Exposure to Bisphenol A increases malignancy risk of thyroid nodules in overweight/obese patients.

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Abstract:

Bisphenol A (BPA) is a widespread thyroid disruptor, but evidence about an association with thyroid cancer is weak. Excess body weight is a risk factor for thyroid cancer and affects activity of endocrine disruptors. Aim of the study was to investigate the association between BPA exposure and thyroid cancer, verifying the effect modification related to body weight.

We performed a multicentre, cross-sectional study including consecutive patients referring for nodular goiter. The quantitative determination of BPA in serum samples was performed through high performance liquid chromatography system, coupled in tandem with ultraviolet and fluorescence detection.

Ninety-six patients were included: 55 benign nodules, 41 thyroid cancers, 28 normal weight, and 68 overweight/obese. BPA was detected in 79 subjects. In the overall study population and in the group with BMI<25 kg/m^2 BPA exposure was not significantly correlated to thyroid cancer (p=0.08 and 0.759, respectively). In the group with BMI≥25 kg/m^2, BPA-exposed subjects showed significantly higher risk of malignancy (OR: 5.3, p=0.028). At multivariate analysis, such association was independent of smoking, alcohol consumption, occupational exposure, and phthalates exposure (p=0.021 and 0.016, respectively), but was lost after adjustment for the presence of metabolic syndrome (p=0.089). In overweight/obese subjects, BPA exposure was significantly associated with higher thyroid stimulating hormone levels.

Our study suggests that BPA exposure is a risk factor for thyroid cancer in overweight/obese subjects.

Keywords: Thyroid cancer, Thyroid Nodules, Thyroid diseases, Environment, Endocrine disrupting chemicals, Bisphenol A, Pollutants, Body mass index.

Introduction

Bisphenols (BPs) are a group of aromatic compounds broadly used as plasticizers and employed in a variety of industrial and commercial activities (Vandenberg et al., 2007).

Bisphenol A (BPA) is the parent compound and, despite the introduction of 16 structurally similar molecules (named BP analogues), still represents the most widespread agent (Chen et al., 2016). Indeed, BPA is the main component of polycarbonates and epoxy resins, which are used for the production of food contact materials, consumer electronics, medical equipment, and as color developer of thermal papers (Sonavane and Gassman, 2019). Therefore, the leaching from these products makes BPA ubiquitous in the environment and determines, through many exposure routes, a massive as well as continuous human contamination (Le et al., 2008).

Endocrine disrupting effect of BPA is known since the 1960s, especially the estrogenic activity (Krishnan et al., 2010). In *in vivo* and *in vitro* experiments, BPA showed capability of impairing thyroid hormones homeostasis at many steps: synthesis, by reducing gland iodine uptake, inhibiting thyroperoxidase activity, and affecting genes expression (Kim and Park, 2019), peripheral activity, by receptors antagonism (Moriyama et al., 2002), and blood transport, by transthyretin binding (Kudo and Yamauchi, 2005). Consistently, some human studies found a positive association between BPA exposure and TSH levels (Andrianou et al., 2016; Geens et al., 2015).

Thyroid cancer is generating worldwide alert, due to the continuously growing incidence, which has triplicated in the last 4 decades (Lim et al., 2017). In the context of thyroid malignancies, differentiated thyroid cancer (DTC) is not only the most frequent (90% of cases), but also represents the unique responsible for such raising incidence.

Despite the deep characterization of its molecular pathogenesis (Marotta et al., 2016), our knowledge of etiologic factors and the impact of environmental contaminants on DTC is still poor. The lead hypothesis is that thyroid disruptors induce chronic thyroid stimulating hormone (TSH) hyperstimulation leading to neoplastic transformation of the thyroid follicular epithelium (Boelaert,

2009). However, other mechanisms such as direct mutagenic activity (Maqbool et al., 2016) and epigenetic modulation (Shafei et al., 2018) are emerging.

