



# Breast Cancer: Why the Environment Matters

A woman has a 1 in 8 chance of developing breast cancer in her lifetime, according to the American Cancer Society. It is the second most common cancer among women in the United States, next to skin cancer. Breast cancer occurs mostly in women who are 50 years old or older.

## Prevention Is Key

Supported by the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI), the Interagency Breast Cancer and Environmental Research Coordinating Committee concluded, in a landmark report<sup>1</sup>, that prevention is key to reducing the emotional, physical, and financial burden of breast cancer.

Research shows, in general, maintaining a healthy weight in adulthood, staying physically active, decreasing alcohol consumption, and consuming a nutritious diet can reduce the chance of developing cancer over your lifetime.

## What Causes Breast Cancer?

Most women who develop breast cancer have no family history of the disease, suggesting an environmental link. In a study, inherited factors, such as the BRCA1 or BRCA2 genes, accounted for only 27% of breast cancer risk.<sup>2</sup>

Although we know of many risk factors that increase women's chances of developing breast cancer, scientists do not completely understand what causes normal cells to become cancerous. But most experts agree that a combination of genetic, hormonal, and environmental factors leads to breast cancer.



## What Does NIEHS Research Tell Us About Breast Cancer?

NIEHS plays a leadership role in funding and conducting studies on the ways in which genetic and environmental factors may affect breast cancer risk. For example, NIEHS scientists discovered women living in areas with higher levels of air pollution may have a higher risk of breast cancer.<sup>3</sup> Research can help determine environmental exposures that are linked to breast cancer. Then, reducing those exposures may help prevent disease.

## The Sister Study

The NIEHS Sister Study includes more than 50,000 sisters of women with breast cancer from the U.S., including Puerto Rico. The study looks at lifestyle and environmental exposures, as well as genetic and biological factors that may affect a woman's chance of developing breast cancer. Women with sisters who had breast cancer may have genetic profiles that make them twice as likely to develop breast cancer themselves. The study design offers the ability to identify environmental exposures over the life course that increase the chance of developing breast cancer, and to identify how genes and the environment interact to increase risk.

The Sister Study commemorates its 20th anniversary in 2023. Some important study findings are described in the following pages.



*"Sisters share many things including genes and early-life environments. By studying these sisters, we have increased the ability to detect health risks that are related to both the environment and genes. Over 20 years, we've conducted a wide range of research on breast cancer and also other diseases that are important for women."*

– Dale Sandler, Ph.D.,  
principal investigator of the NIEHS Sister Study

## Findings From the Sister Study

A wealth of data on exposures, including biological samples, allows the team to address many questions relating to factors associated with disease. In addition to breast cancer, the Sister Study has discovered other important information related to women's health. Key findings from this study are grouped around major themes.

### Air Pollution

Air pollution is a complex mixture of many chemicals, including toxic metals, which can act as carcinogens. Air pollution has been linked to several diseases, such as cardiovascular disease, but less is known about its role in breast cancer.

Sister Study researchers found that higher levels of nitrogen dioxide (NO<sub>2</sub>), a component of air pollution related to traffic, was associated with increased breast cancer risk.<sup>4</sup> Radon gas, which occurs naturally in the environment, can break down into radioactive particles that can mix with air pollutants. Researchers found that exposure to these airborne radioactive particles was associated with a higher risk of estrogen receptor-negative breast cancer.<sup>5</sup>

Women who live in areas of air pollution with higher levels of lead, mercury, and cadmium have a greater chance of developing postmenopausal breast cancer.<sup>6</sup> Researchers evaluated whether dioxin may be associated with breast cancer risk. Publicly available data on industrial emissions at facilities located near participants' homes were used to estimate dioxin exposure levels. They found that long-term exposure to airborne dioxin emissions within 2 miles of participants' residences was associated with increased breast cancer risk. This association was strongest for emissions from municipal solid waste facilities. This finding indicates that living in proximity to industrial emissions may be linked to higher breast cancer rates.<sup>7</sup>



### Diabetes

**Pregnancy.** Sister Study researchers found that developing diabetes during pregnancy, especially multiple pregnancies, increases the risk of type 2 diabetes later in life.<sup>8</sup>

**Metformin use.** While no association between type 2 diabetes and risk of developing estrogen receptor-positive breast cancer was found, there was a small increase in estrogen receptor-negative and triple-negative breast cancer among those with type 2 diabetes. Most women in the study with type 2 diabetes took metformin, a medication widely used to treat type 2 diabetes. These results support the hypothesis that even if type 2 diabetes is associated with increased breast cancer risk overall, metformin may help reduce the risk of developing estrogen receptor-positive breast cancer.<sup>9</sup>

### Diet and Vitamin D

Sister Study research also works to identify the role of individual nutrients, particularly vitamin D, in breast cancer risk.

