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SHORT REVIEW

Endocrine-disrupting chemicals (EDCs) and cancer: new perspectives on an old relationship

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Abstract

Purpose Environmental endocrine-disrupting chemicals (EDCs) are a mixture of chemical compounds capable to interfere with endocrine axis at different levels and to which population is daily exposed. This paper aims to review the relationship between EDCs and breast, prostate, testicle, ovary, and thyroid cancer, discussing carcinogenic activity of known EDCs, while evaluating the impact on public health.

Methods A literature review regarding EDCs and cancer was carried out with particular interest on meta-analysis and human studies.

Results The definition of EDCs has been changed through years, and currently there are no common criteria to test new chemicals to clarify their possible carcinogenic activity. Moreover, it is difficult to assess the full impact of human exposure to EDCs because adverse effects develop latently and manifest at different ages, even if preclinical and clinical evidence suggest that developing fetus and neonates are most vulnerable to endocrine disruption.

Conclusion EDCs represent a major environmental and health issue that has a role in cancer development. There are currently some EDCs that can be considered as carcinogenic, like dioxin and cadmium for breast and thyroid cancer; arsenic, asbestos, and dioxin for prostate cancer; and organochlorines/organohalogens for testicular cancer. New evidence supports the role of other EDCs as possible carcinogenic and pregnant women should avoid risk area and exposure. The relationship between EDCs and cancer supports the need for effective prevention policies increasing public awareness.

Keywords Endocrine-disrupting chemicals (EDCs) · Cancer · Breast · Prostate · Testicle · Ovary · Thyroid

Abbreviations

ADAM33	Metalloproteinase domain 33
AhR	Hydrocarbon receptor
ASR	Age-standardized rate
BPA	Bisphenol A
BPAF	Bisphenol-AF
DEHP	Di(2-ethylhexyl)phthalate
DES	Diethylstilbestrol
DTC	Differentiated thyroid carcinoma
DTT	Dichloro-diphenyl-trichloroethane
EDCs	Endocrine-disrupting chemicals
ERs	Estrogen receptors
ER-α	Estrogen receptor-α
GPI	Glycosylphosphatidylinositol
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ΣLMWP	Low molecular weight phthalates
MBzP	Mono-benzyl phthalate
MEC	Multiethnic cohort
MiBP	Mono-2-isobutyl phthalate
MSWI	Municipal solid waste incinerator
NHANES	National Health and Nutrition Examination Survey
NPCSs	National Priority Contaminated Sites
NG	Nodular goiter
OC	Ovarian cancer

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OR	Odd ratio
PAHs	Polycyclic aromatic hydrocarbons
PBDE	Polybrominated diphenyl ethers
PCa	Prostate cancer
PCBs	Polychlorinated biphenyls
POPs	Persistent organic pollutants
PPAR	Human peroxisome proliferator-activated receptor
PSCA	Prostate stem cell antigen
PTC	Papillary thyroid carcinoma
RR	Relative risk
SERM	Selective estrogen receptor modulator
TCDD	Tetrachlorodibenzodioxin
TGCC	Testicular cancer germ cell
UNEP	United Nations Environment Programme
WC	Waist circumference
WHO	World Health Organization
2-OH-NAP	2-Hydroxynaphthalene

