Environmental Research 142 (2015) 633–643

Contents lists available at ScienceDirect

Environmental Research

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

Serum and adipose tissue as matrices for assessment of exposure to persistent organic pollutants in breast cancer patients

F. Artacho-Cordón [a,c], M. Fernández-Rodríguez [a,c], C. Garde [a], E. Salamanca [a,c], L.M. Iribarne-Durán [a,c], P. Torné [a], J. Expósito [a,b], L. Papay-Ramírez [a], M.F. Fernández [a,c,d], N. Olea [a,c,d], J.P. Arrebola [a,b,c,d,*]

[a] Instituto de Investigación Biosanitaria ibs. GRANADA, Hospitales Universitarios de Granada, Spain
[b] Radiation Oncology Department, Virgen de las Nieves University Hospital, Granada, Spain
[c] Radiology and Physical Medicine Department, University of Granada, Spain
[d] CIBER en Epidemiología y Salud Pública (CIBERESP), Spain

ARTICLE INFO

Article history:
Received 11 June 2015
Received in revised form
14 August 2015
Accepted 18 August 2015

Keywords:
Organochlorine pesticides
Polychlorinated biphenyls
Adipose tissue
Serum
Breast cancer

ABSTRACT

The aim of this study was to assess differences between two biological matrices (serum and breast adipose tissue) in the evaluation of persistent organic pollutant (POP) exposure in breast cancer patients. The study population consisted of 103 women undergoing surgery for newly diagnosed breast carcinoma in a public hospital in Granada, Southern Spain. Independent variables were gathered from questionnaires and clinical records. POP concentrations were quantified in breast adipose tissue and serum samples. Spearman correlation tests were performed between pairs of POP concentrations and stepwise multivariable linear regression analyses were conducted to assess predictors of concentrations in the two matrices. *p,p′*- Dichlorodiphenyldichloroethylene (*p,p′*-DDE) showed the the highest median concentration in both matrices (194.34 and 173.84 ng/g lipid in adipose tissue and serum, respectively). Median wet-basis adipose tissue:serum ratios ranged from 109.34 to 651.62, while lipid-basis ratios ranged from 0.88 to 4.34. In general, we found significant positive correlation coefficients between pairs of POPs in adipose tissue and in serum, which were always higher in adipose tissue. We found positive and statistically significant correlations between serum and adipose tissue concentrations of *p,p′*-DDE and hexachlorobenzene (HCB) but not of polychlorinated biphenyls (PCBs). Age was positively associated with most POPs in adipose tissue and serum, while the body mass index was positively associated with adipose tissue HCB concentrations and negatively associated with serum PCB-153 and PCB-138 concentrations. Recent weight loss was inversely associated with POP residues in adipose tissue and positively associated with POP residues in serum. Serum HCB and PCB-180 concentrations were lower in patients who had received preoperative chemotherapy. According to our results, serum and adipose tissue POP concentrations in breast cancer patients may be differentially affected by external predictors. Taken together, these findings indicate the need to take account of the individual POP(s) under study and the biological matrix used when relating internal POP exposure to breast cancer disease and to make a careful selection of covariates for adjusting the model.

1. Introduction

Persistent organic pollutants (POPs) are a wide group of highly lipophilic environmental pollutants that tend to accumulate and biomagnify in the food chain, resulting in the considerable exposure of living organisms (UNEP, 2003). POPs include organochlorine pesticides (OCPs), such as dichlorodiphenyltrichloroethane (DDT) and its metabolites (notably, *p,p′*-dichlorodiphenyldichloroethylene [*p,p′*-DDE]), hexachlorobenzene (HCB), and polychlorinated biphenyls (PCBs), among others. While DDT and HCB were primarily commercialized for vector control and agricultural purposes, PCBs were mainly used as fluid insulators in electrical transformers and capacitors. Since the early 1970s, most countries have banned or severely restricted the production, handling, and disposal of most POPs. This is due to their high environmental persistence and their proven or suspected adverse human health effects at doses traditionally considered safe, including reproductive disorders, endocrine disruption, and carcinogenicity (Arrebola et al., 2013; Bonefeld-Jorgensen, 2010; Fernandez et al., 2007a, 2007b; Gasull et al., 2010; Krüger et al., 2012; Lee et al., 2014).

* Corresponding author at: Instituto de Investigación Biosanitaria ibs. GRANADA, Hospitales Universitarios de Granada, University of Granada, 18071 Granada, Spain. Fax: +34 958 249953.
E-mail address: jparrebola@ugr.es (J.P. Arrebola).

http://dx.doi.org/10.1016/j.envres.2015.08.020
0013-9351/

Despite their prohibition, POPs are still commonly detected in air, water and soil, among other environmental media (Syed et al., 2013). Besides respiratory and dermal routes, diet is believed to be the main route of exposure to POPs in the general population (Gasull et al., 2010). Due to their lipophilicity, POPs tend to bioaccumulate in fat components, and adipose tissue is therefore acknowledged to be the main deposit of these contaminants, accounting for all routes and sources of exposure and representing a stable and long-term reservoir of these compounds (Kohlmeier and Kohlmeier, 1995).