Among women who identified as Black/African American or non-Black Hispanic/Latina, those with low blood levels of vitamin D were more likely to develop breast cancer than women with adequate levels. These findings, along with prior studies, suggest that adequate vitamin D may be associated with a reduced chance of breast cancer.<sup>10</sup> Women who regularly took vitamin D supplements had lower rates of postmenopausal breast cancer.<sup>11</sup>



### Genes and DNA Modifications

**Genetics.** Breast cancer genetic risk often refers to how the genes a woman is born with can influence her chance of getting breast cancer. However, as researchers showed, breast cancer may also be affected by naturally occurring changes to DNA, known as methylation, that occur after birth.<sup>12</sup> Women who developed breast cancer after joining the study were more likely to have changes in DNA methylation than those who did not have breast cancer, as seen in blood samples collected for the study.

**Predicting risk.** Sister Study researchers developed a new risk prediction score that may improve how women who are at higher risk for developing breast cancer can be identified. This risk score is based on individual changes to DNA methylation associated with breast cancer risk, as well as multiple DNA methylation clocks associated with aging, morbidity and mortality risks, as well as breast cancer. Though this method returned promising results, further investigation and replication is needed to see if it will be useful in a clinical setting.<sup>13</sup>

**Biological age.** Chronological age is a leading risk factor for breast cancer. NIEHS scientists found that measures of biological aging based on combinations of DNA methylation changes, known as methylation-age clocks, may be tied to environmental exposures and the likelihood of developing breast cancer.<sup>14</sup> The researchers later found that women who received breast cancer treatment, particularly radiation therapy, were biologically older than women who were never diagnosed with breast cancer.<sup>15</sup>



### Hair Products

The potential for long-term health effects from certain chemicals in hair products are an interest area for Sister Study researchers.

Women who regularly used hair straighteners and dye were 9% more likely than women who did not to develop breast cancer. Among Black women, using permanent dyes every five to eight weeks or more was associated with a 60% increased chance of developing breast cancer, as compared with an 8% increased risk for white women.<sup>16</sup>

Researchers looked at hair product use during adolescence and found that frequent use of straighteners and perms may be associated with increased breast cancer risk later in life, particularly prior to menopause. This research suggests that some chemicals in such products may be harmful to health, even when used decades before.<sup>17</sup>

**Other cancers.** Frequent use of hair straighteners or relaxers (four or more times per year) was associated with twice the risk of ovarian cancer compared to non-users.<sup>18</sup> An association with uterine cancer was also found for women who frequently used chemical hair straightening products. But no associations between uterine cancer and use of hair dyes, bleach, highlights, or perms were found.<sup>19</sup> These findings are particularly relevant for Black/African American women who are more likely to use certain types of hair products.

### Obesity

Women who were overweight or obese and had one or more metabolic abnormalities (such as elevated triglycerides, high blood sugar, or high blood pressure) had increased risk of postmenopausal breast cancer, as did overweight or obese women with no metabolic abnormalities. Risk of postmenopausal breast cancer was also higher in women with normal weight, but high measures of obesity in the mid-section of their bodies.<sup>20</sup>

### Sleep

**Nighttime light**, from inside the bedroom or shining in from outside the residence, is thought to increase the risk of breast cancer by disrupting the body's natural 24-hour (circadian) rhythms, which serve a wide variety of biologic functions. Sleeping with a television on, or at least one light on in the bedroom, was associated with a small (9%) increase in breast cancer risk.<sup>21</sup>

**Trouble sleeping.** Researchers also found trouble sleeping four or more nights per week was associated with increased breast cancer risk.<sup>21</sup>

### Social and Early-Life Factors

**Activity.** Women who exercised or played sports more than seven hours a week during ages 5-19 had a lower risk of breast cancer as adults.<sup>22</sup>

**Trauma.** Sister Study participants were asked if they experienced certain traumatic experiences during childhood and adolescence, and about half disclosed at least one traumatic experience before age 18. Traumatic events may include sexual, physical, or emotional abuse, and financial hardships. Experiencing either sexual trauma and household dysfunction, or some other early-life trauma, was associated with greater risk of developing breast cancer. But breast cancer risk due to early-life trauma appeared lower among participants who reported constant childhood social support. This research suggests that different types of early-life traumatic experiences may contribute to breast cancer risk.<sup>23</sup>

**Early development.** Earlier age at the first menstrual period (menarche) is known to be associated with increased breast cancer risk. Sister Study researchers found that earlier age of breast development (thelarche) is also associated with breast cancer risk. Experiencing early menarche (before age 12) and early thelarche (before age 10) together was associated with a greater risk than either factor on its own.<sup>24</sup>

### Future Direction for the Sister Study

The Sister Study collects more detailed information than many other studies, allowing researchers to ask and answer more complicated questions. They have been able, and will continue, to partner with researchers all over the world.