Owing to the mentioned evidence, BPA represents a potential thyroid disruptor chemical associated to thyroid cancer. However, studies about the relationship between BPA exposure and occurrence of thyroid cancer in humans are still limited and controversial (Marotta et al., 2020).

Nowadays obesity represents a social and highly widespread disease, with about two third of adults being overweight/obese (Ogden et al., 2014). The adipose tissue acts as an endocrine organ by producing a wide spectrum of biologically active molecules (Fasshauer and Bluher, 2015). In case of adipose tissue excess, the robust release of such substances does heavily affect the endocrine system, including the thyroid axis (Kershaw and Flier, 2004). Owing to these issues, functional activity and health consequences of the endocrine disruptor chemicals (EDCs) should be adjusted for anthropometric parameters (Smith et al., 2020).

Of note, as based on sufficient evidence from prospective studies (Lauby-Secretan et al., 2016), obesity represents a pathogenic risk factor for thyroid cancer development.

Furthermore, many EDCs act as obesogens, having recognized role in the pathophysiology of obesity. These include BPA (Legeay and Faure, 2017), with many studies demonstrating an association between human exposure and obesity (Andra and Makris, 2015; Geens et al., 2015; Liu et al., 2017).

Owing to these observations, to focus the cross talk between EDCs, excess body weight, and thyroid carcinogenesis is an hot topic.

The present multicenter study was aimed at assessing whether the excess body weight acts as effect modifier of the association between BPA exposure and thyroid cancer prevalence, in a population of thyroid nodules patients from an endemic goiter area (the Campania region (Nasti et al., 1998)), characterized by heavy chemical contamination (Mazza et al., 2018) and high prevalence of overweight/obesity (Italian National Institute of Health, Sorveglianza Passi, 2021).

Materials and Methods

Study design

This was an analytical cross-sectional study capturing chemical exposure, clinico-pathological/anthropometric/environmental data, and the presence of thyroid cancer at a single time point, in a population of consecutive thyroid nodules patients advised to cytology (Fig. 1). Three thyroid cancer reference centres from the Campania region were included: University of Salerno, Federico II University, , INT Pascale. Inclusion criteria: a) age ≥ 18 years; b) clinical management and, eventually, surgery performed in one of the involved centres. Exclusion criteria: a) inconclusive cytology (TIR- 3A, 3B, 1 categories); b) clinical and/or cytological and/or histological characteristics consistent with autoimmune thyroiditis (AT); c) clinical and/or cytological and/or histological characteristics consistent with medullary thyroid cancer (MTC); d) modifications in lifestyle and anthropometric variables with possible impact on DTC risk and BPA exposure, as occurred within the previous 5 years (see below).

Upon acceptance from included centres, the study received the approval of the Ethic Committee of the coordination Institute (Federico II University) (protocol number 155/15/ES2). Informed consent was obtained from each enrolled patient.

Clinical management

Work-out of enrolled patients included: internal thyroid ultrasonography (US), determination of serum TSH, FT3, FT4, anti-thyroglobulin and-thyroperoxidase, and calcitonin. Calcitonin stimulation test was planned in case of baseline values > 10 pg ml^{-1} (Wells et al., 2015).

Fine-needle aspiration biopsy (FNAB) was accomplished only in case the American Thyroid Association criteria were met (Haugen et al., 2016). Cytological categorization was based on the latest Italian consensus (Nardi et al., 2014). Patients with TIR-2 cytology were subjected to surveillance, by means of 6-months interval US, unless the development of compressive symptoms

or cosmetic complaints induced physicians to decide upon surgery. All patients with TIR -4 and -5 cytology were subjected to surgery.

Assessment of chemical exposure

EDCs screening included not only BPA, representing the disease-related risk factor tested in our analysis, but also the most commonly used phthalates (PHTs) diethylhexyl phthalate (DEHP) and its monoester metabolite mono (2-ethylhexyl)phthalate (MEHP) (Benjamin et al., 2017), which were used as covariates for the multivariate analysis.

