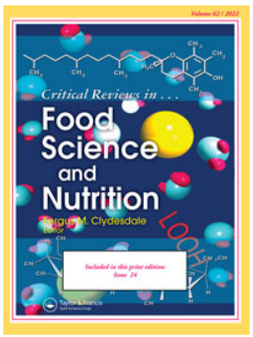

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: www.tandfonline.com/journals/bfsn20

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To cite this article: Murphy Lam Yim Wan, Vanessa Anna Co & Hani El-Nezami (2022) Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies, Critical Reviews in Food Science and Nutrition, 62:24, 6549-6576, DOI: 10.1080/10408398.2021.1903382

To link to this article: https://doi.org/10.1080/10408398.2021.1903382

Published online: 05 Apr 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2022, VOL. 62, NO. 24, 6549–6576
https://doi.org/10.1080/10408398.2021.1903382

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REVIEW

Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies

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ABSTRACT

Background: Endocrine-disrupting compounds (EDCs) are ubiquitous substances that are found in our everyday lives, including pesticides, plasticizers, pharmaceutical agents, personal care products, and also in food products and food packaging. Increasing epidemiological evidence suggest that EDCs may affect the development or progression of breast cancer and consequently lead to life-long harmful health consequences, especially when exposure occurs during early life in humans. Yet so far no appraisal of the available evidence has been conducted on this topic.

Objective: To systematically review all the available epidemiological studies about the association of the levels of environmental exposures of EDCs with breast cancer risk.

Methods: The search was performed in accordance with the PRISMA guidelines. We retrieved articles from PubMed (MEDLINE) until 10 March 2021. The key words used in this research were: "Endocrine disruptor(s)" OR "Endocrine disrupting chemical(s)" OR any of the EDCs mentioned below AND "Breast cancer" to locate all relevant articles published. We included only cohort studies and case-control studies. All relevant articles were accessed in full text and were evaluated and summarized in tables.

Results: We identified 131 studies that met the search criteria and were included in this systematic review. EDCs reviewed herein included pesticides (e.g. p,p′-dichlorodiphenyltrichloroethane (DDT), p,p′-dichlorodiphenyldichloroethylene (DDE), atrazine, 2,3,7,8-tetrachloridibenzo-p-dioxin (TCDD or dioxin)), synthetic chemicals (e.g. bisphenol A (BPA), phthalates, per- and polyfluoroalkyl substances (PFAS), parabens, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), contraceptive pills), phytoestrogens (e.g. genistein, resveratrol), and certain mycotoxins (e.g. zearalenone). Most studies assessed environmental EDCs exposure via biomarker measurements.

Conclusion: We identified certain EDC exposures could potentially elevate the risk of breast cancer. As majority of EDCs are highly persistent in the environment and bio-accumulative, it is essential to assess the long-term impacts of EDC exposures, especially multi-generational and transgenerational. Also, since food is often a major route of exposure to EDCs, well-designed exposure assessments of potential EDCs in food and food packing are necessary and their potential link to breast cancer development need to be carefully evaluated for subsequent EDC policy making and regulations.

KEYWORDS
Breast cancer; dietary; endocrine-disrupting chemicals; environmental; epidemiological studies; systematic review

Introduction

Breast cancer accounts for the majority of the women cancer cases worldwide. According to GLOBOCAN 2020 (2021), there are approximately 2.3 million new breast cancer cases (11%) of all the new cancer cases diagnosed in 2020 and it contributes to the most women cancer death cases globally. The incidence of women breast cancer was the highest in developed countries such as Australia and New Zealand, Western and Northern Europe and Northern America; intermediate in South America, Eastern Europe, Latin America and Caribbean; and lowest in developing areas, such as Central America, Eastern and Middle Africa and South-Central Asia (Sung et al. 2021). This may be attributed to some of the established risk factors for breast cancer, such as early age at menarche, late age at first birth, menopause and other potential reproductive and family histories, but these may only explain breast cancer risk partially (Collaborative Group On Hormonal Factors In Breast 2012). Recently, there has been an increasing interest in whether certain environmental chemicals, especially those with evidence of being hormonally active, play a role in breast cancer risk.

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Endocrine disrupting chemicals (EDCs) are ubiquitous in the environment and accumulating evidence show that estrogenic properties of EDCs are potentially linked to the increasing rates of breast cancer. Young women or girls reaching puberty will have higher susceptibility to cancer if they are constantly exposed to environmental toxicants such as EDCs, even at low concentrations since EDCs perturb the endocrine system in regulating growth and differentiation (Birnbaum and Fenton 2003).

Due to the wide presence of EDCs in the environment, they will end up in food chain and consumed by humans. Humans can be exposed to EDCs through different routes: (i) direct ingestion of contaminated food from packaging materials or additives that are deliberately added in food processing for maintaining the quality and safety of food products; (ii) drinking of contaminated water; and (iii) breathing of air and skin contacting contaminated soil, cosmetics and personal care products, etc. Since food is indispensable for life, it is considered as the major route of EDC exposure. It is worth noting that the choices of diet would affect the levels of exposure to EDCs in humans. For instance, even within the same geographical region, people who consume a large proportion of conventional food in their diet would have higher pesticide exposure than those consume more organic food (Lu et al. 2006). Likewise, people who eat a lot of oily fish, meat and dairy products would have a higher exposure to the more persistent EDCs such as DDT, than those who eat more vegetables, as the lipophilic persistent EDCs are bio-accumulated in the lipid fraction of these food (Darnerud et al. 2006).

Compounds with estrogenic activity (estrogen-mimic), are known as xenoestrogens, and they comprise a broad range of pesticides for agriculture uses (e.g. p,p'-dichlorodiphenyltrichloroethane (DDT), p,p'-dichlorodiphenyldichloroethylene (DDE), atrazine, 2,3,7,8-tetrachloridibenzo-p-dioxin (TCDD or dioxin)), synthetic chemicals (e.g. bisphenol A (BPA), phthalates, per- and polyfluoroalkyl substances (PFAS), parabens, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), contraceptive pills), phytoestrogens (e.g. genistein, resveratrol), and certain mycotoxins (e.g. zearalenone). To assess the potential relationship between EDCs exposure and breast cancer risks, we conducted a systematic review of epidemiologic studies that have evaluated the association between these EDCs exposure (using environmental measures, questionnaires or biomarker measures) and breast cancer incidences.

Methods

Data sources and search strategy: A comprehensive literature search in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) databases was conducted using the following search terms: ("Endocrine disruptor(s)" OR "Endocrine disrupting chemical(s)" OR any of the EDCs mentioned above) AND ("Breast Cancer") to locate all relevant articles published. Titles and abstracts were first scanned; and full articles of potential eligible studies were reviewed independently by two investigators and were carefully examined for any duplicates. Any discrepancies were resolved by consensus. The evaluation of the included studies was conducted in accordance to the criteria defined by Longnecker et al. (1988) and Appel et al. (2002). We confirmed our criteria with the PRISMA checklist for completeness of systematic review findings (Moher et al. 2010).

Data inclusion and exclusion: If all the above criteria were met, the studies were considered eligible for inclusion. Only cohort studies and case-control studies that evaluated the associations between EDCs and breast cancer risks were included, and we excluded non-original reports, review articles, conference abstracts, editorials, commentaries, experimental or pilot studies, case reports and case series, and studies without measures of EDCs exposure. The search was restricted to studies that were published in English. The data extracted from each study include the first author, country of origin, the duration of studies, sample size (number of breast cancer cases and control cases), biological specimen collected, biomarkers measured and breast cancer risk associations. The flowchart of our study selection is presented in Figure 1.

Results

There was a total of 3,276 articles identified through PubMed database till 10 March 2021. 317 articles were first excluded due to the unavailability of full texts. The remaining articles were then assessed independently by two investigators, and 131 studies met our inclusion criteria (Figure 1) and were included in this review. The studies were conducted in the United States, France, Greenland, Sweden, China, Spain, Tunisia, Poland, Mexico, Denmark, Germany, Italy, Japan, Hong Kong, Belgium, Netherlands, Northern Ireland, Switzerland, Korea, Slovakia, South Africa, Canada, India, Indonesia, Jordan, Australia, Greece, United Kingdom, Taiwan, Singapore, Egypt, Norway, Brazil, Iran and Russia. We concluded that majority of the included studies were of limited quality and too diverse in outcome measures and exposure levels to allow for meaningful meta-analysis of all studies (Pittler 2002). Data were extracted and summarized in Tables 1–10.

Pesticides

Regarding links between breast cancer and environmental factors in humans (outside of diet), the most compelling data come from the exposure of pesticides through farming, which is associated with increased breast cancer incidences (Dorgan et al. 1999; Duell et al. 2000; Millikan et al. 2000; Brophy et al. 2002; Mathur et al. 2002; Engel et al. 2005; Xu et al. 2010; Brophy et al. 2012; Tayour et al. 2019). Certain organochlorine compounds, including agricultural pesticides and herbicides, such as p,p'-dichlorodiphenyltrichloroethane (DDT), p,p'-dichlorodiphenyldichloroethylene (DDE), atrazine, 2,3,7,8-tetrachloridibenzo-p-dioxin (TCDD or dioxin) may disrupt the endocrine system owing to their estrogenic properties and may cause breast cancer (Bustos et al. 1988; Ahlborg et al. 1995; Høyer et al. 1998; Zheng et al. 1999; Snedeker 2001).

