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Most women who develop breast cancer do not inherit defective genes from their parents. In fact, fewer than 10% of cases are related to genetic abnormalities. At most, only half of all cases arise in women who have known risk factors.



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Fewer than 1 in ten cases of breast cancer arises in women born with genetic defects.

National Cancer Institute

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The huge proportion of unknown causes may include environmental exposures of pollutants which are avoidable.

Breast cancer arises due to complex interactions between genes, hormones and the physical-chemical environment.

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The breast is mostly fat. Most cases of breast cancer arise in the terminal ductal lobular unit (TDLU) of the breast, in cells that line the milk glands and ducts. (See "All About Breast Cancer," Lawrence Berkeley National Laboratory's ELSI Project.)



Breast cancer arises when cells undergo changes that allow them to proliferate beyond control. This occurs largely because of mutations, damages to genes which would normally regulate cell growth.



Hormones, which act as the body's chemical messengers, and other substances near the cell, may



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Both genetic and hormonal paths can be important for the development of breast cancer.



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Most cases of breast cancer occur in women with few of the known risk factors

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A risk factor is a characteristic which increases the likelihood of disease in a group of people who have the factor compared to an otherwise similar group of people who do not. The relative risk (RR) measures the likelihood of getting disease if exposed to certain risk factors. For example, women who consume 2 or more drinks of alcohol per day will be 1.4 times more likely than those who do not to develop breast cancer. This means that they have 40% more breast cancer than women who do not drink.



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The relative risk (RR) is calculated as the ratio of disease risk in the exposed group compared to the risk in the unexposed group. The higher the RR, the stronger the link between a particular risk factor and disease. Most of the well established risk factors for breast cancer can be linked to hormonal exposures.

Risk factors are not necessarily causes

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Timing of exposure can be more important than dose



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Susceptibility to toxic exposures depends on the rate of cell growth. This means that when exposures occur may be just as important as what levels of exposure occur. High levels of estrogen in utero may predispose the embryo to some types of breast cancer. In adolescence, estrogens may influence developing breast cells in making them more vulnerable to cancer causing agents. And, post-menopausal women may be more susceptible because they have endured longer exposures to the active form of estradiol over the years.



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Contributing risk factors

Exposure to Hormones or Xenohormones





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IGF-1 is a powerful naturallyoccurring growth hormone



Growth factors and breast cancer

Premenopausal women with highest levels of IGF-1 in their blood were 7 times more likely to develop breast cancer 50



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Total Lifetime Exposure to Unbound Hormones



Links Most Known Risk Factors

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There are many lines of evidence - experimental cell culture studies, mounting documentation of wildlife phenomena and human effects - which implicate the role of environmental estrogens in breast cancer. Experimental evidence consists of controlled studies using cell cultures or laboratory animals. Wildlife studies examine natural patterns in free-ranging animals and attempt to link these to environmental factors. Human studies can involve controlled observations of disease in people with and without particular exposures. And, epidemiological studies looking at disease patterns over space and time can provide clues about potential environmental risks



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Cell culture studies have identified numerous compounds that disturb hormones. More than 400 chemicals have been shown to produce mammary tumors in rodents. These tumors are comparable to breast cancer in women, and continuing studies can guide us in evaluating the roles of these chemicals in human disease.



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Estrogen is a hormone that plays a critical role in the development and metabolism of the breast, among other organs. The breast contains receptors for hormones such as estrogen. Receptors resemble locks into which only certain keys can fit. Both the body's own natural estrogen as well as foreign materials, called xenoestrogens, can fit into these locks, or receptors, and alter how much and what types of estrogen the body produces. Once xenoestrogens reach the inside of a cell, they may promote cancer-causing behaviors in a

in a number of ways.



