



THE
SISTER STUDY BREAST CANCER RESEARCH
WOMAN BY WOMAN, SISTER BY SISTER, WE CAN MAKE A DIFFERENCE!

Dear Sisters—

2015 IN REVIEW

Congratulations and sincere thanks are in order for those of you who are celebrating your 10-year anniversary as a Sister Study participant! This is a significant milestone. Your participation over the years has made finding breast cancer risk factors more likely.

When we began the Sister Study, we asked participants to stay with us for at least 10 years. Even then, we knew that our chances of making important discoveries about breast cancer were greater the longer we could follow participants. We chose 10 years as a minimum because we knew we had to prove that we could establish this cohort and use the data in important ways in order to continue longer. Since we started in just a few cities in 2003, we have enrolled the largest ever cohort of women with a sister with breast cancer. Participants come from all 50 states and Puerto Rico, and we exceeded our goal, enrolling 50,884 women. Together, we have completed annual health updates and two comprehensive follow-up cycles with better than 90 percent response each time. We have used the information you provided to answer questions about a range of potential risk factors for breast cancer and other conditions. We partnered with others to better understand how a breast cancer diagnosis affects women and their families. And, we combined forces with other studies to better understand less common conditions like ovarian and thyroid cancers that we cannot study on our own.

Our successes thus far position us for future discovery, and we are excited to continue the study well into the future. There is so much more to learn!

You can find information on the nearly 50 published Sister Study articles to date at sisterstudy.niehs.nih.gov/English/articles.htm. These would not be possible without you, our dedicated participants. You have generously given us your time and information to help us find the causes of breast cancer. We hope you share our pride in the many accomplishments to date.

As we go forward, we will continue to look for ways to make it easier for you to participate—especially for those of you who have been with us a long time and are now finding it more difficult to participate. By continuing to provide updates on any changes to your health, you will be allowing all of us to reap the benefits of the considerable investment you have already made to understanding breast cancer risk. We greatly appreciate your years of dedication to the Sister Study.

With best wishes,

Dale P. Sandler, PhD
Principal Investigator
The Sister Study





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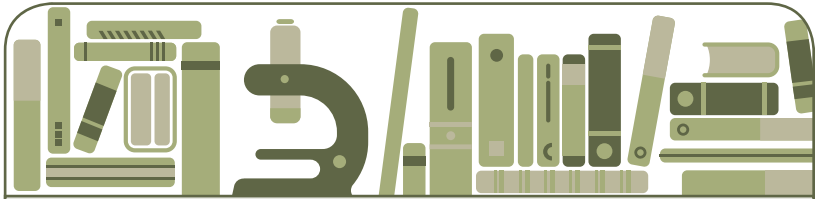
New Researchers Join the Sister Study



Dr. Alexandra (Lexie) White joined the Sister Study in fall 2015 after receiving a doctoral degree in epidemiology from the University of North Carolina at Chapel Hill. During her doctoral studies, Dr. White worked on the Long Island Breast Cancer Study Project, which was one of the first

studies specifically designed to evaluate links between environmental exposures and breast cancer. For her dissertation, Dr. White investigated the association between a common group of chemicals, polycyclic aromatic hydrocarbons (PAHs), and breast cancer risk. PAHs are found in indoor and outdoor air pollution, vehicular traffic, tobacco smoke, and in some foods. She also considered how these chemicals affect DNA methylation, which influences how DNA is expressed and is important for breast cancer. While a graduate student, Dr. White collaborated with the Sister Study to study lifestyle and environmental factors. She is looking forward to expanding and furthering her research on environmental exposures and breast cancer in the prospective Sister Study cohort.

Dr. Yong-Moon (Mark) Park joined the Sister Study in late August 2015. Dr. Park trained in preventive medicine in Seoul, Korea, and received a PhD in epidemiology from the Arnold School of Public Health at the University of South Carolina. His doctoral dissertation evaluated the impact of Mediterranean diet and dietary hypertension interventions on morbidity and mortality. He also showed that weight alone is not a good indicator of future health; other measures of metabolic function may be more important. In the Sister Study, he plans to focus his efforts on understanding environmental contributors to diabetes, obesity, and metabolic function and on evaluating the impact of these outcomes on breast cancer risk.



