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Environmental causes of cancer: endocrine disruptors as carcinogens

Ana M. Soto and **Carlos Sonnenschein**
Department of Anatomy and Cellular Biology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

Abstract

Environmental endocrine disrupting chemicals (EDCs), including pesticides and industrial chemicals, have been and are released into the environment producing deleterious effects on wildlife and humans. The effects observed in animal models after exposure during organogenesis correlate positively with an increased incidence of malformations of the male genital tract and of neoplasms and with the decreased sperm quality observed in European and US populations. Exposure to EDCs generates additional effects, such as alterations in male and female reproduction and changes in neuroendocrinology, behavior, metabolism and obesity, prostate cancer and thyroid and cardiovascular endocrinology. This Review highlights the carcinogenic properties of EDCs, with a special focus on bisphenol A. However, humans and wildlife are exposed to a mixture of EDCs that act contextually. To explain this mindboggling complexity will require the design of novel experimental approaches that integrate the effects of different doses of structurally different chemicals that act at different ages on different target tissues. The key to this complex problem lies in the adoption of mathematical modeling and computer simulations afforded by system biology approaches. Regardless, the data already amassed highlight the need for a public policy to reduce exposure to EDCs.

Introduction

A plethora of synthetic chemicals have been introduced into the environment since World War II under the premise that they would improve standards of living without any negative consequences. The hormone-like effects of these environmental chemicals, including pesticides and industrial chemicals, have surfaced in wildlife and humans. The growing body of evidence on the adverse effects of these chemicals was examined at the 1991 Wingspread Conference, where the term endocrine disruption was coined. This conference aimed to evaluate the adverse effects observed in wildlife in the Great Lakes region in North America as well as in other locations in the Northern hemisphere, and was organized by Dr Theo Colborn, then at the World Wildlife Fund. The participants were experts on diverse disciplines including endocrinology, reproductive and developmental biology, toxicology, marine biology, ecology and psychiatry. Upon reviewing the published evidence, they decided to publish a consensus statement that summarized their findings and expressed their concern about the public and environmental health implications of these findings.

The conference participants proposed that the developmental alterations observed in wildlife and humans were due to exposures to multiple chemicals that disrupted the endocrine

Correspondence to: C. Sonnenschein, carlos.sonnenschein@tufts.edu.

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system of developing organisms through different modes of action. Their focus on alterations in embryonic and fetal development as a result of exposure to these hormones was motivated by the effects of fetal exposure to the synthetic estrogen diethylstilbestrol that for over two decades (1940s to the early 1970s) was prescribed to pregnant women to prevent miscarriages. Clinical use of diethylstilbestrol was restricted in the US when a report linked fetal exposure to diethylstilbestrol to the development of a rare cancer—clear-cell carcinoma of the vagina. Additionally, young women exposed to diethylstilbestrol *in utero* showed genital tract malformations similar to those found in wildlife exposed to pesticides.[1,2]

The Wingspread Conference proceedings generated a hypothesis which proposed that fetal exposure to hormonally active agents may explain epidemiological trends observed in the last half of the 20th century in European and North American populations. These epidemiological observations indicated decreased sperm quality and increased incidence of congenital malformations of the male genital tract, such as undescended testis and hypospadia, and an increased incidence of tumors—uterine leiomyoma, testicular cancer and breast cancer.[3–5] Since this conference, both laboratory research and epidemiological studies have buttressed this hypothesis and have revealed that exposure to environmental endocrine disrupting chemicals (EDCs) during development generates additional effects such as alterations in male and female reproduction, and changes in neuroendocrinology, behavior, metabolism and obesity, prostate cancer, and thyroid and cardiovascular endocrinology.[6–8]

The US Environmental Protection Agency has defined EDCs as exogenous agents that interfere with the normal function of endogenous hormones responsible for the maintenance of homeostasis and the regulation of developmental processes. These agents act by disrupting the synthesis, release, transport, metabolism, binding, action or elimination of natural hormones in the body.[9] This definition encompasses multiple modes of action. Chemicals with estrogen-mimicking activities were the first documented as causing endocrine disruption in the 1950s. Starting in the 1990s, additional mechanisms were found to be affected, which encompassed androgen antagonism and disruption of thyroid hormone transport and action, as well as activities mediated through retinoid and peroxisome proliferator-activated receptors, steroidogenic enzymes and neurotransmitter receptors.[8]