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Some natural products such as plants can produce estrogen, as do synthetic materials such as some pesticides and plastics. In fact, the amount of estrogen produced by plants is typically thousands of times greater than the amount produced by synthetic materials. While most plant estrogens are rapidly excreted from the body, those tied with synthetic estrogens can cumulate for decades. Scientists are asking whether these products could have different effects on humans. Albert R. Cunningham, and Herbert S. Rosenkranz of the University of Pittsburgh and Gilles Klopman, of Case Western Reserve University, have developed

an innovative technique for looking at the chemical structure of natural plant estrogens and synthetic ones (Environmental Health Perspectives, 105:3 (1997) 665-68). They have identified a microscopic structure that occurs in compounds that appear more toxic, tend to be attracted to fat and produce longer lived estrogen exposure in many synthetic estrogens and in the body's own 17-beta and 16-alpha estradiol. In contrast, most natural plant estrogens do not contain this structure, are water soluble and more rapidly excreted from the body. This figure shows that 17 beta, 16 alpha and synthetic estrogens contain large sections of their molecules in purple that are most attracted, while the natural plant estrogens in soy products do not include such sections.



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The compounds listed below are among the better known ones that have been shown in laboratory tests to be xenoestrogens. Of these, DDT . .

Compound	Use	Comment
Atrazine	Weed killer	Widely used today
Chlordane	Termite killer	Widely used before banned in 1988
DDT	Insecticide	Widely used before banned in 1972; still present in virtually evervone's body

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. . and certain PCBs have now been implicated in human studies as causes of breast cancer. The substances that have been banned in the U.S. persist in the environment for many years and are available in some other countries. They may appear in foods imported from abroad and may occasionally travel as air pollution.

Some Proven Xenoestrogens : Chlorinated organic compounds Compound Use Comment Endosulfan Insecticide Widely used today Kepone Bait in ant and roach traps Banned in 1977

Methoxychlor I	nsecticide	A close	relative	of DDT

Some PCBs -	Component of	No longer made in the US but
	electrical	still found in old transformers
	insulation	

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Proven Xenoestrogens:
DlasticsCompoundUseCommentBiosphenol ABreakdown product
of polycarbonateLeaches out into fluids
when hotNonylphenolSoftener for plastics
ceadily at room
temperature

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Proven Xenoestrogens: Pharmaceuticals

Compound	Use	Comment
Synthetic estrogens	Constituent of birth-control pills and estrogen- replacement therapies	One drug, diethylstilbestrol (DES), was given to several million women during pregnancy before it was essentially banned for that use in 1971
Cimetidine	Ulcer treatment	

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Proven Xencestrogens:
Fuel constituentsCompoundUseCommentAromatic
hydrocarbonsComponents
of petroleumCan be inhaled readily from
gasoline and from car exhaust

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A number or recent studies have linked xenoestrogens with reproductive anomalies and other disorders in wildlife. While there are many biological differences between humans and others species of animals, evidence suggests that xenoestrogens which pollute ecosystems can have an impact on the health of the entire food chain. One possible effect is sex reversal in turtles. (See, Our Stolen Future, Evidence from wildlife).



Fish living near outlets from municipal sewers have high levels of vitellogenin, a female protein. Other phenomena include structural damage of DNA and hermaphroditism, possessing both male and female sexual characteristics.



A Florida lake polluted by a nearby pesticide spill has been connected to the occurrence of abnormally small genitalia in alligators hatched there. These alligators' sex organs are functioning poorly as a result.



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The Florida panther is estimated to be nearly extinct because of declining reproductive capacity due to a disorder called cryptorchidism, having undescended testicles, and poor sperm production. The concentrations of heavy metals and persistent chlorinated organic substances in the soil and water in South Central Florida may be involved.



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Agents associated with breast cancer in humans (suspected)

- Alcoholic Beverages
- Pesticides
- Pharmaceuticals
- o Diet

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Sorting out how hormones affect breast cancer is an exciting challenge today. This involves piecing together evidence from studies of wildlife, cell cultures, experimental animals, and humans. Studying humans as models is especially difficult.







