Science of the Total Environment 897 (2023) 165373

Contents lists available at ScienceDirect

Science of the Total Environment

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

Associations of accumulated persistent organic pollutants in breast adipose tissue with the evolution of breast cancer after surgery

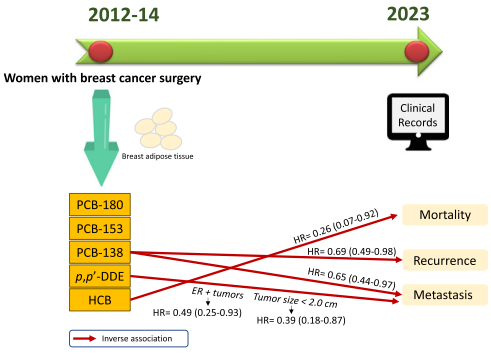
R. Barrios-Rodríguez [a,b,c,1], C. Garde [e,1], F.M. Pérez-Carrascosa [a,b], J. Expósito [b,d], F.M. Peinado [b], M. Fernández Rodríguez [f], P. Requena [a,b,c], I. Salcedo-Bellido [a,b,c,*], J.P. Arrebola [a,b,c,*]

[a] Universidad de Granada, Departamento de Medicina Preventiva y Salud Pública, Granada, Spain
[b] Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain
[c] Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain
[d] Virgen de las Nieves University Hospital, Radiation Oncology Department, Oncology Unit, Granada, Spain
[e] San Cecilio University Hospital, Avenida del Conocimiento s/n, 18016 Granada, Spain
[f] Universidad de Granada, Facultad de Farmacia, Departamento de Farmacia y Tecnología Farmacéutica, Granada, Spain

HIGHLIGHTS

- 5 POPs were analyzed in breast adipose tissue from women under cancer surgery.
- The clinical evolution of participants over 10 years was recorded.
- High HCB levels were associated to lower risk of all-cause mortality.
- PCB-138 was inversely associated with the risk of metastasis and tumor recurrence.
- *p,p′*-DDE was inversely associated with metastasis in ER+ and <2.0 cm tumors.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Lidia Minguez Alarcon

Keywords:
Persistent organic pollutants
Adipose tissue
Metastasis
All-cause mortality
Breast cancer recurrence
Second primary tumor

ABSTRACT

Chronic exposure to persistent organic pollutants (POPs) is suspected to contribute to the onset of breast cancer, but the impact on the evolution of patients after diagnosis is unclear. We aimed to analyze the contribution of long-term exposure to five POPs to overall mortality, cancer recurrence, metastasis, and development of second primary tumors over a global follow-up of 10 years after surgery in breast cancer patients in a cohort study. Between 2012 and 2014, a total of 112 newly diagnosed breast cancer patients were recruited from a public hospital in Granada, Southern Spain. Historical exposure to POPs was estimated by analyzing their concentrations in breast adipose tissue samples. Socio-demographic data were collected through face-to-face interviews, while data on evolution tumor were retrieved from clinical records. Statistical analyses were performed using Cox regression (overall survival, breast cancer recurrence or metastasis) and binary logistic regression models (joint outcome variable). We also tested for statistical interactions of POPs with age, residence, and prognostic markers. The third vs first tertile of hexachlorobenzene concentrations was associated with a lower risk of all-cause mortality (Hazard Ratio, HR = 0.26; 95 % Confidence Interval, CI = 0.07–0.92) and of the appearance of any of the four events (Odds Ratio = 0.37; 95 % CI = 0.14–1.03). Polychlorinated biphenyl 138 concentrations were significantly and inversely associated with risk of metastasis (HR = 0.65; 95 % CI = 0.44–0.97) and tumor recurrence (HR = 0.69; 95 % CI = 0.49–0.98). Additionally, *p,p′*-dichlorodiphenyldichloroethylene showed inverse associations with risk of metastasis in women with ER-positive tumors (HR = 0.49; 95 % CI = 0.25–0.93) and in those with a tumor size <2.0 cm (HR = 0.39; 95 % CI = 0.18–0.87).

* Corresponding authors at: Universidad de Granada, Departamento de Medicina Preventiva y Salud Pública, Facultad de Farmacia, Campus de Cartuja, 18011 Granada, Spain.
E-mail addresses: isalcedo@ugr.es (I. Salcedo-Bellido), jparrebola@ugr.es (J.P. Arrebola).
[1] Equal contribution to this work.

http://dx.doi.org/10.1016/j.scitotenv.2023.165373
Received 30 March 2023; Received in revised form 4 July 2023; Accepted 5 July 2023
Available online 5 July 2023

The observed paradoxical inverse associations of POP exposure with breast cancer evolution might be related to either a better prognosis of hormone-dependent tumors, which have an approachable pharmacological target, or an effect of sequestration of circulating POPs by adipose tissue.

1. Introduction

Breast cancer is currently the most frequently diagnosed cancer worldwide for both sexes combined (Arnold et al., 2022). In fact, breast cancer incidence has surpassed lung cancer, with an estimated 2.3 million new cases (11.7 % of the total) in 2020 (Sung et al., 2021). In recent decades, the incidence of this cancer has increased rapidly, particularly in developed regions like Europe (Yi et al., 2021).

