Environmental Research 160 (2018) 152–182

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms☆

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ARTICLE INFO

Keywords:
Endocrine disruptors
Toxicology
Breast development
Mammary carcinogens
Prevention

ABSTRACT

Background: Many common environmental chemicals are mammary gland carcinogens in animal studies, activate relevant hormonal pathways, or enhance mammary gland susceptibility to carcinogenesis. Breast cancer's long latency and multifactorial etiology make evaluation of these chemicals in humans challenging.

Objective: For chemicals previously identified as mammary gland toxicants, we evaluated epidemiologic studies published since our 2007 review. We assessed whether study designs captured relevant exposures and disease features suggested by toxicological and biological evidence of genotoxicity, endocrine disruption, tumor promotion, or disruption of mammary gland development.

Methods: We systematically searched the PubMed database for articles with breast cancer outcomes published in 2006–2016 using terms for 134 environmental chemicals, sources, or biomarkers of exposure. We critically reviewed the articles.

Results: We identified 158 articles. Consistent with experimental evidence, a few key studies suggested higher risk for exposures during breast development to dichlorodiphenyltrichloroethane (DDT), dioxins, perfluorooctanesulfonamide (PFOSA), and air pollution (risk estimates ranged from 2.14 to 5.0), and for occupational exposure to solvents and other mammary carcinogens, such as gasoline components (risk estimates ranged from 1.42 to 3.31). Notably, one 50-year cohort study captured exposure to DDT during several critical windows for breast development (in utero, adolescence, pregnancy) and when this chemical was still in use. Most other studies did not assess exposure during a biologically relevant window or specify the timing of exposure. Few studies considered genetic variation, but the Long Island Breast Cancer Study Project reported higher breast cancer risk for polycyclic aromatic hydrocarbons (PAHs) in women with certain genetic variations, especially in DNA repair genes.

Conclusions: New studies that targeted toxicologically relevant chemicals and captured biological hypotheses about genetic variants or windows of breast susceptibility added to evidence of links between environmental chemicals and breast cancer. However, many biologically relevant chemicals, including current-use consumer product chemicals, have not been adequately studied in humans. Studies are challenged to reconstruct exposures that occurred decades before diagnosis or access biological samples stored that long. Other problems include measuring rapidly metabolized chemicals and evaluating exposure to mixtures.

Abbreviations: 4-ABP, 4-aminobiphenyl; CI, confidence interval; CrI, credible interval; AA-Hb, acrylamide-hemoglobin; AcE, acetylcholinesterase; AhR, aryl hydrocarbon receptor; APFO, ammonium perfluorooctanoate; AR, androgen receptor; BBMP, 2,2-bis(bromomethyl)-1,3-propanediol; BER, base excision repair; BPA, bisphenol A; COMT, catechol-O-methyltransferase; CYP, cytochrome p450; CYPs, cytochrome p450 enzymes; DCE, 1,2 dichloroethylene; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEHP, bis(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DES, diethylstilbestrol; DnBP, di-n-butyl phthalate; EDCs, endocrine disrupting chemicals; ELISA, enzyme-linked immunosorbent assay; EPA, Environmental Protection Agency; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; ER+/-, estrogen receptor positive/negative; EtO, ethylene oxide; ETS, environmental tobacco smoke; GST, glutathione s-transferase; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HER1, human epidermal growth factor receptor 1; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+/-, hormone receptor positive/negative; HRT, hormone replacement therapy; IARC, International Agency for Research on Cancer; IBCERCC, Interagency Breast Cancer and Environment Research Coordinating Committee; ICC, intraclass correlation coefficient; IOM, Institute of Medicine; MeSH, Medical Subject Headings; NATA, National Air Toxics Assessment; NER, nucleotide excision repair; NIEHS, National Institute of Environmental Health Sciences; NTP, National Toxicology Program; OCPs, organochlorine pesticides; OP, organophosphate; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons; PBB, polybrominated biphenyl; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCE, tetrachloroethylene; PFASs, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFOSA, perfluorooctane-sulfonamide; PM, particulate matter; PPAR, peroxisome proliferator-activated receptor; PPD, p-Phenylenediamine; SIR, standardized incidence ratio; TCDD, 2,3,7,8-Tetrachlorodibenzo-para-dioxin; TCE, trichloroethylene; TDBPP, tris(2,3-dibromopropyl) phosphate; TEB, terminal end bud; TEXB, total xenoestrogen burden; VOCs, volatile organic compounds