The largest increases in breast cancer rates occur in women of all races over the age of 50.



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Breast cancer on Long Island

Women who lived in certain regions of Long Island for 40 or more years had four times as much breast cancer, as those who lived there less than 10 years.



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Breast Cancer Mortality in Developing Countries



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Relative Risk of Breast Cancer Mortality in the Workplace and Community

Exposure	Relative Risk
347 female chemists vs U.S. Population	1.65 (Also: ov, atom, panc. lym, blood increased)
U.S. counties with 2+ waste sites vs. no waste sites	6.5
24,000 blue collar women vs. U.S. population (workers exposed to solvents)	PMR 1.43 in chemical workers 1.64 in pharmaceutical workers
Women workers in FRG pesticide plant vs. E. German population	2.15 2.15
Women in counties with 2+ chem poll.	3.4

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In the past few years, international researchers have reported that male reproductive disorders are on the rise, and there is growing evidence that xenoestrogens may play a role in these alarming trends. The sperm count data vary dramatically worldwide, even within the U.S., and this disparity may reflect the influence of different environmental factors at play. Although breast cancer figures among men are very low, they may also be increasing.



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Puzzling male reproductive health problems

- Testicular cancer
- Hypospadias
- Cryptorchidism
- Infertility
- Reduced sex ratio



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Controlled human studies suggest that DDT increases the risk of breast cancer. Women with higher DDT levels in their blood or fat have been found to have between 2 and 9 times the risk of breast cancer, when compared to women with lower DDT residues.



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In these case control studies, the relative risk (RR) measures the likelihood of getting disease if exposed to a risk factor such as DDT. Ethnicity appears to be important in the disease profile, as Asians tend to have a lower risk of breast cancer than African-American and White women in the U.S.

Some of the early conducted studies on organochlorine residues tended to find a clear association between higher levels of PCB and DDE, either in the blood or in adipose tissue, and breast cancer (Dewailly MS, Dodin S, Verrault R, Ayotte P, Sauve L, Brisson J. High organochlorine body burden in women with estrogen receptor-positive breast cancer. J Natl Cancer Inst 86(3):232-234 (1994)., Glass R, Hoover RN. Rising incidence of breast cancer relationship to stage and receptor status. J Natl Cancer Inst 82(8):693-696 (1990).). In addition, nested case-control prospective studies in this field have tended to yield positive results (Austin H, Keil JE, Cole P. A prospective follow-up study of cancer mortality in relation to serum DDT. Am J Public Health 79:43-46 (1989).), especially those that have looked at estrogen receptor positive cases (Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: A prospective study among white, black, and Asian women. J Natl Cancer Inst 86:589-599 (1994).). Thus, a small case-control study in Canada found that women with elevated levels of DDE had 8.9 times the risk of ER positive disease than did women with relatively lower levels of this metabolite (Hunter DJ, Hankinson SE, Laden F, Colditz GA, Manson JAE, Willet WC, Speizer FE, Wolff MS. Plasma organochlorine levels and the risk of breast cancer. New Engl J Med 337:1253-1258 (1997).). ER positive cases appear to be increasing overall in women over age 60, according to one report from California (56). In some studies, negative results were also described for the total cancer study population or for specific subgroups of breast cancer subjects, such as Asian women (Lopez-Carillo L, Blair A, Lopez-Cervantes M, Cebrian M, Rueda C, Reyes R, Mohar A, Bravo J. Dichlorodiphenyl trichloroethane serum levels and breast cancer risk: a case-control study from Mexico. Cancer Res 57:3728-3732 (1997).,57).