Fortunately, mortality from breast cancer has been reduced by 40 % in the last 30 years in high-income countries due to the advancement of treatments and enhancement in early detection (DeSantis et al., 2019; Siegel et al., 2021). After diagnosis, these women undergo to a close follow-up with a frequency of reviews every 3–6 months during the first 2–3 years (Algara López et al., 2015). However, breast cancer still poses a substantial clinical challenge due to the frequent appearance of recurrence, second primary tumors or metastasis (Kim, 2021; Li et al., 2020; Runowicz et al., 2016). In fact, recent research is being focused on developing new models to improve the clinical decision and preventing underdiagnosis of high-risk tumors and minimising over-treatment of low-risk disease (Amiri Souri et al., 2021). Non-modifiable factors related to a worse prognosis of breast cancer include African-American race, premenopausal status, and clinical variables such as involved margins, high histological grade and high p16 expression (Visser et al., 2019). In addition, previous studies have suggested that environmental exposures might have an important contribution to the development of breast cancer (Rodgers et al., 2018; Zeinomar et al., 2020). Therefore, the identification of these potentially modifiable factors would help to establish strategies for disease prevention and the improvement of the evolution of breast cancer patients.

Persistent organic pollutants (POPs) are an heterogeneous group of chemicals, including polychlorinated biphenyls (PCBs), of industrial origin, and organochlorine pesticides (OCPs), that have been widely used in agriculture for pest control (Arrebola et al., 2013; Echeverría et al., 2021). Despite the legal restrictions on their production and use implemented in recent decades, their lipophilicity and resistance to degradation favor their bioaccumulation and biomagnification in organisms, especially in fatty tissue (Jackson et al., 2017). The main routes of exposure to POPs in the general population are diet and inhalation (Ampleman et al., 2015). Chronic exposure to these environmental chemicals at levels frequently detected in general populations has been positively associated with the risk of cancer, including breast cancer (Arrebola et al., 2015; Leng et al., 2016; Mustieles et al., 2021). In this regard, previous studies have reported associations of high exposure to certain non-dioxin like PCBs such as PCB-138, PCB-153, PCB-180, and pesticides as p,p′-dichlorodiphenyldichloroethylene (p,p′-DDE), hexachlorobenzene (HCB) with increased breast cancer risk (Charlier et al., 2004; Huang et al., 2019). Tumor promotion may occur through different mechanisms as suppression of apoptosis in preneoplastic cells, inhibition of intercellular communication or the production of reactive oxygen species (Knerr and Schrenk, 2006; Mustieles et al., 2021). However, and despite the biological plausibility, the results are still inconsistent (Wan et al., 2022). On the other hand, our research previously evidenced positive associations of PCB-138, PCB-180 and HCB with the expression of estrogen and progesterone receptors, human epidermal growth factor receptor 2 (HER-2), E-Cadherin, or p53 (Arrebola et al., 2016). Nevertheless, the scientific literature on breast cancer prognosis in this context is limited, and specifically, the association between the role of POPs and breast cancer prognosis is highly debated. In this regard, while POPs present levels in blood/serum or breast adipose tissue have often consistently been linked to poorer breast cancer prognosis. Conversely, POPs concentrations detected in adipose tissue outside the breast have frequently been associated with a more favorable prognosis in breast cancer cases (Ennour-Idrissi et al., 2019). Therefore, there is a growing need for further studies to enhance our understanding of these associations (Parada et al., 2016; Roswall et al., 2018).

On the basis of the above mentioned, the objective of this study was to evaluate the potential contribution of long-term exposure to three PCBs and two OCPs on the overall mortality, cancer recurrence, distant metastasis and second primary tumors over a global follow-up of 10 years after surgery in breast cancer patients.

2. Material and methods

2.1. Study design and population

The study participants were newly diagnosed breast cancer patients undergoing breast cancer surgery between January 2012 and June 2014 in a public hospital of the city of Granada (Southern Spain): Clínico San Cecilio University Hospital. It is one of the two reference hospitals covering Granada city and surroundings. The description of the study design and population have been previously published (Arrebola et al., 2016; Artacho-Cordón et al., 2015). Briefly, prior to breast cancer surgery, patients were invited to participate in this study by the research staff. Of the 204 breast cancer patients meeting the selection criteria, 171 (83.8 %) accepted to participate. The final study population comprised 112 participants who provided adequate adipose tissue sample for POP analyses, which is slightly higher than the final population size in the two previous studies conducted in this cohort, i.a., 103 (Arrebola et al., 2016; Artacho-Cordón et al., 2015). The reason was that these studies focused on individuals who had provided both adipose tissue and serum samples. In addition, the analyses with metastasis as outcome of interest were performed in 111 women instead of 112, since one developed metastasis prior to diagnosis.

The data on outcomes from recruitment until 20 January 2023 were retrieved from the DIRAYA® clinical records database. DIRAYA® is the database used in the Andalusian Health Service, that includes all clinical information from each user. DIRAYA® was implemented in 2003 to assist clinical procedures and support epidemiological and clinical research. It integrates every health episode of each patient assisted in Andalusian healthcare centers (Protti, 2007). Mortality over follow-up was gathered from the National Death Index ("Índice Nacional de Defunciones"), a nationwide database supported by the Spanish Ministry of Health (Navarro, 2006). Study protocol was approved by the Ethics Committee of Granada ("Comité de Ética de la Investigación Provincial de Granada", 26th November 2012) including gathering and managing the personal information. All participants included in the study signed an informed consent.