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http://dx.doi.org/10.1016/j.envres.2017.08.045
Received 28 April 2017; Received in revised form 28 August 2017; Accepted 29 August 2017

1. Introduction

Breast cancer is the most common cancer in women worldwide. The U.S. incidence rate is stable but among the world's highest, and incidence is increasing globally (Forouzanfar et al., 2011). The National Cancer Institute estimates that the cost of breast cancer care will reach $20.5 billion in the U.S. in 2020 (Mariotto et al., 2011).

High penetrance inherited genes contribute to 5–10% of breast cancers (Campeau et al., 2008; Martin and Weber, 2000), leaving a substantial portion of overall cases with potential for prevention. Modifiable risk factors include pharmaceutical hormones, lack of exercise, alcohol consumption, weight gain after menopause, nulliparity, late childbearing, and not lactating (Adami et al., 2008). In addition, mechanistic and rodent studies as well as epidemiology suggest that environmental chemicals likely play a role, and chemical links to breast cancer have been identified as a research priority (IBCERCC, 2013; IOM, 2012).

We previously reviewed literature on environmental pollutants and breast cancer in 2007 (Brody et al., 2007) and found the evidence generally supported positive associations with PAHs and polychlorinated biphenyls (PCBs) in combination with certain genetic polymorphisms, and for solvents and dioxins. Methodological problems included lack of highly exposed and unexposed populations for comparisons, inadequate exposure assessment, and study designs that did not capture exposure at the biologically relevant time, so that null results were uninformative. To update our assessment, in this paper we paired a summary of biological evidence with a review of epidemiological studies from the past 10 years. Our goal is to distill results from studies that use the strongest methods to evaluate hypotheses that accord with biological evidence. A limitation of this review is that we did not include several active areas of study relevant to breast cancer prevention: light at night (Gu et al., 2015; Hill et al., 2015; IARC 2010d; Li et al., 2015; Sturgeon et al., 2014; Travis et al., 2016), non-ionizing radiation (NTP, 2016a; West et al., 2013), or metals (Byrne et al., 2013; NIEHS BCERP), because these topics are outside of our mechanistic area of expertise.

1.1. Known risk factors as models for environmental chemicals and breast cancer

Both laboratory and human evidence support a role for chemicals acting by (1) genotoxic action, (2) alteration of mammary gland development or hormone responsiveness, and (3) hormonal tumor promotion. These pathways, described briefly here, provide a helpful framework for considering epidemiological studies of chemically-induced breast cancer. Additional biological evidence for specific chemicals is incorporated in each section of this review.

Genotoxic agents damage genetic material in a cell, which may lead to cancer-causing mutations (Lee et al., 2013). The progression from damaged DNA to cancer includes other processes, such as genomic instability, inflammation, and immune suppression (Hanahan and Weinberg, 2011). Ionizing radiation, which increases breast cancer risk in both males and females (Land et al., 2003; Little and McElvenny, 2016), is a model for the genotoxic action expected from classical carcinogens. Exposure to ionizing radiation most strongly increases breast cancer risk when it occurs in early life (e.g., before age 20 for atomic bomb survivors (Land et al., 2003) and medical radiation (Henderson et al., 2010)). Mammary cells are thought to be most susceptible to damage from carcinogens during adolescence and before pregnancy, when the cells are rapidly proliferating and not yet fully differentiated (Russo and Russo, 2004).