Sister Study Publications 2015

Breast cancer risk in relation to ambient air pollution exposure at residences in the Sister Study cohort (Page 3)

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For information on other published research articles, see sisterstudy.niehs.nih.gov/English/articles.htm

Anthropometry and head and neck cancer: a pooled analysis of cohort data

Fruit and vegetable intake and urinary levels of prostaglandin E₂ metabolite in postmenopausal women

In utero exposure to diethylstilbestrol and blood DNA methylation in women ages 40-59 years from the Sister Study

Hormone therapy and young-onset breast cancer

Lifetime use of nonsteroidal anti-inflammatory drugs and breast cancer risk: results from a prospective study of women with a sister with breast cancer

Migraine and possible etiologic heterogeneity for hormone-receptor-negative breast cancer

Non-steroidal anti-inflammatory drug use and genomic DNA methylation in blood

Post-treatment neurocognition and psychosocial care among breast cancer survivors

Ambient Air Pollution Exposure Is not Associated With Overall Breast Cancer Risk, But May Be Associated With Hormone-Receptor-Positive Breast Cancer

Previous studies have investigated the link between components of air pollution, such as fine particulate matter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and nitrogen dioxide (NO_2), with overall breast cancer, but not with breast cancer defined by estrogen receptor (ER) and progesterone receptor (PR) status. Tumors with ER and/or PR are more responsive to certain growth hormones. To determine if air pollution components affect the risk of breast cancers defined by ER and PR, data from Sister Study participants' residential history were combined with externally measured air pollution data.

Investigators found that overall breast cancer risk was not associated with either $\text{PM}_{2.5}$ or NO_2 . However, data indicated that higher NO_2 levels in the air were associated with ER+/PR+ breast cancer, but not with ER-/PR- breast cancer.

Although results from the Sister Study suggest that air pollution is not associated with an increased risk of overall breast cancer, NO_2 , a marker of traffic-related air pollution, may increase the risk of ER+/PR+ breast cancer. Since NO_2 is not a carcinogenic (cancer-causing) agent itself, further research is needed to understand why NO_2 is associated with breast cancer.

Breast cancer risk in relation to ambient air pollution exposure at residences in the Sister Study cohort.
Reding KW, Young MT, Szpiro AA, Han CJ, DeRoo LA, Weinberg C, Kaufman JD, Sandler DP. *Cancer Epidemiology, Biomarkers & Prevention*. 2015 Dec;24(12):1907-9. doi: 10.1158/1055-9965.EPI-15-0787. Epub 2015 Oct 13.

<http://www.ncbi.nlm.nih.gov/pubmed/26464427>



Long-Term Exposure to Air Pollution Linked to Increased Blood Pressure

Exposure to air pollution is associated with heart disease, a leading cause of death in women. However, the specific mechanisms are not well understood. Sister Study researchers and collaborators at the University of Washington used geographic information system (GIS) data, which is linked to latitude/longitude coordinates, and satellite-based data to predict levels of air pollution from nitrogen dioxide and fine particulate matter at the residences of more than 43,000 Sister Study participants. Predicted air pollution levels were then studied in relation to blood pressure measured at the enrollment home visit for the same participants. The study showed that air pollution-related increases in blood pressure occur at rates high enough to be contributors to the illness and death from cardiovascular disease seen in prior studies.

Long-term air pollution exposure and blood pressure in the Sister Study.

Chan SH, Van Hee VC, Bergen S, Szpiro AA, DeRoo LA, London SJ, Marshall JD, Kaufman JD, Sandler DP. *Environmental Health Perspectives*. 2015 Oct;123(10):951-8. doi: 10.1289/ehp.1408125. Epub 2015 Mar 6.

<http://www.ncbi.nlm.nih.gov/pubmed/25748169>



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Fat Accumulation May Increase Breast Cancer Risk

In this study published in the journal *Cancer*, investigators used data from the Sister Study to evaluate the relationship between adiposity measurements—measurements of fat accumulation in the body—and breast cancer risk. Central adiposity is measured by waist circumference and waist-to-hip ratio [WHR], while overall adiposity is measured by body mass index (BMI).

Waist circumference and WHR are associated with many hormonal and metabolic changes and may be a better predictor of breast cancer risk than BMI in premenopausal women. Central adiposity also has been hypothesized to be a better indicator of metabolically active visceral fat (fat that collects in the liver) among postmenopausal women than BMI.