2.2. Sampling and POP analyses

Samples of approximately 10 g of breast adipose tissue were intraoperatively collected and immediately coded and stored at −80 °C until chemical analysis. To isolate the target analytes from adipose tissue, a chemical extraction process was employed. In brief, the adipose tissue underwent extraction using n-hexane and was then purified via alumina. The dried adipose tissue was fractionated using high-performance liquid chromatography (HPLC). Subsequent chemical analyses were performed using gas chromatography with micro-electron capture detection (GC-ECD) on a VARIAN CP-3800 chromatograph equipped with a ^{63}Ni electron capture detector (Walnut Creek, CA, US) (Rivas et al., 2001). The limit of

detection (LOD) was determined as the smallest amount of the analyte that gave a signal-to-noise ratio ≥3 and was set at 0.05 ng/mL for each analyte. Chromatographic concentrations < LOD were assigned a random value between zero and the LOD as recommended elsewhere (Antweiler and Taylor, 2008). POP concentrations were expressed in lipid basis (ng/g lipid). Residues of the following OCPs were quantified: *p,p′*-DDE (the main metabolite of the pesticide dichloro diphenyl tri-chloroethane [DDT]), HCB, and the PCB congeners −138, −153, and −180.

2.3. Covariates

Baseline covariate information was gathered through face-to-face interviews conducted by trained personnel during the hospital stay prior to surgery. The interviews encompassed socio-demographic data such as age, educational level (none, primary or more than primary), current smoking status (yes or no) and place of residence (rural or urban). Urban residence at recruitment was considered when the participants lived in the city of Granada (with 239,017 inhabitants in 2012, www.ine.es) or in its metropolitan area, and rural residence when they lived in towns or villages (<62,000 in 2012). The height and weight of participants were recorded at recruitment and the body mass index (BMI) was calculated as weight/height squared (kg/m^2). Clinical and reproductive data were collected from the clinical records of the hospital: having children (yes/no), breastfeeding (yes/no), menopausal status (pre/postmenopausal), oral contraceptive consumption (yes/no), and type of breast cancer surgery performed (conservative/radical).

The following data on tumor prognostic markers were obtained from routine pathological anatomy analyses performed at the hospital and recorded in the clinical records (Arrebola et al., 2016): estrogen receptor (ER) (+/−), progesterone receptor (PR) (+/−), expression of HER-2, adhesion molecule E-Cadherin, proliferation index Ki-67, p53 (tumor suppressor) gene mutation, tumor size (continuous), and lymph node involvement. HER-2 expression was based on the intensity of membrane reactivity and number of cells under light microscopy, considering the categories 0 and 1+ as negative, 2+ as equivocal, and 3+ as positive using the fluorescent in situ hybridization to finally categorize 2+ samples. The samples were considered positive for p53 and E-cadherin when ≥10 % of cells were stained and positive for Ki-67 when ≥15 % (Arrebola et al., 2016).

2.4. Data analyses

Mean and standard deviation (SD) or median and interquartile range (IQR, percentil 25-percentil 75) were used for the description of continuous variables and percentages for categorical variables.

Data from questionnaires, chemical analyses, and information from health records were linked by utilizing the unique identification number assigned to each user in the Andalusian Public Health System.

To assess the relationship between the breast adipose tissue POP levels and the risk of either death or breast cancer recurrence, we fitted Cox regression models with time-to-events (all-cause mortality, tumor recurrence or censoring) as the time variable, calculating hazard ratios (HRs) and their corresponding 95 % confidence intervals (CIs). Follow-up time was defined as the time lapse between the date of surgery and either the event of interest, death or the end of the study (20-January-2023), whichever occurred first. Data of those participants reaching the end of follow-up without the event of interest were censored. There were no missing participants during follow-up period. Continuous POP concentrations were log-transformed in order to reduce the skewness in their distributions and improving the functional form, and were also categorized in tertiles (T), considering T1 as the reference category. Selection of confounding variables for multivariable models was based on a directed acyclic graph (Fig. 1) and information from previous studies (Parada et al., 2016; Roswall et al., 2018). In this regard, the models were adjusted for the following variables: age (as the underlying time variable), smoking status, educational level, BMI (categorized as normal weight [<25 kg/m^2] and overweight-obesity [≥25 kg/m^2]), breastfeeding and having children (0/≥1). Due to the low variability in the number of children at recruitment (Table 1) and the low number of events of recurrence (n = 16, 14.3 %), this covariate could not be included in the multivariable models for this outcome. Considering that BMI might also be in the causal pathway between selected POPs and the evolution of breast cancer (Pati et al., 2023; Wood et al., 2016), we repeated the Cox-regression models without adjustment for this variable as a sensitivity analysis, in order to avoid possible model overfitting. Sensitive analyses were also conducted by deleting one participant with previous metastasis because of this circumstance could influence on the posterior evaluation of the illness.