In 2009, The Endocrine Society published a Scientific Statement regarding the probable role of environmental EDCs in human pathology. In it, recommendations were made “to increase understanding the effects of EDCs, including enhancing increased basic and clinical research, invoking the precautionary principle, and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness”.[8]

This Review will preferentially focus on the carcinogenic potential of exposure to EDC in the organs of the male and female genital tract and mammary gland during organogenesis. The main EDCs reviewed are two estrogenic compounds—diethylstilbestrol and bisphenol A (BPA)—and dioxins, which are ligands of the arylhydro-carbon receptor. Diethylstilbestrol was chosen because the effects of fetal human exposure are well known, have been reproduced in rodent models and occurred long ago (1947–1971) to provide solid evidence of an increased risk of breast cancer in women. BPA was chosen because this chemical is one of the most thoroughly studied EDCs owing to its ubiquitous exposure and because its effects in rodent models are quite similar to those found after exposure to diethylstilbestrol. Dioxins were chosen because human data on carcinogenic effects exists, gathered mainly because of the Seveso industrial accident that occurred in Italy in 1976, when a massive amount of dioxins was accidentally released into the environment, and because the mechanism of action of dioxins is different from that of diethylstilbestrol and

BPA. In addition, epidemiological studies linking exposure to EDCs and cancer are briefly discussed.

Theoretical underpinnings

During the three decades following the publication of Lacassagne's observation in 1932 that the administration of estrogens to mice increased the incidence of mammary cancer, a body of evidence was collected which showed that sex hormones were involved in the development of neoplasias and their progression in hormone-target organs such as the prostate and the breast.[10–12] This knowledge was soon applied to cancer treatment. Charles Huggins received the 1966 Nobel Prize in Physiology or Medicine for his pioneering work in the hormonal treatment of prostatic cancer, and, since then, therapeutic hormone withdrawal has been effectively used to induce remissions in breast and prostate cancers.[13]

The hypothesis that prenatal exposure to EDCs might cause cancer arose when two entrenched notions began to be challenged in the 1990s. These notions were that mammalian development was merely the unfolding of a genetic program[14,15] and that only mutagenic agents (physical, chemical and biological agents that induce DNA mutations) can cause cancer.[16,17] An overview of the theoretical underpinnings that are at the core of those old entrenched notions and the novel perspectives in development and cancer are presented below.

Development: an open-ended process

Starting in the 1960s, metaphors such as that genes were in the 'driver's seat' and the introduction of the term 'developmental program' persuaded generations of researchers, teachers and students that development was the mere unfolding of a program encrypted in our genes. This view is now being contested from different perspectives. First, the sequencing of several genomes has revealed that the number of genes in a given genome does not correlate with the complexity of the corresponding organism and that these gene numbers are too low to command development from DNA to phenotype.[18] Second, no univocal correspondence occurs between a DNA 'gene', the several RNAs produced from it by splicing, and the resulting proteins.[19] This issue was referred to as the problem 'of the many and the many', and it pointed out that neither reductionism nor genetic determinism could operate without a clear one-to-one correspondence between gene and protein.[20] Third, experimental biologists who embraced a traditional view referred to as organicism criticized the claims of reductionists and genetic determinists, exposing the many inconsistencies of these stances,[21] and proposed new, dynamic and integrative approaches.[22]

A prevalent philosophical stance in biology is methodological reductionism, which predicates the study of biological systems at the lowest possible level with the objective of uncovering molecular and biochemical causes. In this view, causes act from the bottom-up. Contrary to reductionism, organicism considers both bottom-up and top-down causation. Organicism "has provided the philosophical underpinnings for embryology since the time of Kant"[21] in the 18th century; this view claims that "wholes are so related to their parts that not only does the existence of the whole depend on the orderly cooperation and interdependence of its parts, but the whole exercises a measure of determinative control over its parts."[23] Implicit in this description is the concept of emergence, the idea that at each level of biological organization new properties manifest, which could not have been predicted from the analysis of the lower levels.

