



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

Dear Sisters—

2014

It has been 10 years since the first “vanguard” Sisters joined the Sister Study, though for most of you, this milestone will not come for a few years. For some of you, and for us, being part of the Sister Study has become part of what we do and who we are. For others, it is becoming more challenging to stay active in the study, and we are doing what we can to make participation easier. In this newsletter, you will read how we are trying to shorten questionnaires and reduce the number of things we ask you to do. I am most excited about the addition of our team of Participant Advocates who will partner with those who need a hand with completing study-related activities.

This year, we completed our second round of comprehensive follow-up questionnaires with nearly 92 percent of you providing some information. Unfortunately, we lost a few Sisters to death, major illnesses, or fatigue—but our participation rates continue to amaze. We are the envy of our colleagues because of the dedication of our participants and the richness of the data that you have provided over the years. Some of you have been contacted for a new sample collection, *Sisters Changing Lives*. This will be a unique resource for researchers to learn how biological factors and measures of exposure change over time with or without a diagnosis of breast cancer. Our partnership with the Centers for Disease Control and Prevention (CDC) to focus on quality of life among breast cancer survivors makes us one of the few large studies to ask these important questions that matter to women with breast cancer and those who love them.

Some of you have asked us why we continue to request annual health updates and collect new information about your experiences. It is important—and part of what makes the Sister Study unique and powerful—to learn what may have changed in your life experiences or exposures that could influence your risk for developing breast cancer or other health conditions. Some of you may have retired, or have stopped smoking or taking hormones. Others may have developed high blood pressure, switched jobs, or taken on a second career. I have become a grandmother for the very first time.

I wish you and yours good things in the coming months and thank you again for your continued participation in the Sister Study.

Sincerely yours,

Dale P. Sandler, PhD
Principal Investigator
The Sister Study





RESEARCH

MAKING A DIFFERENCE

Changes in DNA Methylation May Partly Explain Increasing Cancer Risk with Age

DNA methylation is a chemical change to DNA that can alter the way genes function in the cell. Some DNA methylation is inherited, but methylation may be gained or lost over time. Methylation patterns differ between persons with and without cancer, and are thought to change with some environmental exposures and with age. And age is a major risk factor for most cancers.

Sister Study investigators looked for DNA sites that were methylated differently with age (age-related methylation) and with developing cancer. The team analyzed 1,066 DNA samples for methylation changes in the regions of approximately 14,500 different genes. By checking the Sister Study findings against three other independent studies, the investigators identified specific changes that became more common with increasing age. Of the approximately 27,000 DNA locations examined, some sites were methylated more with age, while other sites were methylated less.

When results were compared with data published for seven tumor types (including breast cancer), the age-related, increased-methylation sites identified in the Sister Study were found to be associated with cancer development. In addition, the sites were in genes that are important in known pathways for cancer development. Taken together, these results suggest that age-related increased methylation at these sites may increase cancer risk.

Genome-wide age-related DNA methylation changes in blood and other tissues relate to histone modification, expression, and cancer.

Xu Z and Taylor JA. *Carcinogenesis*. 2014 Feb; 35(2): 356-364. Epub 2013 Nov 28. doi: 10.1093/carcin/bgt391

Obtaining Medical Records and Tumor Tissue To Better Understand a Diagnosis

When a Sister Study participant reports she has been diagnosed with breast cancer or another type of cancer, the Sister Study team follows up to obtain the most useful medical details related to her diagnosis. Once we get signed permission to contact health care providers, we start the process of gathering pathology reports and, for breast cancer, relevant medical records. Although many women can report important details about their diagnosis themselves, the pathology reports and medical records are generally the most complete and accurate sources of information about the tests that were performed and how the diagnosis was made.

When records arrive at the Sister Study office, we assign them a code number and log them into a system that tracks where they are at all times. The documents are then assigned to a specialist who is trained to review medical records. The specialist abstracts information about tumor characteristics, diagnostic tests, surgeries, chemotherapy, radiation treatments, and other therapies and notes information about whether the tumor has spread to lymph nodes or other areas. In all cases, our medical records specialists follow strict guidelines to ensure that every case is reviewed and interpreted in the same way.

