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Phthalate exposure, flavonoid consumption and breast cancer risk among Mexican women

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ABSTRACT

Objective: To evaluate if selected phthalate exposure and flavonoid intake interact on breast cancer (BC) risk.
Material and methods: Interviews and urine samples were obtained from 233 women with histologically confirmed BC and 221 healthy controls matched by age and place of residence, from various states of northern Mexico. Urinary metabolites concentrations of diethyl phthalate (DEP), butyl benzyl phthalate (BBzP) and dioctyl phthalate (DOP) were determined by solid-phase extraction coupled with high-performance liquid chromatography/isotope dilution/tandem mass spectrometry. Using a semiquantitative food frequency questionnaire, consumption of five types of flavonoids (anthocyanidins, flavan-3-ols, flavanones, flavones and flavonols) was estimated according to three food groups: vegetables, fruits and legumes-oil seeds.
Results: A higher intake of anthocyanidins and flavan-3-ols (from vegetables), synergistically increased the negative association between BBzP and BC. No other significant flavonoid-phthalate multiplicative interactions on the risk for BC were found.
Conclusion: The consumption of some flavonoids may interact with exposure to phthalates on the risk of BC. Epidemiological and underlying mechanisms information is still insufficient and requires further investigations.

1. Introduction

The interaction between chemical compounds and diet may explain differences in breast cancer (BC) incidence throughout the world. Phthalates are endocrine disruptors used primarily as plasticizers in a vast amount of products used for food storage and personal care (body lotion, facial cream, etc.) (Braun et al., 2014; Philippat et al., 2015). Our research group previously reported a significant increased risk of BC associated with the exposure to diethyl phthalate (DEP) (OR $_{t3\ vs.\ t1}$ = 2.20 95% CI 1.33, 3.63 P trend = 0.003) among women residing in northern Mexico, as well as significant negative associations between BC and exposure to butyl benzyl phthalate (BBzP) (OR $_{t3\ vs.\ t1}$ = 0.46 95% CI 0.27, 0.79 P trend = 0.008) and dioctyl phthalate (DOP) (OR $_{t3\ vs.\ t1}$ = 0.44 95% CI 0.24, 0.80 P trend = 0.007), respectively (López-Carrillo et al., 2010). It is unknown if the described relationship between the exposure to those phthalates and BC could be modified by the presence of dietary compounds with estrogenic properties such as flavonoids.

Flavonoids are polyphenolic phytoestrogens (>5000), which have been classified based on their chemical structure into anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols and isoflavonoids (Hui et al., 2013). Results from in vitro and in vivo studies have identified that some flavonoids have antiproliferative, antioxidant and antiangiogenic activities as well as the capacity of inhibiting certain enzymes which are responsible for the metabolism of steroid hormones (i.e. estrogen and chemical carcinogens) (Awasthi et al., 2014; Haddad et al., 2006; Kim, 2003; Sen et al., 2013). In addition, certain flavonoids including naringenin, apigenin and kaempferol, have higher affinity for the estrogen receptor (ER) β (Kuiper et al., 1998) than ER α, which has been associated with inhibitory mechanisms of cellular proliferation in breast

Abbreviations: BC, breast cancer; DEP, diethyl phthalate; BBzP, butyl benzyl phthalate; DOP, dioctyl phthalate; MEP, monoethyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono (3-carboxypropyl) phthalate; LOD, limit of detection; TEE, total energy expended.

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tissue (Ng et al., 2014; Rizza et al., 2014). However, at high doses certain flavonoids, such as quercetin and nangerin, can act like mutagens and prooxidants (Skilbola and Smith, 2000).

A meta-analysis which included six longitudinal cohorts and six case-control studies, showed that the ingestion of flavones and flavonols are associated with a decreased risk of BC (Hui et al., 2013). This meta-analysis included a study from central Mexico which reported a protective effect for BC associated with the consumption of flavones and flavonols in post-menopausal women (Torres-Sanchez et al., 2009). Two more recent cohort studies, one on women between the ages of 35 to 70 years old from 10 countries in Europe (n = 334,850), and another study on women older than 55 years old in the Netherlands (n = 3209), found no association between flavonoid consumption and BC. Also, the second study found an increased risk for BC among women older than 70 years old with low total flavonoid consumption (Zamora-Ros et al., 2013; Pantavos et al., 2015). Among the methodological limitations that may explain the inconsistencies among those studies is the heterogeneity of nutrients content in foods from different countries.

The purpose of this study was to evaluate if selected flavonoids from the consumption of vegetables, fruits and legumes-oil seeds modifies the associations between BC and DEP, BBzP and DOP phthalates.

2. Methods and materials

A population based case-control study was performed in northern Mexico in the states of Chihuahua, Coahuila, Durango, Nuevo León, Sonora and Tamaulipas, between 2007 and 2008. The purpose was to evaluate the association between urinary concentrations of various phthalate metabolites and the risk for BC. The study was approved by the Ethics Committee of the National Institute of Public Health (López-Carrillo et al., 2010). This article is a continuation of this study and evaluates the dietary intake of flavonoids among the participants.

