

Present an update on the connection between breast cancer and the environment Executive Summary. Full paper published in Environmental Health September 2017 Janet Gray Ph.D Sharima Rasanayagam Ph.D Connie Engel Ph.D and Jeanne Rizzo RN

State of the Evidence 2017



The Connection Between Breast Cancer and The Environment

Background

On September 2, 2017, this report was published in the scientific journal Environmental Health. You can access the full paper here: https://ehjournal.biomedcentral.com/articles/10.1186/s12940-017-0287-4. In this review, Dr. Janet Gray (Professor Emerita, Vassar College) worked with colleagues from Breast Cancer Prevention Partners to examine the compelling data linking various chemicals and radiation in our environment to the current high incidence of breast cancer.

The review describes our methodology for the literature review, outlines critical concepts that frame the data and then divides the evidence into 7 major areas of exposures linked to breast cancer. This document is a summary of the findings of the review. Full results and citations can be found in the original paper.

Introduction

Since 2002, Breast Cancer Prevention Partners (BCPP, formerly the Breast Cancer Fund) has published nine editions of "State of the Evidence" linking toxic chemicals and radiation with breast cancer incidence. BCPP's comprehensive website www.bcpp.org translates and presents this evidence for everyone.

The scientific journal International Journal of Environmental and Occupational Health (IJOEH) published our comprehensive review of the relevant literature in 2009. Hundreds of new papers published in the 8 years since support the connection between environmental exposures and breast cancer, and the evidence on this topic is even more extensive and of higher quality than that previously available. The evidence cited in the new 2017 review reinforces the conclusion that exposures to a wide variety of toxicants—many of which are found in common, everyday products and byproducts—can lead to increased risk for the development of breast cancer. It makes the case for everything we do at BCPP.

Overarching concepts

The report begins by outlining basic statistics and a brief exploration of the subtypes of breast cancer–recognizing that 'breast cancer' is not a single disease but rather a collection of several genetically, structurally and hormonally distinct diseases. It then introduces the key framing concepts necessary for appreciating the complex evidence linking specific environmental toxicants to an increased risk for developing breast cancer. These framing concepts include: (a) low-dose and non-monotonic responses (where, with hormone disrupting exposures, lower doses may have different or more profound effects than higher doses); (b) the reality that we are not exposed to one environmental toxicant at a time but rather to mixtures of agents which may interact in unanticipated ways; (c) the importance of gene-environment interactions and epigenetic changes which can vary over time even within an individual; (d) the importance of the micro-environment within tissues—cell-cell interactions and the Tissue Organization Field Theory; and (e) the timing of exposures, where exposures at vulnerable life stages (such as prenatally, at puberty and during pregnancy) can have profound impacts on risk of later development of breast cancer. These framing concepts reveal the complexity of research examining relationships between environmental toxicants and risks for developing breast cancer.

Breast cancer does not present with a single biomarker profile; incidence rates differ across ethnic, racial and socioeconomic groups; concentrations of exposures may make a difference, as do possible mixtures and interactions. And specific timing and duration of exposures, especially when they happen early in development, may cause more harmful effects than later exposures.



Summary of the Evidence Linking Environmental Exposures & Breast Cancer



Figure 1. Complexity of factors affecting risk for developing breast cancer.

This synopsis of much of the evidence described in this report demonstrates the complexities of the potential connections between exposures to environmental toxicants and development of breast cancer, all embedded in a web like framework of interconnected factors. Solid arrows indicated connections that have been demonstrated directly between exposures and breast cancer risk, or, as appropriate, mediated through factors described in the framing section of this review. These relationships reflect results of the combined human epidemiological and/or animal studies discussed. Dashed arrows indicate connections between exposures and risk for breast cancer that are more ambiguous, with evidence coming from non-human or animal studies, but without the in vivo data to support more directly the link. Arrows are not weighted to indicate relative strength of links. Rather the purpose of this model is to demonstrate the complexity of the relationships between environmental factors and breast cancer. (Updated and modified from Gray, et al., 2009.11)

01.

Hormones: Pharmaceutical agents & personal care products

For decades, scientists appreciated the positive relationship between lifetime exposures to estrogen and risk for developing breast cancer. More recently it became clear that long-term exposures to progesterone can also influence the possible development of breast cancer. These exposures are often clumped under the category of 'reproductive risk factors' (e.g., age at menarche (first period), first full-term pregnancy, and whether, or not, children were breastfed) in the development of models and simple evaluative tests for determining breast cancer risk.