One reason for the revival of the organicist view since the 1990s has been the resurfacing of ecological and evolutionary developmental biology.[24] The environment was always present in the thought of embryologists in the 19th century, because they worked with species in the

wild, and consequently observed the important role of the environment in the 'making' of the phenotype. For instance, one of those embryologists, August Weissmann, observed that the spring and summer morphs of a butterfly species could be generated just by manipulating the temperature at which the eggs were incubated. This experiment demonstrated that the same genotype generated multiple phenotypes (polyphenism).[25] In the 20th century, the adoption of animal models that reproduce all year long and thrive in laboratories effectively excluded environmental influences, because the vivariums kept animals at well-regulated light cycles and temperatures and provided a controlled diet. This change promoted a narrowly focused concentration on genetics and the exclusion of evolution and ecology from embryology, and consequently it facilitated the ascent of genetics and later of molecular genetics.

In the past few decades, environmental determination of the phenotype acquired renewed relevance when epidemiological studies revealed that undernourishment during fetal development resets the organism for survival in an environment of nutrient deprivation. Exposed to a plentiful supply of food after birth, these children revealed an increased propensity to metabolic syndrome and cardiovascular disease during their adult life.[26] This medical rediscovering of a long tradition in developmental biology acquired the fashionable moniker 'fetal origins of adult disease' and is also referred to as the Barker hypothesis.

An additional reason for adopting an organicist view is the entanglement of the various biological levels of organization. The idea that multicellular organisms are made up of cells that have relinquished their independence became pervasive following the advent of the cell theory in the middle of the 19th century. Nevertheless, in multicellular organisms, single cells are not independent of the whole organism. From the very start of embryonic life, the levels of biological organization are entangled—a zygote is both a cell and an organism. From a reductionist perspective, only bottom-up causation is accepted. Consequently, the advent of multicellularity in the embryo was explained from the perspective that cells made the organism by means of cell proliferation. From an organicist perspective, instead, the embryo is a dynamic open system and causation is bottom-up, top-down, reciprocal and multiple. The organism imposes global constraints, while at the local level biophysical and biochemical interactions among neighboring cells, tissues and extracellular matrices determine shape through differential cell movement, differential cell adhesion, asymmetrical physical forces and morphogenic gradients. This dynamic nature of the organism results in level entanglement, as exemplified by the dual nature of the zygote that is a cell and an organism.[27]

Carcinogenesis: a tissue-based process

For the past 100 years, carcinogenesis has been assumed to be a cell-based process that results from DNA mutations in a single founder cell.[28] This prevalent view is represented by the somatic mutation theory (SMT). Probably owing to the shortcomings of the SMT, and to the fact that nonmutagenic agents cause cancer, some have proposed a course correction for the SMT, namely, that epigenetic changes play a central part in carcinogenesis.[29,30] Regardless of these nuances, both the original SMT and its epigenetic variants are cell-based theories, which suggest that genetic and epigenetic changes will be translated as the loss of cell proliferation control (Table 1). These cell-based theories leave unexplained the long latency period and the regression of hormone-dependent tumors after hormone withdrawal.

Given the shortcomings of the SMT and the introduction of relevant evolutionary concepts related to cell proliferation (namely, that proliferation is the default state of all cells), an alternative theory of carcinogenesis was proposed in 1999. The tissue organization field theory views carcinogenesis at the tissue level of organization, a concept that originated with the advent of pathology as a medical discipline in the last half of the 19th century. Several

German pathologists, including Boll, Ribbert and Cohnheim, realized that neoplasias are characterized by altered tissue organization and thought of cancer development as altered embryonic development.[31,32] Morphogenetic fields are groups of cells from which specific morphological structures and organs develop through the mediation of biophysical and biochemical cues. They orchestrate organogenesis in the embryo and persist into adult life, at which point they facilitate tissue regeneration and wound healing.[16,32] In this theory, neoplasms arise when these fields are disturbed owing to alterations of cell-to-cell communication and tissue interactions mediated by biochemical and biophysical agents (Table 1).[33,34] From this perspective, carcinogens would cause neoplastic development by altering the reciprocal interactions between the cells that would become neoplastic and their microenvironment. In carcinomas, this would be the parenchyma (the distinctive cell type of an organ) and the stroma (the scaffolding to which the parenchymal cells are attached).