Hormone homeostasis is crucial in diseases related to the endocrine system, including the majority of breast cancers. Thus, estrogen signaling and the estrogen receptor (ER) have been implicated in breast cancer progression, and most human breast cancers start out as estrogen dependent (Saha Roy and Vadlamudi, 2011). In fact, ER-alpha antagonism is widely used in the treatment of ER-alpha-positive breast cancer patients. In this regard, some *in vitro* studies have revealed that exposure to some POPs can interact with ERs and cause estrogen-related effects, such as breast cancer cell proliferation. The suspected mechanisms of action have not been fully elucidated, but *in vitro* studies have shown that numerous POPs can interact with estrogen and/or androgen receptors, exerting significant effects at very low doses (Andersen et al., 2002; Bonefeld-Jørgensen et al., 2001; Grünfeld and Bonefeld-Jorgensen, 2004; Soto et al., 1994). In fact, the estrogenic potency of most POPs is approximately six orders of magnitude lower than of estradiol (Soto et al., 1994). Nevertheless, some epidemiological evidence has emerged on the potential role of POP exposure in the etiology of breast cancer, with a wide range of studies reporting positive associations (Aronson et al., 2000; Arrebola et al., 2015, 2014a; Boada et al., 2012; Bonefeld-Jorgensen et al., 2011; Bonefeld-Jørgensen et al., 2014; Ibarluzea et al., 2004), although others found no or even negative associations (Gatto et al., 2007; Itoh et al., 2009; Xu et al., 2010). Key differences among these studies include not only the study design and target population but also the biological matrix used to estimate the exposure, with serum and adipose tissue being the most frequent.

Whereas it is viable to obtain breast adipose tissue from patients undergoing surgery, the difficulties in obtaining these samples from other populations means that blood serum has more frequently been used as a matrix for exposure assessment of the general population. However, although many authors have found a high correlation between POP concentrations in serum and adipose tissue (López-Carrillo et al., 1999; Pauwels et al., 2000; Waliszewski et al., 2004; Whitcomb et al., 2005), it remains unclear whether serum POP concentrations can accurately reflect the body burden of these chemicals in all situations (Aronson et al., 2000; Arrebola et al., 2012a; Mussalo-Rauhamaa, 1991; Rusiecki et al., 2005; Wolff et al., 2000). In fact, it is possible that POP concentrations in the two matrices may be strongly correlated in some cases but not in others, given that serum concentrations are influenced not only by current exposure but also by the recirculation of POPs from adipose tissue due to lipolysis (Crinnion, 2009).

The steady-state partitioning of POPs between serum and breast adipose tissue is an important consideration in attempts to predict adipose tissue concentrations from those found in serum (Rusiecki et al., 2005). Thus, it has been suggested that variations in the lipid content of serum can induce changes in the partitioning coefficient between adipose tissue and serum POP concentrations (Guo et al., 1987). In this regard, most chemotherapy (QT) treatments are believed to reduce concentrations of serum lipid fractions [e.g. triglycerides, total cholesterol and low density lipoprotein (LDL)] in patients with breast cancer (Ray et al., 2001; Shah et al., 2008). It is therefore of interest to assess whether the serum POP concentrations of these patients can always predict the total body burden. Furthermore, given the widespread application of neoadjuvant treatments in breast cancer, it is relevant to assess whether they can act as confounders or effect modifiers in the potential association between POPs and breast cancer risk.

The aim of this study was to assess differences between two biological matrices (serum and breast adipose tissue) in the evaluation of POP exposure in breast cancer patients.

2. Material and methods

2.1. Study population

Breast cancer patients were recruited between January 2012 and June 2014 among newly diagnosed women at San Cecilio University Hospital in the city of Granada (Southern Spain). Out of 204 eligible newly diagnosed breast cancer patients, 33 (16.2%) refused to participate in this study. Among the remaining 171 participants, 68 (39.8%) were excluded due to an inadequate biological sample volume. Therefore, the final study population comprised 103 breast cancer patients. No statistically significant differences in age, BMI, educational level, or histopathological grade were found between included and excluded volunteers (data not shown in tables). All patients signed their informed consent to participate in the study, which was approved by the Ethics Committee of Granada “Comité de Ética de la Investigación Biomédica de la Provincia de Granada”.

2.2. Independent variables

Socio-demographic data, including age, residence, occupation, and educational level, were gathered from a questionnaire completed by each participant before surgery in a face-to-face interview with a trained interviewer during the hospital stay. Questionnaires and research procedures were validated in a previous study (Arrebola et al., 2009, 2010). The height and weight of the participants were recorded, calculating their body mass index (BMI) as weight/height squared (kg/m^2). Residence in the city of Granada or in its metropolitan area at the time of the surgery was considered “urban” and residence in other towns/villages was considered “rural”. Goldthorpe proposed the following occupational classes in Spain: I, managers of companies with ≥ 10 employees, senior technical staff, and free professionals; II, managers of companies with < 10 employees and intermediate occupations; III, administrative personnel, financial management support professionals, self-employed professionals, supervisors of manual workers, and other skilled non-manual workers; IV, skilled and semi-skilled manual workers; and V, unskilled manual workers. A sixth group is formed by those working mainly as homemakers (Regidor, 2001). However, because of sample size limitations, we grouped subjects in two categories: non manual (classes I+II + III) and manual (classes IV + V + homemakers).

Clinical and reproductive data was also gathered from the clinical records of the hospital. The number of pregnancies was recorded as a discrete variable (multiparous/nulliparous). Accumulated breastfeeding time (months) were recorded as a continuous variable. Age of menarche was also recorded. Menopausal status and hormone replacement status were considered as dichotomous variables (pre/post; yes/no, respectively). Clinical data also included information on the neoadjuvant tumor treatment (yes/no), biological aggressiveness (G1/G2/G3), presence of estrogen receptors (negative/positive), tumor stage (0-IIB/IIIA-IIIB/IV), histopathological status (benign/malign), and molecular subtype (Luminal A/Luminal B/Her+/Triple Negative).