In addition to variations in exposures to estrogens and progesterone produced within the body, there are several other sources of natural and synthetic steroids, including those found in a number of pharmaceuticals and personal care products. Most of these hormonal agents have been designated as carcinogens by government bodies such as the World Health Organization's International Agency for Research on Cancer (IARC) and the US National Toxicology Program (NTP). Exposures examined in this section of the review are listed in Table 1:

Table 1.

Regulatory ratings and sources of exposures for hormones in pharmaceuticals and personal care products.

International Agency for Research on Cancer (IARC) rating: K=Known (1), PR=Probable (2A), Po=Possible (2B); U.S. National Toxicology Program (NTP) rating: K=Known, RA=Reasonably anticipated. Source of exposure list contains most common exposure sources.

Product	IARC	NTP	Source of Exposure
Diethylstilbestrol	K	K	Formerly prescribed to pregnant women to sustain viable pregnancies
Hormone Replacement Therapy	K		
Conjugated equine estrogens	PR		Treatment of symptoms experienced
Medroxyprogesterone acetate			in menopause
Bioidentical hormone	К		
	К		Contraception
Infertility treatment drugs			
Clomiphene citrate	К		Infertility treatment
Gonadotropins			
Hormones in personal care products	К		Use of placental extracts in personal care products, especially products marketed to women of color

Exposure to diethylstilbestrol (DES) during pregnancy increases the risk for developing breast cancer in the women who were exposed in utero, their daughters and possibly their grand-daughters. Post-menopausal use of hormonereplacement therapy (HRT) made with synthetic estrogens and progestins also increases the likelihood of developing breast cancer although use of estrogen-only HRT has protective effects for those women who have undergone a hysterectomy. Making HRT drugs with the natural hormone progesterone, does not appear to have detrimental effects on breast cancer risk, although use of the natural estrogen, estradiol, may increase breast cell proliferation and consequent risk for developing breast cancer. There is little consistent evidence that use of hormonal drugs in IVF procedures alters risk for breast cancer, although there are numerous methodological issues in these studies. Finally, several personal care products, especially those marketed primarily to communities of color, have estrogenic and progestin additives, increasing lifetime exposures to these hormones.

02.

Endocrine disrupting compounds (EDCs)

Although intentional use of natural and synthetic hormones has been a practice for decades, if not centuries, it is only in the past two decades that scientists began to recognize that many common products also contain chemicals that are disruptive to the exquisitely sensitive endocrine system. These chemicals, found in products as different as plastics, pesticides, fire retardants and sunscreen, were added to the manufactured products for reasons not intentionally related to their endocrine-related properties. Nevertheless, many compounds have been shown to fit the Endocrine Society's definition of an endocrine disrupting compound (EDC), "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action."

By interfering with the actions of natural hormones, exposures to EDCs have been shown to contribute to the development of a wide variety of disease states. Often these effects are most profound when exposures are low-dose and during early development. The growing literature on the connections between several important EDCs and the risk of developing breast cancer, is built mainly—but not exclusively—from non-human models. It is important to remember that although the research literature looks at these chemicals independently, mixtures of EDCs infuse the products we use, the air we breathe, the water we drink, and the surfaces on which we work and play.

The paper provides a detailed review of the evidence linking the EDCs in Table 2 to breast cancer incidence.

Table 2.

Regulatory ratings and sources of exposures for endocrine-disrupting compounds (EDCs)

International Agency for Research on Cancer (IARC) rating: K=Known (1), PR=Probable (2A), Po=Possible (2B); U.S. National Toxicology Program (NTP) rating: K=Known, RA=Reasonably anticipated. Source of exposure list contains most common exposure sources.

EDC	IARC	NTP	Source of Exposure
Bisphenol A			Polycarbonate plastic, epoxy resins linked food cans, dental sealants, thermal receipt
Phthalates	РО	RA	
di(2-ethylhexyl)phthalate (DEHP)			
di-n-butylphthalate (DNP/DBP)			
monoethyl phthalate (MEHP)			Fragrance ingredients in personal care
diethyl phthalate (DEP)			pharmaceuticals, building materials,
butyl benzyl phthalate, (BBP)			insecticides and food packaging/food
di-n-octyl phthalate, (DOP)			processing.
di-i-butyl phthalate (DiBP)			
monomethyl phthalate			
Parabens			
methyl-paraben			Antimicrobial preservatives in food,
propyl-parabens			personal care products, soaps and detergents, and pharmaceuticals
butyl-parabens			
Alkylpenols			
4-nonylphenol (4-NP)			Detergents and cleaning products,
4-octylphenol (4-OP)			anuoxidants in plastic & rubber products
Triclosan & Triclocarban			Antimicrobials in liquid hand soap, other personal care products and household items
Perfluorooctanoic Acid (PFOA) & Perfluorooctanoic Sulfate (PFOS)	РО		Stain resistant coatings, non-stick coatings, commercial products including firefighting foams

