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

National Cancer Institute

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.
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.

Breast Cancer Biology

Hormones, which act as the body's chemical messengers, and other substances near the cell, may
also contribute to rapid cell multiplication.

Both genetic and hormonal paths can be important for the development of breast cancer.
Most cases of breast cancer occur in women with few of the known risk factors

Known risk factors for breast cancer:
- Radiation
- Late menopause
- Lack of exercise
- History
- Early menses
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.

**Risk factors for breast cancer**

- Risk of breast cancer in those with elevated exposures
- Compared to those without such exposure

**Direct risk factors**

- Radiation
- History of breast cancer
  - (mother or sister pre-menopause) 2-4

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

Timing of exposure can be more important than dose
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.
Vulnerability risk factors

Breast cell growth

- Elevated prenatal hormones  4
- Late menopause          2

Contributing risk factors

- Alter hormonal environment
- Change the ratio of good to bad estrogens
Contributing risk factors

- Alcohol 1.4
- Lack of exercise 2 – 4
- Lack of fiber and vitamin D
- Obesity after menopause 2

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Contributing risk factors

- Age 65+ 17
- Living near a chemical facility 2 – 4
- Lifetime exposure to harmful xenohormones ??? up to 7.0
- Elevated IGF-1 (growth factor) (premenopausal) 7

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IGF-1 is a powerful naturally-occurring 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

Hankinson et al., 1998
Total Lifetime Exposure to Unbound Hormones

Links Most Known Risk Factors

Most important risk factors

- Sex
- Age
Protective factors

- Vegetables
- Soy
- Exercise
- Fish and olive oil
- High fiber

Reduced Lifetime Exposure to Unbound Hormones

Links Most Known Protective Factors
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.
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.

Mammary Cancer in Laboratory Animals

- Benzene
- DBCP
- DDVP
- Atrazine
- Vinyl Chloride
- DMBA
- MNU
- HCA
- PAH

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 number of ways.
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.

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

**Proven Xenoestrogens: Chlorinated organic compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Use</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrazine</td>
<td>Weed killer</td>
<td>Widely used today</td>
</tr>
<tr>
<td>Chlordane</td>
<td>Termite killer</td>
<td>Widely used before banned in 1968</td>
</tr>
<tr>
<td>DDT</td>
<td>Insecticide</td>
<td>Widely used before banned in 1972; still present in virtually everyone's body</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Use</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endosulfan</td>
<td>Insecticide</td>
<td>Widely used today</td>
</tr>
<tr>
<td>Kepone</td>
<td>Bait in ant and roach traps</td>
<td>Banned in 1977</td>
</tr>
<tr>
<td>Methoxychlor</td>
<td>Insecticide</td>
<td>A close relative of DDT</td>
</tr>
<tr>
<td>Some PCBs</td>
<td>Component of electrical insulation</td>
<td>No longer made in the US but still found in old transformers</td>
</tr>
</tbody>
</table>

### Proven Xenoestrogens: Plastics

<table>
<thead>
<tr>
<th>Compound</th>
<th>Use</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphenol A</td>
<td>Breakdown product of polycarbonate</td>
<td>Leaches out into fluids when hot</td>
</tr>
<tr>
<td>Nonylphenol</td>
<td>Softener for plastics</td>
<td>Leaches out into fluids readily at room temperature</td>
</tr>
</tbody>
</table>

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### Proven Xenoestrogens: Pharmaceuticals

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

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### Proven Xenoestrogens: Fuel constituents

<table>
<thead>
<tr>
<th>Compound</th>
<th>Use</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic hydrocarbons of petroleum</td>
<td>Can be inhaled readily from gasoline and from car exhaust</td>
<td></td>
</tr>
</tbody>
</table>

[Slide 38 of 86 slides]
Wildlife evidence

Increases in Disorders are “Sentinel Indicators”

Deformities in frogs

- Grotesquely deformed frogs in Midwest
- Frog populations declining worldwide
A number of recent studies have linked xenoestrogens with reproductive anomalies and other disorders in wildlife. While there are many biological differences between humans and other 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.

Increasing Wildlife Disorders

- Sex reversal in turtles

Increasing Wildlife Disorders

- DNA base lesions in fish
- Vitellogenin (a female hormone) in male fish
- Hermaphroditism in fish
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.

