chen et al., 2003; Chiang et al., 2014; Chung et al., 2011, 2010, 2009, 2008; Gilbert-Diamond et al., 2013; Hsueh et al., 1997; Huang et al., 2008b, 2012, 2008a; Leonardi et al., 2012; López-Carrillo et al., 2014; Melak et al., 2014; Pu et al., 2007; Steinmaus et al., 2010, 2006; Wu et al., 2013a, 2013b, 2012; Yu et al., 2000) met the former criteria. Subsequently, seven articles were excluded because they were secondary analyses of the corresponding original study (Chiang et al., 2014; Chung et al., 2011, 2010, 2008; Huang et al., 2008b; Wu et al., 2013b, 2012) and one more because it only reported odds ratios for a subsample of the study population (Leonardi et al., 2012). Therefore 13 studies were finally described (Chen et al., 2003; Chung et al., 2009; Gilbert-Diamond et al., 2013; Hsueh et al., 1997; Huang et al., 2012, 2008a; López-Carrillo et al., 2014; Melak et al., 2014; Pu et al., 2007; Steinmaus et al., 2006, 2010; Wu et al., 2013a; Yu et al., 2000). Each selected article was analyzed by two members of the research team to extract the following information: author's name(s), publication year, place and year in which the study was conducted, study design, sample size, anatomic location of the included cancers, magnitude of iAs exposure, association measure with its corresponding CI, confounding factors considered in the analysis and reviewer's general comments. No quality criteria were applied for the studies.

Following the PRISMA requirements (Moher et al., 2009), we performed a descriptive meta-analysis of the association between the percentage distribution of urinary iAs metabolites (iAs, MMA and DMA) and type of cancer with the results of 12 studies that comprised 7263 participants (2227 cases and 5036 non-cases). In one of them only measures of association in continuous scale were reported thus, it was not included in this step (Gilbert-Diamond et al., 2013) (Fig. 1).

Summary association measures and 95% CIs between the extreme