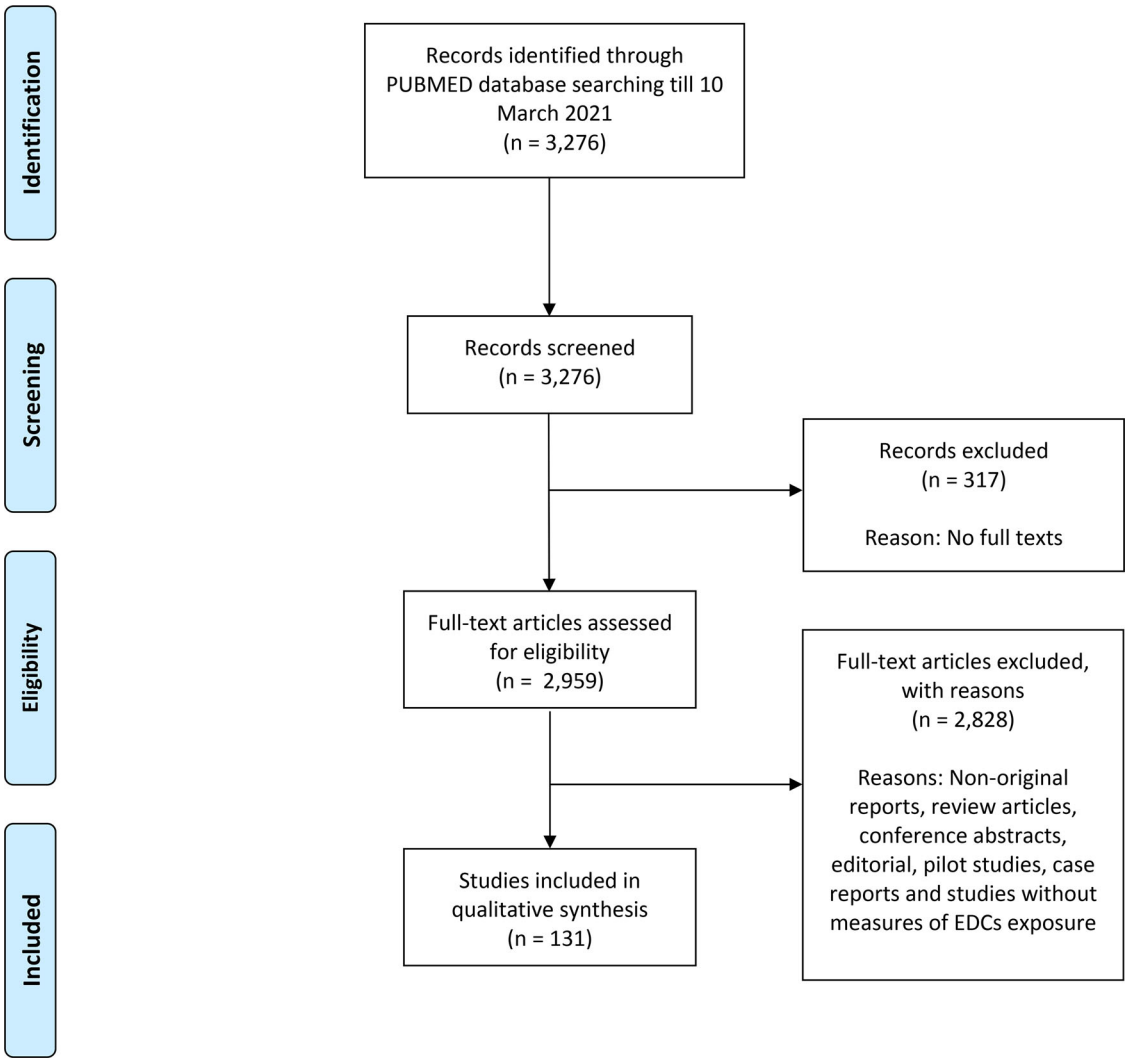

Figure 1. PRISMA flow diagram.

p,p′-dichlorodiphenyltrichloroethane (DDT)/p,p′-dichlorodiphenyldichloroethylene (DDE)

DDT and/or its metabolite DDE are organochlorine pesticides that have always attracted a lot of attention worldwide because they are highly persistent EDCs in the environment. They are able to accumulate along the food chain, and therefore spontaneously be detected in breast milk and adipose tissues. Nowadays most countries impose bans on the use of DTT ever since it was discovered to have endocrine disrupting properties and cause birth defects in human and animals in 1970s (Eskenazi et al. 2009). Similar to most insecticides, DTT is neurotoxic, but DTT and its metabolites also cause reproductive and developmental effects (Faroon and Harris 2002). DDT promoted the growth of mammary tumors in some animal studies (Scribner and Mottet 1981; Robison, Sirbasku, and Stancel 1985; Brown and Lamartiniere 1995; Desaulniers et al. 2001; Johnson et al. 2012). Our search has found forty-three epidemiological studies regarding the DDT or its metabolites exposure on the breast cancer risk, which are summarized in Table 1. Among them, there are eleven epidemiological studies that reported positive associations between DDT or its metabolites in lipid, serum or plasma and breast cancer incidences (Wolff et al. 1993; Stellman et al. 1998; Høyer, Jørgensen, Brock, et al. 2000; Millikan et al. 2000; Mathur et al. 2002; Pavuk et al. 2003; Charlier, Foidart, et al. 2004; Cohn et al. 2007; Arrebola et al. 2015; Cohn, Cirillo, and Terry 2019; Parada et al. 2019). DDT is also shown to adversely affect survival following breast cancer diagnosis in a population-based study (Parada et al. 2016). Nine studies reported higher levels of DDT or DDE among women with breast cancer than among controls (Wassermann et al. 1976; Falck et al. 1992; Aronson et al. 2000; Ahmed, Loutfy, and Shiekh 2002; Charlier et al. 2003; Tang et al. 2014; He et al. 2017; Huang et al. 2019; Kaur et al. 2019). In two studies DDT was found to be linked to women with estrogen-receptor–positive breast cancer (Verreault et al. 1994; White et al. 2013), and in one study DDT increased risk of breast cancer among premenopausal women with CYP1A1 m2 variant genotype (Li et al. 2006). A case-control study by Chang et al. 2008 showed the interaction of genetic polymorphisms of glutathione S-transferase T1 with DDT residues which affected breast cancer risk (Chang et al. 2008). A case-control study showed that daughters whose mothers were exposed to DDT during pregnancy would have a higher risk for breast cancer later in life (Cohn et al. 2015). On the

Table 1. Summary of papers for DDT or its metabolites exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen(s)	Biomarker(s)	Breast cancer risk	Reference
Wolff/ US	1985-1991	Case-control	58	171	Serum	*p, p'*-DDE	↑	WWolff et al. (1993)
López-Carrillo/ Mexico	1994-1996	Hospital based case-control	141	141	Serum	*p, p'*-DDE *p, p'*-DDT	No association	(López-Carrillo et al. 1997)
Hunter/ US	1989-1990, 1992	Case-control	236	236	Plasma	*p, p'*-DDE	No association	(Hunter et al. 1997)
Moysich/ US	1986-1991	Case-control	154	192	Serum	*p, p'*-DDE	No association	(Moysich et al. 1998)
Stellman/ US	1994-1996	Hospital based case-control	362	293	Serum, adipose tissue	*p, p'*-DDE *o, p'*-DDD *p, p'*-DDT	↑	(Stellman et al. 1998)
Høyer/ US	1996-1997	Case-control	240	447	Serum	*p, p'*-DDE *p, p'*-DDT	No association	(Høyer et al. 1998)
Helzlsouer/ US	1974-1989	Nested case-control	235, 105	235, 105	Serum	*p, p'*-DDE *p, p'*-DDT	No association	(Helzlsouer et al. 1999)
Dorgan/ US	1977-1987	Case-control	105	208	Serum	*o, p'*-DDE *p, p'*-DDE *p, p'*-DDD *o, p'-DDT,* *p, p'-DDT*	No association	(Dorgan et al. 1999)
Mendonça/ Brazil	1995-1996	Hospital based case-control	177	350	Serum	*p, p'*-DDE	No association	(Mendonça et al. 1999)
Aronson/ Canada	1995-1997	Hospital based case-control	217	213	Adipose tissue	*p, p'*-DDE *p, p'*-DDT	No association	(Aronson et al. 2000)
Zheng/ US	1995-1997	Case-control	475	502	Serum	*p, p'*-DDE	No association	(Zheng, Holford, Tessari, et al. 2000)
Høyer/ Denmark	1976-1978, 1981-1983	Cohort nested case control	155	274	Serum	*p, p'*-DDT	↑	(Høyer, Jørgensen, Brock, et al. 2000)
Bagga/ US	1995-1996	Case-control	73	73	Adipose tissue	*p, p'*-DDE *p, p'*-DDD *p, p'*-DDT	No association	(Bagga et al. 2000)
Wolff/ US	1987-1992, 1994	Case-control	148	295	Serum	*p, p'*-DDE	No association	(Wolff, Zeleniuch-Jacquotte, et al. 2000)
Wolff/ US	N.A.	Hospital based case-control	175	355	Serum	*p, p'*-DDE *p, p'*-DDT	No association	(Wolff, Zeleniuch-Jacquotte, et al. 2000)
Millikan/ US	1993-1996	Population based case-control	748	659	Plasma	*p, p'*-DDE	↑	(Millikan et al. 2000)
Stellman/ US	1994-1996	Hospital based case-control	232	323	Adipose tissue	*p, p'*-DDE	No association	(Stellman et al. 2000)
Elizabeth/ Norway	1973-1991	Nested case-control	150	150	Serum	*p, p'*-DDE *p, p'*-DDT	No association	(Ward et al. 2000)
Laden/ US	1976, 1989-1990, 1994	Follow up of prospective cohort study	372	372	Plasma	*p, p'*-DDE	No association	(Laden, Collman, et al. 2001)
Woolcott/ Canada	1995-1997	Hospital based case-control	217	213	Adipose tissue	*p, p'*-DDE *p, p'*-DDT	No association	(Woolcott et al. 2001)
Ahmed/ Egypt	1999-2000	Case-control	64	11	Serum	*p, p'*-DDE	↑	(Ahmed, Loutfy, and Shiekh 2002)
Gammon/ US	1886-1997	Population based case-control	646	429	Serum	*p, p'*-DDE	No association	(Gammon et al. 2002)
Mathur/ India	N.A.	Case-control	135	50	Blood	*p, p'*-DDE *p, p'*-DDD *p, p'*-DDT	↑	(Mathur et al. 2002)
Charlier/ Belgium	1999-2000	Case-control	159	250	Serum	Total DDT	↑	(Charlier et al. 2003)
Pavuk/ Slovakia	1997-1999	Case-control	24	88	Serum	*p, p'*-DDE *p, p'*-DDT	↑ for DDE	(Pavuk et al. 2003)