Mammary cancer provides an example of how the competing theories deal with a specific model of carcinogenesis. For decades, under the SMT, researchers hypothesized that the mammary cancers that develop in susceptible rat strains after exposure to chemical carcinogens were due to mutations caused by the carcinogen in the DNA of a 'founder' epithelial cell. In addition, a mutated *ras* gene was found in the majority but not all tumors, so investigators claimed that the carcinogen induced this mutation and that the tumor was caused by this mutation. This interpretation neglects to address the facts that all the cells in the animal were exposed after the carcinogen was injected and that, in addition to DNA, the carcinogen interacted with multiple macromolecules.[35]

In the past decade, tissue recombination experiments were conducted in rodent models to assess which tissue was the target of the carcinogen in the mammary gland. The stroma and epithelium of their mammary glands were separately exposed to carcinogen and to vehicle only (controls) and recombined once the carcinogen was eliminated. Neoplasms developed only when the stroma was exposed to the carcinogen and recombined with unexposed epithelial cells.[36] Carcinogen-exposed epithelial cells failed to produce neoplasms when recombined with unexposed stroma, which suggested that the stroma was the target of the carcinogenic insult. Comparable results were observed by exposing the stroma to radiation.[37] Moreover, the neoplastic phenotype of epithelial cells was reversed when they were placed into a normal (unexposed) stroma in a living animal host.[38] This normalization phenomenon is not exclusive of breast cancer; it was reported multiple times using different neoplasms in various animal models.[39,40] The first publication on this phenomenon dates from 1975 and reported the normalization of teratocarcinoma cells injected into normal blastocysts. These embryos generated normal mice in which the descendants of the teratocarcinoma cell were an integral part of many tissues.[41] Rat liver carcinoma cells grew as tumors when injected subcutaneously, but when injected into the liver they were incorporated into the normal architecture of the organ.[40] In addition, human metastatic melanoma cells acquired a normal phenotype when injected into early zebrafish embryos, but they formed tumors when injected after organogenesis was completed.[39] These results also point to the contextuality of the neoplastic phenotype and the centrality of tissue-interactions in carcinogenesis and its reversal.

EDCs and windows of exposure

A main concern of the 1991 Wingspread Conference was the sensitivity of the developing organism to inappropriate hormone exposure. While hormone effects are, for the most part, activational and reversible in adults, extemporaneous exposure to hormones during organogenesis is mainly organizational. This means that the structure and function of target organs is affected in an irreversible manner.

In rodents, the relative position of a fetus with respect to its male and female siblings influences the adult behavior of the animal[42] and causes morphological differences in the structure of the mammary gland.[43] These intrauterine positioning effects are a result of the small differences in sex hormone levels between fetuses of the same sex placed between female or male siblings.[44] These experiments demonstrate that normal fluctuations in hormonal levels cause morphological and functional variations, and illustrate the sensitivity of the developing organism to hormones. Similarly, effects observed after fetal exposure to EDCs occur at doses significantly lower than those needed to produce an effect later in life. For example, the dose of BPA needed to induce a proliferative effect in the uterus of prepubescent mice is five orders of magnitude higher than the dose needed to produce noticeable changes in the structure of the uterus when administered during organogenesis.[45,46]

EDCs and neoplasia in females

Diethylstilbestrol is considered an EDC because it was released into the environment whilst being used to accelerate weight gain in cattle and poultry. However, its notoriety is due to its unintended deleterious effect on fetal development after being prescribed to pregnant women from the 1940s to the early 1970s to prevent miscarriages. Clear-cell carcinoma of the vagina was reported in young women who had been exposed to diethylstilbestrol *in utero* before the 13th week of gestation.[47]

Adenosis—defined as the presence of islands of glandular tissue in the vagina reminiscent of the glandular tissue in the uterus—has frequently been observed in women exposed *in utero* to diethylstilbestrol. Experiments in mice revealed that prenatal and neonatal diethylstilbestrol blocked stromal induction of stratification of the vaginal epithelium, and resulted in the development of simple columnar epithelium, which is normally present in the uterus.[48] Most of the vaginal epithelium, however, becomes stratified upon discontinuation of diethylstilbestrol exposure, but islands of noninduced epithelium end up developing glands similar to those found in the endometrium which persist throughout adult life. These ectopic glands are believed to be the tissue where clear-cell carcinoma of the vagina originates.[48] This finding is yet another example of how altered tissue interactions lead to carcinogenesis.

