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Most carriers of Fanconi anemia genes are not at a higher risk of cancer

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For almost 50 years, Fanconi anemia has been associated with leukemia. Not just among those who have the genetic disorder but among their family members, whose genes, they were told, made them highly susceptible to a variety of malignancies. But a new study to examine links between 13 specific Fanconi anemia genes and cancer risk has determined that in most cases, their risk of cancer is no greater than that of the rest of the population.

Fanconi anemia is primarily an autosomal recessive genetic condition, which means that in order for it to develop, a person must inherit two mutated Fanconi anemia genes, one from each parent. To date, 13 such genes have been identified and all of them, in Fanconi anemia patients, are associated with a greater than average risk of developing solid as well as blood-based cancers, among other conditions.

The question that Rockefeller University Associate Professor Arleen Auerbach and her team of American and German researchers investigated is one she says has worried families of Fanconi anemia patients for decades: whether a single Fanconi anemia gene increases cancer risk. A pivotal 1971 epidemiological study suggested that cancer risk is, indeed, elevated in Fanconi carriers, although no molecular genetic analysis was performed, Auerbach says. When a 2002 study linked Fanconi anemia to the BRCA2 gene, researchers suggested that inherited mutations in any of several genes might result in cancer risks for Fanconi anemia. “This produced a kind of mass hysteria among family members because they believed carriers were all at increased risk

for cancer in general and breast cancer in particular," Auerbach says.

But the new data, which Auerbach and her colleagues spent six years collecting and analyzing, suggests that besides those with BRCA2 mutations, only one subgroup of Fanconi anemia carriers — older women who carry a single mutated FANCC gene — develop more than the expected amount of cancer. Investigators further found that the cancer these women developed was of one type — breast cancer. In this study, grandmothers of Fanconi anemia patients who carry an FANCC gene were almost 2.5 times more likely to have developed breast cancer compared to women without the gene, says Auerbach, director of the Laboratory of Human Genetics and Hematology and the study's lead investigator.

"This suggests that the FANCC gene is a breast cancer susceptibility gene, and that women who carry it should be screened for breast cancer on a regular basis," Auerbach says. The FANCC gene is the second most common Fanconi anemia gene, accounting for about 15 percent of Fanconi anemia families. Many women may already know they carry a mutated gene because FANCC is part of the routine pre-pregnancy genetic testing panel available for persons of Ashkenazi Jewish descent, she says. Half of all families of this Fanconi subtype (called FA-C) are of Ashkenazi heritage.

"Generally speaking, however, these findings are very good news for many people whose families have been affected by Fanconi anemia, because for many years, the assumption has been that anyone who possesses a single mutated gene associated with the disease is at higher risk of developing cancer," Auerbach says.

The study examined genes from 784 grandparents and 160 other relatives; there were six breast cancers observed among the 33 grandmothers who had a FANCC gene mutation, compared to the 2.5

breast cancers that would be expected. Two other excess breast cancers were found in other female relatives with a mutant FANCC gene.

In addition to quelling the fears of a number of Fanconi anemia gene carriers, the study also cast doubts on theories by which Fanconi anemia genes produce cancer in people who inherit two copies, she says. All 13 genes had been believed to be related to a cancer-causing pathway involving BRCA1 and BRCA2, genes known to be involved in genetic damage repair (but which, when mutated, are breast susceptibility genes) and which are believed to work with Fanconi anemia genes. But this study suggests that only one of the 10 known FA genes found "upstream" of BRCA2, FANCC, may play a role in cancer development.

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