Mucat/ US	1994-1996	Case-control	224	359	Adipose tissue	*p, p′*-DDE *p, p′*-DDT *o, p′*-DDD	No association	(Muscat et al. 2003)
McElroy/ US	1997-2001	Population based case-control study	1481	1301	N.A.	DDT	No association	(McElroy et al. 2004)
Charlier/ Belgium	2001-2002	Case-control	231	290	Serum	*p, p′*-DDE *o, p′*-DDT *p, p′*-DDT	↑ for DDE	(Charlier, Albert, et al. 2004)
Raaschou-Nielsen/ Denmark	1993-1997	Nested case-control	409	409	Adipose tissue	*p, p′*-DDE *p, p′*-DDT	No association	(Raaschou-Nielsen et al. 2005)
Li/ China	2003-2004	Case-control	104	154	Serum	*p, p′*-DDE *p, p′*-DDT	↑ for DTT among premenopausal women with CYP1A1 m2 variant genotype	(Li et al. 2006)
Gatto/ US	1995-1998	Multi-center population-based case-control study	355	327	Serum	*p, p′*-DDE	No association	(Gatto et al. 2007)
Cohn/ US	1959-1967	Prospective nested case-control	129	129	Serum	*p, p′*-DDT	↑	(Cohn et al. 2007)
Iwasaki/ Japan	1990-1995, 2002	Nested case-control	139	139 (24,226)	Plasma	*p, p′*-DDE *p, p′*-DDT	No association	(Iwasaki et al. 2008)
Itoh/ Japan	2001-2005	Matched case-control	403	403	Serum	*p, p′*-DDE *o, p′*-DDT *p, p′*-DDT	No association	(Itoh et al. 2009)
Chang/ China	2006-2007	Case-control	70	30	Serum	*p, p′*-DDT	N.A.	(Chang et al. 2008)
White/ US	1996-1997	Case-control	1,508	1,556	Serum	*p, p′*-DDE *p, p′*-DDT	↑	(White et al. 2013)
Tang/ China	2005-2007	Case-control	78	72	Serum	*p,p′*-DDT *p,p′*-DDE *p,p′*-DDD *o,p′*-DDT *o,p′*-DDE *o,p′*-DDD	↑	(Tang et al. 2014)
Holmes/ US	1999-2002	Case-control	75	95	Serum	*p, p′*-DDE *o, p′*-DDT *p, p′*-DDT	No association	(Holmes et al. 2014)
Cohn/ US	N.A.	Case-control	118	354 (9,300)	Serum	*p, p′*-DDE *o, p′*-DDT *p, p′*-DDT	↑ for *o, p′*-DDT	(Cohn et al. 2015)
Parada/ US	1996-1997, 2011	Population based case-control	224	409	Blood	*p, p′*-DDE *p, p′*-DDT	↑	(Parada Jr. et al. 2016)
He/ China	2015-2016	Hospital based case control	56	46	Adipose tissue	*p, p′*-DDE	↑	(He et al. 2017)
Louis/ US	1993-1997, 2012-2013	Prospective cohort	N.A.	28,909 (2,191 exposed)	N.A.	*p, p′*-DDT	No association	(Louis et al. 2017)
Cohn/ US	1959-1967, 2010	Prospective, nested case-control	153	432	Serum	*p, p′*-DDT	↑	(Cohn, Cirillo, and Terry 2019)
Huang/ China	2014-2016	Hospital-based case-control	209	165	Adipose tissue	*p, p′*-DDE *p, p′*-DDT	↑	(Huang et al. 2019)
Kaur/ India	2015-2016	Hospital-based case-control	42	42	Serum	*p, p′*-DDE *p, p′*-DDT	↑ for DDE	(Kaur et al. 2019)
Paydar/ Iran	2015-2016	Case-control	58	27	Serum	*p, p′*-DDE *p, p′*-DDT	↑	(Paydar et al. 2019)
Parada/ US	1993-1996	Population based case-control	748	N.A.	Plasma	*p, p′*-DDE *p, p′*-DDT	↑	(Parada et al. 2019)

Table 2. Summary of papers for TCDD or dioxin exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen	Biomarker(s)	Breast cancer risk	Reference
Warner/ Italy	1996	Retrospective cohort	N.A.	981	Serum	TCCD	↑	(Warner et al. 2002)
Warner/ Italy	1996	Follow-up	N.A.	981	Serum	TCCD	↑	(Warner et al. 2011)
Danjou/ France	1990-2008	Prospective cohort, Nested case-control	419	716	N.A.	N.A.	No association	(Danjou et al. 2019)
VoPham/ US	1989-2013	Prospective cohort	N.A.	3,840	N.A.	N.A.	No association	(VoPham et al. 2020)

Table 3. Summary of papers for BPA exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen	Biomarker(s)	Breast cancer risk	Reference
Trabert/ Poland	2000-2003	Population-based case-control	575	575	Urine	BPA-G	No association	(Trabert et al. 2014)
Morgan/ US	1999-2004	Cross-sectional	31	115	Serum	BPA	No association	(Morgan et al. 2017)

Table 4. Summary of papers for phthalates or its metabolites exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen	Biomarker(s)	Breast cancer risk	Reference
Reeves/US	1993-1998	Nested case-control	419	838	Urine	13 Phthalates	No association	(Reeves et al. 2019)
Parada/US	1997-1998	Case-control	710	598	Urine	11 Phthalates metabolites	↑ for MCPP, MCNP, MCOP	(Parada et al. 2018)
Holmes/US	1999-2002	Case-control	75	95	Urine	10 Phthalates metabolites	↑ for MEHP, DEHP	(Holmes et al. 2014)
Morgan/US	2003-2004 2005-2006, 2007-2008, 2009-2010	Cross-sectional survey	43	1,964	Urine	13 Phthalates metabolites for 2003-2004, 15 Phthalates metabolites for 2005-2006, 2007-2008, 2009-2010	No association	(Morgan et al. 2017)
Lizbeth López-Carrillo, Merida-Ortega/ Northern Mexico	2007-2008	Population-based case control	233	221	Urine	10 Phthalates metabolites	↑ for López-Carrillo et al. 2010 study; ↑ when interact with dietary flavonoids for Merida-Ortega 2016 study	(López-Carrillo et al. 2010; Mérida-Ortega et al. 2016)

Table 5. Summary of papers for PFOA exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen	Biomarker(s)	Breast cancer risk	Reference
Bonefeld-Jørgensen/ Greenland	2000-2003	Case-control	31	115	Serum	PFOA	↑	(Bonefeld-Jørgensen et al. 2011)
Bonefeld-Jørgensen/ Denmark	1996-2002, 2010	Case-control	250	233	Serum	PFOA	No association	(Bonefeld-Jørgensen et al. 2014)
Wielsøe/ Greenland	2000-2003, 2011-2014	Case-control	3,166	11,562	Serum	PFOA	↑	(Wielsøe, Kern, and Bonefeld-Jørgensen 2017)
Hurley/ US	2011-2015	Nested case-control	902	858	Serum	PFOA	No association	(Hurley et al. 2018)
Mancini/ France	1925-1950, 1990	Nested case-control	194	194	Serum	PFOA	↑	(Mancini et al. 2020)

contrary, thirty-four studies reported no correlation between higher DDT or DDE levels in women and breast cancer risk (Hunter et al. 1997; López-Carrillo et al. 1997; van't Veer et al. 1997; Høyer et al. 1998; Moysich et al. 1998; Dorgan et al. 1999; Helzlsouer et al. 1999; Mendonça et al. 1999; Zheng et al. 1999; Bagga et al. 2000; Cocco, Kazerouni, and Zahm 2000; Demers et al. 2000; Stellman et al. 2000; Ward et al. 2000; Wolff, Berkowitz, et al. 2000; Wolff, Zeleniuch-Jacquotte, et al. 2000; Zheng, Holford, Tessari, et al. 2000; Laden, Collman, et al. 2001; Laden, Hankinson, et al. 2001; Snedeker 2001; Woolcott et al. 2001; Gammon et al. 2002; Muscat et al. 2003; López-Cervantes et al. 2004; McElroy et al. 2004; Raaschou-Nielsen et al. 2005; Gatto et al. 2007; Iwasaki et al. 2008; Itoh et al. 2009; Shakeel et al. 2010; Holmes et al. 2014; Louis et al. 2017; Rusiecki et al. 2020). It is suggested that time of first exposure and the levels of exposure at younger ages are critical for accurate assessment of the breast cancer risk (Johnson et al. 2012).

Atrazine

Atrazine was once one of the most commonly used agriculture herbicides worldwide with potent endocrine disruptor activity. Owing to the ubiquitous and unavoidable water and soil contamination, the use of atrazine was banned by European Union (EU) since October 2003 (Bethsass and Colangelo 2006).