Female rodents exposed during fetal life and neonatally to diethylstilbestrol develop uterine benign neoplasms (leiomyomas) when they reach adulthood.[49,50] Remarkably, perinatal diethylstilbestrol exposure results in altered arrangement of the myometrium, a phenomenon involving Wnt-7a expression in the epithelium and thought to be mediated through mesenchymal–epithelial interactions. These alterations manifest as a thickening and disorganization of the myometrium that provides the substratum for neoplastic organization.[51] Furthermore, epidemiological studies have revealed that women exposed to diethylstilbestrol during fetal life have a significantly increased incidence of this neoplasm.[52] In addition, fetal exposure of rodents to diethylstilbestrol increases their susceptibility to the development of mammary cancer in adulthood.[53,54] Similarly, fetal exposure to diethylstilbestrol has been linked to a significantly increased incidence of breast cancer when women exposed to diethylstilbestrol *in utero* reach the age when breast cancer prevalence is highest.[55] Deleterious effects are not exclusively linked to high estrogen level exposure; epidemiological data support the hypothesis that even small increases in estrogen levels during fetal development may increase the risk of developing breast and prostate cancer.[56–58]

Tamoxifen, a pharmacological agent used in the treatment of breast cancer, is a partial estrogen agonist and antagonist. *In utero* exposure to tamoxifen also increased the incidence

of mammary tumors in rodents when the exposed offspring were challenged with dimethylbenzantracene (a laboratory carcinogen) at puberty.[59]

Bisphenol A—a ubiquitous EDC

The xenoestrogen BPA is one of the EDCs that has been most thoroughly studied. BPA is found in various consumer products including baby bottles, reusable water bottles and reusable food containers, polyvinyl chloride stretch films, papers, cardboards and in the epoxy resins lining the insides of food cans. BPA has been detected in the urine of 92% of a US reference population.[60] Exposure to BPA in the human fetus occurs through maternal exposure, and in the neonate through ingestion of maternal milk, tinned food and infant formula.[61–63]

Rats exposed prenatally to environmentally relevant doses of BPA show an increased number of intraductal hyperplasias (precancerous lesions) that appear during adulthood,[64,65] while high doses induce the development of carcinomas *in situ*.[64,65] Animals exposed during fetal life to BPA develop palpable tumors during early adulthood when treated at 50 days of age with nitrosomethyurea, a chemical carcinogen.[64] Exposure to BPA during nursing followed by exposure at 50 days of age to dimethylbenzantracene resulted in an increased number of tumors per rat and a decreased latency period compared with animals not exposed to BPA during nursing.[66] Regardless of the rat strain, exposure routes and levels, and timings of exposure to BPA, all studies show an increased susceptibility to mammary gland neoplasia that manifests during adulthood.

What are the developmental anomalies that increase the susceptibility to mammary gland neoplasia? Exposure of mouse dams to environmentally relevant levels of BPA during organogenesis results in considerable alterations in the mammary gland. At embryonic day 18, BPA accelerates maturation of the fat pads and increases the density of collagen fibers directly abutting the epithelium. Within the epithelium, BPA exposure leads to a decreased cell size, delayed lumen formation, increased ductal area and ductal extension. At this stage of development, the estrogen receptors are present only in the mesenchyme, and mammary gland development is dependent on reciprocal interactions between the mesenchyme and the epithelium; therefore, the advanced maturation of the adipose tissue pad and changes in the extracellular matrix may be responsible for the effects observed in the epithelium.[43] At puberty, an increased sensitivity to estradiol was observed in the mammary glands of animals exposed fetally to BPA, which led to the induction of progesterone receptors in epithelial cells and to increased duct lateral branching.[67] Moreover, starting at 3 months of age, intraductal hyperplasias—which are considered preneoplastic lesions—were observed in BPA-exposed animals.[68] Thus, perinatal exposure to low doses of BPA results in altered mammary gland morphogenesis, induction of precancerous lesions, and carcinoma *in situ.*

Of note, neoplasias that result from exposures to BPA and diethylstilbestrol during embryogenesis and organogenesis usually appear after sexual maturity is complete. Investigators have hypothesized that this phenomenon is due to the effects of sex hormones on the proliferation and remodeling of these organs.[69] Additionally, over-expression of estrogen receptor-α and progesterone receptor was observed in the endometrial epithelium and lamina propria of adult mice that were exposed to BPA *in utero*;[46] thus, estrogen receptor overexpression may explain enhanced sensitivity to estrogens.[67,70]