Introduction

Scientific interest in environmental endocrine-disrupting chemicals (EDCs) has been growing up through the last half century (Fig. 1). In 1958, Roy Hertz hypothesized that certain chemicals used in livestock feedlots could be absorbed by people's organism and mimic the activity of hormones [1]. Little came until the 1970s, when physicians and researchers found out that diethylstilbestrol (DES), a synthetic non-steroidal selective estrogen receptor modulator (SERM) prescribed from 1940–1971 to millions of women during pregnancy to reduce miscarriage, increased the incidence of a rare tumor in young women (vaginal clear cell adenocarcinoma) and induced reproductive tract anomalies in males exposed in utero with different dose-dependent effects [2–4]. This evidence induced to suppose a possible estrogen-dependent mechanism of EDCs in inducing cancer and pushed the authority to face the problem with specific organization, as summarized in Fig. 1. Nowadays, there are nearly 1,480 chemicals reported to have endocrine effects, but they will probably rise because tests to detect potential EDCs were not often required and data are difficult to obtain, even due to the long latency of many cancers [5]. EDCs are pervasive in the environment, as they are found in plastics and plasticizers (bisphenol A (BPA) and phthalates), in industrial chemicals such as polychlorinated biphenyls (PCBs), pharmaceuticals (parabens) and include some pesticides, herbicides, phytoestrogens, fungicides, chemicals as radon, and even metals such as cadmium, zinc, copper, mercury, and arsenic. Like hormones, EDCs have complex dose–response curves, and they can act at extremely low concentrations, even with synergistic effect [6, 7]. One of the major issues is to prove association between EDCs and human cancer development, together with possible interaction with other environmental chemicals. Nevertheless, in animal models, there is evidence of carcinogenic activity of some EDCs, in particular on endocrine responsive tissues, like breast, prostate, testicle, ovary, and thyroid [8–10]. This paper aims to review available data about the relationship between EDCs and breast, prostate, testicle, ovary, and thyroid cancer, discussing carcinogenic activity of known EDCs (Fig. 2), while evaluating the impact on public health.

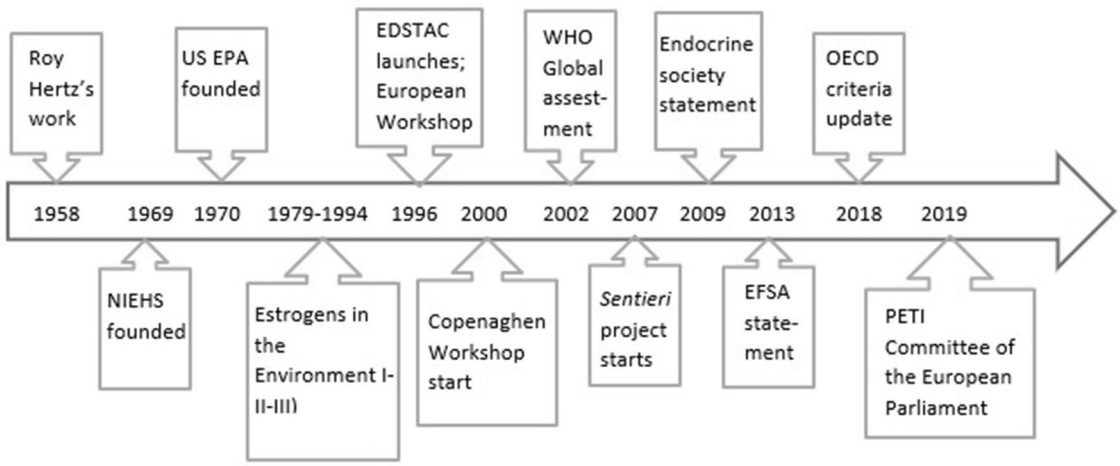

Fig. 1 Milestones in the development of EDCs knowledge. *NIEHS* National Institute of Environmental Health Sciences, *US EPAS* United States Environmental Protection Agency, *EDSTAC* Endocrine Disruptor Screening and Testing Advisory Committee, *WHO* World Health Organization, *EFSA* European Food Safety Authority, *OECD* Organization for Economic Co-operation and Development, *PETI* European Parliament's Committee ob Petitions