In fact, atrazine is not only found in crops that are used as livestock feed but also found in milk and meat (Demarini and Zahm 1999). Atrazine is active and toxic at low

Table 6. Summary of papers for PCBs exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen(s)	Biomarker(s)	Breast cancer risk	Reference
Hunter/ US	1989-1990, 1992	Case-control	230	230	Plasma	Total PCBs	No association	(Hunter et al. 1997)
Moysich/ US	1986-1991	Case-control	154	192	Serum	73 PCB congeners	No association	(Moysich et al. 1998)
Høyer/ US	1996-1997	Case-control	240	477	Serum	28 PCB congeners	No association	(Høyer et al. 1998)
Stellman/ US	1994-1996	Hospital-based case-control	362	293	Adipose tissue, serum	14 PCB congeners	No association	(Stellman et al. 1998)
Dorgan/ US	1977-1987	Case-control	105	208	Serum	27 PCB congeners	No association	(Dorgan et al. 1999)
Helzlsouer/ US	1974, 1989	Nested case-control	235	105	Serum	26 PCB congeners	No association	(Helzlsouer et al. 1999)
Laden/ US	1989-1990, 1992	Nested case-control	240	240	Plasma	16 PCB congeners	Not mentioned	(Laden et al. 1999)
Moysich/ US	1989-1991	Case-control	154	192	Serum	56 PCB congeners	CYP1A1 isoleucine-to-valine substitution may be a risk factor for breast cancer among women with elevated PCB body burden.	(Moysich et al. 1999)
Aronson/ Canada	N.A.	Hospital-based case-control	217	213	Biopsy tissue	14 PCB congeners	↑	(Aronson et al. 2000)
Hoyer/ Denmark	1976-1978, 1981-1983	Nested case-control	155	274	Serum	PCB 118, PCB 138, PCB 153, PCB 180	↑ for PCB118 and PCB138	(Høyer, Jørgensen, Brock, et al. 2000)
Millikan/US	1993-1996	Population-based case-control	748	659	Plasma	35 PCB congeners	↑ for total PCB	(Millikan et al. 2000)
Stellman/ US	1994-1996	Hospital-based case-control	232	323	Adipose tissue	14 PCB congeners	↑ for PCB183	(Stellman et al. 2000)
Ward/ Norway	19973-1991	Nested case-control	150	150	Serum	26 PCB congeners	No association	(Ward et al. 2000)
Wolff/ US	1987-1992, 1994	Prospective cohort, case-control	148	295 (14,275)	Blood	29 PCB congeners	No association	(Wolff, Zeleniuch-Jacquotte, et al. 2000)
Zheng/ US	1995-1997	Case-control	475	502	Serum	9 PCB congeners	No association	(Zheng, Holford, Tessari, et al. 2000)
Zheng/ US	1994-1997	Case-control	304	186	Adipose tissue	9 PCB congeners	No association	(Zheng, Holford, Tessari, et al. 2000)
Hoyer/ Denmark	1976-78, until 1993	Nested case-control	268	536	Serum	28 PCB congeners	No association	(Høyer et al. 2001)
Laden/ US	1976, 1989-1990, follow up through 1994	Nested case-control	370	370	Plasma	PCB 118, PCB 138, PCB 153, PCB 180	No association	(Laden, Collman, et al. 2001)
Woolcott/ Canada	1995-1997	Case-control	217	213	Adipose tissue	14 PCB congeners	↑ and PCBs were associated with poor prognosis	(Woolcott et al. 2001)
Ahmed/ Egypt	1999-2000	Cohort	64	11	Serum	Not specified	No association	(Ahmed, Loutfy, and Shiekh 2002)
Demers/ Canada	1994-1997	Case-control	314	523	Plasma lipid	14 PCB congeners	↑ for dioxin-like PCBs	(Demers et al. 2002)

(*continued*)

Table 6. Continued.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen(s)	Biomarker(s)	Breast cancer risk	Reference
Gammon/ US	1996-1997	Case-control	646	429	Serum	24 PCB congeners	No association	(Gammon et al. 2002)
Laden/ US	1976, 1989-1990 (blood), follow up through 1994	Nested case-control	367	367	Plasma	21 PCB congeners	↑ for women who have the variant CYP1A1-exon7polymorphism.	(Laden et al. 2002)
Lopez-Carrillo/ Mexico	1994-1996	Case-control	95	95	Serum	Not specified	No association	(López-Carrillo et al. 2002)
Muscat/ US	1994-1996	Case-control	224	N.A.	Adipose tissue	14 PCB congeners	↑ recurrence	(Muscat et al. 2003)
Pavuk/ Slovakia	1997-1999	Case-control	24	88	Serum	15 PCB congeners	↓ but not statistically significant	(Pavuk et al. 2003)
Charlier/ Belgium	N.A.	Case-control	60	60	Serum	7 PCB congeners	↑ for PCB153	(Charlier, Albert, et al. 2004)
Li/ US	1993-1996, 1996-2001	Population-based case-control	612	599	Serum	35 PCB congeners	↑ for CYP1A1 M2 and M3-containing genotypes and high levels of PCB exposure	(Li et al. 2004)
McElroy/ Belgium	1997-2001	Population-based case-control	1,481	1,301	N.A.	N.A.	No association	(McElroy et al. 2004)
Rusiecki/ US	1994-1997	Hospital-based case-control	266	347	Adipose tissue, serum	9 PCB congeners	No association	(Rusiecki et al. 2004)
Zhang/ US	1999-2002	Case-control	374	406	Serum	9 PCB congeners	↑ for CYP1A1 M2 and PCB exposure	(Zhang et al. 2004)
Raaschou-Nielsen/ Denmark	1993-1997	Nested case-control	409	409	Adipose tissue	18 PCB congeners	No association	(Raaschou-Nielsen et al. 2005)
Prince/ US	Updated through 1998	Cohort	N.A.	2,572	N.A.	N.A.	No association	(Prince et al. 2006)
Gatto/ US	1995-1998	Multi-center population-based case-control	355	327	Serum	N.A.	No association	(Gatto et al. 2007)
Silver/ US	1970-1999	Occupation cohort	281	5,471	N.A.	N.A.	No association	(Silver et al. 2008)
Itoh/ Japan	2001-2005	Matched case-control	403	403	Serum	More than 41 PCB congeners	No association	(Itoh et al. 2009)
Villeneuve/ France, Denmark	1995-1997	Case-control	104	1,901	N.A.	N.A.	↑	(Villeneuve et al. 2010)
Bonefeld-Jorgensen/ Greenland	2000-2003	Case-control	31	115	Serum	12 PCB congeners	↑ for high PCB exposure (PCBs > 2645 ug/kg lipid)	Bonefeld-Jørgensen et al. 2011)
Recio-Vega/ Mexico	N.A.	Case-control	70	70	Serum	20 PCB congeners	↑	(Recio-Vega et al. 2011)
Cohn/ US	1959-1967	Nested case-control	112	112	Serum	16 PCB congeners	↑ for PCB203 ↓ for PCB167 and PCB187	(Cohn et al. 2012)
Arrebola/ Spain	2003-2004	Cohort	N.A.	368	Adipose tissue	PCB 138, PCB 153, PCB 180	No association	(Arrebola et al. 2015)

Ruder/ US	1957-1977, 1939-1976, 1946-1977, 2008	Cohort	N.A.	24,865	N.A.	N.A.	No association	(Ruder et al. 2014)
Arrebola/ Spain	2012-2014	Cohort	103	N.A.	Adipose tissue, serum	PCB 138, PCB 153, PCB 180	PCB associated with breast cancer aggressiveness	(Arrebola et al. 2016)
Donat-Vargas/ Sweden	1997 (14 years follow-up)	Population-based prospective cohort	1,593	35,184	N.A.	N.A.	No association	(Donat-Vargas et al. 2016)
He/ China	2014-2015	Cohort	N.A.	223	Adipose tissue	7 PCB congeners	↑	(He et al. 2017)
Morgan/ US	1999-2004	Cohort	43	1,964	Serum	6 PCB congeners	↑ for PCB138	(Morgan et al. 2017)
Ruder/ US	1957-1977, 1939-1976, 1946-1977, 2008	Cohort	N.A.	24,865	N.A.	N.A.	No association	(Ruder et al. 2017)
Wielsøe/ Greenland	2000-2003, 2011-2014	Case-control	7	84	Serum	14 PCB congeners	↑	(Wielsøe, Kern, and Bonefeld-Jørgensen 2017)
Huang/ China	2014-2016	Hospital-based case-control	209	165	Adipose tissue	7 PCB congeners	↑ for PCB118, PCB138, PCB153, and PCB180 ↓ for PCB28, PCB52 and PCB101	(Huang et al. 2019)
Rusiecki/ US	1998	Cohort	N.A.	210	Serum	27 PCB congeners	↑	(Rusiecki et al. 2020)

environmentally relevant concentrations, but its mode of action is largely unknown. Atrazine is implicated to be an EDC as it has been demonstrated to cause reproductive dysfunction by inhibiting cAMP-specific phosphodiesterase-4 through the hypothalamic-pituitary-gonadal (HPG) axis (Wirbisky and Freeman 2015). According to IARC (Demarini and Zahm 1999), atrazine is classified as "unlikely to be carcinogenic to humans" but some animal studies have shown that atrazine exposure in adult rats delayed mammary gland growth and development, and long-term exposure of atrazine increased mammary tumor incidence (Laws et al. 2000; Stoker et al. 2000; Ueda et al. 2005; Enoch et al. 2007; Rosenberg et al. 2008; Davis et al. 2011; Hovey et al. 2011). However, epidemiological evidence for the association of atrazine exposure and breast cancer risk is still very limited. Two of them are ecological studies instead of case-control studies so they are not discussed here further (Hopenhayn-Rich, Stump, and Browning 2002; Freeman et al. 2011). There was only one case-control study evaluating the association of the exposure of atrazine and the incidences of breast cancer among women of rural Wisconsin, and the results did not demonstrate an increased breast cancer risk from atrazine exposure (Mcelroy et al. 2007).

2,3,7,8-Tetrachloridibenzo-p-dioxin (TCDD or dioxin)

2,3,7,8-tetrachloridibenzo-p-dioxin (TCDD or dioxin) is one of the most infamous organochlorines that is formed as a result of combustion and manufacturing chemicals. Human can be exposed to dioxins via ingestion of food that are high in fat content such as meat, poultry, milk, egg and their by-products. Dioxins are fat-soluble, very persistent and bio-accumulative in fatty tissues. They are considered as EDCs on the basis that they exert their estrogenic or anti-androgenic effects by binding to the aromatic hydrocarbon receptor (AhR) and inducing epigenetic alterations (Safe 1995).

