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

Sisters— 2013

This is an exciting time for the Sister Study. We have nearly completed the second round of detailed follow-up questionnaires and have information needed to begin addressing important questions about breast cancer. In this newsletter, you will find examples of recent findings and initiatives that illustrate the many ways the Sister Study is contributing to medical research using both the questionnaires and the valuable biological samples you contributed when you joined the study.

Several recent papers from the Sister Study have focused on DNA modifications called methylation that may both result from environmental exposures and influence breast cancer risk. One potentially important finding is that these methylation changes may be detectable before a breast cancer diagnosis and could prove useful for helping to identify women at higher risk for breast cancer who might benefit from interventions.

To enhance this type of research, we are introducing a new initiative called *Sisters Changing Lives*, in which a subset of women in the Sister Study will be asked to provide a second set of biological and environmental samples. Last year, we introduced a partnership with the Centers for Disease Control and Prevention (CDC) that will enable us to better understand topics of interest to women with breast cancer, including quality of life, work-life balance, medical decision making, and barriers to care. This effort began in October 2012, and in less than 9 months 2,540 women had returned completed questionnaires—which was 90 percent of those who were invited to participate. This is a truly amazing feat, and we thank you for your continued commitment and rapid response.

When we started the Sister Study, we knew that some of you would be diagnosed with breast cancer during the study. Sadly, more than 2,000 of you have reported being diagnosed with breast cancer since joining. This is about twice what we would expect in women without a sister with breast cancer. It is encouraging that most of these women reported breast cancer at the very earliest stages.

In order to advance what is known about breast cancer, it is important that we obtain the most accurate information possible about the characteristics and treatment of the cancers that are diagnosed. That is why I am extending a special appeal to those of you who have been diagnosed with cancer to return the requested medical record authorization forms and a copy of your pathology report if you have it. Medical records provide the most detailed and accurate information about your diagnosis. We know that breast cancer is not a single disease, but a collection of related conditions that may have different causes and outcomes. It is important to have the specific clinical information that will help us fill in the research gaps, especially for some of the rarer and more aggressive forms of breast cancer that disproportionately affect African American women.

Lastly, we are pleased to introduce the newly redesigned Sister Study website. We hope you like the new look and find it informative. Please visit **sisterstudy.niehs.nih.gov** to enjoy the new website.

Thank you again for your continued dedication to the Sister Study. We wish you and your family the best and look forward to hearing from you.

Sincerely yours,

Dale P. Sandler PhD
Principal Investigator
The Sister Study

Research
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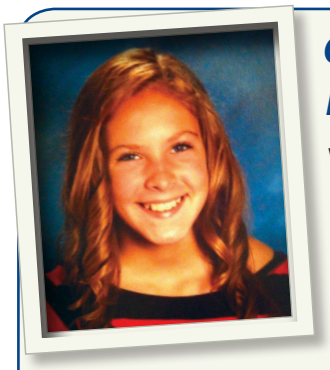
Prenatal and Infant Exposures Are Linked To Starting Menstruation at a Younger Age

Women who start their periods before they are 12 years old are more likely to develop breast cancer than are women who start menstruating later. When menstruation starts may be influenced by prenatal or early childhood factors. Sister Study researchers found that women who started their periods earlier than average (before age 12) reported being born to a teenage mother, being the firstborn child, or having a low birth weight more often than did women who started their periods about the same time as most other girls. These women also reported more often that their mothers smoked, were prescribed diethylstilbestrol (DES), or had high blood pressure or preeclampsia while pregnant with them, or had diabetes that began before pregnancy. Three of these prenatal exposures—maternal DES medication, maternal diabetes, and maternal pregnancy-related high blood pressure or preeclampsia—were most strongly associated with starting menstruation very early—at age 10 or younger. There were also differences in first age at menstruation for women who reported having been fed soy formula during infancy—women either experienced first menstruation very early (age 10 or younger) or later than average (age 14 or older).