Participants in the study are diverse, which allows researchers to study health disparities and the health effects of factors related to where someone lives.

A newer challenge is to understand how changes in the climate may affect breast cancer risk. For example, the researchers are studying the effects of heat and how stressors from experiencing natural disasters may relate to breast cancer risk.

They also are focusing more on the ways that environmental factors may affect how well women fare after diagnosis and treatment for breast cancer.

To learn more about the NIEHS Sister Study, visit <https://sisterstudy.niehs.nih.gov/English/index1.htm>.

### Two Sister Study

A related NIEHS study focuses on women under 50 with young-onset breast cancer and their sisters without breast cancer. This study found certain factors may reduce the risk of young-onset breast cancer, such as older age at menarche, younger age at menopause, premenopausal hysterectomy, and early age at first-term pregnancy.<sup>25</sup>

## Other NIEHS-Funded Research

NIEHS, along with the NCI, studied developmental periods in women's lifespans, such as puberty, pregnancy, and menopause, to identify factors related to breast cancer. As a result, future prevention efforts may be targeted and more effective. Findings include:

- Exposures to common chemicals may change the timing of puberty. For example, girls exposed to high levels of triclosan, used in some antimicrobial soaps, had early breast development. Also, girls exposed to high levels of benzophenone-3, found in some sunscreens, had later breast development.<sup>26</sup>
- The chance of developing breast cancer may increase with exposure to endocrine-disrupting chemicals during these periods: prenatal development, puberty, pregnancy, and menopausal transition.<sup>27</sup>
- About 300 chemicals used in personal care products, flame retardants, food processing, pesticides, and other purposes were tested using *in vitro* assays and found to affect hormones known to increase breast cancer risk.<sup>28</sup>

NIEHS continues to fund grants for breast cancer research. For example, grant recipients are studying:

- Why African American women are more likely to get aggressive forms of breast cancer than other women.
- How disrupting a woman's biological clock or circadian rhythm (through shift work or time zone changes, for example) can affect the risk of developing breast cancer.
- How chemicals like PFAS may affect the chance of developing breast cancer.

## National Toxicology Program (NTP)

An interagency program headquartered at NIEHS, NTP lists six substances in the Report on Carcinogens because they cause or may cause breast cancer in humans: diethylstilbestrol (DES), a synthetic estrogen that was used to prevent miscarriages; steroidal estrogens used for menopausal therapy; X-ray and gamma radiation; alcoholic beverages; tobacco smoking; and ethylene oxide, a sterilizing agent.<sup>29</sup>

After conducting cancer assessments for working at night, NTP found that persistent night shift work that disrupts circadian rhythms can cause breast cancer in women. This type of work is considered frequent and long-term, especially beginning in early adulthood.<sup>30</sup>

For more information on the National Institute of Environmental Health Sciences, visit <https://www.niehs.nih.gov>.

<sup>1</sup> Interagency Breast Cancer and Environmental Research Coordinating Committee. 2013. Breast Cancer and the Environment: Prioritizing Prevention. Available: [https://www.niehs.nih.gov/sites/default/files/about/assets/docs/breast\\_cancer\\_and\\_the\\_environment\\_prioritizing\\_prevention\\_508.pdf](https://www.niehs.nih.gov/sites/default/files/about/assets/docs/breast_cancer_and_the_environment_prioritizing_prevention_508.pdf)

<sup>2</sup> Lichtenstein P, et al. 2000. Environmental and Heritable Factors in the Causation of Cancer: Analyses of Cohorts of Twins from Sweden, Denmark, and Finland. *N Engl J Med* 343(2):78-85.

<sup>3</sup> Niehoff NM, et al. 2020. Outdoor air pollution and terminal duct lobular involution of the normal breast. *Breast Cancer Res.* 24;22(1):100.

<sup>4</sup> White AJ, et al. 2019. Air Pollution, Clustering of Particulate Matter Components, and Breast Cancer in the Sister Study: A U.S.-Wide Cohort. *Environ Health Perspect* 127(10):107002.

<sup>5</sup> White AJ, et al. 2022. Exposure to particle radioactivity and breast cancer risk in the Sister Study: A U.S.-wide prospective cohort. *Environ Health Perspect* 130(4):47701.

<sup>6</sup> White AJ, et al. 2019. Metallic air pollutants and breast cancer risk in a nationwide cohort study. *Epidemiology* 30(1):20-8.