As expected, women who were overweight or obese had increased risk for breast cancer overall and for hormone receptor-positive breast cancer. Increasing waist circumference and increasing WHR were also independently associated with breast cancer risk. In contrast to previous studies that reported that adiposity was not associated with premenopausal breast cancer risk when BMI alone was measured, the Sister Study researchers found that higher waist circumference as a measure of central obesity was associated with increased risk for premenopausal breast cancer even though BMI was not. These results further support the role of fat accumulation and distribution in the body as an independent risk factor for breast cancer.

Overall and central adiposity and breast cancer risk in the Sister Study.

White AJ, Nichols HB, Bradshaw PT, Sandler DP. *Cancer*. 2015 Oct 15;121(20):3700-8. doi: 10.1002/cncr.29552. Epub 2015 Jul 20.

<http://www.ncbi.nlm.nih.gov/pubmed/26193782>

The Sister Study Contributes to Understanding the Relationship Between an Ovarian Hormone and Breast Cancer Risk

With funding from the Avon Foundation, researchers investigated the relationship between anti-Müllerian hormone (AMH) levels in blood and breast cancer risk in a subset of women participating in the Sister Study. AMH is a biomarker of ovarian reserve that is highest in late childhood/early adulthood and begins to decline around age 25 until menopause, when the hormone may no longer be detected. Blood samples provided at enrollment by approximately 1,300 premenopausal Sister Study participants and data from their completed questionnaires were used. The analysis showed that women with the highest AMH levels at time of enrollment had a two-fold increase in the risk of developing breast cancer compared with similar aged women whose levels were too low to be detected. It is already known that late age at menopause is a risk factor for breast cancer. In order to determine if AMH levels are simply a marker for menopause status or if AMH contributes to breast cancer risk directly, the researchers will be combining Sister Study data with data from other studies to have a large enough sample to sort this out. They are also currently exploring links between environmental exposures and AMH levels.

Anti-Müllerian hormone concentrations in premenopausal women and breast cancer risk.

Nichols HB, Baird DD, Stanczyk FZ, Steiner AZ, Troester MA, Whitworth KW, Sandler DP. *Cancer Prevention Research*. 2015 Jun;8(6):528-34. doi: 10.1158/1940-6207.CAPR-14-0377. Epub 2015 Apr 14.

<http://www.ncbi.nlm.nih.gov/pubmed/25873369>

Exposure to Certain Workplace Chemicals Linked to Increased Risk of Breast Cancer

Researchers analyzed more than 47,000 Sister Study participants' self-reported occupational exposure information—including whether they ever used acids, dyes or inks, gasoline or other petroleum products, glues or adhesives, lubricating oils, metals, paints, pesticides, soldering materials, solvents, and stains or varnishes—and compared the exposures of women who did and did not develop breast cancer later. The researchers found no overall associations between having ever used any of the 11 agents and increased breast cancer risk. However, they did observe that women with the highest overall

exposures to gasoline and petroleum products had an elevated risk of breast cancer compared with the women with the lowest exposures. Exposure to soldering materials was associated with an increased risk of premenopausal breast cancer. The findings demonstrated the need for more research on the relationship between workplace chemical exposures and breast cancer.

Chemical exposures in the workplace and breast cancer risk: A prospective cohort study.

Ekenga CC, Parks CG, Sandler DP. *International Journal of Cancer*. 2015 Oct 1;137(7):1765-74. doi: 10.1002/ijc.29545. Epub 2015 Apr 27.

<http://www.ncbi.nlm.nih.gov/pubmed/25846061>

Former Sister Study Fellow Receives Grant to Continue Breast Cancer Research



Now an Assistant Professor of Epidemiology at the University of North Carolina at Chapel Hill, former Sister Study research fellow Dr. Hazel Nichols recently received a \$200,000 grant from the Avon Foundation to study pregnancy-associated breast cancer. Unlike rates among older women, advanced-stage breast cancer rates among reproductive-age women have increased in recent years. Breast cancers diagnosed within a few years of childbirth are more likely to be at an advanced stage—a fact that has drawn greater attention to breastfeeding and weaning as processes that may temporarily make breast tissue more vulnerable to cancer cell growth and spread. However, breastfeeding also lowers risk of specific tumor subtypes, including triple-negative or basal-like tumors that are more aggressive.