These results support the notion that factors present very early in life, even before birth, can influence outcomes that occur much later.

Researchers generally believe that early menstruation affects breast cancer risk by exposing a woman to a higher dose of cycling hormones, especially estrogens, over her lifetime. Since early menstruation is associated with adult breast cancer, factors that affect when puberty occurs also may influence risk of adult breast cancer. We are currently looking at whether early-life factors that were associated with earlier age at first menstruation are associated with greater risk of breast cancer.

Prenatal and infant exposures and age at menarche.
D'Aloisio AA, DeRoo LA, Baird DD, Weinberg CR, Sandler DP.
Epidemiology. 2013 Mar; 24(2):277–84.



Gratitude From the Next Generation

When many of you enrolled in the Sister Study, you told us that one of your primary reasons for joining was to help ***future generations*** avoid facing the same disease your sister faced. The Sister Study team receives many heartfelt letters and e-mails not only from participants, their family members, and friends, but also from others who learn about our work. We can't resist sharing one such e-mail (with her permission) from a seventh grader who had been working on a school project about breast cancer. Carolyn sent an e-mail to the Sister Study to let us know that she was researching the topic for school, because over the past 18 months four close family friends had battled breast cancer. Carolyn said, "I have always had questions about breast cancer and your site really encouraged me, knowing people are really trying to make a difference and help the world. I hope the sisters who joined this program not only understand this can help them, but it helps me. It helps every single person breast cancer has affected. **I would love to thank all those women who took and are still taking their time to help this research.**"

It takes great dedication to participate in a long-term study. Please know that your dedication is recognized and appreciated. As Carolyn stated, it is a great contribution to future generations!

How long will the Sister Study last?

The Sister Study completed enrollment in 2009, although some women joined the study as early as 2004. We believe it is important to follow each participant for at least 10 years. Therefore, the study will last through 2019 or longer. That seems like a long time, but the longer we can continue the study, the more we will learn. It is important for us to continue to follow all women—including those who develop breast cancer—so we can also learn how genes and the environment might influence health after a breast cancer diagnosis.

Sister Study Young Investigator Awarded Grant To Study Biomarkers That May Predict Breast Cancer Development in Premenopausal Women

Information provided by Sister Study participants is the foundation for an innovative research study by Hazel Nichols, PhD, a research fellow at NIEHS. Under the mentorship of Dale Sandler, PhD, Dr. Nichols was awarded a grant from the Avon Foundation to study the role that a novel reproductive hormone called anti-Müllerian hormone (AMH) plays in the development of breast cancer. It is thought that this hormone, a marker of ovarian reserve, may have different effects on premenopausal and postmenopausal breast cancer risk. The study also will investigate oxidative stress and central adiposity ("belly fat") in premenopausal breast cancer. Biological markers will be measured in the urine and serum provided at enrollment by approximately 1,500 women sampled from the Sister Study. The grant Dr. Nichols received from the Avon Foundation was funded in part by the proceeds raised during the 8th annual Avon Walk for Breast Cancer, held October 27–28, 2012, in Charlotte, North Carolina. Dr. Nichols personally accepted the award during the Avon Walk festivities.

The Avon Foundation grant and the extensive information women in the Sister Study provide make it possible for me to focus my research on understanding breast cancer in premenopausal women. Breast cancer rates have fallen in recent years for women over 50, but not among younger women. This research will give us new clues about risk factors unique to younger women and will provide a critical first step toward preventing future disease.

— **Hazel Nichols, PhD**
NIEHS Research Fellow

When will you start reporting on environmental exposures and breast cancer?

Studies of environmental factors and breast cancer require large numbers of women with the disease in order to generate statistically meaningful results. We are now in a position to be addressing questions about environment and breast cancer. Some of the projects we have started focus on air pollution, occupational exposures, and the man-made environment. We hope to share findings with you in the near future.