The cases (n = 233) were women with histopathologically confirmed BC from 17 tertiary hospital units, at least 18 years old, without a history of any other type of cancer, and residents of the selected geographical area for at least one year prior to the study. The response rate was 94.8%.

The controls (n = 221) were women matched by place of residency and age (±5 years) of the case. They were identified through the master sample framework used by the Ministry of Health in national surveys, which consists of a housing list from urban and rural areas that are grouped into primary sampling units. A sample of those units was randomly selected for the purpose of this study. Selected homes were visited systematically, until an eligible woman was identified. In households where no eligible women were found or consent was not received, another home was systematically identified. If there was more than one eligible woman in a household, then one of them was randomly selected. The response rate was 99.5%.

2.1. Interviews and urine samples

After providing informed consent, women were interviewed in person to obtain information on medical and reproductive history, sociodemographics, diet, physical activity and anthropometric measures to calculate the body mass index (BMI). Patients were interviewed on average 2 months after their diagnosis. A first morning void urine samples was collected in phthalate free sterile disposable polypropylene urine collection cups (Medegen®). Among cases the samples were collected before receiving any type of treatment. Four milliliter aliquots were prepared in Cryovials and stored in −20 °C until shipped to the Center for Disease Control (CDC) where they were stored at −40 °C until they were analyzed.

2.2. Evaluation of urinary concentration of phthalate metabolites

For this report, three phthalate metabolites that were significantly associated with BC were included, from a total of nine metabolites that were assessed in the original study (López-Carrillo et al., 2010). The urinary concentrations of monoethyl phthalate (MEP), monobenzyl phthalate (MBzP) and mono (3-carboxypropyl) phthalate (MCPP) which are the urinary metabolites of DEP, BBzP and DOP were measured by solid-phase extraction coupled with high-performance liquid chromatography/isotope dilution/tandem mass spectrometry. Of the measured metabolites, only MCPP had values below the limit of detection (LOD) (MCPP < LOD: 3% cases, 2% controls) and were assigned a value equal to LOD divided by two, according to the methodology suggested by Barr et al. when the percentage < LOD is low and the distribution of data is skewed (MCPP skewness = 14.77) (Barr et al., 2006). The urinary creatinine concentration (mg/dL) was measured using the enzymatic method of Kit Randox according to the instructions of the manufacturer (RADOX, 2010).

2.3. Evaluation of dietary flavonoid consumption

The frequency of consumption of 119 foods and 14 meals over the past 12 months was obtained through validated semi-quantitative food frequency questionnaire (Galvan-Portillo et al., 2007). The frequency of consumption of predetermined portions for each food item included 10 options ranging from “never” up to “6 or more times a day”. Predetermined portions were as follows: a glass (for milk and wine), a cup (for yogurt, some fruits and vegetables, tea, juices, alcoholic and nonalcoholic beverages), a spoon (for oils, sour cream, sauces and nuts), a slice (for chesses, some fruits and meats), a plate (for legumes and local dishes) and a piece (for some fruits and breads).

Our group has previously showed an agreement of the foods included in our questionnaire, with the nutrient composition reference tables no. 20 of the United States Department of Agriculture (USDA, 2007), from which the nutritional value of each food item was obtained. The nutritional composition of two local food items (quince and Mexican hawthorn) are not included in those reference tables and were obtained from tables established by the National Institute of Nutrition Salvador Zubiran in Mexico. Also, information of five types of flavonoids and its subtypes was obtained from the database of flavonoid composition version 3.1 from the USDA: (1) anthocyanidins: cyanidin, petunidin, delphinidin, malvidin, pelargonidin, peonidin; (2) flavan-3-ols: catechin, epigallocatechin, epicatechin, epicatechin 3-gallate, epigallocatechin 3-gallate, theaflavin, thearubigins, theaflavin 3,3′digallate, theaflavin 3-gallate, gallocatechin; (3) flavanones: eriodictyol, hesperetin, naringenin; (4) flavones: apigenin, luteolin; (5) flavonols: isorhamnetin, kaempferol, myricetin, quercetin (USDA, 2014).

Daily or weekly consumption, total energy, nutrients and flavonoids were estimated based on the participants' report of frequency of food consumption. The consumption of flavonoids were estimated according to the principal food groups: vegetables (cauliflower, broccoli, purslane, corncob, potato, carrot, spinach, zucchini, chayote, lettuce, avocado, squash blossom, beetroot, onions, garlic and nopal that is a local cactus leaf), fruits (banana, cherry, peach, apple, orange juice, orange, grape, blackberry, strawberry, melon, watermelon, mango, pear, mamey, sapodilla, prickly pear, papaya, pineapple, guava, figs, quince, Mexican hawthorn and tuna that is a local cactus fruit) and legumes-oil seeds (beans, pea, lentils, lima bean, dry bean, pistachios and walnuts). The frequency of fruit and vegetable consumption was adjusted according to the annual market supply. For example, only half the consumption of plums was accounted for because they are only available during 6 months of the year. The consumption of isoflavones was not calculated due to the limited consumption of soya and derivatives in the study region.

As quality control of the dietary information the percentage of adequacy was calculated for all the participants. This is the proportional