As previously performed elsewhere, we tested the potential modifying effect of age (above/below median [52 years]), residence (rural/urban),

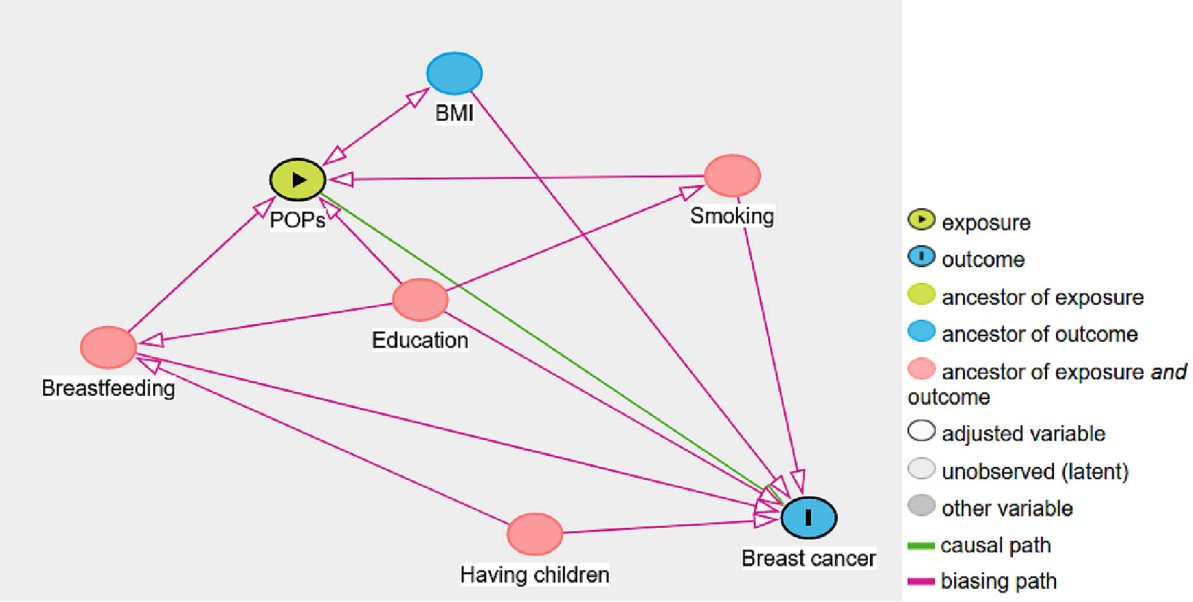


Fig. 1. Directed acyclic graph about the association between persistent organic pollutants (POPs) and breast cancer.
BMI: body mass index. Cite: Johannes Textor, Benito van der Zander, Mark K. Gilthorpe, Maciej Liskiewicz, George T.H. Ellison. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. International Journal of Epidemiology 45(6):1887–1894, 2016.

Table 1
Baseline characteristics of the study population (n = 112).

Variable	
Age, mean (SD)	53.9 (11.9)
Education level, n (%)	
None/primary	62 (55.4)
More than primary	50 (44.6)
Residence, n (%)	
Rural	82 (73.2)
Urban	30 (26.8)
Smoker (yes), n (%)	28 (25.0)
Body mass index, mean (SD)	27.0 (4.9)
<25 kg/m^2, n (%)	45 (40.2)
≥25 kg/m^2, n (%)	67 (59.8)
Menopausal status, n (%)	
Premenopausal	45 (40.2)
Postmenopausal	67 (59.8)
Breastfeeding (yes), n (%)	79 (70.8)
Having children (yes), n (%)	99 (88.4)
Oral contraceptive use (yes), n (%)	62 (55.4)
Estrogen receptor (+), n (%)	91 (81.3)
Progesterone receptor (+), n (%)	81 (72.3)
Ki67 (+)	61 (54.5)
HER-2 (+)	20 (17.9)
p53 (+)	42 (37.5)
E-Cadherin (+)	84 (75.0)
Lymph node involvement, n (%)	42 (37.5)
Tumor size (cm), median (IQR)	2.0 (1.3–3.2)
Type of breast cancer surgery, n (%)	
Conservative	84 (75.0)
Radical	28 (25.0)
Overall mortality, n (%)	26 (23.2)
Recurrence, n (%)	16 (14.3)
Metastasis, n (%)	19 (17.1)

SD: standard deviation; IQR: interquartile range.

prognostic markers (estrogen receptor [+/−], tumor size [above/below median, 2.0 cm], menopausal status, smoking, BMI, and lymph node involvement [yes/no]) by including in each model the product term of each variable*POPs levels as well as by means of stratified analyses. The rationale for these approach is based on previous investigations supporting that the aforementioned prognosis variables could modify the effect of POP concentrations on breast cancer evolution (Soerjomataram et al., 2008). Besides, it is been previously reported that age, residence, smoking and BMI may have an effect in the burden of breast cancer (Kenzik et al., 2020; Liu et al., 2021; Phung et al., 2019) and in the levels of POPs (Artacho-Cordón et al., 2015; Echeverría et al., 2021; Moon et al., 2017). Again, the number of children at recruitment could not be included in the multivariable in the stratified models.

Due to the low incidence of second primary tumors (n = 7, 6.3 %), they were only considered in the statistical analyses as a joint outcome variable (including exitus, tumor recurrence, metastasis), using binary logistic regression models.