Research
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Partnership Gathers Information About Cancer Awareness and Treatment

As reported last year, the Sister and Two Sister Studies partnered with the Centers for Disease Control and Prevention (CDC) to help reach goals of the 2010 EARLY Act, intended in part to increase knowledge and awareness of breast cancer in young women.

In 2011, Sister Study participants who had never been diagnosed with breast cancer themselves completed a special survey about the impact that having a sister with breast cancer has had on them and their families. The survey also covered topics such as breast cancer screening and women's personal beliefs about breast cancer. More than 20,000 sisters participated. Among those completing the survey—

- 69 percent of participants perform breast self-exams on a regular basis.
- 87 percent of participants have talked with their doctors about what their family history of breast cancer might mean for their own health and cancer risk.
- 44 percent of participants eat healthy foods, and 30 percent take vitamins or supplements more often than they did before their sisters were diagnosed.

From October 2012 through May 2103, a new questionnaire was introduced to both Sister Study and Two Sister Study participants who had been diagnosed with breast cancer to offer the perspective of breast cancer survivors. The survivorship questionnaire completed by 2,540 women focused on women's personal experiences with breast cancer and the impact that a diagnosis has had on their lives. These two surveys will offer valuable information about both the firsthand experience of going through a breast cancer diagnosis and treatment and the experiences of family members. The CDC and Sister Study research teams met in September 2013 to plan the reports they hope will come from this research. Having this knowledge can serve as the foundation for developing programs and providing resources to meet the needs of breast cancer survivors and their families. We look forward to sharing results with you soon.

Menopausal Symptoms Are Associated With a Reduced Risk of Developing Breast Cancer Before Age 50

As a woman approaches menopause, levels of estrogen and other hormones decline; this decline can cause many of the symptoms commonly associated with menopause. Women with menopausal symptoms are reported to have a lower risk of breast cancer, which could reflect differences in hormone levels. To learn if the same relationship exists for young-onset breast cancer (breast cancer before age 50), we compared women in the Two Sister Study who developed breast cancer before age 50 with their breast cancer-free sisters in the Sister Study. We examined information on history and age when menopausal symptoms such as hot flashes, poor sleep, irritability, and night sweats first started. Our results suggest that having menopause-associated symptoms at a younger age was associated with a reduced risk of young-onset breast cancer.

Menopausal symptoms and the risk of young-onset breast cancer.
Fei C, DeRoo LA, Sandler DP, Weinberg CR. *European Journal of Cancer.* 2013 Mar;49(4):798–804.

Sister Study Papers 2012–2013

Prenatal and infant exposures and age at menarche.
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Menopausal symptoms and the risk of young-onset breast cancer.
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Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood.
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Epigenome-wide association study of breast cancer using prospectively collected Sister Study samples.
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Global DNA methylation and one-carbon metabolism gene polymorphisms and the risk of breast cancer in the Sister Study.
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Additional Publications This Year

Association between urinary prostaglandin E2 metabolite and breast cancer risk: a prospective, case-cohort study of postmenopausal women.
Kim S, Taylor JA, Milne GL, Sandler DP. *Cancer Prevention Research.* 2013 Jun; 6(6):511–8.

Early-life exposure and early onset uterine leiomyomata in black women in the Sister Study.
D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP. *Environmental Health Perspectives.* 2012 Mar;120(3):406–12.

Fertility drugs and young-onset breast cancer: results from the Two Sister Study.
Fei C, DeRoo LA, Sandler DP, Weinberg CR. *Journal of the National Cancer Institute.* 2012 Jul 3;104(13):1021–1027.

Serum microRNA expression as an early marker for breast cancer risk in prospectively collected samples from the Sister Study cohort.
Godfrey AC, Xu Z, Weinberg CR, Getts RC, Wade PA, DeRoo LA, Sandler DP, Taylor JA. *Breast Cancer Research.* 2013 May 24; 15(3):R42.