For study groups comparison, chemical exposure was assessed as a qualitative parameter: exposed (detectable serum EDC levels) *versus* not exposed (undetectable EDC levels) subjects. We considered subject as not exposed to the analyzed EDCs if the concentration level was below the Limit of Detection (LOD) values, as reported below.

Blood samples were obtained from included subjects in the same day of FNAB performance, after overnight fasting. Five mL were collected in Vacu-test® tubes from the antecubital vein, and centrifuged at 3000 rpm for 20 min. Detection and quantification of the mentioned pollutants were performed on the supernatant, which was previously transferred to a clean glass vial, frozen and stored at -20°C until the analysis. Plastic labware was kept in contact with a solution 50/50n-hexane:tetrahydrofuran for at least three hours before use (Olivieri et al., 2012) to avoid any contamination. The sample preparation and the chromatographic analysis were performed according to a method, already reported in the literature (Russo et al., 2019) and fully applied. In brief, a high-performance liquid chromatography (LC-20 AD VP; Shimadzu Corp., Kyoto, Japan), equipped in tandem with an ultraviolet–visible detector (UV, λ 220 nm) (Shimadzu Model SPD10 AV) and Fluorescence detector (excitation wavelength of 263, emission wavelength of 305 nm (FLD)) was used for serum determination of the total amount of each analyte under investigation. A reversed-phase LC column Kinetex phenyl-hexyl (100 Å, 150 × 4.6 mm, 5.0 μm particle size), with a precolumn (4 × 3.0 mm) (Phenomenex, Torrance, CA, USA) was used. Each sample was added of

15 µL of a biphenyl solution in ethyl acetate of a stock solution (10 µg/mL) as internal standard (IS) to determine the concentration of other analytes by calculating response factor. LOD and Limit of Quantification (LOQ) of the analytical method resulted, respectively: 4.34 and 14.47 ng/mL for BPA, 2.10 and 6.29 µg/mL for DEHP, 0.43 and 1.53 µg/mL for MEHP. Recovery was performed fortifying the serum samples at low, medium and high values, achieving an average recovery of 99.64, 102.28, and 109 %, respectively.

Reagents and chemicals: For the analysis of organic pollutants, analytical standards, BPA (CAS No.80-05-7), DEHP (CAS No.117-81-7), and MEHP (CAS 4376-20-9), were purchased from Sigma-Aldrich (Dorset, United Kingdom). Methanol (HPLC analytical grade) and formic acid (minimum purity ≥ 95%) were both purchased from Sigma-Aldrich (Milan, Italy). Methanol (High performance liquid chromatography analytical grade) and formic acid (minimum purity ≥98%) were both purchased from Sigma Aldrich (Milan, Italy). Milli Q water was produced in-house and its conductivity was found to be 0.055 µS cm^{-1} at 25 °C (resistivity equals 18.2 MΩ·cm).

Assessment of clinico-pathological/anthropometric/metabolic/environmental data

All data relevant to the analysis were captured at the time of cytology.

Clinico-pathological features: The number of thyroid nodules (uni-/multi- nodularity) and the thyroid volume (as calculated by means of the ellipsoid formula (Dighe et al., 2017)). Thyroid hormones profile. Ongoing levothyroxine treatment.

BMI: For BMI computation, weight (kg) was divided by height (m) squared.

Parameters related to metabolic syndrome: systolic and diastolic blood pressure; waist circumference; glycemia; serum levels of total, high-density lipoprotein (HDL-C), and low-density lipoprotein (LDL-C) -cholesterol; serum levels of triglycerides. For the diagnosis of metabolic syndrome, criteria from the National Cholesterol Education Program were adopted (2001).

Environmental factors: information relevant to the study were obtained through self-reported questionnaires.

The following variables were considered, as included in the statistical analysis: a) smoking status: current vs never/former smokers; b) alcohol consumption: moderate/heavy consumers (1 drink/day for women and 2 drinks/day for men were used as upper limits (Bergmann et al., 2013)) vs slight/never/former consumers; c) occupational exposure: jobs with close chemical exposure (e.g. shoe manufacture, preserving industry, building activities, pulp/papermaker industry, wood processing, agricultural activities, chemists, pharmacists) identified occupationally exposed subjects.