EDC	IARC	NTP	Source of Exposure	
EDCs found in sunscreens	РО	RA		
3-(4-methylbenzylidene)-camphor (4-MBC)				
octyl-methoxycinnamate			LIV filters	
octyl-dimethyl-PABA (OD-PABA)				
benzophenone-3 (Bp-3)				
homosalate (HMS)				
Polycyclic Aromatic Hydrocarbons (PAHs)		RA	Byproducts of combustion resulting from	
Pyrene			fossil fuel production, diesel exhaust,	
benz[a]anthracene	РО	RA	grilled meats, cigarettes.	
benzo[a]pyrene	К	RA		
Triazine herbicides				
Atrazine				
Simazine			vveed control for corn and sorgnum crops.	
Cyanazine				
Other Pesticides & Herbicides				
Heptachlor	РО		Insecticide, now banned	
Dieldrin and Aldrin	PR		Insecticide for corn & cotton, now banned	
Chlordane	РО		Home termites, general crop pesticide	
Malathion	PR		Residential, recreational, crop pesticide	
2,4-D	РО		Broadleaf weed herbicide	
2,4,5-trichlorophenoxypropionic acid (2,4,5-TP)			Woody plant and broadleaf weed herbicide, now banned	

EDC	IARC	RC NTP Source of Exposure		
Persistent organochlorines				
Dichloro-diphenyl-trichloroethane (DDT)/DDE	PR	RA	Insecticide, now banned	
PCBs	K	RA	Electrical insulation, fluid coolants, plasticizer in paints, dyes & inks	
Dioxins: 2,3,7,8-tetra chlorodibenzo-para-dioxin (TCDD)	K		Byproduct of burning of chlorine-based chemicals	
Polybrominated Diphenyl Ether (PBDEs)			Flame retardants, previously used in furniture and electronics; most have been banned or voluntarily phased out	
Aromatic amines				
o-toluidine	К	K	Hair dyes	
4-aminobiphenyl (ABP)	K	К	Azo dyes in textiles	
p-phenylenediamine			Hair dyes	
2-amino-phenylimidazo[4,5-b] pyridine (PhIP)			Cooked meats	
heterocyclic aromatic amines			Hair dyes	
Metals				
Copper				
Cobalt	РО	RA		
Nickel	РО			
Lead	PR	RA		
Mercury			in naturally derived colorants, clays, and	
Methylmercury	РО		other metals, found in cosmetics, toys,	
Tin			and other products.	
Cadmium	К	К		
Zinc				
Iron	К			

The growing literature on exposures to EDCs, especially early in development, indicates an increased risk of developing breast cancer following exposure to many of these compounds, either alone or in combination. The most substantial human epidemiological data supporting this relationship come from prospective studies on women exposed to DDT during gestation or early childhood and increased development of premenopausal breast cancer. The largest animal and cell-based literature connects early, low-dose exposures to bisphenol A (BPA) to increased risk for developing mammary tumors. Both types of studies have added substantially to our understanding of the complex mechanisms underlying these relationships. Although not as robust as for DDT and BPA, links between exposures, especially early in development, and many other EDCs have also been documented.

03.

Hormones in food: Natural and additives

The prevailing evidence against synthetic estrogens must also be understood alongside evidence about the effects of plant estrogens (phytoestrogens) on risk for developing breast cancer. While most of the research in this area has focused on possible protective effects of soy-based isoflavones in a normal diet, a growing literature is also examining the potential protective effects of lignans (another class of phytoestrogens).

Mycoestrogens (estrogens found in fungal species) can contaminate agricultural and meat products, and this contamination may increase susceptibility to developing breast cancer. Also, exposures to growth enhancing compounds given to meat-producing and dairy animals have been linked to increased risk for developing breast cancer.