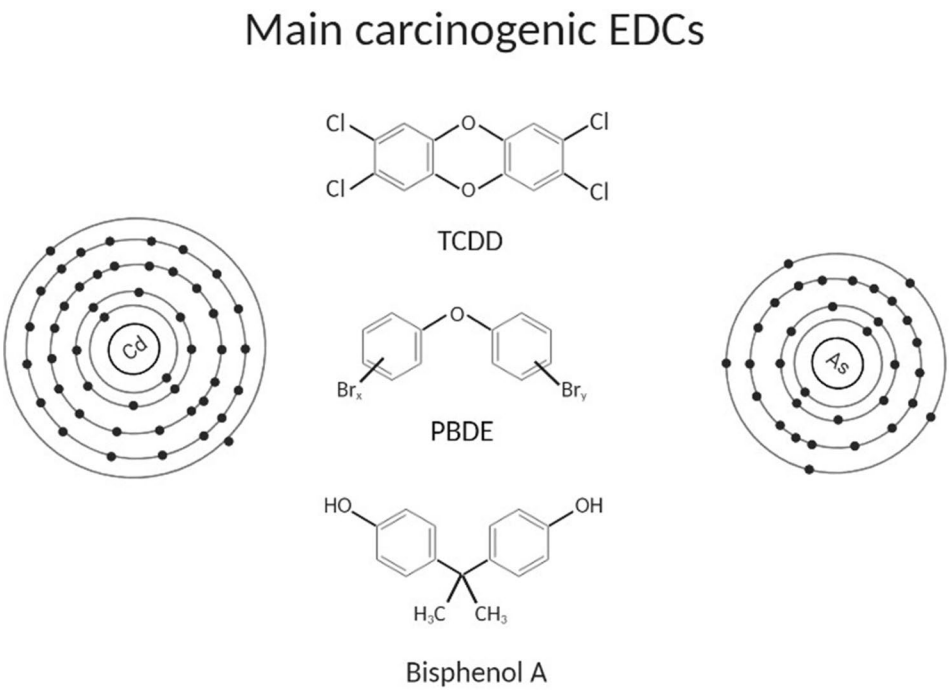

Fig. 2 Main carcinogenic EDCS. *PBDE* polybrominated diphenyl ethers, *TCDD* tetrachloridibenzodioxin, *CD* Cadmium, *AS* arsenic

Material and methods

Deepened research on "Pubmed" using terms "endocrine-disrupting chemicals", "EDCs", "phthalates", "TCDD", "dioxin", "polychlorinated biphenyls", "PCB", "bisphenol A", "BPA", "nitrate", "nitrite" and "breast cancer" or "prostate cancer" or "thyroid cancer" or "ovarian cancer" or "testicle cancer" was carried out. All articles between 1958 and 2022 were considered, with particular interest on meta-analysis and human studies. Moreover websites of scientific institutions and advisory committees have been accessed [11–16].

Definition According to the World Health Organization (WHO) in 2002 [15] "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny or (sub)populations". This definition includes just observation on "intact organism", that means only "in vivo" observations are accepted and the term "adverse health effects" is non-specific, thus it has been detailed as "a change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences". Ten years later, the Endocrine Society proposed to define an EDC as: "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action" [16]. Subsequently, the European commission proposed an evidence-based classification of EDCs, just as International Agency for Research on Cancer (IARC) has done for carcinogenic substance [17]. This represents an important step forward in systematic EDCs classification, dividing chemicals into three categories:

- "Known EDCs", category 1A: All the substance with certain activity as endocrine disruptors. They should respect all three criteria: showing an adverse effect in an intact organism or its progeny or (sub) populations; showing clear endocrine activity; showing biological plausible link between the showed adverse effect and the endocrine activity.
- "Presumed EDCs", category 1B: Lower level of evidence than 1A or not all criteria have been proved.
- "Suspected EDCs", category 2: Lower level of evidence than 1B.

Nowadays, European Society distinguished between substances "identified" as EDCs reported in List I [12], "under evaluation" to be classified as EDCs in List II [13], and "considered by National Authority as EDCs" in List III [14].

Another effort should be done to find specific criteria to certify carcinogenic activity of some EDCs. IARC criteria have been used with some difficulty to prove clear relationship between human EDCs exposure and tumor development.