In addition to the medical records, we request relevant samples of breast tumor tissue from the pathologists who helped make the diagnosis. After tumor tissue is biopsied to make a diagnosis, it is saved by hospitals in paraffin (wax) blocks that preserve the tissue. We take tiny samples of the tumor tissue from the blocks to use in critical genetic studies, and then the original tissue blocks are stored or returned to the pathologist, if needed.

All medical records and pathology tissue samples are stored securely. Medical records are filed numerically by your Study ID in locked fireproof file cabinets within a secure room and building. Only qualified medical records staff ever have access to your records.

Genetic Variants from Mother’s Side of the Family May Affect the Development of Breast Cancer

We know that women with a family history of breast cancer are more likely to develop breast cancer themselves. Variations in genes (“genetic variants”) that are passed down from grandparents to parents to children are thought to account for much of this increased risk, but genes may act in other ways to increase the chances of developing breast cancer.

Studying patterns in family history of breast cancer may help researchers understand just how genes influence cancer risk. If most of a family’s cancers occurred on one side—either the mother’s side or the father’s side—it may suggest other ways that risk is passed down in families. For example, a mother’s genes may influence her pregnancies in ways that affect her daughter’s risk. It is also possible that the development of breast cancer may depend on whether certain genetic variants were inherited from the mother or the father.

Using family history data from Sister Study participants, we were able to find about 5,000 families in which the participants could tell us about both of their grandmothers, and one of those grandmothers had breast cancer. If it does not matter how the genes that lead to breast cancer are inherited, we would expect that about one-half of those grandmothers with breast cancer would have been on the mother’s side and one-half from the father’s side. Instead, we found that breast cancer was more likely to have been diagnosed in the maternal grandmother (mother’s mother) than in the paternal grandmother (father’s mother). These findings support the theory that genetic variants inherited from the mother’s side of the family may influence the development of breast cancer.

Asymmetry in family history implicates nonstandard genetic mechanisms: application to the genetics of breast cancer.

Weinberg CR, Shi M, DeRoo LA, Taylor JA, Sandler DP, Umbach DM. *PLOS Genetics*. 2014; 10(3): e1004174. Epub 2014 Mar 20. doi:10.1371/journal.pgen.1004174

Lightening Your Load and Tailoring Your Experience

We know that we ask much of you. Without your dedication and commitment to the Sister Study, we never could have established this groundbreaking cohort. We also know that staying in a study like this for many years can be challenging. We want you to know that we hear you! We hope you will notice that we are finding ways to lighten your load and are making changes in response to your feedback.

For example, we are changing how often we ask you to do something for the study, and we are working to make our questionnaires shorter. If you have indicated how you prefer to complete questionnaires—online, on paper, or by telephone—we want to give you that option first.

We have introduced a new team of Participant Advocates whose role will be to make it easier for some of you to participate. These advocates have been specially trained to work with Sisters who need help completing follow-up questionnaires. An advocate and a participant partner to work through any barriers to participating.

Our goal is to listen to you, and to do everything possible to make remaining in the study as easy as possible.



Kalimah, Storme, Lourdes, Jannie, and Brenda are part of the Participant Advocates team.



RESEARCH

MAKING A DIFFERENCE

Timing of Workplace Exposure to Solvents May Influence Breast Cancer Risk

Women who use solvents in their jobs may have a higher risk for breast cancer, especially if this use took place before their first full-term childbirth.

“The time between puberty and first birth is important in breast tissue development. It is a time when the breast may be more vulnerable to chemical exposures,” said Dr. Christine C. Ekenga, a Sister Study researcher and postdoctoral fellow at NIEHS. “We observed that women who started working with solvents before their first full-term birth had a higher risk for breast cancer.”