The complicated profiles of exposures to food-based estrogens and risk for developing breast cancer is explored in this section of the review. There has been no determination on potential carcinogenicity of these substances by IARC or NTP. The exposures covered are:

Phytoestrogens

- Lignans
- Soy and soy derivatives
- Mycoestrogens

Natural, synthetic and genetically engineered hormones used in food production

- Zeranol (Ralgro®)
- rBGH/rBST

In summary, when incorporated into regular nutritious diets, lignans and soy-based foods have been shown to be protective against breast cancer in numerous epidemiological studies. This protection is especially clear when dietary intake begins in childhood. On the other hand, both mycoestrogens and the stock animal growth enhancer zeranol are estrogenic in their interactions with human breast cells, including cells derived from cancers, in cell culture environments—an indicator that they may increase risk of breast cancer. The data are more ambiguous on possible effects of elevated IGF-1 levels, found after drinking cow's milk.

04.

Non-EDC industrial chemicals

Not all chemicals associated with increased risk for breast cancer exert their effects through endocrine disrupting mechanisms. This section examines the literatures linking an increased risk for developing breast cancer to a few industrial chemicals, all of which have been determined to be carcinogenic by IARC. These compounds and/or the DNA adducts formed following exposures to the compounds, are directly mutagenic.

Table 3.

Regulatory ratings and sources of exposures of chemicals found in non-EDC industrial chemicals

International Agency for Research on Cancer (IARC) rating: K=Known (1), PR=Probable (2A), Po=Possible (2B); U.S. National Toxicology Program (NTP) rating: K=Known, RA=Reasonably anticipated. Source of exposure list contains most common exposure sources.

Chemical				
Non-EDC Industrial Chemicals				
Benzene (71-43-2)	К			
Vinyl chloride (75-01-4)	K			
1,3-Butadiene (106-99-0)	К			
Ethylene oxide (75-21-8)	K			

NTP	Source of Exposure
K	Petrochemical solvent
K	Monomer used in polyvinyl chloride (PVC) plastic
K	Byproduct of combustion
K	Sterilizer, byproduct contaminant in some cosmetics

Epidemiological studies show that both men and women exposed occupationally to benzene or vinyl chloride, such as those working in manufacturing, with organic solvents, or in petroleum extraction and refinement, have higher risk for developing breast cancer. Limited human evidence also indicates that exposures to 1,3-butadiene increase risk for breast cancer. More robust evidence links exposure to ethylene oxide with increased breast cancer risk.

05.

Tobacco smoking: Active and passive

Increasing evidence indicates that exposure to the many chemicals included in tobacco smoke, both through active (first hand) and passive (second hand) means, can increase risk for developing breast cancer. While exposures to smoke are often clustered with alcohol consumption and other lifestyle factors, in this category we only focus on tobacco smoke exposures as these are from chemicals polluting the environment, and the exposures are often involuntary.

- Active smoking
- Passive smokings

Table 4.

Regulatory ratings of chemical exposures found in cigarette smoke

International Agency for Research on Cancer (IARC) rating: K=Known (!), PR=Probable (2A), Po=Possible (2B); U.S. National Toxicology Program (NTP) rating: K=Known, RA=Reasonably anticipated.

Chemical	IARC	NTP
Tobacco smoking: Active and passive		K
Polycyclic aromatic hydrocarbons (PAHs)		RA
Polonium-210		
Benzene	К	К
Vinyl chloride	К	K
1,3-butadiene	К	K
nitrosamine ketone (NNK)		

There is now substantial research indicating that past and current active cigarette smoking is associated with a higher risk for developing breast cancer. For women who are smokers at the time of diagnosis, there is also an increased risk in mortality from breast cancer. These effects are complicated by interactions with race/ethnicity, history of alcohol consumption and subtype of breast cancer.

06.

Shift work, light-at-night and melatonin

In 2007, IARC concluded that shift work is 'probably carcinogenic to humans' based in large part on the growing association between shift working and increased incidence of breast cancer. Several occupational studies have demonstrated that women who consistently work night shifts have increased breast cancer risk, although not all reports have found evidence for this relationship. Methodological differences between studies, including varied definitions of "shift work" and "night," as well as lack of consistent attention to confounding factors may explain some of the differences in results between individual studies.

In summary, extensive experience with night-shift work, and therefore higher exposure to light-at-night (LAN), has been shown to increase risk for breast cancer, although there may be ethnic differences in this response. The most studied underlying mechanism for the effect of LAN exposures is the accompanying change in patterns of melatonin secretion. Other lifestyle and physiological factors associated with shift work have also been proposed to alter risk for developing breast cancer.

07. Radiation

Exposure to ionizing radiation, from both military and medical sources, is the best known and longest established environmental cause of breast cancer in both women and men. Exposures early in life, during childhood through adolescence, are particularly important. Data for potential links between electromagnetic fields, or non-ionizing radiation, and breast cancer are mixed and inconclusive.