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Recently published studies on breast cancer have produced inconsistent results regarding breast cancer and organochlorine exposures. These recent studies have not addressed the broad array of other suspect xenohormones, many of which leave no biologic markers, such as benzo-a-pyrene, some plastics and fuels. Nor have protective factors, such as genistein and other isoflavones, been widely studied. Susan Hankinson and colleagues at the Harvard School of Public Health have recently reported that premenopausal cases of breast cancer with the highest levels of insulin-like-growth factors-1 (IGF-1) as measured 4 years or more before diagnosis had nearly a 7-fold greater risk of breast cancer compared to those without the disease (Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M. Circulating concentrations of insulin-like growth factor I and risk of breast cancer. Lancet 351: 1393-96 (1998).). This finding indicates the importance of looking at a broad array of potential protective and disruptive factors, as well as the value of conducting longer term prospective studies that permit their identification. Studies which consider current levels of metabolites of pesticides in cancer patients have been described as analogous to "looking under the nearest lamppost for lost keys because that is where there is light" (63). Two critical questions must be raised: what were exposures to xenohormones during critical windows of development, including the prenatal and pre-pubescent periods, and what was the lifetime exposure to hormonally active parent compounds? Studies which look at contemporaneous measures of lipophilic metabolites of organochlorine compounds cannot resolve these questions. For more information see, D.L.Davis et al., "Rethinking Breast Cancer Risk and the Environment: The Case for the Precautionary Principle."



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Normal Cell Communication



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Abnormal Cell Communications after DDT



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Disrupted cell communication after pesticides



Source: Kang, *et al.*, 1995.

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Important Things You Can Do to Reduce the Risk of Breast Cancer

Take Care of Yourself

- » Eat vegetables, fruit and calcium
- » Reduce your fat intake
- » Get moderate exercise
- » Take caution in undergoing long-term estrogen-replacement therapy
- » Avoid long-term use of oral contraceptives before giving birth

Educate Yourself

» Raise your awareness about the connections between cancer and environmental toxins

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Important Things You Can Do to Reduce the Risk of Breast Cancer

Take Care of Your Children

- Before and during pregnancy, avoid exposures to estrogens, hazardous chemicals, cigarettes, alcohol, etc...
- » Reduce the use of toxic chemicals in household and school
- » Use public transportation, bike, or walk

Empowerment

» Become actively involved in a health promotion group to identify what you can do to help reduce the risk of breast cancer related to environmental factors

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Important Things Your Family Can Do

- Educate your children about protective behaviors during breast development
- Encourage your children to exercise
- Get regular mammograms when over age 50.
- Support one another
- Encourage family discussions on reducing contaminants
- 🔹 Maintain a healthy, low-fat diet

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Important Things Your Community Can Do

- Be a breast cancer resource person in your community and help educate those around you
- Encourage school sports for everyone
- Inform local/state representatives of your concern over suspect toxic materials and encourage precautionary action
- Exercise your right to know
- Get involved with organizations promoting sound national and international environmental and economic policies to promote healthy behaviors

Important Things the Private Sector Can Do

- Promote integrated pest management (IPM)
- Reduce, reuse, and recycle materials
- Encourage pollution prevention
- Promote workplace safety

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 Never forget that the only thing that changes public policy is a group of concerned citizens

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• Environmental Health Perspective is a journal devoted to exploring the links between the environment and health, and has information on breast cancer. <u>http://ehpnet1.niehs.nih.gov/docs/1998/106-9/toc.html</u>

• Environmental Health Perspective Supplement: Volume 105 Supplement 3, April 1997 Hormones, Hormone Metabolism, Environment, and Breast Cancer. <u>http://ehpnet1.niehs.nih.gov/docs/1997/Suppl105-3/toc.html</u>

• The University of Pennsylvania Cancer Center maintains a list of comprehensive information sites on breast cancer. http://oncolink.upenn.edu/templates/types/index.cfm

• The Our Stolen Future website provides regular updates

• about the cutting edge of science related to endocrine disruption. It also posts information about ongoing policy debates and new suggestions about what you can do as a consumer and citizen to minimize risks related to hormonally-disruptive contaminants. <u>http://www.ourstolenfuture.org/</u>

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