EDCs can act through various signalling pathways modulating the action of androgenic thyroid and retinoid receptors, as well as interacting with estrogen receptors (ERs) and other non-nuclear receptors, such as membrane ERs,

non-steroid receptors, and orphan receptors [18–21]. Genetic and epigenetic changes, such as DNA methylation and/or acetylation and histone modifications, appear to be involved in mechanisms related to endocrine disruption, as well as cancer development. They could act even with non-receptor-dependent mechanism, through free radical generation, that are known to promote cancer growth [22, 23].

Breast cancer

Breast cancer accounts for about 30% of female cancers and has a mortality-to-incidence ratio of 15%. Worldwide incidence varies between 27 in 100 000 (Africa and east Asia) and 97 in 100 000 (North America), reflecting the association between breast cancer incidence and the degree of economic development and lifestyle factors [24, 25]. In high-income countries, more than a third of cases of breast cancer seems to be preventable through lifestyle and environmental changes [26]. Through years, different scientific institutions/advisory committees for tumors have established some EDCs as breast carcinogenic (Table 1). Of interest, both WHO and Endocrine Society stressed the carcinogenic role of dioxin, even if a recent systematic review reveal just a weak link between its exposition and breast cancer development [27]. There are more than 400 types of dioxin-related compounds, about 30 of which are significantly toxic to human health, with 2,3,7,8-tetrachlorodibenzodioxin (TCDD) being the most toxic [28]. TCDD can bind the aryl hydrocarbon receptor (AhR) and function as a signal transducer with anti-estrogenic actions [21]. In vitro study proved that just 50 nM TCDD induced proliferation of an ERα-positive breast epithelial carcinoma cell line (MCF-7) by AhR and BRCA1 activation [29]. In Seveso, Italy, an industrial accident in 1976 resulted in the highest contamination of TCDD known in human residential populations. Women who were infants at the time of the accident had a tenfold increase in serum TCDD, which was associated with a twofold increase in breast cancer incidence, but follow-up data are needed to draw any conclusions [30, 31]. Moreover, in an USA prospective cohort study, authors suggested a positive relationship between dioxin produced by any municipal solid waste incinerator (MSWI)'s exposure and invasive breast cancer, with higher risk for women nearer than 5 km from MSWI (Hazard ratio, HR: 125; confidence interval, CI: 95% 104–152) [32]. However, in a case–control study nested within the French E3N prospective cohort, no increased risk of breast cancer was shown from higher airborne dioxin exposure, probably due to the small population size [33]. Being dioxin classified as a known human carcinogen by IARC and its pathogenic mechanism plausible, it is reasonable to propose a possible role in breast cancer development [34]. Regarding cadmium, a recent meta-analysis of cohort studies found just a marginal positive relation between dietary cadmium intake and breast cancer, with no clear mechanism [35, 36]: in vitro and in animal models, this heavy metal has estrogen-like properties, can increase migration and epithelial–mesenchymal transition of breast cancer cell, and can increase active oxygen species (ROS) production, but their possible effect in human is unclear [37–41]. Interestingly, an epidemiological Italian study started in 2007, *"Italian Epidemiological Study of Residents in National Contaminated Sites (SENTIERI Project)"*, in an update of 2017–2019, revealed the presence of cadmium in three National Priority Contaminated Sites (NPCSs) in which breast cancer incidence was higher than the expected in the same age group [42, 43].

Nevertheless, even between other confirmed and emerging EDCs, there is evidence of a possible carcinogenic role on breast. BPA shares some structural similarity to estradiol and binds to ER-α with weak affinity [44]. In vitro BPA induced the proliferation of MCF-7 cells [45]. Human in vivo evidences are hard to achieve, maybe because of the short half-life of the chemical and the difficulty in assessing exposure during susceptible life stages. Indeed, animal studies have proved that BPA carcinogenic effect would be relevant if exposition occur during peri-gestational period [46, 47]. BPA given orally during gestation and through 90 days of age induced a significant increase in ductal hyperplasia in female rats at 21 days of different grade depending on dose exposition [48]. Anyway, a recent meta-analysis including 9 case–control studies (5 high quality, 4 medium quality) on human, consisting of 7,820 breast cancer, finds no associations between BPA and breast cancer [49]. Moreover,

