Sister Studies Aim To Shed Light on Breast Cancer Risk

By Susan Jenks

Two years after surpassing an enrollment goal of 50,000, the Sister Study is on track for investigators to analyze urine, blood samples, toenails, and even particles of dust for clues about how breast cancer develops.

But with the study’s long-term design—4 years for recruitment and 10 years of follow-up (through 2018)—it’s far too early to single out a definitive reason why the disease strikes one sister and not the other, according to researchers at the National Institute of Environmental Health Sciences conducting the study.

“The Sister Study is designed to be somewhat open-ended in the sense that we’re trying to address a lot of different hypotheses,” said Lisa DeRoo, Ph.D., a lead investigator and staff scientist at NIEHS, who ticks off a long list of possible environmental and hormonal triggers whose interaction with a woman’s genetic history may lead to breast cancer.

Although the list includes (among other factors) exposure to pesticide residues, air pollution, and heavy metals, “it’s too soon to suggest which factors are strongest,” she said.

When the study first began in 2004, none of the enrolling women had breast cancer. But each had a sister or sisters with the disease, elevating her personal risk, based on genetics alone, to 2.5 times that of the general population. Some 1,600 of the women since have developed breast cancer, slightly more than anticipated.

DeRoo and other investigators say that baseline data from the Sister Study’s extensive questionnaires are providing a rich resource for examining early-life exposures even in the perinatal environment that may influence breast tissue development and later risk of breast cancer. A companion project begun in 2008, the Two Sister Study, focusing only on women younger than 50 years with breast cancer, has already yielded preliminary data on the use of fertility drugs and early-onset breast cancer. However, its findings still await publication.

Because the women in the Two Sister Study have been diagnosed with cancer, “we can do case-control analyses” such as this, said Dale Sandler, Ph.D., principal investigator of the Sister Study and chief of the epidemiology branch at NIEHS. “We looked at fertility drugs first not because we consider this the greatest risk for early-onset breast cancer but because we had an interest. Fertility drugs convey a big dose of hormones.”

Sandler described the two studies as complementary, because the Two Sister Study consists mostly of women with breast cancer who were the sisters of women in the first study. Some 1,400–1,600 women are now enrolled in this spin-off effort, meeting researchers’ target goal. Observations from the cancer cohort then will be tested in the larger group to see whether they hold.

“‘The idea is to carry out efficient and more affordable studies, by analyzing samples for cases along with a random sample of the study cohort.’”

“‘There’s been a big push to make the cohort as representative of the general population as possible,’” said Clarice Weinberg, Ph.D., principal investigator of the Two Sister Study and chief of the biostatistics branch at NIEHS. She said about 9% of the study group are black, 5% are Hispanic, and 3% are in other racial groups.

NIEHS scientists have not yet analyzed specimens for the breast cancer susceptibility genes BRCA1 and BRCA2, but they have used peripheral blood samples to see whether the presence of shorter telomeres in these chromosome regions statistically correlated with breast cancer risk. It did not.

“We know telomeres are shorter in cancer tissue, although breast cancer literature is all over the place as to the specific risk for breast cancer,” Sandler said. “In our study, we found no relationship, even though [a shorter length] is associated with other risk factors that raise the risk of breast cancer,” such as obesity.

These results appeared in the July issue of Cancer Causes and Control. Researchers compared telomere length in 342 women who later developed breast cancer with telomere length in a random sample of 735 women in the Sister Study who did not develop the disease.

Weinberg said she hopes to delay genotyping women in the Two Sister Study to secure additional funding for more extensive testing than just the typical candidate genes long associated with cancer risk, such as p53 or DNA-repair genes.

“If you look only at known genes, you find out only what’s known,” she said. “We want to find new things. We want to look at genetic factors that predict long-term health in cancer patients.”

Nationwide Study

The 50,884 women enrolled in the studies live in all 50 states and Puerto Rico. They range in age from 35 to 74 years, with a mean age of 50 years. About 16% are minorities.

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Survival and Other Issues

As part of a recent interagency agreement with the Centers for Disease Control and Prevention, NIEHS is combining data

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from survivors in the Two Sister Study and the Sister Study to examine how breast cancer affects families’ emotional and financial health, along with what enables one woman to survive and causes another to succumb.

“I think anybody who knows somebody like my husband’s great-aunt, who lived to 99 and never stopped smoking, wants to know why,” Weinberg said. “No, she never got cancer. She just wore out. But predictors of good health are important.”

Sandler also stressed the Sister Studies’ ongoing ability to look at these predictors of good health, as well as other diseases that develop besides breast cancer.

“The idea is to carry out efficient and more affordable studies by analyzing samples for cases along with a random sample of the study cohort,” she wrote in a follow-up e-mail. “In this way we can keep the cost of assays manageable.”

So far, the initial cost has been around $50 million to create data repositories and collect initial samples, according to Sandler. But it could ultimately cost $90 million, she said, despite funding from other sources, including the Susan G. Komen Foundation and the National Center on Minority Health and Health Disparities.

The future of funding is as uncertain as the potential needs of the study.

“We have the ability to look at a whole range of environmental and hormonal factors, but before we do that, we have to make sure that a single blood sample is enough,” Sandler stressed. “And the timing of when a sample is drawn is also an issue.”