Besides, changes in the following lifestyle and anthropometric items, as occurred during the 5 years prior enrolment, were assessed: residence, occupation, therapeutic regimen (of note, due to the possible role of estrogenic activity in thyroid carcinogenesis (Moleti et al., 2017), assumption of oral contraceptives was considered as an exclusion criterium); dietary habits: consumption of vegetables/fruit (≤2 *vs* >2 times daily) and processed meat (≤3 *vs* >3 times weekly); smoking status; alcohol consumption; weight change (greater than 10%).

Study groups definition

BPA exposure was compared between patients with benign goiter and subjects with DTC. The benign nodules group included: a) patients with TIR-2 cytology with no evidence of clinical progression in the following 12 months. We considered as clinical progression the rise in at least two nodule diameters, each ≥ 2 mm and ≥ 20% of the baseline diameter (Durante et al., 2015), or the *de novo* occurrence of cervical lymph nodes suggestive of secondarisms (Ito et al., 2014); b) patients with TIR-2 cytology subjected to surgery, with histology report confirming benignity. The DTC group included the patients with TIR-4 and -5 cytology advised to surgery, with histology finding of DTC.

To assess the effect modification related to excess body weight, two BMI groups were identified using 25 as cut-off: <25 kg/m^2 (normoweight) versus ≥ 25 kg/m^2 (overweight/obese).

Statistical analysis

Statistical analysis was performed by using the software SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL). For the comparison of categorical variables, chi-square test was used and, in case of sample size less than 5, Fisher's exact test (Lydersen et al., 2009). Odds ratios (OR) were calculated according to Altman (Altman, 1991). When the computation of the ORs and 95% CIs was altered by zeros, 0.5 was added to all cells of the contingency tables (Pagano and Gauvreau, 2000). Due to the small sample size, we applied the Shapiro-Wilk test for studying the distribution of continuous variables. Continuous variables were compared by means of T-test when the distribution was normal, whereas the Mann Whitney U test was used in case of non-normal distribution. When the univariate analysis showed significant association between BPA exposure and DTC risk, a multivariate model of binary logistic regression analysis was applied for evaluating whether this represented an independent predictor of malignancy. Multivariate analysis included three models: "environment-adjusted", where environmental factors with possible impact on both cancer risk and BPA exposure were included; "PHTs-adjusted", where exposure to one or both of the PHTs DEHP and MEHP was included; "metabolic syndrome-adjusted", where the diagnosis of metabolic syndrome was considered. Assessment of the effect modification related to BMI was performed by analyzing separately the normoweight and overweight/obese group.

All tests were two sided, and p-values of less than 0.05 were considered significant.

Results

Flow chart of the study was reported in Fig 1. Overall, 199 patients carrying thyroid nodules were subjected to cytology from May 2017 to May 2019. Among them, 103 subjects were excluded due to exclusion criteria. Particularly, 17 patients showed inconclusive cytology, 26 were diagnosed with AT, 4 revealed both inconclusive FNAB and AT, 2 subjects were diagnosed with MTC. Among the remaining 150 patients, 54 subjects were not included due to modifications of variables potentially affecting EDCs exposure in the prior 5 years: change of residence for 11 patients, change of occupation for 10 subjects, modification of smoking status for 7 cases, changes in therapeutic regimen for 11 patients, dietary modifications (particularly different fruit/vegetables consumption) for 3 cases, weight change greater than 10% within 5 years before study entry for the remaining 12 subjects .

Ultimately, the study sample included 96 patients (30 males and 66 females; median age 51 yrs [SD 14.9]). Detectable BPA was found in 79 cases (82.3%). Among BPA-exposed patients, median serum concentration was 734.68 ng/ml (range 94.93-1088.31). At the time of cytology, 68 subjects (70.8%) were overweight/obese (BMI $\geq 25 < 30$ kg/m^2 in 38 cases; BMI ≥ 30 kg/m^2 in 30 cases). Forty-one subjects (42.7%) resulted to be affected with DTC.