Solvents are chemicals in paints, adhesives, degreasing agents, and cleaning products. They also are used in manufacturing plastics, medicines, fabrics, computer parts, and other goods. Dr. Ekenga and her colleagues used data from the Sister Study to explore the relationship between breast cancer risk and use of solvents in the workplace. The team identified several jobs—including laboratory technicians, maids or housekeepers, and factory workers—in which women who used these chemicals had a higher risk for breast cancer. Dr. Ekenga noted, “All women should be familiar with the chemicals and hazards in their workplace, use

personal protective equipment properly, and limit exposures when appropriate.”

Overall, there was no increased risk for breast cancer from *lifetime* exposure to solvents, but the researchers found that women who worked with solvents *before* their first full-term birth had about a 40 percent higher risk for developing hormone-related breast cancer. They also found that women whose jobs required working with solvents before 1980—when Federal workplace safety and health regulations were not yet in place—had a 28 percent higher risk for developing hormone-related breast cancer.

“Our study is an important first step toward understanding how the *timing* of chemical exposures may affect breast cancer risk,” said Dr. Ekenga. “Our findings suggest a need for future studies that focus on vulnerable time windows and the types of solvents women use in different job settings. We hope our study will generate additional interest in the possible role solvents and other chemicals play in causing breast cancer.”

Breast cancer risk after occupational solvent exposure: the influence of timing and setting.

Ekenga CC, Parks CG, D’Aloisio AA, DeRoo LA, Sandler DP. *Cancer Research*. 2014 Jun 1; 74(11);3076-3083. doi:10.1158/0008-5472.CAN-13- 2430

Sister Study Fellow Receives Grant To Study Vitamin D and Breast Cancer Prevention

Vitamin D has been shown to have powerful anti-cancer effects, but evidence on whether taking vitamin D supplements can reduce risk for cancer, including breast cancer, is not clear. Dr. Katie O’Brien, a postdoctoral fellow working with Dr. Clarice Weinberg in the NIEHS Biostatistics Branch and a member of the Sister Study research team, recently received funding from the NIH Office of Dietary Supplements to study whether vitamin D can reduce the risk of developing breast cancer. In addition to supplements, vitamin D comes from sunlight and foods like some types of fish, fortified milk and cereal, eggs, and dairy products. Dr. O’Brien will measure levels of vitamin D in serum from the blood samples women provided when they joined the study. She will combine the results with information from Sister Study questionnaires, medical records from women who developed breast cancer since joining the study, and laboratory data from other Sister Study research—such as the studies of DNA methylation—to evaluate whether women with higher levels of vitamin D are less likely to develop breast cancer.



What Do We Mean When We Talk About “Genetic Tests”?

The tests performed by Sister Study investigators are used for research, not diagnoses. Tests for medical decision-making or “clinical” tests—such as for mutations in the BRCA1 or BRCA2 genes—must be licensed by the U.S. Food and Drug Administration (FDA) and performed in laboratories with Clinical Laboratory Improvement Amendments (CLIA) certification. The Sister Study does not do clinical testing. If you have concerns or questions about your health, you should ask your doctor about appropriate medical tests.

The types of genetic tests performed in the Sister Study are focused on identifying new markers that can be developed for use in the future—not on testing markers that are currently available (such as BRCA1 and BRCA2). Most research tests are intended to help us understand how and why cancer develops, not to diagnose or treat it. To achieve this, researchers examine large numbers of genetic analyses. They are looking to see if women with a certain genetic variation are more likely (or less likely) to get breast cancer than are women with different variations. If this turns out to be the case, these findings could be an extremely valuable clue for researchers and could serve to guide other researchers and test developers in the most productive directions.

The goal of research is to understand breast cancer and discover better ways to prevent it. Your benefit is the knowledge that the information from your research tests may lead to new tests that will help women achieve this goal. The women you help could be your daughters, daughters-in-law, nieces, or granddaughters. Research is a slow process, but your generous participation in the Sister Study is helping to speed it up.