Despite the significance level was set at the traditional $p < 0.05$, the results were also interpreted on the basis of the confidence intervals, magnitude of the associations and biological plausibility. R statistical computing environment v4.1.1 (R Core Team, 2021) was used to analyze the statistical power and Stata program v.15 (Stata Corp., College Station, TX, USA, 2017) for the rest of the data analyses.

3. Results

The baseline characteristics of the study subjects are summarized in Table 1. The mean age (SD) was 53.9 (11.9) years. 44.6 % had secondary or university studies, the majority lived in a rural area (73.2 %) and 25.0 % were smokers. Participants were predominantly overweight or obese (59.8 %), postmenopausal (59.8 %), had children (88.4 %), had breastfed their children (70.8 %), and had used oral contraception (55.4 %). In regards to tumor prognostic markers, the majority of the 112 women had ER+ (81.3 %), PR+ (72.3 %) and E-Cadherin (75.0 %). 37.5 % had lymph node involvement and the median of tumor size was 2.0 cm (IQR: 1.3–3.2). Breast conserving surgery was carried out in 75 % of participants. More detailed information about the type of surgery is shown in supplementary material (Table S1).

A total of 26 (23.2 %) participants died during follow up, with median follow-up time (until event or censure) of 114.3 months (IQR: 109.7–127.9 months). A total of 16 (14.3 %) participants had tumor recurrence and 19 (17.09 %) developed metastasis, with median follow-up time of 117.0 months (IQR: 110.8–128.1 months) and 116.8 months (IQR: 110.3–128.4 months), respectively. For the 7 (6.3 %) patients with second primary tumors, the median follow-up time was 117.5 months (IQR: 111.8–128.6 months). A total of 41 (36.6 %) participants developed any of these adverse outcomes.

POP concentrations median adipose tissue ranged from 44.7 ng/g lipid for PCB-180 to 221.4 ng/g lipid for *p,p′*-DDE (Fig. 2) and the detection frequency ranged from 98.2 % for PCB-180 to 100 % for PCB-153 and *p,p′*-DDE. More details of POP detection rates were reported elsewhere (Artacho-Cordón et al., 2015).

Table 2 summarizes the associations between POP concentrations with all-cause mortality. There was a general pattern of non-significant inverse associations, with the exception for HCB categorized in tertiles (p-trend = 0.030), for which the likehood of all-cause mortality was a 74 % lower in the third tertile that in the first tertile (p = 0.036). The associations of breast adipose tissue POP concentrations with tumor recurrence and metastasis are displayed in Tables 3 and 4, respectively. PCB-138 concentrations were associated to a lower risk of breast cancer recurrence (HR = 0.69; 95 % CI = 0.49–0.98) and metastasis (HR = 0.65; 95 % CI = 0.44–0.97). These associations did not substantially change in BMI-unadjusted models (supplementary material, Tables S2–S4) as well as in those without the participant with previous metastasis (data no shown).

The above mentioned negative association of PCB-138 with the risk of tumor recurrence was stronger in women older than 52 years (n = 58)

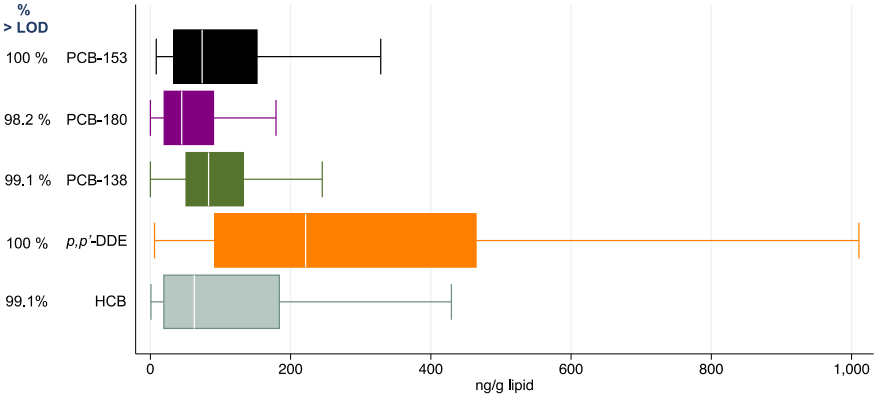


Fig. 2. Baseline breast adipose tissue persistent organic pollutant concentrations in the study population (n = 112).

Table 2
Associations of adipose tissue POP concentrations with the risk of all-cause mortality (23.2 %). Cox regression analysis.

