AOP ID and Title:

SNAPSHOT

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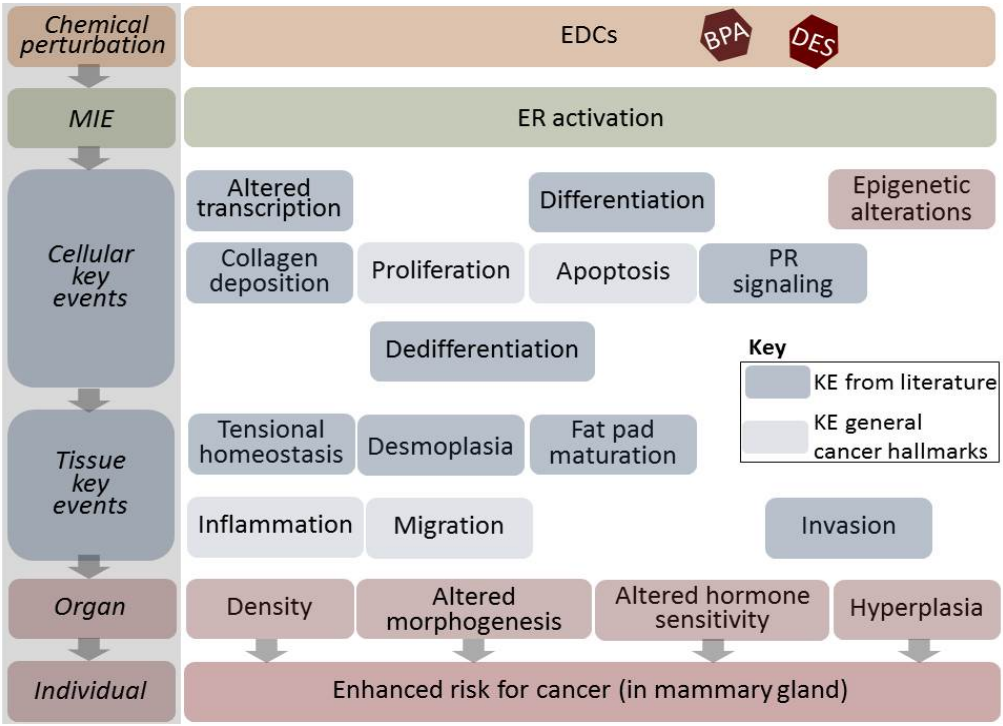
AOP 295: Early-life stromal estrogen receptor activation by endocrine disrupting chemicals in the mammary gland leading to enhanced cancer risk

Short Title: Early-life stromal ER-activation by EDCs leads to mammary cancer risk

Graphical Representation



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Status

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Under development: Not open for comment. Do not cite	Under Development	1.79	Included in OECD Work Plan

Abstract

This adverse outcome pathway (AOP) links gestational EDC exposure to enhanced breast cancer risk. The molecular initiating event (MIE) is gestational estrogen receptor (ER) activation; particularly, stromal activation at in utero time of exposure. The ER is a master transcriptional regulator, with proliferation as its primary effect, and is the main mediator of breast development [24, 25]. Human-relevant EDC exposure triggers transcriptional activity that promotes altered signaling between the epithelial and stromal tissue compartments leading to disrupted tensional homeostasis [26] and tissue architecture. Inflammation and altered cellular differentiation are major cell- and tissue-level key events (KEs) mediating these disruptions. The pathway converges on the following mammary gland adverse outcomes (AOs) at the tissue- and organ-levels: altered density, structure and hormone sensitivity along with hyperplasia. Epigenetic alterations are a cellular-level AO that propagate gestational EDC exposure to later-life risk through cellular memory that directs ER-mediated gene expression and altered mammary development. Risk of tumorigenesis follows from these AOs.

The industrial estrogen, bisphenol A (BPA) is one of the most data-rich chemicals related to breast cancer and altered mammary gland development [11]. As such, studies in model rodent strains following gestational EDC exposure to bisphenol A (BPA) or DES provide experimental support for this AOP and human-relevance. A thorough search of the literature yielded experimental evidence for this AOP as directed by a mix of natural and MeSH term search logic specifying rodents and non-human primates (population); human-relevant, in utero exposure to BPA or DES (exposure); and mammary gland AOs (outcome) [27-32] (see PECO statement, Table 1 below). Most studies investigating EDC-effects on mammary development heavily describe altered growth and structure, resulting in limited mechanistic understanding. This AOP integrates knowledge and tools from investigations of established breast cancer risk factors such as density and obesity to enhance understanding of the molecular- and cellular-driven etiologies of altered mammary structure and growth. Integrating this knowledge promotes the development of in vitro assays capable of predicting high-risk phenotypes and offers efficient alternatives to in vivo mammary gland evaluation. Ultimately, making these links in the knowledge base will improve screening to identify chemicals that act on gestational development and will more specifically target chemical contributions to later-life breast cancer risk in toxicity testing. Productive intermediate testing endpoints would follow ER-binding, -activation and steroidogenesis (OECD TG-455; EDSP TG-890[33, 34]), precede carcinogenicity (OECD TG-451, and -453) and connect these with EDC-effects on breast cancer due to prenatal exposure (OECD TG-414, -415, -416, -422, -443). This AOP will also describe 'missed opportunities' in the existing evidence; not reporting or measuring traditional toxicity testing endpoints, like uterine weight and body weight alongside more sensitive mammary gland growth and structural changes. Failure to do this in parallel within the same study undermines the sensitivity of these endpoints to predict later-life breast cancer risk.