Sister Study and CDC Investigators Begin Analyses To Advance EARLY Act Goals and Better Understand Life After Breast Cancer



Sister Study and Centers for Disease Control and Prevention (CDC) investigators met last fall in Research Triangle Park, North Carolina, to plan analyses using two special surveys completed by Sister Study participants. Some 20,000 women answered questions on breast cancer screening, family communication about cancer, and how having a sister with breast cancer affected them and their families. This first survey was conducted in part to address goals of the Education and Awareness Requires Learning Young (EARLY) Act—passed by Congress in 2010 to advance the awareness and understanding of breast cancer in young women. The second survey asked important questions about quality-of-life

and other areas of concern for women who have experienced a breast cancer diagnosis and treatment. Topics included medical decision-making, work–life balance, and barriers to care or healthy behaviors.

Dr. Mary C. White, Chief of the Epidemiology and Applied Research Branch in the CDC’s Division of Cancer Prevention and Control, described our unique partnership to address Sister Study and EARLY Act goals at the 7th Biennial Cancer Survivorship Research Conference, “Advancing Survivorship Care through Multilevel Collaborations,” which was held in Atlanta in June. Also at the conference, Dr. Hazel Nichols, Assistant Professor in the Department of Epidemiology at the University of North Carolina at Chapel Hill and a member of the Sister Study team, presented preliminary results evaluating mastectomy, reconstruction patterns, and treatment satisfaction among Sister Study participants with breast cancer. We look forward to sharing results about this project and many others in the future. Thank you for providing the valuable questionnaire information that makes survivorship research possible.



RESEARCH

MAKING A DIFFERENCE

Air Pollution and Asthma in the Sister Study

Women who joined the Sister Study reported detailed information about where they have lived at different ages. Addresses can be translated into “geocodes,” which use the latitude and longitude of the location of the street address. The geocodes can then be linked to geographic information on environmental exposures such as air pollution.

One of the first Sister Study analyses using these geocoded addresses looked at whether air pollution was associated with the development of asthma. Prior research has suggested a relationship with air pollution from traffic and asthma, but no published studies have focused specifically on particulate matter of very small (<2.5 micrometers) diameter (PM_{2.5}). Researchers studied these small air pollution particles, as well as nitrogen dioxide (NO₂), and the development of doctor-diagnosed asthma and respiratory symptoms in the Sister Study. More than 250 women in the Sister Study reported being diagnosed with asthma since they joined the study. In addition, more than 1,000 reported wheeze and 1,500 reported cough—both are symptoms associated with asthma. Asthma and wheeze were associated with increasing levels of PM_{2.5} exposure at enrollment addresses. NO₂ was associated with developing wheeze but not asthma.

Most air pollution research to date has focused on mortality, lung disease, and heart disease. Research on air pollution and breast cancer is limited, but conflicting. We plan to use the Sister Study data to look at other health outcomes, including breast cancer, in the near future.

Ambient air pollution exposure and incident adult asthma in a nationwide cohort of US women.

Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. *American Journal of Respiratory and Critical Care Medicine*. 2014 Aug 29. Epub ahead of print. doi:10.1164/rccm.201403-0525OC

Your Participation in the Sister Study Becomes Even More Valuable Over Time

When NIEHS scientists began the Sister Study, we chose a cohort design because of its many advantages over other designs, even though we knew it would take a lot longer than other types of research. A cohort design is a prospective study that collects information about experiences people have before they develop an outcome of interest—in our study, breast cancer. This makes it easier to interpret findings that link these experiences to getting breast cancer later. If information about past exposures is collected only after breast cancer is diagnosed, there is a chance that a woman’s exposures may have changed, or the way she remembers the past may have changed, because she has already been diagnosed.

By collecting new information every few years, we also are able to update what we know about exposures that could change over time. For example, women may stop smoking or start eating more vegetables. By continuing to collect information about factors that may be related to the chances of getting breast cancer, we can be sure that we are correctly characterizing women in terms of potential level of risk. Data from multiple points in time provide a more complete understanding of how exposures may lead to outcomes such as breast cancer—much in the same way a video gives a more complete picture of what is happening as compared with a single photograph. Finally, the chances of developing breast cancer or other diseases, such as heart disease, increase with age. So the longer we follow women, the more we can learn.

We appreciate each and every follow-up activity you complete, because it adds one more piece to solving the complex puzzle of how our life-long experiences affect our health.