Dioxins

Dioxins are byproducts of combustion and of multiple industrial processes; they have been identified as a class 1 carcinogen by the International Agency for Research on Cancer[71] and have also been identified as reproductive and endocrine toxicants.[72] They bind to the aryl

hydrocarbon receptor. TCDD, 2,3,7,8-tetrachlorodibenzodioxin, is the most potent dioxin of the series. In cell culture studies, TCDD, by binding to the aryl hydrocarbon receptor, interacts with estrogen receptors, and thus behaves either as an estrogen agonist or antagonist. Furthermore, in mice, TCDD blocks estrogen-induced responses in several tissues.[73] TCDD exposure during organogenesis alters mammary gland morphogenesis as evaluated by the persistence of terminal end buds in exposed rats.[74] These transient structures are considered the loci where cancer arises. Exposure of these rats to the carcinogen dimethylbenzantracene at puberty increases their tumor incidence and shortens the latency period as compared to animals not exposed to TCDD.[75]

Exposures during puberty and adulthood

Most epidemiological studies have explored the link between a single chemical exposure and breast cancer by measuring exposure at the time of diagnosis. These studies have generated inconsistent results. By contrast, when exposure was measured several years before cancer diagnosis, a positive link between breast cancer and exposure to the estrogenic pesticides toxaphene[76] and dichlorodiphenyltrichloroethane (DDT)[77] became evident. DDT exposure was found to be associated with an increased risk of breast cancer, particularly in women in the US who were aged ≤14 years in 1945—the year when DDT use became widespread in the US. However, individuals are exposed to a mixture of hormonally active chemicals and their exposure profile is also affected by diet and migration history. A single chemical can, therefore, hardly be considered as a marker of total exposure. Of relevance, a case–control study has reported a positive correlation between total xenoestrogen exposure and breast cancer.[78]

How does xenoestrogen exposure during the period of sexual maturity result in mammary gland carcinogenesis? One possibility is that xenoestrogens may lengthen the period of ductal growth and acinar development during each menstrual cycle. Xenoestrogens would act additively with ovarian estrogens and, therefore, advance the period of ductal growth by a few days.[8] An explanation consistent with the SMT would be that a small and sustained increase of estrogenic activity at the beginning of the cycle, when the ovarian output of estrogen is low, could be sufficient to promote carcinogenesis by increasing the number of cells that undergo proliferation in each menstrual cycle. An explanation consistent with the tissue organization field theory, however, would be that estrogens acting as morphogens enhance tissue remodeling through stroma–epithelium interactions, thus increasing the probability of abnormal tissue organization.[8]

EDCS and neoplasia in males

Testicular dysgenesis syndrome

Skakkebaek *et al.*[79] have suggested that the association of diminished semen quality, male genital tract malformations, and testicular germ line cancer share a common cause. They hypothesized that fetal exposure to EDCs may have lead to this triad through a mechanism involving altered Leydig and Sertoli cell function and impaired germ cell development. Unlike the effects described above in females, no animal model has been found, so far, in which the testicular cancer component of the triad can be tested directly. However, epidemiological studies have shown a strong correlation between anomalies of the male genital tract and residence in agricultural areas. In regard to testicular cancer, a small study has found that blood organochlorine levels in mothers, measured decades after they gave birth to sons, correlated with the sons' increased risk of testicular germ cell cancer.[80]

Prostate development and cancer

Similar to the mammary gland, the fetal development of the prostate is affected by exposure to estrogens and TCDD.[81,82] Fetal exposure to xenoestrogens, such as BPA, increase the adult prostate size. That androgens play a major part in the development of prostate cancer has been inferred from the fact that men castrated at an early age do not develop prostate cancer, and regression of prostate cancer is observed upon androgen withdrawal.[10] Animal experiments have confirmed this concept, and also revealed that estrogens have a significant role in the induction of prostate cancer.[83] The developing prostate has been shown to be sensitive to minute doses of estrogens, which suggests that altered morphogenesis may predispose the prostate to neoplastic development.[84,85] Neonatal exposure to estradiol and diethylstilbestrol in rodent models increases the incidence of prostate intraepithelial hyperplasias (PIN), which are considered preneoplastic lesions. Exposure to environmentally relevant doses of BPA did not result in the induction of PIN, but increased the sensitivity of the gland to develop PIN following a second hit of hormonal exposure during adulthood.[29]