**Increasing Wildlife Disorders**

- Altered sex ratios and genitalia in alligators

**Deformed Alligator Penis**
**Alligator Hormones**

![Bar chart showing hormone levels in clean and polluted environments]

**Increasing Wildlife Disorders**

**Military Dogs in Vietnam Compared to Non-Vietnam**

- Testicular cancer
- Testicular atrophy
- Reduced sperm

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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.
Human evidence

Agents associated with breast cancer in humans (suspected)

- Alcoholic Beverages
- Pesticides
- Pharmaceuticals
- Diet
Factors associated with breast cancer in humans (suspected)

- Plastics
- Fuel Constituents
- Solvents
- EMF
- Smoking

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.

Studying Humans is Difficult

- Human studies are difficult to conduct
- People seldom know what they have been exposed to, especially early in life
- Both good and bad xenoestrogens exist
- Looking at residues in people after they have cancer can be misleading; the development of the disease can change what sorts of toxic compounds are stored in the body.
Geographic hot spots for breast cancer

Geographic Patterns Provide Clues

- Within the U.S. white population, rates of breast cancer vary by nearly 50%.
- Highest rates occur in San Francisco, New York, and areas near the Great Lakes.
- Death rates are higher for blacks than whites, because of unequal access to screening and treatment.
The largest increases in breast cancer rates occur in women of all races over the age of 50.

**Female Breast Cancer Incidence Trends (United States)**

- **Percent Change 1973-1991**
  - All Races
  - All Races < 50
  - All Races > 50
  - All White Females
  - White Females < 50
  - White Females > 50
  - All Black Females
  - Black Females < 50
  - Black Females > 50

**Source:** SEER Cancer Statistics Review 1973-1991, National Cancer Institute

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**Evidence in New York**

Post-menopausal women living near two or more chemical plants had twice the risk of developing breast cancer compared with women who lived in areas with no such facilities.
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.

Breast Cancer Mortality in Developing Countries

Percent Change 1973-1987

Source: International Agency for Research on Cancer.

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[Slide 58 of 86 slides]
### Breast Cancer Mortality in Developed Countries

#### Percent Change 1973-1987

<table>
<thead>
<tr>
<th>Country</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** International Agency for Research on Cancer.

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### Relative Risk of Breast Cancer Mortality in the Workplace and Community

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>347 female chemists vs U.S. Population</td>
<td>1.65</td>
</tr>
<tr>
<td>(Also: ov., atom, panc. lym, blood increased)</td>
<td></td>
</tr>
<tr>
<td>U.S. counties with 2+ waste sites vs. no waste sites</td>
<td>6.5</td>
</tr>
<tr>
<td>24,000 blue collar women vs. U.S. population (workers exposed to solvents)</td>
<td>PMR</td>
</tr>
<tr>
<td>1.43 in chemical workers</td>
<td></td>
</tr>
<tr>
<td>1.64 in pharmaceutical workers</td>
<td></td>
</tr>
<tr>
<td>1.51 in electronic equipment</td>
<td></td>
</tr>
<tr>
<td>Women workers in FRG pesticide plant vs. E. German population</td>
<td>2.15</td>
</tr>
<tr>
<td>Women in counties with 2+ chem poll</td>
<td>3.4</td>
</tr>
</tbody>
</table>
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. (See, Our Stolen Future, Human evidence).

**Increasing Human Male Reproductive Disorders**

- Dropping sperm count
- Testicular cancer
- Malformation of genitalia
- Undescended testes
- Breast cancer?

**Puzzling male reproductive health problems**

- Testicular cancer
- Hypospadias
- Cryptorchidism
- Infertility
- Reduced sex ratio
Testicular cancer trends  
(Nordic countries)

Hypospadias trends  
(United States)
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.
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).
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."
Disrupted cell communication after pesticides

Source: Kang, et al., 1995.
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

[Slide 77 of 86 slides]

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

[Slide 78 of 86 slides]
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

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

Never forget that the only thing that changes public policy is a group of concerned citizens.
NO ONE EVER SAID THE FIGHT TO END BREAST CANCER WOULD BE A WALK IN THE PARK.

One step at a time


The University of Pennsylvania Cancer Center maintains a list of comprehensive information sites on breast cancer.  [http://oncolink.upenn.edu/templates/types/index.cfm](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.  [http://www.ourstolenfuture.org/](http://www.ourstolenfuture.org/)

World Resources Institute, 10 G Street, NE (Suite 800), Washington, DC 20002