• Ionizing radiation

• Non-Ionizing radiation (EMFs)

Table 5.Regulatory ratings and exposure sources of light-at night and radiation

International Agency for Research on Cancer (IARC) rating: K=Known (!), PR=Probable (2A), Po=Possible (2B); U.S. National Toxicology Program (NTP) rating: K=Known, RA=Reasonably anticipated. Source of exposure list contains most common exposure sources.

Exposure	IARC	NTP	Use
Shift Work, Light-at-Night	PR		Shift work or ambient light pollution
Ionizing Radiation	K	K	Diagnostic medical tests; nuclear medicine procedures; nuclear power plants, research protocols
Non-ionizing radiation (electromagnetic fields)			Lighting, computers, cell phones and other electronic sources

Exposure to ionizing radiation is a known cause of increased risk for breast cancer. Victims of military use of nuclear bombs have increased risk, as do women who had X-ray treatments for medical purposes, especially when they were young. Women carrying the BRCA1/2 mutations are particularly susceptible to the effects of X-rays, including those emitted by routine mammography.

More mixed results come from studies of women exposed to non-ionizing radiation, either because of occupational or residential exposures.

Conclusions

Exposures linked to breast cancer

In the 8 years since we last published an extensive review of the relevant literature, hundreds of new papers have been published supporting a link between exposures to environmental toxicants and an increased risk for developing breast cancer. This literature expanded in size and also in depth, breadth and complexity. The growing literature on developmental exposures to EDCs and later development of breast cancer is especially strong.

Epidemiological (human) data strongly supports the link between increased risk of developing breast cancer and early developmental exposures to the synthetic estrogen DES, the pesticide DDT and ionizing radiation, as well as adult exposures to oral contraceptives and hormone-replacement therapy (HRT). A growing body of literature also implicates engaging in night-shift work as an important factor leading to increased risk for breast cancer. On the other hand, substantial literature examining the effects of consuming soy products and lignans as part of a regular diet, especially starting early in life, indicates they can have a protective effect against later development of breast cancer.

Animal and other in vitro models support the hypothesis that many other chemicals found in commonly used consumer products, as well as in our air, water and dust, are all associated with increased risk for predisposing mammary tissue to develop tumors. This data supports the strong links described above for endocrine disrupting compounds (EDCs).

Recommendations for future research

Data from human studies (epidemiology) suggests connections between exposures and later development of cancer. Limitations in the data collected in these studies often constrain the conclusions that can be drawn. Of particular concern is the lack of direct measurement of toxicant exposure levels in individuals, especially in the years (or decades) prior to diagnosis of the breast cancer. There is often a long latency between exposures and diagnosis, and earlier developmental exposures can be especially powerful in affecting development of breast cancer, even decades later. To enlarge the body of relevant work, it will be important for large cohort studies (ones that follow a group for a long period of time) to regularly collect exposure information across much of the lifespan, and to develop the technology necessary to quantify exposure levels, biomarkers, and health outcomes at large-scale levels.

Importantly, scientists are beginning to understand mechanisms by which exposures to various toxicants may lead to increased risk for developing cancer. This literature has been slow to develop because regulatory toxicological studies examining reproductive and developmental consequences of exposures to various drugs or potential toxicants have not required examination of mammary tissue endpoints. There are no standardized protocols for determining appropriate times of exposures, ranges of doses, or mammary gland endpoints to study and later potential carcinogenic, genotoxic, or endocrine disrupting effects of these exposures. In order to demonstrate the connections between the many chemicals that have been implicated in increased risk for development of breast cancer and causal links to the disease, it will be important to develop a series of endpoints to study routinely. Critical endpoints to be evaluated include altered mammary gland development; activity of various biomarkers including PR, HER, other endocrine factors; and different subtypes of various hormone receptors, each of which can have different effects on cellular activity when activated.

Final thoughts

Despite these critical methodological limitations and concerns, the breadth and strength of the evidence cited in this review reinforces the conclusion that exposures to a wide variety of toxicants—many of which are found in common, everyday products and byproducts—can lead to increased risk for development of breast cancer. As concluded by the reports of the Presidential Cancer Panel and the Interagency Breast Cancer and Environment Research Coordinating Committee, it is critical to recognize the growing literature demonstrating connections between exposures to environmental toxicants and later development of disease, including breast cancer, and to prioritize prevention both at the research and the public health levels.

Breast Cancer Prevention Partners (BCPP) is the leading science-based policy and advocacy organization working to prevent breast cancer by eliminating our exposure to toxic chemicals and radiation.

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