Second, exposure to endocrine disrupting chemicals (EDCs) in early life may alter breast development and increase adult susceptibility to breast cancer. For example, the synthetic estrogen diethylstilbestrol (DES) causes alterations in mammary gland structure and gene expression in rodents and was associated with breast cancer after age 40 in a U.S. cohort of women who were exposed in utero (Hoover et al., 2011). Animal studies have found that perinatal exposure to DES can increase terminal end bud (TEB) and ductal formation during puberty (Fielden et al., 2002; Hovey et al., 2005; Rudel et al., 2011a), suggesting a mechanism for increased breast cancer risk. Prenatal exposure to hormones and some chemicals that alter mammary development also increase mammary tumors when animals are challenged with a carcinogen during puberty (reviewed in Rudel et al., 2011a). The prenatal period, puberty, and pregnancy, when cells proliferate and differentiate, are critical windows for exposures that alter mammary gland development, as reviewed in Rudel et al. (2011a) and Russo and Russo (2004), although the relationship between mammary morphological changes and breast cancer risk is not well understood (Rudel et al., 2011a).

Third, some EDCs may act closer to the time of diagnosis by promoting tumor growth through estrogen- or progesterone-mediated pathways or other hormonal responses (Lee et al., 2014; Rudel et al., 2014). Increased breast cancer in women taking hormone replacement therapy (HRT) is a model for this pathway. The increase in risk persists for five years after stopping therapy and then diminishes (Roth et al., 2014). Higher levels of estradiol are also a risk factor for postmenopausal breast cancer via a genomic response that increases cell proliferation or inhibits apoptosis, leading to tumor growth (Yager and Davidson, 2006). Further, chemicals that activate enzymes involved in estradiol metabolism or synthesis, such as cytochrome p450 enzymes (CYPs), may contribute to breast cancer through downstream effects on endogenous estrogen, and progesterone is also important in controlling cell proliferation in the adult breast (Brisken et al., 2015).

An additional consideration for biological hypotheses is that breast cancer is a heterogeneous disease. While the link between tumor subtype (e.g. hormone receptor (HR) positive vs negative) and prognosis/responsiveness to treatment is well-established, differences in etiologic pathways underlying tumor subtypes and disease types (e.g. pre- vs postmenopausal) are not well understood.

Further, our review includes breast cancer incidence, mortality, and survival as outcomes. The mechanistic pathways outlined above are relevant to consider for incidence, the outcome of interest in the majority of the studies we reviewed. From a biological perspective, breast cancer mortality and survival are related to tumor aggressiveness and treatability. Because HR positive tumors have better survival due to hormone-targeted treatment, hormone-dependent tumor promotion may also be a relevant pathway for survival. However, the current lack of understanding of the etiological factors that lead to aggressive tumors, including HR negative tumors, limits hypotheses about relevant mechanisms for survival and mortality.

2. Methods

2.1. Study identification and selection

We searched PubMed for peer-reviewed articles published in English from June 2006 through June 2016 that reported on human studies of breast cancer and environmental pollutants. Searches included "breast cancer" in combination with terms for specific chemicals (excluding pharmaceuticals), chemical groups, and product classes, from the following sources: (1) terms used in Brody et al. (2007), (2) three chemicals identified as mammary carcinogens by the National Toxicology Program (NTP) since 2007, (3) chemicals classified as potential mammary carcinogens with substantial population exposure by Rudel et al. (2014), (4) chemicals identified as mammary gland developmental disruptors by Rudel et al. (2011a), (5) "xenoestrogen burden," and (6) terms for consumer products (consumer products, flame retardant, hair dye, personal care products). We truncated certain terms (occupation, air pollution) to make the search more flexible; added MeSH terms (such as "hazardous waste") from relevant articles; and employed an "etiology filter" (Harvey Cushing/John Jay Whitney