Conclusions

The endocrine disruptor hypothesis was postulated in the early 1990s when the only evidence for developmental carcinogenicity of estrogens in humans was the very rare clear-cell carcinoma of the vagina. In the past decade, an increased incidence of breast cancer among women exposed *in utero* to diethylstilbestrol has been reported, an effect comparable to that observed three decades ago when rats were exposed to diethylstilbestrol. Since then, animal studies have repeatedly shown that fetal and neonatal exposure to EDCs, including BPA, result in an increased susceptibility to mammary and prostate neoplasms. The close parallelism between the effects of diethylstilbestrol and BPA in rodents, and between the effects reported in women exposed *in utero* to diethylstilbestrol with those observed in rodents strongly suggests that exposure to these chemicals throughout life, particularly during early developmental stages, may be the cause of the increased incidence of these cancers reported in the industrialized world. Additionally, EDCs induce other deleterious effects that are cause for concern, such as obesity, altered behaviors and infertility.[86]

The consequences of exposure to a single EDC are dependent on the sex and gonadal status of the individual, the dose level and the time and length of exposure. For example, some xenoestrogens, such as BPA and diethylstilbestrol, increase[87–89] or decrease[88,90] body weight or lead to increased insulin secretion followed by development of insulin insensitivity.[91] Overlapping mechanisms of action among EDCs contribute to the similarity of their effects.[92] In addition to their better-known endocrine effect, certain EDCs act through additional mechanisms. For example, BPA also interferes with thyroid hormone signaling.[93]

Humans and wildlife are exposed to a mixture of EDCs. To explain this mindboggling complexity will require the design of novel experimental approaches that integrate the effects of different doses of widely structurally different chemicals acting at different ages on different target tissues having different susceptibilities to those diverse EDCs. Mathematical modeling tools and computer simulations afforded by system biology approaches[94] may help in the understanding of this complex problem. At the beginning of this Review, we addressed the epistemological problems inherent to reductionist thinking, which strives to achieve a representation of reality free of complexity. From the perspective of organicism, the complexity inherent to the subject of this Review should instead be acknowledged and dealt with. We hope that the present analysis will persuade researchers to heed Whitehead's advice to seek simplicity and distrust it.[21]

In terms of medical practice and public health, the proposition by The Endocrine Society to adopt the pre-cautionary principle when dealing with EDCs is meritorious and timely. Studying the details of the complex interactions outlined above is an intellectually rewarding proposition, but not a necessary condition for action. On the contrary, abundant scientific evidence of the harmful effects by EDCs has accumulated to support a swift change in public health and environmental policies aimed at protecting the public in general, and, in particular, the developing fetus and women of reproductive age.

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Key points

- The embryo is an open system and the environment is a co-determinant of phenotypes, such that the embryo 'reads' environmental cues as a forecast of the postnatal environment
- Hormones act as morphogens: extemporaneous exposure to even low doses of hormonally active chemicals increases the susceptibility to various diseases, including cancer
- Neoplasia is a tissue-based disease caused by various deleterious exposures that interfere with the reciprocal communication between cells and between cells and their surrounding extracellular matrix
- The effects of developmental exposure to diethylstilbestrol observed in humans have been reproduced in rodent models; thus, rodents are relevant models for assessing the human toxicity of environmental endocrine disruptors
- Endocrine disrupting chemicals act additively—their multiple and complex effects are dose-dependent and contextual; therefore, a systems biology approach should be adopted to tackle this complexity
- Sufficient supporting data have been gathered on the deleterious effects of endocrine disrupting chemicals to warrant immediate action to decrease human and wildlife exposure to these agents

Review criteria

This Review is based on a search in PubMed for full-length articles published up to April 2010. The authors used the search terms “endocrine disruptors and cancer”, “endocrine disruptors and neoplasia”, “BPA and cancer”, “DES and cancer”, “dioxins and cancer”. Additionally, the author’s perspective on the subject of endocrine disruption in general and in relation to carcinogenesis was enriched through participation in several groups and committees that evaluated these issues, particularly among them the Wingspread Conference, the National Research Council Committee on Hormonally Active Chemicals, The Chapel Hill Conference on BPA and the committee charged with writing The Endocrine Society Statement.

Table 1

Differences between the SMT and the tissue organization field theory

Aspects of the theories	The SMT	The tissue organization field theory
Premises	The default state of metazoan cells is quiescence The target of carcinogens is an epithelial cell	The default state of all cells is proliferation (consistent with evolutionary theory) The target of carcinogens are tissues
Definition	Cancer is a disease of the control of cell proliferation	Cancer is a disease of tissue organization (organogenesis gone awry)
Corollaries	Cancer cells proliferate autonomously from organismal control Cancer is irreversible	Cancer is not independent from organismal control Cancer is reversible

Abbreviation: SMT, somatic mutation theory.