According to IARC, dioxin is classified as a known human carcinogen, primarily based on occupational studies of increased mortality from all cancers combined (Dibenzofurans 1997). Overall, epidemiological studies did not provide a consistent link between dioxin exposure and risk of breast cancer in women. Our search has identified seven human studies about the dioxin exposure with breast cancer risk or mortality (Table 2). It was found that a higher incidence of breast cancer in women in Seveso, Italy which was associated with an elevated serum level of dioxin (Warner et al. 2002; Warner et al. 2011). The long-term effects of occupational exposure to dioxins, particularly with regards to cancer mortality, were also examined in a follow-up 23 years after closure of a German pesticide plant. An increase in breast cancer mortality was found among women workers exposed to herbicide and insecticide (Brody et al. 2007; Manuwald et al. 2012). Positive associations were found among Russian women living near a chemical plant, compared with women from a non-contaminated region (Revich et al. 2001). Similar results were observed in US women who resided close to incinerator plants for longer duration compared to those who lived farther (VoPham

et al. 2020). 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 included in this study (Danjou et al. 2019).

Synthetic chemicals

Bisphenol A (BPA)

Bisphenol A (BPA) is a synthetic chemical used in manufacturing of polycarbonate plastics for food and beverage storage. Humans usually expose to BPA at low levels through eating food or drinking water stored in containers that contain BPA. BPA is a known endocrine disruptor, and it was considered as a relatively weak environmental estrogen because of their ability to bind either ERα and ERβ, or their capacity to activate ER-dependent transcription (Kuiper et al. 1998; Lemmen et al. 2004). Despite BPA has relatively lower binding affinity for ERs compared to estradiol (E_2), some studies have demonstrated that BPA can trigger cellular responses even at very low concentrations. In some cases, BPA has similar potency as E_2 (Quesada et al. 2002; Alonso-Magdalena et al. 2005; Hugo et al. 2008; Bouskine et al. 2009; Ge et al. 2014).

Due to its wide availability in the environment, adverse effects of BPA exposure on human health are possible. There are numerous studies examining BPA and human reproduction as well as other health outcomes (reviewed by Vandenberg et al. (2013)). Furthermore, BPA is considered as a potential risk factor for breast cancer (Smith-Bindman 2012). Indeed there were some associations of BPA with breast cancer risks reported as summarized by Yang, Ryu, et al. (2009) and in Table 3. It has been hypothesized that exposure of BPA during the early development may be the underlying cause of the increased incidence of infertility, genital tract abnormalities and breast cancer (Sharpe and Skakkebaek 1993; Yang, Ryu, et al. 2009). Also, BPA was shown to induce tumor aggressiveness in breast cancer patients, which may be associated with poor prognosis (Dairkee et al. 2008). There were, however, no significant associations between BPA and breast cancers found in two other studies (Trabert et al. 2014; Morgan et al. 2017). Considering potential linkages between BPA exposure and breast cancer risks, further biomonitoring studies of BPA are necessary for effective prevention against breast cancer.

Phthalates

Phthalates are a large class of chemicals that are constantly detected in food through food packaging materials and food contact substances used during processing and storage (Petersen and Jensen 2010). Their use is normally considered as harmless, but they are also known to induce cancer owing to its potential endocrine disrupting properties- the ability to interfere with the action or metabolism of androgens, thyroid hormones and glucocorticoids (Grindler et al. 2018). Majority of animal studies show that phthalates induce adverse effects on the male reproductive system (reviewed by Yost et al. (Yost et al. 2019)), however the precise underlying mechanisms remains largely unclear. In our search we identified six epidemiological studies that investigated the correlation of phthalates exposure and breast cancer risk by measuring different urinary phthalate metabolites as biomarkers (Table 4). Among them, four studies showed a positive association of phthalates with breast cancer risk (López-Carrillo et al. 2010; Holmes et al. 2014; Mérida-Ortega et al. 2016; Parada et al. 2018). In the study by Mérida-Ortega et al. (2016), it reported the synergistic interactions of some flavonoid from vegetables (anthocyanidins, flavan-3-ols and flavones) with phthalate exposure on the risk of breast cancer, but it was inconclusive due to the small population size.

Per- and polyfluoroalkyl substances (PFAS)

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals that can contaminate drinking water. They can enter the food chain and be consumed by human through food packaging materials and contaminated soil. It has been reported that PFAS can mimic fatty acid and bio-accumulate in adipose tissues, therefore exposure to PFAS chemicals can cause adverse health effects. Furthermore, PFAS bind to plasma proteins, which can then be passed on to the offspring via the placenta and breast milk (Inoue et al. 2004).

The most-studied PFAS are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). They are considered as potential EDCs, since they have been shown to cause endocrine disruption by binding and activating the peroxisome proliferator activated receptor (PPAR)-α/γ signaling pathways, which then increases hepatic aromatase concentrations and subsequent estrogen levels (DeWitt et al. 2009). Reproductive and developmental toxicities of PFAS have been documented in animals and humans (Lau et al. 2006; Yang, Tan, et al. 2009; Zhao et al. 2010; Macon et al. 2011; Dixon et al. 2012; Tsai et al. 2015; Anderko and Pennea 2020; Blake and Fenton 2020). After gestational exposure of rodents, PFOA was found in the placenta, amniotic fluid, breast milk and fetus (Fenton et al. 2009). The maternal level of PFOA was found to be associated with various reproductive and child health outcomes (Fei et al. 2007).

Currently, there are only five epidemiological studies about the association of PFOA with breast cancer risk (Table 5). A study of Inuit women showed a positive association of serum perfluorinated compounds along with other persistent organic chemicals and breast cancer risk (Bonefeld-Jørgensen et al. 2011). It was found that the genetic polymorphisms in CYP 1A1(Val) and CYP 17(A1) may increase the breast cancer risk among Inuit women, and that the risk increases with higher serum levels of PFOA and another persistent environmental contaminant, PFOS (perfluorooctane sulfonate). Three studies found positive associations between breast cancer risk and perfluoroalkylated substances, including PFOA, in Danish premenopausal women, Greenlandic Inuit and French women, respectively (Bonefeld-Jørgensen et al. 2014; Wielsøe, Kern, and Bonefeld-Jørgensen 2017; Mancini et al. 2020). However, a

recent nested case-control study within the California Teachers showed no correlation of serum PFAS levels measured after diagnosis with breast cancer risk (Hurley et al. 2018).

Parabens

Parabens are synthetic chemicals that are commonly used as preservatives in many foods, for examples, beer, sauces, jams, soft drinks, as well as personal care products such as cosmetics (Golden, Gandy, and Vollmer 2005). In spite of their relatively low toxicity profiles and a long history of safe uses, these chemicals are considered as potential carcinogens and endocrine disruptors, because they can mimic estrogen in the body and disrupt the hormone balances (Golden, Gandy, and Vollmer 2005). In animal studies, parabens have been shown to affect both male and female reproductive developments (Oishi 2001; Kang et al. 2002; Kawaguchi et al. 2009; Vo et al. 2010; Ahn et al. 2012; Guerra, Sanabria, Cagliarani, et al. 2017; Guerra, Sanabria, Leite, et al. 2017; Fisher et al. 2020). In humans, parabens have been detected in normal breast cells and maternal urine and breast milk (Barr et al. 2012; Fisher et al. 2017; Amin et al. 2019). These studies have revealed that the estrogenic properties of parabens may perturb the mechanism of normal breast cells and potentially contribute to their abnormal growth and thus increase the risk of the breast cancer (Barr et al. 2012; Fisher et al. 2017; Amin et al. 2019). By far there are only one epidemiological study that reported the association of paraben exposures and breast cancer risk and mortality following breast cancer (Parada et al. 2019).

Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are a halogenated aromatic group of ubiquitous, persistent environmental pollutants, and they can be present in high concentrations in fatty foods such as such as meat, fish and dairy products (Guo et al. 2019). Similar to DTT and dioxins, these chemicals are lipophilic, bio-accumulate in adipose tissue, persistent in animal tissues and excreted in breast milk (Jackson et al. 2017).

PCBs are a class of 209 possible congeners, and they are different from each other in the numbers and positions of chlorine atoms substituted on the aromatic rings. However, not all PCBs act alike. Some congeners seem to be estrogenic, especially those that contain less than 48% chlorine, in particular after hydroxylation (Ahlborg et al. 1995; Negri et al. 2003), with the ability to mimic and induce metabolism of different hormones such as estradiol E_2, that can lead to infertility, cancers and other hormone-related disorders (Bonefeld-Jørgensen et al. 2001; Negri et al. 2003). These congeners, such as Aroclor 1221, were shown to increase uterine weight and cause precocious puberty (Gellert 1978). Some can also bind to the estrogen receptor (Korach et al. 1988) and enhance the proliferation of MCF-7 cells, as well as induction of gene expression (Nesaretnam et al. 1996; Andersson et al. 1999; Arcaro et al. 1999; Ptak, Mazur, and Gregoraszczuk 2011). Other congeners, however, bear structural similarities to dioxins, which exhibit anti-estrogenic activity via AhR which induces down-regulation of ER, interfere with ligand activated ER binding to DNA response element and/or induction of cytochrome P450 monooxygenase 1A1, 1A2 or 1B1 activities that are involved in the metabolism of E_2 (Bonefeld-Jørgensen et al. 2001).

One of the most studied PCBs, 3,3,4,4,5-pentachlorobiphenyl (PCB 126), is classified as a "dioxin-like compound". A study by Muto et al. (2002) showed that prenatal exposure to a relatively low dose of PCB126 increased the rate of DMBA-induced rat mammary carcinoma, while a high dose decreased it. In addition exposures at these levels also reduced serum E_2. In vitro studies have demonstrated that PCB126, and other congeners, including PCB77, PCB88 and PCB169 inhibited E_2-stimulated cell proliferation dose-dependently in estrogen-responsive breast tumor T47D and ZR-75-1 cells (Oenga, Spink, and Carpenter 2004). Clearly, this complex array of potential PCB effects could be missed by evaluating solely the total level of PCBs instead of individual congeners.