Early-Life Conditions May Influence the Development of Rheumatoid Arthritis in Adulthood

Rheumatoid arthritis (RA) affects approximately 1 million adult women in the United States. RA is a chronic inflammatory condition affecting the small joints in the hands and feet that is more common in women than in men. Some research suggests that women with RA are less likely to develop breast cancer, although the reasons for this are not known. Therefore, research about RA may be of special interest to the Sister Study.

RA has been associated with lower adult socioeconomic status (SES). Although there is reason to think that SES in childhood may be important, there has been little research. Because of the extensive life histories provided by Sister Study participants, we were able to study the impact of SES factors during childhood and even before birth on developing RA as an adult. We found that RA was more common in participants who reported factors such as being born to a teenage mother, not having enough to eat at times as a child, being raised in a family with a relatively low income, or having all parents/guardians in the household who had less than a high school education. RA was most common among women who reported at least two of these low childhood SES factors and had less than a college education. In addition, women who weighed less than 5.5 pounds at birth, or whose fathers smoked 3 months before their mothers became pregnant with them, were more likely to develop RA as adults. Overall, this tells us that research on early-life factors and RA is on the right track. Future research can try to pinpoint how these factors may increase risk of RA.

Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood.
Parks CG, D'Aloisio AA, DeRoo LA, Huiber K, Rider LG, Miller FW, Sandler DP. *Annals of the Rheumatic Diseases.* 2013 Mar; 72(3):350–6.

Research
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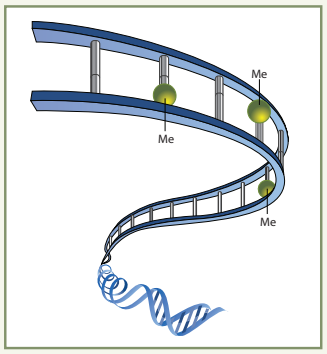

What Is DNA Methylation and Why Is it Important?

DNA methylation (Me) is a chemical modification to DNA that can change the way genes are turned on and off to form proteins. Some DNA methylation can be inherited, but methylation also appears to be gained or lost over time in response to age, lifestyle, and environmental exposures. Studying the links between environmental exposures (which may be modifiable), methylation changes, and risk of cancer is an exciting new area of research.

Overall DNA Methylation May Be Related to Physical Activity

Sister Study investigators used blood DNA global methylation information to evaluate the relationship between overall DNA methylation and physical activity among women. We studied physical activity for three different time periods: childhood (ages 5–12), teenage years (ages 13–19), and currently (the previous 12 months). Physical activity was measured by combining information on recreational physical activity, such as sports or walking for exercise, with data on daily activities that require physical exertion, such as house cleaning or gardening. Women at or above the median physical activity level for one, two, or all three time periods had higher levels of overall methylation when compared with women with below median levels of physical activity. Results were even stronger for women with higher than average physical activity in more than one period of their lives. These results provide a valuable clue to a precise biological mechanism linking exercise and lower cancer risk, and extend our understanding of how exercise at all ages may help prevent breast cancer.

Recreational and household physical activity at different time points and DNA global methylation.
White AJ, Sandler DP, Bolick SCE, Xu Z, Taylor JA, DeRoo LA. *European Journal of Cancer.* 2013 Jun;49(9):2199-2206.

I need my Study ID to access a web survey. Can you e-mail it to me?

Your Study ID is found on printed study materials (forms, questionnaires, and letters). For your privacy, we are unable to e-mail the ID number; please call the Sister Study Help Desk toll-free at 877-4SISTER (877-474-7837) if you need assistance.

Sister Study Samples Show That Methylation Patterns Hold Promise for Breast Cancer Risk Prediction

Age as well as reproductive, family, and medical histories can be used to estimate the risk of developing breast cancer using a method called the Gail model, but this estimate is only about 58 percent accurate. Information about common genetic polymorphisms (inherited changes in the sequence of DNA) has an accuracy rate of about 60 percent, and together the Gail model and common polymorphisms have an accuracy rate of 62 percent—better, but still in need of improvement.