<sup>7</sup> Rhee J, et al. 2023. Residential proximity to dioxin emissions and risk of breast cancer in the sister study cohort. *Environ Res* 222:115297.

<sup>8</sup> Diaz-Santana MV, et al. 2022. Persistence of risk for type 2 diabetes after gestational diabetes mellitus. *Diabetes Care*; doi:10.2337/dc21-1430

<sup>9</sup> Park YM, et al. 2021. A prospective study of type 2 diabetes, metformin use, and risk of breast cancer. *Ann Oncol* 32(3):351-359

<sup>10</sup> O'Brien KM, et al. 2022. Vitamin D concentrations and breast cancer incidence among Black/African American and non-Black Hispanic/Latina women. *Cancer* 128(13):2463-2473.

<sup>11</sup> O'Brien KM, et al. 2017. Serum Vitamin D and Risk of Breast Cancer Within Five Years. *Environ Health Perspect* 125(7):077004.

<sup>12</sup> Xu Z, et al. 2020. Blood DNA Methylation and Breast Cancer: A Prospective Case-Cohort Analysis in the Sister Study. *J Natl Cancer Inst* 112(1):87-94.

<sup>13</sup> Kresovich JK, et al. 2022. Blood DNA methylation profiles improve breast cancer prediction. *Mol Oncol* 16(1):42-53.

<sup>14</sup> Kresovich JK, et al. 2019. Methylation-based biological age and breast cancer risk. *J Natl Cancer Inst* 111(10):1051-8.

<sup>15</sup> Kresovich JK, et al. 2023. Changes in methylation-based aging in women who do and do not develop breast cancer. *J Natl Cancer Inst* djad117.

<sup>16</sup> Eberle CE, et al. 2019. Hair dye and chemical straightener use and breast cancer risk in a large US population of black and white women. *Int J Cancer* 147(2):383-391.

<sup>17</sup> White AJ, et al. 2021. Adolescent use of hair dyes, straighteners and perms in relation to breast cancer risk. *Int J Cancer* 148(9):2255-63.

<sup>18</sup> White AJ, et al. 2021. Use of hair products in relation to ovarian cancer risk. *Carcinogenesis* 42(9):1189-95

<sup>19</sup> Chang CJ, et al. 2022. Use of Straighteners and Other Hair Products and Incident Uterine Cancer. *J Natl Cancer Inst* 114(12):1636-1645

<sup>20</sup> Park YM, et al. 2017. The association between metabolic health, obesity phenotype and the risk of breast cancer. *Int J Cancer* 140(12):2657-66.

<sup>21</sup> White AJ, et al. 2017. Sleep characteristics, light at night and breast cancer risk in a prospective cohort. *Int J Cancer* 141(11):2204-2214.

<sup>22</sup> Niehoff NM, et al. 2017. Childhood and teenage physical activity and breast cancer risk. *Breast Cancer Res Treat* 164(3):697-705.

<sup>23</sup> Woo JMP, et al. 2022. Latent class models of early-life trauma and incident breast cancer. *Epidemiology* 33(5):729-38.

<sup>24</sup> Goldberg M, et al. 2020. Pubertal timing and breast cancer risk in the Sister Study cohort. *Breast Cancer Res* 22(1):112.

<sup>25</sup> O'Brien KM, et al. 2015. Risk factors for young-onset invasive and in situ breast cancer. *Cancer Causes Control.* 26(12):1771-8.

<sup>26</sup> Wolff MS, et al. 2015. Breast Cancer and Environment Research Program. 2016. Environmental phenols and pubertal development in girls. *Environ Int* 84:174-180.

<sup>27</sup> Terry MB, et al. 2019. Environmental exposures during windows of susceptibility for breast cancer: a framework for prevention research. *Breast Cancer Research*; doi: 10.1186/s13058-019-1168-2

<sup>28</sup> Cardona B, Rudel RA. 2021. Application of an *in Vitro* Assay to Identify Chemicals That Increase Estradiol and Progesterone Synthesis and Are Potential Breast Cancer Risk Factors. *Environ Health Perspect.* 129(7):77003.

<sup>29</sup> National Toxicology Program. 15th RoC Dashboard. DOI: <https://doi.org/10.22427/NTP-DATA-ROC-15> [accessed 17 July 2023].

<sup>30</sup> National Toxicology Program. 2021. Cancer Hazard Assessment Report on Night Shift Work and Light at Night. Available: [https://ntp.niehs.nih.gov/ntp/results/pubs/cancer\\_assessment/lanfinal20210400\\_508.pdf](https://ntp.niehs.nih.gov/ntp/results/pubs/cancer_assessment/lanfinal20210400_508.pdf)