In a review of epidemiology studies, the association between total PCBs and breast cancer risk was found to be inconsistent, regardless of the exposure measure (Table 6). While there are 29 studies showing no correlation of PCBs with breast cancer risk (Hunter et al. 1997; Høyer et al. 1998; Moysich et al. 1998; Stellman et al. 1998; Dorgan et al. 1999; Helzlsouer et al. 1999; Aronson et al. 2000; Bagga et al. 2000; Demers et al. 2000; Ward et al. 2000; Wolff, Berkowitz, et al. 2000; Zheng, Holford, Mayne, et al. 2000; Zheng, Holford, Tessari, et al. 2000; Høyer et al. 2001; Laden, Hankinson, et al. 2001; Woolcott et al. 2001; Gammon et al. 2002; López-Carrillo et al. 2002; Muscat et al. 2003; Pavuk et al. 2003; Raaschou-Nielsen et al. 2005; Prince et al. 2006; Gatto et al. 2007; Itoh et al. 2009; Bonefeld-Jørgensen et al. 2011; Holmes et al. 2014; Donat-Vargas et al. 2016; Li et al. 2019; Rusiecki et al. 2020), 19 studies found a positive association between certain PCB exposures and elevated incidence for breast cancer (Moysich et al. 1999; Høyer, Jørgensen, Grandjean, et al. 2000; Millikan et al. 2000; Stellman et al. 2000; Ahmed, Loutfy, and Shiekh 2002; Laden et al. 2002; Charlier, Albert, et al. 2004; Li et al. 2004; McElroy et al. 2004; Zhang et al. 2004; Silver et al. 2009; Villeneuve et al. 2010; Recio-Vega et al. 2011; Cohn et al. 2012; Zimeri et al. 2015; He et al. 2017; Morgan et al. 2017; Wielsøe, Kern, and Bonefeld-Jørgensen 2017; Huang et al. 2019). It is suggested that certain polymorphisms, such as cytochrome P450 1A1 (CYP1A1) M2-containing genotypes modify the association between PCB exposure and risk of breast cancer, and genotyping of *CYP1A1* could help to resolve inconsistencies in past epidemiologic studies (Moysich et al. 1999; Laden et al. 2002; Li et al. 2004; Zhang et al. 2004).

Polybrominated diphenyl ethers (PBDEs)

Polybrominated diphenyl ethers (PBDEs) are a group of synthetic halogenated compounds that have been widely distributed as environmental contaminants due to their

Table 7. Summary of papers for PBDEs exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen	Biomarker(s)	Breast cancer risk	Reference
Holmes/ US	1999-2002	Case-control	75	95	Urine	8 PBDE congeners	↑ for BDE-47	(Holmes et al. 2014)
Hurley/ US	2006-2014	Nested case-control	902	936	Serum	19 PBDE congeners	No association	(Hurley et al. 2019)
Hurley/ US	2006-2014	Case-control	78	56	Adipose tissues	5 PBDE congeners	No association	(Hurley et al. 2011)
Mancini/ France	1994-1999, identified up to 2013	Nested case-control	197	197	Plasma	6 PBDE congeners	No association	(Mancini et al. 2020)
McElroy/ US	1996-2000	Case-control	3,753	5,155	N.A.	N.A.	No association	(McElroy et al. 2004)
He/ China	2014-2016	Case-control	209	165	Adipose tissues	14 PBDE congeners	↑	(He et al. 2018)
Kachuri/ Canada	2012-2015	Case-control	305	144	Serum	8 PBDE congeners	↑	(Kachuri et al. 2018)

extensive uses as additive flame retardants in many household products, such as furniture, hard plastic coating in appliances, etc (Pohl et al. 2017). They are highly persistent, and they can enter the food chain and be accumulated in wildlife such as fish, and other higher predators that are eventually consumed by humans (Ross et al. 2009). Due to their structural similarities to PCBs, they are also known to be suspected human chemical carcinogens. According to IARC (2012), PCBs are not classified as carcinogenic to humans.

However, there is a raising concern over the use of PBDEs in humans as several animal studies have shown that PBDEs are able to cause endocrine disruptions and affect sexual, reproductive functions and developments (Branchi, Alleva, and Costa 2002; Kuriyama et al. 2005; Lilienthal et al. 2006; Tseng et al. 2008). This is largely due to their interference with estrogen and androgen signaling pathways. High levels of PBDEs are consistently detected in human breast tissues (She et al. 2002; Petreas et al. 2011).

Moreover, owing to their endocrine-disrupting effects, PBDEs attract a lot of interest in their connection with breast cancer. Certain PBDE congeners were shown to stimulate the proliferation of human breast cancer cells (Li, Liu, et al. 2012; Kanaya et al. 2019), In mouse models, PBDE congeners were able to promote breast tumor growth as indicated by influencing cell cycle regulation as well as increasing expression of Ki-67, a cancer proliferation marker (Kanaya et al. 2019). A recent study by Wei et al. (2020) has revealed a positive correlation of breast cancer growth with exposure to BDE-47, one of the PBDE congeners with intense focus, owing to its extensive existence in the environment and adverse health effects. Human data are still limited but our search has identified seven case-control studies (Table 7). Among them, five studies showed no significant associations with PBDEs (McElroy et al. 2004; Hurley et al. 2011; Holmes et al. 2014; Hurley et al. 2019; Mancini et al. 2020). A case-control study, in contrast, showed that the BDE-47 levels in adipose tissue were positively correlated with breast cancer risk in Chinese women (He et al. 2018). A similar possible association of PBDE levels and breast cancer risk was observed in young women from the Ontario Environment and Health Study (Kachuri et al. 2018). However, significant difference in PBDE levels were not observed when examining malignant and benign tumor tissues (Li et al. 2019).

Oral contraceptive pills

Oral contraceptives, which contain both levonorgestrel (a progestin) and ethinyl estradiol (an estrogen), are considered as toxic EDCs because they alter normal reproductive function by mimicking the action of estrogen and thus preventing normal hormone production. A large body of evidence showed that the ethinyl estradiol in oral contraceptive pills not only affect the fertility and sexual behavior of mice but also affects fetal growth and survival, as well as causes disruption of the fetal development of the prostate, urethra, especially when the mice were exposed to ethinyl estradiol during early pregnancy (Yasuda, Kihara, and Nishimura 1981; Vom Saal et al. 1997; Timms et al. 2005; Della Seta et al. 2008; Derouiche et al. 2015; Kolla et al. 2018; Meyer et al. 2019).

Due to wide availability and prevalent usage of oral contraceptives among women nowadays, there are considerable interest in investigating the linkage between contraceptive pills consumption and breast cancer risk. Seven prospective and retrospective studies identified an increased breast cancer risk associated with contraceptive pills use, regardless of contraceptive pills type (Table 8) (Rosenberg et al. 1996, 2009; Hunter et al. 2010; Bethea et al. 2015; Soroush et al. 2016; Wahidin, Djuwita, and Adisasmita 2018; Bardaweel et al. 2019), but only one study reported no such association (Vessey and Yeates 2013). However, there were controversies on whether duration of oral contraceptive use affect cancer risk. Bethea et al. (2015) demonstrated that recency and duration of oral contraceptive use increased breast cancer risk. While discontinued use would lower the risk slightly, the risk was still higher compared to non-users. In addition, the increase in risk was more pronounced in overweight or obese women, though the authors did not suggest an explanation for this. The studies by Mørch et al. (2017) and Van Hoften et al. (2000) also reported that long term use of oral contraceptive increased breast cancer risk, but their studies also suggested that the increased risk would gradually reduce after discontinuation. On the other hand, three studies showed that the duration of oral contraceptive use was not associated with increased breast cancer risk

Table 8. Summary of papers for oral contraceptive pills exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen	Breast cancer risk	Reference
Kumle/ Norway, Sweden	1991-1999	Prospective cohort	1,008	106,844	N.A.	↑	(Kumle et al. 2002)
Rosenberg/ US	1976-1996, 1993-2007	Case control	907	1,711	N.A.	↑	(Rosenberg et al. 2009)
Urban/ South Afirca	1995-2006	Hospital-based prospective case control	1,664	1,492	N.A.	↑ with use but no association with duration of use	(Urban et al. 2012)
Bethea/ US	1995-2011, 1993-2001, 2003	Prospective cohort; Population-based case control; Population-based case control	N.A.; 1,424; 370	59,000; 2,020; 207	N.A.	↑ with dosage, recency and duration of use	(Bethea et al. 2015)
Nur/ Sweden	1993-2012	Population-based prospective cohort	2,120	N.A.	N.A.	No association with breast cancer-related mortality	(Nur et al. 2019)
Mørch/ Denmark	1995-2012	Prospective cohort	N.A.	1,797,932	N.A.	↑	(Mørch et al. 2017)
Wahidin/ Indoesia	2013	Hospital-based case control	381	381	N.A.	↑ with use and duration of use	(Wahidin, Djuwita, and Adisasmita 2018)
Bardaweel/ Jordan	2017	Case control	225	225	N.A.	↑	(Bardaweel et al. 2019)

(Hankinson et al. 1997; Urban et al. 2012; Bardaweel et al. 2019). Moreover, Rosenberg et al. (1996) and Meirik et al. (1986) reported that use of oral contraceptive pills at young ages increased breast cancer risk, but opposing results were observed in other studies (Hennekens et al. 1984).

Phytoestrogens

The chemicals that have been discussed by far are synthetic compounds that disrupt the endocrine system by mimicking or inhibiting endogenous hormones. However, there are also some naturally occurring chemicals that can mimic or inhibit the effects of endogenous hormones. Phytoestrogens are naturally occurring estrogens that can be found abundantly in plants. They are considered to be EDCs. In contrast to industrial or communal EDCs, some believe that in some cases, phytoestrogens can be beneficial, such as to treat and/or prevent breast cancer. Yet, negative effects associated with phytoestrogens were also reported. Life-long exposure to estrogenic substance, especially during critical periods of development, can lead to the severe long-term consequences, for instance, leading to the formation of malignancies and several abnormalities of the reproduction systems (Pryor et al. 2000).