	HR[a] (95 % CI)	p-Value	Tertiles (T) (min-max)	HR[a] (95 % CI)	p-Value
PCB-138	0.92 (0.65–1.29)	0.621	T1 (0.1–55.7)	1.00	
			T2 (56.0–116.4)	0.83 (0.29–2.35)	0.722
			T3 (119.6–1127.4)	0.73 (0.25–2.14)	0.563
			p-trend		0.566
PCB-153	0.94 (0.62–1.45)	0.803	T1 (8.4–41.2)	1.00	
			T2 (43.4–108.0)	0.56 (0.19–1.65)	0.292
			T3 (114.1–706.1)	0.78 (0.29–2.12)	0.633
			p-trend		0.617
PCB-180	0.87 (0.69–1.10)	0.246	T1 (0.0–26.7)	1.00	
			T2 (27.6–69.7)	0.52 (0.18–1.51)	0.232
			T3 (72.2–312.2)	0.59 (0.22–1.62)	0.308
			p-trend		0.296
HCB	0.79 (0.58–1.08)	0.142	T1 (0.9–29.3)	1.00	
			T2 (30.7–127.3)	0.45 (0.16–1.21)	0.114
			T3 (127.3–2159.7)	0.26 (0.07–0.92)	0.036
			p-trend		0.030
p,p′-DDE	0.91 (0.65–1.28)	0.596	T1 (6.0–121.1)	1.00	
			T2 (130.9–382.9)	1.11 (0.40–3.07)	0.834
			T3 (388.9–3614.3)	0.91 (0.32–2.60)	0.856
			p-trend		0.870

HR: hazard ratio; CI: confidence interval; PCB: polychlorinated biphenyls; *p,p′*-DDE: *p,p′*-dichlorodiphenyldichloroethylene; HCB: hexachlorobenzene; T: tertile.
[a] Age as underlying time variable in all analyses and additionally adjusted for smoking (yes/no), educational level (none or primary/more than primary), body mass index (normal weight/overweight-obesity), breastfeeding (yes/no), to have children (yes/no).

Table 4
Associations of adipose tissue POP concentrations with the risk of metastasis (17.1 %). Cox regression analysis.

	HR[a] (95 % CI)	p-Value	Tertiles (min-max)	HR[a] (95 % CI)	p-Value
PCB-138	0.65 (0.44–0.97)	0.036	T1 (0.1–55.7)	1.00	
			T2 (56.0–116.4)	1.09 (0.37–3.24)	0.879
			T3 (119.6–1127.4)	0.65 (0.18–2.38)	0.515
			p-trend		0.549
PCB-153	1.09 (0.69–1.73)	0.702	T1 (8.4–41.2)	1.00	
			T2 (43.4–108.0)	1.74 (0.55–5.55)	0.350
			T3 (114.1–706.1)	1.20 (0.34–4.20)	0.775
			p-trend		0.720
PCB-180	1.13 (0.77–1.67)	0.534	T1 (0.0–26.7)	1.00	
			T2 (27.6–69.7)	1.64 (0.54–5.04)	0.386
			T3 (72.2–312.2)	1.32 (0.38–4.61)	0.664
			p-trend		0.613
HCB	1.01 (0.72–1.42)	0.937	T1 (0.9–29.3)	1.00	
			T2 (30.7–127.3)	0.54 (0.17–1.72)	0.297
			T3 (127.3–2159.7)	1.04 (0.29–3.66)	0.952
			p-trend		0.893
p,p′-DDE	1.21 (0.83–1.77)	0.314	T1 (6.0–121.1)	1.00	
			T2 (130.9–382.9)	1.24 (0.36–4.27)	0.734
			T3 (388.9–3614.3)	1.77 (0.55–5.65)	0.336
			p-trend		0.337

HR: hazard ratio; CI: confidence interval; PCB: polychlorinated biphenyls; *p,p′*-DDE: *p,p′*-dichlorodiphenyldichloroethylene; HCB: hexachlorobenzene; T: tertile.
[a] Age as underlying time variable in all analyses and additionally adjusted for smoking (yes/no), educational level (none or primary/more than primary), body mass index (normal weight/overweight-obesity), breastfeeding (yes/no), to have children (yes/no).

(HR = 0.52; 95 % CI = 0.33–0.83, p-interaction = 0.076). Associations of PCB-138 with the risk of metastasis were also stronger in rural vs urban women (n = 81) (HR = 0.56; 95 % CI = 0.32–0.97, p-interaction = 0.823) (data not shown in tables). Similarly, concerning the concentration of HCB, the probability of all-cause mortality was found to be lower in the third tertile compared to the first tertile among women in the overweight/obesity stratum (HR = 0.09; 95 % CI = 0.01–0.65, p-interaction = 0.191). In the stratified analyses *p,p′*-DDE was also found to be inversely associated with the tumor recurrence in women with ER positive tumors (n = 91)

Table 3
Associations of adipose tissue POP concentrations with the risk of tumor recurrence (14.3 %). Cox regression analysis.

	HR[a] (95 % CI)	p-Value	Tertiles (min-max)	HR[a] (95 % CI)	p-Value
PCB-138	0.69 (0.49–0.98)	0.041	T1 (0.1–55.7)	1.00	
			T2 (56.0–116.4)	0.96 (0.28–3.24)	0.948
			T3 (119.6–1127.4)	0.69 (0.18–2.61)	0.589
			p-trend		0.595
PCB-153	1.22 (0.73–2.03)	0.453	T1 (8.4–41.2)	1.00	
			T2 (43.4–108.0)	1.88 (0.48–7.43)	0.368
			T3 (114.1–706.1)	1.90 (0.55–6.57)	0.312
			p-trend		0.315
PCB-180	1.30 (0.83–2.04)	0.251	T1 (0.0–26.7)	1.00	
			T2 (27.6–69.7)	2.04 (0.51–8.11)	0.311
			T3 (72.2–312.2)	2.01 (0.57–7.08)	0.280
			p-trend		0.290
HCB	0.84 (0.58–1.21)	0.354	T1 (0.9–29.3)	1.00	
			T2 (30.7–127.3)	0.93 (0.29–3.05)	0.910
			T3 (127.3–2159.7)	0.35 (0.08–1.62)	0.180
			p-trend		0.190
p,p′-DDE	0.78 (0.51–1.18)	0.242	T1 (6.0–121.1)	1.00	
			T2 (130.9–382.9)	1.45 (0.45–4.61)	0.532
			T3 (388.9–3614.3)	0.37 (0.07–1.92)	0.237
			p-trend		0.290