Table 1 Recognized EDCs carcinogenic for breast, prostate, testicular, thyroid. POPs: persistent organic pollutants; PBDE: polybrominated diphenyl ethers

WHO/UNEP [11]	European Commission [12]	The Endocrine Society (103)
Breast cancer		
Dioxins, Furans, PCBs	Cadmium	Dioxins
Prostate cancer		
Arsenic, Cadmium, PCBs	Arsenic, Cadmium, PCBs	Cadmium, PCBs
Testicular cancer		
Fungicides, Pesticides, PBDE, Prenatal exposure to POPs	Organochlorine chemicals, PCBs	Arsenic, Cadmium, PCBs
Thyroid cancer		
Pesticides, TCDD	PCBs, Pesticides	

the authors find out a negative correlation between some phthalates metabolites—in particular mono-benzyl phthalate (MBzP) and mono-2-isobutyl phthalate (MiBP)—and breast cancer (odds ratio, OR 0.73, 95% CI: 0.60–0.90; OR 0.75, 95% CI 0.58–0.98, respectively). This could be explained by other effect of these chemicals. In fact, it is proved that they could activate human peroxisome proliferator-activated receptor (PPAR) α and γ, and it has a detrimental effect on growth of breast cancer cell [50]. Moreover, they could upregulate disintegrin and metalloproteinase domain 33 (ADAM33) expression, which play an important role in reducing breast cancer risk [51]. A study examined the association between pre-diagnostic urinary phthalates and breast cancer in a nested case–control study within the Multiethnic Cohort (MEC): breast cancer risk was higher for those in tertile 2 and tertile 3, more exposed to phthalates, than those in tertile 1 (respective OR 1.32 and 1.26, $p = 0.05$). Moreover, they considered immunohistochemical subtypes: exposure above the median of low molecular weight phthalates (ΣLMWP) was associated with an increased risk of ER-positive breast cancer (OR 1.30, 95% CI 1.05–1.60) while above the median exposure to phthalic acid was associated with an increased risk of ER-negative breast cancer (OR 1.59, 95% CI 1.01–2.48) [52].

These data support the hypothesis that dioxin and cadmium are plausible to be carcinogenic for breast, maybe with an estrogen-dependent mechanism. BPA exposition during pregnancy could be a risk factor at least for ductal hyperplasia, while role of phthalates is still unclear.

Prostate cancer

Prostate cancer (PCa) is the second most common solid tumor in men and the fifth cause of cancer mortality worldwide, with 375,304 estimated number of deaths in the year 2020. Thanks to early detection strategies, Europe has an all-age incidence ASR (age-standardized rate) of 63 per 100 000 males (473,334 estimated new cases in the year 2020) with a lifetime cumulative risk of only 16% [53]. As for breast cancer, even for prostate, there are some well-known EDCs that have a carcinogenic role (Table 1). Regarding arsenic, a recent meta-analysis proved that any exposure is statistically significantly associated with prostate cancer risk (relative risk, RR 1.18, 95% CI 1.06–1.30), regardless of medium such as water or soil [54] and it shows a dose-dependent mechanism [55], probably working by changing stromal tumor microenvironment and microRNA expression (57,58). On the other hand, even if cadmium seems not to have "driving" mutational capacity on prostate tissue [58, 59], its exposure could concur to determine higher grade and more aggressive tumor rather than not exposed people [60]. Moreover, European Association of Urology has reported some EDCs exposition as major risk factor for prostate cancer developing in their 2021 update, including chromium, organochlorine pesticides, and asbestos, whose role is confirmed by a systematic review and meta-analysis [61–63]. At least, PCBs exposure seems to be linked with a high-grade prostate tumor at diagnosis, but not with a higher incidence compared with not exposed subjects [64, 65].