Genistein

Genistein is a naturally occurring phytoestrogen found in most soy products. In spite of the fact that it is a polyphenol, genistein shares structural similarity with E_2 and has been shown to act in a similar way as an estrogen. In vivo and in vitro data indicate that genistein can signal through both ERα and ERβ (Mueller et al. 2004). It has also been suggested that whether or not genistein exerts its beneficial or adverse effects depends on the timing of exposure, dose levels and endpoints examined. For example, prepubertal exposure to genistein prevented carcinogen-induced mammary gland cancer in rats (Murrill et al. 1996; Lamartiniere, Zhang, and Cotroneo 1998; Hilakivi-Clarke, Onojafe, et al. 1999), whereas another study showed that maternal exposure to genistein during pregnancy increased carcinogen-induced mammary tumorigenesis (Hilakivi-Clarke, Cho, et al. 1999). Neonatal exposure to genistein resulted in a higher incidence of uterine adenocarcinoma in mice, similar to that following diethylstilbestrol exposure (Newbold et al. 2001). In two multigenerational studies conducted by the National Toxicology Program, developmental genistein exposures in rats increased incidence of adenomas, adenocarcinomas and mammary hyperplasia in male offspring compared to controls (National Toxicology Program 2008; Latendresse et al. 2009). In ovariectomized athymic mice implanted with MCF-7 breast cancer cells, dietary genistein stimulated mammary gland growth and enhanced the growth of MCF-7 cell tumors, which was similar to that seen in vitro (Hsieh et al. 1998; Ju et al. 2001).

There are only sparse human data regarding the relationship between dietary exposure of soy products containing phytoestrogens such as genistein and breast cancer risk (Table 9). Although ten studies have shown that a high soy diet/supplementation reduced breast cancer risk in women (Lee et al. 1991; Wu et al. 1996, 2002, 2008; Yamamoto et al. 2003; Trock, Hilakivi-Clarke, and Clarke 2006; Do et al. 2007; Korde et al. 2009; Dong and Qin 2011; He and Chen 2013), the causative role of soy food intake in reducing breast cancer risk is still controversial. Several of these studies reported that Asian women who consumed a traditional diet (high in soy products) had lower incidence of breast cancer compared to Western women (Lee et al. 1991; Wu et al. 1996; Yamamoto et al. 2003; He and Chen 2013). Interestingly, the incidence of breast cancer in Asian-American populations was higher than native Asians, suggesting that breast cancer occurrence is not solely due to genetics but also diet or environmental factors, for example, due to reduced intakes of soy products (Wu et al. 1996). A case-control study by Veheus et al. (2007) also showed that increased levels of isoflavones in blood samples are associated with lower risk of breast cancer among Dutch women.

Table 9. Summary of papers for genistein exposure and breast cancer risk.

Study/ Country	Study year	Study design	Cases	Controls (or cohorts)	Biological specimen	Biomarker(s)	Breast cancer risk	Reference
Ingram/ Australia	1992-1994	Case-control	144	144	Urine	Genistein	No association	(Ingram et al. 1997)
Murkies/ Australia	1997-1998	Case-control	25	155	Urine	Genistein	↓	(Murkies et al. 2000)
Dai/ China	1996-1998	Population-based case control	1,459	1,556	N.A.	N.A.	↓	(Dai et al. 2001)
Horn-Ross/ US	1995-1998	Population-based case-control	1,326	1,657	N.A.	N.A.	No association	(Horn-Ross et al. 2001)
Tonkelaar/ Netherlands	1974-1984, 1977-1985	Nested case-control	88	268	Urine	Genistein	No association	(Tonkelaar et al. 2001)
Peterson/ Greece	1989-1991	Case-control	820	1,548	N.A.	N.A.	No association	(Peterson et al. 2003)
Yamamoto/ Japan	1990-1999	Population-based prospective cohort	179	21,852	N.A.	N.A.	↓	(Yamamoto et al. 2003)
Keinan-Boker/ Netherlands	1993-1997	Population-based prospective cohort	280	15.555	N.A.	N.A.	No association	(Keinan-Boker et al. 2004)
Sartippour/ US	1999-2001	Pilot	17	N.A.	Serum	Genistein	No association	(Sartippour et al. 2004)
Silvia/ United Kingdom	1995-1999	Population-based case-control	240	477	N.A.	N.A.	↓	(Silva et al. 2004)
Wu/ US	1995-1998	Population-based case-control	97	97	Plasma	Genistein	↓	(Wu et al. 2004)
Bosetti/ Italy	1991-1994	Case-control	2,569	2,588	N.A.	N.A.	↓	(Bosetti et al. 2005)
Hirose/ Japan	1988-2002	Population-based case-control	167	854	N.A.	N.A.	↓ for premenopausal women	(Hirose et al. 2005)
Lee/ Taiwan	1996-1999	Population-based case-control	250	219	N.A.	N.A.	↓ for older subjects (>40), but not for younger subjects (<40)	(Lee et al. 2005)
Shannon/ China	1989-1991, 1995-2000	Population-based case-control	378	1,070	N.A.	N.A.	No association	(Shannon et al. 2005)
Ho/ Hong Kong	1998	Population-based case-control	174	10,968	N.A.	N.A.	↓	(Ho et al. 2006)
Thanos/ Canada	2002-2003	Population-based case-control	3,024	3,420	N.A.	N.A.	↓	(Thanos et al. 2006)
Touillaud/ France	1990-1991, 1993-1995	Population-based prospective cohort	402	117,652	N.A.	N.A.	No association	(Touillaud et al. 2006)
Do/ Korea	1999-2003	Population-based case-control	359	708	N.A.	N.A.	↓	(Do et al. 2007)
Fink/ US	1996-1997	Population-based case-control	1,434	1,440	N.A.	N.A.	↓ for postmenopausal breast cancer	(Fink et al. 2007)
Nishio/ Japan	1988-1990	Population-based prospective cohort	N.A.	30,454	N.A.	N.A.	No association	(Nishio et al. 2007)
Verheus/ Netherlands	2003	Nested case-control	383	383	Plasma	Genistein	↓	(Verheus et al. 2007)
Ward/ United Kingdom	1993-1997, 1993-2006	Population-based prospective cohort	237	952	Serum, urine	Genistein	No association	(Ward et al. 2008)
Wu/ Singapore	1993-2005	Population-based prospective cohort	629	35,303	N.A.	N.A.	↓	(Wu et al. 2008)
Guha/ US	1997-2000, 2000-2002	Prospective cohort	N.A.	1,954	N.A.	N.A.	↓ breast cancer recurrence	(Guha et al. 2009)
Iwasaki/ Japan and Brazil	2001-2005, 2001-2006	Hospital-based case-control	850	850	N.A.	N.A.	↓ for Japanese Brazilians, non-Japanese Brazilians, and premenopausal Japanese; ↓ for all three populations combined	(Iwasaki et al. 2009)
Toi/ Japan	2007-2009	Population-based case-control	306	662	N.A.	N.A.	↓	(Toi et al. 2013)
Wada/ Japan	1992-2008	Population-based prospective cohort	172	15,607	N.A.	N.A.	↓ for postmenopausal breast cancer, but no association for premenopausal breast cancer	(Wada et al. 2013)
Wei/ China	2004-2008	Prospective cohort	N.A.	300,852	N.A.	N.A.	No association	(Wei et al. 2019)

Table 10. Summary of papers for mycoestrogen exposure and breast cancer risk.

Study/Country	Study year	Study design	Cases	Controls (or cohorts)	Exposure	Biological specimen	Biomarker(s)	Breast cancer risk	References
Pillay/ South Africa	N.A.	Case-control	28	24	Dietary	Serum	ZEA, α-ZOL, β-ZOL	No association	(Pillay et al. 2002)
Belhassen/ Tunisia	2012	Case-control	69	41	N.A.	Urine	ZEA, α-ZOL, β-ZOL, α-ZAL, β-ZAL, ZAN	↑ for α-ZAL; no association for ZON and other metabolites	(Belhassen et al. 2015)

Yuan et al. (Yuan et al. 1995), however, reported no protection against breast cancer from soy consumption. A retrospective cohort study found that young women fed soy-based infant formula reported slightly longer duration of menstrual bleeding and menstrual discomfort than those who were fed a non-soy based formula (Strom et al. 2001). On the other hand, in an epidemiological study, pregnant women consuming vegetarian diets (with high soy isoflavones levels) during pregnancy gave birth to a male offspring with a higher incidence of hypospadias (North, Golding, and Team 2000).

Resveratrol (RES)

Resveratrol (3,4′,5-trihydroxy-trans-stilbene) (RES) is one of the polyphenols abundant in red wine and grape skin. In recent years, RES has been proven to have numerous health-promoting benefits, for examples, inhibiting inflammation, viral infection, oxidative stress, and platelet aggregation and the growth of a variety of cancer cells (Athar et al. 2009), as well as breast cancer (Levi et al. 2005).

RES is structurally similar to E_2 and has endocrine disrupting properties. Unlike other phytoestrogens, RES binds ERβ with higher affinity than ERα (Bowers et al. 2000). In the absence of E_2, resveratrol exerts mixed estrogen agonist/antagonist activities in some mammary cancer cell lines, but in the presence of E_2, RES functioned as an anti-estrogen (Bhat et al. 2001). Whether the RES-bound ER has agonist or antagonist activity in breast cancer is not clear. RES was shown to increase the expression of native estrogen-regulated genes and stimulated the proliferation of estrogen-dependent T47D breast cancer cells, and that the stimulation was blocked by the estrogen antagonist ICI 182, 780 (Gehm et al. 1997). Other studies have shown that RES decreased proliferation of both ER-positive (MCF-7, T47D and KPL-1) and ER-negative (MDA-MB-231 and MKL-F) breast cancer cells (Mgbonyebi, Russo, and Russo 1998; Lu and Serrero 1999; Damianaki et al. 2000; Nakagawa et al. 2001), implying that the interaction of RES with ER may not fully explain its inhibitory effect on proliferation.