To address this problem, a team of Sister Study researchers hypothesized that patterns of DNA methylation might be better predictors for breast cancer. The team, led by Jack Taylor, MD, PhD, used DNA extracted from blood samples of Sister Study participants to look at more than 27,000 different methylation sites on DNA and compared methylation patterns of women who later developed breast cancer with those of women who did not. Results showed that methylation patterns had an accuracy rate of 66 percent—better than the Gail model and common polymorphisms combined. Although a 4 percent change in accuracy is small, this is highly statistically significant and suggests that a broader look at many more methylation sites might lead to further improvements in breast cancer prediction.

Epigenome-wide association study of breast cancer using prospectively collected Sister Study samples.
Xu Z, Bolick SCE, DeRoo LA, Weinberg CR, Sandler DP, Taylor JA. *Journal of the National Cancer Institute.* 2013 May 15; 105(10):694–700.

In a related study, Sister Study investigators also used blood DNA to estimate the overall or "global" level of methylation across the genome, again comparing samples from women who later developed breast cancer with those who did not. In a paper that was recently accepted for publication, they show that women with the lowest levels of global methylation have almost twice the risk of developing breast cancer compared with women with the highest levels.

Global DNA methylation and one-carbon metabolism gene polymorphisms and the risk of breast cancer in the Sister Study.
DeRoo LA, Bolick SCE, Xu Z, Umbach DM, Shore D, Weinberg CR, Sandler DP, Taylor JA. *Global Carcinogenesis 2013.* doi: 10.1093/carcin/bgt342

New 2013–2014 Sisters Changing Lives *Initiative Coming Soon*

Some Sister Study members will be asked to be a part of an important new initiative involving the collection of a second set of biological and environmental samples. Both the Sister Study Scientific Advisory Board and our Steering Committee have stressed the importance of having more than one set of samples from individuals in the study to help identify the factors that contribute to breast cancer risk.

The Sisters Changing Lives initiative will include two groups of participants: those who have developed breast cancer since enrolling in the Sister Study and a random sample of everyone else in the study. About 4,000 women will be asked to participate. The second set of samples from women with breast cancer will help researchers identify changes in biological factors that may be associated with breast cancer development or treatment. The samples collected from those without breast cancer will allow researchers to evaluate how exposures change over time and to help determine if biological changes seen in breast cancer patients are due to age and natural variation rather than to breast cancer *per se*. The repeated dust samples will help determine how exposures change over time and if the baseline samples can be used as a measure of usual exposures or just exposures at the time they were collected. The sample collection will be almost identical to what was done at enrollment except there will be ***no*** long questionnaires to complete! Stay tuned for further information and invitations over the coming months.

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The Sister Study is conducted by the National Institute of Environmental Health Sciences—one of the National Institutes of Health of the U.S. Department of Health and Human Services.

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

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 new website: **sisterstudy.niehs.nih.gov**

Is it possible to get my test results?

Individual blood tests are not available. All of the tests are for research purposes only and are not intended to be used as diagnostic tests or to make decisions about your medical care. Most tests are not done for all participants, and it may be years before we test your blood sample; having stored blood samples allows researchers to take advantage of future advances in science and technology and to do the tests that are most likely to give us new information about breast cancer. If you have concerns about your health, please discuss them with your health care provider.

I was contacted by the Sister Study about participating in another effort. I thought I was already participating in the Sister Study and my data would not be shared with others.

The Two Sister Study and the Young Women's Breast Cancer Project are examples of additional studies that are associated with the Sister Study. These studies are being conducted by members of the Sister Study team and collaborators. As we promised when you joined the study, we allow only qualified collaborators to use the valuable data you provided, and strict privacy protections are followed. You and the study team have made a significant investment in the Sister Study. It is important that we take full advantage of the information that has been collected to contribute new knowledge about breast cancer and other conditions.