Sister Study Papers 2013–2014

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Tubal ligation in relation to menopausal symptoms and breast cancer risk
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Additional Publication This Year

CpG sites associated with cigarette smoking: analysis of epigenome-wide data from the Sister Study.
Harlid S, Xu Z, Panduri V, Sandler DP, Taylor JA. *Environmental Health Perspectives*. 2014 Jul. doi:10.1289/ehp.1307480

Articles in Press

Risk-benefit profiles of women using tamoxifen for chemoprevention.
Nichols HB, DeRoo LA, Scharf D, Sandler DP. *Journal of the National Cancer Institute*. In press.

Hormone replacement therapy and young-onset breast cancer.
O'Brien KM, Fei C, Sandler DP, Nichols HB, DeRoo LA, Weinberg CR. *American Journal of Epidemiology*. In press.

Tubal Ligation Followed by Hysterectomy May Lower Risk for Invasive Breast Cancer

Tubal ligation is a surgical procedure used to prevent a woman from becoming pregnant. Some women experience changes in their menstrual cycles after a tubal ligation. Some types of tubal ligation surgery may lead to inflammation at the site of the surgery and other changes that could affect how the ovaries function. Researchers have wondered if such changes lead to early menopause or decrease a woman's chances of getting cancers, like breast cancer, that are associated with hormones such as estrogen that come from the ovaries.

Sister Study researchers analyzed data on tubal ligation, menopause, and breast cancer. Nearly 30 percent of women in the Sister Study reported having tubal ligation. Those who did were more likely to experience hot flashes and other menopause symptoms. But their age at menopause was similar to women without tubal ligation.

Overall risk of breast cancer was unaffected by tubal ligation. A small decreased risk for invasive breast cancer that was estrogen-receptor-positive and progesterone-receptor-positive (ER+/PR+) was thought to be explained by the fact that many women with tubal ligation had a hysterectomy with removal of both ovaries at a later time, which lowered the risk of ER+/PR+ tumors.

Tubal ligation in relation to menopausal symptoms and breast cancer risk.

Nichols HB, Baird DD, DeRoo LA, Kissling GE, Sandler DP. *British Journal of Cancer*. 2013 Sep 3; 109(5):1291-1295. Epub 2013 Aug 6. doi:10.1038/bjc.2013.433



Introducing Dr. Elizabeth Hodgson

Dr. Elizabeth Hodgson has joined the Sister Study team as a Senior Research Analyst at Social & Scientific Systems, Inc., in Research Triangle Park, North Carolina. Dr. Hodgson trained at the University of North Carolina at Chapel Hill, earning her doctorate under the guidance of the late Dr. Robert Millikan, Principal Investigator of the Carolina Breast Cancer Study (CBCS) and a good friend to the Sister Study. With the CBCS, Dr. Hodgson focused on gene–environment interaction, specifically on improving methods to detect breast cancer. She also worked at GlaxoSmithKline, where she developed her interests in co-morbidity and its effects on cancer risk, treatment, and outcomes. Dr. Hodgson will continue her interest in these research areas with the Sister Study. "Working on the Sister Study feels like 'coming home' to me. I am delighted to be working again on this important and challenging problem that affects so many."



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Working together, making a difference.

You can update your current e-mail address and other contact information anytime by e-mailing info@sisterstudy.org or calling toll-free: **877-4SISTER (877-474-7837)**.

Visit our website: sisterstudy.niehs.nih.gov

Sisters Changing Lives!



We are truly thankful to those of you who provided another set of samples for our *Sisters Changing Lives* initiative. Participants like Julie Kaufman continue to remind all of us why sticking with the Sister Study is important. She wrote, "I am so happy that the Sister Study exists, and it is my pleasure to participate by giving you toenail clippings, dust from the tops of my doors, blood, and other samples.

I love so many who have or had breast cancer, including my beloved sister. To know that I may be helping someone else in some small way by participating in this study makes it easy to say 'yes' when you'all call. The sample collection went just fine. Everyone was very accommodating, on time, and professional. My feedback is all positive."