

CONTENTS

All in the Family

BY CHARLOTTE HUFF

Registries reveal links for cancer that runs in the family.

Joyce Calabria describes her aggressive battle with breast cancer not as an isolated diagnosis, but rather as the latest branch on a vulnerable family tree.

Her aunt died of breast cancer at age 35. Her sister was diagnosed about seven years ago, in her early 50s. Calabria first sat down with an oncologist in 1990, at age 33, when she was diagnosed with stage 3 inflammatory breast cancer. She fought the cancer successfully then and in 2002 when another primary cancer appeared in her opposite breast.

Rather than shy away from those family connections, Calabria wants to mine and share whatever information she can to assist her family and others. She was screened for genetic markers in 2000 and tested positive for a mutation in the BRCA2 gene, which markedly increases a woman's lifetime risk of breast and ovarian cancers, as does a mutation in the BRCA1 gene. She has encouraged both of her daughters, now in their 20s, to get tested. And she's been enrolled for at least 10 years in the Fox Chase Cancer Center's family registry, one of six breast cancer sites participating in the National Cancer Institute's breast and colon cancer family registries.

"I thought the more information I have, even if it didn't help me, it would help the rest of my family," says Calabria, a 51-year-old New Jersey resident. "You can't have enough research when it comes to family."

By 2006, nearly 26,000 people had enrolled in the NCI's breast and colon cancer family registries, an international coalition that includes 12 primary sites, along with other affiliated sites. The registries, first formed in the mid-1990s, include participants from Australia and Canada, among other countries. In addition, many other U.S. medical centers also run family registries, targeting a variety of malignancies, including melanoma, pancreatic, and prostate.

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—Alice Whittemore, PhD

Their goal: to track individual cancer patients and sprawling families, ideally over the course of decades. By collecting detailed lifestyle and medical information, along with blood and other samples, researchers hope to develop a multifaceted picture of not only which genes influence cancer's development, but also how those genes interact—for better or worse—with environmental influences and lifestyle choices. That information, they say, can provide crucial cancer-fighting clues for all families, whether they carry known genetic markers or not.

“Some women who carry BRCA mutations, for example, reach the age of 75 or 80 without ever developing breast or ovarian cancer,” says Alice Whittemore, PhD, a Stanford University professor and co-investigator of the Northern California Cooperative Family Registry for Breast Cancer. “What is protecting those women? Is it their lifestyle or some other genes they carry?”

Whittemore and other investigators are assisted in their research by increasingly sophisticated techniques— from epidemiological analyses to gene sequencing—to sift through the vast data and complex biology to unlock some of cancer's secrets. “I think we are at the tip of the iceberg,” says Mary Daly, MD, PhD, principal investigator of the Margaret Dyson Family Risk Assessment Program at Fox Chase Cancer Center in Philadelphia. “We spent a lot of time for the first 10 years collecting the resources. Now we are in the explosion phase of doing this research.”

Making the Connections

Family registries break down into two primary types, population-based registries or clinic-based settings. And both approaches, Whittemore says, are vital to better understanding cancer's development.

Population-based registries, which typically draw from cancer registries operated by state governments or other public entities, collect information across a broader crosssection of patients, since the diagnosis is usually a reportable disease. Clinic-based registries, which draw participants from high-risk clinics, are not as reflective of the overall cancer population, attracting people with a higher education and income level, Whittemore says. But those clinics remain a rich repository of information about BRCA1, BRCA2, and other genetic markers, because carriers are disproportionately represented, she says.

Specifics can vary, but registry participants are typically asked to fill out detailed questionnaires, answering queries about not only family medical history but also diet, alcohol consumption, and other behaviors. Samples, including blood and tumor tissue, may be taken.

Unraveling differences between cancer survivors and closely related family members, such as siblings, can be particularly illuminating. “They are the closest, not only genetically, but also in shared diet, because they grew up together and have a shared socioeconomic status,” Whittemore says. “This allows researchers to look at differences within families and between families.”

Researchers hope the sophisticated assembly of genetic information coupled with lifestyle, environmental, and long-term clinical information will allow greater ability to counsel and treat people with predispositions through personalized activity, dietary recommendations, and customized screening techniques.

Bearing Fruit

Already, the cancer family registry research is starting to produce results.

Information collected by the NCI's Breast Cancer Family Registry, along with a couple other research coalitions, has spawned some initial insights into the impact of certain behaviors on carriers of BRCA1 or BRCA2. One recent study identified no added breast cancer risk among carriers who had taken oral contraceptives for at least a year. But they found longer-term use, at least five years, may be associated with increased risk for BRCA2 carriers, according to the results published in 2006 in the journal *Cancer Epidemiology Biomarkers & Prevention*. Another research analysis, also published in 2006 in the same journal, found no increased risk related to alcohol consumption.

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Polly Newcomb, PhD, co-investigator of the Fred Hutchinson Cancer Research Center's Colon Cancer Family Registry, describes research in which she's involved that strives to identify relative survival for those who inherit genetic markers for colon cancer. So far, the results are encouraging, she says.

The research shows genetic carriers might have a better survival than the general population that develops colon cancer. But research is still ongoing and family registries, like the Seattle site at the Fred Hutchinson Cancer Research Center, are vital not only to resolving that question, but also other strategies that could improve colon cancer longevity, she says.

A multitude of other research projects continue. By this spring, nearly 90 research projects had emerged from the Breast Cancer Family Registry and about 110 were connected to the Colon Cancer Family Registry, according to data provided by Sheri Dixon Schully, PhD, a program director with the Epidemiology and Genetics Research Program at the NCI.

Clarifying genetic links can pave the way to new drug therapy. A better understanding of the von Hippel-Lindau, or VHL, gene malfunction has resulted in new drugs, such as Nexavar (sorafenib) and Sutent (sunitinib), to inhibit the blood supply that fuels kidney cancer's growth. Researchers discovered a mutation in the VHL tumor suppression gene in many clear-cell renal cell carcinomas, one which they believed encourages the growth of cancer-promoting blood vessels.

Sharing Information

As registries proliferate, many have made an effort to boost enrollment among under-represented minority groups to ensure a diverse genetic profile. Steps also have been taken to protect the interests of participants. To that end, the NCI family registries use patient advocates called community representatives. “I think it’s really important that the consumer goes into this with their eyes open,” says Sylvia Rickard, a community representative and breast cancer survivor. “And that they get the counseling they need and their family needs.”

Privacy is protected by replacing names with unique numerical identifiers. “I am pleased to say I know of no names whatsoever in my research,” Whittemore says.

But what if participants want to know their genetic results? Dr. Daly estimates about 20 genetic markers— associated with a wide variety of cancers—have been identified that might have clinical value to patients.

In the early years, registries generally didn’t share genetic details, Dr. Daly says. “People used to argue, what’s the point of telling someone because they can’t do anything about it?” she recalls. Now some interventions are available, such as removal of the ovaries for women with BRCA1 or BRCA2. Most registries, including Fox Chase, share validated genetic markers with participants if they want to know, Dr. Daly says. Other results, if it’s unclear what they mean, are not disseminated.

Registry participants, if willing, may be followed for years. Calabria continues to fill out annual questionnaires updating her family’s information. Her 29-year-old daughter, Gina Groves, was just tested in June and learned that she also carries the BRCA2 mutation. As a result, she’ll receive rigorous mammography screening in the years ahead.

“It’s my hope that my children and their children will continue [registry participation] after I’m gone,” Calabria says. “I feel like we are finally starting to get somewhere as a family. Perhaps by the following generation, they will be closer to finding the solution.”