Association of clinico-pathological/anthropometric/metabolic/environmental characteristics and PHTs exposure with DTC prevalence

Results for such analysis were reported in Table 1.

Clinico-pathological features: The likelihood of being affected with DTC was significantly higher for solitary nodules, as compared with multinodularity (p=0.012; OR 2.89 95% CI 1.24-6.7), and in case of thyroid volume within the normal range, as compared with increased (p<0.001; OR 8.41 95% CI 3.04-23.24). Although TSH levels did not differ between benign and malignant nodules, the subjects under levothyroxine therapy, all showing TSH semi-suppression (below 1 μUI/ml), had a significantly lower risk of DTC (p=0.003; OR 0.12 95% CI 0.02-0.58).

BMI: The parameter BMI was analyzed by a double model comparison: overweight/obese (BMI≥25 kg/m^2) versus normal weight (BMI<25 kg/m^2); obese (BMI≥30 kg/m^2) versus normal weight/overweight (BMI<30 kg/m^2). In both models, no significant relationship with the malignancy risk was found. However, when using ≥30 kg/m^2 as BMI cut off, a trend emerged, with obese subjects having higher likelihood of malignancy, as compared with normal weight/overweight (OR 1.87 95% CI 0.78-4.48).

Metabolic syndrome: Neither significant nor a trend of association with the DTC risk were observed for metabolic syndrome.

Environmental factors: Neither significant nor trends of association with the DTC risk were observed for the included environmental factors (smoking status, alcohol consumption, and occupational exposure).

PHTs exposure: Both DEHP and MEHP exposure were related to higher DTC risk (p<0.001; OR 13.74 95% CI 2.91-64.89 and p=0.043; OR 2.65 95% CI 1.01-6.94, respectively).

Comparison of demographic/anthropometric/metabolic/environmental characteristics and PHTs exposure between subjects exposed and not exposed to BPA

Results for such analysis were reported in Table 2.

None of the analyzed variables showed association with higher likelihood of BPA exposure. Even, the current smoker status and the occupational exposure were related to a lower risk.

Association between BPA exposure and malignancy risk

Results for such analysis were reported in Table 3.

Univariate analysis: In the overall study population, exposure to BPA was not significantly related to the risk of malignancy, even though there was a trend to a positive association (p=0.08; OR 2.86 with 95% CI 0.85-9.55). In the BMI<25 kg/m^2 group, such trend completely disappeared. Even, BPA-exposed subjects had a slightly lower DTC risk (p=0.759; OR 0.71 with 95% CI 0.08-5.95).

By contrast, in the BMI≥25 kg/m^2 group, a statistically significant association emerged, with BPA-exposed subjects having higher risk of malignancy (p=0.028; OR 5.3 with 95% CI 1.07-26.18).

Multivariate analysis: Such analysis involved solely the BMI≥25 kg/m^2 group, for which a significant association was found. "Environment-adjusted" model: after adjustment for smoking status, alcohol consumption, and occupational exposure, BPA exposure retained the significant association with high DTC risk (p=0.021). "PHTs-adjusted" model: after adjustment for DEHP and/or MEHP exposure, the significant association between BPA exposure and DTC prevalence was confirmed (p=0.016); "Metabolic syndrome-adjusted" model: after adjustment for metabolic syndrome, BPA exposure lost the significant association with high DTC risk (p=0.089).

Association of BPA exposure with TSH levels

Results from such analysis were reported in Table 4.

BPA exposed subjects showed higher TSH levels in the overall study population and in the BMI≥25 kg/m^2 group (p=0.006 and 0.004, respectively), whereas no significant difference was found when focusing on the BMI<25 kg/m^2 group (p=0.305).

Discussion

To date, most studies linking exposure to chemicals with human disease does not account for anthropogenic parameters as effect modifiers. The statement of novelty of our study was to shed light about the possible interplay between BPA exposure and BMI in allowing thyroid cancer development. To the best of our knowledge, this approach was never adopted before.