HR: hazard ratio; CI: confidence interval; PCB: polychlorinated biphenyls; *p,p′*-DDE: *p,p′*-dichlorodiphenyldichloroethylene; HCB: hexachlorobenzene; T: tertile.
[a] Age as underlying time variable in all analyses and additionally adjusted for smoking (yes/no), educational level (none or primary/more than primary), body mass index (normal weight/overweight-obesity), breastfeeding (yes/no).

(HR = 0.49; 95 % CI = 0.25–0.93, p-interaction = 0.082) and in women with a tumor size <2.0 cm (n = 54) (HR = 0.39; 95 % CI = 0.18–0.87, p-interaction = 0.013). No relevant results were found when exploring interactions with menopausal status, smoking or lymph node involvement.

Regarding the analyses of adipose tissue POP concentrations with the incidence of any adverse outcome (joint outcome variable: overall mortality, recurrence, metastasis or second primary tumor), the direction of the estimations was highly variable in comparison to the analyses with individual outcomes (supplementary material Table S5). Of note, the likelihood of having an adverse event was lower with the increase of HCB concentrations (T3 vs. T1, OR = 0.37; 95 % CI = 0.14–1.03, p-trend = 0.051).

4. Discussion

This is one of the very first studies investigating the associations between breast adipose tissue POP concentrations and the evolution of breast cancer patients after surgery in women previously exposed to POPs. Our findings suggested a lower likelihood of presenting any of the analyzed events with higher concentrations of these contaminants, being particularly significant for PCB-138 and HCB. Interactions were found, confirming the inverse associations in aged, rural or women with overweight/obesity, as well as those with an increased tumor size or ER+ tumors.

For such inverse association, we hypothesize that a POP-related estrogenic microenvironment might promote the expression and activation of ER (Ennour-Idrissi et al., 2019; Muñoz-de-Toro et al., 2006). However, ER+ breast cancers are known to have a better prognosis because of the available pharmacological treatment blocking this specific therapeutic target (den Hollander et al., 2013). This might result on the observed paradoxical associations of a lower risk of death in patients with higher POP concentrations. Interestingly, these results complement previous cross-sectional findings in the same study population showing positive associations of mammary adipose tissue POP concentrations with the expression of ER (Arrebola et al., 2016).

Up to our knowledge, no previous study has evaluated the associations between POPs measured in breast adipose tissue and the risk of death or the incidence of any adverse event measured as a joint outcome, hampering

comparisons of our results. Roswall et al. (Roswall et al., 2018) found similar negative associations between buttock adipose tissue PCB and some pesticide concentrations and adverse breast cancer prognostic factors, such as ER-tumor, lymph node involvement, or increased tumor size. These authors suggested, as a possible biological mechanism, the sequestration of POPs by adipose tissue and consequent reduced bioavailability. This interpretation could also partially explain our overall findings and, specifically, the stronger association of HCB concentrations and all-cause mortality in women with overweight or obesity since breast adipose tissue might decrease the blood levels of the hydroxylated metabolites with described potentially-carcinogenic actions in *in vitro* studies (Gregoraszczuk et al., 2008; Ptak et al., 2010). In fact, previous studies measuring POP concentrations in blood sample in breast cancer patients have described an increased risk of mortality with higher levels of PCBs (Høyer et al., 2001; Parada et al., 2016). However, as it has been highlighted, the comparison between studies using different biological matrices to measure POP exposure should be interpreted with caution, since each compartment might have a dissimilar biological meaning (Artacho-Cordón et al., 2015; Salamanca-Fernández et al., 2021). Conversely, it is important to consider that the most significant factor in the association between adiposity and chronic diseases is the location and function of adipose tissue (Goyal et al., 2014). However, the measurement of BMI does not provide this distinction.

It is noteworthy the significant inverse association with the risk of breast cancer recurrence of *p,p′*-DDE and PCB-138, and this last, moreover, with the risk of metastasis. In addition to our above mentioned associations of POPs with hormone receptor expression in this cohort (Arrebola et al., 2016), previous studies have described associations of breast adipose tissue PCB-138 levels with increased ER expression (Dewailly et al., 1994; He et al., 2017). These findings could potentially be explained by the availability of pharmacological targets in this tumor subtype, particularly given the high prevalence of ER positive breast cancers (81 %) in our sample compared to what is typically observed in the general population (65–75 % in high-income populations) (Brinton et al., 2017). Indeed, our findings show a stronger inverse association between POPs and selected outcomes in women with smaller tumor sizes and older ages at diagnosis. Interestingly, these two factors, smaller tumor sizes and older ages at diagnosis, have been associated with lower tumor recurrence in previous studies (Lyman et al., 1996; van der Leij et al., 2012). Noteworthy, the only previous study using breast adipose tissue POP concentrations as the exposure biomarker did not find a significant association between PCB-138 and breast cancer recurrence (Muscat et al., 2003). The differences in concentrations of POPs, in the place of the study (USA vs. Spain) or in the follow-up duration (up to 5 years in the compared study) could partially explain these discrepancies. In addition, previous research evidenced positive associations between POP internal levels and the risk of breast cancer metastasis (Koual et al., 2020). However, there is very little research on these outcomes using breast adipose tissue as the exposure assessment matrix.