TCDD exposure during the peri-gestational period could promote the trans-differentiation of prostate adenocarcinoma's cell in neuroendocrine ones. Herein in a recent study, male B6-TRAMP mice (animals genetically designed to develop prostate adenocarcinoma) containing zero, one, or two functional copies of the Ahr gene were exposed in utero and via lactation to a single oral maternal dose of corn oil (vehicle, 5 ml/kg—control group) or TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin 1 μg/kg). IUL (in utero and lactation) TCDD exposure significantly increased the incidence of NEPC (neuroendocrine prostate carcinomas) in Ahr + /+ + mice, showing that its effect is mediated by Ahr pathway [66]. As for women in Seveso, also men were exposed to high dose TCDD. During the Vietnam conflict (1962–1971), the herbicide Agent Orange, an equal mixture of 2, 4-di-chlorophenoxyacetic acid and 2, 4, 5-trichlorophenoxyacetic acid was widely used; the second compound was, however, contaminated by TCDD during production. Increased prostate cancer rates in Agent Orange-exposed veterans have been identified, with a RR increase of 2.3–6.0 in the highest exposure group (Air Force Ranch Hand sprayers) compared to non-exposed veterans [67, 68]. Furthermore, this highly exposed group developed the disease earlier rather than the others [69]. Moreover, prostate biopsy in exposed veterans, compared to non-exposed veterans, found a 2.1-fold increased risk in detecting prostate cancer with a Gleason score ≥ 8, including both aggressive and potentially lethal forms of the disease [70]. All these observations suggest that even TCDD should be consider carcinogenic for prostate.

Regarding BPA exposition, it could have a role in early onset prostate cancer. It has been proved that early life exposure to low-dose BPA increased rat prostate cancer risk with aging and alters adult prostate stem cell homeostasis [71, 72]. A human study analyzed BPA-glucuronide urinary levels in patients with or without prostate cancer. Subjects with cancer and younger than 65 years had higher **BPA-glucuronide levels than non-cancer patients, whereas there was no difference in BPA levels in cancer vs non-cancer patients in men over 65 years old [73]. Larger case-controlled studies are needed to confirm this observation.

There is no accordance on the role of phthalates. Di (2-ethylhexyl)phthalate (DEHP) exposure has been studied in mice peri-gestational period. Herein, female mice were treated with 0,01 or 0,1 or 1 DEHP mg/kg body weight/day from 5th gestational day to 21st postnatal day and compared to a control group that received just corn oil: all treatment

groups' male birth had hypomethylation of prostate stem cell antigen (PSCA), that is a glycosylphosphatidylinositol (GPI)-anchored cell surface protein associated with malignant progression of pre-malignant prostate lesions and advanced clinical stage and metastasis of prostate cancer [74, 75]. Moreover, a recent study considered phthalates' urinary metabolites in men with prostate carcinoma: presence of DEHP, mono-n-butyl and mono-benzyl phthalate (MBzP, MiBP) was positively associated with prostate cancer in men with waist circumference (WC) ≥ 90 cm but not in the leans: the upper tertile of DEHP's level compared to lower ones had an odds ratio (OR) of 7.76 (95% CI 1.95–30.9; $p = 0{,}03$) for WC ≥ 90 cm to develop prostate cancer [76]. There are two main explanations for this observation: PPAR-γ may be oncogenic in prostate cancer development and progression, and it could be activated by phthalates [77, 78]; DEHP is a weak AhR agonist [79] and AhR is constitutively active in advanced prostate cancer cells [80].

Arsenic, asbestos and dioxin could be considered carcinogenic for prostate. Cadmium, PCBs and dioxin are associated with high-grade prostate cancer diagnosis. BPA and phthalates could have a role in early prostate cancer development if exposure occurs during pregnancy.