A strength point of the study was represented by the reference population, coming from the Campania region. Firstly, such area has long been plagued by the illegal dumping and burning of wastes, leading to widespread environmental and, expectedly, human contamination by chemicals (Mazza et al., 2018). Furthermore, as reported by the most recent data of the Italian National Institute of Health (Italian National Institute of Health, Sorveglianza Passi, 2021), the prevalence of overweight/obesity in the over 18 years population overcomes 50% and is the highest of all Italian regions. Therefore, Campania represents an ideal scenario for assessing the intersection between chemical contamination and excess body weight in producing harmful effects for humans.

In our previous study (Marotta et al., 2019), significant relationships between some EDCs and the risk of thyroid cancer in a different population of thyroid nodules patients emerged when comparing exposed *versus* not exposed subjects. Therefore, in the present analysis, exposure to the involved pollutants was considered as a qualitative parameter. However, no significant differences of BPA serum concentrations between benign nodules and DTC were observed both in the overall study population and in the different BMI groups (data not shown).

Due to the epidemiological and clinical features of thyroid nodular disease, we used subjects with benign nodules as control group. Indeed, up to 70% of the general population presents thyroid lesions at US examination (Ezzat et al., 1994), with the vast majority of them being benign (Papini et al., 2002). Of note, the Campania region is still characterized by iodine deficiency despite the long standing iodine prophylaxis (Mazzarella et al., 2009), so the prevalence of benign goiter is expected to be high. Furthermore, benign thyroid nodules demonstrated negligible risk of malignancy development overt time and low risk of size increase (Durante et al., 2015). Therefore,

benign thyroid lesions represent a widespread (particularly in iodine deficient areas such as the reference region) and clinically insignificant finding, to be classified as a paraphysiological cancer-unrelated phenomenon rather than a real pathological entity.

In our series, the prevalence of BPA contamination was 82.3%. This was in line with the other available prevalence studies of BPA exposure in the general adult population (Colorado-Yohar et al., 2021).

Overweight/obesity was reported in 70.8% of the study sample. This is fully consistent with the mentioned prevalence data reported for the Campania region (Italian National Institute of Health, Sorveglianza Passi, 2021).

The DTC prevalence was significantly higher for solitary nodules compared to multinodular goiter and in case of normal thyroid volume. These findings are consistent with the enduring iodine-deficiency reported for Italy (Olivieri et al., 2017) and, specifically, for the Campania region (Mazzarella et al., 2009).

TSH semi-suppression in subjects receiving levothyroxine treatment was associated with a lower cancer prevalence. This was consistent with the most accepted thesis of a positive association between TSH level and DTC risk in patients carrying thyroid nodules (Ventrice et al., 2013).

Exposure to the PHTs DEHP and MEHP was associated to higher DTC risk. This is consistent with many previous studies (Liu et al., 2020; Miao et al., 2020), including our previous experience on the same reference population, where a significant independent association was found for DEHP, and a trend for MEHP (Marotta et al., 2019).

Neither the demographic/anthropometric/metabolic/environmental features nor the contamination by PHTs were associated with high prevalence of BPA exposure. Therefore, it can be assumed that the correlation analysis between BPA exposition and malignancy is not biased by any interfering variables.

We found that BMI exerted effect modification on the association between BPA exposure and thyroid cancer risk. Indeed, detectable serum BPA levels were related to significantly higher risk

(5.3 fold) of DTC only in overweight/obese subjects. Two multivariate analyses were performed to substantiate the result obtained in the overweight/obese subgroup. The "environment-adjusted" model included three major environmental factors with recognized impact on cancer induction and chemical exposure: smoking status, alcohol consumption, and occupational exposure. After adjustment for such parameters, BPA exposure retained the significant association with the DTC risk. The "PHTs-adjusted" model included exposure to DEHP and/or MEHP, the two main compounds of the PHTs category. The relevance of such analysis relies on the fact that real-life human exposure to chemicals consists in the concomitant contamination of a variety of pollutants with compensatory, multiplicative, or synergistic activity. Therefore, it was important to exclude that our results were related to EDCs other than BPA. We chose PHTs based on the demonstrated thyroid disruptor activity (Kim et al., 2019) and also on the emerging evidence of a relationship with thyroid cancer (Marotta et al., 2020). Of note, the relationship between BPA exposure and DTC prevalence was retained upon PHTs adjustment.