Understanding the short- and long-term effects of pregnancy and breastfeeding on breast cancer risk has been difficult because few studies have enough young women with breast cancer to carefully

consider each factor. Dr. Nichols' research will combine information from the Sister Study with data from more than 18 other studies around the world to specifically focus on cancer diagnosed in reproductive-age women. In addition to the funding from the Avon Foundation grant, the study is supported by NIEHS and The Institute of Cancer Research, Royal Cancer Hospital, London, UK, and being carried out through the National Cancer Institute Cohort Consortium, which was organized to foster the large-scale collaborations needed to quicken the pace of research and provide urgently needed answers. Ultimately, the study will include more than a million women and provide some of the best evidence to date on risk factors for premenopausal breast cancer.





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Two Studies Investigate the Link Between Physical Activity at Work and Impact on Leisure-Time Activity and Potential Breast Cancer Risk

Using information on self-reported levels of occupational and leisure-time physical activity from about 26,000 currently employed women participating in the Sister Study, researchers evaluated associations between three levels of occupational activity (sitting, standing, or manually active) and leisure-time physical activity (insufficient, moderate, or high). They found that only about half of the women met or exceeded minimum recommended levels of leisure-time physical activity, and that women who reported sitting or standing most of the time at work were less likely than active workers to meet the requirements for high leisure-time physical activity. The study's findings suggest that women who are not active at their workplace would likely benefit from strategies to promote leisure-time physical activity, which may decrease breast cancer risk.

These results led to a follow-up study to evaluate the relationship between occupational physical activity and breast cancer in the study population.

Sister Study participants with three-quarters or more of their occupational history spent in active jobs had a 28 percent reduced risk of breast cancer, even after adjusting for recreational physical activity. The impact of occupational physical activity was most pronounced for overweight and postmenopausal women. In the end, the researchers concluded that while additional research is needed to understand the mechanisms underlying the relationships between occupational activity, body size, and breast cancer, occupational physical activity can be an important contributor to a healthy lifestyle.

Leisure-time physical activity in relation to occupational physical activity among women.

Ekena CC, Parks CG, Wilson LE, Sandler DP. *Preventive Medicine*. 2015 May;74:93-6. doi: 10.1016/j.ypmed.2015.03.003. Epub 2015 Mar 12.

<http://www.ncbi.nlm.nih.gov/pubmed/25773471>

A prospective study of occupational physical activity and breast cancer risk.

Ekena CC, Parks CG, Sandler DP. *Cancer Causes Control*. 2015 Dec;26:1779-89. doi: 10.1007/s10552-015-0671-8. Epub 2015 Oct 8.

<http://www.ncbi.nlm.nih.gov/pubmed/26450605>

Some "Known" Breast Cancer Risk Factors Do Not Increase Risk in Younger Women

When breast cancers occur at an earlier age, these tumors tend to be more aggressive than later-onset tumors and may be associated with different risk factors. Researchers evaluated the association between several potential risk factors and young-onset breast cancer in the Two Sister Study, which is an offshoot of the Sister Study. The Two Sister Study included pairs of sisters—one in the Sister Study who did not have breast cancer and a sister who was diagnosed with breast cancer before age 50 and no more than 4 years before the study was carried out.

The researchers found that, similar to studies of women diagnosed at older ages, older age at menarche, younger age at menopause, and premenopausal hysterectomy were associated with reduced risk of breast cancer in young women. However, in contrast to studies of older women, early age at first-term pregnancy, obesity, and moderate consumption of alcohol—commonly considered to be risk factors for breast cancer—were not associated with breast cancer in young women.

Risk factors for young-onset invasive and in situ breast cancer.

O'Brien KM, Sun J, Sandler DP, DeRoo LA, Weinberg CR. *Cancer Causes Control*. 2015 Dec;26:1771-8. doi: 10.1007/s10552-015-0670-9. Epub 2015 Sep 25.

<http://www.ncbi.nlm.nih.gov/pubmed/26407954>

Sister Study Launches Effort to Retrieve Mammograms

Breast density, a mammographic measure of the proportion of the breast that is made up of breast tissue (e.g., milk ducts, lobules, and connective tissue) versus fat, is considered a marker for breast cancer risk. In general, younger women tend to have dense breasts, and breast density typically decreases as a woman gets older. Women with high breast density are more likely to get breast cancer than women with low breast density. Mammograms of dense breasts are harder to read than mammograms of fatty breasts, but this alone does not explain why women with dense breasts whose mammograms are read as normal have a greater chance of later being diagnosed with breast cancer.