Table 1. PECO statement [27, 28]. A statement of the Population, Exposure, Comparators and Outcomes was prepared to direct objective experimental study collection for this AOP synthesis on breast cancer risk from early-life EDC exposure. The Organization for Economic Co-operation and Development does not cite systematic review methods or objective identification of included evidence in its guidance for AOP development. A narrowed survey of review articles in PubMed, published after 2006 and until November 2018, was performed to assess the state of mechanistic evidence connecting EDC exposure to breast cancer risk and altered mammary gland growth and structure. This step assisted problem formulation by situating human-relevant EDC exposures in the hallmarks of cancer via 'important reviews.' There were no systematic reviews. This initial survey of the review literature assisted search logic development and supported an initial sketch of the AOP.

INCLUSION CRITERIA	**EXCLUSION CRITERIA**
Population (Experimental animal, *in vivo* studies) • Female laboratory rodents • Female laboratory non-human primates	• Human and non-rodent animals and organisms, including wildlife, aquatic species and plants • Males
Exposure • Human-relevant exposure to BPA, related BPA analogues or DES • *In utero* exposure. *In utero* exposure is a requirement but studies that extend exposure to the perinatal period are also included • Exposure to controlled doses of BPA via an exposure method (e.g. – diet, drinking water, gavage, injection)	• High-dose or pharmacological-dose exposures to BPA or DES • Any other EDC • Exposure to chemical mixtures in animals • Exposures during other developmental windows of risk
Comparators • Vehicle-only, concurrently run treatment controls	• No controls • Historical controls
Outcomes • Determination of mammary gland disruption via any methodology intended to address mechanisms mapped in the AOP (see Figure) including to alterations of tissue density, epigenetics, gland morphology, hormone sensitivity and hyperplasia as precursors to tumorigenesis • Assessed in virgin, female laboratory rodents or non-human primates at any stage-of-life (e.g. - postnatal, pubertal or adult development) • Uterine weight • Body weight	• Any other organs • Any other stage-of-life

Publication parameters • Peer-reviewed • Original data • Studies must be published in English	• Non-peer reviewed; gray literature (e.g. - conference presentations or other studies published in abstract form only, grant awards/ proposals and theses/ dissertations • Retracted articles • Review articles (only considered for the initial survey of available mechanistic data)

Background

Breast cancer risk background: Breast cancer is a significant health concern as the second leading cause of death in women [1]. Only 5-10% of breast cancers are attributable to genetic predisposition and substantial evidence indicates many lifestyle and environmental factors contribute to lifetime risk [2-5]. Early-life developmental disruption by hormone-like, or endocrine disrupting chemicals (EDCs), heightens age-related breast cancer risk. A human model of this disruption emerges from the treatment of pregnant women with synthetic estrogen, diethylstilbestrol (DES), beginning in the 1940's with the intent to prevent miscarriages. This practice ceased when women exposed in gestation – "DES Daughters" – had a 40x increased incidence of cervical and vaginal cancers [6, 7], highlighting in utero development as a critical window of exposure. The later finding that "DES Daughters" also had a 2-fold increased incidence of breast cancer only detected in women ≥30 years post-exposure, underscores the latency of this disruption in causing disease [7-9]. Studies of the reproductive tract and mammary gland of rodent models have recapitulated these increased risks [10-12]. While synthetic estrogens are no longer prescribed to pregnant women, human biomonitoring data show widespread exposure to EDCs that include weak estrogens [13, 14] and their ability to cross the placental barrier [14-18]. Many EDCs are present at human-relevant exposures in the environment, but these chemicals can act together on the same adverse health outcomes [19], including estrogen action as a relevant target for breast cancer [20-23]. Taken together, this evidence raises concerns that early-life EDC exposure enhances later-life breast cancer risk.

Summary of the AOP

Events

There are no Events associated with this AOP

Key Event Relationships

There are no Relationships associated with this AOP

Overall Assessment of the AOP

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Appendix 1

Appendix 2

List of Key Event Relationships in the AOP

There are no Relationships associated with this AOP