Described results strongly suggests an interaction between BPA exposure and adipose tissue excess in promoting thyroid carcinogenesis. Actually, the presence of a link between body fat excess, exposure to EDCs, and cancer has been proposed by many studies, and currently represents one of the most intriguing frontiers in the context of preventive oncology (Bokobza et al., 2021).

Lipophilic agents (La Merrill et al., 2013), such as BPA (Wetherill et al., 2007), can accumulate into the adipose tissue (as stored into lipid droplets), and are slowly released over time following lipolysis. Therefore, the adipose tissue may be considered as a dynamic EDCs deposit, generating a continuous low level systemic exposure. This may enhance the strength and duration of EDCs biological effects.

At the same time, the adipose tissue is biologically modulated by EDCs, with many of them showing effects on physiological functions (proliferation/differentiation/secretion) (Papalou et al., 2019) and on the inflammatory status (Rolle-Kampczyk et al., 2020). Concerning BPA, there is wide *in vitro* and *in vivo* evidence of a stimulating activity on adipocytes

388 proliferation/differentiation and lipid storage (Desai et al., 2018), and of a pro-inflammatory effect
389 (Cimmino et al., 2019), as occurring through genomic (nuclear receptors), non genomic (membrane
390 receptors), and epigenetic mechanisms (Cimmino et al., 2020). Therefore, in overweight/obese
391 subjects, EDCs, including BPA, exposure is expected to worsen adipocytes hyperplasia/hypertrophy
392 and the adipose tissue chronic inflammation. This may produce a boosting effect on the so-called
393 adipocyte secretome, namely the mixture of hormones, adipokines and growth factors with
394 paracrine and endocrine activity, considered as able to impair the natural cell growth and survival
395 and promote cancer development (Thompson et al., 2021).
396 Recently, a large prospective trial showed that metabolic syndrome was related to a significantly
397 higher risk of developing thyroid cancer, even though only in obese subjects (Park et al., 2020). In
398 our multivariate model adjusting for the presence of metabolic syndrome, the association between
399 BPA exposure and DTC in overweight/obese group of thyroid nodules patients was lost. This
400 indicates that concomitant metabolic syndrome is necessary for BPA to elicit promotion of thyroid
401 carcinogenesis, suggesting that BPA may favour thyroid cancer development by further worsening
402 the impairment of insulin sensitivity and the metabolic changes typical of this condition.
403 In the overweight/obese group, but not in the normal weight, subjects exposed to BPA showed
404 higher serum TSH, as compared with the not exposed ones. This can sustain the hypothesis that
405 BPA role in DTC development is mediated by the impaired thyroid function, which in turn leads to
406 TSH hyperstimulation and increased thyroid cancer risk (Fiore and Vitti, 2012; Ventrice et al.,
407 2013).
408 Limitations of the study are as follows: a) the cross-sectional design, which hampers to capture
409 BPA exposure as occurring prior of DTC development. Therefore, a causal relationship cannot be
410 established; b) the small sample size; c) the use of BMI for assessing body fat excess, as it does not
411 carefully reflect the exact amount of adipose tissue.
412
413

Conclusions

Our study reports an association between BPA exposure and the risk of DTC in patients with nodular goiter, occurring solely in case of overweight/obesity. Overweight/obese subjects exposed to BPA had higher serum TSH, as compared with the not exposed ones, leading to the hypothesis that the oncogenic effect of BPA is mediated by an increased TSH stimulation. The association between BPA exposure and DTC was dependent on the concomitant metabolic syndrome.

Declaration of interest

Authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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