Several animal studies have shown that RES is protective against mammary tumorigenesis (Bhat et al. 2001; Banerjee, Bueso-Ramos, and Aggarwal 2002; Nikaido et al. 2004; Provinciali et al. 2005; Whitsett and Lamartiniere 2006). Anti-breast cancer effects of RES were also documented in animals. A significant decrease in tumor growth and angiogenesis, as well as an increase in apoptotic index was demonstrated in mice treated with RES (Garvin, Öllinger, and Dabrosin 2006). However, RES had no effect on tumor growth or metastasis in mice administered intraperitoneally daily with RES (Bove, Lincoln, and Tsan 2002). Castillo-Pichardo et al. reported that RES accelerated mammary tumor growth and metastasis in nude mice, which was accompanied by a significant induction of tumoral Rac activity and a trend of increased expression of the Rac downstream effector PAK1 and other tumor promoting molecules (Castillo-Pichardo, Cubano, and Dharmawardhane 2013). However, there was only one case-control study in the Swiss Canton of Vaud, which reported an inverse correlation between resveratrol and breast cancer risk (La Vecchia and Bosetti 2006). Taken together, although RES has shown remarkable promise as a potent chemopreventive and anti-cancer drug in breast cancer, however low concentrations of RES may potentially promote breast cancer as demonstrated in animal studies. Further studies are needed to establish its usefulness as a chemopreventive agent.

Mycotoxins

Mycotoxins are highly toxic secondary metabolites of fungi. Human are exposed to these mycotoxins through ingestion of contaminated foods and feeds. Among the most important mycotoxin producing fungi are *Fusarium*, *Aspergillus* and *Penicillium* spp. Out of the many classes of mycotoxins produced by *Fusarium* fungi, resorcyclic acid lactones (RALs) are of particular concern with respect to endocrine disruption. The most prominent representative of the RALs is zearalenone (ZEA).

Zearalenone (ZEA) and its metabolites

Zearalenone (ZEA) is a macrocyclic β-RAL produced by *Fusarium spp*. It is a common plant and crop contaminants around the world. The oestrogenicity of ZEA and its metabolites, particularly α-zearalenol (ZOL), are attributed to their ability to bind to human estrogen receptors, although an action through a disturbance of the steroid metabolism cannot be excluded. In vitro and in vivo studies have demonstrated that ZEA and its metabolites are capable of binding to ERs which initiate estrogenic effects (Celius et al. 1999; Takemura et al. 2007; Frizzell et al. 2011; Li, Burns, et al. 2012). The binding affinity and potency are in the order of $\alpha\text{-ZOL} \sim E_2 \gg \text{ZEA} > \beta\text{-ZOL}$ (Celius et al. 1999; Shier et al. 2001; Cozzini and Dellafiora 2012). Due to the structural similarity with E_2, its direct estrogenic effects are expected to be similar to that of E_2, and its oestrogenicity is orders of magnitudes higher than those of synthetic endocrine disruptors such as BPA, DTT, etc (Coldham et al. 1997). In fact,

ZEA has been found to activate a variety of estrogenic genes (Parveen, Zhu, and Kiyama 2009) via the nuclear ERs (Frizzell et al. 2011) and secondary signaling (Ahamed et al. 2001). As a result, ZEA would increase the estrogen burden in the animals, disrupt the endocrine systems and possibly have a role in the cancer development. In vitro exposure to relatively low dose in the nano-molar range of ZEA caused proliferation of breast cancer cells (Dees et al. 1997; Yu et al. 2005; Yip et al. 2017); and exposure to ZEA related compound α-zeralanol (zeranol; ZAL) increased proliferation of rat breast epithelial and stroma cells (Zhong et al. 2011), and pre-adipocytes in young cow in vivo (Ye et al. 2009). However, a study has revealed that α-ZAL could exert a biphasic behavior by stimulating breast cancer at low doses but increasing apoptosis and cell cycle arrest at high doses (Yuri et al. 2006).

Among the few epidemiological studies on this topic (Table 10), the findings on ZEA exposure and breast cancer risk were also controversial. A case-control study in Tunisia suggested a positive association between urinary α-zeralanol concentration and breast cancer risk (Belhassen et al. 2015). Another study also found that ZEA promoted the growth of mammary gland tumors, and the authors advised ZEA as a potential risk factor for breast cancer (Kuciel-Lisieska et al. 2008). On the other hand, Pillay et al. (2002) found no significant difference between plasma concentrations of ZEA, α-ZOL and β-ZOL in breast cancer patients and healthy volunteers. One possible explanation for the different conclusions could be inconsistencies in measuring the in vivo levels of ZEA and its metabolites, where some studies measured only the free forms of the mycotoxin while others accounted for the total levels in the biological samples (Bandera et al. 2011; Belhassen et al. 2015).

Discussion

This paper provides a comprehensive review of all the epidemiological studies about the association of common EDCs found in pesticides, herbicides, plant crops and food additives/packaging and breast cancer risks.

From these studies, it is first worth mentioning that for EDCs to cause impairment of endocrine functions, time of exposure is as important as dose, duration and age at exposure. Indeed, an EDC can have different effects in different cell/tissue types, species, and at different time during the life cycle (Zoeller et al. 2012). Moreover, the relationship between EDC exposure and breast cancer risk is not always clear-cut. Several studies suggest that genetics could play a vital role, and genotypes could determine whether EDC exposure affects host susceptibility and risks. One example is the polymorphism of the CYP1A1 gene, which is responsible for estrogen metabolism. Two case-control studies reported the association of CYP1A1 genotype to one's susceptibility to increased breast cancer risk following PCB exposure (Moysich et al. 1998; Laden et al. 2002). Women with at least one valine CYP1A1 allele are more likely to be affected by high serum PCBs levels compared to other CYP1A1 genotypes (Moysich et al. 1998). However, there are only a few studies considering the effects of genetic variations on EDC and breast cancer risk. Further research on this topic is needed to gain a more comprehensive understanding of the relationship between EDC exposure and breast cancer.

Moreover, there are not many of the population-based case-control studies reporting an increased risk of breast cancer with exposure to chemicals such as DDT and PCBs. The inconsistency and heterogeneity of the studies could be attributed to potential confounders or modifiers that might affect the relationship between DDT or PCBs and breast cancer incidences such as the collection time of biological samples, instruments of measurements and misclassification of the exposure. For example, DDT can stay in the body for an extended period of time, thus it is difficult to accurately identify the latent period of exposures during diagnosis (Park et al. 2014). For PCBs, some of the PCB congeners have short life and are quickly metabolized. Therefore, the results of existing studies may not be able to assess the exposure of short-lived organochlorine compounds accurately (Calle et al. 2002).

Furthermore, most of studies regarding the association of EDCs and breast cancer risk were case-control studies. Although case-control studies are an efficient method for the study of rare outcomes, they incur several limitations, for example, bias can occur during recollection of samples for exposure estimations (Melamed and Robinson 2019). Also, case-control studies are always retrospective which are often started with an outcome then traced back to investigate exposures. In other words, case-control studies may only prove an association but they do not reveal any causation (Lewallen and Courtright 1998).

The other limitation of the existing research studies is the negligence of interactive effect of different chemicals in the natural environment. For example, many persistent organic pollutants, including DDT can have either an agonistic role in estrogenic effects, or an antagonistic role. Current estimations may rule out the possibility that there is a more pronounced adverse effect resulting from interactions of several chemicals. To make things worse, there are quick emergence of thousands of new and untested synthetic chemicals in addition to the numerous naturally existing ones, and the adverse effects that could be caused by these EDCs, especially the mixture, are still not fully known. As a result, the WHO/UNEP (2013) urged the development of validated test methods for identification of EDCs, which target larger range of endocrine disrupting effects, and also the investigation of the mixture effects of EDCs.

Traditionally biomarkers of exposure are usually based on the costly and time-consuming measures of certain chemicals or chemical metabolites in the body or after excretion from the body. In this review we find that the assessment of breast cancer risk is mainly based on the measurement of EDCs and their metabolites in urine, serum, plasma or adipose tissues. However, these methods do not account for the delayed effects or multigenerational effects of EDCs on disease development. During the developmental stages, humans are usually more sensitive to stressors, and exposure to stressors in this time could lead to more

devastating or permanent changes that will increase the susceptibility to some other diseases. Therefore, timing of collection of the biomarker, together with patient conditions will need to be delineated more clearly for more precise prediction of cancer risks. Also, in certain occasions, for example, when estimating the levels of exposure to oral contraceptive pills, the only source of information was based on self-reported questionnaires, which may lead to biased and imprecise estimation of breast cancer risks.

Finally, it is important to note that epidemiological studies on the association between EDCs exposure and breast cancer risk are usually diverse. Thus, one could not easily apply meta-analysis as well as graphical or statistical methods to accurately assess any publication-related biases. Large-scale well-designed studies with long-term follow-up are necessary to document the clinical importance of exposure to environmental chemicals, by taking into considerations all the relevant confounders and characterization of the exposure.

Conclusion and future perspectives

In conclusion, exposure of these EDCs via food appears to be inevitable and this can indeed significantly result in long-term adverse consequences to human health and well-being, especially in pregnant women, developing fetuses and young children, who are often considered as highly susceptible populations to EDC exposures. Accumulating body of evidence from epidemiology studies has already shown that many EDCs may influence the development or progression of breast cancer. However, owing to the co-existence of multiple EDCs in the environment, more research studies are necessary in order to adequately evaluate the human risk for breast cancer upon the exposure to mixtures of EDCs in the environment.

To date, with the extraordinary advance in next-generation technologies, such as genome sequencing, proteomics or epigenomics, these can help identify the key molecular changes associated with EDC exposure which can then be developed as potential exposure biomarkers with better sensitivity and specificity. These technologies will also pave way to better assessment of past exposure and prediction of future risks, by taking into account an individual's genetic profile. However, for a biomarker to be used clinically, it needs to be validated in multiple and large population cohorts to ensure its reliability and demonstrate the ability to provide incremental prognostic information over conventional marker.

Acknowledgements

M.W. and V.C. performed the systematic review and wrote the paper. H.E. checked the extracted data and provided input and suggestions for revision.

Competing interests

The authors declare they have no actual or potential competing financial interests.

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