Testicular cancer

The incidence of testicular cancer germ cell (TGCC), which represents 95% of all testicular cancer cases, has increased in recent decades. It has been suggested that TGCC has a fetal origin with pre-neoplastic lesion, and that hormonal stimulation from puberty onward stimulates tumor development [81], with a peak incidence in young men, as testicular cancer is the most common malignancy in men 15–44 years old worldwide (60% in this age group). Some EDCs are reported as carcinogenic for testicle (Table 1). Preclinical evaluation conducted on Leydig cells exposed to arsenic proved an induction of genomic instability and an increased proliferation rate [82]. Because of this tumor epidemiology and the epigenetics' EDCs mechanism, most of in vivo studies have focused on mother's exposition during gestational period. Regarding organochlorines, like dichloro-diphenyl-trichloroethane (DTT), and organohalogens, like PCBs, a recent meta-analysis takes in account ten papers (all measuring EDCs directly in serum): maternal exposure to combined EDCs was associated with a higher risk of testicular cancer in male offspring (HR 1.63 for organochlorines and 2.53 for organohalogens). Moreover, authors considered effects of these EDCs in seminoma or non-seminoma tumor development and a possible effect of exposition after birth. Maternal exposure to organohalogens or to organochlorines was associated with elevated risk of non-seminoma (HR: 2.96, 95% CI 2.32–3.76 and HR: 2.41, 95% CI 1.61–3.61 respectively) and seminoma (HR: 1.82, 95% CI 1.35–2.45 and HR: 2.24, 95% CI 1.38–3.62 respectively) testicular cancer. Postnatal adult male exposure to organohalogens was associated with decreased risk of non-seminoma (HR 0.57, 95% CI 0.48–0.68) and seminoma (HR 0.74, 95% CI 0.63–0.88) testicular cancer; otherwise in the same group, organochlorines exposition was associated with higher risk of non-seminoma (HR 1.32, 95% CI 1.14–1.53) and seminoma (HR 1.46, 95% CI 1.22–1.73) testicular cancer but without statistical significance [83]. Also PCBs' congeners level in mother's blood showed a clear association with testicle cancer in their children (OR 2.4, 95% CI 0.95–6.0), and, in particular, exposure to a group of them considered potentially estrogenic, proved to increase seminoma/non-seminoma risk in a case–control study (OR 2.5, 95% CI 1.3–4.7)[84–86].

Exposure to organochlorines or organohalogens compounds, as well as to PCBs, increases the risk of progeny to develop testicular cancer.

Ovarian cancer

Worldwide, ovarian cancer (OC) is the seventh most common type of malignant neoplasm in women and the eighth cause of mortality in them. The global incidence of OC has been stable during the last decades, without any screening program. The majority of ovarian tumors overexpress ERα, and this facilitates tumor growth through estrogen signaling [87].

There is no established EDCs clearly carcinogenic for ovary, but some evidence suggests that there could be a higher risk to develop disease in people exposed to dioxin and to chlorotriazine herbicides. Herein, a study conducted in rats demonstrated that chronic exposure to TCDD promotes the development of ovarian tumors in female [88]. On the other hand, in a case–control study, women previously exposed to these EDCs showed a significant 2.7-fold increased risk for ovarian neoplasms [89]. A similar result was obtained by the Agricultural Health Study conducted in North Carolina [90].

Regarding EDCs assumed trough food ingestion, in a meta-analysis of 62 observational studies, 49 studies for consumption of nitrates and 51 studies for nitrites, just 3 have studied ovarian cancer, finding no statistically significant correlation [91].

Further investigations are needed about relationship between female reproductive cancer and EDCs, like DES, BPA, or phthalates. TCDD and chlorotriazine herbicides seem to be carcinogenic for ovary.

Thyroid cancer

Thyroid cancer is the most common endocrine tumor, currently responsible for 567,000 cases worldwide (F > M; 5.1% of the total estimated female cancer burden) [92, 93].

Meanwhile detrimental EDCs effect on thyroid function has been deepened, a little is known about their carcinogenic role. Nevertheless, there are some EDCs reported as carcinogenic for thyroid (Table 1). A descriptive ecological assessment conducted on people who lived in Staten Island revealed a higher incidence of differentiated thyroid carcinoma (DTC) compared to that of New York City (NYC). That area has got a proved high concentration of some EDCs in air, water, and soil, in particular cadmium, PCBs, and dioxins [94]. Another study in Spain suggested an association between proximity to coal instillation and thyroid cancer [95].