Many states have passed laws requiring doctors to report breast density scores to women following their mammogram, presumably so women can decide on further screening tests or make lifestyle changes in hopes of reducing breast cancer risk. However, while dense breasts are associated with a greater chance of developing breast cancer, it is not clear if reducing breast density will decrease breast cancer risk. It is also not clear how one would go about reducing her breast density. Getting older and gaining weight after menopause are both related to lower breast density, but are also related to an increase in breast cancer risk. There is also concern that women with higher density scores could receive unnecessary extra testing. Therefore, it is important to better understand what breast density means in terms of breast cancer risk and to identify which potentially modifiable factors, if any, might be associated with having denser breasts.

Change in breast density over time may be more informative than a single measure for risk prediction. For example, women whose breast tissue remains dense for several years after menopause may have a different degree of risk compared with women whose breast density declines gradually or rapidly as they approach menopause.

The Sister Study is now pilot testing procedures to collect participant's past mammograms. We have already found that if women give us permission, doctors are willing to share the mammograms for research studies. We also found that most women have had many mammograms since age 45 and that these can often be retrieved—sometimes electronically—from the same medical facility. These repeated records will allow us to track changes over the years. We now plan to reach out to a larger percentage of Sister Study participants so that we can study the importance of change in breast density over time as well as the impact of environmental exposures on breast density.

If you are contacted and asked to give us permission to retrieve your mammograms, we hope you will say yes! It should take you only a few minutes to complete the permission forms, and you'll be making an important contribution to breast cancer research. By combining the information from your screening mammograms with data you have already shared about lifestyle, family history, and other breast cancer risk factors, we can make great strides in understanding the value of breast density measures over time for risk prediction and breast cancer prevention.

The Sister Study Examines the Risks and Benefits of Tamoxifen Use for Preventing Breast Cancer

Tamoxifen has been approved for prevention of breast cancer since 1998 but has not been widely adopted, in part because of sometimes unpleasant side effects (e.g., hot flashes) as well as less common but serious side effects (e.g., endometrial and uterine cancer). Researchers used data from women in the Sister Study who reported on their tamoxifen use to examine risk/benefit profiles. Data from 788 tamoxifen users and about 3,000 nonusers were compared. Results showed that for about 20 percent of the tamoxifen users, there was not sufficient evidence, based on published risk/benefit indices, that the benefits of tamoxifen outweighed the risk of serious side effects. On the other hand, some women who might have benefitted were never prescribed the drug. Results also showed that 46 percent of the women who used tamoxifen stopped early.

Risk-benefit profiles of women using tamoxifen for chemoprevention.

Nichols HB, DeRoo LA, Scharf DR, Sandler DP. *Journal of the National Cancer Institute*. 2014 Dec 3;107(1):354. doi: 10.1093/jnci/dju354. Print 2015 Jan.

<http://www.ncbi.nlm.nih.gov/pubmed/25475563>



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The Sister Study receives additional support from research grants and other U.S. Government agencies.



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Visit our website: sisterstudy.niehs.nih.gov

48 Zn zinc 65.39	49 Cd cadmium 112.4	69 Ga gallium 69.72
79 Au gold 196.967	80 Hg mercury 200.59	

Metals in Toenails

Have you ever wondered why the Sister Study and Two Sister Study collected toenail clippings when you enrolled? We are using toenails to measure your typical exposures to specific chemicals and environmental agents. In particular, metals such as cadmium, lead, nickel, manganese, and arsenic can be measured in toenails and represent a biological marker of exposures over the previous 6 to 12 months, depending on the chemical and which toenail is used (the big toenail takes the longest to grow out). Researchers from the Two Sister Study are collaborating with researchers from Dartmouth College, who have extensive experience studying metals in toenail samples, to study the potential relationship between cadmium and other elements and breast cancer risk. Several studies have reported increased risk for breast cancer in women with higher exposure to cadmium in the diet or as measured in urine, but other studies have not found such a link. Sources of cadmium exposure include air pollution and contaminated soil and water from mining and manufacturing. Other sources of exposure for women in the United States are cigarette smoking and some components of diet. In general, leafy green vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds may contain relatively higher levels of cadmium.