Importantly, the scope of this investigation was limited to a selection of non-dioxin-like PCBs and organochlorine pesticides. The mechanistic pathways of carcinogenic action and the spectrum of toxicity differ considerably among distinct POPs (Koual et al., 2020; Leng et al., 2016) and, therefore, our results might not be generalized to other POPs.

Our study has some limitations: 1) The sample size was relatively small, thus hampering our power to detect significant associations, particularly in certain subgroups of the stratified analyses, e.g., ER-. 2) The collection of some data through the clinical records could lead to information bias because of the potential underdiagnosis. However, all patients were users and treated in the public health system and under strict clinical follow-up by their clinicians. 3) The generalizability of our results might be limited by the relatively small sample size. Although there is no evidence to support that the associations found cannot be observed in other populations, our results still need to be further confirmed in future studies in persons with different POP concentrations, lifestyles or tumor characteristics. In this regard, only women with breast cancer susceptible to be operated were included, which might affect the extrapolation of our results. However, the prevalence of conservative and radical breast cancer surgery was very similar to those published in previous studies (Blay et al., 2019; Escribà et al., 2014). Indeed, our population showed a relatively high prevalence of ER and PR positive breast cancers and small tumor sizes, as well as a moderately high incidence of metastasis (n = 26) and local recurrence (n = 16). 4) Results with the joint variable might be biased since the outcomes might have different etiologies, even more when death was not related to breast cancer. 5) Underdiagnosis of our target outcomes may exist. However, the rigorous follow-up regimen for breast cancer patients could mitigate this potential bias. Specifically, in the hospitals of the province of Granada, the follow-up protocol includes a physical examination, analytical control with tumor markers, and annual mammography. For the first two years, these are conducted every three months; from the third to the fifth year, they are done every six months; and from the fifth to the tenth year, they occur annually. Even so, this limitation could introduce a bias towards the null, potentially diluting the observed association. And 6) Due to the study design, residual confounding in the observed associations may occur due to unmeasured third variables, changes in covariates and/or exposure over follow-up period. Additionally, there is a possibility of unmeasured co-exposure to other lipophilic and potential hormone-active pollutants, such as polybrominated diphenyl ethers, polybrominated biphenyls, metals and metalloids, or polycyclic aromatic hydrocarbons, which could potentially have an impact on the outcomes.

Among the strengths of the present study are the longitudinal design, the relatively long follow-up, and the detailed clinical information. Another strength of our study is the use of adipose tissue as the exposure biological matrix, as it has been proposed to more accurately reflect long-term lipophilic POP exposures in relation to the more accessible blood. In fact, it has been suggested as the most appropriated matrix to evaluate long-term POP exposures (Kohlmeier and Kohlmeier, 1995; Mustieles and Arrebola, 2020). Specifically, the use of breast adipose tissue to measure POP concentrations could be especially relevant due to be proximity to the biological target.

5. Conclusion

Our results suggested that historical POP exposure might be related to a better evolution of breast cancer patients after surgery. Further research is warranted on the basis of the highly explorative nature of our study, the scarce existing literature on this issue and the complexity of the hypothesized associations. Future investigations ought to take into consideration potential other confounding variables or effect modifiers, such as dietary factors, physical activity, or the (joint) effects of other POP families.

Funding sources

Dr. JP Arrebola is under contract within the Ramón y Cajal Program (RYC-2016-20155, Ministerio de Economía, Industria y Competitividad, Spain). This study was supported by research grants from Instituto de Salud Carlos III, Junta de Andalucía and European Regional Development Fund – FEDER (PI-0513/2012, PI16/01858, PI18/01573, PI20/01568).

CRediT authorship contribution statement

R. Barrios-Rodríguez: Data curation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **C. Garde:** Data curation, Methodology, Formal analysis, Writing – review & editing. **F.M. Pérez-Carrascosa:** Data curation, Writing – review & editing. **J. Expósito:** Writing – review & editing. **F.M. Peinado:** Writing – review & editing. **M. Fernández Rodríguez:** Writing – review & editing. **P. Requena:** Writing – review & editing. **I. Salcedo-Bellido:** Methodology, Writing – review & editing. **J.P. Arrebola:** Conceptualization, Project administration, Funding acquisition, Supervision, Writing – review & editing.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

These results would not have been achieved without the selfless collaboration of the staff from San Cecilio Hospitals and the participants who took part in the study. This paper will form part of the doctoral thesis developed by Carlos Garde in the context of the "Clinical Medicine and Public Health Program" of the University of Granada (Spain). Funding for open access charge: University of Granada / CGUA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.165373.

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