Polycyclic aromatic hydrocarbons (PAHs) are a class of organic pollutants containing two or more fused aromatic rings. Urinary metabolites of PAHs were analyzed in people with nodular goiter (NG) or papillary thyroid carcinoma (PTC) and compared to controls: seven metabolites were significantly higher in PTC, than in control and goiter. [96]. Interestingly for five metabolites, higher levels corresponded to a higher risk to develop PTC. Regarding 2-hydroxynaphthalene (2-OH-NAP), an increased risk was reported for levels corresponding to 150–329 mg/g creatinine. The National Health and Nutrition Examination Survey (NHANES) in 2017 reported that the median urine concentrations of 2-OH-NAP was approximately 3 mg/g creatinine among the U.S. adult population, so more than 50% of population in U.S. has got an higher risk to develop PTC. Clearly this observation should be verified with other studies, but it should be an alert [96, 97].

Another study compared serum presence of bisphenol-AF (BPAF) or of di(2-ethylhexyl)phthalate (DEHP) between people with benign noduls or DTC. A significant relationship was found between malignancy and the detection of both BPAF and DEHP: their presence confers a more than 14 times higher risk of developing DTC ($p = 0{,}018$). Relationship was dose-independent and not mediated by higher thyroid stimulating hormone levels [98]. Anyway, a recent review underlined how relationship between BPA and thyroid cancer, both in animal model and human, is almost unexplored [99].

Even with the lack of meta-analysis on this field, it is likely that dioxin, cadmium, PCBs, and PAH can contribute in thyroid cancer development, while more research is needed to explore BPA and phthalate role.

Perceived risk and estimated costs

A recent study explored public knowledge and awareness of EDCs. Interestingly, despite the relevance of this problem, most participants were totally unaware of EDCs, maybe due to lack of attention, information or educational resources. Anyway, after reading an "information pocket", risk perception of EDCs varied greatly among participants on the basis of perceived severity, perceived control, inevitability, pre-existing health conditions, children's health [100]. Besides the negative impact on public health, the economic costs that can be reasonably attributed to EDCs represent a relevant issue, as it has been estimated that approximately 160 billion euro is the cost of EDCs on European population [101]. Consequently, increasing awareness of risks related to EDCs may positively impact both on public health and costs.

Conclusion

EDCs represent a major environmental and health issue that has a role in cancer development. Preclinical studies have been essential to prove possible mechanisms of action, often regarding estrogenic-receptor pathway. New interesting findings underline the possible role of genetic instability and epigenetic changes induced by EDCs in cancer development. The possibility to carry out case–control study in humans is difficult due to EDCs' variability both in levels and time to exposure, and even due to their lipophilic structure, making them accumulate in the white adipose tissue [102]. There are currently some EDCs that can be considered as carcinogenic, like dioxin and cadmium for breast and thyroid cancer; arsenic, asbestos, and dioxin for prostate cancer; and organochlorines/organohalogens for testicular cancer. New evidence supports the role of other EDCs as possible carcinogenic, in particular phthalates and BPA for breast, prostate, and thyroid and TCDD for ovary. Gestational period is a vulnerable moment for EDCs effect on fetus, and pregnant women should avoid risk area and exposure. More studies are needed to clarify these associations, but, despite the uncertainties, the relationship between EDCs and cancer supports the need for effective prevention policies, paying attention to public awareness.

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Data availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors have no financial or non-financial competing interests to disclose.

Ethical approval The authors have no ethical conflict to disclose. The study was performed in accordance with the principles of the Declaration of Helsinki. Local Ethics Research Committee approval was obtained.

Informed consent Written informed consent was obtained from the patients for publication of this case series.

Research involving human participants and animals No animals were used for this study.

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